

AN ABSTRACT OF THE DISSERTATION OF

Carolyn M. Poutasse for the degree of Doctor of Philosophy in Toxicology presented on February 19, 2020.

Title: New Configurations of Silicone Passive Sampling Devices: Quantifying Feline and Firefighter Chemical Exposures

Abstract approved:

Kim A. Anderson

Silicone wristbands are passive sampling devices (PSD) that sequester bioavailable organic chemicals in the environment. In environmental health studies, silicone wristbands are easy to wear and can provide personal exposure data about complex chemical mixtures. This dissertation includes an overview of PSD technology, a literature review of current wristband research publications, and two original studies using new silicone PSD configurations to assess personal chemical exposures. For the first configuration, we designed the silicone pet tag for use on companion animals and demonstrated its use in a case-control study investigating feline hyperthyroidism. We determined that concentrations of the flame retardant tris(1,3-dichloro-2-isopropyl) phosphate (TDCIPP) were higher among pet tags worn by hyperthyroid compared to non-hyperthyroid cats, and we correlated TDCIPP pet tag concentrations with thyroid hormone levels in healthy cats. These results provided converging lines of evidence implicating TDCIPP flame retardant exposures as a risk factor for feline hyperthyroidism. For the second configuration, we developed the military-style silicone dog tag to wear around the neck and investigated occupational and non-occupational firefighter exposures to polycyclic aromatic hydrocarbons (PAHs), phthalates, and industrial-related chemicals. Of the 44 PAHs detected, this study was the first to identify personal firefighter exposures to 18 unique PAHs. We further determined that the dog tag

concentrations were higher for the on- compared to off-duty samples and at the high compared to the low call volume fire department. PAH concentrations were strongly correlated with the number of fire attacks a firefighter participated in during the sampling period, compared to firefighter rank and years in the fire service. This suggested that quantitative data, rather than job descriptions and other surrogate data, should be employed for future firefighter chemical exposure assessments. This dissertation demonstrated that silicone wristbands and silicone PSDs can be applied to epidemiological studies to investigate the links between chemical exposures and adverse health outcomes.

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New Configurations of Silicone Passive Sampling Devices:
Quantifying Feline and Firefighter Chemical Exposures

by
Carolyn M. Poutasse

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APPROVED:

Major Professor, representing Toxicology

Head of the Department of Environmental and Molecular Toxicology

Dean of the Graduate School

I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my dissertation to any reader upon request.

Carolyn M. Poutasse, Author

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CONTRIBUTION OF AUTHORS

In Chapter 1, Carolyn M. Poutasse and Holly M. Dixon equally contributed in writing this chapter. Kim A. Anderson assisted in the book chapter writing, preparation, and review.

In Chapter 2, Carolyn M. Poutasse performed the chemical and statistical analyses, created tables and figures, and wrote the manuscript. Mark E. Peterson, Jana Gordon, and Peter H. Soboroff recruited the hyperthyroid and non-hyperthyroid cats. Julie B. Herbstman, Darrell Holmes, and Dezere Gonzalez digitally uploaded the questionnaire data and assisted in the statistical analyses. Lane G. Tidwell assisted with the chemical analysis. Kim A. Anderson and Carolyn M. Poutasse conceived and co-designed the study. All authors assisted in manuscript review.

In Chapter 3, Carolyn M. Poutasse performed the chemical and statistical analyses, created tables and figures, and wrote the manuscript. Walker S.C. Poston and Sara A. Jahnke recruited the firefighters and digitally uploaded the questionnaire data. Christopher K. Haddock assisted with the statistical analyses. Lane G. Tidwell assisted with the chemical analyses. Peter H. Hoffman assisted with the silicone dog tag sampler construction. Kim A. Anderson conceived and designed the study and oversaw the chemical analyses. All authors assisted in manuscript review.

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New Configurations of Silicone Passive Sampling Devices:
Quantifying Feline and Firefighter Chemical Exposures

Chapter 1 – Silicone Wristbands and Wearables to Assess Chemical Exposures

Holly M. Dixon,* Carolyn M. Poutasse,* and Kim A. Anderson

*These co-authors contributed equally

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1.1 Abstract

First described in 2014, silicone wristband technologies have gained increasing interest as personal chemical monitors. Silicone wristbands are low cost, easy-to-use, sensitive to low chemical concentrations, and sequester a wide range of bioavailable organic chemicals. Wristbands are comfortable, rugged, and do not interfere with daily activities. Between 2014 and early 2019, wristband results have been included in 23 peer-reviewed articles and have been worn by several thousand volunteers on six continents. This chapter provides an overview of silicone wristband passive sampling, considerations for laboratory processing, and research applications. Investigations have ranged from agricultural pesticide exposures in Africa to prenatal polycyclic aromatic hydrocarbon exposures in North America to consumer product-related chemical exposures in South America. Other silicone wearables include pet tags, which have been used to examine flame retardant exposures in context of feline hyperthyroidism. Future directions for wristbands include further investigating chemical mixtures, behavioral health interventions, and disaster-related chemical exposures. As an accessible exposure assessment tool, wristbands will complement research initiatives on the exposome and total exposure health, as well as promote collaborations between researchers and communities.

1.2 Personal Chemical Exposures

Chemicals in our everyday environment may have unintended effects on human health. Increasing evidence indicates that environmental exposures impact the risk of disease,¹ but researchers and community members often lack knowledge about the frequency and magnitude of personal exposures to many chemicals. In order to monitor such exposures, low-cost and easy-to-use technologies are critical tools to inform cutting-edge research in toxicology and environmental epidemiology. These exposure assessment tools will further complement recent research initiatives, such as understanding total exposures

throughout a person's lifespan ('exposome') and pairing personal exposure data with genetic information ('total exposure health' and 'precision medicine').

1.3 Passive Sampling

1.3.1 Passive Sampling Background

Passive sampling devices (PSDs) for organic chemicals are lipophilic polymers that mimic biological cellular membranes (Figure 1.1).^{2,3} Via simple diffusion, unbound chemicals in environmental media (e.g. air, sediment, soil, and water) are sequestered into PSD polymers.^{3,4} Researchers can then extract and quantify the chemicals in the polymer. PSDs do not sequester all chemicals in the environment, but rather the fraction biologically available to transport across cellular membranes.⁵⁻⁷ A chemical's bioavailability is not an inherent property. Rather, bioavailability is dependent upon physiological uptake processes and physical-chemical properties.^{3,8} When examining the relationship between chemical exposures and health effects, it is important to characterize the bioavailable fraction of chemicals.

Over 16,700 scientific publications have mentioned passive sampling since 1980, and over 45 percent of those papers were published between 2014 and 2018 (Google Scholar search; accessed January 4, 2019). Growing interest in passive sampling is partly attributed to low cost, ease of deployment, high sensitivity to low chemical concentrations, and ability to sequester a wide range of bioavailable chemicals.^{9,10} In addition, PSD chemical concentrations represent an average chemical concentration over the study period (i.e. time-weighted average).^{6,9,11} A time-weighted average can be a benefit in comparison to conventional chemical assessment methods, such as taking water or soil grab samples. Grab samples, which represent a snapshot of chemicals at one time point, require repeated sampling campaigns to characterize long-term exposures, resulting in comparatively high costs.³ For chemical monitoring programs, passive sampling is an effective long-term solution compared to grab sampling.⁴

1.3.2 Silicone Wristbands

Many different types of polymers, including silicone, have been optimized for use as PSDs. A novel application of PSDs are silicone wristbands, first described by O'Connell et al. in 2014. Wristbands are used to characterize personal exposure to organic chemicals. As of March 2019, wristband results have been included in 23 peer-reviewed manuscripts and have been worn by several thousand volunteers on six continents. To date, several different chemical classes including flame retardants, pesticides, polycyclic aromatic hydrocarbons (PAHs), phthalates, and consumer product-related chemicals, have been detected and quantified in silicone wristbands. The ability to concurrently monitor all these different chemical classes offers a unique opportunity to assess the effect of chemical mixtures on human health.

1.4 Silicone Wristband Characterization

1.4.1 Wristband Advantages

Silicone wristbands are a robust, simple technology used to characterize an individual's chemical exposures from dermal, inhalation, and limited ingestion exposure pathways. Due to their small size and mass (less than five grams), wristbands are comfortable, rugged, and do not interfere with daily activities (Figure 1.2). Wristbands also do not require a battery or maintenance, allowing an individual to continuously wear the sampler. Finally, as a noninvasive chemical monitor, wristband studies have high volunteer compliance.¹²⁻¹⁶

Silicone wristbands, or other silicone wearables, sequester a wide range of bioavailable chemicals, including volatile organic chemicals (VOCs) and semi-volatile organic chemicals (SVOCs). Depending on physical-chemical properties, different chemicals will sequester at different rates into the wristband, which can be characterized by chemical partition coefficients (e.g. octanol-air partition coefficient, $\log K_{oa}$).^{17, 18} Wristbands can sample chemicals that span over twelve orders of magnitude for octanol-air partition

coefficients, with log K_{oa} values ranging from 3.3 to 16 (toluene to di(2-ethylhexyl)tetrabromophthalate).¹⁹ As an analogy for several orders of magnitude, the temperature of water freezing at 0 °C (log 0) and the temperature at the sun center is 15,000,000 °C (log 7). This wide range enables the PSD to function as a broad, nonspecific organic chemical sampler.

1.4.2 Chemical Uptake

Uptake into the silicone wristband is unique to each chemical based on its physical-chemical properties, environmental concentrations, and exposure time. The uptake of organic chemicals into the wristband over time includes linear, curvilinear, and equilibrium phases (Figure 1.3).^{2, 9, 20} In the linear phase, a chemical's concentration in the wristband is lower than in the environment and the uptake rate is constant. In the curvilinear phase, a chemical's concentration in the wristband increases and the uptake rate is reduced. In the next phase, the wristband is in equilibrium with the surrounding environment; the chemical concentration in the wristband becomes constant if the environmental concentration is not changing. Regardless of whether a chemical is in the linear, curvilinear, or equilibrium phase, chemical uptake is dynamic and chemicals are actively moving in and out of the silicone wristband during the entire sampling period.

Although the process of chemical uptake depends on several factors, researchers have tools to determine chemical uptake rates in wristbands. Performance reference compounds (PRCs) can be added to wristbands prior to deployment and they allow researchers to calculate a chemical's uptake rate and phase specific to each sampler's environment.²¹ There is significant precedence for using PRCs with PSDs.^{9, 10, 18, 20}

Some chemicals will reach equilibrium between the wristband and the environment, representing the estimated average concentration of the chemical over the time worn. This is the case for small, volatile chemicals (e.g. naphthalene). Saturation of the wristbands is not a concern at equilibrium; the wristbands have been tested in highly contaminated environments for long deployment times with no evidence of saturation. At

equilibrium, wristbands can detect changes in a chemical's concentration and will accurately reflect the average concentrations over the period worn. The chemicals are sequestered within the silicone polymer via simple diffusion (Figure 1.1), but the polymer pores do not behave like enzymatic binding sites (e.g. lock-and-key mechanism). Wristbands do not fill up nor stop sequestering chemicals during uptake; rather, chemicals can move freely between the environment and silicone wristband, resulting in relevant chemical concentrations.

