Healthier Materials in Buildings: Assessments of Global Chemical Exposures, Hormonally Active Dust, and Product Interventions

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Hormonally Active Dust, and Product Interventions

Anna Young

A dissertation submitted to the faculty of the

Harvard Graduate School of Arts and Sciences and

Harvard T.H. Chan School of Public Health

in partial fulfillment of the requirements

for the degree of Doctor of Philosophy

in the department of Population Health Sciences

in the Environmental Health area of study

Harvard University

Cambridge, Massachusetts

May 2020

Advisor: Joseph Allen Anna Young

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ABSTRACT

We spend 90% of our time inside buildings, where we are exposed to many semi-volatile organic chemicals harmful to human health. Polybrominated diphenyl ethers (PBDEs), organophosphate esters (OPEs), per- and polyfluoroalkyl substances (PFAS), and polychlorinated biphenyls (PCBs) are four classes of persistent chemicals that have been commonly found in building materials, migrate out into air and dust, and have been detected in the blood or urine of over 90% of Americans. With a focus on these chemical classes in office buildings, the aims of this dissertation were to assess 1) global differences in chemical exposures, 2) the hormonal activity of indoor dust due to its chemical components, and 3) the impact of a "healthier" materials intervention on levels of chemicals in dust.

First, we evaluated exposures of 130 office workers in the USA, UK, China, and India to PBDEs, OPEs, and PCBs using silicone wristbands to sample chemical exposures during work hours. Our findings showed substantial differences across the four countries, which have varying regulations for each chemical class. Some office workers were exposed to legacy PCBs and PBDEs decades after chemical phase-outs due to the long lifespans of building materials. We also found frequent exposures to PCB-11, a contemporary, unintentional byproduct (not banned) in pigments. Exposures to DecaBDE were higher than PentaBDE due to either later phase-outs

or restriction exemptions in all four countries. Seven OPEs were detected in nearly all wristbands. Participants in the USA and UK often had higher BFR and OPE exposures, at least partially due to the older and more strict flammability regulations compared to China and India.

Second, we quantified hormonal activities of 46 university building dust samples in novel cell-based assays and evaluated associations with measured concentrations of PFAS, PBDEs, and OPEs. We assayed estrogen receptor activation, androgen receptor suppression, peroxisome proliferator-activated receptor suppression, thyroid hormone receptor suppression, and thyroid hormone transport interference. All dust samples were hormonally active, and every assay endpoint had significant or suggestive associations with at least one chemical class.

Third, in the same buildings, we evaluated the impact of "healthier" furniture and carpet materials on the chemical concentrations in dust. Rooms with full "healthier" materials interventions were associated with substantially lower dust levels of PFAS and OPEs and suggestive evidence of lower PBDE levels compared to rooms with no intervention or a partial intervention. We found that old buildings continued to contaminate dust with legacy chemicals, even if the chemicals had since been phased out. We also identified electronics and exposed insulation as two other important product categories to address next.

In summary, we found that global office buildings influence worker exposures to both legacy and contemporary chemicals, that these chemicals contribute to hormonally active dust in buildings, and that "healthier" materials can reduce the chemicals in building dust. There are actionable solutions to reduce these chemicals indoors and prevent future legacy chemicals. The decisions we make today on healthier materials in buildings will influence the health of generations to come.

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ACKNOWLEDGMENTS

This dissertation is dedicated to all my mentors, collaborators, and peers who made this research possible. First, I'd like to thank my advisor, Dr. Joseph Allen, who first mentored me during the Master of Science program and who showed me the value of high-impact, solutions-driven, and fast-paced academic research. Dr. Allen always challenged the Healthy Buildings team to think up "the next big idea" for public health impact in our fields and consistently guided us in not only research but also skills training for media interviews, stakeholder engagement, and translation of science for public communication. I would not have pursued this PhD or a career in academia without his mentorship and guiding example.

I'd also like to thank the other faculty members on my dissertation committee: Drs. Russ Hauser, Tamarra James-Todd, and Brent Coull. It's been an honor to work with Dr. Hauser, whose research has formed the foundation of much of our knowledge about the health impacts of hormone-disrupting chemicals and who has provided invaluable feedback on the novel exposure assessment methods. Dr. James-Todd has been an inspiration and role model to me and has continually offered unique perspectives on drivers of chemical exposure disparities and challenged me to think holistically about key takeaway messages and communication back to populations. I've also deeply appreciated Dr. Brent Coull's guidance on statistical analyses. Dr. Coull's ability to clearly explain complex concepts was critical for understanding different approaches to reduce the dimensions of a large, multilevel 100-chemical exposure dataset.

Thank you to all our collaborators who have helped us develop this research and have served as my mentors: Drs. Heather Stapleton, Thomas Zoeller, Peter Behnisch, Nick Herkert, Kurunthachalam Kannan, Hongkai Zhu, and Aaron Specht. I'd especially like to thank Heather Henriksen, who has been an incredible leader in the healthier materials movement and has

demonstrated the power of translating science into real public health action; you are a force to be reckoned with. Thank you to other mentors who have helped guide me during my training: John Ullman, Drs. Elsie Sunderland, Keith Houck, Russell Thomas, and Carmen Messerlian.

I want to acknowledge the Healthy Buildings team, who make it a dream to come into work every single day. Thank you especially to all the previous graduates who have advised me throughout the PhD process and have served as my inspiration – Drs. Erika Eitland, Jie Yin, Memo Cedeño, Piers MacNaughton, and Parichehr Salimifard. I also want to thank our Global Buildings study team who have worked together to pull off a massive feat of sampling logistics, led by Memo Cedeño and Piers MacNaughton and including Emily Jones, Maya Bliss, Skye Flanigan, Jose Vallarino, Xiaodong Cao, Marianne Lahaie Luna, and Sammi Chung. Thank you to everyone on the Healthy Buildings team who also helped with field sampling, which was never a glorious task and often included *very* early mornings of vacuuming: Maya Bliss, Marianne Lahaie Luna, Kaitlyn Ponti, Quentin Campbell, Emily Jones, Erika Eitland, Jose Vallarino, Parichehr Salimifard, Sydney Robinson, Ian Leavitt, and Aaron Specht.

A special thanks to all my friends who have supported me during this time, especially my fellow cohort members Dina Goodman, Cristina Gago, Nazleen Khan, Emily Jones, and Erika Eitland, as well as other friends including Laura Miyares, Philile Shongwe, Onella Dawkins, Esther Lim, Suna Park, Bethany Hull, Carey Marr, Lucy Dempsey, and Meredith Shanoski. It means the world to me to have such a community of strong, brilliant, fierce women. Thank you also to my parents Kenlyn and John Young, who taught me hard work (especially when completing a degree with high school children) and meticulousness (always "getting our ducks in a row") and who never doubted for a second that I could try to pursue a career in STEM. Thank you to my grandparents Ann and Stanley Riggs–the original PhD in the family–who always

provided our family with a swampland escape “back to the earth” and have spent their lives advocating for the health of the planet. Thanks to my cousin Caitlin Baumann, who is a fierce woman in global health always down to nerd out on scientific research–or beach reads–with me.

Finally, I’d like to acknowledge the funders of this research. Study 1 was funded by NIOSH Grant T42 OH008416, NIEHS Grant ES000002, and the Marilyn Hoffman Program on Chemicals and Health at Harvard. The research in Studies 2 and 3 was made possible by the Harvard Office for Sustainability’s Campus Sustainability Innovation Fund, NIH Grant P30ES000002, NIOSH Grant T42 OH008416, NIH Grant P30ES000002, and NIOSH Grant 1K01 OH011648.

CHAPTER 1: Introduction

Harmful Chemical Classes in Building Materials

We spend an average 90% of our time inside buildings,[1] where we are exposed to many harmful chemicals, as well as many more chemicals that have not been independently tested for safety. Only a small fraction of 550,000 catalogued chemicals have any health hazard information (20%), exposure data (4%), or human biomonitoring data (0.07%).[2] Even the chemicals we know to be harmful to human health still ubiquitously expose populations. For example, polybrominated diphenyl ethers (PBDEs), organophosphate esters (OPEs), per- and polyfluoroalkyl substances (PFAS), and polychlorinated biphenyls (PCBs) are four classes of anthropogenic chemicals that are widely found in building materials and have been well-documented as human endocrine-disruptors or carcinogens.[3–7] Nonetheless, these chemicals have been detected in the blood or urine of over 90% of Americans.[8–12] Buildings, and the materials that reinforce or furnish them, are a critical but often overlooked determinant of health.

Due to their use in building materials, PBDEs, OPEs, PFAS, and PCBs are frequently found in building air and dust that occupants breathe, touch, and ingest.[13,14,23–31,15–22] PBDEs and OPEs have been used as flame retardants in furniture, carpet, electronics, and building insulation,[32–37] and OPEs are also added as plasticizers to furniture, floor finishes, plastic, rubber, paints, and other products.[38,39] Both chemical classes have been shown in epidemiologic research to be associated with harmful impacts on thyroid function,[5,6,48–50,40–47] fertility, pregnancy outcomes,[5–7,48,51–56] and brain development.[5,6,43,57–61] PFAS are a class of highly fluorinated, stain-resistant, and water-repellant chemicals applied as coatings to furniture, carpet, other building materials, and many consumer products.[4,62–66] Human exposure to PFAS is associated with thyroid disease,[41,67–70] elevated cholesterol,[71–75] impairment of fetal development,[69,76]

suppression of the immune system,[68,77,78] cardiometabolic disorders such as obesity and diabetes,[4,71,72,79–81] and kidney and testicular cancers.[82–88] Finally, PCBs are human carcinogens[3,89,90] and endocrine disruptors[91–93] and were historically used in caulking, adhesives, paints, plastic, and many other materials in building construction and design.[15,94–97] Despite the known and concerning health impacts of these four chemical classes, there have been several barriers to success of regulatory and market-based approaches to reduce population exposures.

First, chemicals are often treated separately and addressed one at a time, which can lead to so-called 'regrettable substitution' of an eliminated chemical for another less widely known chemical with a similar toxicological profile.[98] For example, two of the most common and well-studied PFAS, perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS), were largely phased out by manufacturers in the United States (USA) and European Union (EU) in the last two decades.[4,99] However, PFOA and PFOS were often simply substituted with similarly concerning alternatives from the same chemical class, including new short-chain PFAS as well as other PFAS that break down into PFOA and PFOS.[100–102] In fact, there are more than 4,700 different PFAS commercially available.[103] Flame retardants have a similar history. PBDEs were historically used as flame retardants in the USA and EU until many of them were voluntarily phased out or banned in 2004 due to concerns about their health impacts.[22,104] However, another common mixture of PBDEs, DecaBDE, was not removed from production until 2013 in the USA and 2019 in the EU.[22,105] Additionally, PBDEs were often replaced with OPEs, which are also hormone disruptors but do not undergo the same restrictions for building materials.[9,22,25,35,98]

Second, chemical regulations and phase-outs can vary widely worldwide. For example, PCBs were banned or removed from production in the 1970s and 1980s in the USA, EU, and China,[106–108] but India only officially banned PCB production and importation in 2016.[109] In

addition, production of PFOA and other types of PFAS have continued to increase in low- and middle-income countries (LMICs) such as China and India, possibly even offsetting the declines achieved from restrictions in certain high-income countries (HICs).[110] Although PBDEs are on the list of banned substances by the global Stockholm Convention (which China and India have ratified),[111,112] China and India have technically only passed restrictions on certain PBDEs for electronic products.[113–117] Due to country disparities in restrictions, exposures to phased-out chemicals can still largely persist globally despite eliminations in a particular region.

Third, even if a chemical is removed from production, products containing that chemical can still be found in buildings for several decades. In particular, pre-existing materials containing PCBs are still present in older buildings despite bans implemented 40 years ago,[106–108] and PCBs continue to leach out of the materials into indoor environments.[13,14,95,97,106,118,119] Furthermore, the recycling of products, such as electronics with PBDEs, can cause phased-out chemicals to carry over into new products, thus prolonging exposures to chemicals originally used in older materials.[120–122] Such semi-volatile organic chemicals can persist indoors for many years due to their slow release rate from materials and their partitioning into sorbed states.[123] Many PFAS, PCBs, PBDEs, and OPEs are environmentally persistent chemicals.[38,45,124] In fact, a common subclass of PFAS called perfluoroalkyl acids (PFAAs) are so extremely persistent that they will never appreciably degrade under environmental conditions.[4,102,125] Because we are exposed to persistent chemical classes in building materials long after restrictions of certain chemicals in certain countries, the decisions we make about materials have lasting impacts.

Strategies that target entire chemical classes seek to prevent regrettable substitution of persistent chemicals, but there is currently very little research that has scientifically evaluated the benefits of class-based chemical interventions inside buildings. For example, to our knowledge,

no studies have assessed an intervention on PFAS indoors. Only two studies have investigated the benefits of a class-based intervention to eliminate flame retardants in childcare nap mats[126] or gymnastics pit foam.[127]

The goal of this dissertation is to evaluate, in the buildings where we work and learn, 1) global disparities in chemical exposures, 2) hormonal activity of indoor dust due to its chemical components, and 3) an intervention on chemical classes in building furnishings. The research framework of our aims in context of the conceptual exposure-related disease model is presented in Figure 1.1.

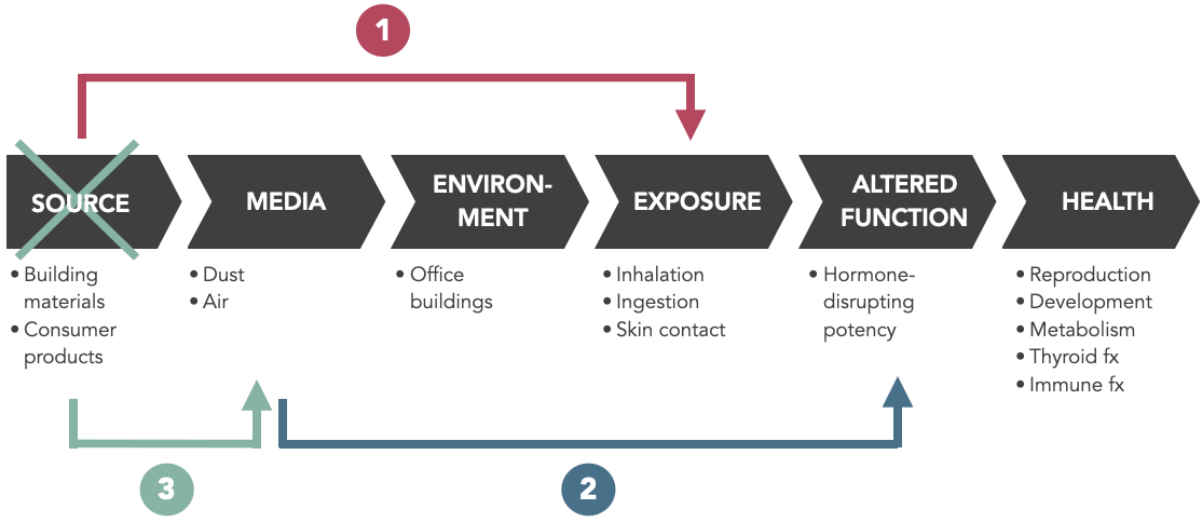

Figure 1.1: Dissertation research framework in context of the conceptual exposure-related disease model.

Novel Exposure Assessment Techniques

To address our three primary dissertation research goals and to fulfill a secondary aim of advancing the field of exposure science, we utilized several novel exposure assessment techniques. These methods included the use of non-invasive silicone wristbands as passive personal samplers, hormone cell-based assays on indoor dust mixtures, high-throughput chemical screening data to associate potency-weighted concentrations of chemicals in dust with total

hormonal potencies of the dust, and portable instruments to scan materials in situ for chemical indicators.

Silicone Wristband Samplers

Silicone wristband samplers are a recent innovation used in the last decade to passively measure personal exposures to semi-volatile organic chemicals (SVOCs).[128–130] While worn by participants, the wristbands collect chemicals from the air, dust, and materials people interact with and reflect both inhalation and dermal exposure routes.[131,132] SVOC concentrations on silicone wristbands have been found to significantly correlate with levels in blood and urine,[128,132–135] but wristbands offer several advantages over traditional blood or urine samples. First, they are simple, non-invasive, and inexpensive. Second, silicone wristbands allow for control over the exposure time window and the exposure microenvironment(s) of interest in a study. For example, by utilizing wristbands in this research, we could instruct participants to only wear their wristband while working in the office building and only during one work week. In that way, we could better isolate participant exposures due to their office building and avoid contributions from the dietary exposure pathway. This dissertation presents the first study to use silicone wristbands to pinpoint chemical exposures inside office buildings. Importantly, SVOCs collected on the silicone wristbands have also been shown to be stable at high temperatures during transport for at least a month.[129] This property facilitates the use of silicone wristbands in large, global studies such as in this dissertation, where transport or shipment back to the home laboratory can take several weeks. The wristbands' simplicity, and the ability of participants to collect samples on their own without the assistance of a health professional, can also enable

remote sample collection as participants simply mail their wristbands back to the laboratory after the study.

Cell-Based Assays of Dust

Cell-based assays are another technique that can be used in a novel application–dust–to assess the indoor environmental quality of a building. Compared to traditional targeted laboratory analyses that measure individual chemicals in dust, cell-based assays are inexpensive and rapid and reflect the impact of all chemicals in the dust mixture, even those chemicals that are unknown or not quantifiable in the laboratory.[136–138] Cell-based assays also capture mixture effects of chemicals in the dust, which arise when the hormonal activity of one particular chemical is altered in the presence of another chemical.[137,139,148,140–147] Evaluating the hormonal activity of indoor dust helps us better understand the "health" of an indoor space and the impact of building characteristics without having to conduct multi-year epidemiologic studies that would be challenged to link transient workforces' time spent in specific rooms to their health (especially within complex university campuses). This dissertation presents the first research linking cell-based assays of dust to concentrations of PFAS and several chemical classes.

Potency-Weighted Chemical Concentrations

In addition, novel statistical approaches for cell-based assay results can identify which chemicals are driving the hormonal activity of indoor dust. The recently available Tox21 database of high-throughput screening assay data for ten thousand chemicals enabled us to combine information on the measured concentrations of chemicals in our dust samples *and* the previously known potencies of those measured chemicals in cell-based screening assays.[149–154]

This was the first study of indoor dust to calculate the sum of potency-weighted concentrations for each chemical within a chemical class for statistical models in order to identify chemical classes influencing each assay endpoint, develop more biologically relevant covariates, and reduce the dimensions of the data.

In Situ Product Screening

Measuring chemicals in dust alone does not enable comprehensive evaluations of the product sources of those chemicals in buildings. However, laboratory measurements of chemical concentrations in products are often expensive, time-consuming, labor-intensive, and destructive to the product. To more easily identify products of concern in situ and to inform interventions, handheld x-ray fluorescence (XRF) instruments can non-destructively scan materials in real time for concentrations of elements. For example, XRF measurements of elemental bromine have been reliably used in several studies to screen products for the potential content of PBDEs (brominated flame retardants)[36,37,120,155–159] and to identify which product categories are associated with PBDEs in house dust or human blood.[155,158] To our knowledge, only one published study has used XRF technology to scan furniture for elemental phosphorus as a potential indicator for OPEs (organophosphate chemicals).[156] Although XRF measurements cannot conclusively determine whether one particular product contains a certain chemical class or not, this dissertation summarized loadings of elements in various product categories in studied buildings to assess statistical patterns in product sources of the chemicals found in dust. This approach reduces exposure misclassification in statistical models that instead only evaluate raw counts of products in spaces regardless of whether those products may actually contain the chemicals of interest.[155]

Research Framework

In the first study of this dissertation, we evaluated exposures of 130 office workers in the USA, UK, China, and India to PBDEs, OPEs, novel brominated flame retardants (BFRs), and PCBs using silicone wristbands. We aimed to better understand exposures specifically in office buildings and the country disparities in chemical uses across two HICs and two understudied LMICs with different regulations. Participants were instructed to wear their wristbands only during work hours for four consecutive days. The findings indicated substantial differences in office worker chemical exposures by country and showed that certain previously phased-out chemicals still persist in buildings, have unintentional contemporary sources, and/or have been substituted with other harmful chemical replacements.

In the second study, we quantified the hormonal activities of 46 indoor dust samples using human cell-based assays for interference with the activation of estrogen receptor α (ERα), androgen receptor (AR), peroxisome proliferator-activated receptor γ2 (PPAR), and thyroid hormone receptor β (TRβ), and with the transport of thyroid hormone thyroxine (T4). We also measured the concentrations of PBDEs, OPEs, and PFAS in the dust samples. This chapter showed that all indoor dust samples were hormonally active, and the activities were significantly associated with concentrations of the three chemical classes. Publicly available high-throughput chemical screening data to calculate potency-weighted chemical concentrations was useful for enhancing the statistical identification of important chemical components in the dust.

In the third study, we aimed to scientifically evaluate a real-world, chemical class-based solution to both PFAS and flame retardants in furniture for the first time. Specifically, we assessed the impact of "healthier" materials in buildings on concentrations of PBDEs, OPEs, and

PFAS in indoor dust, using the same 46 samples. We also used portable XRF instruments to screen products in the studied rooms for potential flame-retardant content. The results indicated that rooms with full "healthier" materials interventions had substantially lower levels of chemicals in dust compared to rooms with no intervention, and the product screening helped us identify electronics and exposed building insulation as two important product categories contributing to chemicals in the dust.

Overall, this dissertation hopes to advance our understanding of 1) global exposures to chemicals used in building materials, 2) the influence of chemicals on the "health" of an indoor space, and 3) the benefits, and next targets, of "healthier" material choices to reduce toxic chemical loads in buildings.

CHAPTER 2: Brominated Flame Retardants, Organophosphate Esters, and Polychlorinated Biphenyls in Silicone Wristbands Worn by Office Workers in the USA, UK, China, and India

Anna S. Young[1,2], Nicholas Herkert[3], Heather M. Stapleton[3], Jose Guillermo Cedeño Laurent[1], Piers MacNaughton[1], Brent A. Coull[1], Tamarra James-Todd[1], Russ Hauser[1], Emily Jones[1], Joseph G. Allen[1]

[1] Harvard T.H. Chan School of Public Health, Boston, MA, USA

[2] Harvard Graduate School of Arts and Sciences, Cambridge, MA, USA

[3] Duke Nicholas School of the Environment, Durham, NC, USA

Abstract

Semi-volatile organic chemicals such as polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), novel brominated flame retardants (BFRs), and organophosphate esters (OPEs) have been widely used in building materials, including caulking, furniture, carpet, electronics, and insulation. To better understand exposures in commercial buildings, we used silicone wristbands as personal passive samplers of these chemicals for 130 office workers in the USA, UK, China, and India. Participants were instructed to wear the wristbands for four consecutive days only during work hours to isolate exposures in office buildings. We found legacy PCB-28 and PCB-101 were detected in wristbands decades after bans in the USA (38% and 39%, respectively) and UK (8% and 20%). PCB-11, an unintentional byproduct in pigments, was detected more frequently (70%) across countries and was not correlated with legacy PCBs. Wristbands from China and India were estimated to have approximately 7-fold and 10-fold higher levels of PCB-11 compared to the USA in multilevel regression models adjusted for building age (p=0.005 and p<0.001). The flame-retardant mixture PentaBDE (including BDE-47 and BDE-99) was phased out in the USA by 2004, but these legacy PBDEs were still detected in 95% and 89% of wristbands from the USA, respectively. By contrast, DecaBDE (BDE-209) was frequently detected in all countries (59–88%) at higher levels. In adjusted models, BDE-209 was estimated to be nearly 3-fold (p=0.002) and 2-fold (p=0.01) higher in wristbands from the UK and India, where there were few restrictions, compared to the USA, which phased out DecaBDE by 2013. Often used as PBDE substitutes, novel BFRs and OPEs were ubiquitously detected in over 95% of wristbands, with varying chemical profiles by country indicative of different use patterns. The higher concentrations of many BFRs and OPEs in the USA and UK may partially be because their flammability standards

date back to 1975–1988. Overall, we found persistent legacy chemicals in buildings, unintentional contemporary sources of banned chemicals, and prevalent substitutes to legacy chemicals. Significant country-level differences in exposures reflected disparate chemical restrictions, flammability regulations, and preferences of specific chemicals.

Introduction

Chemical additives in building materials play an important role in defining our indoor exposures. These materials can contain complex profiles of many potentially harmful semi-volatile organic chemicals (SVOCs) that can migrate to the air and dust to which occupants are exposed.[15,123,155,160–163] Polychlorinated biphenyls (PCBs), brominated flame retardants (BFRs), and organophosphate esters (OPEs) are examples of three chemical classes used in building materials and which are commonly found in air and dust inside buildings.[13,14,23–28,15–22] These compounds are commonly detected at higher levels in offices than homes.[15,16,26,164] Typical office workers working eight hours per weekday[165] would spend about one quarter of their time in their office building alone, where they have little to no control over their chemical exposures from building materials.

In buildings, PCBs were historically used as additives in joint sealants, caulking and many other building materials for their plasticizer, flame resistance, insulation, durability, and chemical stability properties.[15,94–97] Some PCB congeners, such as PCB-11, have also been found to currently be produced as unintentional byproducts in pigments and in production processes for silicone and polyester polymers.[14,166–169] PCBs have been classified as known human carcinogens as a group by the International Agency for Research on Cancer[3,89,90] and have been linked to hormone disruption and impaired brain development.[91–93]

Polybrominated diphenyl ethers (PBDEs), other novel BFRs, and OPEs have been used as flame retardants in foam furniture, carpet, electronics, and building insulation.[32–37] OPEs have an additional important use as plasticizers in furniture, floor finishes, plastic, rubber, paints, coatings, wallpaper, and other materials.[38,39] Research has found both PBDE and OPE exposure in humans to be associated with adverse effects on the thyroid,[5,6,48–50,40–47] fertility, pregnancy outcomes,[5–7,48,51–56] and brain development.[5,6,43,57–61]

Even though PCBs were banned in the 1970s–1980s in many countries,[106–108] large reservoirs of these chemicals exist in many older buildings. For example, half of the current office buildings in the USA are estimated to have been built in 1979 or earlier, the year PCB production was banned.[170] Several studies have documented that legacy PCBs are still being emitted from old building materials.[13,14,95,97,106,118,119] Certain PBDEs are another group of legacy chemicals phased out of production in some countries in the early 2000s.[22,104] However, PBDEs were often simply replaced with similarly concerning OPEs, which do not face the same restrictions.[9,22,25,35,98] In addition, the recycling of old materials that have legacy chemicals can cause contamination of new products containing recycled content[120–122] and can lead to environmental contamination in regions near electronic waste recycling and waste dumping sites, especially in low- and middle-income countries (LMICs) like China and India, to which recycling is often exported from high-income countries (HICs).[171–176]

Human exposures to SVOCs are vastly understudied in LMICs, which comprise 84% of the global population.[177] Even among LMICs, most of the focus in chemical exposure research is on China, not India or other countries.[178–181] From what we do know, PCBs, BFRs, and OPEs are ubiquitously found in people and environments across the globe, but concentrations, profiles, and

sources of chemicals within a chemical class can vary significantly depending on the country and its regulations, enforcement, practices, and degree of industrialization.[178–180,182–185]

In the last decade, silicone wristbands have emerged as novel, non-invasive personal passive samplers for estimating SVOC exposures[128–130] and have since been employed in over a dozen published studies.[49,128,191–196,132–134,186–190] The wristbands adsorb chemicals from the air (both gas-phase and particle-bound), dust, and products that people interact with, capturing inhalation and dermal pathways of exposure.[131,132] Concentrations of PBDEs, OPEs, and other chemicals on silicone wristbands have been found to be significantly correlated with both serum and urinary biomarkers of exposure, demonstrating their usefulness as indicators of exposure for compounds with short and long half-lives in the body.[128,132–135]

The objectives of this study were to: 1) evaluate exposures of 130 office workers to PCBs, BFRs, and OPEs in their office buildings using silicone wristband samplers; and 2) assess country differences in the chemical exposures of the office workers across the USA, UK, China, and India. To our knowledge, this was the first study to use silicone wristbands to sample chemical exposures in office buildings, which are often understudied environments compared to homes.[181] We also sought to better understand SVOC exposures in two LMICs to address major gaps in research about indoor environmental levels and human biomonitoring.[177,178,181]

Methods

Study Population

In this study, we assessed exposures of office workers (n=130) to semi-volatile chemicals in office buildings across the USA, UK, China, and India using silicone wristbands as personal passive samplers.

Participants were recruited through email or on-site visits from the preexisting cohort of office workers as part of the CogFx study. Briefly, the CogFx cohort of buildings included a convenience sample of architecture, technology, real estate investment, coworking, and engineering companies. The inclusion criteria for buildings were the presence of at least 10 workers, the occupancy in urban commercial real estate (i.e. no retail or manufacturing sites), and that employees generally worked at least three days a week in the office. Within each building of the CogFx study, 10 participants were randomly selected among employees that met the following eligibility criteria: between the ages of 18 and 65, uses a smartphone, is a permanent full-time employee, works at least three days per week in the office, is a non-smoker, and is not color blind (due to other cognitive function tests that are not relevant to this current study). For the participants in China, all study materials were translated to Chinese by native and fluent members of the research team. In India, the sampled offices used English as the language at work and the participants were all fluent in English. We invited all of the original study participants in these buildings to participate in our nested study. In China, we also extended recruitment to other employees in the same office who were not original participants in the parent study in order to increase our population size.

In total, 255 office workers from study buildings in the USA, UK, China, and India participated in this nested study of chemical exposures. After sample collection, three (1%) of the 255 participants were excluded because they did not report the amount of time for which they wore the wristband samples, which was necessary in order to weight the chemical concentrations by sampling duration. Analytical results from an additional 122 samples are not presented in this paper as a result of laboratory shutdowns during the COVID-19 pandemic. Thus, the final sample subset henceforth discussed in this paper consisted of 130 office workers. By country, the

sample sizes were 61 in the USA, 25 in the UK, 31 in India, and 13 in China. The samples that have not yet been analyzed in the laboratory yet cover an additional 25 in the USA, 17 in the UK, 23 in India, and 57 in China, and these omissions were random with blinded quality control measures in place.

Table 2.1 summarizes building factors, workstation characteristics, and personal demographic information for the participants. The 130 participants worked at 34 different buildings, including 15 in the USA, six in the UK, eight in India, and five in China. The average number of participants per building was 3.8 (4.1 in USA, 4.2 in UK, 3.9 in India, and 2.6 in China). The USA buildings were located in the following cities (states): Chicago (IL), Cleveland (OH), Phoenix (AZ), Overland Park (KS), Los Angeles (CA), Minneapolis (MN), Omaha (NE), Denver (CO), Seattle (WA), Washington DC, San Francisco (CA), Clearwater (FL), and Boston (MA). The UK buildings were located in Cambridge (East of England), London (Greater London), Sheffield (Yorkshire and the Humber), Birmingham (West Midlands), and Croydon (Greater London). The buildings in China were located in Shanghai (municipality) and Chengdu (Sichuan Province). The buildings in India were in Bengaluru (KA), Mumbai (MH), Gurugram (HR), and Hyderabad (TS).

Study Design

Table 2.1. Summary of available information on personal, workstation, and building characteristics overall and by country (USA: n=61; UK: n=25; China: n=13; India: n=31).

Personal Factors						
Age (years)	Med [Range]	31 [22-61]	32.5 [23-61]	31 [22-58]	28 [23-40]	30 [24-53]
Gender Identity	n (%)					
Female		58 (51%)	35 (62%)	5 (25%)	7 (70%)	11 (41%)
Male		55 (49%)	21 (38%)	15 (75%)	3 (30%)	16 (59%)
Hours work per week in building	Med [Range]	40 [10-90]	40 [20-90]	38 [23-45]	49 [32-70]	45 [10-55]
Highest education level	n (%)					
High school graduate		3 (2.7%)	0 (0%)	0 (0%)	0 (0%)	3 (11%)
Some college		6 (5.4%)	2 (3.6%)	2 (11%)	1 (10%)	1 (3.7%)
2 year degree		1 (0.89%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)
4 year degree		28 (25%)	19 (34%)	3 (16%)	0 (0%)	6 (22%)
Professional degree		17 (15%)	9 (16%)	1 (5.3%)	0 (0%)	7 (26%)
Master		10 (8.9%)	2 (3.6%)	1 (5.3%)	7 (70%)	0 (0%)
Doctorate		47 (42%)	24 (43%)	12 (63%)	1 (10%)	10 (37%)
Workstation Characteristics						
Type of workstation	n (%)					
Open space without partitions		74 (65%)	43 (77%)	14 (70%)	3 (30%)	14 (52%)
Open space with partitions		28 (25%)	6 (11%)	6 (30%)	6 (60%)	10 (37%)
Shared private office		7 (6.2%)	5 (8.9%)	0 (0%)	1 (10%)	1 (3.7%)
Single person private office		3 (2.7%)	2 (3.6%)	0 (0%)	0 (0%)	1 (3.7%)
Other		1 (0.88%)	0 (0%)	0 (0%)	0 (0%)	1 (3.7%)
Foam Workstation Chair	n (%)					
Yes		97 (78%)	39 (65%)	25 (100%)	13 (100%)	20 (74%)
No		28 (22%)	21 (35%)	0 (0%)	0 (0%)	7 (26%)
Carpeting in Workstation	n (%)					
Yes		98 (78%)	52 (87%)	25 (100%)	6 (46%)	15 (56%)
No		27 (22%)	8 (13%)	0 (0%)	7 (54%)	12 (44%)
Building Characteristics						
Year Constructed	Med [Range]	2003 [1898-2017]	1979 [1898-2015]	1990 [1987-2015]	2014 [2009-2016]	2011 [2003-2017]
Mean Temperature During Study (C)	Med [Range]	24.4 [22.3-30.0]	23.5 [22.3-28.3]	24.3 [24.1-24.9]	26.3 [23.1-30.0]	26.8 [24.7-28.3]
Mean Relative Humidity During Study (%)	Med [Range]	37.8 [20.0-64.4]	37.3 [19.8-53.7]	35.1 [32.8-37.4]	49.0 [46.5-64.4]	45.9 [36.3-51.6]

During a predefined study week for each office building in 2019, participants were instructed to wear their silicone wristbands on either wrist for four consecutive business days, Monday–Thursday, only during work hours. Some participants skipped certain sampling days if they were out of the office. Most participants (75%) wore the wristband for four workdays, and another 16% wore it for three days. The median number of hours the participants wore the wristbands was between 31 and 34 hours for all countries (32 hours is equivalent to four typical 8-hour workdays). The overall range was 7.7 to 56 hours worn.

Participants wore the wristbands only during their workdays in order to isolate the office building as the microenvironment of interest. For each day during the study period, participants were told to put on their wristbands when they arrived at their workplace and then to wear it continuously until leaving the office building after their work shift. On paper time log sheets that we provided, participants filled out the exact times they placed on and removed their wristbands.

Participants wore the wristbands continuously during any lunch breaks or external meetings since exposures during those times may be 'brought back' to the building on their clothes, skin, and other materials. Overnight and at the end of the study, the participants stored their wristbands wrapped in clean aluminum foil and sealed in the plastic bags at their desk.

Most buildings within a country were sampled during the same study week. The UK buildings were sampled in February 2019, the USA buildings were sampled in late April (except one in January), the buildings in India were sampled in May (except one in June), and the buildings in China were sampled in July. At the end of the study week, wristbands were sent back to Boston. For all buildings, the samples arrived back and were stored at -13°C within two weeks after the end of the study week. Sample packages from most buildings (92%) arrived within one week. SVOCs have been experimentally shown to be stable on wristbands at high temperatures (30°C) in transport for at least one month.[129]

During the study week, participants responded to one baseline survey about their workstation characteristics (such as the presence of foam furniture and type of flooring) as well as a daily survey about their time activities while wearing their wristband (such as what time they put on and took off their wristband the day before). Qualtrics-based surveys were administered through email or the ForHealth custom research app developed for the CogFx study. We asked a few contacts from the buildings in India or China to review the English or Chinese surveys in advance to check for understanding and appropriate terminology.