1.4.3 Wristband Data Applications

Understanding the process of chemical uptake is essential when making conclusions about chemical exposure. Wristband results are often used to make comparisons between different groups of study volunteers. For exposure comparisons, chemical concentrations can be reported as ng/wristband, ng/g wristband, or pmol/g wristband.^{15, 22} Even if specific uptake rates are not known, the uptake rate of a given chemical will be approximately equivalent for the same type of silicone sampler, enabling direct comparisons of the given chemical. Because different chemicals have unique uptake curves, researchers have to be cautious when making comparisons between different chemicals (e.g. toluene compared to benzo[a]pyrene), either within a wristband or between different wristbands.¹⁵ Screening for the presence and absence of a large number of chemicals can also be an efficient way to make comparisons between groups of volunteers and inform future toxicology and exposure science studies.^{13, 23}

Current research is addressing how environmental concentrations can be calculated from silicone wristbands via partition coefficients.¹⁸ For PAHs, partition coefficients between wristbands and air have been reported from two paired studies: one using wristbands and active air samplers¹⁸ and one using wristbands and low-density polyethylene, another common PSD.²⁴

Another application of wristband data sets is to predict chemical concentrations in biological matrices. This is similar to environmental research that has used PSD data to

predict chemical concentrations in organisms such as crayfish, clams, mussels, and aquatic worms.^{7, 25-27} Data from Dixon et al. (2018) was used to generate a linear regression model of phenanthrene in wristbands and associated metabolites in urine from participants in an urban environment (Figure 1.4). When looking at the sum of phenanthrene urinary metabolites, the associated R-squared value for the line of best fit was 0.62 (Figure 1.4). This type of approach could be used with other chemicals and types of biological matrices (e.g. blood and breast milk) to predict internal biomarker concentrations.

1.4.4 Silicone Wristband Limitations and Additional Considerations

While wristbands and other silicone wearables offer many opportunities to examine personal chemical exposures, wristbands are not real-time samplers (e.g. do not change color nor notify the wearer when chemical exposure occurs). A sampler must be sent back to a laboratory for chemical analysis. Wristband extracts from either liquid extraction or thermal desorption methods can be stored and reanalyzed later with other analytical methods after sampling has occurred.

Additionally, when worn on the wrist, chemical concentrations in wristbands represent a combination of several exposure routes (e.g. dermal and inhalation).^{23, 28, 29} Although determining the contribution from specific exposure routes may be difficult, it can be advantageous to evaluate chemical exposures from multiple routes to address human health questions.

There are other types of methodologies beyond silicone wristbands that are currently available to monitor personal organic chemical exposures.³⁰ Stakeholders (e.g. researchers, communities, non-government organizations) need to consider which method aligns best with their objectives. For example, biomonitoring samples are traditionally analyzed to monitor chemical exposures.³¹ However, biomarker concentrations can vary due to several factors, such as individual variability in metabolism, gender, age, and health status.^{32, 33} Additionally, some chemicals remain in the body for a long time or lack

a clear link to an internal biomarker.³⁴ These factors complicate efforts to evaluate chemical exposures, to assess intervention strategies, and to set regulatory limits via biomonitoring samples. The characteristics of any chemical exposure assessment method must be fit-for-purpose to best address stakeholder questions.

1.5 Laboratory Practices

1.5.1 Wristband Preparation and Shipment

Silicone wristband stock material is low cost and commercially available. Yet, the stock material must be properly prepared in order to remove chemicals that can adversely impact analysis and chemicals that are in the analytical method. To minimize solvent use, wristband preparation can occur via vacuum oven conditioning when prepared according to Anderson et al. (2017). Alternatively, wristband preparation can also occur using Soxhlet extraction.^{17, 35, 36} Following preparation processes, wristbands can be analyzed using chromatography and spectrometry to ensure removal of chemicals.¹⁸

Silicone wristbands can be individually transported to study locations in airtight, impermeable containers, such as airtight polytetrafluoroethylene (PTFE) bags (Figure 1.5).¹⁸ Each PTFE bag can be labelled with necessary study information, such as sample identification number and the sampler on and off dates and times. Wristbands can be transported to each study location at ambient temperature through standard mail services (Figure 1.5).

1.5.2 Chemical Stability in Wristbands

When stored in PTFE bags, both VOCs and SVOCs have been demonstrated to be stable in the wristbands for extended periods of time.¹⁸ Under simulated transport conditions (30 °C), 17 VOCs were stable in the wristbands for 7 days and 131 SVOCs for up to 1 month.¹⁸ Because there was no chemical loss in wristbands stored in PTFE bags at elevated temperatures, wristbands and other wristbands can be shipped long distances at ambient temperature, reducing transportation costs. Similarly, during long-term storage at

-20 °C, all chemical levels were stable for up to 3 months for VOCs and 6 months for SVOCs,¹⁸ and this dataset has since been extended to 21 months. The transport and storage stability of organic chemicals provides time and cost advantages over other exposure assessment methods. By comparison, the US EPA SVOC method 8270 for water samples maintains that extractions be completed in 14 days. Storage stability of chemicals in wristbands allows greater flexibility for stakeholders.

1.5.3 Chemical Extraction

The extraction of chemicals from wristbands can vary depending upon study design and analytes of interest. The majority of literature on wristbands include a post-deployment cleaning step to remove surface particulates.^{4, 12-16, 18, 23, 37, 38} Particle-bound contaminants, which are generally not bioavailable for dermal exposure, can be removed by washing the wristbands.^{3, 18} Following post-deployment cleaning, wristbands are amenable to a wide variety of chemical extraction procedures. Solvent extractions are currently the most common method.¹⁸ For example, wristbands can be extracted with ethyl acetate.^{4, 18, 29} Alternatively, thermal desorption onto sorbent tubes is another option which can significantly decrease extraction time compared to solvent extractions.

For any extraction method, researchers must consider the number and amount of chemicals that are removed by the silicone preparation step compared to the extraction steps after use. If the silicone preparation process removes fewer interference chemicals than the post-use extraction process, researchers are potentially analyzing chemicals left over from the original silicone manufacturing process. In practice, the silicone preparation steps should be more rigorous (e.g. higher temperature) than the post-use solvent extraction.

1.5.4 Chemical and Biological Analysis

Solvent extracts from wristbands can be analyzed for chemicals on a wide variety of different analytical methods, using both gas and liquid chromatography. One analytical

method is a quantitative screen for 1530 target organic chemicals with only 50 minutes of instrument time per sample.¹⁹ Experienced chemists spend under 20 minutes per sample reviewing the chromatographic results. The target analytes include pesticides, PAHs, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), phthalates, and fragrances, which can all contribute to chemical mixtures. Although this method is a targeted screen, there is interest in applying non-targeted chemical analysis to extracts from wristbands as demonstrated by Manzano et al. (2019)³⁹ and Ulrich et al. (2019).⁴⁰

For biological analysis, extracts can be applied to bioassays and investigated using an effects-directed analysis.^{11, 41} For instance, the developmental zebrafish model has allowed researchers to test multiple toxicity endpoints, such as physiological deformities and neurobehavioral changes, with chemical extracts from PSDs.⁴¹ The zebrafish developmental model, or other bioassays, paired with extracts from wristbands offers countless opportunities for chemical risk assessment.

1.6 Human Research Ethics

Silicone wristbands can be easily integrated into studies requiring Institutional Review Board (IRB) approval. At academic institutions, IRB approval is required for all studies involving human participants. This process ensures volunteers understand the risks, benefits, and expectations of participating in a research study. As determined by Oregon State University's IRB on silicone wristband research, "The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life." For other stakeholders interested in using silicone wristbands outside of a research study, IRB approval might not be required.

In several studies from Oregon State University, volunteers are given the option to have their wristband chemical results returned to them. Returning chemical results gives volunteers opportunities to learn more about scientific studies, reduce their chemical exposures, and engage in public discourse.⁴²⁻⁴⁴ Even if chemical exposure limits and potential health effects of exposure are not known, previous research has demonstrated

that participants report benefits from receiving their chemical results.^{23, 42, 45, 46} For example, members of the Swinomish Indian Tribal Community received their wristband results and volunteers reported that this information helped them become more aware of potential PAH sources in their community.⁴⁷ Several volunteers also reported changing their behaviors to try to reduce their exposure to PAHs.⁴⁷

1.7 Silicone Wristband Applications

Since 2014, researchers have demonstrated the applicability of wristbands, compared wristbands with other conventional exposure assessment methodologies, and investigated associations between wristband results and health effects (Table 1.1). Together, these studies demonstrate silicone wristband applications across diverse communities.

1.7.1 Initial Field Applications

In two occupational settings with hot asphalt applications in O'Connell et al. (2014), silicone wristbands were worn by roofers (n=8) at an outdoor and indoor training facility and analyzed for PAHs and oxygenated-PAHs. Average PAH concentrations were three times higher at the indoor worksite compared to the outdoor worksite.⁴ This initial wristband publication garnered significant interest in applications in areas of exposure science, occupational health, and epidemiology.

Paulik et al. (2018) focused on personal PAH exposures in non-occupational settings (n=19) of rural Ohio, using both silicone wristbands and stationary air PSDs nearby. With the expansion of natural gas extraction (NGE) in the United States, this was one of few studies documenting personal PAH exposures with NGE occurring nearby. Wristbands from participants with active NGE wells on their properties had a significantly higher sum of 62 PAHs than participants without (Wilcoxon ranked sum, $p<0.005$).³⁸ Furthermore, PAH concentrations in wristbands were positively correlated with PAH concentrations sampled in air near participants' homes (simple linear regression, $p<0.0001$). This linear relationship underestimated and overestimated some personal

PAH exposures based on stationary air monitors, indicating the importance of personal wristband data.

In Aerts et al. (2018), volunteers (n=30) in Leuven, Belgium wore silicone wristbands to assess non-occupational pesticide exposures in an urban setting, while a second wristband was placed near each volunteer's home.²⁹ Researchers analyzed wristband extracts for 200 polar pesticides. Thirty-one pesticides were detected, with 48% of those pesticides being detected only in the wristbands worn by volunteers and not detected in the wristbands placed outside. Volunteers with diets featuring increased vegetable consumption were associated with increased pesticide detections, demonstrating that wristbands capture ingestion and dermal exposures. Aside from five wristbands with only DEET detected, all other wristbands had a unique profile of pesticide detections, revealing how highly individualized chemical exposures can be and the importance of personal monitoring.²⁹

As further evidence of individualized exposures, Donald et al. (2016) found that no two wristbands worn by different volunteers (n=35) had the exact same pesticides detected. In this study, volunteers from rural farming families in Diender, Senegal wore wristbands in the first assessment of personal occupational pesticide exposures in West Africa.¹⁵ Each volunteer wore a wristband for two separate periods, for a total of 70 wristbands in the study (100% compliance). Although inter-individual differences were large between different volunteers for the 65 pesticides in the analysis, the pairs of wristbands worn by the same individuals revealed that intra-individual differences were small. Within each individual's paired wristbands, neither the number of detections nor concentrations were significantly different (Wilcoxon signed-rank, $p < 0.003$). These results may be attributable to consistent behaviors and activities of individuals from week to week, whereas behaviors can vary widely between different people. Researchers can use wristbands to detect inter- and intra-individual chemical exposure patterns.

In the remote region of Alto Mayo, Peru, volunteers (n=68) from rural and urban communities wore wristbands, as described in Bergmann et al. (2017). Wristbands were screened for the presence of 1397 chemicals and chemical patterns based on demographics were identified.¹³ For example, wristbands from rural communities had a higher number of pesticide and PAH detections than urban communities, and wristbands from urban communities had higher personal care product chemical detections than rural communities (chi-square likelihood ratio test, $p < 0.05$).

1.7.2 Comparisons with Conventional Exposure Assessment Technologies

Concentrations in silicone wearables (i.e. wristband) have been directly compared to concentrations in paired conventional exposure assessment technologies, including hand wipes, active air samplers, serum, and urine. These studies all demonstrated strong correlations between wristband chemical concentrations and paired biological metabolite concentrations, providing further evidence that wristbands sequester the bioavailable fraction.