In addition to the participant surveys, we had access to surveys of building managers from the CogFx study. This information included building characteristics such as age of construction and cleaning practices, which were almost always reported as daily. CogFx participants were provided with low-cost air quality sensors at their workstations, which

provided real-time data on temperature, relative humidity, fine particulate matter ($PM_{2.5}$), and carbon dioxide.

In the laboratory, we also analyzed 10 field blanks from different buildings. Field blanks were silicone wristbands pre-cleaned and prepared in the same way as the sample kits, but not worn by a participant. Field blanks were shipped to and from buildings in the same packages as the samples but were not opened. The study protocols were reviewed and approved by the Institutional Review Board of the Harvard T.H. Chan School of Public Health.

Wristband Sample Preparation

Our wristband sample preparation, storage, and analysis followed previously published protocols.[128,132,133] Red silicone wristbands were purchased from 24hourwristbands.com (Houston, TX, USA), pre-cleaned in a solvent extraction, wrapped in clean aluminum foil, and double sealed in two plastic Ziploc bags. We sent each participant an envelope with the wristband sample bag, instructions, and extra clean foil.

Laboratory Analytical Methods

We analyzed the wristband samples for 11 PCBs, 13 BFRs, and 31 OPEs in the laboratory based on previously described methods.[128,132,133,192] The PCB analytes included congeners 11, 28, 47, 51, 52, 68, 101, 118, 138, 153, and 183. The BFR analytes included bis (2-ethyl hexyl)-2,3,4,5-tetrabromophthalate (BEHTBP), decabromodiphenyl ethane (DBDPE), 2-ethyl hexyl-2,3,4,5-tetrabromobenzoate (EHTBB), and PBDE congeners 28, 47, 66, 85, 99, 100, 153, 154, 183, and 209. The OPE analytes included triethyl phosphate (TEP), triisopropyl phosphate (TiPP), tripropyl phosphate (TPrP), tri-iso-butyl-phosphate (TiBP), tri-n-butyl-

phosphate (TnBP), tris (2-chloro-ethyl) phosphate (TCEP), tris (1-chloro-isopropyl) phosphate (TCIPP), tripentyl phosphate (TPeP), tris (2,4-dichloro-isopropyl) phosphate (TDCIPP), triphenyl phosphate (TPHP), 2-ethylhexyl diphenyl phosphate (EHDPP), tris(2-ethylhexyl) phosphate (TEHP), tri-o-cresyl phosphate (ToCP), tri-m-cresyl phosphate (TmCP), tri-p-cresyl phosphate (TpCP), and tris(3,5-dimethyl phenyl) phosphate (TDMPP); several tertbutylated triaryl phosphates (TBPPs) including 2-tert-butylphenyl diphenyl phosphate (2tBPDPP), 4-tert-butylphenyl diphenyl phosphate (4tBPDPP), bis(2-tert-butylphenyl) phenyl phosphate (B2tBPPP), bis(4-tert-butylphenyl) phenyl phosphate (B4tBPPP), and tris(4-tert-butylphenyl) phosphate (T4tBPP); as well as several isopropylated triaryl phosphates (ITPs): 2-isopropylphenyl diphenyl phosphate (2IPPDPP), 3-isopropylphenyl diphenyl phosphate (3IPPDPP), bis(2-isopropylphenyl) phenyl phosphate (B2IPPPP), 4-isopropylphenyl dipheynyl phosphate (4IPPDPP), 2,4-diisopropylphenyl diphenyl phosphate (24DIPPDPP), bis (3-isopropylphenyl) phenyl phosphate (B3IPPPP), bis (4-isopopylphenyl) phenyl phosphate (B4IPPPP), bis (2,4-diisopropylphenyl) phenyl phosphate (B24DIPPPP), tris(4-isopropylphenyl) phosphate (T4IPPP), and tris(3-isopropylphenyl) phosphate (T3IPPP).

Approximately one-fifth of each wristband was used for analyses, with sample masses around 0.75 g. The wristband segments were transferred to a clean 50 mL glass centrifuge tube and spiked with isotopically-labeled compounds. The wristband samples were extracted via sonication (15 minutes repeated three times) with 10 mL of a 50:50 mixture (v:v) of hexane:dichloromethane for a final extraction volume of 30 mL. Samples were then concentrated to ~ 1 mL using purified nitrogen. Extracts were purified using 8 g of water deactivated, 100-200 mesh Acros Organics Florasil (Thermo Fisher Scientific, Waltham, MA, USA). Two fractions (F1 and F2) were collected together using hexane and ethyl acetate,

respectively, concentrated to near dryness, and reconstituted in 1 mL of hexane. Most target analytes were analyzed using a Q Exactive GC Hybrid Quadrupole-Orbitrap GC-MS/MS system (Thermo Fisher Scientific, Waltham, MA, USA) operated in full scan Electron Ionization (EI) mode. BEHTBP, BDE 183 and BDE 209 were analyzed using a single quadrupole GC-MS (Agilent 6890N and 5975, respectively) (Agilent Technologies, Inc., Santa Clara, CA, USA) operated in electron capture negative chemical ionization (ECNI) mode.

Quality Assurance and Quality Control

Field blanks and lab blanks were processed and analyzed with each batch of wristbands for quality assurance and quality control. A six-point calibration curve was used to quantify each individual SVOC in samples and blanks. Method detection limits (MDLs) were calculated as three times the standard deviation of the field and lab blank responses. MDLs ranged from 0.01 to 1.26 ng/g-wristband for OPEs, 0.01 ng/g for BFRs, and 0.01 to 0.06 ng/g for PCBs.

The average recovery for all isotopically label standards was 88% (± 39%) and ranged from 43% (± 7%) for ^{13}C PCB 52 to 162% (± 7%) for ^{13}C EHTBB. Target analyte concentrations were recovery-corrected with an appropriate internal standard to account for loss during laboratory processing.

Prior to sample analysis, the QE-GC was tuned and calibrated to ensure maximum mass accuracy (<0.5 ppm). The tune was examined after samples had run to ensure no significant sensitivity loss had occurred. Additionally, a standard mixture of all target analytes was injected periodically (every 15 injections) to monitor response stability during the instrument run.

Statistical Analyses

We first blank-corrected the chemical concentrations of the wristband samples by subtracting the average field blank concentrations. We also substituted non-detect values with one-half the chemical MDL.[197] Because each participant wore their wristband for a different reported sampling duration, we normalized the chemical concentrations to a 32-hour time period (equivalent to four 8-hour workdays).

To evaluate whether there were differences in the proportions of chemical detections based on country, we conducted two-sided Fisher's exact tests for the chemicals detected in at least 50% of samples in at least one country. Only if the global tests were significant did we then perform post hoc pairwise tests. We evaluated significance for the Fisher's exact tests at the α_{BH_F}= 0.026 significance level based on the Benjamini-Hochberg procedure to decrease the false discovery rate due to multiple testing issues.[198]

To identify chemical groupings, we conducted principal component analysis and calculated a Spearman correlation coefficient matrix among the analytes detected in over one-third of samples in a country. We used a lower detection threshold for these evaluations of chemical relationships because there were several important types of less frequently detected chemicals (such as any legacy PCBs) that we sought to better understand in relation to other analytes. In the correlation matrix, we only presented correlations that were statistically significant at the α_{BH_C}=0.028 level (based on the post hoc Benjamini-Hochberg procedure). Then, we conducted principal component analysis on the concentrations of those same chemicals detected in over one-third of samples in a country. The chemical concentrations were scaled to unit variance and zero-centered before the principal component analysis so that the chemicals with the highest magnitudes of concentrations did not overwhelm the analysis. We evaluated the

principal components (PCs) that together explained a cumulative variance of over 70% and that each had eigenvalues of at least one.

For formal statistical modeling (final *n*=119), we excluded five participants who did not respond to the baseline workstation survey (4%) and six participants who occupied one building with an unknown construction age (5%). Before modeling, we calculated the natural log of the chemical concentrations since the data were not normally distributed (as determined from histograms and Shapiro-Wilk tests). We developed multilevel regression models of chemical concentrations with building-specific random intercepts to account for possible correlation among samples collected from the same building and to determine the proportion of variation explained by the building relative to that at the individual level. The multilevel models allowed us to control for year of building construction (because of differences by country), presence of a foam office chair (for flame retardants), and flooring type (for flame retardants and plasticizers).

We included country as the primary predictor of interest. However, in some cases we could only conduct the model on the subset of countries that had greater than 0% detection of the chemical. Model estimates were transformed to percent differences because we used log-transformed outcomes.

To avoid multiple testing issues that would arise from statistical models on 55 chemicals, we used the principal component analysis results to select key chemicals. We chose one to two tracer chemicals per principal component. We prioritized the chemical(s) with the highest contributions to each component, then among those, the chemicals with the highest detection frequencies in the samples, while ensuring we included a second chemical if it is used in a different product application. We did not calculate summations of chemicals in a class (such as the sum of all OPEs) due to the differences in physical-chemical properties of chemicals that

would influence their uptake efficiency into the silicone wristband material. Statistical significance in the models was evaluated at the α=0.05 level.

In sensitivity analyses, we conducted the same multilevel regression models with additional control for indoor air quality measurements, which were available for 31 of the 34 study buildings. The data from the real-time sensors from the CogFx study in the remaining three buildings were missing completely at random due to sensor technological issues. For the analyses, we calculated average temperature and relative humidity during each building's four-day study period during business hours (9:00–17:00). We did not include these parameters in the main models because of the missing data and thus lower statistical power. All analyses were conducted in R (version 3.3.1).

Results

Fifty-two (95%) of the 55 measured chemical analytes were detected in wristband samples (Table 2.2). Sixteen (29%) were widely detected in over half of all wristband samples. The overall detections, magnitudes, and profiles of chemical classes varied by country. Wristbands from the USA and/or UK tended to have more frequent detections and higher magnitudes of OPEs and BFRs compared to China and India, except that the concentrations of one specific PBDE congener (BDE-209) were lowest in the USA (Figure 2.1; Table 2.2). Of note, the UK samples had an orders of magnitude higher geometric mean concentration of one OPE than the other three countries. On the other hand, India and China had higher concentrations and detection rates of the most frequently detected PCB in wristbands compared to the USA or UK.

Table 2.2. Summary of detections (shaded) and Fisher's exact tests of their country-level differences for chemicals on silicone wristband samples worn by 130 office workers (USA: n=61; UK: n=25; China: n=13; India: n=31).

		Percent Detected (%)					Fisher's Exact Tests for Country Differences in Detection Percents (p)[a]						
Abbreviation	**Chemical Name**	**All**	**USA**	**UK**	**China**	**India**	**Overall**	**US–UK**	**US–CH**	**US–IN**	**UK-CH**	**UK-IN**	**CH-IN**
Polychlorinated biphenyls													
PCB-11	3,3'-Dichlorobiphenyl	70	57	64	92	90	**0.0016 ***	0.63	**0.024 ***	**0.0017 ***	0.12	**0.023 ***	1
PCB-28	2,4,4'-Trichlorobiphenyl	22	39	20	0	0							
PCB-47	2,2',4,4'-Tetrachlorobiphenyl	12	21	4	7.7	0							
PCB-51	2,2',4,6'-Tetrachlorobiphenyl	0.77	0	0	7.7	0							
PCB-52	2,2',5,5'-Tetrachlorobiphenyl	12	21	8	0	3.2							
PCB-68	2,3',4,5'-Tetrachlorobiphenyl	2.3	3.3	0	0	3.2							
PCB-101	2,2',4,5,5'-Pentachlorobiphenyl	21	38	8	0	6.5							
PCB-118	2,3',4,4',5-Pentachlorobiphenyl	8.5	13	0	0	9.7							
PCB-138	2,2',3,4,4',5'-Hexachlorobiphenyl	6.2	11	4	0	0							
PCB-153	2,2',4,4',5,5'-Hexachlorobiphenyl	5.4	9.8	0	0	3.2							
PCB-183	2,2',3,4,4',5',6-Heptachlorobiphenyl	1.5	3.3	0	0	0							
Brominated flame retardants													
BDE-28	2,4,4'-tribromodiphenyl ether	0	0	0	0	0							
BDE-47	2,2',4,4'-tetrabromodiphenyl ether	48	95	20	0	0	**2.7e-28 ***	**4.1e-12 ***	**5.4e-12 ***	**2e-21 ***	0.14	**0.014 ***	1
BDE-66	2,3',4,4'-tetrabromodiphenyl ether	1.5	3.3	0	0	0							
BDE-85	2,2',3,4,4'-pentabromodiphenyl ether	0	0	0	0	0							
BDE-99	2,2',4,4',5-pentabromodiphenyl ether	48	89	32	0	0	**1.9e-22 ***	**4e-07 ***	**7.4e-10 ***	**4.2e-18 ***	0.034	**0.00076 ***	1
BDE-100	2,2',4,4',6-pentabromodiphenyl ether	19	41	0	0	0							
BDE-153	2,2',4,4',5,5'-hexabromodiphenyl ether	4.6	9.8	0	0	0							
BDE-154	2,2',4,4',5,5'-hexabromodiphenyl ether	3.1	4.9	0	0	3.2							
BDE-183	2,2',3,4,4',5',6-heptabromodiphenyl ether	3.1	3.3	4	0	3.2							
BDE-209	Decabromodiphenyl ether	71	59	88	69	81	**0.026 ***	**0.011 ***	0.55	0.061	0.2	0.72	0.45
BEHTBP	Bis (2-ethyl hexyl)-2,3,4,5-tetrabromophthalate	95	100	96	77	90	**0.0028 ***	0.29	**0.0044 ***	0.036	0.11	0.62	0.34
DBDPE	Decabromodiphenyl ethane	22	21	36	23	9.7							
EHTBB	2-ethyl hexyl-2,3,4,5-tetrabromobenzoate	45	89	12	0	3.2	**2.7e-23 ***	**1.5e-11 ***	**7.4e-10 ***	**1.9e-16 ***	0.54	0.31	1
Organophosphate esters													
EHDPP	2-Ethylhexyl diphenyl phosphate	99	100	100	100	97	0.53						
TCEP	Tris (2-chloro-ethyl) phosphate	72	67	80	100	65	0.04						
TCIPP	Tris (1-chloro-isopropyl) phosphate	99	100	100	100	97	0.53						
TDCIPP	Tris (2,4-dichloro-isopropyl) phosphate	96	100	100	100	84	**0.0024 ***	1	1	**0.0035 ***	1	0.058	0.3
TDMPP	Tris(3,5-dimethyl phenyl) phosphate	6.2	4.9	4	31	0							
TEHP	Tris(2-ethylhexyl) phosphate	98	100	100	100	90	0.043						
TEP	Triethyl phosphate	19	15	16	31	26							
TiBP	Tri-iso-butyl-phosphate	38	39	76	31	6.5	**5.9e-07 ***	**0.0039 ***	0.75	**0.0011 ***	**0.013 ***	**9.5e-08 ***	0.053
TiPP	Triisopropyl phosphate	1.5	0	8	0	0							
TmCP	Tri-m-cresyl phosphate	8.5	15	8	0	0							
TnBP	Tri-n-butyl-phosphate	52	75	64	15	9.7	**1.6e-10 ***	0.3	**8.8e-05 ***	**1.2e-09 ***	**0.0064 ***	**3.5e-05 ***	0.62
ToCP	Tri-o-cresyl phosphate	3.1	1.6	8	0	3.2							
TpCP	Tri-p-cresyl phosphate	96	97	96	100	94	0.9						
TPeP	Tripentyl phosphate	0.77	1.6	0	0	0							
TPHP	Triphenyl phosphate	99	100	100	100	97	0.53						
TPrP	Tripropyl phosphate	0	0	0	0	0							
Organophosphate esters: tertbutylated triaryl phosphates													
2tBPDPP	2-tert-butylphenyl diphenyl phosphate	2.3	1.6	4	0	3.2							
4tBPDPP	4-tert-butylphenyl diphenyl phosphate	82	98	92	54	52	**7.8e-09 ***	0.2	**5.9e-05 ***	**5.9e-08 ***	**0.011 ***	**0.0012 ***	1
B2tBPPP	bis(2-tert-butylphenyl) phenyl phosphate	0.77	0	4	0	0							
B4tBPPP	bis(4-tert-butylphenyl) phenyl phosphate	51	72	52	7.7	26	**1.2e-06 ***	0.084	**2.3e-05 ***	**4.2e-05 ***	**0.012 ***	0.056	0.24
T4tBPP	Tris(4-tert-butylphenyl) phosphate	9.2	9.8	4	0	16							
Organophosphate esters: isopropylated triaryl phosphates													
24DIPPDPP	2,4-Diisopropylphenyl diphenyl phosphate	12	11	12	38	3.2							
2IPPDPP	2-Isopropylphenyl diphenyl phosphate	95	97	100	100	87	0.13						
3IPPDPP	3-Isopropylphenyl diphenyl phosphate	25	31	36	31	0							
4IPPDPP	4-Isopropylphenyl diphenyl phosphate	82	98	92	77	45	**4.2e-09 ***	0.2	**0.016 ***	**2.8e-09 ***	0.31	**0.00022 ***	0.096
B24DIPPPP	Bis (2,4-diisopropylphenyl) phenyl phosphate	1.5	0	0	15	0							
B2IPPPP	Bis(2-isopropylphenyl) phenyl phosphate	60	74	80	54	19	**6.5e-07 ***	0.59	0.19	**7.2e-07 ***	0.14	**9.1e-06 ***	0.033
B3IPPPP	Bis (3-isopropylphenyl) phenyl phosphate	1.5	0	4	7.7	0							
B4IPPPP	Bis (4-isopopylphenyl) phenyl phosphate	38	38	56	54	19	**0.022 ***	0.15	0.36	0.097	1	**0.0058 ***	0.033
T3IPPP	Tris(3-isopropylphenyl) phosphate	0	0	0	0	0							
T4IPPP	Tris(4-isopropylphenyl) phosphate	2.3	0	4	15	0							

[a] Only chemicals detected in over half of samples in at least one country were tested. Post-hoc pairwise tests were only conducted when the overall test was significant. Statistical significance (*) was evaluated at $p<0.026$.

Polychlorinated Biphenyls

Three PCB congeners were found in over 20% of the silicone wristbands worn by 130 office workers (Table 2.2). The most commonly detected congener, PCB-11, significantly differed in detection frequency by country (Fisher's exact $p=0.0016$). PCB-11 was detected in

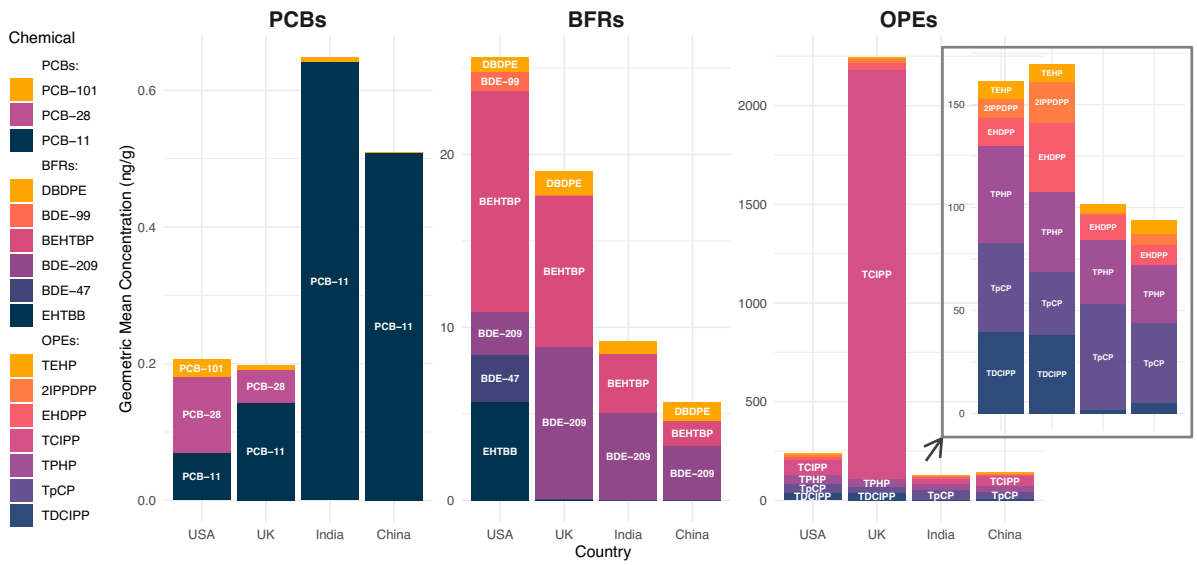

Figure 2.1. Profiles of three classes of chemicals in wristband samples worn by 130 office workers in the USA, UK, China, and India.

PCBs = polychlorinated biphenyls; BFRs = brominated flame retardants; OPEs = organophosphate esters.
Note: only chemicals contributing to more than 1% of the height of the tallest bar in the chemical class (in at least one country) are shown. Chemical classes are presented on different y-axis scales. Caveat: the different physical-chemical properties of the analytes may influence their respective sampling uptakes and thus concentrations on the wristbands.

70% of all samples, but more frequently in China (92%) and India (90%) than in the USA (57%) or UK (64%). For nearly all other PCB congeners, wristbands worn by participants from the USA were more likely to have measurable levels. PCB-28 and PCB-101 were detected in 39% and 38% of samples from the USA, respectively, but only 20% and 8% in samples from the UK, 0% and 6.5% in India, and never in China.

The magnitudes, not just detections, of PCBs on the wristbands also varied by country. Concentrations of PCB-11 were much higher in China and India than in the USA or UK (Figure 2.2). Moreover, the PCB profiles of samples from China and India were almost entirely dominated by PCB-11, whereas the USA had evident contributions from PCB-101 and PCB-28 too (Figure 2.1). A multilevel linear regression model of the log concentrations of PCB-11, controlling for building age, found that country of origin was a significant predictor (Table 2.3). Compared to the USA, PCB-11 levels were estimated to be 676% higher in wristbands worn by office workers in China (95% confidence interval [CI]: 121–2,600%; p=0.005) and 999% higher

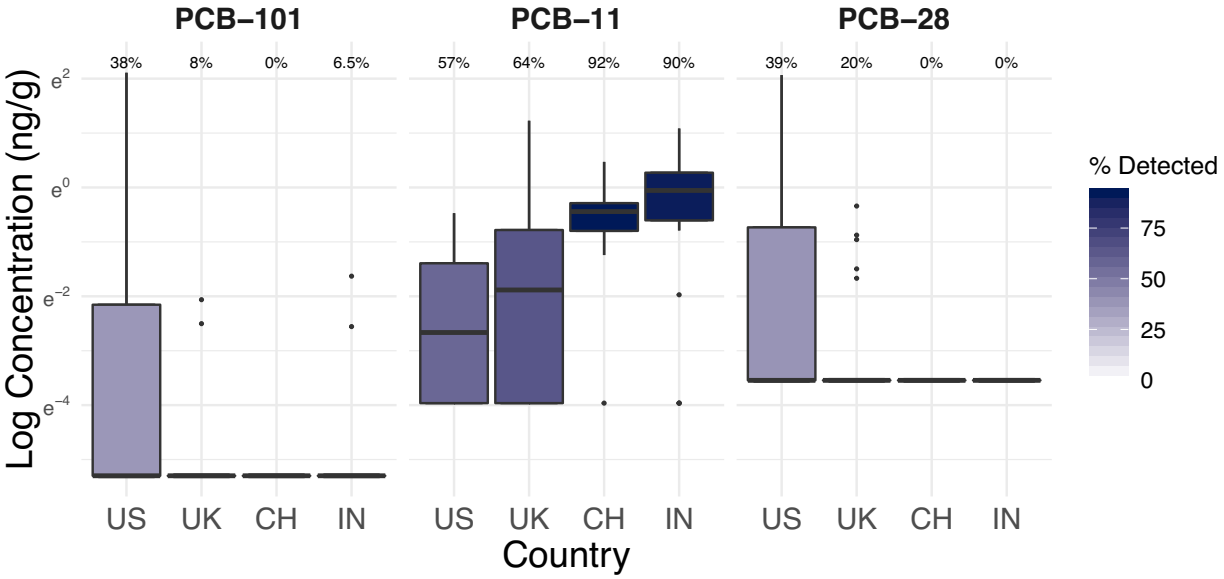

Figure 2.2. Log concentrations (ng/g-wristband, standardized to 32 hours of sampling) of main polychlorinated biphenyls on silicone wristbands worn by 130 office workers.

Table 2.3. Results of multilevel linear regression models of log concentrations of key chemicals (as determined by principal component analysis) in silicone wristbands (n=119).

	Polychlorinated Biphenyls				*Brominated Flame Retardants*					
	PCB-11		**PCB-101**		**BDE-47**		**BDE-209**		**BEHTBP**	
Variable	% Change	*p*	% Change	*p*	% Change	*p*	% Change	*p*	% Change	*p*
Country (ref: USA)										
UK	117%	0.20	-42.5%	0.38	**-97.6% *****	<0.0001	**270% ****	0.0020	19.2%	0.66
China	**676% ****	0.0052	*No detections*		*No detections*		24.1%	0.65	**-92.8% *****	<0.0001
India	**999% *****	0.00028	-30.2%	0.55	*No detections*		**171% ***	0.012	**-71.9% *****	0.00089
Year of Building Construction	-0.226%	0.76	**-2.35% ****	0.0047	0.469%	0.34	-0.216%	0.63	-0.0778%	0.86
Foam Chair at Workstation					3.63%	0.93	41.0%	0.19	48.7%	0.19
Carpeting in Workstation					11.3%	0.85	-26.0%	0.31	**-63.7% ****	0.0013

	Organophosphate Esters											
							ITPs		*TBPPs*			
	TPHP		**TiBP**		**TCIPP**		**2IPPDPP**		**4tBPDPP**		**B4tBPPP**	
Variable	% Change	*p*	% Change	*p*	% Change	*p*	% Change	*p*	% Change	*p*	% Change	*p*
Country (ref: USA)												
UK	-2.48%	0.95	**178% ****	0.0043	**3100% *****	<0.0001	177%	0.28	-63.7%	0.14	**-83.8% .**	0.062
China	-34.2%	0.43	-29.9%	0.39	-35.1%	0.38	-6.89%	0.95	**-94.8% ****	0.0012	**-96.4% ****	0.0082
India	-5.81%	0.89	**-45.4% .**	0.065	**-54.7% .**	0.061	-73.6%	0.15	**-89% ****	0.0028	**-87.2% ***	0.033
Year of Building Construction	-0.236%	0.65	0.0951%	0.80	0.182%	0.71	-0.225%	0.84	-0.663%	0.41	-0.882%	0.40
Foam Chair at Workstation	-9.6%	0.71	-11.7%	0.62	13%	0.60	-16.3%	0.73	31.6%	0.51	**290% ***	0.046
Carpeting in Workstation	18.1%	0.62	2.47%	0.92	-3.72%	0.90	**439% ***	0.02	**715% *****	0.00026	**440% ***	0.028

ITPs = isopropylated triaryl phosphates; TBPPs = tertbutylated triaryl phosphates; ref = reference category.
Model outcomes were log-transformed before analysis, so model estimates were transformed to percent differences.

in India (95% CI: 285–2,980; $p<0.001$). The higher levels of PCB-101 in samples from the USA did not reach statistical significance in the model ($p=0.38$–0.55).

While the year of building construction did not significantly impact PCB-11 in wristbands, there were 21.1% lower PCB-101 concentrations (95% CI: -31.5– -9.24%; $p=0.005$) associated with a 10-year increase in the construction year, controlling for country. The

differences between buildings, as opposed to between individuals within buildings, explained 34% and 18% of the variability in log concentrations of PCB-11 and PCB-101 respectively. Table 6.1 summarizes the geometric means, geometric standard deviations, and ranges of chemical concentrations by country.

Polybrominated Diphenyl Ethers

Almost all wristband samples (90%) had at least one detectable PBDE (Table 2.2). The detection of congeners BDE-47 and BDE-99 significantly differed by country ($p<0.0001$), with the highest detection frequencies in samples from the USA. In fact, BDE-47, BDE-99, and BDE-100 were found exclusively in the USA (at 89%, 95%, and 41% respectively) and/or UK (20%, 32%, and 0%), while not in any samples from China or India. By contrast, the most commonly detected PBDE congener, BDE-209, was detected in 71% of samples overall and its detection significantly varied by country ($p=0.026$), but the lowest detection frequencies occurred in the USA (USA: 59%; UK: 88%; China: 69%; India: 81%).

There were also evident country-level differences in the magnitude of concentrations of PBDE congeners in wristbands. The PBDE profiles show that the wristbands from the USA were dominated by BDE-47, BDE-209, and BDE-99, whereas wristbands from the UK, India, and China were only dominated by BDE-209 (Figure 2.1). The boxplots demonstrate that the USA had the highest concentrations of BDE-47 and BDE-99, even compared to the UK which had the second most frequent detection rates of the congeners (Figure 2.3). The results from the multilevel regression models confirmed that the UK had 97.6% lower levels of BDE-47 (95% CI: -99.0– -94.3%; $p<0.0001$) in wristbands compared to the USA, adjusted for the construction year of the building and the presence of a foam chair and carpeting (Table 2.3). On the other

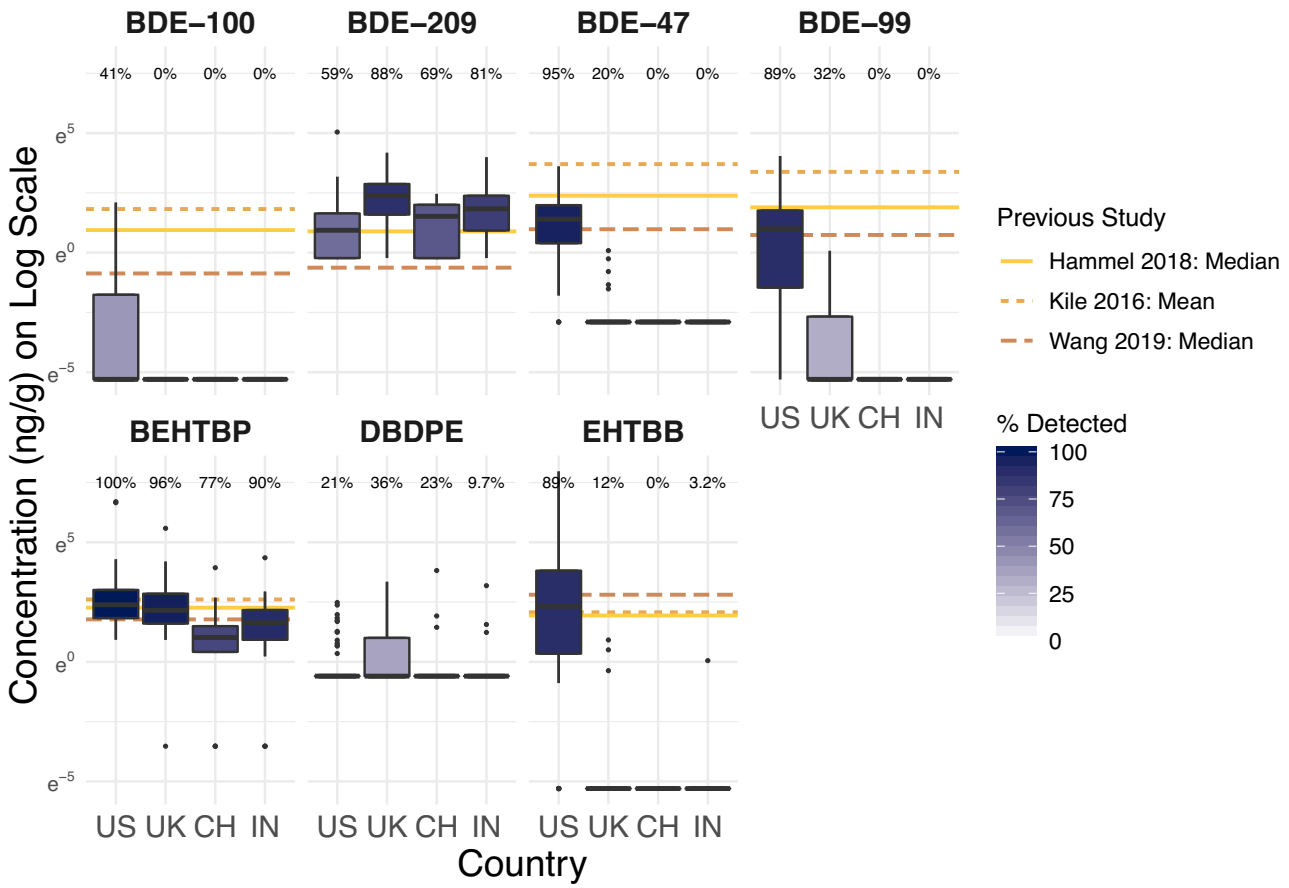

Figure 2.3. Log concentrations (ng/g-wristband, standardized to 32 hours of sampling) of key brominated flame retardants on silicone wristbands worn by 130 office workers, with comparison to concentrations (standardized to 32 hours) from previous wristband studies.

Caution: some previous studies did not employ the same lab analysis methods. We standardized reported means/medians to 32 hours.
Hammel et al. 2018: general population in North Carolina, USA (*n*=30; compatible lab methods; sampled 2016; wristbands worn for 7 days).
Kile et al. 2016: preschool children in Oregon, USA (*n*=72; sampled 2012-2013; wristbands worn for 7 days and concentrations scaled by time).
Wang et al. 2019: community in rural Appalachia, USA (*n*=101; sampled 2017-2018; wristbands worn for 7 days).

hand, BDE-209 tended to be higher in both magnitude and detection in the UK and India than the USA or China (Figure 2.3). In fact, there were 270% and 171% higher concentrations of BDE-209 in wristbands from the UK (95% CI: 85.1–631%; p=0.002) and from India (95% CI: 38.8–422%; p=0.012), respectively, compared to the USA in the multilevel regression model (Table 2.3). In the models, most of the variability in log concentrations of BDE-47 and BDE-209 were explained by differences between individuals within buildings (100% and 88%), as opposed to between buildings.

Novel Brominated Flame Retardants

Novel brominated flame retardants were frequently detected in the wristband samples as well (Table 2.2). In particular, bis (2-ethyl hexyl)-2,3,4,5-tetrabromophthalate (BEHTBP) was found in the vast majority of all samples (95%) and samples within each country (USA: 100%, UK: 96%, India: 90%, China: 77%). BEHTBP detections did vary significantly by country (p=0.0028), with China experiencing the lowest detection frequencies. There were also significantly more frequent detections of 2-ethyl hexyl-2,3,4,5-tetrabromobenzoate (EHTBB) in wristbands from the USA (89%) compared to the UK (12%), India (3.2%), and China (0%) (p<0.00001). Decabromodiphenyl ethane (DBDPE) was detected in 22% of samples overall, which did not significantly differ by country (p=0.12).

There were clear differences in the magnitude of wristband concentrations of EHTBB and BEHTBP across countries. Compared to all three other countries, levels of EHTBB were drastically higher in the USA, which was also the country with the highest detection frequency (Figure 2.3). In addition, wristband concentrations of BEHTBP in the USA and UK were higher than in China or India (Figure 2.1 and Figure 2.3). China had both the lowest concentrations and least frequent detections of BEHTBP. In a multilevel model for one novel BFR, BEHTBP, we estimated that there were 92.8% lower levels in China (95% CI: -97.2– -81.9%; p<0.0001) and 71.9% lower levels in India (95% CI: -86.2– -42.7%; p=0.00089) than in the USA, adjusted for building construction year, foam furniture, and carpeting. Carpeted flooring in the participant's workstation was also associated with a 63.7% decrease in BEHTBP concentrations in wristbands (95% CI: -79.8– -34.7%; p=0.0013), adjusted for country, construction year, and foam furniture. All (100%) of the variability in log BEHTBP concentrations was explained by differences between individuals as opposed to between buildings. Furthermore, the USA was the only

country that had samples with EHTBB concentrations greater than BEHTBP concentrations, indicative of unique commercial flame-retardant mixtures. By country, the median EHTBB:BEHTBP ratios were 1.1 (range: 0.00020–7.3) in the USA, 0.00068 (0.000019–0.46) in the UK, 0.0018 (0.00010–0.17) in China, and 0.0012 (0.000064–0.17) in India.

Organophosphate Esters

OPEs were detected in nearly every (99%) silicone wristband sample (Table 2.2). Seven specific OPE chemicals were detected in 95% or more of samples: TCIPP, TPHP, EHDPP, TEHP, TpCP, TDCIPP, and 2IPPDPP. Another six OPEs were detected in over half of samples. Despite the ubiquity of many OPEs, some still had significantly different detection frequencies across countries, usually with higher frequencies in the USA and/or UK. For example, samples from the USA (75%) and UK (64%) had significantly more frequent detections of TnBP than China (15%) and India (9.7%) (p<0.01). Two ITPs, 4IPPDPP and B2IPPPP, had significantly different (more) detections in the USA (98% and 74%, respectively) and UK (92% and 80%) compared to India (45% and 19%; p<0.0004). Two types of TBPPs, 4tBPDPP and B4tBPPP, had significantly different (more) detections in the USA (98% and 72%) and/or UK (92% and 52%) than in China (54% and 7.7%) or India (52% and 26%; p<0.012).

The magnitudes of wristband concentrations of several OPEs were also substantially different across countries. Of particular note, the concentrations of TCIPP in wristbands from the UK were orders of magnitude higher than for any other country (Figure 2.4) or any other OPE (Figure 2.1). TiBP also exhibited higher concentrations and detection frequencies in the UK than other countries (Figure 2.4). In addition, log concentrations of TnBP were higher in the USA and

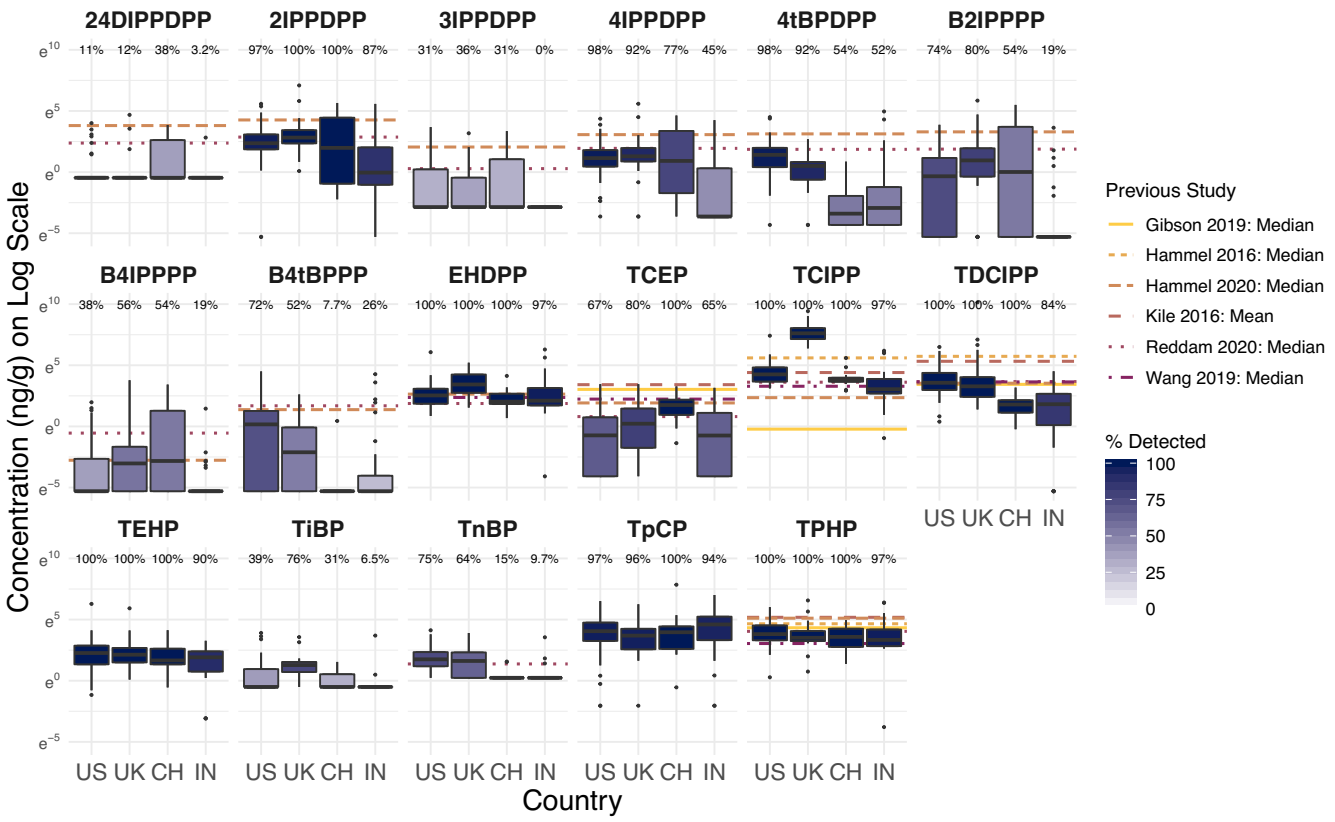

Figure 2.4. Log concentrations (ng/g-wristband, standardized to 32 hours of sampling) of select organophosphate esters on silicone wristbands worn by 130 office workers, with comparison to concentrations (standardized to 32 hours) from previous wristband studies.

Caution: some previous studies did not employ the same lab analysis methods. We standardized reported means/medians to 32 hours.
Gibson et al. 2019: mothers in New York, USA (*n*=38; sampled 2015; wristbands worn for 7 days).
Hammel et al. 2016: general population in North Carolina, USA (*n*=40; compatible lab methods; sampled 2015; wristbands worn for 5 days).
Hammel et al. 2020: children in North Carolina, USA (*n*=77; compatible lab methods; sampled 2015; wristbands worn for 7 days).
Kile et al. 2016: preschool children in Oregon, USA (*n*=72; sampled 2012-2013; wristbands worn for 7 days).
Reddam et al. 2020: undergraduate students in California, USA (*n*=88; sampled 2019; wristbands worn for 5 days).
Wang et al. 2019: community in rural Appalachia, USA (*n*=101; sampled 2017-2018; wristbands worn for 7 days).

UK, while TCEP tended to be higher in China than other countries. TDCIPP concentrations in wristbands from China and India were slightly lower than those from the USA or UK.

In multilevel regression models of a subset of OPEs, there were 3,100% higher concentrations of TCIPP on wristbands from the UK than from the USA (95% CI: 1,480–6,400%; $p<0.0001$), adjusted for construction year, foam furniture, and carpeting (Table 2.3). TCIPP concentrations in samples from India were also 54.7% lower than in the USA (95% CI: -77.8– -11.0%; $p=0.061$), although this only had suggestive statistical evidence. In the adjusted

models, TiBP levels were 178% higher in the UK than in the USA (95% CI: 49.7–413%; p=0.0043), with suggestive evidence that India had 45.4% lower levels than the USA (95% CI: -69.6– -2.22%; p=0.065).

For ITP chemicals, wristbands from India consistently had lower concentrations and fewer detections than those from the other countries. The median concentrations of ITPs in samples from the USA, UK, and China tended to be similar except that 24DIPPDPP was most frequently detected in China (Figure 2.4). In fact, in the adjusted regression model of 2IPPDPP, country was not significantly associated with the wristband concentrations (Table 2.3). Among the two primary chemicals in the TBPP commercial mixture (4tBPDPP and B4tBPPP), both showed higher median concentrations (and detection frequencies) in the USA and UK than in China or India (Figure 2.4). There were 94.8% lower levels of 4tBPDPP in China (95% CI: -98.7– -78.1%; p=0.0012) and 89.0% lower levels in India (95% CI: -96.7– -67.5%; p=0.0028) compared to the USA, adjusted for building construction year, carpeting, and foam furniture. B4tBPPP concentrations in wristbands were also 96.4% lower in China (95% CI: -99.5– -73.6%; p=0.0082) and 87.2% lower in India (95% CI: -97.6– -45.4%; p=0.033) than the USA. Wristbands from the UK had suggestive evidence of lower concentrations of B4tBPPP compared to the USA (-83.8%; 95% CI: -97.2– -23.8%; p=0.062).

The presence of carpeting and/or foam chairs at participant workstations significantly impacted concentrations of 2IPPDPP, 4tBPDPP, and B4tBPPP in wristbands (Table 2.3). There were 439% higher 2IPPDPP concentrations (95% CI: 51.8–1,520%; p=0.02), 715% higher 4tBPDPP concentrations (95% CI: 230–1,840%; p=0.00026), and 440% higher B4tBPPP concentrations (95% CI: 53.0–1,880%; p=0.028) for participants that had carpeting in their workstation compared to no carpeting, adjusted for country, building construction year, and

presence of a foam chair. The use of a foam office chair by participants was associated with 290% higher B4tBPPP concentrations (95% CI: 16.5–1,330%; p=0.046) in wristbands compared to a non-foam office chair.

Chemical Relationships

Many chemicals within each chemical class were correlated in the wristband samples, and there were relationships that differentiated contemporary versus legacy chemicals across different classes (Figure 2.5; Figure 6.1 by country). For example, legacy PCB-28 and PCB-101 were significantly and positively correlated with each other, but PCB-11 was not. BDE-47 and BDE-99, components of the commercial flame-retardant mixture PentaBDE,[199] were also highly positively correlated with legacy PCB-28 and PCB-101, while BDE-209 (DecaBDE) was not.

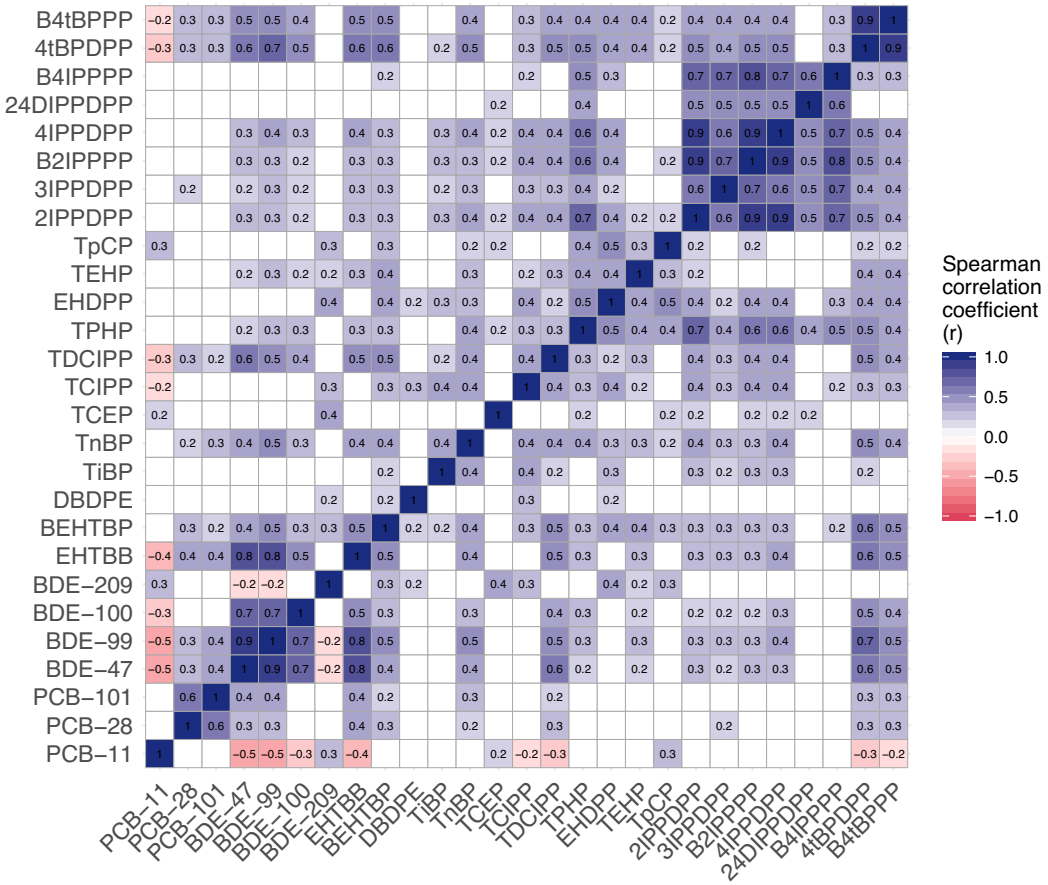

Figure 2.5. Significant (p<0.028) Spearman correlation coefficients for chemicals detected in at least one-third of silicone wristband samples within a country (n=130).

There were strong correlations within each group of the novel BFRs, ITPs, and TBPPs, as well as between ITPs and TPHP, indicative of co-occurrences in commercial flame-retardant mixtures.

Principal component analysis on the 27 chemicals detected in over one-third of samples in a country resulted in seven principal components that together explained over 70% of the variance and that had eigenvalues greater than one (Figure 2.6). The first component (PC1), explaining 24% of the total variance, was mostly influenced by OPEs. Specifically, all the evaluated ITPs and TPHP exhibited high contributions to PC1. The second component (PC2), explaining 13% of the variance, had the highest absolute coordinates for BDE congeners 47, 99, and 100. The third component (PC3; 9%) was dominated by BDE-209 and two novel BFRs: EHTBB and BEHTBP. PC4 (8%) was mostly explained by the two TBPPs: 4tBPDPP and B4tBPPP. PC5 (6%) was not as distinct but had the most influence from PCB-11 and TpCP. PC6

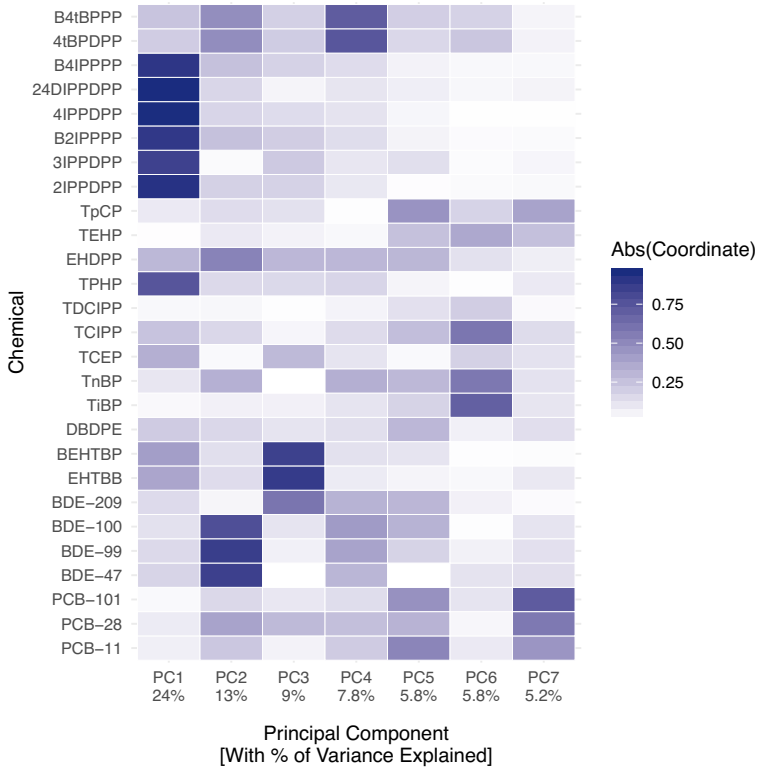

Figure 2.6. Contributions of chemicals in the seven principal components explaining over 70% of variance from analysis of analytes detected in over one-third of silicone wristband samples in a country (n=130).

(6%) mostly reflected contributions of TiBP, TCIPP, and TnBP. Finally, PC7 (5%) was well-explained by PCB-101, PCB-28, and slightly by PCB-11 and TpCP. Figure 6.2 presents principal component analysis results by country.

Sensitivity Analyses with Indoor Air Quality Parameters

For sensitivity analyses, we conducted the same multilevel regression models as in Table 2.3 but with additional adjustments for the average temperature and relative humidity measured during each building's study week (during business hours only). The significant predictors of chemical exposure, including countries, were mostly robust in our sensitivity analyses. One appreciable difference was that India no longer had a suggestive effect on TiBP concentrations in the sensitivity analysis (-11.9%; p=0.76) compared to in the primary model (-45.4%; p=0.065). The few other estimates with minor differences were still similar in magnitude as before but now just had slightly higher p-values (0.05–0.06), possibly due to the reduction in sample size (and increase in number of covariates) and thus limited statistical power. Importantly, the effects of the UK, which was usually sampled the earliest in the year, and of China, which was sampled the latest (in summer), were all still statistically significant, except that the estimate for China for 4tBPDPP maintained the same magnitude (-88.3% versus -94.8%) with only a suggestive p-value now (p=0.063 versus 0.0012).

Discussion

All but three of the 55 measured semi-volatile chemicals commonly used in building materials were detected in the silicone wristbands worn by office workers in the USA, UK, China and India. The variation between countries in exposures to polychlorinated biphenyls,

brominated flame retardants, and organophosphate esters highlights differences in use and regulations. We found that office workers are still being exposed to legacy chemicals that were phased out decades ago, and some contemporary, unintentional sources of chemicals (such as PCB-11) are present at elevated levels even though their direct production is banned. Our findings also show that participants from the HICs with historically more rigorous flammability standards (the USA and UK) tended to have higher exposures to most flame-retardant chemicals compared to the LMICs (China and India), except for some flame retardants (such as BDE-209) that were not phased-out in the LMICs as thoroughly or as early as they were in HICs. The ubiquitous exposures of the studied office workers to novel BFRs and OPEs demonstrate the increasing use of chemicals that may be used as regrettable substitutes to phased-out PBDE flame retardants and/or as plasticizers. The silicone wristband samplers proved to be useful, novel tools for evaluating global chemical exposures in office buildings.

Polychlorinated Biphenyls

PCBs were banned in the USA and UK by 1979[106] and 1986,[107] respectively, yet office workers in this study were still exposed to several legacy PCBs. In particular, PCB-28 and PCB-101 were found in the silicone wristbands at higher detection frequencies and geometric mean concentrations in the USA compared to the other countries. In fact, these two PCBs were detected in 0% of samples from China and less than 7% of samples from India. The sampled buildings in China and India were all constructed after 2003, which likely explains the relatively lower detections of legacy PCBs compared to the USA and UK. PCBs were added to the Stockholm Convention's banned substances in 2004, although China reportedly stopped PCB production gradually between 1974 and the 1980s,[108] and India officially banned their production

and import in 2016.[109] By contrast, the USA study population occupied some of the oldest buildings in our study, dating back to 1898 (eight of the 15 were constructed in or before the 1979 ban), and three of the six study buildings in the UK were constructed between 1987–1990 (right after the 1986 ban). The detected concentrations of legacy PCBs were likely a result of PCB-containing materials in older buildings constructed before regulatory bans, since pre-existing materials were generally allowed to remain in use (and often have not been tested for PCBs). The significant positive association between PCB-101 and building age in our regression models confirmed that exposures to this chemical are likely due to legacy building materials and are declining over time. Several studies have similarly documented the continued presence of legacy PCBs in buildings in the USA and Europe decades later due to their use in building materials such as joint sealants.[13–15,95–97,118,200,201]

PCB-11, on the other hand, is a contemporary, non-legacy PCB congener that was not historically added to commercial mixtures at appreciable levels and has been an emerging concern in buildings.[14,202] In this study, PCB-11 was frequently detected in 70% of wristbands from all the countries. PCB-11 was detected in at least 90% of wristbands from China and India, where the study buildings were all constructed more recently (after 2007 in China and after 2002 in India). As expected because of more recent building constructions, wristbands from China and India had substantially and significantly higher concentrations of PCB-11 than those from the USA. In addition, while the legacy congeners PCB-28 and PCB-101 were significantly positively correlated with each other, PCB-11 was negatively correlated with each. In the principal component (PC5) we classified as driven by PCB-11, the two legacy congeners contributed to the principal component in the direction opposite of PCB-11. These findings suggest that PCB-11 in the office buildings has a non-legacy source. Studies have more recently found

unexpectedly high levels of PCB-11 in outdoor air and water that were not driven by the dechlorination process of heavier congeners and continued even as other legacy PCBs declined.[14,167,203,204] Research has shown that PCB-11 is an unintentional manufacturing byproduct in certain pigments that are used in wall paint, product packaging, textiles, and other materials with pigments.[14,166–169,205] Even though PCB manufacturing was banned in many countries, that does not apply to the *unintentional* presence of PCB congeners as a byproduct of manufacturing processes.[14]

Polybrominated Diphenyl Ethers: PentaBDE

Similar to PCBs, PBDEs were still present in the study buildings as legacy phased-out chemicals used in furniture, electronics, carpet, and insulation. The PBDE congeners 47, 99, and 100 were detected at the highest frequencies in wristbands from the USA and at low to moderate frequencies in those from the UK, while most other congeners (except BDE-209) were rarely detected. BDE-47, BDE-99, and BDE-100 were components of the historically common commercial flame-retardant mixture PentaBDE.[199] By 2004, major manufacturers in the USA voluntarily phased out PentaBDE and OctaBDE[22] (which included BDE-153, BDE-154, and BDE-183),[199] and the state of California banned them in 2006.[206] Similarly, the UK banned PentaBDE in 2004 (and separately in 2006 for electronics).[104] Thus, the office workers in this study were still exposed to PentaBDE chemicals 15 years after their phase-out. Unlike the USA and UK, the presence of PentaBDE was non-existent in samples from China and India, possibly due to the contrasting lack of similar flammability regulations and/or the more recent construction of the study buildings (2009 or later in China; 2003 or later in India). For example, while the USA and UK first mandated rigorous flammability tests for upholstered furniture in

1975[156,207] and 1988,[208] respectively, China only recently implemented a flammability standard effective 2008, which applied to products in public (not residential) facilities.[114] This standard may have come after PentaBDE fell out of favor due to the addition of PentaBDE and OctaBDE to the Stockholm Convention global elimination list in 2004.[111,112]

As expected, given their co-presence in PentaBDE mixtures, concentrations of the PBDE congeners 47, 99, and 101 in our wristband samples were very highly positively correlated with each other and were the primary chemicals of the second principal component that explained 13% of the variability in chemical concentrations. BDE-47 and BDE-99 were also significantly positively correlated with PCB-28 and PCB-101, indicating they are all legacy chemicals phased out of building materials. In addition, the median concentrations of PentaBDE components in this study were mostly lower (especially in non-USA countries) than have been found in previous studies of silicone wristbands worn by adults or children in the USA,[49,190] including one study that employed similar laboratory methods (Figure 2.3).[132] This may indicate exposures to these legacy PBDE congeners are declining over time or that home and work environments differ.

Polybrominated Diphenyl Ethers: DecaBDE

Unlike the PentaBDE chemicals, DecaBDE largely consists of BDE-209 and was found in over half of our samples across all four countries. The higher presence, and difference in trends, of BDE-209 compared to the other PBDEs could have resulted from its more recent restrictions and/or differences in physical-chemical properties. BDE-209 concentrations on the wristbands were much higher in the UK and India than the USA. Detection frequencies and

median concentrations of BDE-209 were also higher in China than the USA, although the difference did not reach statistical significance. While DecaBDE was voluntarily phased out by manufacturers in the USA by 2013, the UK only banned it in March 2019, after our study sampling period ended[105] (and in 2008 ended its exemption in restrictions of PBDEs in electronics).[209,210] India restricted PBDEs in electronic products since 2014,[113] but not in other products to our knowledge. In China, DecaBDE is not restricted, as it's exempted from the electronics regulation of PBDEs, and it remains a high production-volume flame retardant there.[114–117] The fact that the wristbands from the UK tended to have the highest BDE-209 concentrations of the four countries aligns with previous research reporting the high use and detection of BDE-209 in the UK compared to other countries.[211] The median BDE-209 concentrations in our samples from the UK, India, and China were higher than those from a previous sample of wristbands worn by 30 people in the USA and analyzed with compatible laboratory methods, whereas concentrations in our study from the USA were similar to this previous study (Figure 2.3).[132] BDE-209 was not positively correlated with the legacy PCBs and was negatively correlated with the legacy PentaBDE components, suggesting that BDE-209 is a more contemporary chemical that has not yet declined as much in use. BDE-209, along with two novel BFR substitutes (EHTBB and BEHTBP), also loaded onto a different principal component than PentaBDE. Our findings of BDE-209 in wristbands worn in office buildings across the USA, UK, China, and India reveal the lags between regulations and exposure reductions as well as the gaps in government restrictions that do not treat chemicals as an entire class.

Novel Brominated Flame Retardants

Even though certain harmful chemicals like PBDEs were largely phased out, they are frequently replaced with other similarly concerning regrettable substitutes.[98] Novel BFRs and OPEs are two classes of unrestricted flame retardants commonly used as substitutes in the same product applications as PBDEs.[28,35,38,178,212,213] For example, BEHTBP and EHTBB are two novel BFRs often used in commercial flame retardant mixtures together.[24,28] The concentrations of these two chemicals in our wristband samples were significantly and positively correlated with each other and contributed heavily to the same distinct principal component. However, EHTBB was primarily detected in the USA (and at much higher magnitude), while BEHTBP was detected in the vast majority of samples across all four countries. The concentrations of BEHTBP were significantly higher in the USA than China or India. The USA was also the only country with any samples having higher concentrations of EHTBB than BEHTBP. This suggests that in our study, the USA may be the only one of the four countries that has contributions from commercial flame-retardant mixtures such as Firemaster (FM) 550, BZ-54, and FM 600, which contain both BEHTBP and EHTBB.[24,214–217] The other countries may have higher relative use of other commercial flame-retardant mixtures, such as DP-45, which consists exclusively of BEHTBP.[214–216] Even in the USA, the median EHTBB:BEHTBP ratio of 1.1 (max 7.3) suggests that FM 550 (with an approximate ratio between 2:1 and 4:1),[24,212,215,216,218] BZ-54 (ratio of 5:2),[212,219] and FM 600 (ratio of 1.5:1)[212,218] are not the only mixtures used as PBDE replacements in products.[35,212] This finding aligns with two previous studies of dust in the USA and UK that found ratios indicating the presence of additional non-FM 550 mixtures.[24,220] The median concentrations of BEHTBP and EHTBB in the USA were both similar to previous wristband studies (Figure 2.3).[49,132,190] In our regression models, the presence of carpeting was negatively associated with BEHTBP concentrations, which may be driven by the alternative

presence of vinyl or other non-carpeted floor types as a source. In addition to flame retardant applications, BEHTBP can be used as a plasticizer in polyvinyl chloride plastic and neoprene.[28]

Organophosphate Esters

OPE concentrations also provided insights into varying uses of flame-retardant mixtures. TPHP did not load on the same principal component as BEHTBP and EHTBB, and TPHP was only moderately correlated with those two chemicals. This indicates that FM 550 (of which TPHP is another component)[24,212,218] may not be the only or primary mixture used. Instead, EHTBB and BEHTBP were significantly and highly correlated with two TBPPs: 4tBPDPP and B4tBPPP. The relationship with these two TBPPs indicates the likely use of FM 600, in which they each may comprise up to 20-30% of the mixture by weight,[212,218] at least in the USA and UK where the TBPP wristband concentrations were significantly higher than in India or China. On the other hand, TPHP was significantly correlated with ITPs and together they tightly formed the first principal component overall and within each country, suggesting prevalent use of the so-called ITP flame retardant mixture that consists of TPHP and a suite of ITPs.[218] India typically had lower wristband concentrations of OPEs than the other countries, which aligns with previous research of OPEs in dust from India (which has less strict flammability standards) compared to industrialized countries.[221] These results demonstrate the differences in flame retardant profiles and trends across countries. In our regression models, the association between higher exposures of office workers to certain ITPs and TBPPs and the presence of carpeting and/or a foam office chair in the workstation reinforces our understanding that OPEs are used as regrettable substitutes to traditional PBDEs in similar product applications.

TCIPP is a common substitute flame retardant in foam furniture that we found in nearly every sample and at substantially higher levels in wristbands from the UK than all three other countries. In addition, we observed higher median levels of TCIPP as compared to six previous studies using silicone wristbands (Figure 2.4).[49,128,133,190,192,222] These findings align with previous research that found preferential use of TCIPP in the UK compared to other countries.[223,224] By contrast, TCEP was much higher and more frequently detected in our wristbands from China than other countries. This result is consistent with previous research reporting that TCEP comprises a larger proportion of OPEs in indoor dust from China and other Asian countries compared to the USA and European countries where TCEP has dropped in production.[221] In fact, TCEP was listed as a human carcinogen by the California Environmental Protection Agency in 1992.[225] The chlorinated OPEs are typically used in polyurethane foam applications but can also be added as plasticizers to PVC, plastic, wallpaper, textiles, coatings, and paints.[39]

Public Health Implications

This study demonstrated several limitations in market and regulatory approaches that should be addressed to reduce indoor chemical exposures from building materials. First, chemical restrictions do not always occur, or apply equally, in every country. For example, DecaBDE was phased out in the USA in 2013, but it still does not have any restrictions in China, has only very limited restrictions in India, and was only recently phased out in the UK in 2019. Given substantial country-level differences in certain chemical exposures and their regulations, this study highlights the importance of conducting more research to fill gaps about exposure disparities in understudied low- and middle-income countries (LMICs).[177] Second, even when

chemicals are eliminated from the market, many buildings still contain legacy chemicals for decades. This is especially evident for the office workers still exposed to legacy PCBs and PBDEs from building materials present in older buildings in the USA and UK despite bans implemented decades ago. Third, chemical classes phased out from certain uses may appear in other applications. We found that PCB-11 was an important contemporary, non-legacy contaminant in the office buildings. This PCB is inadvertently produced in the manufacturing of pigments for paint and other materials, despite bans on intentional uses of legacy PCBs. In addition, the recycling of discarded products, such as PBDE-containing plastic electronics, could cause phased-out chemicals to re-enter the material resource stream during manufacturing of new products.[120–122] Fourth, phased-out chemicals are usually replaced with other similar, harmful regrettable substitutes.[98] This study found significant exposures of office workers to replacements to legacy PBDEs in several countries, including novel brominated flame retardants and possibly organophosphate esters (also used as plasticizers). Our results reinforce that buildings and the products within them last for many decades. Thus, the decisions we make today about chemicals in materials will influence population exposures for decades to come.

Advantages of Silicone Wristband Samplers

Sampling with silicone wristbands offered several key advantages for our study design. Compared to urine or blood samples, wristbands are simple, non-invasive, and relatively inexpensive.[128] Importantly, they can also help isolate environmental exposures in a specific microenvironment of interest (such as the office), since the wristbands can easily be worn by participants only in the desired location(s) as instructed, and the results do not have interference from dietary exposures. In addition, wristbands allow for control over the exact exposure time

window that the sample concentrations reflect. In comparison to hand wipes, wristbands have been shown to provide better a measure of cumulative exposures.[128] Finally, the stability of wristband samples facilitates the use of sample shipment kits in large, global studies such as this one. Previously, semi-volatile chemicals on wristbands were experimentally shown to be stable at high temperatures (30°C) for at least one month during transport and when stored frozen (-20°C) for at least six months (the longest time studied),[129] but possibly up to 500 days based on another study.[190]

Strengths and Limitations

This study has several other key strengths in addition to the novel use of silicone wristbands. It is the first study to use silicone wristbands to study people's exposures specifically in their office environments. This was also the only study to report chemical exposures from wristbands in the UK and in two understudied LMICs: India and China. Compared to previous wristband studies, the amount of information we had on building factors and workstation characteristics for the participants was unique. This information and our large sample size allowed us to conduct statistical modelling of a few predictors of chemical exposures with wristbands and to control for air quality factors in sensitivity analyses. An important strength was that participants were instructed to wear their wristbands only during work hours at their office buildings, which allowed us to isolate exposures specifically in this indoor environment where workers often spend a quarter of their time.

Limitations include the fact that this study was a convenience sample of Class A office buildings. Therefore, we cannot generalize to all types of office environments in these countries. Due to differences in physical-chemical properties that would influence each chemical's uptake

efficiency onto the silicone wristband material, we could not accurately compare concentrations across different chemicals. However, we did have internal validity within each chemical, so could compare a chemical's concentrations by country and other factors. In addition, the silicone wristbands were able to capture both primarily gas-phase (e.g. BDE-47) and particle-bound chemicals (e.g. BDE-209). Finally, we sampled participants from the four countries in different sampling weeks, with the UK during February and China (last) during July. However, our indoor air quality sensor data allowed us to control for differences in temperature and relative humidity, and the sensitivity analyses showed that the multilevel model results were robust after adjusting for these factors (with some reductions in statistical power). Furthermore, a range of temperatures similar to that in China (median: 24.7°C; range: 23.1–30.0°C) occurred in buildings from the USA (median: 23.5°C; range: 22.3–28.2°C) and India (median: 26.9°C; range: 24.7–28.3°C) during their study weeks. The UK had a smaller range of average temperature during its study week (median: 24.4°C; range: 24.1–24.9°C).

Conclusions

The use of novel silicone wristband samplers allowed us to isolate and measure chemical exposures inside office buildings across four countries–the USA, UK, China, and India. We found that certain PCB, BFR, and OPE chemicals used in building materials were frequently detected in wristbands worn by office workers from all countries. Even legacy PCBs and PBDEs that were phased out decades ago in some countries still persisted inside buildings and exposed occupants due to the continued use of older building materials. In addition, historically common PBDEs were often simply replaced with other concerning flame retardants, such as OPEs, which were detected in nearly every wristband sample in this study. The decades-long life span of

building materials and the semi-volatile chemicals in them urges the need for forward-looking decisions on healthier materials. The substantial variation in semi-volatile organic chemical exposures across countries also highlights the need for more research in understudied low- and middle-income countries.

CHAPTER 3: Indoor dust affects multiple human nuclear hormone receptors in cell-based reporter assays

Anna S. Young[1,2], Thomas Zoeller[3], Russ Hauser[1], Tamarra James-Todd[1], Brent Coull[1], Peter A. Behnisch[4], Abraham Brouwer[4], Hongkai Zhu[5], Kurunthachalam Kannan[5], Joseph G. Allen[1]

[1] Harvard T.H. Chan School of Public Health, Boston, MA, USA

[2] Harvard Graduate School of Arts and Sciences, Cambridge, MA, USA

[3] University of Massachusetts Amherst, Amherst, MA, USA

[4] BioDetection Systems, Amsterdam, The Netherlands

[5] New York University School of Medicine, New York, NY, USA

Abstract

Building occupants are exposed to complex mixtures of hormone-disrupting chemicals, including per- and polyfluoroalkyl substances (PFAS), organophosphate esters (OPEs), and polybrominated diphenyl ether flame retardants (PBDEs). These chemicals are in furniture, carpet, and electronics and can migrate from products into air and dust. Our objectives were to: 1) quantify hormonal activities of 46 indoor dust samples using cell-based luciferase reporter assays, and 2) determine if specific chemicals in dust were driving any observed hormonal activity, using both raw measured concentrations of 42 PFAS, OPEs, and PBDEs as well as potency-weighted concentrations of the chemicals, mostly derived from Tox21 high-throughput chemical screening data. We quantified dust activation of estrogen receptor α (ERα); suppression of androgen receptor (AR), peroxisome proliferator-activated receptor γ2 (PPARγ), and thyroid hormone receptor β (TRβ); and competitive binding interference with thyroid hormone thyroxine (T4) serum transport on transthyretin. All dust samples were hormonally active in at least two assays, showing antagonistic activity towards PPARγ (100%), TRβ (89%), and AR (87%); agonist activity on ERα (96%); and binding competition with T4 on TTR (98%). Effects were observed with as little as 4 μg of dust; for reference, people aged 12 years or older ingest an average 20,000 μg/day of dust. In regression models, we found that an interquartile range (IQR) increase in the potency-weighted ΣPFAS or ΣOPE concentration in dust increased TRβ suppression by 28% (p<0.01) or 27% (p=0.08), respectively, adjusted for the summed concentrations of chemicals in the class that were classified as inactive in the Tox21 screening data or that were not screened. We also found evidence that an IQR increase in potency-weighted ΣPBDEs significantly increased TRβ suppression by 20% (p<0.05) and ERα activation by 8% (p=0.08). T4 transport interference was 34% higher (p<0.05) for an IQR increase in ΣOPEs, all

analytes of which had unknown potencies towards this endpoint. All indoor dust samples exhibited hormonal activities, which were substantially influenced by dust concentrations of PFAS, PBDEs, and OPEs. Reporter gene cell-based assays are relatively less expensive and are health-relevant to evaluate toxic loads of chemicals and their mixtures that building occupants are exposed to.