In Hammel et al. (2016), adults (n=40) from Durham, North Carolina wore wristbands and provided one hand wipe and three spot urine samples. Pooled urine was analyzed for metabolites of four organophosphate ester (OPE) flame retardants: TDCIPP, TCIPP, TPHP, and mono-ITP. Concentrations of TDCIPP and TCIPP in the wristbands strongly correlated with the associated urinary metabolites ($r_s = 0.5$ to 0.65 , $p < 0.001$), suggesting wristbands predict internal exposure to OPEs.³⁶ Wristbands may be an improved OPE exposure assessment tool compared to hand wipes.

In follow-up to Hammel et al. (2016), Hammel et al. (2018) continued the validation study by examining wristbands for PBDE exposures. PBDEs, which also act as household flame retardants, biomagnify and have longer half-lives in the body compared to OPEs. Participants (n=30) provided serum samples to correlate PBDE biomarkers with wristband data.¹⁷ Between wristbands and serum biomarkers, BDE-47, -99, -100, and -

153 were positively correlated ($r_s=0.39-0.57$, $p<0.05$), demonstrating that silicone wristbands can quantify personal PBDE exposures, as well as OPE exposures.

In Dixon et al. (2018), pregnant women ($n=22$) in a birth cohort in New York City wore a wristband, provided a urine sample, and wore an active air sampler (i.e. polyurethane foam (PUF) and filter housed in a personal backpack). Researchers compared concentrations of PAHs and PAH metabolites between wristbands, PUFs, filters, and urine. Researchers found three times more positive, significant correlations between PAH and PAH metabolite pairs in wristbands and urine samples than between PUF-filters and urine samples.³⁷ Specifically, concentrations of six PAHs in the wristbands strongly correlated with concentrations of the associated urinary metabolites ($r_s=0.44$ to 0.76 , $p=0.04$ to <0.001), indicating that wristband PAH exposures are predictive of internal biomarkers.

In Quintana et al. (2019), children in California ($n=31$) wore silicone wristbands and provided a urine sample to investigate nicotine exposures between smoking and nonsmoking homes. Similar to Hammel et al. (2016), Hammel et al. (2018), and Dixon et al. (2018), Quintana et al. reported strong significant correlations between concentrations in the wristbands and in the urine ($r^2=0.85$, $p<0.001$), further demonstrating that wristbands are reflecting the bioavailable chemical fraction and body burden.⁴⁸

1.7.3 Health Effects

Several studies have begun to examine chemical concentrations from wristbands in association with adverse health effects. In Kile et al. (2016) and Lipscomb et al. (2017), wristbands quantified preschool-aged children's flame retardant exposures ($n=72$) and examined exposures in the context of emotional and social behaviors. Children from Corvallis and Eugene, Oregon enjoyed wearing the wristbands, with one child referring to it as "their own personal science bracelet."¹⁶ Flame retardant concentrations and sociodemographic data were correlated for multiple variables, such as house age and vacuuming frequency. In the companion article, social behaviors were measured using

the Social Skills Improvement Rating Scale as rated by a child's teacher.⁴⁹ Higher flame retardant exposures were associated with less responsible behavior and increased externalizing behavior problems.⁴⁹ This study suggested that the correlation of higher flame retardant exposures with poorer social skills may impact a child's ability to succeed academically and socially.

Vidi et al. (2017) also characterized children's chemical exposures, but focused on para-occupational pesticide exposures and DNA damage in hair follicles. The long-term effects of pesticide exposures on health and development are poorly understood, but indirect exposures (e.g. shared housing with an agricultural worker) may lead to adverse health effects.¹⁴ Latino children (n=10) from farmworker households in rural North Carolina were recruited as part of a community-based participatory research project. Each child wore a wristband to quantify pesticide exposures and provided plucked hair follicle samples to quantify DNA damage. An increasing number of pesticide detections was significantly associated with DNA damage in the papilla region of the hairs, indicative of DNA damage to epithelial cells.

Rohlman et al. (In Review) developed the novel Exposure, Location and lung Function (ELF) tool to concurrently collect daily individualized chemical exposure (silicone wristbands), location (cell phone), and respiratory health outcomes (spirometer and questionnaires).⁵⁰ An ELF phone app collected questionnaire data about personal behavior, potential exposure sources, and respiratory health symptoms. Volunteers also used a handheld, Bluetooth-linked spirometer to assess lung function throughout the study. In an initial pilot study using this ELF technology in Eugene, Oregon, volunteers used the ELF with high compliance (>90%).⁵⁰

1.7.4 Additional Configurations of Silicone Wristbands

Since the first report of silicone wristbands in 2014, new configurations of silicone PSDs have also been developed. Multiple pilot studies have demonstrated the use of novel silicone PSDs that are not worn on the wrist (e.g. wearables).

To characterize chemical exposures in animal health studies, horses have worn silicone wearables on their halters and cats have worn silicone pet tags. The horse cohort study evaluated broodmare PAH exposures in New York and Pennsylvania in relationship to the incidence of foal dysphagia.⁵¹ A silicone wearable was secured to the horses' halter (Figure 1.6A). A cat case-control study evaluated flame retardant exposures using pet tags (Figure 1.6B) worn by geriatric cats diagnosed with feline hyperthyroidism. Community cat owners volunteered their cats (n=78) to wear the tag. With extremely positive feedback from the owners ("The tag didn't bother her/him at all!"), the results indicated that elevated exposures to tris(1,3-dichloro-2-isopropyl) phosphate were correlated with feline hyperthyroidism (see Chapter 2).²² These two examples demonstrate the widespread applicability of silicone wearables to answer chemical exposure questions for animals, as well as humans.

Additional configurations for human volunteers include lapels and military-style dog tags. A lapel configuration on top of clothing (Figure 1.6C) selectively samples inhalation exposures, as demonstrated in O'Connell et al. (2014). By altering where and how the silicone sampler is worn, the lapel minimizes dermal uptake. Similarly, a military-style dog tag (Figure 1.6D) can be worn around the neck to assess firefighter chemical exposures. The exposure study was driven by firefighter concern over high incidences of cancer diagnoses,⁵² and firefighter participants had significant input in developing the dog tag sampler. Dog tags can be worn under or over clothing to address different chemical exposure questions (see Chapter 3). Examining occupational chemical exposure mixtures provides unique opportunities for assessing behavioral health interventions.

1.8 Future Directions

1.8.1 Chemical Mixtures

The ability to analyze personal chemical samplers for many chemical classes at one time allows for efficient and realistic mixture analysis on a global scale. With more research studies including silicone wristbands, researchers can use PSDs as population screening

tools as demonstrated in Dixon et al. (2019). The presence of 1,530 chemical detections was reported for 262 wristbands worn on three continents.²³ Common chemical mixtures were identified, and the characterization of such mixtures offers significant advances for toxicological testing. When certain chemicals co-occur, there can be synergistic, antagonistic, or additive effects,⁵³ and wristbands allow for the identification of realistic chemical mixtures.

1.8.2 Disaster-Related Exposures

Wristbands can be worn in disaster situations to characterize chemical exposures because they do not interfere with important activities, such as response and recovery to a flood or fire (Figure 1.7). After Hurricane Harvey made landfall in Texas in 2017, over a dozen federal Superfund sites were flooded and/or experienced possible storm damage.^{54, 55} Communities were concerned about chemicals in the floodwater.⁵⁶ People involved in the hurricane recovery process wore wristbands within four weeks post-Hurricane Harvey. Even in the aftermath of Harvey, wristband compliance was 85%, illustrating the approachability of this technology. Although only a small, non-random sample of wristbands was analyzed, wristbands worn after Harvey had a higher mean number of chemical detections compared to several other geographic regions unaffected by recent disasters.²³ In the future, wristbands can be worn by people impacted by other disasters, such as people in close proximity to wildfire smoke.

1.8.3 Behavioral Health Interventions

Identifying risk factors associated with elevated chemical exposures provides insight into how exposures can be mitigated in the future via behavioral interventions. Harley et al. (2019) used silicone wristbands to characterize pesticide exposures among 14-to-16-year-old girls (n=97) living in the Salinas Valley, California. California's Salinas Valley (Monterey County) is an extremely productive agricultural region, but some pesticide exposures are associated with various adverse health effects (e.g. disruption of hormonal function). In this study, the majority of detected pesticides were used only for residential

pest control, suggesting that this community experiences pesticides exposures beyond agriculture.¹² Higher odds of detecting select pesticides were associated with living within 100 m of agricultural fields, having carpet in the home, and having an exterminator treat the home within the past 6 months. The study volunteers reported these major findings to the larger agricultural community and recommended lifestyle changes for reducing pesticide exposures.¹² In the future, wristband studies could assess the impact of behavioral health interventions on personal chemical exposure.

1.8.4 Precision Health and Precision Prevention

Individualized chemical exposure data obtained from silicone wristbands can be paired with personalized genomic data. A combination of chemical exposure and genetic data is necessary to understand human health. The cost to sequence an individual's genome has decreased dramatically in the past decade,⁵⁷ and the cost to assess personal chemical exposures is dropping with the development of silicone wristbands. Wristbands can fulfill the need for large chemical dataset generation in the emerging field of precision health and precision prevention.⁵⁸ The power of large-scale chemical datasets enables researchers to improve overall understanding of exposures, to improve health through reducing certain chemical exposures, and to answer health-related questions previously unable to be addressed with genetic information alone. Silicone wristbands can be an integral piece of the collaborative strategy that shifts the current healthcare paradigm from retroactively curing disease to proactively preventing disease.

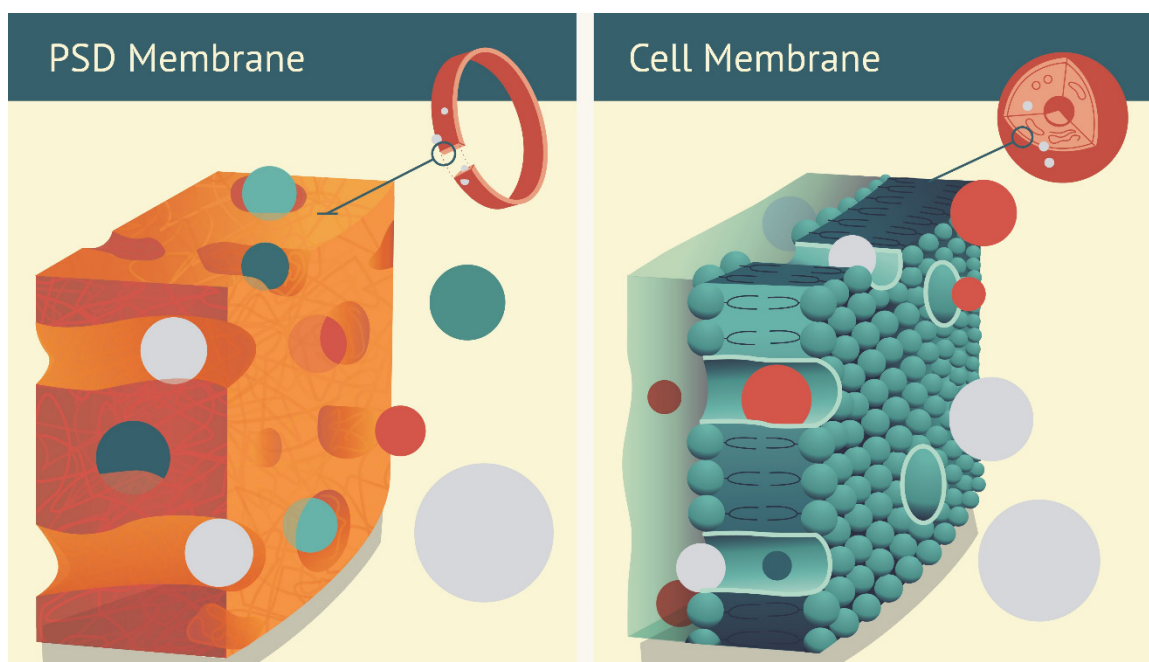


Figure 1.1. Simplified representation of a passive sampling device (PSD) membrane and biological cell membrane, illustrating functional similarities. Both membranes are lipophilic and have similar pore sizes (estimated 10 Å for PSD membrane and 9.5 Å for cell membrane).³ Chemicals are represented by spheres, with some chemicals able to cross the membranes (bioavailable fraction) and some chemicals unable to cross the membranes (adapted from Anderson and Hillwalker 2008).



Figure 1.2. Silicone wristbands can be worn during normal daily activities, such as showering, driving, smoking, sleeping, swimming, and interacting with animals.

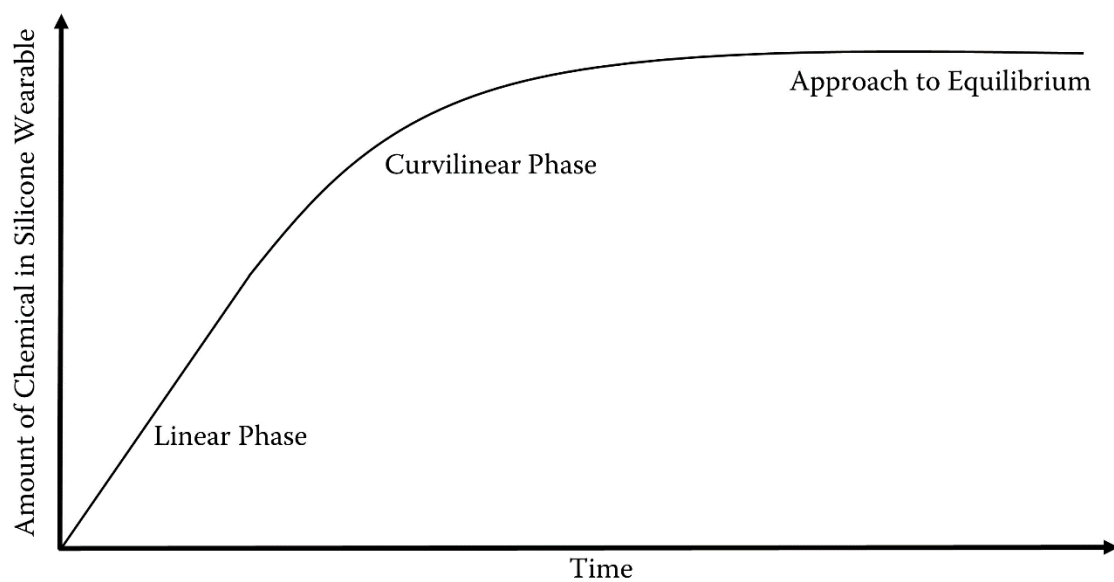


Figure 1.3. Theoretical chemical uptake curve for silicone wearables over time. Each chemical will have a different uptake curve.

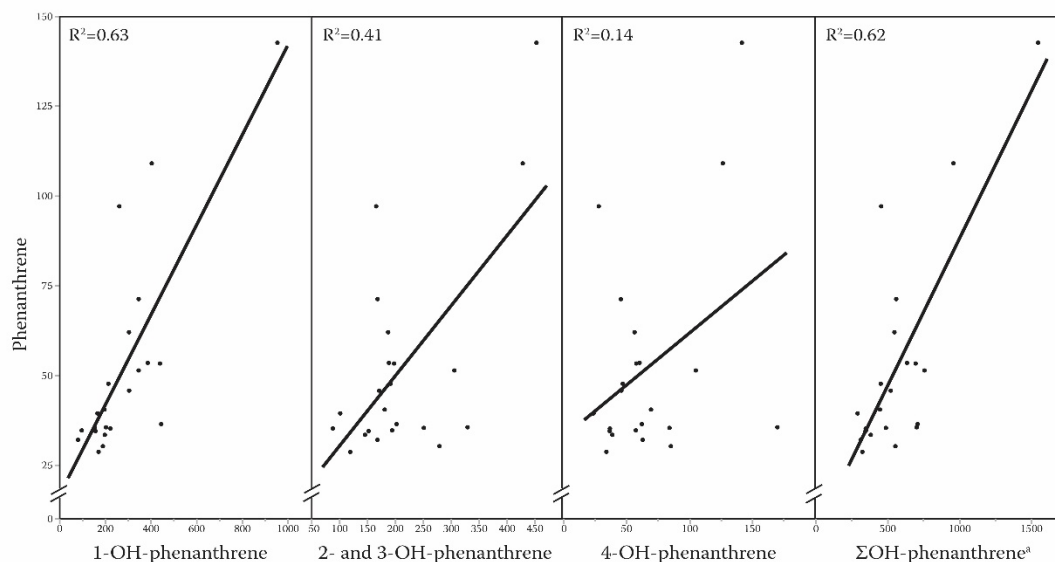


Figure 1.4. Linear regression model of phenanthrene in wristbands and associated phenanthrene metabolites in urine from data in Dixon et al. 2018. ^a Sum of 1-OH-phenanthrene, 2-OH- and 3-OH-phenanthrene, 4-OH-phenanthrene concentrations.



Figure 1.5. Silicone wristbands can promote collaborations between diverse stakeholders. Process steps to assess personal chemical exposures can include preparation in the laboratory, study volunteer participation, sampler transport, chemical extraction and analysis, and community engagement.



Figure 1.6. Silicone wearable options: (A) horse halter, (B) pet tag, (C) lapel, and (D) military-style dog tag.



Figure 1.7. Silicone wristbands can be used to assess personal chemical exposure in several disaster scenarios, including flooding, hurricanes, and fires.

Table 1.1. Silicone wearable references as of March 2019, organized by chemical class.

	Chemical Class	Analytical Instrument	References
Targeted Chemical Analysis	Polycyclic aromatic hydrocarbons (PAHs)	GC-MS ^a	(O'Connell et al. 2014a, Donald et al. 2016, Bergmann et al. 2017a, Bergmann et al. 2018, Romanak et al. 2018, Dixon et al. 2019)
		GC-MS/MS	(Anderson et al. 2017, Paulik et al. 2018, Dixon et al. 2019, Rohlman et al. 2019, Rohlman et al. In Review)
		GCxGC/ToF-MS ^b	(Manzano et al. 2018)
	Polychlorinated biphenyls (PCBs)	GC-MS	(O'Connell et al. 2014a, Anderson et al. 2017, Bergmann et al. 2017a, Bergmann et al. 2018, Dixon et al. 2019)
	Flame Retardants • Polybrominated diphenyl ethers (PBDEs) • Novel brominated flame retardants (BFRs) • Organophosphate esters (OPEs)	GC-MS	(O'Connell et al. 2014a, Hammel et al. 2016, Kile et al. 2016, Anderson et al. 2017, Bergmann et al. 2017a, Lipscomb et al. 2017, Bergmann et al. 2018, Hammel et al. 2018, Romanak et al. 2018, Dixon et al. 2019, Donald et al. 2019)
	Pesticides • Organochlorines • Organophosphates • Neonicotinoids • Pyrethroids • Amides • Pyrazoles • Other	GC-MS	(O'Connell et al. 2014a, Bergmann et al. 2017a, Bergmann et al. 2018, Dixon et al. 2019, Donald et al. 2019, Harley et al. 2019)
		GC-ECD ^c	(O'Connell et al. 2014a, Donald et al. 2016, Bergmann et al. 2017a, Vidi et al. 2017, Bergmann et al. 2018, Harley et al. 2019)
		UHPLC-MS/MS ^d	(Aerts et al. 2018)
	Phthalates	GC-MS	(O'Connell et al. 2014a, Bergmann et al. 2017a, Bergmann et al. 2018, Dixon et al. 2019)
		GCxGC/ToF-MS	(Manzano et al. 2018)
	Consumer product-related chemicals	GC-MS	(O'Connell et al. 2014a, Bergmann et al. 2017a, Bergmann et al. 2018, Dixon et al. 2019, Donald et al. 2019)
		LC-MS/MS	(Quintana et al. 2019)
	Industrial-related chemicals	GC-MS	(O'Connell et al. 2014a, Bergmann et al. 2017a, Bergmann et al. 2018, Dixon et al. 2019, Donald et al. 2019)
		GCxGC/ToF-MS	(Manzano et al. 2018)
	Volatile organic compounds (VOCs)	GC-MS	Anderson 2017, Donald 2019 (Anderson et al. 2017, Donald et al. 2019)
	Dioxins and Furans	GC-MS	(Bergmann et al. 2017a, Bergmann et al. 2018, Dixon et al. 2019)
Nontargeted Analysis		GCxGC/ToF-MS	(Manzano et al. 2018)
		Assorted LC analyses (interlaboratory comparison study)	(Ulrich et al. 2019)

Chapter 2 – Silicone Pet Tags Associate Tris(1,3-Dichloro-2-Isopropyl) Phosphate
Exposures with Feline Hyperthyroidism

Carolyn M. Poutasse, Julie B. Herbstman, Mark E. Peterson, Jana Gordon, Peter H.
Soboroff, Darrell Holmes, Dezere Gonzalez, Lane G. Tidwell, and Kim A. Anderson

Environmental Science and Technology

American Chemical Society

1155 16th Street

Washington, DC 20036

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2.1 Abstract

Feline hyperthyroidism is the most commonly diagnosed endocrine-related disease among senior and geriatric housecats, but the causes remain unknown. Exposure to endocrine-disrupting compounds with thyroid targets, such as flame retardants (FRs), may contribute to disease development. Silicone passive sampling devices, or pet tags, quantitatively assessed the bioavailable FR exposures of 78 cats (≥ 7 y) in New York and Oregon using gas chromatography mass spectrometry. Pet tags were analyzed for 36 polybrominated diphenyl ethers, six organophosphate esters (OPEs), and two alternative brominated FRs. In non-hyperthyroid cats, serum free thyroxine (fT₄), total T₄ (TT₄), total triiodothyronine, and thyroid-stimulating hormone concentrations were compared with FR concentrations. Tris(1,3-dichloro-2-isopropyl) phosphate (TDCIPP) concentrations were higher in hyperthyroid than non-hyperthyroid pet tags (adjusted odds ratio, $p < 0.07$; Mantel-Cox, $p < 0.02$). Higher TDCIPP concentrations were associated with air freshener use compared to no use ($p < 0.01$), residences built since 2005 compared to pre-1989 ($p < 0.002$), and cats preferring to spend time on upholstered furniture compared to no preference ($p < 0.05$). Higher TDCIPP concentrations were associated with higher fT₄ and TT₄ concentrations ($p < 0.05$). This study provides proof-of-concept data for the use of silicone pet tags with companion animals and further indicates that bioavailable TDCIPP exposures are associated with feline hyperthyroidism.

2.2 Introduction

Feline hyperthyroidism is the most commonly diagnosed endocrine-related disease among senior and geriatric housecats (≥ 10 years).⁵⁹ First clinically diagnosed in 1979, the prevalence of feline hyperthyroidism among US housecats 10 years or older increased from 1 in 200 to 1 in 10 between 1980 and 2014.^{60, 61} Similar prevalence statistics are reported worldwide.⁶²⁻⁶⁵ In North America, an estimated two million cats are currently diagnosed with hyperthyroidism.⁶¹ The growing number of diagnoses is likely

attributable to a true increase in prevalence, although increased awareness, improved diagnostic tools, and increased feline longevity may contribute.

Domestic cats are the only nonhuman species frequently diagnosed with hyperthyroidism, known as toxic nodular goiter (TNG) in humans.⁶¹ Feline hyperthyroidism and TNG result from excessive circulating concentrations of the thyroid hormones thyroxine (T₄) and triiodothyronine (T₃).^{59, 61} These progressive diseases, which also share clinical symptoms, exhibit adenomatous hyperplasias with autonomous cell growth and hormone secretion.^{61, 66} Because of these similarities, hyperthyroid cats are recommended as animal models for TNG.