Introduction

We are increasingly exposed to complex mixtures of hormone-disrupting chemicals from the products and materials inside buildings.[29,181,226–228] Flame retardants (FRs) and fluorinated stain repellants are two types of chemicals that are ubiquitously used in building furnishings and that have been detected in the urine or blood of over 90% of Americans.[8–11] As unbound additives, these chemicals can leach out of products[66,155,160,161,229–231] and accumulate in dust.[20–26,29,232] Ingestion and dermal absorption of dust (and less so, inhalation) have been estimated to be the most important routes of exposure for flame retardants[233–239] and usually only preceded by dietary consumption for common stain repellants.[30,31]

Per- and polyfluoroalkyl substances (PFAS) are a class of anthropogenic, fluorinated chemicals applied as surface coatings on materials to repel stains, grease, and water.[4] PFAS are commonly used in carpet, furniture upholstery, outdoor clothing, non-stick cookware, and disposable food packaging.[62–66] Owing to their extreme persistence, the perfluoroalkyl acids will practically never degrade under environmental conditions.[4,102,125] Research has linked PFAS to adverse human health effects on thyroid function,[41,67–70] metabolism (including overweight/obesity, diabetes, insulin resistance, and high cholesterol),[4,71–75,79,80] fetal development,[69,76] the immune system,[68,77,78] and possibly kidney and testicular cancer.[82–88] Even

though two of the most widely known toxic PFAS were voluntarily phased out of production by manufacturers in the U.S. starting in the early 2000s, there are over 4,700 different PFAS 'regrettable substitutes' available on the market.[98,99,103] Toxicological research indicates that studied replacement PFAS are also of concern to human health.[100–102]

Chemical flame retardants have been added to polyurethane foam furniture, carpet, electronics, and building insulation to meet fire codes and product flammability standards.[22,25,227,240–242,32–38,159] One historically common type of flame retardant, polybrominated diphenyl ethers (PBDEs), are associated with thyroid dysfunction,[5,6,48,49,40–47] reproductive health issues (including poor pregnancy outcomes, infertility, and altered hormone levels),[5,6,48,51–53] and impairment of reproductive and cognitive development.[5,6,43,45,57–59] Three common commercial mixtures of PBDEs were largely phased out by manufacturers between 2004 and 2013 in the U.S.[22] However, products containing old PBDE formulations will still be used for many years, and PBDEs can re-enter the material resource stream through recycling of old products.[243] In addition, similar to PFAS, phased-out PBDEs were often substituted with other flame retardants with similar toxicological profiles. This includes the emerging use of organophosphate esters (OPEs), which recent research has found to be associated with adverse effects on thyroid function,[49,50,56] development,[60,61] pregnancy outcomes, and fertility.[7,54–56]

There is considerable evidence that both PFAS and flame retardants are endocrine-disrupting chemicals. These chemicals can replace natural hormones in the body and thus disrupt their fine-tuned regulation of many physiologic systems.[244] Some PFAS have been shown to activate estrogen receptor α (ERα)[245–248] and peroxisome proliferator-activated receptor γ (PPARγ),[245,246,249–252] suppress thyroid hormone receptor β (TRβ),[150,247] PPARγ,[150,253] and androgen receptor (AR),[147] and interfere with thyroid hormone serum transport.[254–257] Similarly,

PBDEs can also activate ERα,[150,258–261] suppress TRβ[137,150,258,262–264] and AR,[150,258–260] and interfere with thyroid hormone serum transport.[257,259,263,265–267] OPEs have been found to activate ERα[150,260,268–273] and PPARγ[273–276] and suppress AR,[150,260,268,277] TRβ,[137,150,277] and PPARγ.[150]

Because nuclear hormone receptors regulate critical genes, their signaling disruption can lead to reproductive (e.g. infertility), developmental (e.g. abnormal fetal growth), metabolic (e.g. obesity or diabetes), and proliferative diseases (e.g. breast cancer).[244] For example, estrogen receptor α, normally activated by the endogenous estrogen hormone 17β-estradiol (E2), regulates the development and maintenance of the breast tissue, uterus, cardiovascular system, female reproductive cycle, and bone density. Androgen receptor, under signaling control by testosterone and dihydrotestosterone, plays an important role in male sexual development and differentiation as well as spermatogenesis. Peroxisome proliferator-activated receptor γ, mainly activated by fatty acid metabolites, is the key regulator of fat storage, lipid metabolism, and insulin sensitivity and can produce anti-inflammatory effects. Thyroid hormone receptor β, usually activated by thyroid hormones (thyroxine [T4] and tri-iodothyronine [T3]) throughout the body, is crucial for normal development, growth, metabolism, and brain function.[244,249,258,278–282] Some chemicals can also disrupt action of thyroid hormones by competitively binding to their serum transporters, such as transthyretin, which is important for delivering T4 across the blood-brain barrier and placenta. When not bound to transporters, free T4 is available for elimination from the body, which thus decreases circulating levels of the hormone. The competitive binding by a particular toxic chemical may also facilitate the transport of that chemical into important target tissues.[254,257,266,283,284]

Cell-based assays are an emerging high-throughput method to quantify the total hormone receptor activity of complex environmental mixtures of hormone-disrupting chemicals.

Compared to traditional targeted laboratory approaches that measure each chemical in a mixture individually, cell-based assays of dust are inexpensive, rapid, statistically simple to model, and representative of the total mixture.[136–138,285] Hormonal activities in assays of dust reflect combined effects from co-exposures of *all* hormone-disrupting chemicals in the sample, including unmeasurable chemicals and unknown 'regrettable substitutes.' The assays account for any mixture effects that cannot be predicted from the isolated hormonal activity of each individual chemical, such as when a chemical's effect is triggered, enhanced, or reduced when in the presence of another substance.[137,139,148,140–147]

Many cell-based assay approaches work by introducing into the cell line a reporter gene, such as firefly luciferase, whose expression is controlled by activation of a certain nuclear hormone receptor. For example, when a chemical binds to and either activates (agonizes) or suppresses (antagonizes) a hormone receptor, light will be proportionally produced and can be measured as an indicator of receptor activation.[286–289] Normally in the body, once the right hormone binds to and conformationally changes a nuclear hormone receptor, the receptor can bind to its target gene (if not already bound), and corepressors on the receptor are replaced with coactivators that facilitate transcription of the target gene (also called a hormone response element).[244,249,278,282,290,291]

Only a few studies have previously measured any hormonal activities of indoor dust using cell-based assays.[136–138,257,260,275,292] Suzuki et al. reported that certain measured PBDEs or OPEs were probable contributors to the levels of ERα activation and AR suppression in dust from homes in the U.S. and four Asian countries.[260] Kollitz et al. found significant correlations between PBDE or OPE levels and TRβ antagonism in dust from 137 homes in the U.S. even though the 12 measured flame retardants were not active when tested in isolation, demonstrating

possible mixture effects and influence from unmeasured chemicals.[137] Vandermarken et al. found a significant relationship between phthalate levels and estrogenic activity in dust from kindergartens in Belgium.[136] There are currently no published studies that have related PFAS concentrations to bioactivities in dust.

Hormone receptor activity in a cell-based assay is not only a function of the chemical concentration, but also a function of the chemical potency. The increase in available high-throughput screening assay data, such as the Tox21 database for individual potencies of almost ten thousand chemicals,[149,150] has recently enabled water monitoring studies to integrate information on chemical concentrations and their respective potencies in order to identify key contaminants driving the total bioactivities of water samples.[151–154] This type of potency-weighted exposure evaluation using high-throughput screening data has not been done with chemicals in dust to our knowledge.

The objectives of this study were to: 1) quantify hormonal activities of indoor dust, 2) identify associations between measured PFAS, PBDE, and OPE chemicals and hormonal activities of dust, and 3) evaluate potency-weighted chemical concentration calculations as a method to determine which of the measured chemicals are driving the effects of dust mixtures.

Methods

Study Design

We collected indoor dust samples from 46 rooms across 21 different buildings at a university located in the northeastern United States during January to March 2019. The rooms included 22 common spaces or study areas, 6 office suites, and 18 classrooms, conference rooms, or auditoriums across campus. Approximately half of the samples (n=22) were collected from

rooms renovated between 2017 and 2019 with upholstered foam furniture and carpet specified to be free of flame retardants and PFAS. The remaining samples (*n*=24) were collected from carpeted rooms that made up an equivalent distribution of room types and that had been renovated with conventional furniture as recently as possible. For all sampled rooms, the building construction years ranged from 1863 to 2018 (median 1966) and the years of last renovation ranged from 2001 to 2019 (median 2017).

Dust Sample Collection

Before sampling, we asked each building's custodial crew to leave the space unvacuumed for two to three days, often over the weekend, so that enough dust could accumulate. In each selected building room, we split the space into three equally sized, equivalently furnished areas. We then collected three separate dust samples, one in each of the three designated areas, to have sufficient dust mass for concurrent analysis by three different laboratories (for chemical concentrations, for cell-based assays, and for elements).

For each sampling area, we vacuumed all floor surfaces, including underneath furniture, for 10 minutes. We collected a sample by vacuuming dust into a cellulose extraction thimble secured with a nitrile rubber o-ring in a crevice tool attached to a vacuum cleaner (Dyson CY18), following a previously published protocol.[23,232] Thus, the dust only came into contact with the crevice tools, which were cleaned with hot water and isopropyl alcohol between samples. The thimbles were stored in polypropylene centrifuge tubes in polyethylene bags at -13°C until laboratory analysis. For field blanks, we also carried four unopened centrifuge tubes with thimbles to the field sites on various sampling days.

Cell-Based Luciferase Reporter Gene Assays

The dust samples and field blanks were analyzed for hormonal activities in chemically activated luciferase gene expression (CALUX) assays by BioDetection Systems (Amsterdam, The Netherlands). Based on known or suspected mechanisms of human toxicity for PFAS and flame retardants, we chose to conduct the following five assays: antagonism of thyroid hormone receptor β, antagonism of androgen receptor, antagonism of peroxisome proliferator-activated receptor γ2, agonism of estrogen receptor α, and interference of binding thyroxine to the plasma transport protein transthyretin. We had performed an initial test of 10 samples for both agonism and antagonism on PPARγ, but no agonism was detected and so we only measured antagonism for the remaining samples. Furthermore, we measured cytotoxicity using CALUX assays to ensure that we only evaluated dilutions of dust sample that were not cytotoxic.

These luciferase reporter gene assays employ human female osteosarcoma cell lines (U2OS) stably transfected with the firefly luciferase reporter gene that is regulated by specific hormone response elements under study.[286,287,293] When an agonistic ligand (e.g. a chemical) binds to and activates a specific receptor, it will trigger transactivation of the associated genes, including the firefly luciferase reporter gene. Expression of luciferase then increases, and that enzyme will produce light (luminescence) in the presence of added luciferin substrate. If the ligand is instead an antagonist that binds to but does not activate the receptor, it will compete with an added reference agonist and less light will be produced. The intensity of light is measured with a luminometer and is directly proportional to the degree of receptor activation. In the TTR-T4 interference assay, the chemicals in the dust sample compete with a fixed concentration of T4 to bind the transport protein TTR, and some T4 will be replaced. The

amount of T4 still bound to TTR is then separated out and quantified in the TRβ agonism assay based on the amount of light produced due to TRβ activation by T4.

The measured luminescence is benchmarked against a reference compound to calculate a final result for each sample in units of μg-eq/g, or the mass of equivalent reference compound per unit mass of dust. This unit can be interpreted as: for a given mass of dust, the mass of the reference compound that produces the same level of activity. The reference compounds are potent and selective agonists or antagonists that are measured alongside the samples in the assays. We used deoxynivalenol, flutamide, GW9662, 17β-estradiol, and perfluorooctanoic acid (PFOA) as the reference compounds for the TRβ antagonism, AR antagonism, PPARγ antagonism, ERα agonism, and TTR-T4 binding interference assays, respectively. For the reference compounds, a full dose-response curve is fitted from the activities of eight separate serial dilutions using the Hill equation. Benchmarked activities (μg-eq/g) are calculated by interpolating a certain concentration of dust sample extract onto the calibration curve of the reference compound, as demonstrated in Figure 6.3. For agonistic activity for each sample, we used the data point for the lowest sample concentration that produces a response above the limit of quantification (LOQ). The result is then the ratio of the reference compound concentration in medium to the sample concentration at that same measured response level. Whereas an actual measured point is used for the sample concentration, the reference concentration is interpolated from the calculated dose-response curve. For antagonism, we used the lowest sample concentration that produces the highest response below 80% of the maximal response (i.e. more than 20% inhibition) of the reference compound. The result is then the ratio of the reference to sample concentration at that measured response level for that sample. Although different response levels are used in the calculations for different samples, the results are comparable

because of the interpolation onto the reference curve and because the chosen response levels are targeted to be in the linear range of the reference curve. Dose-response curves further to the left indicate higher potency.

Exposure of Cell-Based Assays to Dust Extracts

The dust samples were sieved with a 1 mm mesh and extracted by accelerated solvent extraction (ASE) using hexane and acetone (1:1, v/v). An average 0.43 g of dust was extracted for each sample. After gentle evaporation under nitrogen, the hexane/acetone extracts were dissolved in 100 µL of dimethyl sulfoxide (DMSO). Five-point serial dilutions (1x, 3x, 10x, 30x, and 100x) of each final extract were then prepared in DMSO. The final DMSO concentration during exposure of the cells to the prepared serial dilutions was 0.1% in the hormone receptor assays.

Before evaluating the samples in the assays for nuclear hormone receptor disruption, the serial dilutions (with 1% DMSO) were first evaluated for cytotoxicity in a CALUX assay. Unlike the other assays, the cell line in the cytotoxicity assay continuously expresses luciferase, and cell death reduces the amount of light emitted. Sample extract dilutions that caused a 20% reduction in light were considered cytotoxic and excluded from assessment because reductions in the light signal due to lack of cell viability could be misinterpreted as antagonism.[294] General cytotoxicity of the samples was also reported in µg-eq/g values using the reference compound tributyltin acetate. These values reflect non-specific cell stress and interference with luciferase in the test system.[295]

For the hormone receptor assays, the cells were cultured in an incubator for 24 hours at 37°C, 5% CO_2, and high humidity with medium (DMEM-F12 without phenol red and non-

essential amino acids). The cells were then seeded (at 10,000 cells/well) in 96-well microtiter plates and incubated for another 24 hours. After pre-incubation, the medium was removed from the cells, and the solution of dust extract or reference compound were added to the cells for testing along with DMEM-F12 medium, with stripped fetal bovine serum, and without phenol red. For assays of antagonism, the cells were also incubated in the presence of a fixed concentration of an agonist (EC_{50}: effective concentration that produces 50% of its maximal response). The agonists used were triiodothyronine (T3), rosiglitazone, and dihydrotestosterone (DHT) for TRβ, PPARγ, and AR, respectively. After 24 hours of exposure, the medium was removed, the cells were lysed (broken open), luciferin was added, and the plate was placed in the luminometer for measurement of light.

To study the potency of dust sample extracts to interfere with TTR-T4 binding, serial sample dilutions in DMSO were incubated in Tris-buffer (pH 8.0) overnight at 4ºC in the presence of TTR (0.058 μM) and a fixed concentration of T4 (0.052 μM). The final concentration of DMSO in the incubations was 3.2%. After incubation, TTR-bound T4 was separated from free T4 on a Bio-Gel P-6DG column. The eluate (TTR-bound T4) was added to assay medium after which TRβ CALUX cells were exposed for 24 hours as described above. More details on the CALUX assay procedures have been described previously.[136,259,260,288,289,296–300]

For quality assurance and quality control (QA/QC), all dust sample extracts, reference compound series, and solvent blanks were analyzed in triplicate with an acceptable maximum coefficient of variation defined as below 15%. Each plate contained its own reference compound series and solvent blanks. The four field blanks for the dust samples were almost all below the LOQ for all five assays (plus cytotoxicity) or otherwise well below the minimum detected

response of the samples, except that one field blank had a detected response against TRβ that was about half the median of the samples (all three other blanks had responses below the LOQ). We subtracted average field blank responses from the sample responses, as described in statistical analyses.

The method LOQs for antagonism were defined as the concentration of reference compound resulting in 80% of its maximal response. For agonism, the LOQs were calculated as the average of the DMSO solvent blank plus 10 times the standard deviation of the triplicate measurements of the solvent blank. Each plate had separate solvent blanks, so different samples could have a slightly different LOQ depending on which plate they were analyzed on. For samples with no dilutions producing a response above the LOQ, the LOQ was reported.

Chemical Analysis of Dust

The dust samples and field blanks were analyzed for 15 PFAS, 19 OPEs, and eight PBDEs by following previously published protocols.[233,238,301,302] Specifically, the measured PFAS were perfluorooctane sulfonate (PFOS), PFOA, perfluorohexanoate (PFHxA), perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonamide (FOSA), perfluoroheptanoate (PFHpA), perfluoropentanoate (PFPeA), perfluorononanoate (PFNA), perfluorobutane sulfonate (PFBS), perfluorodecane sulfonate (PFDS), perfluorobutanoate (PFBA), perfluorodecanoate (PFDA), perfluoroundecanoate (PFUnDA), perfluorododecanoate (PFDoDA), and n-methyl perfluorooctane sulfonamidoacetic acid (N-MeFOSAA). The PBDE analytes were 2,4,4'-tribromodiphenyl ether (BDE-28), 2,2',4,4'-tetrabromodiphenyl ether (BDE-47), 2,2',4,4',5-pentabromodiphenyl ether (BDE-99), 2,2',4,4',6-pentabromodiphenyl ether (BDE-100), 2,2',4,4',5,5'-hexabromodiphenyl ether (BDE-153), 2,2',4,4',5,6'-hexabromodiphenyl ether (BDE-

154), 2,2',3,4,4',5',6-heptabromodiphenyl ether (BDE-183), and decabromodiphenyl oxide (BDE-209). The OPE analytes were tris(2-butoxyethyl) phosphate (TBOEP), tris(1-chloro-2-propyl) phosphate (TCIPP), tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), triphenyl phosphate (TPHP), tris(2-chloroethyl) phosphate (TCEP), 2-ethylhexyl diphenyl phosphate (EHDPP), isodecyl diphenyl phosphate (IDDP), tri-iso-butyl phosphate (TIBP), tripropyl phosphate (TPP), cresyl diphenyl phosphate (CDPP), tert-butylphenyl diphenyl phosphate (BPDP), tri-n-butyl phosphate (TNBP), tetrakis(2-chloroethyl) dichloroisopentyl diphosphate (V6), bisphenol a bis(diphenyl phosphate) (BDP), resorcinol bis(diphenyl phosphate) (RDP), tris(2-ethylhexyl) phosphate (TEHP), tris(methylphenyl) phosphate (TMPP), triethyl phosphate (TEP), and tris(p-tert-butylphenyl) phosphate (TBPHP).

First, the dust samples were sieved through a 150-μm stainless steel mesh. Then, the samples (0.2-0.5 g) were spiked with 30 ng each of labeled surrogate standard mixture and extracted using methanol (3 mL) with mechanical oscillation (1 h) followed by ultrasonication (30 min). Resultant extracts were centrifuged (3500g, 10 min) and transferred into a new polypropylene tube. The extraction procedure was repeated twice with acetonitrile (3 mL) and ethyl acetate (3 mL), and then the extracts were combined and evaporated to 3 mL under a gentle stream of nitrogen and divided into three aliquots for analysis of OPEs, PBDEs, and PFAS. The aliquots were evaporated to near dryness and were reconstituted with 200 μL of different solvents: water/methanol (4/6; v/v) for OPEs, hexane for PBDEs, and methanol for PFAS. The extracts were filtered through 0.2 mm nylon filters into glass vials prior to instrumental analysis.

OPEs were analyzed with high-performance liquid chromatography (HPLC) coupled with electrospray triple quadrupole mass spectrometry (ESI-MS/MS), using electrospray positive ionization multiple reaction monitoring. PBDEs were analyzed using a gas chromatographer

coupled with a mass spectrometer (GC-MS) under electron impact ionization mode. PFAS were analyzed using HPLC coupled with ESI-MS/MS. Target PFAS were monitored by multiple reaction monitoring mode under negative ionization. Limits of detection (LODs) ranged from 0.1–0.8 ng/g for OPEs, 0.09–4.5 ng/g for PBDEs, and 0.06–1.5 ng/g for PFAS.

Chemical concentrations in the field blanks were all either below the LOD or far below the measured concentrations in dust samples. Duplicate analysis of seven dust samples showed that median relative percent differences were 0% (range: -96 to 52%) for OPEs, -3.2% (range: -50 to 80%) for PBDEs, and 0% (range: -62 to 190%) for PFAS. This variability likely reflects the natural heterogeneity of indoor dust.

Potency-Weighted Concentrations of Chemicals

To account for differential activities of individual chemicals in dust, we collected previously published information on the potencies of the individual chemicals. From these data, we first calculated relative potency factors (RPFs), which are weights for each chemical based on its bioactivity in a given assay compared to the other chemicals.

For the four main antagonism or agonism assays, we used Tox21 data on the *in vitro* toxicity screening of thousands of chemicals.[303] We downloaded the data from the Environmental Protection Agency (EPA) ToxCast Chemistry Dashboard in late 2019. We chose one reporter gene assay per endpoint based on relevance, availability, and cell line sensitivity. For PPARγ antagonism, TRβ antagonism, AR antagonism, and ERα agonism, we used the following assays of chemicals: “TOX21_PPARg_BLA_antagonist_ratio” (beta-lactamase reporter; human embryonic kidney cells), “TOX21_TR_LUC_GH3_Antagonist” (luciferase reporter; rat pituitary tumor cells), “TOX21_AR_LUC_MDAKB2_Antagonist_0.5nM_R1881”

(luciferase; human breast cells), and "TOX21_ERa_LUC_VM7_Agonist" (luciferase; human ovarian cancer cells), respectively.

As measures of potency in the Tox21 tests, we used the activity concentrations at cutoff (ACCs) because they are point of departure estimates based on the potency of a chemical at a threshold that is predefined for all chemicals for the given assay.[151–154,304] The cutoff is defined for each assay as a multiplier of the baseline median absolute deviation.[152,153,305] This approach has been recently employed in studies instead of using more traditional AC50s (the chemical concentration at 50% of its own maximal response), where concentrations are estimated at different response thresholds for different chemicals.[306–308] Unlike AC50s, ACCs are relative potencies and are not biased by the efficacy (maximal response) of a chemical, so they can be more appropriately compared across chemicals in an assay. The ACC is indicated by "MODL_ACC" in the ToxCast database. Because a higher ACC indicates a lower potency, we first inverted each analyte's ACC and then applied Equation 1 to calculate a unitless RPF for each assay. The "HIT_CALL" and "FLAGS" columns in the database were used to classify chemicals as active (including if borderline) or inactive in an assay.

Equation 3-1

$$RPF_{chemical} = \frac{potency_{chemical}}{\max\left(potency\right)_{all\ analytes}}$$

For the TTR-T4 binding interference assay, we used data from the laboratory to calculate RPFs for PFAS in the exact same luciferase assay,[309] as there was no available Tox21 information. These RPFs were calculated as the IC_{50} of the chemical (the concentration at which 50% of its maximal response is observed) divided by the max IC_{50} observed among our analytes, following Equation 3-1. We classified a chemical as "active" if the IC_{50} was greater than zero.

The RPFs allowed us to develop sum of potency-weighted chemical concentrations for each chemical class in dust for each assay endpoint (Equation 3-2), instead of just an unweighted sum that does not take into account the fact that chemicals in each class have differing degrees of both concentrations and hormonal potencies. We could also then calculate the percent that each chemical contributes to the potency-weighted class sum to identify important drivers of differences in dust bioactivities. We adapted the methods from Exposure-Activity Ratios (EARs) that have been used in previous studies of chemicals in water[151,153,154,310] and from Toxicity Equivalents (TEQs) that have been used in studies of dioxin-like activities of chemicals in dust.[285,311,312]

Equation 3-2

$$Potency\text{–}Weighted\ Sum\ of\ Chemical\ Class_{\mu g/g} = \sum_{analytes} Concentration_{\mu g/g} * RPF$$

Statistical Analyses

Before statistical analyses, we blank-corrected the chemical concentrations and dust potencies by subtracting the average of all field blanks. We substituted non-detect values with half the LOD.[197] Before modelling, the potencies were log-transformed due to the lack of normality of the data (based on Shapiro-Wilk tests and histograms). We conducted several stages of linear regression to first evaluate the unweighted impact of the three chemical classes on the bioactivities for five assays and then to model the contributions of the chemicals designated as active, unknown, or inactive for those endpoints.

We did not have sufficient sample size or statistical power to determine the impact of the type of building materials renovation on dust bioactivities, given the many measured and unmeasured covariates about other chemicals and products in the rooms that we would have

liked to control for. However, we did conduct a simple model with a three-level categorical variable to determine if renovation and product selection influenced hormone potency: 1) spaces in older buildings (built before the 2004 PBDE phase-out) and meeting historic, stringent flammability standards; 2) partially renovated spaces that likely have less contamination from legacy building materials or furniture; and 3) spaces in post-2004 or fully renovated buildings with furniture and carpet specified as free of PFAS and FRs. Partial 'healthier' interventions included conventional rooms in newer buildings or with furniture unintentionally free of FRs (now possible with the newest flammability standard), as well as rooms with 'healthier' materials but that are located in older buildings or have exposed insulated pipes in the room.

Statistical significance was evaluated at the α=0.05 level, with suggestive evidence at α=0.10. All analyses were conducted in R (version 3.3.1).

Results

Hormonal Activities of Dust Samples

All 46 dust samples were hormonally active in at least two of the cell-based assays. Approximately 83% percent of the dust samples activated or suppressed all four nuclear hormone receptors assayed. Specifically, 100% of the dust samples suppressed PPARγ, 96% activated estrogen receptor α, 89% suppressed thyroid hormone receptor β, 87% suppressed androgen receptor, and 98% interfered with the binding of T4 to one of its serum transport proteins (Table 3.1). All active dust samples also usually exhibited dose-response monotonic relationships for each assay. Four dust samples exceeded the maximal response (efficacy) observed for the endogenous estrogen hormone, 17β-estradiol. Forty-four samples (96%)

Table 3.1. Summary statistics for the hormonal activities of 46 indoor dust samples in luciferase reporter gene assays.

Assay Endpoint	Abbreviation	Reference Compound	% Active	GM (GSD)	Median	Range for Active	Units
Peroxisome proliferator-activated receptor γ2 antagonism	PPARγ	GW9662 (chemical)	100%	0.554 (1.92)	0.580	0.150–2.90	μg-eq/g
Estrogen receptor α agonism	ER	17β-estradiol (natural hormone)	96%	2.21 (2.38)	1.76	0.287–22.0	ng-eq/g
Thyroid hormone receptor β antagonism	TR	Deoxynivalenol (mycotoxin)	89%	68.7 (2.30)	80.8	12.8–370	μg-eq/g
Androgen receptor antagonism	AR	Flutamide (medication)	87%	105 (2.26)	104	27.5–434	μg-eq/g
Thyroid hormone transport interference	TTR-T4	Perfluorooctanoate (PFAS chemical)	98%	104 (2.90)	141	15.2–626	μg-eq/g
Cytotoxicity (as a control for cell death)		Tributyltin acetate (chemical)	100%	25.7 (1.92)	24.0	6.20–100	μg-eq/g

μg-eq/g = μg of reference compound equivalents per g of dust.

produced a response above half the efficacy of 17β-estradiol (n=21) or could not be evaluated at the highest concentration in the dilution series due to cytotoxicity (n=23).

The median hormonal activities measured in the dust samples in the luciferase assays for PPARγ suppression, ERα activation, TRβ suppression, AR suppression, and TTR-T4 transport interference were: 0.580 μg GW9662 reference per g of dust, 1.76 ng-17β-estradiol/g, 80.8 μg-deoxynivalenol/g, 104 μg-flutamide/g, and 141 μg-PFOA/g, respectively (Table 3.1). We observed detectable effects in the assays with as little as 3.66, 5.20, 16.1, or 17.9 μg of dust per well for ERα, PPARγ, AR, and TRβ, respectively, as well as 30 μg of dust per incubate for TTR activity. Suppressions of PPARγ and thyroid hormone receptor by the dust samples were significantly correlated (Spearman r=0.54, p<0.001). Interference with thyroid hormone transport was also significantly correlated with suppression of PPARγ (r=0.43, p<0.01), and moderately correlated with thyroid hormone receptor antagonism (r=0.26, p=0.08). All other pairs of nuclear hormone receptor activity were not significantly correlated, with correlation coefficients ranging between 0.13 and 0.25.

Table 3.2. Results of linear regression models[1] of percent differences in hormonal activities (µg-eq/g or ng-eq/g)[2] for an interquartile range (IQR) increase in concentrations (ng/g)[3] of three chemical classes in 46 dust samples: per- and polyfluoroalkyl substances (PFAS), organophosphate esters (OPEs), and polybrominated diphenyl ethers (PBDEs).

	Thyroid hormone receptor β antagonism (µg-eq/g)				PPARγ antagonism (µg-eq/g)				Androgen receptor antagonism (µg-eq/g)				Estrogen receptor α agonism (ng-eq/g)				Thyroid hormone transport interference (µg-eq/g)			
Covariate	**ΔIQR**	***p***	**IQR**	***n***	**ΔIQR**	***p***	**IQR**	***n***	**ΔIQR**	***p***	**IQR**	***n***	**ΔIQR**	***p***	**IQR**	***n***	**ΔIQR**	***p***	**IQR**	***n***
Model 1: Unweighted Effects of Chemicals	*(R^2=0.22)*				*(R^2=0.17)*				*(R^2=0.11)*				*(R^2=0.0014)*				*(R^2=0.14)*			
Sum of PFAS	**7.00% ****	0.01	267	*15*	1.06%	0.6	267	*15*	**5.58% ***	0.04	267	*15*	–0.674%	0.8	267	*15*	1.86%	0.6	267	*15*
Sum of OPEs	**25.7% ***	0.02	29000	*8*	**25.2% ****	0.01	29000	*8*	8.83%	0.4	29000	*8*	0.193%	1	29000	*8*	**38.5% ***	0.01	29000	*8*
Sum of PBDEs	–3.93%	0.4	1020	*19*	–1.28%	0.7	1020	*19*	–3.8%	0.4	1020	*19*	–0.313%	1	1020	*19*	–4.22%	0.5	1020	*19*
Model 2: Potency-Weighted Effects of PFAS	*(R^2=0.22)*				*(R^2=0.013)*				*(R^2=0.083)*				*(R^2=0.039)*				*(R^2=0.006)*			
Potency-weighted sum of PFAS	**27.5% ***	0.01	116	*4*	–1.21%	0.7	57	*4*	No RPFs[5]	-	0	*0*	–5.05%	0.2	13.2	*1*	0.637%	0.8	41.2	*12*
Sum of PFAS with unknown potencies	0.7%	0.9	14.7	*7*	3.37%	0.5	14.7	*7*	0.856%	0.9	36.2	*8*	–2.63%	0.7	14.7	*7*	–2.45%	0.7	14.9	*3*
Sum of PFAS designated as inactive[4]	–12.0%	0.2	218	*4*	0.182%	1	172	*4*	5.11%	0.3	261	*7*	1.88%	0.8	261	*7*	Few detects[7]	-	0	*0*
Model 3: Potency-Weighted Effects of OPEs	*(R^2=0.18)*				*(R^2=0.18)*				*(R^2=0.086)*				*(R^2=0.016)*				*(R^2=0.12)*			
Potency-weighted sum of OPEs	**26.8% .**	0.08	81500	*7*	–2.22%	0.5	2450	*4*	–14.1%	0.3	5500	*6*	–4.14%	0.5	3190	*4*	N/A	-	0	*0*
Sum of OPEs with unknown potencies	**10.9% ***	0.02	189	*6*	1.97%	0.6	189	*6*	**12.7% .**	0.06	243	*7*	–0.543%	0.9	189	*6*	**34.4% ***	0.02	29000	*19*
Sum of OPEs designated as inactive[4]	2.54%	0.2	5450	*6*	**24.6% ****	0	28600	*9*	7.2%	0.5	28600	*6*	1.59%	0.9	28400	*9*	N/A	-	0	*0*
Model 4: Potency-Weighted Effects of PBDEs	*(R^2=0.18)*				*(R^2=0.024)*				*(R^2=0.022)*				*(R^2=0.071)*				*(R^2=0.00012)*			
Potency-weighted sum of PBDEs	**20.2% ***	0.02	316	*2*	No RPFs[5]	-	0	*0*	–2.78%	0.6	301	*3*	**7.71% .**	0.08	173	*1*	N/A	-	0	*0*
Sum of PBDEs with unknown potencies	–4.55%	0.3	963	*5*	0.210%	1	963	*5*	4.41%	0.5	66.2	*4*	–1.59%	0.7	963	*5*	–0.423%	0.9	1020	*8*
Sum of PBDEs designated as inactive[4]	–3.05%	0.8	14.5	*1*	4.82%	0.3	160	*3*	–2.16%	0.6	909	*1*	Collinear[6]	-	94.1	*2*	N/A	-	0	*0*

PPARγ = peroxisome proliferator-activated receptor γ2; *n* = number of chemicals contributing to the sum for that covariate.
[1]Assay activities were log-transformed in the models, but the estimates are transformed and presented as the percent difference in activity for an IQR increase in the chemical covariate.
[2]Mass of reference compound equivalents per gram of dust.
[3]Mass of chemical per gram of dust; parts per billion.
[4]Designated as inactive in Tox21 assays of the chemicals (for antagonism/agonism) or in the exact luciferase assays by the laboratory (for transport interference).
[5]None had relative potency factors (RPFs) available so this covariate could not be included in the model.
[6]This covariate was very collinear (Spearman r=0.9) so excluded from the model.
[7]The few inactive PFAS in this assay were too infrequently detected and excluded from the model.

Unweighted Effects of Chemicals on Dust Hormonal Activities

Table 3.2 presents results from the statistical models evaluating the impact of unweighted sums of the chemical classes on hormonal activities of the dust. We found that for an interquartile range (IQR) increase in the ΣPFAS concentration (from the 25th to the 75th percentile), dust had 7.00% significantly higher levels of suppression of thyroid hormone receptor activation (95% CI: 1.73–12.5%, p<0.01) and 5.58% significantly higher suppression of androgen receptor (95% CI: 0.137–11.3%, p<0.05), adjusted for ΣOPEs and ΣPBDEs. For an IQR increase in the ΣOPE concentration, dust had an estimated 25.7% significantly higher suppression of thyroid hormone receptor (95% CI: 3.79–52.2%, p<0.05), 25.2% significantly higher suppression of PPARγ (95% CI: 7.22–46.1%, p<0.01), and 38.5% significantly higher interference of thyroid hormone transport (95% CI: 7.02–79.2%, p<0.05), adjusted for ΣPFAS

and ΣPBDEs. Unweighted ΣPBDEs were not significantly associated with the hormone-disrupting potencies of the dust samples in this test system. As shown in Table 3.2, these models using unweighted concentrations of the chemical classes explained 22%, 17%, 14%, and 11% of the total variability in dust suppression of thyroid hormone receptor, PPARγ, TTR-T4 binding, and androgen receptor, respectively.

Hormonal Potencies of Chemicals

Many of our 42 targeted chemical analytes were also active in previous chemical screening assays, which employed similar gene reporter assays as this study's but not necessarily the same cell lines.[303] The bioactivity classifications and relative potency factors of each analyte in each assay are provided in Table 3.3. Twenty-six percent of the analytes were not screened in any of the five assays and therefore had no comparative data. Of the chemical analytes with available screening data, 77% were found to be active in at least one of the five endpoints we measured in dust. Only one analyte (triphenyl phosphate) was designated as active in all four nuclear hormone receptor assays. Of all pairs of the chemicals and four nuclear hormone receptor assays, 21% exhibited evidence for activity, 36% were classified as inactive, and 42% had not been analyzed.

Table 3.3. Relative Potency Factors (RPFs) and potency-weighted exposure contributions for each chemical measured in this study's dust samples (n=46), using Tox21 data on activity concentrations at cutoff (ACCs) and hit calls for the agonism/antagonism assays or using the laboratory's data on RPFs for the transport interference assay ("unknown" indicates the chemical did not have available screening data).