The underlying causes of feline hyperthyroidism remain unknown, but its development involves more than one risk factor.⁵⁹ As with TNG,⁶⁷ feline hyperthyroidism does not develop due to dietary iodine deficiency alone.⁵⁹ However, iodine deficiency may function synergistically with other factors.^{59, 68} Reported risk factors for feline hyperthyroidism include increasing age,^{63-65, 69} canned cat food consumption,^{60, 62, 65, 69} and litter box use.^{62, 63}

Researchers have hypothesized another risk factor for feline hyperthyroidism is household flame retardant (FR) exposures.⁷⁰⁻⁷⁴ The hypothesis emerged because the earliest diagnoses coincided with the introduction of polybrominated diphenyl ethers (PBDEs) as FRs during the mid-1970s.⁷⁵ FRs are commonly used in textiles, polyurethane foam, plastics, and electronics to delay the ignition of a fire.⁷⁵⁻⁷⁷ To meet flammability standards, PBDEs emerged as a major FR series with the common commercial mixtures of pentaBDE, octaBDE, and decaBDE.^{75, 76} In 2004, the pentaBDE and octaBDE mixtures were voluntarily phased out of US manufacturing due to concerns of persistence, bioaccumulation, and potential to cause adverse health effects.^{76, 78} The decaBDE mixture phase-out began in 2010, but PBDEs detections continue in dust and biomonitoring samples.⁷⁹⁻⁸¹ Additionally, products containing PBDEs are infrequently replaced, such that PBDE exposures will likely continue despite the phase-outs.^{75, 76, 82}

In response to the PBDE phase-out, organophosphate ester (OPE) production has increased over the past 10 years.⁸³ OPEs have been considered suitable alternatives to PBDEs for decades^{31, 83, 84} and include analytes such as tris(1,3-dichloro-2-isopropyl) phosphate (TDCIPP), tris(1-chloro-2-propyl) phosphate (TCIPP), tris(2-chloroethyl)phosphate (TCEP), and triphenyl phosphate (TPHP). Evidence suggests that both PBDEs^{75, 85} and OPEs⁸⁶⁻⁹⁰ act as endocrine-disrupting chemicals (EDCs) with thyroid targets.

A fraction of household PBDEs and OPEs remain unbound and freely dissolved in the gaseous phase.^{83, 91, 92} These biologically relevant, or bioavailable, FRs are significant for inhalation and dermal contact exposure routes.^{3, 16, 28, 92} By contrast, FRs bound to particulate matter (e.g. dust) are more significant for the ingestion pathway,⁹¹ but all three exposure routes can lead to potential adverse health effects. Both cats⁷⁰⁻⁷² and young children^{85, 92} are hypothesized to experience FR exposures predominantly via dust ingestion and inhalation of gaseous phase FRs, such that researchers should consider using cats as sentinels for human FR exposures in the home.

To quantify the bioavailable FR exposures of housecats, this study used a novel silicone passive sampling devices (PSDs). PSDs sequester unbound volatile and semi-volatile organic compounds (VOCs, SVOCs) via diffusion because the PSD polymer mimics an organism's phospholipid membrane.^{3, 4, 16} PSDs capture the bioavailable fraction of lipophilic organic chemicals and researchers can quantify exposures. Compared to active sampling devices, PSDs are lightweight, low cost, and easy to use.⁴ Stationary PSDs may underestimate individual exposures,³⁸ leading to an increased interest in personalized PSDs.

In 2014, silicone wristbands were first modified to function as personalized PSDs.^{4, 12-19, 23, 29, 36-38, 49} Worn against the skin, wristbands are capable of sequestering over 1530 chemicals, including pesticides,^{12-15, 29} polycyclic aromatic hydrocarbons,^{4, 18, 37, 38} personal care products,^{4, 13, 18, 19, 23} and FRs.^{16, 17, 23, 36, 49} In Hammel et al. 2016 (n=48),

TDCIPP, TCIPP, and TPHP urinary metabolite concentrations were more strongly correlated with parent OPE concentrations in wristbands compared to hand wipes. In Hammel et al. 2018 (n=30), BDE-47, -99, -100, and -153 concentrations were strongly correlated between wristbands and serum. Together, these studies suggest that wristbands can act as strong predictors of FR body burden.^{17, 36}

In this study, silicone pet tags are introduced as a new configuration of personalized PSDs and compare bioavailable FR exposures between hyperthyroid and non-hyperthyroid senior and geriatric cats. The objectives of this study were to (1) demonstrate the use of silicone PSDs on companion animals, (2) compare FR exposures of hyperthyroid and non-hyperthyroid cats, and (3) correlate FR concentrations associated with feline hyperthyroidism to household variables and behaviors. This study further recommends the use of housecats as sentinels for human bioavailable FR exposures.

2.3 Materials and Methods

2.3.1 Materials

Solvents were Optima-grade and purchased from Fisher Scientific (Pittsburgh, PA, USA). All analytical standards were purchased from Accustandard (New Haven, CT) as single analyte or composite solutions. For the full list of individual FR analytes and extraction surrogates, see Table A1. Prior to use, glassware was rinsed in a base bath, washed with detergent in an automatic dishwasher, rinsed with 18 M Ω ·cm water, and baked at >300 °C for 12 h. Air-tight polytetrafluoroethylene (PTFE) storage bags and closures were purchased from Welch Fluorocarbon, Inc. (Dover, NH, USA).

2.3.2 Silicone Tag Preparation

The silicone pet tags (3.0 cm wide by 2.5 cm long by 0.3 cm thick; ~2.7 g; <https://24hourwristbands.com>, Houston, TX, USA; Figure 2.1) were prepared as previously reported with minimal modifications.¹⁸ Briefly, the tags were conditioned in a

vacuum oven at 270-300 °C for six hours at 0.1 Torr (Vacuum Oven, Blue-M, model no. POM18VC, with Welch Duo-seal pump, model no. 1405). Quality control (QC) samples were selected to evaluate for data quality objectives prior to storing the tags in sealed metal containers at 4 °C (see Appendix A). Pet tags were transferred to PTFE bags before deployment.

2.3.3 Cat Population and Recruitment

Cat recruitment (n=78) occurred between December 2017 and October 2018. All protocols involving cats were approved by the Institutional Animal Care and Use Committees at Oregon State University (OSU ACUP 4963) and Columbia University (CU ACUP AC-AAAT5454). Hyperthyroid cats were recruited from the Animal Endocrine Clinic (n_{NY,hyperthyroid}=22) and OSU's Animal Teaching Hospital (n_{OR,hyperthyroid}=17). Non-hyperthyroid cats were recruited from the New York Cat Hospital (n_{NY,non-hyperthyroid}=16) and OSU's Animal Teaching Hospital (n_{OR,non-hyperthyroid}=23). For more details on cat recruitment, see Appendix A and Table A2.

2.3.4 Flame Retardant Extraction and Analysis

The pet tags were cleaned, extracted, and analyzed as previously reported⁴ (see Appendix A for details on extraction procedures, instrument analysis, and quality control). Additional details on instrument parameters, target analytes, and limits of detection and quantitation (LOD, LOQ) are given in Appendix A and Table A1.

2.3.5 Statistical Analysis

Statistical analyses were performed using SAS statistical software (JMP Pro version 13.0.0; SAS Institute Inc., Cary, NC) and R free software (CRAN R Project version 3.5.2) for analytes detected in at least one pet tag. All FR concentrations were normalized to the average pet tag sampler mass (2.7 g), or the mass recorded during post-deployment cleaning if the tag was partially chewed. We substituted FR concentrations below the method LODs with a value equal to one-half the LOD. All concentrations were converted

to moles per gram pet tag (pmol/g tag). During the PBDE congener comparison between cat tag and commercial mixture profiles, all concentrations were normalized using octanol-air partition coefficients to simulate the silicone-air partition coefficients.¹⁷

FR concentrations and thyroid hormone concentrations were approximately log-normally distributed (Kolmogorov's test, $p < 0.05$). Spearman's correlation coefficients assessed bivariate comparisons for FR concentrations. Adjusted odds ratios for FR concentrations were calculated using logistic regression,⁹³ where covariates were included if associated with the independent variable at $p < 0.15$.

To confirm the significance of the adjusted odds ratios, we performed two alternative analyses. A Kaplan-Meier procedure for censoring non-detected values compared hyperthyroid and non-hyperthyroid FR tag concentrations (Mantel-Cox χ^2).⁹⁴ Weighted quantile sum (WQS) regression for high-dimensional datasets assessed mixture effects in association with feline hyperthyroidism as the binary disease outcome.⁹⁵⁻⁹⁷ The WQS regression considered correlations between FR variables, enabled a generalized inference about the mixture effect, and identified individual FRs most strongly associated with feline hyperthyroidism.⁹⁵⁻⁹⁷ Chemical exposures occur as complex mixtures,²³ yielding high-dimensional datasets in which some individual exposures may increase the risk of disease. During univariate analysis, identifying chemicals with the strongest association with the disease outcome can be complicated by strong correlations with other chemicals in the dataset.⁹⁶ Because the FR dataset from this study demonstrated strong variable-variable correlations (Table A3, Table A4), WQS method application was appropriate as an alternative statistical approach. For the 21 FR components, the WQS method estimated a weighted linear index.^{96, 97} The 21 FR components were scored as ordinal variables into quantiles ($n=4$; quartiles) prior to being combined into the weighted index. The FR weights, which sum to 1, were empirically determined with bootstrap sampling ($B=100$). FRs with higher contributor weights had stronger associations with the outcome of feline hyperthyroidism.

A subset of FRs (adjusted odds ratio, $p < 0.10$) were selected from the logistic regressions for investigation with questionnaire variables using generalized linear models. For all multivariate linear models, we $\log_{10}$ -transformed both FR and hormone concentrations to produce a more normal distribution. Again, covariates were included if associated with the independent variable at $p < 0.15$.

2.4 Results

2.4.1 Participant Population

Of the 78 tags distributed, all tags were worn for seven days and all were returned (100% compliance). One cat owner did not complete a questionnaire (99% compliance). Select questions had up to 16 missing answers (79% compliance). All pet tags were included in the logistic regressions, but tags with missing questionnaire answers were excluded from the generalized multivariate linear models. All pet tags detected at least one FR above LOQ. A summary of cat population demographics is given in Table 2.1.

Potential confounding variables included location, age, bite marks on the pet tag, time spent outdoors, living in the same household as other recruited cats, and sampling season. Multiple pet tags ($n=10$, 13%) were returned with bite marks. Of the bitten tags, two tags (4%) were returned with sections missing, presumably chewed off by the recruited cat. Neither was found to be a confounder for any FRs (ANOVA, $p > 0.05$; logistic regression, $p > 0.15$). Unadjusted odds ratios are shown in Table A5.

2.4.2 Flame Retardant Concentrations among Case-Control Cats

2.4.2.1 OPEs

All six OPEs in the analytical method were detected in at least one tag (Table 2.2). TPHP, TDCIPP, and TCIPP were detected in over 90% of pet tags in each group. TCEP and tri-n-butyl phosphate (TNBP) were detected over 50% of samples each, and tri-n-ethyl phosphate (TNEP) in fewer than 50% of samples. For the Spearman's correlation,

we included all six OPEs for a total of 15 coefficients, of which seven were significant (Table A3). This suggested the OPEs were unlikely to originate from a common source.