Chemical	Exposure Levels in Dust Samples			Bioactivity Classification (Relative Potency Factor) [Median % Contribution to Potency-Weighted Concentration Sum of Chemical Class]				
	% of Samples >MDL	Median [Range] in ng/g	Median % of Class Sum	PPARγ Antagonism *(Source: Tox21)*	Thyroid Hormone Receptor β Antagonism *(Source: Tox21)*	Androgen Receptor Antagonism *(Source: Tox21)*	Estrogen Receptor α Agonism *(Source: Tox21)*	Thyroid Hormone Transport Interference *(Besselink 2020)* [1]
Per- and polyfluoroalkyl substances (PFAS)								
PFHxA	97.8	193 [<MDL–2980]	66	Inactive	Inactive	Inactive	Inactive	Active (0.044) [22%]
PFOS	97.8	15.2 [<MDL–296]	5.4	Active (0.55) [51]	Active (0.52) [50]	Inactive	Inactive	Active (0.81) [41%]
PFOA	73.9	7.63 [<MDL–1520]	4.5	Active (0.4) [25]	Inactive	Inactive	Inactive	Active (0.37) [15%]
PFHxS	63.0	1.82 [<MDL–23.7]	<1	*Unknown*	*Unknown*	*Unknown*	*Unknown*	Active (1) [4.1%]
FOSA	60.9	3.26 [<MDL–236]	1.5	Inactive	Active (0.59) [14]	Inactive	Active (0.39) [100]	*Unknown*
PFHpA	52.2	0.918 [0–1760]	<1	Inactive	Inactive	Inactive	Inactive	Active (0.35) [2.1%]
PFPeA	32.6	<MDL [<MDL–455]	<1	*Unknown*	*Unknown*	*Unknown*	*Unknown*	Active (0.013) [<1%]
PFNA	30.4	<MDL [<MDL–1480]	<1	Active (0.76) [2.3]	Active (0.47) [1.2]	Inactive	Inactive	Active (0.12) [<1%]
PFBS	30.4	<MDL [<MDL–16.1]	<1	*Unknown*	*Unknown*	*Unknown*	*Unknown*	Active (0.028) [<1%]
PFDS	10.9	<MDL [<MDL–12.5]	<1	*Unknown*	*Unknown*	*Unknown*	*Unknown*	*Unknown*
PFBA	4.35	<MDL [<MDL–155]	<1	*Unknown*	*Unknown*	*Unknown*	*Unknown*	Active (0.001) [<1%]
PFDA	4.35	<MDL [<MDL–35.0]	<1	Inactive	Active (0.29) [<1]	Inactive	Inactive	Active (0.032) [<1%]
PFUnDA	0	<MDL [<MDL–<MDL]	<1	Active (1) [4.2]	Inactive	Inactive	Inactive	Active (0.017) [<1%]
PFDoDA	0	<MDL [<MDL–<MDL]	<1	*Unknown*	*Unknown*	*Unknown*	*Unknown*	Active (0.0037) [<1%]
N-MeFOSAA	0	<MDL [<MDL–<MDL]	<1	*Unknown*	*Unknown*	*Unknown*	*Unknown*	*Unknown*
Polybrominated diphenyl ethers (PBDEs)								
BDE-209	100	830 [34.8–13000]	70	*Unknown*	*Unknown*	Inactive	*Unknown*	*Unknown*
BDE-99	100	124 [10.6–734]	11	Inactive	Active (0.63) [69]	Active (0.64) [52]	Inactive	*Unknown*
BDE-47	100	60.9 [6.55–1470]	5.5	Inactive	Active (0.53) [31]	Active (1) [43]	Active (1) [100]	*Unknown*
BDE-100	100	26.9 [6.12–202]	2.4	*Unknown*	*Unknown*	*Unknown*	*Unknown*	*Unknown*
BDE-183	89.1	24.2 [<MDL–817]	2	*Unknown*	*Unknown*	*Unknown*	*Unknown*	*Unknown*
BDE-28	89.1	3.55 [<MDL–104]	<1	*Unknown*	*Unknown*	*Unknown*	*Unknown*	*Unknown*
BDE-153	84.8	18.9 [<MDL–78.5]	1.5	Inactive	Inactive	Active (0.46) [5.2]	Inactive	*Unknown*
BDE-154	80.4	10.6 [<MDL–53.5]	<1	*Unknown*	*Unknown*	*Unknown*	*Unknown*	*Unknown*
Organophosphate esters (OPEs)								
TBOEP	100	15300 [1250–118000]	65	Inactive	Active (1) [92]	Inactive	Inactive	*Unknown*
TCIPP	100	3130 [675–139000]	12	Inactive	Inactive	Inactive	Inactive	*Unknown*
TDCIPP	100	970 [220–6440]	3.5	Inactive	Active (0.54) [2.9]	Active (0.84) [57]	Inactive	*Unknown*
TPHP	100	817 [238–10600]	3.0	Active (0.74) [67]	Active (0.4) [2]	Active (0.47) [21]	Active (1) [76]	*Unknown*
TCEP	100	214 [2.31–3170]	<1	Inactive	Inactive	Inactive	Inactive	*Unknown*
EHDPP	100	184 [4.65–2480]	<1	Inactive	Active (0.54) [<1]	Active (0.42) [3.9]	Inactive	*Unknown*
IDDP	100	88.1 [0.699–612]	<1	Active (0.6) [5.4]	Active (0.64) [<1]	Active (0.5) [2.5]	Inactive	*Unknown*
TIBP	100	32.8 [5.28–804]	<1	Inactive	Active (0.45) [<1]	Inactive	Inactive	*Unknown*
TPP	100	11.1 [1.52–63.3]	<1	*Unknown*	*Unknown*	*Unknown*	*Unknown*	*Unknown*
CDPP	97.8	192 [<MDL–11500]	<1	Active (0.69) [15]	Inactive	Active (0.46) [6.3]	Active (0.72) [13]	*Unknown*
BPDP	97.8	88.4 [<MDL–371]	<1	Active (0.77) [5.6]	Active (0.52) [<1]	Active (0.52) [2.3]	Inactive	*Unknown*
TNBP	97.8	41.1 [<MDL–1060]	<1	Inactive	Inactive	Inactive	Active (0.76) [2.6]	*Unknown*
V6	95.7	23.2 [<MDL–216]	<1	*Unknown*	*Unknown*	*Unknown*	*Unknown*	*Unknown*
BDP	93.5	26.3 [<MDL–494]	<1	*Unknown*	*Unknown*	*Unknown*	*Unknown*	*Unknown*
TEHP	91.3	40.4 [<MDL–1680]	<1	Inactive	Inactive	Inactive	Active (0.68) [2.2]	*Unknown*
RDP	91.3	36.6 [<MDL–3270]	<1	*Unknown*	*Unknown*	*Unknown*	*Unknown*	*Unknown*
TMPP	91.3	28.8 [<MDL–486]	<1	*Unknown*	*Unknown*	*Unknown*	*Unknown*	*Unknown*
TEP	60.9	18.2 [<MDL–416]	<1	Inactive	Inactive	Inactive	Inactive	*Unknown*
TBPHP	19.6	<MDL [<MDL–10.7]	<1	*Unknown*	*Unknown*	*Unknown*	*Unknown*	*Unknown*

PPARγ = peroxisome proliferator-activated receptor γ2; MDL = method detection limit.
[1]Analysis conducted by the same laboratory as assayed our dust samples.[309]
Note: Chemical concentrations below the MDL in dust were substituted with the MDL/2 for analyses and calculations of class sums.

Table 3.3 shows the median percent, respectively, that each chemical for each assay contributed to the aggregated potency-weighted concentration of its parent chemical class. For each chemical class, a few chemicals dominated the potency-weighted concentration profiles in dust. For example, TBOEP was responsible for a median 92% of the potency-weighted ΣOPEs for TRβ suppression because it was the chemical with the highest potency towards that endpoint

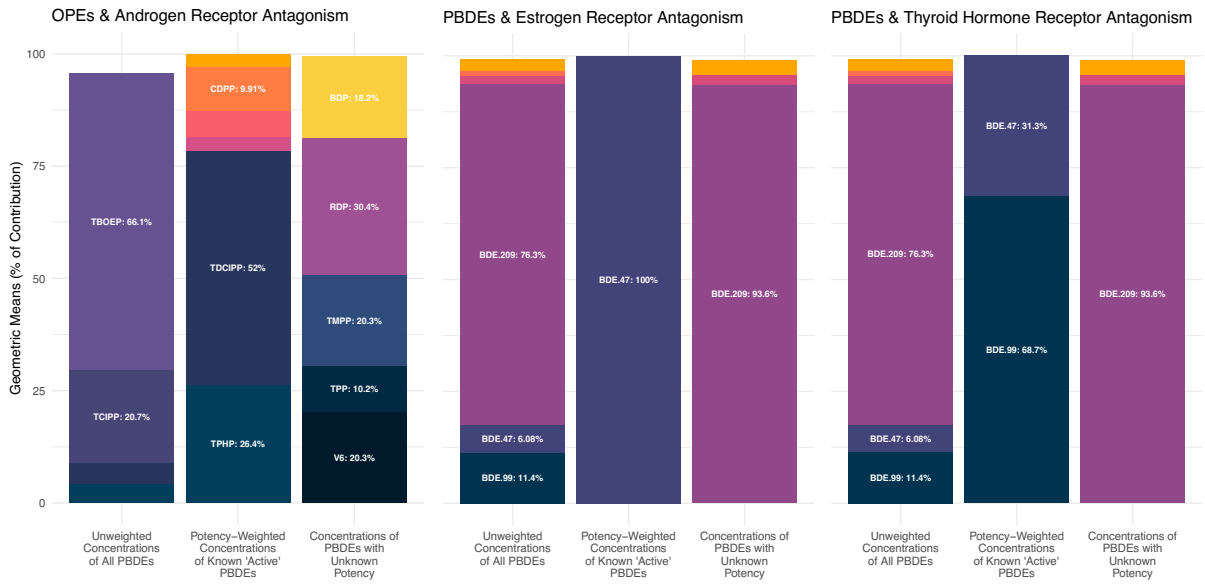

Figure 3.1. Comparison of profiles of chemicals with any versus active versus unknown designations for select pairs of assay endpoints and chemical classes, using Tox21 high-throughput screening data.

in Tox21 data and the highest concentration in the dust samples. By contrast, TBOEP and TCIPP (the two OPEs detected at the highest concentrations in dust) were designated as inactive towards AR suppression, so the OPE profile for just the active chemicals was dominated by TDCIPP. As another example, BDE-209 was detected at substantially higher concentrations in dust than any other measured PBDE, but other PBDEs had higher or better known bioactivities in Tox21 screening assays and thus were weighted to contribute more to the total potency-weighted sum of the class for various assay endpoints than BDE-209. Figure 3.1 visualizes these examples of differences in chemical profiles between unweighted and potency-weighted concentrations.

Potency-Weighted Effects of Chemicals on Dust Hormonal Activities

We then used total potency-weighted concentrations for each chemical class to model the separate impacts of chemicals with active, inactive, or unknown potency classifications, with the goal of 1) improving the explanatory power of our models, 2) assessing the usefulness of exposure- and potency-scaled chemical concentration calculations, and 3) evaluating the extent

of missing data issues (Table 3.2). In these models, PBDEs had significant or borderline significant effects on thyroid hormone receptor and estrogen receptor activity. For an IQR increase in the potency-weighted ΣPBDEs, dust had 20.2% significantly higher levels of suppression of thyroid hormone receptor (95% CI: 3.27–39.9%, $p<0.05$) and had 7.71% higher activation of estrogen receptor (95% CI: -0.914–17.1%, $p=0.08$) with borderline statistical significance, adjusted for the sums of PBDEs with inactive or unknown potencies.

For an IQR increase in the potency-weighted ΣPFAS, dust had 27.5% significantly higher suppression of thyroid hormone receptor (95% CI: 5.37–54.2%, $p<0.01$), adjusted for the sums of PFAS with inactive or unknown potencies. There were no PFAS with available RPFs for androgen receptor activity and modeling the impact of only sums of PFAS with inactive or unknown potencies did not yield a significant result for that assay endpoint.

The sum of OPEs with unknown potencies had 10.9% significantly higher suppression of thyroid hormone receptor (95% CI: 1.58–21.0%, $p<0.05$) for an IQR increase in concentration, adjusted for potency-weighted and inactive ΣOPEs. In that model, the potency-weighted ΣOPEs had a similar effect estimate as the unweighted ΣOPEs did on thyroid hormone receptor inhibition in the previous model, with borderline statistical significance (26.8% per IQR increase, 95% CI: -3.08–65.8%, $p=0.08$). An IQR increase in the sum of OPEs with unknown potencies also had 12.7% higher suppression of androgen receptor, with very borderline statistical significance (95% CI: -0.527–27.8%, $p=0.06$). For thyroid hormone transport interference, the ΣOPEs with unknown potencies (which consisted of all OPE analytes) in its own model had a similar impact as the unweighted ΣOPEs in the previous model with all three chemical classes (34.4%, 95% CI: 5.27–71.6%, $p<0.05$). Finally, there was only one significant association between any inactive chemicals and an assay endpoint. For an IQR increase in the

sum of OPEs designated as inactive in the Tox21 data, dust had 24.6% higher suppression of PPARγ (95% CI: 7.54–44.5%, $p<0.01$).

The R^2 values in Table 3.2 show that each chemical class can individually explain substantial amounts of variation in thyroid hormone disruption or PPARγ inhibition. The model for OPEs explained 18% of the total variability in both thyroid hormone receptor and PPARγ suppression in the dust samples. The model for PFAS and for PBDEs also explained 22% and 18% of the total variability in thyroid hormone receptor antagonism, respectively. The model for OPEs explained 12% of the variability in interference of T4 binding to its transporter. Variabilities in estrogen receptor activation in the dust samples were not as highly explained by these three chemical classes in any of the models (at most 7.1%).

Effects of Room Factors on Dust Hormonal Activities

In our secondary, albeit statistically underpowered, modeling of the impact of two room factors on dust bioactivities, we found that common spaces had 81.6%, 62.6%, and 98.1% significantly higher dust levels of inhibition of thyroid hormone receptor (95% CI: 7.71–206%, $p<0.05$), PPARγ (95% CI: 8.26–144%, $p<0.05$), and TTR-T4 binding (95% CI: 0.11–292%, $p=0.05$) respectively than classrooms did, adjusted for renovation status (which did not achieve statistically significant effects).

Discussion

Hormonal Activities of Dust Samples

In our study of chemical mixtures and bioactivities in dust in buildings across a university, we found that all dust samples were hormonally active in at least two CALUX assays.

Importantly, hormonal effects of the dust samples were observed at exposure-relevant concentrations, with as little as 4 to 18 μg of dust across the five cell-based assays. For reference, people (aged 12 years to adult) ingest an estimated average of 20 mg (upper percentile of 60 mg) of indoor dust per day, equivalent to 20,000 μg.[313]

Every sample suppressed the activation of PPARγ, whose interference has the potential to cause obesity, diabetes, and other metabolic disorders.[244,249] The vast majority of samples also disrupted estrogen and androgen receptors, which play important roles in reproductive health and development.[249,281] Finally, all dust samples interfered with action of thyroid hormones, either through suppression of the receptor or displacement of T4 from a serum transport protein. Disruption of thyroid hormones can adversely affect development, metabolism, the brain, and the cardiovascular system.[249,279]

Effects of Chemicals on Dust Hormonal Activities

Many of the individual chemicals we measured in the dust samples were also active towards the nuclear hormone receptors when tested in isolation (Table 3.3),[314–317] and we found that chemical profiles significantly explained the hormonal activities of dust in the cell-based assays. The potency of dust samples to inhibit thyroid hormone receptor activation was significantly explained by all three types of chemicals (PFAS, OPEs, and PBDEs), which have been associated with thyroid disruption and developmental impairment in human epidemiologic studies.[5,41,45,49,60,125,258] The OPEs also significantly impacted thyroid-disrupting activities in dust via substantial displacement of T4 thyroid hormone from the TTR transporter, which prevents the thyroid hormone from being delivered to essential brain issues or the placenta and makes T4 more readily excreted from the body.[257,283] To our knowledge, OPEs have been under-

investigated as potential disruptors of thyroid hormone binding to that transporter, unlike PFAS and PBDEs (which actually did not yield statistically significant effects in this assay for dust).

PPARγ suppression was also significantly associated with OPE concentrations. Some OPEs were linked in epidemiologic studies to obesity and related metabolic effects, although more research in humans is needed.[318–320] There were statistically significant or close to significant impacts of PFAS and OPE levels in dust on androgen receptor inhibition, and in epidemiologic studies, PFAS chemicals may be associated with birth size[69,76] and OPEs may be associated with brain development[60,61] and infertility.[54,321]

There was limited evidence that estrogen receptor activation of the dust was associated with the potency-weighted concentration of all PBDEs, which was driven by BDE-47. Epidemiologic studies have found PBDEs to be associated with adverse effects on fertility, pregnancy outcomes, and development.[5,6,51–53,258] Of all the assay endpoints, estrogen agonism had the least amount of variability explained by the measured chemical classes (R^2 up to 7.1%), perhaps because there are so many other important unmeasured chemicals in dust that influence estrogenicity (including unmeasured flame retardants, phthalate plasticizers, bisphenol plasticizers, chlorinated pesticides, and polychlorinated biphenyls).[136,281,322–325]

We found that levels of PPARγ suppression were significantly correlated with both thyroid hormone receptor suppression and thyroid hormone transport interference by the dust samples. This indicates that chemicals can be bioactive against several hormone receptors and transporters. Regulatory assessments often treat each chemical and mechanism separately, but interactions are much more complex in our bodies.[146] The same chemical can bind multiple different types of receptors (at different affinities), many different chemicals can bind to or influence signaling of the same type of receptor, the presence of multiple chemicals can jointly

elicit greater-than or less-than-expected effects, and many different types of receptors can contribute to the same adverse health outcome.[137,139,148,244,326–328,140–147]

Indoor Sources of Key Chemicals

The combined information we synthesized on each chemical's concentrations in our dust samples and relative potency in screening cell-based assays suggested that combinations of a select few PFAS (PFOS and FOSA), OPEs (TBOEP, TCIPP, TDCIPP, and TPHP), or PBDEs (BDE-47 and BDE-99) may largely explain the significant effects of each chemical class on some hormonal potencies in dust. PFOS and its precursor compound FOSA have been found in furnishings such as carpet, textiles, and leather, as well as food packaging and non-stick cookware.[63,329,330] The four OPEs are found as flame retardants in foam furniture, electronics, carpet, and/or building insulation and as plasticizers in plastic products.[25,34,242,35–38,159,227,240,241] BDE-47 and BDE-99 have been used as flame retardants in foam furniture, textiles, electronics, and plastic toys.[25,32,33,35] Therefore, chemicals in furnishings are important contributors to hormonal activities in indoor dust in buildings.

We also found that common building spaces had significantly higher activities against thyroid hormone receptor, PPARγ, and thyroid hormone transport in dust than classrooms did. Given the higher utilization and foot traffic in common areas, the more potent activities may indicate that people track in, and/or bring in personal products with, hormone-disrupting contaminants.

Method Evaluation of Potency-Weighted Concentrations of Chemical Classes

Potency-weighted chemical concentration assessments helped us better characterize the impacts of the chemical mixtures on hormonal activities of indoor dust. For example, the unweighted sum of all PBDEs in the dust samples did not have statistically significant effects on the assay endpoints. However, one dominant chemical, BDE-209, contributed a median 70% to the total PBDE concentrations in dust but was only designated as unknown or inactive in the chemical screening assays. When we instead conducted models for the associations between dust activities and the potency-weighted sums of bioactive PBDEs based on Tox21 data (which excluded BDE-209), we found significant or near-significant effects on interference with thyroid hormone and estrogen receptors, whereas we did not for the sum of PBDEs with unknown potencies (which included BDE-209). Therefore, in the unweighted models, the null effect of BDE-209 was masking the effect of individual PBDEs that had lower dust concentrations but might be more potent in the screening assays. In addition, the potency-weighted exposure models showed there was suggestive evidence that the covariate for the unweighted sum of OPEs with missing Tox21 screening data was associated with androgen receptor suppression. We did not observe this association based on the unweighted concentration of all OPEs, likely because two specific OPEs heavily dominated the chemical profiles for all OPEs but were classified as inactive in the Tox21 database. In addition, the sum of OPEs with unknown activities was significantly associated with the potencies of the dust samples to inhibit thyroid hormone receptor. These findings support the importance of efforts to continue high-throughput screening of chemicals in cell-based assays and of using screening results to weight chemical concentrations in samples by chemical potencies.

Chemical screening data may become increasingly useful for environmental exposure research as the number of chemicals needed to be assessed increase and as future studies analyze

samples for more and more analytes, such as with non-targeted laboratory approaches.[331] Potency-weighted chemical exposure indicators can 1) act as more biologically relevant covariates in models, 2) improve the explanatory power of statistical models to identify and prioritize causative chemicals of concern, 3) reduce the dimensions of mixture data, and 4) parse the contributions of chemicals with known bioactivities versus with missing data versus with inactivity when assayed in isolation.

However, models of the unweighted chemical exposures are still also useful for several reasons. The unweighted sum of a chemical class does not exclude chemicals that did not reach an active designation when tested in isolation but that may enhance (or reduce) mixture effects when present with other chemicals.[137,139,148,140–147] This could be one possible explanation for why the concentrations of OPEs designated as inactive in Tox21 screening assays had statistically significant impacts on PPARγ antagonism in our dust samples. That result could also be partly explained by the fact that the inactive-designated OPEs are sometimes correlated with other unmeasured flame retardants or phthalate plasticizers[137,138,332–334] or could be influenced by the small error that could be introduced from analyzing chemical activity designations based on a PPARγ antagonism assay with a different reporter gene (beta-lactamase) and human cell line tissue type (embryonic kidney) than our dust assays. However, another previous study that measured PPARγ antagonism of OPEs using the same luciferase reporter gene assays and human osteosarcoma cell lines as our study was consistent in classifying the four Tox21-inactive chemicals found in our samples at the highest concentrations as inactive.[260] The Tox21 data on the other three nuclear hormone receptor assays used the same luciferase reporter. The modeling of unweighted chemical concentrations has the advantage of not introducing error in calculating

potency-weighted sums for chemical classes, although we do in effect have to assume that each chemical has equal potency.

Comparison to Previous Literature

Only two previous studies quantified bioactivities of indoor dust in some of the same cell-based assays with comparable units. Vandermarken et al. measured estrogenic activity in dust in 12 kindergartens in Belgium using the similar luciferase cell-based assay and found a median potency of 1.34 ng-E2/g-dust (range: 0.426–8.71).[136] These bioactivities are comparable to, if not slightly less potent than, the results from our study in the U.S. (median: 1.76 ng-E2/g-dust; range: 0.287–22.0). A study by Suzuki et al. used three of our same cell-based assays to measure the bioactivities of 13 house dust samples pooled from 66 homes across the U.S. and four Asian countries. However, they reported results in units of μg of dust per well needed to achieve 5% of the maximal response of the reference compound, and we were able to convert our results similarly to μg/well needed to achieve an effect above the LOQ. The dust samples in our study were similar to their global house dust samples for estrogen receptor activation (our study: median 32.0 μg/well [range among active 3.66–201]; Suzuki et al.: 39 [12–120]), androgen receptor inhibition (our study: 56.2 [16.1–172]; Suzuki et al.: 72 [38–120]), and PPARγ inhibition (our study: 29.3 [5.20–121]; Suzuki et al.: 70 [11–120]).[260]

Strengths and Limitations

Our study was novel in the use of cell-based assays of indoor dust as an inexpensive, rapid, holistic, health-driven method to evaluate the toxic load in buildings from chemicals. This is the first study to measure multiple important chemical classes and to evaluate and use the

Tox21 data to develop potency-weighted concentrations of chemical classes in indoor dust as a means to determine important chemical contributors to hormonal disruption. A key strength of this study is also the summary of bioactivities across a diverse range of hormonal activity endpoints in the largest sample size of indoor dust samples (n=46). We used units relative to reference compounds (μg-eq/g-dust) that we hope can be best used as a benchmark in future research studies. Finally, the luciferase cell-based assays did not measure only receptor binding as some previous studies have done,[275,335] but actual transcriptional effects due to activation or suppression of the receptor upon binding.

The limitations of this study include that there were likely many other unmeasured hormone-disrupting chemicals in the dust samples that may have influenced the cell-based assay results.[336,337] Given the sample size, we had too limited statistical power to be able to develop complex models with many covariates at once. In addition, the cell-based assays were conducted on dust samples taken from a different split of each room than the chemical analyses (although collected at the same time), so the natural heterogeneity of dust may have limited the explanatory power of our models too. The cytotoxicity of some dust extracts at their highly concentrated dilutions prevented our ability to evaluate all five serial dilutions for each sample, which resulted in several samples with values reported as below the LOQ.

Finally, we calculated relative potency factors for chemicals based on Tox21 data, although their gene reporter assays used different cell types (although still mostly human) compared to our assays. Chemicals can sometimes have slightly different effects in different cell lines depending on the species and tissue type.[287,338–341] Suzuki et al. measured ERα agonism, PPARγ antagonism, and AR antagonism of some of our flame retardant analytes in the exact same luciferase gene reporter assays and human cell lines as our study, and they had discordance

with the Tox21 data for six of 31 chemical–assay pairs.[260] Acknowledging some level of possible uncertainty, high-throughput chemical screening data are still useful for understanding large patterns in the types of chemicals contributing to bioactivities in very complex environmental mixtures. Although a causal link between cell-based assays and human health effects has not been determined, the assays are useful for identifying key chemical characteristics that indicate potential endocrine-disrupting activity, and some studies have found that results from in vitro assays of well-studied chemicals accurately reflect their known health effects.[342–347]

Conclusions

This study found that all the indoor dust samples were hormonally active and that PFAS and flame retardants significantly contributed to the hormonal activities in the dust. We also found publicly available high-throughput chemical screening data useful for incorporating both potency and exposure into enhanced evaluations of chemical drivers of hormonal activities in dust samples. Because indoor dust is a complex, hormonally potent mixture of many endocrine-disrupting compounds, more research needs to be done to identify important contaminants and evaluate successful interventions to reduce them indoors.

CHAPTER 4: Impact of "healthier" materials intervention on dust concentrations of per- and polyfluoroalkyl substances, polybrominated diphenyl ethers, and organophosphate esters

Anna S. Young[1,2], Russ Hauser[1], Tamarra James-Todd[1], Brent A. Coull[1], Hongkai Zhu[3], Kurunthachalam Kannan[3], Aaron Specht[1], Maya S. Bliss[1], Joseph G. Allen[1]

[1] Harvard T.H. Chan School of Public Health, Boston, MA, USA

[2] Harvard Graduate School of Arts and Sciences, Cambridge, MA, USA

[3] New York University School of Medicine, New York, NY, USA

Abstract

Per- and polyfluoroalkyl substances (PFAS), polybrominated diphenyl ether (PBDE) flame retardants, and organophosphate esters (OPEs) are three ubiquitous chemical classes used in furniture, carpet, and building materials. They have been linked to thyroid disease, infertility, cancer, and adverse developmental effects. In this study, we evaluated an intervention at a university to eliminate all types of PFAS and flame retardants from carpet and furniture during office renovations. We compared concentrations of 15 PFAS, 8 PBDEs, and 19 OPEs in dust from offices, common areas, and classrooms having undergone either no intervention (conventional rooms in older buildings meeting strict fire codes; n=12), a full "healthier" materials intervention (rooms with "healthier" materials and in buildings constructed more recently or gut-renovated; n=7), or a partial intervention (other rooms with at least "healthier" foam furniture but more potential building contamination; n=28). To characterize potential sources in situ, we scanned all materials in the rooms for bromine and phosphorus as surrogates of PBDEs and OPEs respectively, using two portable x-ray fluorescence instruments. We conducted multilevel regression models and for PBDEs and OPEs, we adjusted for covariates related to insulation, electronics, and furniture. We used two different referent groups: no intervention or partial intervention (due to its larger sample size). We found that the rooms with a full "healthier" materials intervention had 78% lower levels of PFAS and 65% lower levels of OPEs in dust than rooms with no intervention (p<0.01). PBDEs were 45% lower in rooms with the full "healthier" intervention when compared to rooms with only a partial intervention (p<0.10). The partially renovated rooms did not have significantly different dust concentrations of the chemical classes than those with no intervention (p=0.2–0.7). Bromine loadings from electronics in the studied rooms were associated with PBDE concentrations in dust (p<0.05), and

the presence of exposed insulation in the room was significantly associated with OPE dust concentrations (p<0.001), suggesting other chemical sources besides furniture and carpet. The full "healthier" materials intervention was successful at reducing chemical classes in indoor dust. Future interventions should target more product types and should consider cross-contamination from the building and attached non-renovated spaces.

Introduction

The products that furnish buildings contain complex mixtures of chemicals.[29,181,228] Research has shown that many chemicals are unbound additives that can migrate out of the products and into indoor environments,[66,155,160–162,229–231] exposing people via dust ingestion, inhalation, and dermal sorption.[22,24,239,348,29–31,233–236,238] Several studies have linked the concentrations in dust and air to higher body burdens of these chemicals.[30,33,349–356] Thus, the pathway from source to environmental media, exposure, and body burden has been well established for chemicals used in building products. An upstream intervention on the product sources of harmful chemicals presents a public health opportunity to reduce exposure. Several classes of chemicals found in building furnishings are of particular concern, including per- and polyfluoroalkyl substances (PFAS) and flame retardants (FRs).

PFAS are a class of highly fluorinated aliphatic chemicals widely used as stain- and water-repellant coatings in furniture upholstery, carpet, clothing, disposable food packaging, non-stick pans, and building materials.[4,62–66] Incidental ingestion of dust and inhalation are estimated to be the most important routes of human exposure to PFAS, after dietary consumption.[30,31,357] Research has found PFAS exposure to be associated with thyroid disease,[41,67–70] impairment of fetal development,[69,76] high cholesterol,[71–75] and immune system

suppression.[68,77,78] There is also some evidence linking PFAS to metabolic disorders such as obesity, insulin resistance, and diabetes,[4,71,72,79–81] as well as kidney and testicular cancer.[82–88] The characteristic, extremely strong carbon–fluorine bond that makes these human-made chemicals so useful as stain- and water-repellants also imparts their extreme environmental persistence. In fact, the perfluoroalkyl acids (PFAAs) will never appreciably break down under environmental conditions.[4,99,125]

Polybrominated diphenyl ethers (PBDEs) are a class of 209 congeners used as chemical flame retardants in foam furniture, carpet, electronics, and insulation to comply with fire codes.[32–37] The increasing use of PBDEs in foam products across the United States market was catalyzed by California's first flammability standard for upholstered furniture (Technical Bulletin [TB] 117) passed in 1975.[156,207] TB 117 required a smolder test and a 10-second small open-flame test for fire retardance of interior foam filling in furniture.[358] In 1991, a new standard, TB 133, was created that required more strict flammability tests under larger open flames for furniture in publicly occupied spaces.[207] Ingestion or skin absorption of indoor dust has been shown to be the largest route of exposure to flame retardants, followed by inhalation.[233–236,238,239] Human exposure to PBDEs is associated with adverse health effects on thyroid function,[5,6,48,49,40–47] reproduction (including pregnancy outcomes and fertility),[5,6,48,51–53] and reproductive and brain development.[5,6,43,45,57–59]

Even when certain chemicals in the PFAS and PBDE classes were found to be harmful and were largely removed from production, they have often been replaced with other similar chemicals with human health concerns, in a phenomenon called regrettable substitution.[98] For example, two of the most well-studied and widely known PFAS, perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS), were voluntarily phased out by manufacturers in the early

2000s in the U.S.[99] However, new replacement PFAS, including short-chain alternatives and precursors that break down into legacy PFAS, may be just as concerning for health.[100–102] In fact, over 4,700 different PFAS are currently available.[103] Due to the health concerns of PBDEs, two commercial flame retardant mixtures, penta-BDE and octa-BDE, were also voluntarily phased out in the U.S. in 2004, followed by deca-BDE in 2013.[22] Similar to the substitution of legacy PFAS, PBDEs were often simply replaced with other organohalogenated flame retardants and organophosphate esters (OPEs), which have been found in recent research to be associated with similar adverse effects on thyroid function,[49,50,56] pregnancy outcomes, fertility,[7,54–56] and development.[60,61]

Recently, changes to furniture flammability regulations have laid the foundation to enable reductions in the use of these flame retardants in upholstered furniture. Effective in 2014, TB 117 was updated to require furniture to only pass a smolder resistance test (TB 117-2013),[359] and TB 133 was repealed in 2019.[360] Despite efforts to eliminate some specific chemicals within the PFAS and FR chemical classes and to update flammability standards, three issues remain: 1) new, sometimes unknown, regrettable substitute chemicals are still used; 2) even the old products containing phased-out flame retardants and PFAS will continue to be used for many years; and 3) the recycling of discarded products could cause legacy chemicals to be carried over into new materials on the market.[35,120,121,243]

PFAS, PBDEs, and OPEs have been used ubiquitously in building furnishings, have been found in the blood or urine of over 90% of Americans as a result,[8–11] and will persist in the material resource stream for years to come. Despite widespread concerns about these chemical classes, only a few research studies have been able to evaluate the success of interventions to remove the chemicals from products. Stubbings et al. swapped in FR-free nap mats in six

childcare centers in Seattle and found that several OPEs were significantly reduced in dust samples three months after the intervention.[126] Another study reported a significant decline in FRs on hand wipes of 10 gymnasts after an intervention to replace pit foam with FR-free alternatives.[127] Other studies evaluated the impact of changing furniture flammability standards or PBDE phase-outs on the emerging use of OPEs and other replacement FRs.[22,24,207,227] To our knowledge, no studies have assessed interventions to reduce PFAS indoors.

One of the current limitations with intervention studies is the inability to screen chemicals in products in situ in order to identify important driving product sources and to inform future interventions. Handheld x-ray fluorescence (XRF) instruments can non-destructively and in real-time analyze many elements, such as bromine and phosphorus, as indicators of the total content of chemical classes like PBDEs and OPEs, respectively. Several studies have used XRF measurements of bromine to reliably screen products for potential content of PBDEs and some other brominated FR chemicals, but not in the context of "healthier" materials interventions.[36,37,120,155–159] In fact, XRF-measured bromine levels in furniture and/or electronics have been significantly associated with PBDE concentrations in house dust[155] and in human blood samples.[158] One study has also measured phosphorus in furniture using XRF. Although the authors recommended caution in classifying a product as OPE-free based on XRF data alone (the probability of XRF to predict a true negative was 96% for phosphorus, compared to 100% for bromine),[156] phosphorus measurements should be a useful surrogate to statistically model patterns in sources of OPEs. Analyzing bromine and phosphorus in products with portable XRF can help address the exposure misclassification errors that arise from models relying on raw counts of foam furniture and electronics in spaces.[155]

For this study, we evaluated a chemical class-based "healthier" materials intervention at a university which, since 2017, has renovated over a dozen buildings with furniture, carpet, and other products specified by manufacturers as free of the entire classes of PFAS and flame retardants (often customized as so for the first time). The objectives of this study were to: 1) measure levels of 42 PFAS, PBDEs, and OPEs in indoor dust from spaces with "healthier" materials compared to analogous samples from conventional spaces, and 2) identify important sources of flame retardants in the buildings using XRF product screening for bromine and phosphorus.

Methods

Study Design

We sampled indoor dust in 47 rooms from 21 buildings across eight schools at a university in the northeastern United States. Specifically, we studied six office suites, 23 common rooms, and 18 classrooms (including seminar rooms, conference rooms, and class auditoriums).

We first selected as many rooms as possible that had been renovated with "healthier" materials (n=22), including furniture and carpet specified by manufacturers as free of the entire classes of PFAS and flame retardants. Renovated "healthier" furniture includes seating and most non-fixed furnishing items purchased for the rooms, excluding attached materials like cabinets, electronics, and any existing furniture that was kept. The trace contamination thresholds for the "healthier" designation in product procurement agreements were 100 ppm for PFAS and 1000 ppm for FRs by weight (the same FR threshold as TB 117-2013). The furniture also could not contain polyvinyl chloride (PVC) above 1% by weight. All of these interventions were

implemented starting in 2017 through 2019, and most of them (86%) were conducted in existing buildings. The interventions did not target renovation of fixed materials inherent to the building, such as insulation.

We then selected an approximately equal set of rooms that did not undergo the "healthier" materials intervention, had also been refurnished as recently as possible, comprised an equivalent distribution of room types, were carpeted, had similar room characteristics as the "healthier" rooms, and we had permission from schools and building managers to access (n=25). In five cases, we were able to sample a conventional room in a building that had a "healthier" room on a different floor in order to maximize comparability (although these rooms sometimes had different renovation dates). Sampling multiple rooms within the same building, if different enough in function or characteristics, helped to increase the limited sample size of available "healthier" rooms and recently renovated conventional spaces.

The building construction years were similar for "healthier" rooms (median 1970; range 1863–2018) and conventional rooms (median 1965; range 1863–2017). The years of last refurnishing, as reported by building managers and/or labeled on furniture purchase tags, ranged from 2017 to 2019 (median 2018) for "healthier" rooms and 2001 to 2019 (median 2016) for conventional rooms. The rooms all had the floors vacuumed at least twice weekly and never had new stain-repellant coatings applied to carpets. Only two conventional rooms were naturally, not mechanically, ventilated.

"Healthier" Materials Intervention Classifications

Given the spectra of "healthier" materials statuses in the studied rooms, we decided to categorize the spaces into the following three groups: no intervention, partial intervention, and

full “healthier” materials intervention. We avoided defining more than three categories in order to ensure a reasonable sample size within each group and parsimony for statistical modeling.

- “No intervention” = rooms located in older (but possibly renovated) buildings constructed before the 2004 phase-out of most PBDEs and that had foam furniture meeting historically stringent flammability standards (TB 117 or 133).
- “Full ‘healthier’ materials intervention” = rooms that 1) were renovated with furniture and carpet specified to be free of PFAS and FRs, and 2) resided in buildings built after the 2004 PBDE phase-out or that had renovated the entire floor to be “healthier” (i.e. no adjacent contamination from conventional spaces).
- “Partial intervention” = All other rooms, including 1) conventional spaces in newer buildings built after the 2004 PBDE phase-out or likely with fewer flame retardants in foam furniture (under the TB 117-2013 option), and 2) rooms with “healthier” materials that would have cross contamination from the old building and connection to adjacent conventional spaces.

Dust Sample Collection

We collected dust samples in each room between January and March 2019. Dust samples were not collected until at the very least two months after the “healthier” materials interventions. Before sampling, we asked the custodial crew to leave the space unvacuumed for two to three days so that we could capture enough mass of dust. In each room, we collected three different dust samples to send to different analytical laboratories (one sample for chemical analysis for this study and two other samples archived for future analyses). We split the room into equally sized thirds with equivalent furnishings. For each dust sample, we vacuumed floor dust

(including under pieces of furniture) in the designated space for 10 minutes using a vacuum cleaner (Dyson CY18) with an attached crevice tool that housed a cellulose extraction thimble (secured with a nitrile rubber o-ring) to collect dust. We used several identical crevice tools that were pre-cleaned in our laboratory with isopropyl alcohol and tap water before each sampling day. We used a different cleaned crevice tool for each room. The sample collection procedure ensured that the dust only came into contact with the cleaned crevice tools and followed previously published protocols.[23,232] After vacuuming, the thimbles were stored in polypropylene centrifuge tubes in polyethylene bags in a -13°C freezer until shipment on ice to laboratories for analysis. We also collected five field blanks by carrying unopened centrifuge tubes into the field on multiple different sampling days.

PFAS and FRs in Dust

Dust samples and field blanks were analyzed for 15 PFAS, eight PBDEs, and 19 OPEs, following previously published methods.[233,238,301,302] The PFAS analytes included PFOS, PFOA, perfluorohexanoate (PFHxA), perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonamide (FOSA), perfluoroheptanoate (PFHpA), perfluoropentanoate (PFPeA), perfluorononanoate (PFNA), perfluorobutane sulfonate (PFBS), perfluorodecane sulfonate (PFDS), perfluorobutanoate (PFBA), perfluorodecanoate (PFDA), perfluoroundecanoate (PFUnDA), perfluorododecanoate (PFDoDA), and n-methyl perfluorooctane sulfonamidoacetic acid (N-MeFOSAA). The PBDE analytes included 2,4,4'-tribromodiphenyl ether (BDE-28), 2,2',4,4'-tetrabromodiphenyl ether (BDE-47), 2,2',4,4',5-pentabromodiphenyl ether (BDE-99), 2,2',4,4',6-pentabromodiphenyl ether (BDE-100), 2,2',4,4',5,5'-hexabromodiphenyl ether (BDE-153), 2,2',4,4',5,6'-hexabromodiphenyl ether (BDE-154), 2,2',3,4,4',5',6-heptabromodiphenyl ether

(BDE-183), and decabromodiphenyl oxide (BDE-209). The OPE analytes included tris(2-butoxyethyl) phosphate (TBOEP), tris(1-chloro-2-propyl) phosphate (TCIPP), tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), triphenyl phosphate (TPHP), tris(2-chloroethyl) phosphate (TCEP), 2-ethylhexyl diphenyl phosphate (EHDPP), isodecyl diphenyl phosphate (IDDP), tri-iso-butyl phosphate (TIBP), tripropyl phosphate (TPP), cresyl diphenyl phosphate (CDPP), tert-butylphenyl diphenyl phosphate (BPDP), tri-n-butyl phosphate (TNBP), tetrakis(2-chloroethyl) dichloroisopentyl diphosphate (V6), bisphenol a bis(diphenyl phosphate) (BDP), resorcinol bis(diphenyl phosphate) (RDP), tris(2-ethylhexyl) phosphate (TEHP), tris(methylphenyl) phosphate (TMPP), triethyl phosphate (TEP), and tris(p-tert-butylphenyl) phosphate (TBPHP).

Concentrations of the PFAS were measured using high-performance liquid chromatography (HPLC) coupled with electrospray triple quadrupole tandem mass spectrometry (ESI-MS/MS) and monitored by multiple reaction monitoring mode under negative ionization. OPEs were measured with HPLC coupled with ESI-MS/MS, using monitoring by electrospray positive ionization multiple reaction monitoring. PBDEs were measured with a gas chromatographer coupled with a mass spectrometer (GC-MS) using electronic impact ionization mode. The limits of detection (LODs) ranged from 0.1–0.8 ng/g for OPEs, 0.09–4.5 ng/g for PBDEs, and 0.06–1.5 ng/g for PFAS.

For preparation of samples before instrumental analysis, the dust samples were first sieved through a 150-μm stainless steel mesh. The samples (with masses ranging from 0.2 to 0.5 g) were then spiked with 30 ng each of labeled surrogate standard mixture. The samples were extracted with methanol (3 mL) under mechanical oscillation (1 h) followed by ultrasonication (30 min). Then, the dust extracts were centrifuged (3500g, 10 min) and transferred into new polypropylene tubes. The extraction was repeated twice with acetonitrile (3 mL) and ethyl

acetate (3 mL), after which the extracts were combined and evaporated to 3 mL under a gentle stream of nitrogen. The extracts were split into three aliquots for the measurement of PFAS, PBDEs, and OPEs. The extracts evaporated to near dryness and were then reconstituted with 200 μL of solvents: methanol for PFAS, hexane for PBDEs, and water/methanol (4/6; v/v) for OPEs. Before instrumental analysis, the sample extracts were filtered through a 0.2 μm nylon filter into glass vials.

All field blanks either had values below the LOD or detected concentrations well below the levels in samples. The spiked recovery results were 67.4–104% for PFAS, 55.9–128% for OPEs, and 101–115% for PBDEs, respectively. We split and analyzed duplicates of seven dust samples for quality assurance and quality control (QA/QC) and calculated median relative percent differences of 0% (range: -62–190%) for PFAS, -3.2% (range: -50–80%) for PBDEs, and 0% (range: -96–52%) for OPEs. There was some variability in chemical levels in the duplicates, likely mostly due to the natural heterogeneity of indoor dust.

Screening Products for Br and P (XRF)

We returned to all the studied rooms between September and October 2019 to characterize potential sources of these chemicals. Only two of the 47 rooms had some missing furniture pieces since the dust sampling earlier in the year. In each room, we first took another inventory of all the products and recorded their counts, material types, surface areas, and manufacturing information (if available). For upholstered foam furniture, we looked for flammability tags (if still present) and recorded which regulatory standard the product complied with. In a few cases, multiple different standards were labeled on separate tags of one product, in which case we recorded the most stringent standard (unless labeled to contain no added FRs).

We also noted whether or not there was an adjacent conventional space connected to a "healthier" room. Except for a few foam furniture pieces in two rooms, we were able to study the same products that were in the rooms previously during dust sampling (as noted from previous field sheets and photos).

We then screened the products and materials within each room for bromine and phosphorus content (as surrogates for PBDEs and OPEs, respectively) using two handheld, non-destructive XRF instruments. Fluorine, as a surrogate for PFAS, was too light an element to be detectable by either of the instruments. The first instrument, an Olympus Innov-x XRF with a consumer product (RoHS) testing mode, was used to measure bromine concentrations in the products, but could not detect lighter elements like phosphorus. We took minimum 15-second measurements with this instrument by holding it still against the surface of the product. The second instrument, a more sensitive Thermo Fisher Scientific Niton xl3t GOLDD+ XRF, was used to measure phosphorus. For the Niton XRF, we could only use the TestAllGeo mode (hereby referred to as "geo"), which automatically selects the right testing mode for geological samples. Spectral data from this instrument can also be analyzed for bromine concentrations, so we were able to assess differences between the two instruments/modes (as described in results). We programmed the Niton XRF to collect measurements with 15 seconds in the main element range and 30 seconds in the light element range (an advanced feature to capture phosphorus). The XRF measurements penetrate deep enough to capture concentrations inside foam filling of furniture. The LODs were expected to be approximately 10 ppm for bromine and 20 ppm for phosphorus.

We focused on foam furniture, carpet, insulation, and electronics for XRF measurements, as these are the products known to be primary sources of flame retardants.[32–37] For each type of

foam furniture, we took four measurements (with each XRF): on both the seat cushion and seatback (if cushioned) for two different items of the same model. For carpet, we took two measurements in different spots. For televisions, we took two repeat measurements on the back plastic casing for two different items of the same model (if present). For other electronics, we took at least one measurement for each product type, and again measured the back plastic for computers. In some cases, when the instruments could not fit behind, under, or to the side of the television for measurements of the plastic casing, we scanned the front. Some products in the room could not be scanned because they were out of reach, such as exposed insulation, routers, and ceiling speakers in rooms with high ceilings. In addition to these primary products of interest, we also took a measurement of most other products or materials in the rooms, including tables/desks, non-upholstered chairs, window treatments, walls, wall base, ceilings, floorings, white or chalk boards, countertops, drawers, and cabinets.

Statistical Analyses

We first blank-corrected the concentrations of chemicals in the dust samples by subtracting the average value of the field blanks. Chemical concentrations below the LOD in dust were substituted with half the LOD.[197] For statistical models, we also log-transformed the chemical concentrations because the data were not normally distributed (based on histograms and Shapiro-Wilk tests). First, we performed principal component analysis on scaled and centered concentrations of the eight PBDE congeners in order to identify how the congeners grouped according to commercial flame-retardant mixtures. We evaluated principal components that together explained at least 70% of the variance.

To prepare covariates for statistical modeling of the chemicals in dust, we calculated room loadings of bromine and phosphorus from foam furniture and electronics separately by taking the sum of each unique product type's mean element concentration multiplied by its surface area and the number of that product type in the room (Equation 4-1). This approach followed a previously published protocol.[155] For upholstered foam furniture loadings, we included chairs (with cushioned seats), armchairs (fully cushioned), couches, foam ottomans, foam pillows, and foam tops on metal drawers. For electronics, we included televisions, computers, projector systems and screens, routers, keyboards, computer mice, telephones, speakers, TV remotes, tablets, power strips, plug ports, printers, portable scanners, floor outlets, server kits, audio radiators, and DVD or video game players. Non-detect XRF measurements were conservatively substituted with zero for loading calculations, but we added one to all the concentrations so we could transform the non-normally distributed data to the log scale for modeling. In addition, occasionally when some ceiling electronics (such as routers) were not able to be measured, we borrowed the result for the same product of the same manufacturer if available for a different room in the same building.

Equation 4-1

$$Loading = \sum_{products} (mean\ concentration * surface\ area * count)$$

We conducted multilevel models for the chemical classes in dust, with a random intercept for the building because some rooms were sampled within the same building. As covariates, we included the three-category "healthier" materials intervention status (conducted with the reference as "none" and as "partial" based on interpretability and largest sample size, respectively), a binary variable for the presence of exposed insulation in or immediately adjacent

to the room (reference=no), the element loading from foam furniture (reference=low), and the element loading from electronics (reference=low). The element loadings were categorized into low, medium, and high based on terciles. We did not use an element loading variable for insulation because insulated pipes on ceilings were not always accessible for XRF measurement. To present results from the models, we transformed the estimates back to the linear scale and report them as percent differences (since the dependent variables were log-transformed before modeling).

To model the association between furniture characteristics and XRF-measured element concentrations in the products, we conducted multilevel models with two random intercepts for the room and the specific products (we took repeated measurements on two different spots of two identical furniture items of the same product model). We included random intercepts to 1) account for expected correlation between products within the same room, as well as replicate items or cushions of the same furniture product; and 2) evaluate the amount of variability in element concentrations within versus between specific products. In the models for bromine and phosphorus in products, we included three categorical covariates: the university or Californian flammability standard the furniture was labeled to be in compliance with (reference group of "healthier"; TB 117-2013 with no added FRs; TB 117 or 117-2013 with added FRs; TB 133; and unlabeled), the type of foam furniture (reference group of chair; fully upholstered armchair; couch; ottoman), and the location of the measurement (reference category of the seat; the seatback cushion). We evaluated statistical significance at $\alpha=0.05$ and suggestive evidence at $\alpha=0.10$. All statistical analyses were performed in R (version 3.3.1).

Results

Per- and Polyfluoroalkyl Substances in Dust

PFAS were detected in 100% of our dust samples (n=47) from offices, common areas, and classrooms (Table 6.2). The most frequently detected PFAS were PFHxA at 98%, PFOS at 98%, PFOA at 75%, PFHxS at 64%, FOSA at 60%, and PFHpA at 51%. The maximum detected concentrations across all analytes were 2,980 ng/g (PFHxA), 1,760 ng/g (PFHpA), 1520 ng/g (PFOA), and 1,480 ng/g (PFNA).

The geometric mean total Σ_{15}PFAS concentrations were 262 ng/g (range: 18.1–8,310 ng/g) in all rooms, 481 ng/g (225–1,140 ng/g) in the rooms with no intervention, 252 ng/g (18.1–8,310 ng/g) in the rooms with a partial "healthier" materials intervention, and 108 ng/g (43.6–243 ng/g) in the rooms with a full "healthier" materials intervention (Table 6.2). PFHxA, PFOS, and PFOA dominated the geometric mean profiles of PFAS analytes in dust across intervention statuses, although the concentrations were much lower in the "healthier" rooms (Figure 4.1). Geometric mean concentrations of PFHxA were 326, 127, and 64.3 ng/g in rooms with no intervention, rooms with a partial "healthier" intervention, and rooms with a full "healthier"

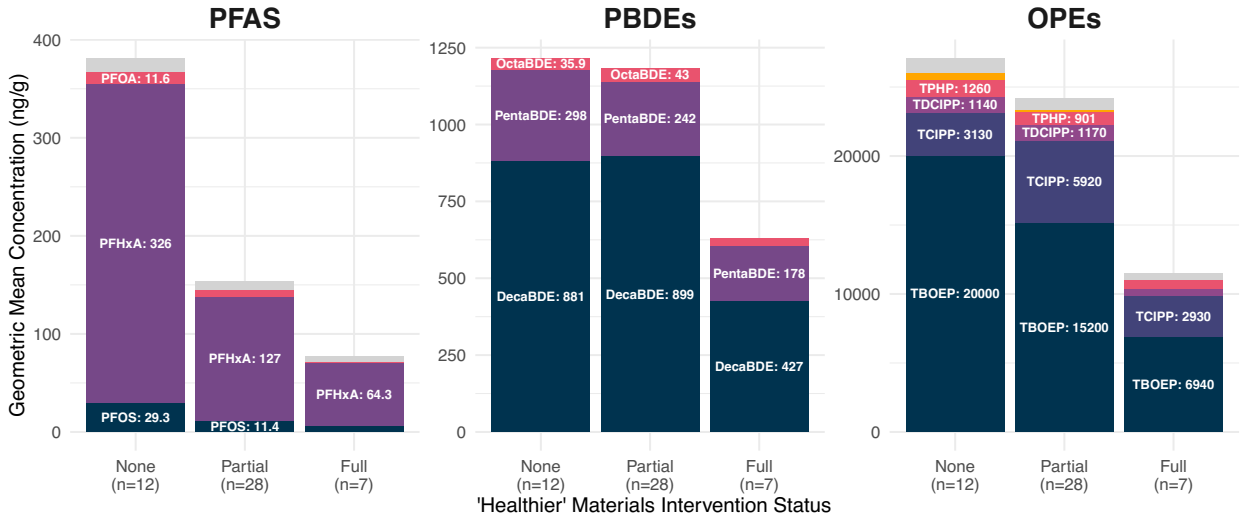

Figure 4.1. Geometric mean concentrations (ng/g) of each main PFAS, PBDE, and OPE analyte in indoor dust samples (n=47) by "healthier" materials intervention status.

Penta-BDE was defined from principal component analysis to include BDEs 28, 47, 99, 100, and 153. Octa-BDE includes BDE-154 and BDE-183. Deca-BDE is BDE-209.

Table 4.1. Results from multilevel models of the impact of "healthier" materials intervention status, presence of exposed insulated pipes, flame retardant-related element loadings in furniture, and element loadings in electronics (bromine [Br] for PBDEs; phosphorus [P] for OPEs) on total concentrations (ng/g) of 15 PFAS, 8 PBDEs, and 19 OPEs in indoor dust samples (n=47).

		% Change (p value)[a]					
Covariate	***n***	**Sum of 15 PFAS**		**Sum of 8 PBDEs**		**Sum of 19 OPEs**	
'Healthier' Materials Intervention Status							
No intervention	*12*	Reference	47% (0.3)	Reference	-33.7% (0.2)	Reference	7.93% (0.7)
Partial intervention	*28*	-32% (0.3)	Reference[b]	50.7% (0.2)	Reference[b]	-7.34% (0.7)	Reference[b]
Full intervention	*7*	**-77.9% (0.006) ****	**-67.5% (0.02) ***	-17.4% (0.6)	**-45.2% (0.09) .**	**-65.0% (<0.001) *****	**-62.2% (<0.001) *****
Exposed Insulation in Room							
No	*41*	Not included		Reference		Reference	
Yes	*6*	Not included		24.8% (0.5)		**176% (<0.001) *****	
Br or P Loading[c] from Foam Furniture				*For bromine:*		*For phosphorus:*	
Low	*16*	Not included		Reference		Reference	
Medium	*15*	Not included		-12.6% (0.6)		-26.8% (0.2)	
High	*16*	Not included		**86.2% (0.04) ***		0.393% (1.0)	
Br or P Loading[c] from Electronics							
Low	*16*	Not included		Reference		Reference	
Medium	*15*	Not included		42.1% (0.2)		**43.9% (0.09) .**	
High	*16*	Not included		**169% (<0.001) *****		-3.32% (0.9)	

PFAS = per- and polyfluoroalkyl substances; PBDEs = polybrominated diphenyl ethers; OPEs = organophosphate esters.
[a] Chemical concentrations were log-transformed in the multilevel models, but estimates are presented as the percent change on the linear scale.
[b] The models were conducted a second time with 'partial intervention' as the reference category in order to assess any improvements of the full intervention over the partial one and to increase statistical power by using the group with the largest sample size.
[c] Loadings were calculated as the sum across foam furniture or electronics products of the average element concentration of each unique product type multiplied by its surface area and count in the space.
. $p < 0.10$
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

intervention, respectively. The geometric means of PFOS were 29.3, 11.4, and 6.17 ng/g and the geometric means of PFOA were 11.6, 6.25, and 1.07 ng/g for rooms with no intervention, with a partial intervention, and with a full intervention, respectively. presents additional summary statistics by room type (offices, common areas, and classrooms).

In a multilevel regression model with a random intercept for the building, rooms with a full "healthier" materials intervention had 78% (95% CI: 38–92%) lower Σ_{15}PFAS concentrations in dust than rooms with no intervention (p=0.006) (Table 4.1). The spaces with a full "healthier" materials intervention even had 68% (95% CI: 15–88%) lower Σ_{15}PFAS concentrations in dust than rooms with a partial intervention (p=0.02). About 71% of the variability in log PFAS concentrations was attributable to differences between rooms within a building, while the remaining 30% was explained by differences across buildings.

Polybrominated Diphenyl Ethers in Dust

As shown in Table 6.2, BDE-209, BDE-99, BDE-47, and BDE-100 were each detected in 100% of our dust samples at geometric mean concentrations of 800 ng/g (max 13,000), 120 ng/g (max 734), 63.7 ng/g (max 1,470), and 27.1 ng/g (max 202), respectively. The other four PBDE congeners were detected in at least 80.9% of samples at up to 817 ng/g. In principal component analysis (Figure 6.4), the PBDE congeners grouped into three main components (explaining 75% of variance) that aligned well with commercial flame retardant mixture formulas: penta-BDE (congeners 28, 47, 99, 100, and 153), octa-BDE (congeners 154 and 183), and deca-BDE (congener 209). The PBDE profiles in dust were mostly influenced by deca-BDE (BDE-209), followed by the penta-BDE group (Figure 4.1). The geometric mean concentrations of BDE-209 were 881, 899, and 427 ng/g and the maximum concentrations were 5,410, 13,000, and 1,400 ng/g in rooms with no intervention, with a partial intervention, and with a full "healthier" intervention, respectively. Two new buildings were built after the 2013 voluntary phase-out of BDE-209. In the new building with full "healthier" materials interventions, three sampled rooms had detectable levels of BDE-209 in dust ranging from 52.9 to 1,340 ng/g. In the new building containing rooms classified as a partial intervention, three rooms had dust concentrations of BDE-209 between 369 and 2,680 ng/g.

Total PBDE dust concentrations were similar between rooms with no intervention and rooms with a partial intervention, but the full "healthier" rooms had lower levels (Figure 4.2). The geometric mean concentrations of Σ_8PBDEs in dust were 1,360 ng/g (range: 452–5,930 ng/g) in rooms with no intervention, 1,390 ng/g (179–14,200 ng/g) in rooms with a partial

"healthier" intervention, and 839 ng/g (414–1,570 ng/g) in rooms with a full "healthier" materials intervention (Table 6.2).

In the multilevel model adjusted for exposed insulation, bromine loading from foam furniture, and bromine loading from electronics (Table 4.1), there was suggestive evidence that rooms with a full "healthier" materials intervention had 45% (95% CI: -1.7–71%) lower Σ_8PBDEs concentrations when compared to rooms with only a partial intervention (p=0.09). The rooms with a full intervention also had 17% lower Σ_8PBDEs concentrations in dust than rooms with no intervention, but this did not reach statistical significance (p=0.68), perhaps because of the lower sample size of the no-intervention reference group. The rooms with partial versus no interventions also did not have significantly different Σ_8PBDE dust levels (p=0.16). The PBDE concentrations in dust were significantly associated with bromine loadings from both electronics and from foam furniture. Rooms with high bromine loadings in electronics had 169% (95% CI: 51–362%) higher levels of Σ_8PBDEs in dust than rooms with low electronic loadings (p=0.0008). Rooms with high bromine loadings in foam furniture had 86% (95% CI: 2–226) higher Σ_8PBDEs concentrations in dust than rooms with low loadings (p=0.04). Differences

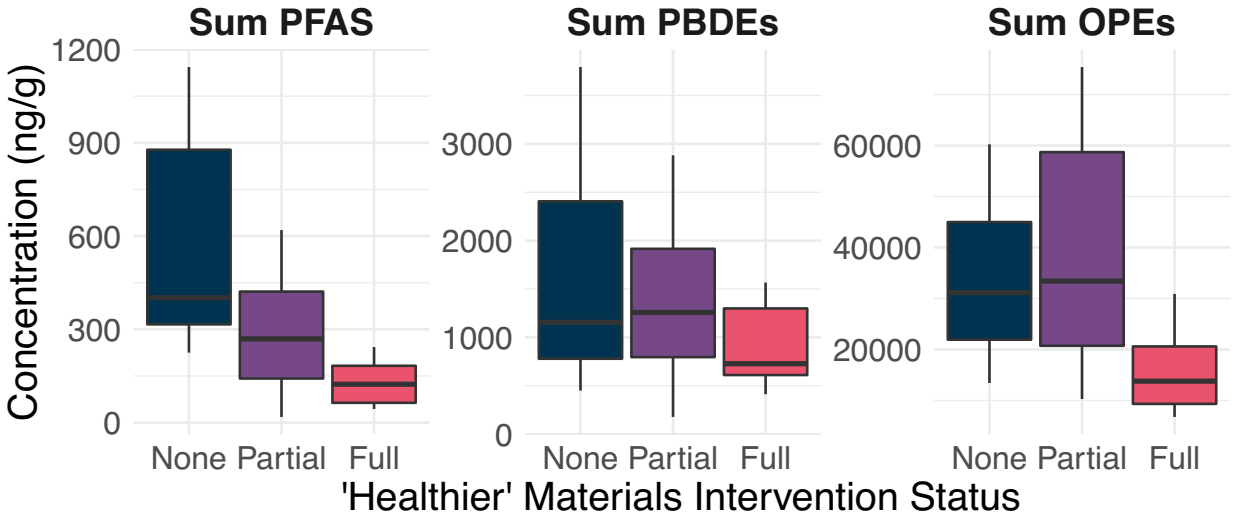

Figure 4.2. Boxplots of concentrations (ng/g) of Σ_{15}PFAS, Σ_8PBDEs, and Σ_{19}OPEs in indoor dust samples by "healthier" materials intervention status, with outliers excluded to obtain tighter y-axis scales (n=47).

between rooms within a building (as opposed to between buildings) explained 83% of the variability in log PBDE concentrations in dust.

Organophosphate Esters in Dust

Nine OPEs were detected in 100% of dust samples, and another eight were detected in at least 91% of samples (Table 6.2). The most frequently and highest detected chemicals were TBOEP (geometric mean 14,500; max 118,000 ng/g), TCIPP (4,530; 139,000 ng/g), TDCIPP (1,030; 6,440 ng/g), and TPHP (927; 10,600 ng/g). Figure 4.1 shows that these four chemicals make up the vast majority of the geometric mean profiles of OPE analytes.

The OPE concentrations were generally lowest in dust from the full "healthier" rooms, while the rooms with no intervention or a partial intervention had similar concentrations to each other (Figure 4.2). The geometric mean concentrations of Σ_{19}OPEs in dust were 30,400 ng/g (range: 13,400–60,300 ng/g) in rooms with no intervention, 37,500 ng/g (10,300–182,000 ng/g) in rooms with a partial "healthier" intervention, and 14,000 ng/g (6,760–30,900 ng/g) in rooms with a full "healthier" materials intervention (Table 6.2).

In a multilevel model controlling for insulation presence, furniture phosphorus loading, and electronics phosphorus loading, the rooms with a full "healthier" materials intervention had 65% (95% CI: 37–80%) lower total levels of OPEs in dust than rooms with no intervention (p=0.0006) (Table 4.1). Rooms with only a partial materials intervention did not have significantly lower Σ_{19}OPEs concentrations in dust than rooms with no intervention (p=0.7). Rooms with the presence of exposed insulation had 176% higher Σ_{19}OPEs levels in dust than rooms without visible insulation (95% CI: 55–396%; p=0.0005), adjusted for intervention status, furniture loading, and electronics loading. There was suggestive evidence that rooms with

medium phosphorus loadings from electronics, compared to rooms with low loadings, had 43.9% higher Σ_{19}OPEs concentrations in dust (95% CI: -7–118%; p=0.09). Phosphorus loadings in foam furniture were not statistically significant predictors of Σ_{19}OPEs concentrations. All (100%) of the variability in log OPE concentrations could be attributed to differences between rooms within a building, so between-building differences did not play a significant role.

Bromine in Products

We collected 1,230 measurements of bromine in 845 products in the 47 studied rooms using a portable Olympus XRF in its consumer product mode. We analyzed bromine in 105 unique upholstered foam seating furniture items (N=293 including replicate measurements on different spots of the product), 54 carpets (N=91 measurements), and 170 electronic products (N=240). Table 4.2 provides summary statistics of the bromine concentrations by product type. Median bromine concentrations were higher in carpet in conventional spaces (21.2 μg/g; max 305 μg/g) compared to "healthier" carpet specified as free of flame retardants (7.6 μg/g; max 153 μg/g). In an unadjusted multilevel regression model, the conventional carpet had 210% (95% CI: 65–484%) higher bromine levels than "healthier" carpet (p=0.001).

The bromine concentrations in upholstered foam furniture varied by flammability standard as labeled on the furniture tag. The conventional foam furniture meeting the historic and most stringent flammability standard, TB 133, had the highest median bromine concentration (917; max: 65,910 μg/g). Foam furniture meeting other stringent flammability standards, including TB 117 or TB 117-2013 (with added chemical FRs), had a lower median bromine concentration of 27.2 μg/g (max: 46,120 μg/g). Foam furniture that met the newest flammability standard's (TB 117-2013) option of not adding chemical flame retardants above 1000 ppm

(µg/g) had the lowest median bromine levels (7.70; max: 848 µg/g). The 1000 µg/g limit for PBDEs would be equivalent to at most 833 µg/g of bromine (based conservatively on the most brominated congener, BDE-209), so the bromine concentrations in TB 117-2013 furniture with 'no added FRs' seem to mostly be below that regulatory limit, unlike the furniture that instead

Table 4.2. Summary of concentrations (µg/g) of bromine and phosphorus in different product types in the 47 studied spaces, as measured using portable x-ray fluorescence (XRF).

	Bromine (µg/g)		Phosphorus (µg/g)	
	XRF in product mode		*XRF in geo mode*	
Product Type	***n***	**Median [Range]**	***n***	**Median [Range]**
Upholstered foam furniture[a]	*293*	21.5 [ND, 79240]	*284*	585.8 [ND, 22880]
By flammability standard				
'Healthier': no added FRs (or PFAS)	*122*	10.05 [ND, 4820]	*114*	457.4 [ND, 4827]
Conventional: TB 117-2013 with no added FRs	*39*	7.7 [ND, 848]	*40*	732 [ND, 18430]
Conventional: FRs at TB 117 or 117-2013	*25*	27.2 [5.9, 46120]	*25*	915.9 [ND, 2416]
Conventional: FRs at TB 133	*30*	917 [2.6, 65910]	*30*	493 [ND, 22880]
Conventional: unlabeled	*77*	141 [2.2, 79240]	*75*	1124 [ND, 13140]
By product type				
Chair with cushioned seat	*75*	25.8 [ND, 38440]	*73*	491 [ND, 4450]
Armchair	*126*	14.95 [ND, 76270]	*120*	864.1 [ND, 18430]
Couch	*62*	94.6 [2, 79240]	*61*	557.7 [ND, 22880]
Ottoman	*30*	9.9 [2, 55510]	*30*	512.6 [ND, 13010]
Carpet	*91*	10.6 [0.2, 305]	*91*	ND [ND, 1840]
'Healthier': no added FRs (or PFAS)	*44*	7.6 [0.2, 153.1]	*44*	99.12 [ND, 1840]
Conventional	*47*	21.2 [1.9, 305]	*47*	ND [ND, 1835]
Electronics[b]	*240*	20.35 [ND, 147800]	*229*	719 [ND, 128800]
Televisions	*51*	26 [ND, 133500]	*50*	2025 [ND, 42680]
Computer monitors	*30*	57.2 [ND, 965]	*28*	917.2 [ND, 128800]
Projector systems	*13*	2.4 [0.4, 5285]	*12*	25230 [887.8, 34740]
Keyboards	*32*	381.5 [ND, 2931]	*32*	202.6 [ND, 878]
Mouses	*24*	247.4 [0.9, 821]	*23*	426.9 [ND, 5941]
Telephones	*12*	9.05 [1.1, 395]	*12*	412 [239.9, 1183]
Audio/video devices	*15*	2.3 [ND, 147800]	*13*	711.8 [154.8, 44780]
Printers/copiers	*5*	7.3 [1, 224]	*6*	39790 [17030, 43250]
Routers/modems	*16*	0.5 [ND, 108100]	*14*	25020 [ND, 39450]
Floor outlets	*11*	4.7 [ND, 23820]	*9*	668.6 [ND, 1458]
Projector screens	*3*	ND [ND, ND]	*3*	11490 [ND, 48350]
Foam pillows	*12*	5.45 [0.7, 106]	*13*	418 [ND, 10240]
Foam drawer tops	*5*	10.2 [1.7, 12.8]	*6*	652.1 [551, 883.6]
Exposed insulation	*10*	16080 [5.4, 21030]	*10*	ND [ND, 1308]
Window shades	*24*	1.85 [ND, 94630]	*21*	471.5 [ND, 49720]
Fabric walls or dividers	*26*	2.75 [ND, 61]	*26*	431.2 [ND, 14530]
Wall paint	*48*	5.75 [ND, 263]	*49*	895 [ND, 1436]
Ceiling tile	*16*	6.2 [ND, 49.9]	*17*	ND [ND, 17400]
Wall base	*32*	ND [ND, 13.2]	*32*	ND [ND, 3884]
Plastic tables	*69*	ND [ND, 6.9]	*69*	550.8 [ND, 4777]
Plastic chairs	*52*	1.6 [ND, 30330]	*52*	169.4 [ND, 3469]
Plastic flooring	*14*	ND [ND, 14.6]	*14*	192.2 [ND, 20840]
Wood flooring	*9*	ND [ND, 3.1]	*9*	229.9 [ND, 1282]
White boards	*21*	2.8 [ND, 8.7]	*20*	22130 [ND, 213800]
Chalk boards	*4*	15.2 [13.9, 20.8]	*6*	98850 [91760, 108700]

ND = not detected
n = number of XRF measurements (including duplicates on same product)
[a] Including only chairs, armchairs, couches, and ottomans with foam filling.
[b] Including the specifically mentioned product types, as well as DVD players, tablets, power strips, scanners, TV remotes, audio radiators, plug ports, monitor-free computer systems, and one server kit.

meets the stricter regulations. The "healthier" furniture in this study that was specified as FR-free by manufacturers had similarly very low levels compared to furniture meeting the stringent regulations (median 10.1; max 4,820 μg/g). The model of "healthier" furniture with the maximum bromine level was labeled in the manufacturer's product specification to be "FR-free" and "bromine-free" but to contain recycled content; we did not have this information for most other furniture models.

In a multilevel regression model adjusted for type of furniture product and measurement spot, upholstered foam seating furniture that met the most stringent flammability standard, TB 133, had 2,940% (95% CI: 458–16,200%) higher levels of bromine than "healthier" furniture specified by manufacturers as free of all flame retardants (p=0.0002) (Table 4.3). Foam seating furniture that met the other stringent flammability standards had 922% (95% CI: 45–7,210%) higher bromine levels than "healthier" furniture specified as FR-free (p=0.026). Conventional furniture that was not tagged with a flammability label also had significantly higher bromine levels compared to "healthier" furniture (1510%; 95% CI: 311–6,190%; p=0.0004). As expected, the conventional furniture labeled under TB 117-2013 to not contain chemical FRs above 1000 ppm did not have significantly different bromine content compared to the university's "healthier" furniture that followed the same FR restrictions. By including two random intercepts in the multilevel model for the room and for the specific product type, we found that 26% of the variability in log bromine concentrations in foam furniture were explained by differences between rooms. About 83% of the variability was attributable to differences between product types across rooms, while conversely 17% was explained by differences in repeated measurements within a product type (from a different spot of the same item or different item of the same product type in the room).

Table 4.3. Results from multilevel models of the impact of flammability standard, furniture type, and type of cushion measured on concentrations (µg/g) of bromine and phosphorus in foam furniture in 47 studied spaces as measured with a portable x-ray fluorescence (XRF) instrument.