TDCIPP concentrations were higher in hyperthyroid than non-hyperthyroid tags (Table 2.2; adjusted odds ratio, $p < 0.07$). The Mantel-Cox χ^2 confirmed this result (Table 2.2; Figure A1; Mantel-Cox, $p < 0.02$). The weighted quantile sum regression also indicated that TDCIPP was the largest contributor to the FR mixture effect and the FR most strongly associated with feline hyperthyroidism (contributor weight > 0.20), although the entire FR mixture was not associated with the disease outcome ($\beta = 0.07$; $p > 0.90$). The remaining five OPE concentrations and Σ_6 OPEs demonstrated no difference between hyperthyroid and non-hyperthyroid tags (Table 2.2; adjusted odds ratio, $p > 0.10$; Mantel-Cox, $p > 0.10$). This result suggested that besides TDCIPP, hyperthyroid and non-hyperthyroid cats experience similar OPE exposures.

2.4.2.2 PBDEs

Of 36 PBDEs in the analytical method, 15 congeners were detected in at least one pet tag (Table 2.2). Low molecular weight (LMW) congeners (e.g. one through five bromines) were more frequently detected than high molecular weight (HMW) congeners (e.g. six through 10 bromines).

PBDE congeners were detected with similar frequency between hyperthyroid and non-hyperthyroid tags (Table 2.2). BDE-47 was the most frequently detected congener ($> 80\%$) in both hyperthyroid and non-hyperthyroid tags, followed by BDE-99 ($> 65\%$). BDE-100 and -153 were detected between 25% and 50% of samples in each group, while BDE-154, -49, -66, -28&-33, -8, -12, and -25 were detected in $< 25\%$ of samples. The PBDE congener concentrations and Σ_{36} PBDEs demonstrated no difference between hyperthyroid and non-hyperthyroid tags (Table 2.2; adjusted odds ratio, $p > 0.10$; Mantel-Cox, $p > 0.10$). This result suggested that hyperthyroid and non-hyperthyroid cats experience similar PBDE exposures.

For the Spearman's correlation, we included the six most frequently detected PBDE congeners for a total of 15 coefficients, all of which were statistically significant (Table A4). In contrast to the OPEs, this result suggested pet tag PBDE congener profiles likely originated from a common source, such as a commercial mixture. For example, the Bromkal series were common PBDE commercial formulations⁹⁸ treated a wide variety of consumer products prior to the phase-outs.^{75, 76} The Bromkal congener compositions were compared to the mean hyperthyroid and non-hyperthyroid congener profiles from this study (Figure 2.2).⁹⁸

2.4.2.3 Alternative BFRs

Two alternative BFRs were included in the analysis, of which only EH-TBB was detected. EH-TBB was detected less frequently in hyperthyroid than non-hyperthyroid tags. Neither EH-TBB nor Σ_2 BFR concentrations were different between the hyperthyroid and non-hyperthyroid pet tags (Table 2.2; adjusted odds ratio, $p > 0.10$). This indicated that the measured BFR exposures were not associated with feline hyperthyroidism. However, future studies may benefit by including additional BFRs.

2.4.3 Thyroid Hormone Concentrations

We investigated serum thyroid profile results from non-hyperthyroid cats ($n=39$) to assess correlations between FR concentrations and thyroid function. Only non-hyperthyroid cats were included in this analysis due to potential bias from hyperthyroid cat weight loss (see Section 2.5.4). Summary statistics for fT₄, TT₄, TT₃, and thyroid-stimulating hormone are reported in Table A2.

Multivariate associations between log₁₀-transformed concentrations of OPEs and thyroid hormones (Table 2.3) were calculated for models with no covariates (Model A), models with cholesterol as the only covariate (Model B), and models with all covariates (Model C). Model C contained the largest number of statistically significant and predominantly positive associations. Compared to other OPEs in Model C, TDCIPP demonstrated the

largest effect estimates (10^{β}). For example, a 10% increase in TDCIPP pet tag concentrations corresponded with a 1.38% increase in fT_4 hormone concentrations (95% CI: 1.15, 1.66; $p < 0.002$). For fT_4 , TDCIPP and TPHP were positively associated (Table 2.3, $p < 0.002$; $p < 0.03$) and TCIPP negatively associated (Table 2.3, $p < 0.001$). For TT_4 , TDCIPP and TCEP were positively associated (Table 2.3, $p < 0.01$; $p < 0.002$), with similar results for TT_3 (Table 2.3, $p < 0.10$; $p < 0.002$).

2.4.4 Associations with Household and Feline Variables

TDCIPP $\log_{10}$ -transformed concentrations from pet tags were associated with specific household and behavioral variables in a multivariate linear model, adjusted for confounders (Table 2.4). Reference groups are indicated in the effect estimate column ($10^{\square}$). For instance, the median TDCIPP pet tag concentrations in homes with weekly air freshener use was 61% higher compared to median concentrations in homes with no air freshener use (95% CI: 1.18, 2.20; $p < 0.002$). For cleaning-related variables, TDCIPP concentrations were positively associated with monthly to weekly air freshener use ($p < 0.01$), but not associated with vacuum frequency ($p > 0.05$). Residence-specific variables associated with higher TDCIPP concentrations were residences built since 2005 compared to those built prior to 1989 ($p < 0.002$) and residences containing upholstered furniture purchased between 2007 and 2012 compared to purchases prior to 2006 ($p < 0.01$). Feline behavioral variables positively associated with TDCIPP were any consumption of commercial dry food ($p < 0.001$) and cats who preferred to sleep on furniture compared to cats with no location preference ($p < 0.05$).

2.4.5 Intra-Household Comparison

Of 78 recruited cats, four pairs of cats lived in the same household, enabling direct comparisons of feline exposures within a shared living space. Because household factors (e.g. air freshener use) were identical between cat pairs, FR exposure differences were attributable to specific feline behaviors. There were two pairs of hyperthyroid/non-hyperthyroid cats and two pairs of two non-hyperthyroid cats living in the same

household. All FR concentrations were normalized using log K_{oa} values to account for variable FR-silicone affinity.¹⁷ Each pet tag FR profile was unique, regardless of the shared household environment (Figure 2.3). Higher TDCIPP concentrations for one cat were observed between three of the four pairs (OR-H-01, OR-H-02, OR-H-04). In all three pairs, the cat with higher TDCIPP tag concentrations spent an additional one to six hours/day on upholstered furniture. Consistent with the results in Table 2.4, this suggested an association between elevated TDCIPP exposures and increased time spent on upholstered furniture ($p < 0.05$).

2.5 Discussion

2.5.1 Owner Feedback

The owner responses to this study were extremely positive. The most common written feedback were variations of “The tag didn’t bother her/him at all!” Some recruited cats did not wear a collar on a daily basis, but owners frequently reported their cat became accustomed to wearing the collar and tag. This feedback indicated that pet tag use is low-stress and simple for both cat and owner when monitoring companion animal chemical exposures.

2.5.2 TDCIPP

2.5.2.1 This Study

To our knowledge, this is the first study to investigate bioavailable household OPE exposures between hyperthyroid and non-hyperthyroid cats. Of the OPEs, PBDEs, and BFRs detected in this study, TDCIPP concentrations were higher in pet tags from hyperthyroid compared to non-hyperthyroid cats (Table 2.2; adjusted odds ratio, $p < 0.07$; Mantel-Cox, $p < 0.02$). In Table 2.3, TDCIPP concentrations were also positively associated with fT_4 ($p < 0.002$), TT_4 ($p < 0.01$), and TT_3 ($p < 0.10$) concentrations among non-hyperthyroid cats. TDCIPP also had the largest 10^B coefficients, and therefore impacted fT_4 , TT_4 , and TT_3 more strongly, compared to other OPEs in Table 2.3. This

result was further suggestive of a link between TDCIPP exposure and thyroid function. Combined with historic use and altered thyroid hormone function in various organisms, this study provides new evidence that bioavailable household TDCIPP exposures may be linked to feline hyperthyroidism.

2.5.2.2 Background

Prior to the earliest diagnoses of feline hyperthyroidism, manufacturers introduced TDCIPP as a household FR.^{84, 86, 99} Known as Fyrol FR2,^{77, 84, 100} TDCIPP was initially applied to children's sleepwear to meet US flammability standards in the mid-1970s. Concerns of mutagenicity^{84, 101} led to its discontinuation from sleepwear products in May 1977.^{86, 100} However, TDCIPP use continued in other consumer products, particularly upholstered furniture containing polyurethane foam.^{86, 102, 103} Annual US demand for TDCIPP expanded from an estimated 450 tons in 1997 to 22,700 tons in 2006.^{83, 90} TDCIPP use has continued to grow in the past decade with the subsequent PBDE phase-out.^{81, 102, 103}

Additionally, a growing body of evidence has implicated TDCIPP as an EDC with thyroid targets.^{83, 86-88} TDCIPP exposures have been correlated with altered thyroid hormone levels in human men,¹⁰⁴ as well as suspected neurotoxicity, developmental toxicity, and hepatotoxicity in various model organisms.^{83, 88} Although TDCIPP mechanisms of action remain unknown, there is particular interest in the downregulation of messenger RNA expression and ribosome protein genes along the hypothalamic-pituitary-thyroid axis.⁸⁸⁻⁹⁰ Ribosome biogenesis is suggested to drive cell growth, and the downregulation of ribosome protein genes may be important in TDCIPP-induced phenotypic alterations (e.g. decreased cell quantity).⁹⁰ With historic TDCIPP use and exposure differences observed in this study, evidence of ECD mechanisms presents a converging line of evidence for the association of household bioavailable TDCIPP exposures with feline hyperthyroidism.

Widespread TDCIPP exposures among human populations, as documented by NHANES data,³¹ can potentially be monitored using cats as sentinels.^{105, 106} Such TDCIPP and other chemical exposure data may be particularly useful in homes with either a cat at risk of developing feline hyperthyroidism and/or a human at risk of developing TNG.

2.5.2.3 Household and Behavioral Variables

Associations between TDCIPP pet tag concentrations and household and behavioral variables suggested future preventative health interventions that could be implemented to reduce TDCIPP exposures (Table 2.4). With cleaning-related variables, elevated TDCIPP concentrations with air freshener use may indicate OPE applications beyond flame retarding (e.g. plasticizers, anti-foaming agents).^{4, 31, 83} For instance, OPE use as anti-foaming agents^{4, 31} may have applications in gel air fresheners. However, to the authors' knowledge, published studies have not reported emissions of SVOCs from gel air fresheners. Unexpectedly, vacuum frequency did not affect TDCIPP tag concentrations, in contrast to previously published results analyzing wristbands worn by preschool-aged children for FRs.¹⁶ Residence-specific variables (residences built since 2005 or which contain upholstered furniture purchased between 2007 and 2012) were potentially reflective of increasing OPE production volume in recent decades.⁸³

More interestingly, select feline behaviors were associated with TDCIPP. Higher TDCIPP concentrations were associated with any consumption of commercial dry food ($p < 0.001$), a result potentially related to chemical applications in pet food packaging^{28, 59, 60, 63} and warrants further study. TDCIPP concentrations were also positively associated with cats that preferred to sleep on furniture ($p < 0.05$) compared to cats with no location preference in the home, a result attributable to high flammability standards for human consumer products.¹⁰²

FR concentrations beyond TDCIPP were not investigated using multivariate linear models because this study focused on FRs associated with feline hyperthyroidism. Exploring the remaining FRs may provide greater insight into how specific household

and behavioral variables affect the pattern of bioavailable FR exposures among mature, senior, and geriatric cats.

2.5.3 PBDEs

2.5.3.1 Congeners

Similarities between the pet tags and the pentaBDE mixture (Figure 2.2) suggested that hyperthyroid and non-hyperthyroid cats experience similar PBDE exposures and that bioavailable PBDE exposures are not associated with feline hyperthyroidism. Both hyperthyroid and non-hyperthyroid pet tag profiles closely matched the pentaBDE mixture (Bromkal 70-5DE), compared to the octaBDE (Bromkal 79-8DE) and decaBDE (Bromkal 82-0DE) mixtures.⁹⁸ These three profiles were dominated by BDE-47, -99, and -100, with minor contributions from BDE-153 and -154. By comparison, BDE-209 and other HMW congeners dominated the octa- and deca- mixtures, but were undetected in the pet tags. However, additional HMW congener exposures may occur via dust ingestion (e.g. feline grooming habits).^{72, 74} Although hyperthyroid and non-hyperthyroid pet tags demonstrated similar PBDE concentrations in this study, silicone pet tags may still be applied in the future to identify risk factors associated with elevated PBDE concentrations in human home environments.