		% Change (*p* value)[a]	
Covariate	***n***	**Bromine**	**Phosphorus**
Intervention			
'Healthier': no added FRs (or PFAS)	125	Reference	Reference
Conventional: TB 117-2013 with no added FRs	40	-25.2% (0.7)	**2200% (0.001) ****
Conventional: FRs at TB 117 or 117-2013	25	**922% (0.03) ***	566% (0.1)
Conventional: FRs at TB 133	30	**2940% (<0.001) *****	103% (0.5)
Conventional: unlabeled	77	**1510% (<0.001) *****	**495% (0.02) ***
Foam Furniture			
Chair	75	Reference	Reference
Armchair	129	-17.2% (0.7)	28.3% (0.7)
Couch	63	**632% (0.004)****	58.3% (0.6)
Ottoman	30	56.1% (0.5)	-45.3% (0.5)
Spot Measured			
Seat Cushion	199	Reference	Reference
Seatback Cushion	98	-11.9% (0.4)	**-59.9% (<0.001) *****

FRs = flame retardants; TB = technical bulletin of California furniture flammability standard.
[a] Element concentrations were log-transformed in the multilevel models, but estimates are presented as the percent change on the linear scale.
* $p < 0.05$
** $p < 0.01$
*** $p < 0.00$

Electronics and insulation were two other main product types with bromine in the studied rooms. Bromine levels in exposed insulation (mostly hot water pipes) were detected at a median 16,080 µg/g (max 21,030 µg/g). Televisions had a median bromine level of 26 µg/g and a max of 133,500 µg/g in one room. Other electronic types sometimes reached high maximum bromine levels, such as 147,800 µg/g for a speaker, 108,200 µg/g for a router, and 23,820 µg/g for a floor outlet.

Phosphorus in Products

We collected 1,210 phosphorus measurements in 840 products in the rooms using a portable Niton XRF in its geo mode, as summarized in Table 4.2. We measured phosphorus in 105 unique upholstered foam seating items (*N*=284 measurements), 54 carpets (*N*=91), and 163 electronic products (*N*=229).

Median phosphorus concentrations were lowest in "healthier" upholstered foam seating furniture that were specified by manufacturers to be free of flame retardants (457.4; max 4,827 μg/g). Compared to the "healthier" furniture, the conventional furniture labeled to have no added FRs had higher phosphorus levels (median 732; max 18,430 μg/g), and levels were even higher in conventional furniture meeting more stringent standards (median 915.9; max 2,416 μg/g) but not the most stringent TB 133 (median 493; max 22,880). The 1000 μg/g limit for furniture with no added FRs (whether "healthier" or conventional under TB 117-2013) would be equivalent to up to 170 μg/g phosphorus for our OPE analytes (specifically TEP). The geometric mean concentrations of phosphorus for all furniture standards were above that limit, although organophosphate chemicals may also technically be present in the products as plasticizers.

In a multilevel model adjusted for the type of furniture and the measurement spot, conventional furniture labeled to have no added flame retardants under the TB 117-2013 option had 2,200% (95% CI: 309–12,800%) higher levels of phosphorus than "healthier" furniture (p=0.001). Conventional furniture with no flammability standard tag also had 495% (95% CI: 48–2,300%) higher phosphorus levels than "healthier" furniture (p=0.02). In the multilevel model, 7% of the variability in log phosphorus levels was explained by differences between rooms. About 40% of the variability was attributable to differences in repeated measurements within a product type.

Electronics also had relatively high phosphorus levels, especially in televisions (median 2,025; max 42,680 μg/g), projector systems (25,230; 34,740 μg/g), printers (39,790; 43,250 μg/g), computer monitors (917.2; 128,800 μg/g), and routers (25,020; 39,450 μg/g). Window shades had a median phosphorus level of 471.5 μg/g (max 49,720 μg/g). Phosphorus

concentrations in conventional and "healthier" carpets were not significantly different in a multilevel regression model.

Although phosphorus was a light element that could only be measured in a geo soil mode on the Niton XRF, the extremely strong correlation (for foam furniture: Spearman r=0.91, p<0.0001; for all product categories: r=0.65, p<0.0001) between bromine from the Niton XRF soil mode and bromine from the consumer product mode on the Olympus XRF (even when taken on different spots of the product) suggested that the soil mode did not produce interference in foam furniture product measurements for modeling purposes.

Discussion

In indoor dust from 47 office, class, or common rooms at a university, we found that a "healthier" furniture and carpet intervention substantially reduced total levels of 42 measured PFAS, PBDEs, and OPE chemicals relative to conventional spaces.

Per- and Polyfluoroalkyl Substances

In particular, compared to rooms with no intervention, PFAS were 78% lower in dust in rooms with the full "healthier" materials intervention, which included carpet and furniture specified by manufacturers to be free of all PFAS and flame retardants. The specific PFAS detected in dust from the studied rooms mostly included PFHxA, PFOS, and PFOA. These three chemicals have all been used as coatings on furniture and carpet, so their substantial reductions in dust align with the "healthier" materials that were intervened on in this study.

The dust concentrations of the two historically widely used legacy chemicals, PFOS and PFOA, were mostly much lower than in previous studies of indoor dust in the United States

(Figure 4.3).[232,349,361–365] Some residual contamination of these two legacy PFAS still persists in the studied buildings despite their voluntarily phase-out by major manufacturers in the early 2000s,[99,100] suggesting that products with long life spans as well as materials inherent to the building continue to be used even after phase-outs.

At the same time, the newer, short-chain replacement chemical PFHxA tended to be found at higher dust concentrations in our study (even in "healthier" rooms) than have been previously measured in dust collected from homes or offices in the United States between 2000 and 2013 (Figure 4.3). The substantially higher levels are likely due to the increasing use of PFHxA over time and our sampling of mostly recently refurnished buildings (unlike the case for many homes). It's possible our studied university buildings also had a higher density of furniture and carpeting than homes. PFHxA contamination was still found in the rooms with "healthier" furniture and carpet, likely from other types of building materials that were not intervened on, furnishings from any conventional spaces adjacent to the "healthier" room, and consumer products that people carry in. Other than upholstered furniture and carpet, PFHxA (and/or PFOA and PFOS) has been found in clothing, disposable food packaging, floor waxes, wood sealants,

paints, and other products with water-repellant or stain-repellant coatings.[62,63,65,66,329] A previous study found that soil tracked inside on people's shoes is not a major contributor to PFAS in

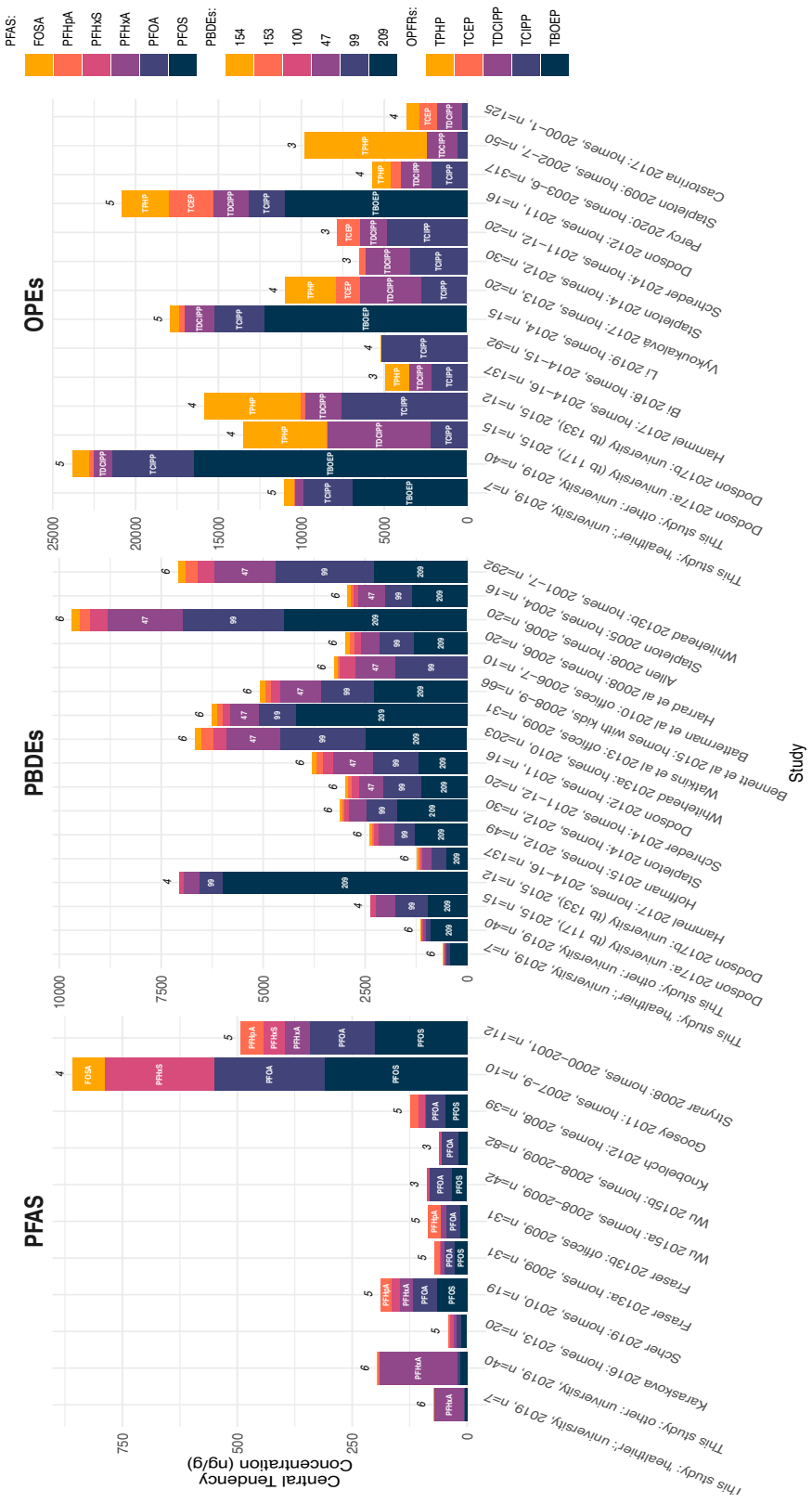

Figure 4.3. Central tendency concentrations (medians or geometric means) of select PFAS, PBDE, and OPE analytes (ng/g) in indoor dust in this study (the two bars on the left for full "healthier" spaces versus other spaces), compared to select previous studies of dust in the United States, sorted chronologically by sampling year.

Note: Numbers on top of stacked bars indicate the number of the selected analytes that were measured in the study (a few studies did not measure all visualized chemicals).

indoor dust, as interior materials are the dominate sources.[364] Overall, the comparisons of our study to previous studies reflect the phase-out of legacy PFAS and the emerging substitution of other PFAS chemicals like PFHxA.

Polybrominated Diphenyl Ethers

We found suggestive evidence that PBDE levels in dust were 45% lower in rooms renovated with the full "healthier" materials intervention that those with only a partial intervention. BDE-209 was the congener detected at the highest geometric mean concentrations by far and with the highest absolute reduction due to the full "healthier" materials intervention, which reflects its relatively recent phase-out by manufacturers a decade after the other measured PBDEs.

The PBDE dust concentrations were significantly higher in rooms with high bromine loadings from foam furniture compared to rooms with low loadings, indicating that upholstered foam furniture is indeed an important source of flame retardants. The XRF measurements of products in the studied rooms also verified that there were very low levels of bromine, a surrogate for PBDEs, in most "healthier" furniture specified by manufacturers to be free of all flame retardants for the intervention. In fact, the foam furniture meeting the historic, most stringent flammability standard (TB 133) had substantially higher bromine levels than the "healthier" furniture. Similarly, the "healthier" carpet specified as FR-free had significantly lower bromine levels than the conventional carpet. The mean bromine concentrations in "healthier" foam furniture and carpet in this study were lower than a few previous studies that employed XRF measurements.[36,155,157,158] The intervention on "healthier" furniture and carpet

specified as free of all flame retardants was associated with lower levels of a PBDE surrogate in the furniture and carpet as well as lower resulting levels of PBDEs in dust.

Other sources besides furniture and carpet likely contributed to the presence of PBDEs in dust, which motivates the need to continue developing interventions on other product categories. For one, plastic electronics like televisions in the studied rooms often had very high bromine levels compared to foam furniture. In addition, the rooms with high bromine loadings from electronics had higher PBDE levels in dust than those with low loadings. Electronics have often contained flame retardants in their plastic housings since the products operate at higher temperatures and can accumulate concentrated amounts of dust in small spaces.[366] Since PBDEs have been added to electronics as additive (not reactive) flame retardants, they are not covalently bound to the polymer and can migrate out of the product during normal use. For the very low-volatile congeners like BDE-209, the two major mechanisms of migration into dust are direct contact between the product and dust as well as physical abrasion and weathering of the product.[162,367,368]

The building itself, and the materials behind its walls, may be an important source of PBDE contamination, not just the furnishings inside it. PBDEs, especially BDE-209, have been historically used in polyurethane foam wall insulation, insulated hot water pipes, and other construction materials.[369,370] Although we may not have had enough statistical power to evaluate the impact of visibly exposed insulation (mostly hot water pipes) in six of the studied rooms on dust levels of PBDEs, we did measure high levels of bromine in the insulation that were comparable to concentrations in conventional foam furniture. In addition, we did not see a significant difference between the rooms with no intervention and the rooms that only had a partial intervention; PBDEs were only lower in dust in the spaces with a full intervention

("healthier" materials *and* either located in a newer building or not connected to adjacent conventional rooms). Furthermore, we found that 17% of the variability in log PBDE concentrations could be explained by differences across buildings as opposed to between different rooms within a building, suggesting that the building does play a role. By contrast, 0% was explained by between-building differences for OPEs, which are relatively newer substitute flame retardants.

The geometric mean PBDE levels in our dust samples from recently refurnished conventional or "healthier" buildings were substantially lower than most previous studies of dust in homes or offices in the United States (sampled between 2000 and 2015), reflecting the voluntarily reduction in manufacturing of these chemicals in the country (Figure 4.3).[22,23,375–377,27,33,207,348,371–374] However, in the two newly constructed buildings in our study that opened a few years after the 2013 phase-out of BDE-209, the dust concentrations were still detectable at up to 2,680 ng/g. So, there were residual PBDEs in even the newest buildings that theoretically should not be contaminated. Despite phase-outs, PBDEs may take some time to be replaced with new products in warehouse stocks, can persist in older buildings, and have re-entered the material resource stream through the recycling of older plastics.[120,121,243,370] Thus, these flame retardants will likely contaminate buildings and products at some level for years to come.

Organophosphate Esters

We found that OPEs in dust were significantly lower (65%) in spaces with the full "healthier" materials intervention than rooms with none. The presence of exposed insulation in the studied rooms was also significantly associated with OPE contamination in dust, and phosphorus-containing electronics in the rooms may be another contributing source too. Our

findings are supported by what we know of product sources of these chemicals. The main OPE chemicals present in the dust samples were TBOEP, TCIPP, TDCIPP, and TPHP, which are used as flame retardants in upholstered foam furniture, carpet, electronics, and/or building insulation.[25,34,241,242,35–38,159,221,227,240] The rooms with only a partial intervention did not significantly differ from those with no intervention, demonstrating the importance of cross-contamination of "healthier" single rooms from adjacent conventional spaces and/or the contributions from other materials besides FR-free foam furniture in partially renovated conventional rooms.

Phosphorus loadings from foam furniture in the rooms were not statistically significant predictors of OPE levels in dust. However, the intervention on "healthier" furniture (and carpet) did produce a significant reduction in OPEs in dust. In addition, the XRF product measurements did confirm that the "healthier" furniture items had relatively low levels of phosphorus. In fact, the conventional foam furniture items that met TB 117-2013 without the use of added flame retardants still had significantly higher levels of the phosphorus surrogate than the "healthier" furniture that was specified by manufacturers to not contain FRs. This difference could arise from the additional avoidance of polyvinyl chloride (and thus plasticizers) to at least below 1% in the "healthier" furniture. The conventional furniture meeting older, more stringent flammability standards did not have statistically higher phosphorus levels than the "healthier" foam furniture (except for the 'unlabeled' group), which is likely due to the historic preference towards PBDEs, which were only more recently substituted with OPEs. Furthermore, the mean (476 ppm) and maximum (4,830 ppm) XRF-measured phosphorus levels in the "healthier" foam furniture items were lower than were found in furniture by one previous study using an

Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OES) instrument (mean: 2,060; max: 8,830 ppm).[156]

We also may not have seen a statistically significant impact of phosphorus loadings from foam furniture on OPE dust levels because there are so many more product sources (with added flame retardants or plasticizers) than for PBDEs. This may also explain why the studied rooms had significantly higher OPE concentrations compared to previous studies of home indoor dust in the United States, although we studied non-residential buildings that may have higher densities of furniture and more recent renovations than many homes (Figure 4.3).[22,33,379,207,221,227,333,334,371,372,378] Compared to previous research of homes sampled between 2000 and 2015, our study did have lower geometric mean or median levels of TDCIPP, which has been suggested to be phased out in favor of TCIPP in foam products after TDCIPP was recently added as a carcinogen to California's Proposition 65 list.[35] TBOEP was the most dominant analyte in our study, and it may be a flame retardant substitute (or plasticizer) increasing in use, too. Although many prior studies did not measure TBOEP, median levels of TBOEP in dust in our studied rooms (median: 16,500; max: 118,000 ng/g), excluding the full "healthier" rooms, were higher than medians from three previous studies of dust in homes collected between 2011 and 2015 (medians: ND, 11,000, and 12,200; maxes: 51,100, 121,000, and 170,000 ng/g).[22,221,334] TBOEP is used in furniture, floor finishes, rubber, plastic, lacquers/paints, and wallpaper.[38,39,221,380]

Alternative Strategies to PFAS and Flame Retardants

Because these chemicals are usually non covalently bound additives, they can be removed as ingredients without sacrificing the functional integrity of the product. Also, the costs

of the furniture to the university were lower when chemical flame retardants were not added. There is even evidence that disputes the hypothesized effectiveness of using chemical flame retardants in furniture foam filling to protect against residential fires.[381–383] At the building level, public spaces often have extensive measures to protect against fires, including smoke detectors, smoking prohibitions, and sprinkler systems. At the ignition source level, cigarettes that self-extinguish after a few minutes and fire-safe candles can help prevent fires from starting.[381,383] At the furniture level, safer flame retardants, other filling materials, naturally fire-resistant fabrics (such as wool), and fire barriers between the fabric and foam filling have been investigated as alternative strategies.[381,382,384] One of the manufacturers that furnished the "healthier" carpet in this study reported to use aluminum hydroxide (ATH) as a non-halogenated mineral filler flame retardant to meet fire codes. ATH is generally thought to be safer than chemical flame retardants, although there are limited studies.[385] In fire scenarios, mineral fillers work by absorbing heat, producing inert water or carbon dioxide gases that help extinguish flames, building up a barrier on the surface of the decomposing product, and reducing the amount of filling that is combustible.[386]

The same carpet manufacturer also described their approach for eliminating PFAS for the studied university. To repel stains and soil, they make the nylon fibers cationic (positively charged) and alter the microscopic geometry so that the top of the nylon fiber loop partially flattens out. These were reported to be long-term stain-repellency properties that do not wear off over time. Water-repellant alternatives on the market may include paraffin, silicone, dendrimer, and polyurethane chemistries.[387] For any potential alternative solution, health risks should be carefully studied and balanced.

Strengths and Limitations

This is the first study to evaluate an intervention on "healthier" building materials without PFAS. A key strength was the university's holistic, class-based intervention to remove three classes of chemicals in a practical, scalable solution. Our thousands of portable XRF product measurements enabled us to assess the importance of different product categories based on bromine and phosphorus concentrations and to characterize sources of phosphorus for the first time.

There were a few limitations in this study. First, the "healthier" materials interventions did not address all products or building materials in a given room, occurred at different timings across the buildings, and were often conducted in rooms next to conventional spaces not renovated. Our categorization of rooms into no, partial, or full intervention helped capture some of the nuances. We also could not feasibly measure all the chemicals in each class, of which some could be used as unknown substitutes to legacy chemicals. Another limitation is that some OPEs can be used as plasticizers in addition to flame retardants, so we could not disentangle these separate OPE functions in the buildings. However, we did observe significant reductions in OPEs in dust due to the intervention that focused mainly on their elimination as flame retardants. In addition, the natural heterogeneity of dust could have limited the power of our statistical models to detect certain effects. For example, PBDEs in dust are spatially heterogenous, with higher levels closer to the product sources.[368] For the product scanning with XRF, phosphorus is not a perfect indicator of the amount of OPEs in one particular product, however, calculations of phosphorus loadings were useful for evaluating overall product sources in statistical models and how concentrations in furniture tend to vary by flammability standard. The XRF measurements of phosphorus and bromine not only capture the PBDE and OPE analytes we report in this study,

but also the unknown chemicals in those classes. This is an advantage of the technology, although it may have limited statistical power in our models to relate elements in products (including furniture and electronics) to the chemical analytes in dust. Other sources of phosphorus besides organophosphate esters and plasticizers include soil, pesticides, fertilizers, nerve agents, pharmaceuticals, industrial solvents, and fuel additives, but we do not expect these chemicals to significantly differ in furniture products or by intervention status in indoor dust.[388,389] Similarly, other sources of bromine besides PBDEs could include other brominated flame retardants (which should also be reduced in the intervention), biocides, fuel additives, pharmaceuticals, polymers, halons, rubber, and dyes,[390,391] but these should not significantly interfere with our results, and bromine has been shown to be highly correlated with FRs for indoor sources.[155] Although the flame retardant levels in a product would not necessarily be homogenous, we took averages of multiple XRF measurements on the products and then calculated categorical room-level loadings for furniture and electronics.

Conclusions

This study demonstrates the effectiveness of a chemical class-based "healthier" furniture and carpet intervention on reducing levels of PFAS and flame retardants in dust indoors. The scanning of products in situ in the studied rooms for element surrogates using XRF proved helpful to identify electronics and exposed insulated pipes as additional important sources of flame retardants in buildings. Future interventions should target more product categories and should consider strategies to limit the use of, or reduce occupant exposures to, legacy materials of the building. Overall, we observed significant indoor chemical reduction benefits from the use of "healthier" materials in buildings.

CHAPTER 5: Conclusions

The goal of this dissertation was to evaluate sources, exposures, and solutions for semi-volatile organic chemicals used in materials in office buildings. The dissertation findings emphasize the important role of the building in our indoor exposures to hormone-disrupting chemicals and demonstrate that real-world solutions to eliminate those chemicals in materials can lead to appreciable reductions in toxic chemical loads inside buildings.

Summary of Findings

In Study 1, the results of chemical exposure sampling of office workers in the USA, UK, India, and China demonstrated the complexity of limitations in regulatory and market approaches to chemical reductions. For example, we found that building occupants in the USA were still exposed to legacy PCBs that were banned 40 years ago and certain PBDEs that had been phased out 15 years ago, which highlights the long lifespan of buildings and the materials within buildings. In addition, PBDEs were not restricted as an entire chemical class, and we saw that there were higher exposures to DecaBDE in all four countries due to its later phase-outs (in the USA and UK) or lack of restrictions in most consumer products (in India and China). Another evident issue was that even though *intentional* PCB production has been banned or phased-out in all four countries, the office workers were frequently exposed to higher amounts of one PCB congener that has a contemporary, non-legacy source as a byproduct in pigments. Finally, we found ubiquitous exposures of the office workers to novel brominated flame retardants and OPEs that are unrestricted in these countries and that are known to be used as harmful substitutes to PBDE flame retardants (in addition to additional plasticizer uses for OPEs). The results of this chapter show the importance of building materials in occupant chemical exposures as well as the

difficulties in strategies to reduce those exposures. These findings urge action to reduce and replace harmful chemical additives in building materials as soon as possible, since these decisions will have lasting impacts on the health of building occupants for decades to come.

In Study 2, we took exposure assessment one step farther to evaluate the "health" of an indoor space and the influential role of chemicals. Specifically, we found that every indoor dust sample was hormonally active in human cell-based assays, and we observed the effects with very small amounts of dust – orders of magnitude less than the amount of dust people ingest on average in a day. The degrees of hormonal activity in the dust samples were influenced by concentrations of three classes of hormone-disrupting chemicals: PBDEs, OPEs, and PFAS. In human bodies, disruption of the action of estrogen receptor, androgen receptor, thyroid hormone receptor, PPARγ, and thyroid hormone transport can lead to reproductive, developmental, metabolic, and proliferative diseases.[244]

While Studies 1 and 2 demonstrated that office workers are exposed to building material chemicals that contribute to hormonally active dust inside buildings, Study 3 scientifically evaluated the benefits of an actual solution to reduce PBDEs, OPEs, and PFAS in building materials in a real-world setting. We found that "healthier" materials indeed substantially reduced chemicals in building dust. Our results also highlight the importance of next considering electronics, exposed insulation, other materials, and the building itself as important factors influencing indoor chemical loads.

Implications for Public Health

This dissertation demonstrates that there are beneficial, actionable solutions to improve the health of indoor environments and thus reduce exposures of building occupants to

hormonally active mixtures of chemicals from building materials. The findings emphasize the importance of addressing certain chemicals as an entire class and preemptively conducting health assessments of alternative chemical replacements in order to prevent the regrettable substitution of toxic chemicals for other similar toxic chemicals. Our results showed the benefits of interventions on flame-retardant and stain-repellant chemicals in furniture and carpet, but we will also need continued innovations in practical solutions for other types of building materials and other types of harmful chemicals, too. We must consider multi-faceted strategies not only to eliminate the use of harmful chemicals in materials in new construction, but also to intervene on and reduce occupant exposures to pre-existing materials in current buildings. The urgency to make healthier choices on building materials and consumer products is heightened by the fact that so-called forever chemicals, including many PFAS, will never break down under environmental conditions.[4,99,125] As documented in Study 1, phased-out chemicals still expose people in buildings decades after action was taken to eliminate them. In fact, half of the office buildings in the USA are estimated to be constructed before the PCB ban 40 years ago,[170] so large reservoirs of old building materials persist in many of our indoor environments for decades. The decisions we enact today impact the chemical exposures and health of generations to come, and we should make healthier material solutions the default for buildings.

Recommendations for Future Research

This dissertation advances multiple methodologic approaches to chemical exposure assessment research, and we offer several recommendations for future studies. Study 1 highlights the utility of silicone wristband personal samplers to more precisely determine indoor chemical exposures in specific microenvironments of interest, such as office buildings. This method could

be applied in future studies to other vulnerable populations in workplaces or homes. Furthermore, the silicone wristbands are simple, non-invasive, and stable in shipment, which can facilitate the remote sampling for very large sample sizes across the world. This advantage would be useful for further research we need on chemical exposures in vastly understudied low- and middle-income countries. As we saw in Study 1, office workers in China and India had substantially different exposures to certain chemicals than the USA and UK, probably at least partially related to differences in chemical restrictions and product flammability regulations. Although there are over a dozen published studies about silicone wristband samples, we also need more research about 1) thresholds of chemical concentrations in the wristbands that would be considered harmful to health, and 2) experimental estimates of the different uptake efficiencies of chemicals into the silicone material based on physical-chemical properties so that we can make informed comparisons of concentrations across different chemicals.

Study 2 demonstrates the importance of cell-based assays of indoor dust to better capture the chemical-related "health" of a building without expensive, multi-year human epidemiologic studies. Although this study measured many assay endpoints and many chemical classes in dust samples, future studies could expand on this even more to include other human cell impacts (including on other hormone receptors) and other hormone-disrupting chemicals (including phthalate and bisphenol plasticizers). In addition, even larger sample sizes of dust would enable statistical evaluations of the impact of building factors on the hormonal activities of dust. Study 2 also emphasizes the importance of high-throughput chemical screening data for synthesizing information on the potency *and* amount of a chemical in dust to better investigate associations between chemical components and dust potencies, which we recommend for any future studies of assays of dust to address. We should also continue to conduct high-throughput screening on

more common hormone-disrupting chemicals to close the missing data gaps. Finally, we need further research to translate the levels of hormonal potencies of dust in human cell assays *in vitro* to the amount of hormone disruption that would actually occur in human bodies *in vivo*.

Study 3 presents the first study of a class-based intervention on PFAS and flame retardants in building materials. We recommend future research studies to scientifically evaluate the benefits of solutions for more product categories (such as electronics and exposed insulation) and more harmful substances (such as phthalates, bisphenols, antimicrobials, fly ash, and others). We also need more research to quantify the benefits of these building interventions on reducing human chemical exposures and health outcomes.

In conclusion, this dissertation found that buildings and their materials play an important role in our exposures to harmful chemicals, but that there are actionable solutions to reduce these chemicals indoors. The decisions we make today on healthier materials in buildings can either harm or enhance the health of generations to come.

CHAPTER 6: Supplementary Materials

Table 6.1. Summary of percent detects (shaded) and concentrations (ng per g wristband, standardized to 32 hours of sampling) of chemical analytes in wristbands worn by 130 office workers in the USA, UK, China, and India.

	Geometric Mean (Geometric Standard Deviation) [Range]				
Abbreviation	**All**	**USA**	**UK**	**China**	**India**
Polychlorinated biphenyls					
PCB-28	0.0596 (4.4) [<0.06, 8.74]	0.11 (6.4) [<0.06, 8.74]	0.0474 (2.8) [<0.06, 0.651]	<0.06 (1) [<0.06, <0.06]	<0.06 (1) [<0.06, <0.06]
PCB-47	0.00684 (2.6) [<0.01, 0.58]	0.0088 (3.3) [<0.01, 0.483]	0.00527 (1.3) [<0.01, 0.0202]	0.00732 (4) [<0.01, 0.58]	<0.01 (1) [<0.01, <0.01]
PCB-51	0.0051 (1.3) [<0.01, 0.0566]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	0.00612 (2.1) [<0.01, 0.0566]	<0.01 (1) [<0.01, <0.01]
PCB-52	0.00847 (4.4) [<0.01, 3.27]	0.0133 (7.2) [<0.01, 3.27]	0.00632 (2.3) [<0.01, 0.099]	<0.01 (1) [<0.01, <0.01]	0.0055 (1.7) [<0.01, 0.105]
PCB-68	0.00533 (1.5) [<0.01, 0.251]	0.00547 (1.7) [<0.01, 0.251]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	0.00546 (1.6) [<0.01, 0.064]
PCB-11	0.166 (5.3) [<0.04, 3.65]	0.0702 (3.6) [<0.04, 0.607]	0.143 (5.9) [<0.04, 3.65]	0.508 (3) [<0.04, 1.3]	0.642 (3.7) [<0.04, 2.75]
PCB-101	0.0117 (6) [<0.01, 4.89]	0.0249 (9.7) [<0.01, 4.89]	0.00636 (2.3) [<0.01, 0.0915]	<0.01 (1) [<0.01, <0.01]	0.00615 (2.2) [<0.01, 0.209]
PCB-118	0.00698 (3.2) [<0.01, 2.25]	0.00892 (4.7) [<0.01, 2.25]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	0.0065 (2.3) [<0.01, 0.146]
PCB-138	0.00629 (2.5) [<0.01, 0.985]	0.00782 (3.6) [<0.01, 0.985]	0.00556 (1.7) [<0.01, 0.0755]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]
PCB-153	0.00624 (2.6) [<0.01, 1.75]	0.00773 (3.9) [<0.01, 1.75]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	0.00538 (1.5) [<0.01, 0.052]
PCB-183	0.00535 (1.8) [<0.01, 2.59]	0.00577 (2.3) [<0.01, 2.59]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]
Brominated flame retardants					
BDE-28	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]
BDE-47	0.374 (8.8) [<0.1, 19.6]	2.74 (4.4) [<0.1, 19.6]	0.0843 (2.5) [<0.1, 1.09]	<0.1 (1) [<0.1, <0.1]	<0.1 (1) [<0.1, <0.1]
BDE-66	0.00523 (1.4) [<0.01, 0.0587]	0.0055 (1.7) [<0.01, 0.0587]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]
BDE-85	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]
BDE-99	0.0768 (22) [<0.01, 23.6]	1.07 (11) [<0.01, 23.6]	0.0151 (5.6) [<0.01, 1.27]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]
BDE-100	0.0109 (5.3) [<0.01, 3.36]	0.0265 (8.3) [<0.01, 3.36]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]
BDE-153	0.00621 (2.7) [<0.01, 1.58]	0.00794 (4.2) [<0.01, 1.58]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]
BDE-154	0.00565 (2) [<0.01, 0.436]	0.00615 (2.6) [<0.01, 0.436]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	0.00555 (1.8) [<0.01, 0.154]
BDE-183	0.00603 (2.9) [<0.01, 4.91]	0.00611 (3) [<0.01, 2.88]	0.00601 (2.5) [<0.01, 0.548]	<0.01 (1) [<0.01, <0.01]	0.00636 (3.8) [<0.01, 4.91]
BDE-209	3.82 (3.5) [<2, 97.4]	2.45 (3.1) [<2, 97.4]	8.8 (3.3) [<2, 59.7]	3.18 (2.9) [<2, 12.2]	5.06 (3.2) [<2, 31.7]
BEHTBP	6.97 (5.5) [<0.06, 691]	12.8 (3) [1.7, 691]	8.74 (5.1) [<0.06, 285]	1.43 (11) [<0.06, 54.7]	3.4 (6) [<0.06, 82.3]
DBDPE	0.906 (2.8) [<1, 48.6]	0.839 (2.4) [<1, 11]	1.35 (3.9) [<1, 29.3]	1.1 (4.1) [<1, 48.6]	0.707 (2.3) [<1, 14.2]
EHTBB	0.161 (61) [<0.01, 2550]	5.68 (23) [<0.01, 2550]	0.00985 (6.6) [<0.01, 2.1]	<0.01 (1) [<0.01, <0.01]	0.00594 (2.6) [<0.01, 0.896]
Organophosphate esters					
24DIPPDPP	0.946 (3.1) [<1, 109]	0.903 (2.9) [<1, 48.7]	0.996 (3.8) [<1, 109]	2.19 (5.5) [<1, 38.3]	0.699 (1.8) [<1, 14.3]
2IPPDPP	6.17 (10) [<0.01, 1220]	9.51 (6) [<0.01, 239]	19.9 (4.1) [1.23, 1220]	5.24 (17) [0.115, 231]	1.1 (16) [<0.01, 225]
2tBPDPP	0.00386 (1.6) [<0.007, 0.244]	0.00377 (1.5) [<0.007, 0.0849	0.00395 (1.6) [<0.007, 0.0183	<0.007 (1) [<0.007, <0.007]	0.0041 (2.1) [<0.007, 0.244]
3IPPDPP	0.148 (5.9) [<0.1, 35.3]	0.185 (6.4) [<0.1, 35.3]	0.207 (6.8) [<0.1, 24.3]	0.264 (11) [<0.1, 23.3]	<0.1 (1) [<0.1, <0.1]
4IPPDPP	1.49 (10) [<0.05, 271]	2.98 (4.1) [<0.05, 70]	3.44 (7.3) [<0.05, 271]	1.5 (21) [<0.05, 83.1]	0.194 (12) [<0.05, 59.6]
4tBPDPP	0.795 (12) [<0.03, 143]	3.25 (4.2) [<0.03, 98]	1.02 (5.3) [<0.03, 15]	0.0689 (7) [<0.03, 2.96]	0.114 (15) [<0.03, 143]
B24DIPPPP	0.383 (1.6) [<0.7, 19]	<0.7 (1) [<0.7, <0.7]	<0.7 (1) [<0.7, <0.7]	0.642 (4.1) [<0.7, 19]	<0.7 (1) [<0.7, <0.7]
B2IPPPP	0.228 (30) [<0.01, 351]	0.381 (18) [<0.01, 42.6]	1.19 (24) [<0.01, 351]	0.488 (100) [<0.01, 198]	0.0158 (13) [<0.01, 32]
B2tBPPP	0.0158 (1.1) [<0.03, 0.0634]	<0.03 (1) [<0.03, <0.03]	0.0165 (1.3) [<0.03, 0.0634]	<0.03 (1) [<0.03, <0.03]	<0.03 (1) [<0.03, <0.03]
B3IPPPP	0.00531 (1.6) [<0.01, 0.573]	<0.01 (1) [<0.01, <0.01]	0.00604 (2.6) [<0.01, 0.573]	0.00632 (2.3) [<0.01, 0.118]	<0.01 (1) [<0.01, <0.01]
B4IPPPP	0.0259 (11) [<0.01, 44.3]	0.0226 (9.2) [<0.01, 6.4]	0.055 (15) [<0.01, 44.3]	0.135 (34) [<0.01, 24.9]	0.00918 (4.3) [<0.01, 3.64]
B4tBPPP	0.104 (25) [<0.01, 87.7]	0.423 (21) [<0.01, 87.7]	0.0785 (18) [<0.01, 13.8]	0.00778 (4.9) [<0.01, 1.97]	0.0245 (21) [<0.01, 72.3]
EHDPP	15.1 (3.5) [<0.03, 543]	13.3 (2.5) [1.58, 179]	33.6 (2.6) [4.02, 189]	10.1 (2.3) [2.35, 50.3]	12 (6.2) [<0.03, 543]
T3IPPP	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]
T4IPPP	0.00576 (2.6) [<0.01, 5.77]	<0.01 (1) [<0.01, <0.01]	0.00662 (4.1) [<0.01, 5.77]	0.0119 (9.1) [<0.01, 5.57]	<0.01 (1) [<0.01, <0.01]
T4tBPP	0.00829 (5.2) [<0.01, 14.1]	0.00865 (5.7) [<0.01, 14.1]	0.00625 (3) [<0.01, 1.32]	<0.01 (1) [<0.01, <0.01]	0.0119 (7.9) [<0.01, 5.02]
TCEP	0.496 (11) [<0.03, 37.6]	0.328 (11) [<0.03, 28.1]	0.65 (11) [<0.03, 37.6]	4.5 (3.6) [0.273, 21.4]	0.357 (13) [<0.03, 22.5]
TCIPP	106 (6.1) [<0.8, 9260]	76 (2.3) [13.1, 1480]	2070 (2.1) [269, 9260]	49.9 (2) [12.4, 218]	25.3 (4.1) [<0.8, 407]
TDCIPP	15.7 (9.9) [<0.01, 25500]	39.5 (3.2) [1.46, 525]	38.4 (7.4) [3.8, 25500]	5.23 (2.5) [0.89, 18.1]	1.98 (20) [<0.01, 108]
TDMPP	0.00682 (3.6) [<0.01, 9.35]	0.00615 (2.7) [<0.01, 2.62]	0.00646 (3.6) [<0.01, 3.07]	0.0259 (16) [<0.01, 9.35]	<0.01 (1) [<0.01, <0.01]
TEHP	6.85 (4) [<0.09, 501]	8.29 (3.6) [0.337, 501]	8.66 (3.1) [1.04, 418]	6.57 (3.3) [0.687, 50.3]	3.96 (5.5) [<0.09, 27.3]
TEP	1.75 (2.7) [<2, 118]	1.55 (2.4) [<2, 49.3]	1.92 (3.6) [<2, 118]	2.41 (3.3) [<2, 24.4]	1.81 (2.3) [<2, 13.9]
TiBP	1.25 (3) [<1, 45.4]	1.29 (3.1) [<1, 45.4]	2.77 (3) [<1, 18.1]	0.916 (2) [<1, 5.86]	0.711 (2.2) [<1, 42.9]
TiPP	0.00524 (1.5) [<0.01, 0.0749]	<0.01 (1) [<0.01, <0.01]	0.00639 (2.4) [<0.01, 0.0749]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]
TmCP	0.00743 (3.8) [<0.01, 1.91]	0.0104 (6.1) [<0.01, 1.91]	0.00661 (2.7) [<0.01, 0.282]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]
TnBP	3.39 (3) [<3, 48.6]	5.39 (2.8) [<3, 48.6]	4.39 (3) [<3, 25.3]	1.55 (1.6) [<3, 5.14]	1.54 (2) [<3, 33.3]
ToCP	0.708 (1.6) [<1, 10.9]	0.683 (1.4) [<1, 8.24]	0.811 (2.1) [<1, 10.9]	<1 (1) [<1, <1]	0.705 (1.5) [<1, 8.75]
TpCP	41.5 (6.1) [<0.3, 2080]	43.1 (5.4) [<0.3, 722]	30.3 (5.2) [<0.3, 556]	38.8 (7.1) [0.692, 2080]	51.2 (8.3) [<0.3, 1260]
TPeP	0.00515 (1.4) [<0.01, 0.262]	0.00533 (1.6) [<0.01, 0.262]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]
TPHP	39.3 (3.4) [<0.05, 720]	47.5 (2.8) [1.46, 366]	38.9 (3) [2, 720]	28 (3) [4.72, 117]	31.3 (5.4) [<0.05, 619]
TPrP	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]	<0.01 (1) [<0.01, <0.01]

Table 6.2. Summary of concentrations (ng/g) of chemicals in indoor dust samples (n=47) overall and by healthier materials intervention status: none (n=12), partial (n=28), and full (n=7).