2.5.3.2 Previous Literature

Previous studies on feline PBDE exposures included samples of cat serum,^{70-74, 106-110} household dust,^{71, 72, 74, 108} and commercial cat food.^{70-72, 107} However, only three publications have positively associated hyperthyroidism diagnoses, serum PBDE concentrations, and dust PBDE concentrations.⁷²⁻⁷⁴

The strongest evidence for a link between PBDE exposures and feline hyperthyroidism came from Guo et al. 2016, a longitudinal California case-control study ($n_{\text{total}}=22$), where the median serum concentrations of 19 PBDE congeners were higher in pet tags worn by hyperthyroid compared to non-hyperthyroid cats.⁷³ Separately, Engdahl et al. 2017

demonstrated a significant association between dust and serum PBDE concentrations in homes with non-hyperthyroid cats ($n_{\text{total}}=17$), but this was solely applicable for BDE-47, -99, and -153.⁷⁴ To date, studies have only examined dust ingestion as the primary FR exposure route for indoor cats.⁷²⁻⁷⁴

2.5.4 Potential Biases of Serum Concentrations

Studies including serum PBDE and thyroid hormone concentrations from hyperthyroid cats may introduce unintentional bias. Serum concentrations represent body burden,^{78, 111} but over 90% of hyperthyroid cats experience moderate to extreme weight loss prior to treatment.¹¹² Weight loss introduces potential overestimation bias into serum PBDE concentrations for hyperthyroid cats because PBDEs stored in fat can be released into serum.⁷⁵ In contrast, the silicone pet tags effectively avoid bias resulting from weight loss while still being indicative of body burden.^{17, 36, 37} Silicone pet tags may serve as a supplement to cat serum samples for future studies.

2.5.5 Intra-Household Variations

Every pet tag featured unique FR exposures for each cat in a shared household (Figure 2.3). These results suggested that silicone pet tags are highly sensitive to individual feline behaviors within a given household. In particular, elevated TDCIPP concentrations among cat pairs were associated with an additional one to six hours/day on upholstered furniture, consistent with results from Table 2.4. Despite the small sample size, this data also suggested that silicone pet tags and other personalized PSDs can effectively assess preventative health interventions.

The intra-household comparisons provide future opportunities to explore other feline chemical exposures, particularly into additional EDCs with thyroid targets. As seen in Figure 2.3, among the hyperthyroid/non-hyperthyroid pairs, the non-hyperthyroid pet tags featured higher concentrations of TDCIPP, TNBP, and EH-TBB. Other potential EDCs,

such as phthalates,²³ were not captured by the flame retardant analytical method and such data may provide insight into additional household chemical exposures

2.5.6 Study Limitations

There were several limitations to this study. First, the study population was composed of non-random recruitments and therefore may not be representative of the wider US senior and geriatric cat population. The small sample size also limited the consideration of potential confounders. However, this is now the largest case-control study on feline hyperthyroidism related to household FR exposures. Second, silicone pet tags sample VOCs and SVOCs in the bioavailable phase, which can incorporate inhalation, dermal contact, and limited ingestion exposure pathways. For instance, silicone wristbands can detect caffeine after it has been ingested and sweat through the skin.⁴ However, the study objectives did not include isolating the FR concentrations attributed to specific exposure routes. Third, this study did not use performance reference compounds as in situ calibration standards to estimate environmental concentrations.²¹ Background air concentrations are difficult to calculate without the use of performance reference compounds, but this study investigated entire external exposures in the context to feline hyperthyroidism. Finally, feline behaviors in the home environment may change over time. Cats may reduce physical activity as they age and as the household dynamic changes (e.g. new furniture).

2.6 Conclusions

The results of this silicone pet tag study demonstrated that cats are exposed to bioavailable household FRs and elevated TDCIPP exposures are associated with the occurrence of feline hyperthyroidism. This study also demonstrated that TDCIPP pet tag concentrations positively associated with thyroid hormone concentrations among non-hyperthyroid cats. Evidence of EDC mechanisms and historic household use further strengthened these results linking TDCIPP exposures with feline hyperthyroidism. In

future studies, cats can wear silicone pet tags to assess preventative health interventions and to act as sentinels for FR and EDC human exposures.

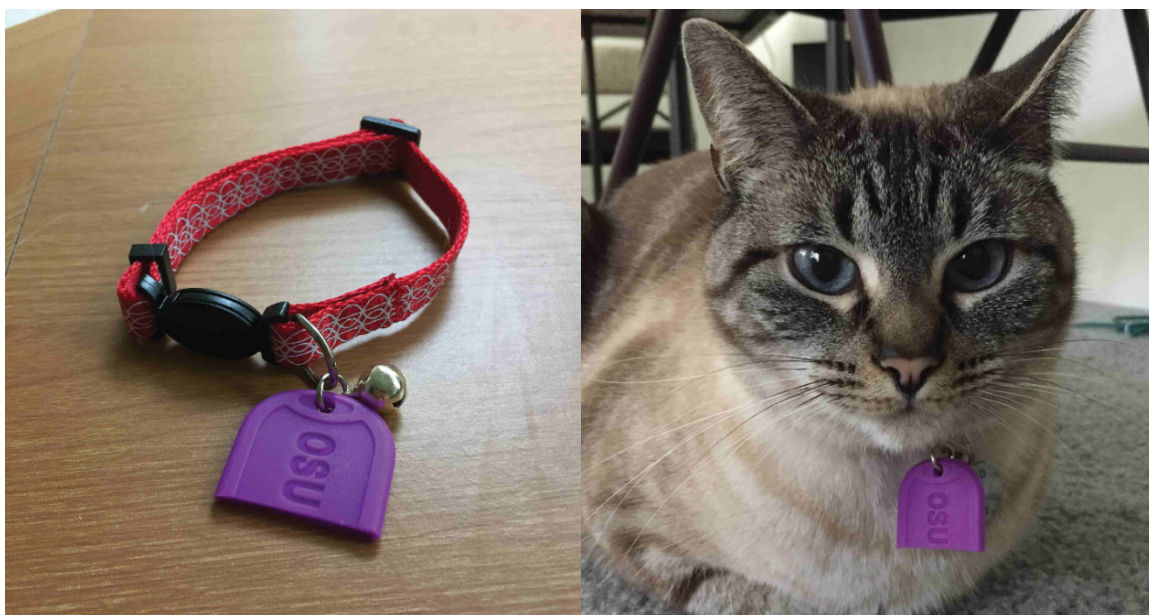


Figure 2.1. The study compared flame retardant exposures using silicone pet tags between hyperthyroid ($n=39$) and non-hyperthyroid ($n=39$) mature, senior, and geriatric cats (e.g. ≥ 7 years).

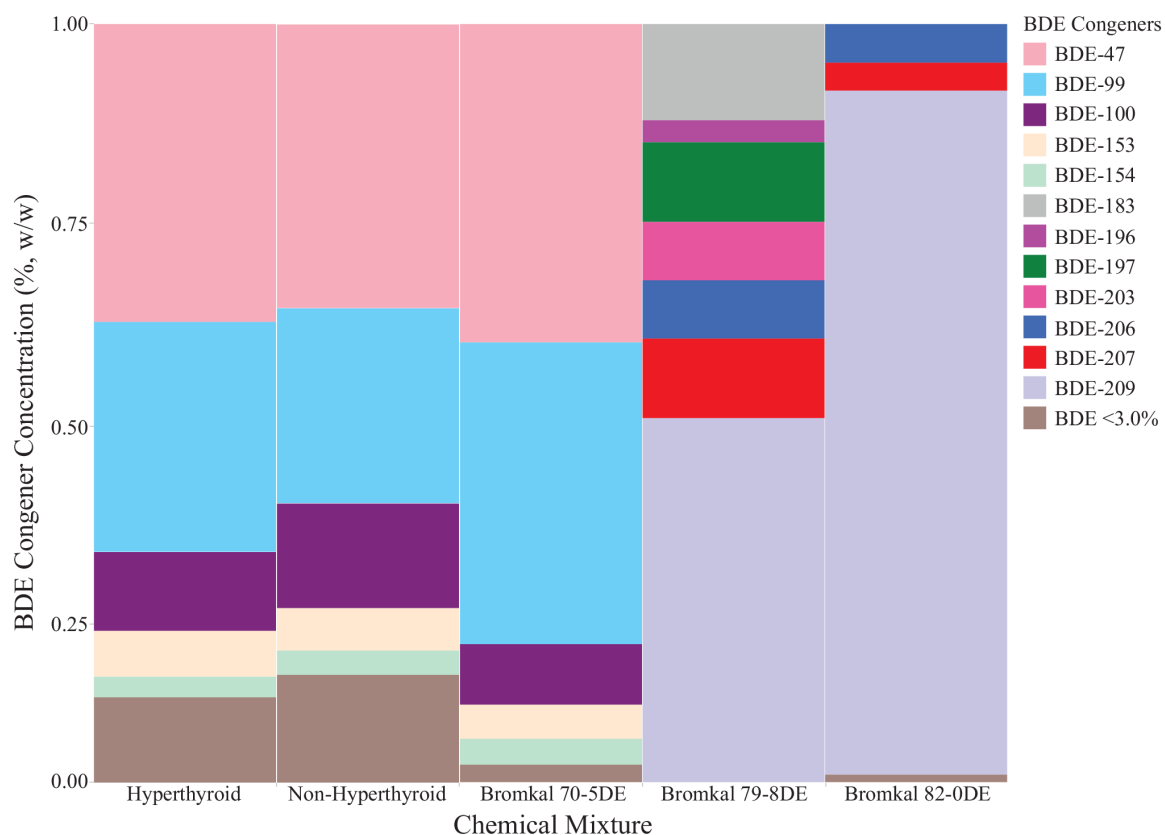


Figure 2.2. The mean PBDE congener profiles identified from hyperthyroid and non-hyperthyroid tags are compared to three commercial PBDE mixtures, known as the Bromkal formulation series.⁹⁸ The pentaBDE mixture (Bromkal 70-5DE) matched the pet tag congener profiles more closely than the octaBDE (Bromkal 79-8DE) and decaBDE (Bromkal 82-0DE) mixtures