By intervention:	% Detected				Geometric Mean				Geometric Standard Deviation				Range			
Analyte	***All***	***None***	***Partial***	***Full***	***All***	***None***	***Partial***	***Full***	***All***	***None***	***Partial***	***Full***	***All***	***None***	***Partial***	***Full***
Sum of 15 PFAS	100	100	100	100	262	481	252	108	2.91	1.75	3.2	1.94	18.1–8310	225–1140	18.1–8310	43.6–243
PFHxA	97.9	100	96.4	100	146	326	127	64.3	4.25	1.80	5.2	2.78	<MDL–2980	164–788	<MDL–2980	10.0–216
PFOS	97.9	100	96.4	100	13.2	29.3	11.4	6.17	4.28	3.29	4.75	2.22	<MDL–296	6.30–296	<MDL–166	2.26–24.2
PFOA	74.5	83.3	75.0	57.1	5.62	11.6	6.25	1.07	11.7	8.98	13.1	6.57	<MDL–1520	<MDL–86.1	<MDL–1520	<MDL–8.50
PFHxS	63.8	75.0	67.9	28.6	0.672	1.43	0.751	0.117	12.5	14.1	11.0	10.3	<MDL–160	<MDL–160	<MDL–23.7	<MDL–3.78
FOSA	59.6	50.0	67.9	42.9	1.39	0.481	2.57	0.731	21.0	12.7	21.5	33.2	<MDL–236	<MDL–13.3	<MDL–236	<MDL–48.8
PFHpA	51.1	75.0	46.4	28.6	2.2	4.91	2.09	0.689	7.55	6.13	8.78	2.98	<MDL–1760	<MDL–54.4	<MDL–1760	<MDL–5.65
PFPeA	34.0	66.7	25.0	14.3	0.745	2.89	0.541	0.263	10.8	10.6	10.8	4.42	<MDL–455	<MDL–67.4	<MDL–455	<MDL–7.67
PFNA	31.9	41.7	25.0	42.9	0.93	1.79	0.712	0.882	13.3	18.0	13.5	7.89	<MDL–1480	<MDL–150	<MDL–1480	<MDL–16.6
PFBS	31.9	41.7	35.7	0	0.159	0.241	0.181	0.045	6.83	8.64	7.18	1	<MDL–16.1	<MDL–7.91	<MDL–16.1	<MDL–<MDL
PFDS	12.8	25.0	10.7	0	0.048	0.0875	0.0417	0.03	3.76	8.11	2.68	1	<MDL–12.5	<MDL–12.5	<MDL–1.14	<MDL–<MDL
PFBA	4.26	0	7.14	0	0.746	<MDL	0.864	<MDL	2.85	1	3.84	1	<MDL–155	<MDL–<MDL	<MDL–155	<MDL–<MDL
PFDA	4.26	0	3.57	14.3	0.355	<MDL	0.356	0.471	2.28	1	2.46	3.3	<MDL–35.0	<MDL–<MDL	<MDL–35.0	<MDL–7.08
PFUnDA	0	0	0	0	<MDL	<MDL	<MDL	<MDL	1	1	1	1	<MDL–<MDL	<MDL–<MDL	<MDL–<MDL	<MDL–<MDL
PFDoDA	0	0	0	0	<MDL	<MDL	<MDL	<MDL	1	1	1	1	<MDL–<MDL	<MDL–<MDL	<MDL–<MDL	<MDL–<MDL
N-MeFOSAA	0	0	0	0	<MDL	<MDL	<MDL	<MDL	1	1	1	1	<MDL–<MDL	<MDL–<MDL	<MDL–<MDL	<MDL–<MDL
Sum of 8 PBDEs	100	100	100	100	1280	1360	1390	839	2.33	2.22	2.52	1.66	179–14200	452–5930	179–14200	414–1570
BDE-209	100	100	100	100	800	881	899	427	3.19	2.56	3.36	3.47	34.8–13000	171–5410	34.8–13000	52.9–1400
BDE-99	100	100	100	100	120	138	124	82	2.14	2.13	1.98	2.84	10.6–734	40.1–734	25.7–639	10.6–291
BDE-47	100	100	100	100	63.7	88	62.7	39.1	2.31	2.81	1.92	2.75	6.55–1470	23.6–1470	13.0–238	6.55–127
BDE-100	100	100	100	100	27.1	33.4	26.7	20.4	1.85	2.11	1.8	1.46	6.12–202	13.3–202	6.12–124	12.9–34.1
BDE-183	89.4	91.7	89.3	85.7	19.4	19.9	21.9	11.3	6.23	4.94	7.00	6.54	<MDL–817	<MDL–87.9	<MDL–817	<MDL–46.2
BDE-28	89.4	100	85.7	85.7	2.8	7.48	2.62	0.674	6.91	2.85	8.38	4.11	<MDL–104	1.98–104	<MDL–93.7	<MDL–3.55
BDE-153	85.1	83.3	82.1	100	10.5	12.8	8.61	17.1	5.64	7.01	6.32	1.48	<MDL–78.5	<MDL–68.0	<MDL–78.5	9.53–27.8
BDE-154	80.9	75.0	78.6	100	5.34	3.55	5.99	6.81	5.96	6.39	7.04	2.06	<MDL–53.5	<MDL–17.8	<MDL–53.5	2.04–21.3
	100	100	100	100	30700	30400	37500	14000	2.06	1.62	2.07	1.74	6760–182000	13400–60300	10300–182000	6760–30900
TBOEP	100	100	100	100	14500	20000	15200	6940	2.70	1.88	2.84	2.83	1250–118000	8320–51200	1390–118000	1250–25400
TCIPP	100	100	100	100	4530	3130	5920	2930	3.50	2.24	4.33	1.84	675–139000	946–13300	675–139000	1100–6030
TDCIPP	100	100	100	100	1030	1140	1170	518	2.06	1.57	2.14	1.91	220–6440	673–2520	223–6440	220–1310
TPHP	100	100	100	100	927	1260	901	614	2.31	2.23	2.38	1.96	238–10600	473–6670	238–10600	264–1590
TCEP	100	100	100	100	203	475	209	41.6	4.06	2.33	3.66	3.83	2.31–3170	114–1470	2.31–3170	2.71–112
EHDPP	100	100	100	100	164	254	198	36.8	3.36	2.77	2.65	4.03	4.65–2480	26–2480	48.1–2210	4.65–174
IDDP	100	100	100	100	87.2	148	85.3	38.2	2.95	1.68	2.46	6.39	0.699–612	70.9–459	10.9–612	0.699–131
TIBP	100	100	100	100	35.7	27.3	38.9	39.8	2.58	2.64	2.16	4.55	5.28–804	7.32–128	5.28–259	6.28–804
TPP	100	100	100	100	10.8	8.19	12.1	11	2.42	2.77	2.40	1.96	1.52–63.3	2.29–44.7	1.52–63.3	4.26–23.3
CDPP	97.9	100	96.4	100	217	280	225	119	5.10	3.13	7.03	1.70	<MDL–11500	63.2–3740	<MDL–11500	47.2–244
BPDP	97.9	100	96.4	100	72.1	149	63.1	35.6	3.56	1.85	3.99	3.15	<MDL–371	57.5–371	<MDL–324	5.57–170
TNBP	97.9	100	96.4	100	42.2	40.5	40.8	51.8	3.74	1.98	4.98	2.50	<MDL–1060	16.4–117	<MDL–1060	19.9–239
V6	95.7	100	92.9	100	21.4	41.5	18.9	11.2	3.47	2.68	3.82	2.12	<MDL–216	7.46–158	<MDL–216	5.08–48.6
BDP	93.6	91.7	96.4	85.7	19.2	22.7	20.1	12.1	4.82	7.88	3.30	8.23	<MDL–494	<MDL–494	<MDL–104	<MDL–56.8
RDP	91.5	75.0	96.4	100	32.1	12.2	42.5	54.6	6.22	8.98	5.59	2.52	<MDL–3270	<MDL–81.1	<MDL–3270	19.5–173
TEHP	91.5	91.7	92.9	85.7	25.1	35.3	29.6	7.16	7.55	6.98	7.08	9.33	<MDL–1680	<MDL–273	<MDL–1680	<MDL–51.8
TMPP	91.5	100	85.7	100	21.5	36.9	18.5	15.4	6.44	1.98	10.2	2.16	<MDL–486	16–127	<MDL–486	6.33–57.6
TEP	61.7	50.0	60.7	85.7	5.01	1.98	5.18	21.4	15.9	13.3	17.8	9.29	<MDL–416	<MDL–151	<MDL–416	<MDL–168
TBPHP	19.1	33.3	17.9	0	0.609	0.915	0.568	<MDL	2.47	3.56	2.18	1	<MDL–10.7	<MDL–10.7	<MDL–5.26	<MDL–<MDL

Table 6.3. Summary of concentrations (ng/g) of chemicals in indoor dust samples (n=47) by room type.

Analyte	Geometric Mean (Geometric Standard Deviation)				Median [Range]			
	All Samples	**Office Suites**	**Classrooms**	**Common Areas**	**All Samples**	**Office Suites**	**Classrooms**	**Common Areas**
	n=47	*n=6*	*n=18*	*n=23*	*n=47*	*n=6*	*n=18*	*n=23*
Sum of 15 PFAS	262 (2.91)	685 (4.04)	215 (2.19)	238 (2.97)	273 [18.1-8310]	590 [192-8310]	207 [53.9-1750]	317 [18.1-1140]
PFBS	0.159 (6.83)	0.211 (12.4)	0.14 (6.86)	0.162 (6.27)	<MDL [<MDL-16.1]	<MDL [<MDL-16.1]	<MDL [<MDL-7.91]	<MDL [<MDL-4.97]
PFHxS	0.672 (12.5)	0.313 (13.3)	0.753 (12)	0.751 (13.7)	1.88 [<MDL-160]	1.07 [<MDL-5.53]	2.03 [<MDL-14.9]	1.88 [<MDL-160]
PFOS	13.2 (4.28)	40.2 (2.5)	11.4 (2.9)	11.1 (5.6)	16.1 [<MDL-296]	24.6 [19-160]	10.6 [2.26-166]	11.1 [<MDL-296]
PFDS	0.048 (3.76)	0.03 (1)	0.0478 (3)	0.0544 (5.1)	<MDL [<MDL-12.5]	<MDL [<MDL-<MDL]	<MDL [<MDL-1.14]	<MDL [<MDL-12.5]
FOSA	1.39 (21)	0.167 (7.76)	2.28 (20.8)	1.64 (23)	3.08 [<MDL-236]	<MDL [<MDL-3.44]	8.58 [<MDL-98.7]	4.78 [<MDL-236]
PFHxA	146 (4.25)	436 (3.1)	109 (5.14)	138 (3.58)	204 [<MDL-2980]	344 [145-2980]	156 [<MDL-971]	216 [10-783]
PFHpA	2.2 (7.55)	11.7 (19.2)	1.24 (5.94)	2.23 (5.78)	1.46 [<MDL-1760]	6.48 [<MDL-1760]	<MDL [<MDL-49.3]	3.72 [<MDL-46.5]
PFOA	5.62 (11.7)	22.6 (20.6)	3.45 (9.92)	5.72 (11.2)	8.5 [<MDL-1520]	29.1 [<MDL-1520]	4.69 [<MDL-229]	20.5 [<MDL-150]
PFNA	0.93 (13.3)	4.84 (51.3)	0.859 (14)	0.643 (7.73)	<MDL [<MDL-1480]	5.09 [<MDL-1480]	<MDL [<MDL-215]	<MDL [<MDL-47.7]
PFDA	0.355 (2.28)	<MDL (1)	<MDL (1)	0.423 (3.21)	<MDL [<MDL-35]	<MDL [<MDL-<MDL]	<MDL [<MDL-<MDL]	<MDL [<MDL-35]
PFUnDA	<MDL (1)	<MDL (1)	<MDL (1)	<MDL (1)	<MDL [<MDL-<MDL]	<MDL [<MDL-<MDL]	<MDL [<MDL-<MDL]	<MDL [<MDL-<MDL]
PFDoDA	<MDL (1)	<MDL (1)	<MDL (1)	<MDL (1)	<MDL [<MDL-<MDL]	<MDL [<MDL-<MDL]	<MDL [<MDL-<MDL]	<MDL [<MDL-<MDL]
PFBA	0.746 (2.85)	<MDL (1)	0.777 (3)	0.764 (3.18)	<MDL [<MDL-155]	<MDL [<MDL-<MDL]	<MDL [<MDL-63.2]	<MDL [<MDL-155]
PFPeA	0.745 (10.8)	8.69 (27.6)	0.522 (8.19)	0.519 (7.43)	<MDL [<MDL-455]	25.1 [<MDL-455]	<MDL [<MDL-32.3]	<MDL [<MDL-54.8]
N-MeFOSAA	<MDL (1)	<MDL (1)	<MDL (1)	<MDL (1)	<MDL [<MDL-<MDL]	<MDL [<MDL-<MDL]	<MDL [<MDL-<MDL]	<MDL [<MDL-<MDL]
Sum of 8 PBDEs	1280 (2.33)	741 (1.89)	1530 (2.18)	1290 (2.49)	1180 [179-14200]	628 [452-2490]	1270 [617-12900]	1180 [179-14200]
BDE.28	2.8 (6.91)	3.62 (10.4)	3.25 (8.08)	2.32 (5.85)	3.56 [<MDL-104]	8.1 [<MDL-35.3]	3.98 [<MDL-93.7]	2.53 [<MDL-104]
BDE.47	63.7 (2.31)	53 (1.8)	59.1 (2.02)	71 (2.7)	60.7 [6.55-1470]	48.8 [23.6-112]	60.9 [6.55-170]	74.1 [13-1470]
BDE.99	120 (2.14)	137 (2.38)	113 (2.01)	121 (2.25)	121 [10.6-734]	129 [40.1-437]	127 [10.6-272]	115 [25.7-734]
BDE.100	27.1 (1.85)	22.2 (1.5)	26.7 (1.51)	29 (2.18)	26.9 [6.12-202]	21 [13.3-37]	27.2 [12.9-61.1]	26.7 [6.12-202]
BDE.153	10.5 (5.64)	8.74 (6.12)	7.5 (7.11)	14.4 (4.6)	19.2 [<MDL-78.5]	19.5 [<MDL-21.9]	18.3 [<MDL-46]	20.2 [<MDL-78.5]
BDE.154	5.34 (5.96)	2.26 (7.66)	4.11 (8.47)	8.2 (3.75)	10.2 [<MDL-53.5]	5.31 [<MDL-17.6]	9.18 [<MDL-53.5]	12.3 [<MDL-37.5]
BDE.183	19.4 (6.23)	70.9 (2.69)	15.3 (3.53)	16.6 (9.4)	23.4 [<MDL-817]	51.6 [33.9-466]	19.5 [<MDL-71.4]	23.4 [<MDL-817]
BDE.209	800 (3.19)	315 (3.07)	1140 (2.57)	773 (3.41)	827 [34.8-13000]	381 [52.9-1360]	958 [347-12700]	827 [34.8-13000]
Sum of 19 OPFRs	30700 (2.06)	20400 (1.73)	31100 (1.88)	33800 (2.26)	28700 [6760-182000]	20500 [10500-50900]	32000 [8090-134000]	28700 [6760-182000]
TEP	5.01 (15.9)	1.35 (20.5)	2.87 (19.2)	10.9 (11.2)	16.6 [<MDL-416]	<MDL [<MDL-168]	1.08 [<MDL-283]	28.8 [<MDL-416]
TPP	10.8 (2.42)	14.5 (1.86)	10.7 (2.88)	10 (2.25)	10.7 [1.52-63.3]	12.7 [7.59-44.7]	11.1 [2.1-63.3]	10.3 [1.52-43.3]
TNBP	42.2 (3.74)	14.6 (17.9)	50.9 (1.9)	48.1 (2.82)	40.9 [<MDL-1060]	31.1 [<MDL-117]	46.5 [19.3-239]	39.5 [8.88-1060]
TIBP	35.7 (2.58)	24.2 (2.33)	44.3 (1.79)	33.3 (3.22)	32.3 [5.28-804]	17.2 [14-128]	41.6 [15.7-259]	29.8 [5.28-804]
TBOEP	14500 (2.7)	8020 (3.17)	12800 (2.71)	18600 (2.47)	15100 [1250-118000]	8660 [1390-43800]	16300 [1250-53800]	19100 [4240-118000]
TEHP	25.1 (7.55)	9.68 (30.9)	33.3 (2.7)	25.7 (8.94)	40.4 [<MDL-1680]	56.1 [<MDL-148]	40.6 [4.26-139]	40.1 [<MDL-1680]
TCEP	203 (4.06)	817 (2.94)	206 (2.88)	139 (4.56)	203 [2.31-3170]	1220 [104-1980]	287 [23.8-837]	159 [2.31-3170]
TCIPP	4530 (3.5)	2770 (1.61)	4710 (3.98)	5000 (3.66)	3330 [675-139000]	2650 [1320-4690]	2520 [946-119000]	4300 [675-139000]
TDCIPP	1030 (2.06)	1500 (1.84)	1040 (1.85)	917 (2.27)	948 [220-6440]	1420 [805-4120]	1050 [246-4040]	757 [220-6440]
TPHP	927 (2.31)	1510 (1.78)	1200 (2.35)	668 (2.17)	817 [238-10600]	1390 [818-3020]	1040 [264-6670]	579 [238-10600]
TMPP	21.5 (6.44)	17.5 (12.2)	39.7 (2.68)	14 (8.49)	29.2 [<MDL-486]	43.9 [<MDL-115]	34 [11.5-486]	23.5 [<MDL-356]
EHDPP	164 (3.36)	341 (4.79)	145 (3.31)	150 (3.06)	185 [4.65-2480]	203 [58.8-2480]	184 [15.6-1430]	189 [4.65-1040]
CDPP	217 (5.1)	37.4 (12.2)	433 (3.65)	199 (3.53)	214 [<MDL-11500]	84.7 [<MDL-245]	368 [47.2-7220]	169 [12.4-11500]
IDDP	87.2 (2.95)	103 (1.69)	86.4 (4.32)	84.1 (2.33)	88.3 [0.699-612]	101 [54.9-249]	95.2 [0.699-612]	83.7 [10.9-573]
BPDP	72.1 (3.56)	119 (2.28)	82.5 (2.27)	56.8 (4.94)	92 [<MDL-371]	105 [48.1-371]	83.4 [12.8-324]	92 [<MDL-301]
TBPHP	0.609 (2.47)	<MDL (1)	0.758 (3.03)	0.572 (2.26)	<MDL [<MDL-10.7]	<MDL [<MDL-<MDL]	<MDL [<MDL-10.7]	<MDL [<MDL-5.26]
RDP	32.1 (6.22)	72 (18.4)	32.2 (6.95)	25.9 (4)	33.5 [<MDL-3270]	91.5 [<MDL-3270]	43 [<MDL-1150]	19.5 [<MDL-312]
BDP	19.2 (4.82)	54.9 (4.56)	27.4 (1.9)	11.1 (6.69)	26 [<MDL-494]	49.6 [5.22-494]	23.8 [7.17-164]	19.7 [<MDL-104]
V6	21.4 (3.47)	18.1 (1.6)	27.3 (2.71)	18.5 (4.61)	23.2 [<MDL-216]	20.9 [7.59-27.6]	27.5 [5.08-216]	23.2 [<MDL-134]

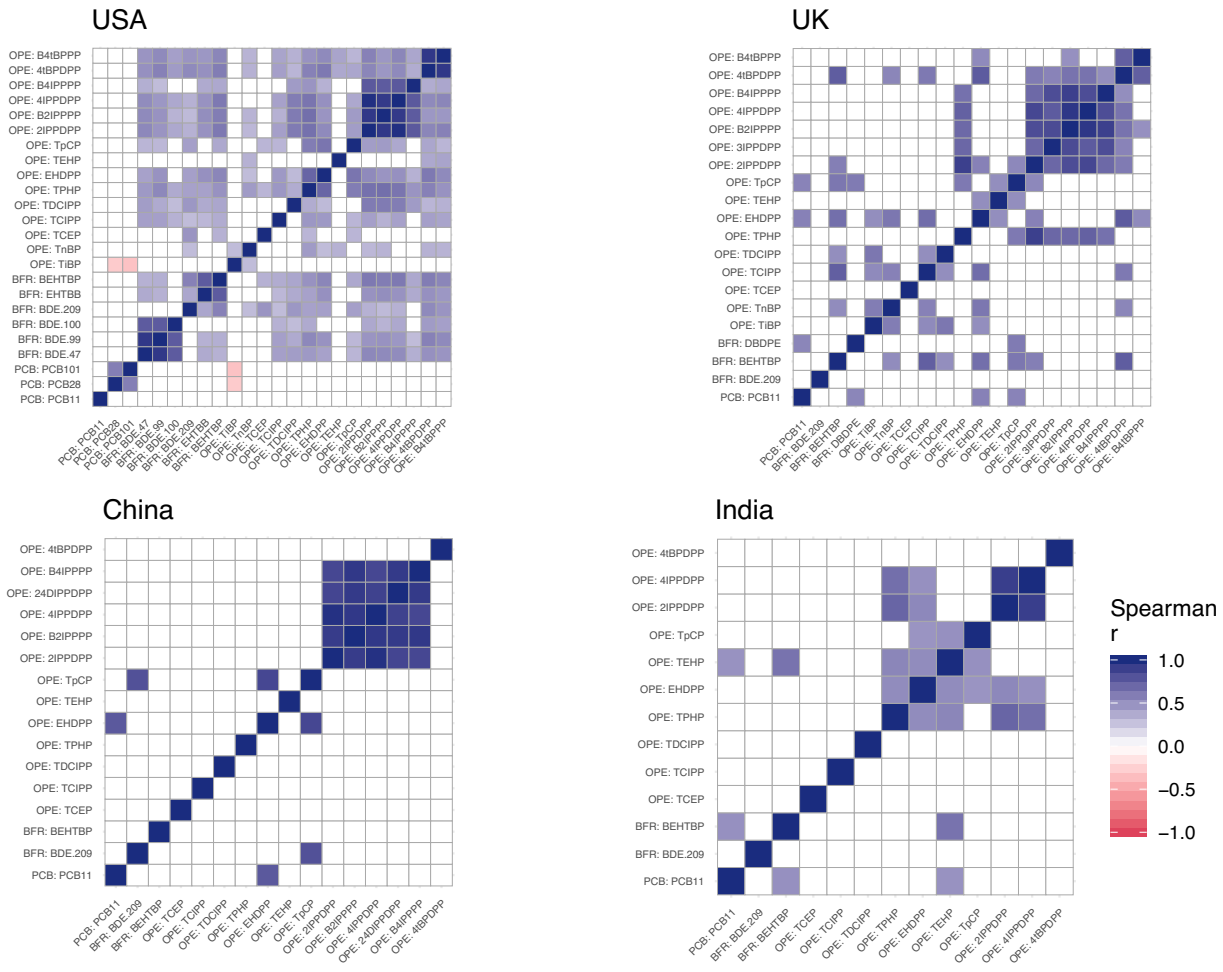

Figure 6.1. Spearman correlation coefficients for chemicals detected in at least one-third of silicone wristband samples by country (USA: n=61; UK: n=25; China: n=13; India: n=31), with only significant relationships presented based on the Benjamini-Hochberg procedure by country.

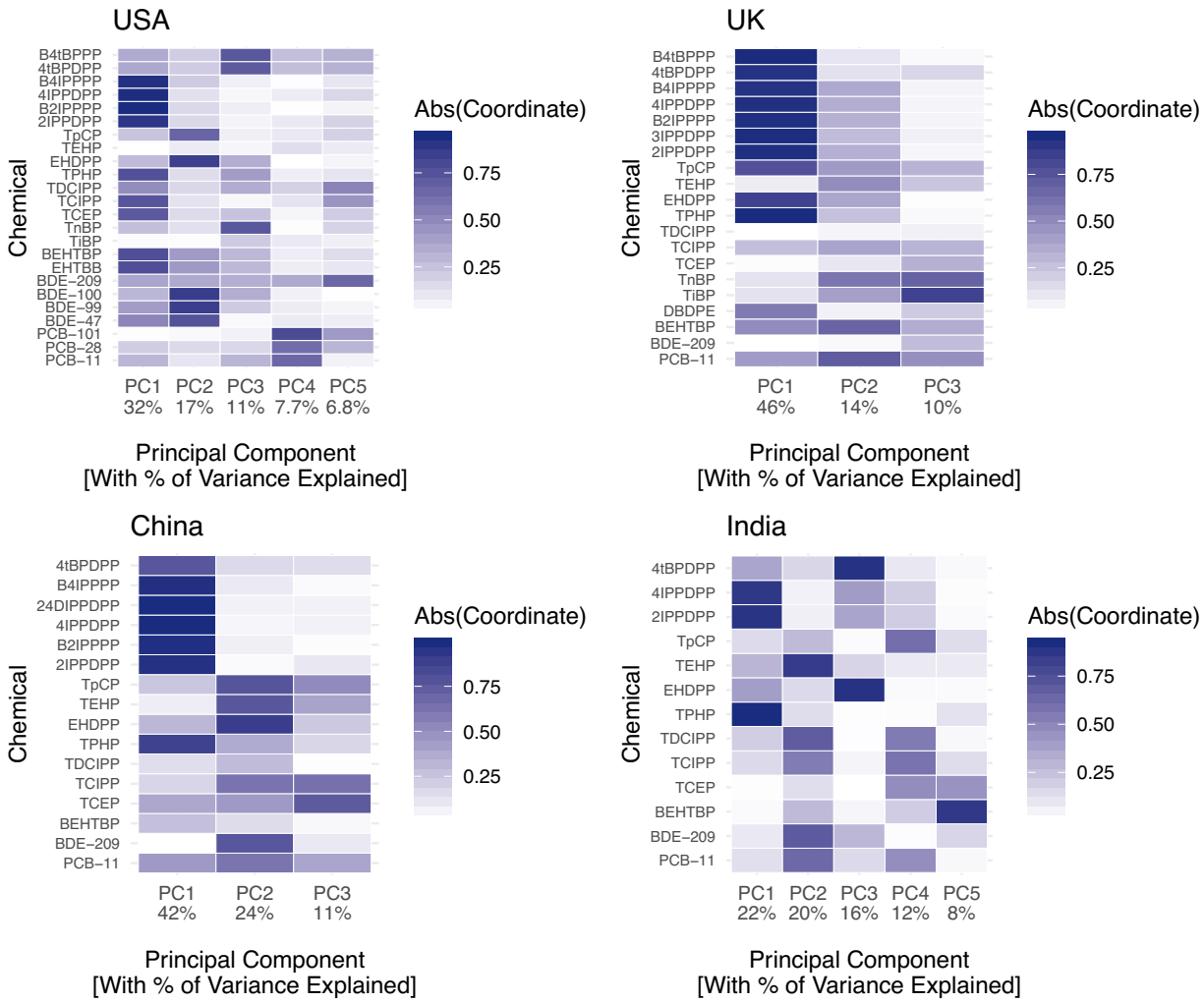

Figure 6.2. Contributions of chemicals in the principal components explaining over 70% of variance from analysis of analytes detected in over one-third of silicone wristband samples, by country (USA: n=61; UK: n=25; China: n=13; India: n=31).

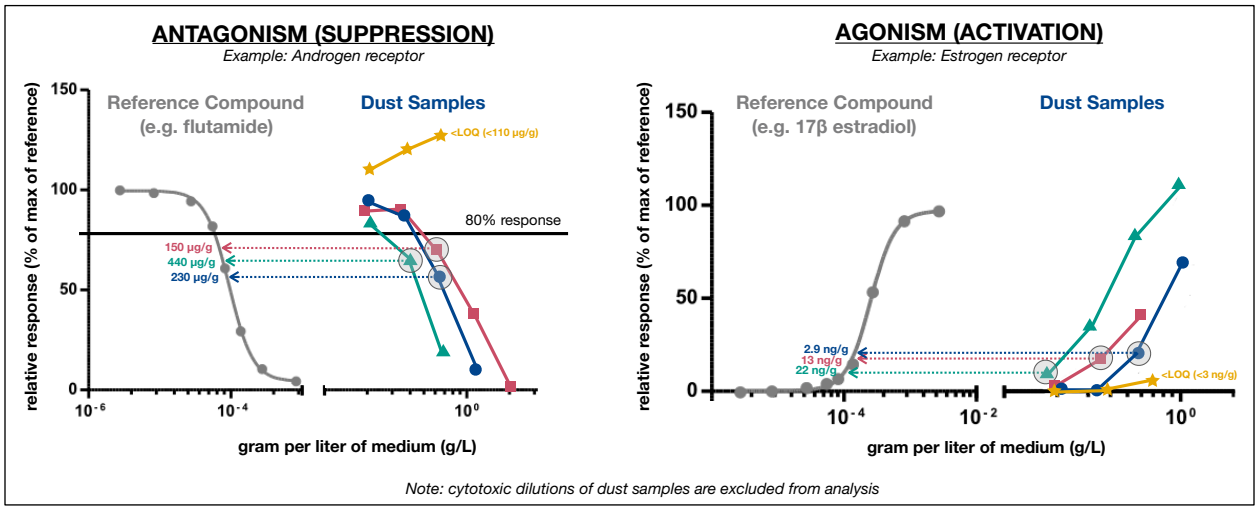

Figure 6.3. Methods used to calculate the hormonal activities (µg-eq/g) of dust samples in luciferase reporter gene assays for either a) antagonism, where the result is the ratio of the extrapolated equivalent reference compound concentration to the measured dust sample concentration at the sample's highest recorded relative response below 80%; or b) agonism, where the result is the ratio of the extrapolated reference compound concentration to the measured sample concentration at the sample's lowest recorded response above the limit of quantification (LOQ).

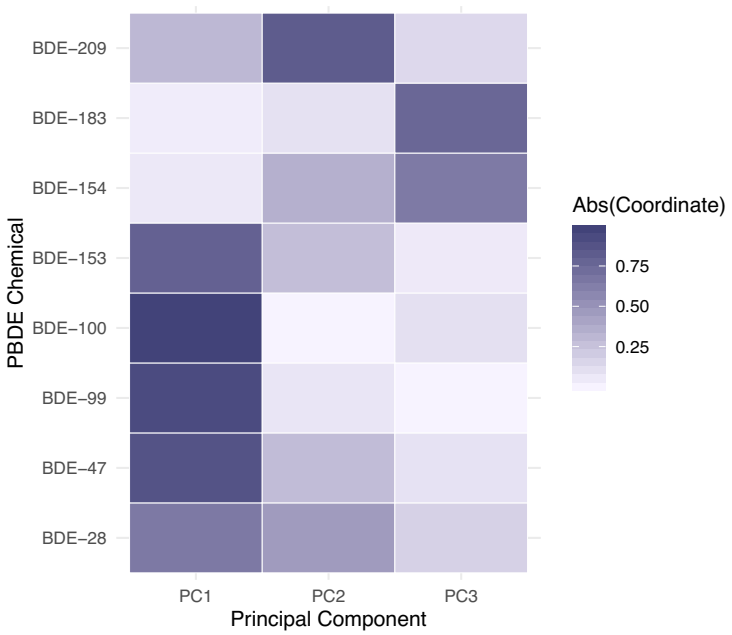

Figure 6.4. Results of principal component analysis of polybrominated diphenyl ether (PBDE) concentrations in indoor dust samples (n=47).

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