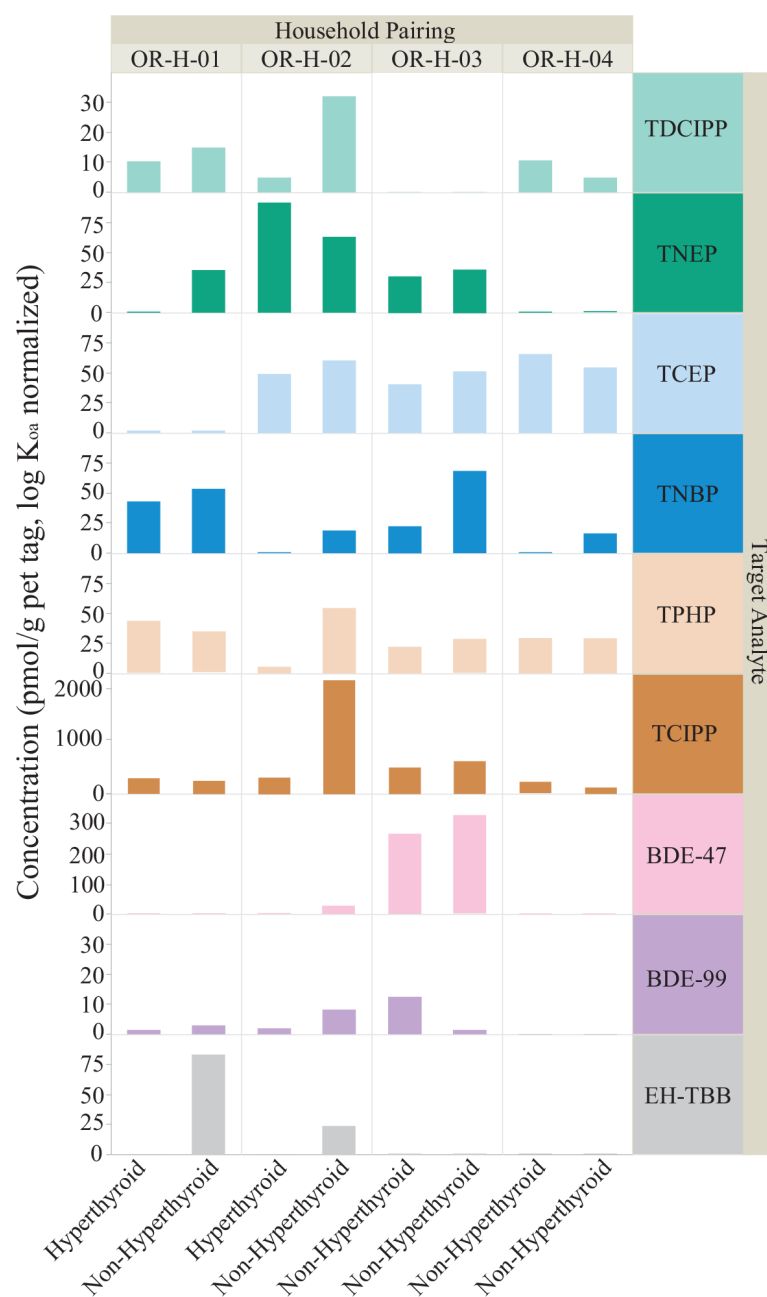


Figure 2.3. The FR profiles from four pairs of cats living in the same household were compared to identify individual variations. The FR profiles between non-hyperthyroid cats in a household (OR-H-03, OR-H-04) were visually more similar than profiles between a hyperthyroid and non-hyperthyroid cat (OR-H-01, OR-H-02). Each individual FR profile was unique, indicative of the sampler sensitivity to individual feline behaviors.

Table 2.1. Population demographics are reported between hyperthyroid and non-hyperthyroid study participants.

Characteristic	Hyperthyroid n=39	Non-Hyperthyroid n=39	P-value
Location			0.176
New York	22 (56%)	16 (41%)	
Oregon	17 (44%)	23 (59%)	
Sex			0.644
Female	20 (51%)	22 (56%)	
Male	18 (46%)	16 (41%)	
Age$\pm$SD (y)	13.1 $\pm$ 2.46	13.4 $\pm$ 2.22	0.591
Weight$\pm$SD (kg)	4.99 $\pm$ 1.46	4.85 $\pm$ 1.78	0.699
Year adopted$\pm$SD	2006 $\pm$ 4.12	2007 $\pm$ 4.22	0.511
Time in residence$\pm$SD (y)	7.50 $\pm$ 4.61	6.00 $\pm$ 4.56	0.169
Breed			0.999
Domestic Short Hair	31 (79%)	26 (67%)	
Domestic Medium Hair	4 (10%)	5 (13%)	
Domestic Long Hair	2 (5.1%)	3 (10%)	
Manx	1 (2.6%)	0 (0.0%)	
Russian Blue	0 (0.0%)	1 (2.6%)	
Siamese/Siamese mix	1 (2.6%)	2 (5.1%)	

Table 2.2. Detection frequencies, summary statistics, and adjusted odds ratios for flame retardants detected in at least one tag. Mantel-Cox χ^2 values and WQS contributor weights are included as alternative analyses to confirm the adjusted odds ratio result.^{95-97, 113} Larger WQS index weights indicate a larger contribution to the mixture effect and a stronger association with feline hyperthyroidism. **Bold***: $p < 0.10$; **Bold****: $p < 0.05$.

Target Analyte	Detection Frequency (% samples)		Median (pmol/g tag)		Geometric Mean (pmol/g tag)		Adjusted Odds Ratio (95% CI)	P-value (odds ratio)	Mantel-Cox χ^2	P-value (χ^2)	Weighted Quantile Sum Contribution
	Hyperthyroid	Non-Hyperthyroid	Hyperthyroid	Non-Hyperthyroid	Hyperthyroid	Non-Hyperthyroid					
TNBP ^{a,b,c}	71.8%	74.4%	160	160	66.6	68.5	0.711 (0.107, 4.61)	0.716	0.549	0.459	0.137
TNEP ^{a,d,e}	41.0%	35.9%	<LOD	<LOD	20.8	23.4	0.921 (0.852, 9.24)	0.943	0.078	0.780	0.070
TCEP ^{a,c,f}	51.3%	56.4%	212	222	56.4	76.0	0.206 (0.014, 2.58)	0.222	1.17	0.280	0.016
TCIPP ^{a,c,g,h}	100%	94.9%	1810	2410	2070	1860	1.01 (0.926, 1.11)	0.870	0.008	0.929	4.51*10 ⁻³
TDCIPP ^{a,d,f,h}	94.9%	97.4%	113	114	146	126	1.37 (0.986, 2.26)	0.060*	6.25	0.012**	0.215
TPHP ^a	94.9%	100%	234	243	164	256	1.09 (0.427, 3.23)	0.840	0.596	0.440	1.67*10 ⁻⁸
Σ OPEs ^{a,c,g,h}	100%	100%	3060	3280	3270	3260	1.01 (0.932, 1.11)	0.822	0.113	0.737	--
BDE-8	2.6%	0.0%	<LOD	<LOD	<LOD	<LOD	--	--	--	--	0.035
BDE-12	2.6%	0.0%	<LOD	<LOD	<LOD	<LOD	--	--	--	--	0.035
BDE-15	0.0%	2.6%	<LOD	<LOD	<LOD	<LOD	--	--	--	--	0.035
BDE-17	0.0%	5.1%	<LOD	<LOD	<LOD	<LOD	--	--	--	--	0.035
BDE-25	2.6%	0.0%	<LOD	<LOD	<LOD	<LOD	--	--	--	--	0.035
BDE-28& BDE-33 ^e	5.1%	10.3%	<LOD	<LOD	<LOD	<LOD	0.949 (0.810, 1.02)	0.186	2.60	0.107	0.035
BDE-47 ^e	89.7%	84.6%	29.8	23.9	24.5	24.8	0.998 (0.990, 1.00)	0.138	0.941	0.332	0.080
BDE-49 ^e	10.3%	10.3%	<LOD	<LOD	<LOD	<LOD	0.975 (0.881, 1.02)	0.338	2.70	0.101	0.035

Table 2.2. Flame retardants detected in at least one tag (Continued)

BDE-66	2.6%	2.6%	<LOD	<LOD	<LOD	<LOD	0.966 (0.773, 1.13)	0.647	1.00	0.317	0.035
BDE-99 ^{d,g}	74.4%	69.2%	19.8	23.4	12.4	12.1	0.997 (0.987, 1.00)	0.356	1.37	0.243	0.090
BDE-100 ^g	25.6%	35.9%	<LOD	<LOD	2.45	4.11	0.991 (0.977, 1.00)	0.098	2.25	0.134	9.09*10 ⁻³
BDE-138	0.0%	2.6%	<LOD	<LOD	<LOD	<LOD	--	--	--	--	0.035
BDE-153 ^g	43.6%	46.2%	<LOD	<LOD	1.56	2.05	0.975 (0.911, 1.01)	0.150	2.71	0.100	6.44*10 ⁻⁸
BDE-154 ^g	23.1%	28.2%	<LOD	<LOD	<LOD	1.14	0.955 (0.832, 1.01)	0.121	2.40	0.121	0.022
$\Sigma_{36}BDES^g$	92.3%	89.7%	106	108	111	130	0.280 (0.005, 1.31)	0.142	1.14	0.285	--
EH-TBB ^{a,f,i}	7.7%	17.9%	<LOD	<LOD	<LOD	9.39	0.998 (0.993, 1.00)	0.142	0.073	0.787	0.035
$\Sigma_2BFRs^{a,f,i}$	7.7%	17.9%	<LOD	<LOD	<LOD	10.8	0.998 (0.993, 1.00)	0.142	0.073	0.787	--

^aOdds ratio calculated using nmol/g tag concentrationsCovariates included ^bage, ^cbreed, ^dsampling season, ^eyears in current residence, ^fyear adopted, ^glocation, ^htime spent outdoors, ⁱweight

Table 2.3. Exponentiated beta (β) coefficients are shown for the multivariate linear models of $\log_{10}$ -transformed OPE and thyroid hormone concentrations. The model was constructed using a stepwise variable selection procedure based on Akaike information criterion optimization. **Bold:** $p < 0.05$.

Model	TNBP		TNEP		TCEP		TCIPP		TDCIPP		TPHP	
Hormone	10^β (95% CI)	p	10^β (95% CI)	p	10^β (95% CI)	p	10^β (95% CI)	p	10^β (95% CI)	p	10^β (95% CI)	p
fT ₄ (ng/dL)												
Model A	1.07 (0.982,1.17)	0.116	0.954 (0.872,1.05)	0.309	1.00 (0.896,1.12)	0.976	1.01 (0.885,1.15)	0.877	0.958 (0.683,1.34)	0.801	0.926 (0.706,1.21)	0.571
Model B	0.996 (0.933,1.06)	0.909	0.969 (0.909,1.03)	0.329	1.03 (0.952,1.11)	0.458	0.897 (0.817,0.986)	0.026	1.10 (0.869,1.39)	0.418	1.21 (0.999,1.47)	0.052
Model C	1.04 (0.945,1.14)	0.422	1.00 (0.929,1.08)	0.949	0.990 (0.927,1.06)	0.763	0.806 (0.738,0.881)	<0.001	1.38 (1.15,1.66)	0.001	1.27 (1.04,1.56)	0.020
TT ₄ (ug/dL)												
Model A	1.12 (0.910,1.37)	0.283	0.954 (0.776,1.17)	0.645	1.11 (0.859,1.43)	0.422	1.12 (0.831,1.52)	0.437	1.26 (0.583,2.72)	0.550	0.809 (0.436,1.50)	0.491
Model B	1.03 (0.846,1.25)	0.784	0.994 (0.823,1.20)	0.953	1.13 (0.901,1.43)	0.277	1.03 (0.780,1.37)	0.817	1.36 (0.675,2.74)	0.381	0.974 (0.549,1.73)	0.928
Model C	1.04 (0.861,1.25)	0.678	0.891 (0.764,1.04)	0.132	1.25 (1.10,1.43)	0.001	0.853 (0.715,1.02)	0.076	1.70 (1.18,2.46)	0.006	1.22 (0.816,1.82)	0.323
TT ₃ (ng/dL)												
Model A	1.56 (0.869,2.79)	0.133	0.725 (0.402,1.31)	0.276	1.32 (0.643,2.73)	0.437	1.98 (0.836,4.69)	0.117	2.46 (0.274,22.2)	0.411	0.429 (0.074,2.50)	0.338
Model B	1.27 (0.717,2.23)	0.407	0.804 (0.461,1.40)	0.431	1.40 (0.715,2.76)	0.315	1.60 (0.706,3.64)	0.252	2.99 (0.384,23.2)	0.287	0.682 (0.127,3.67)	0.648
Model C	0.876 (0.499,1.54)	0.636	0.784 (0.496,1.24)	0.286	2.10 (1.41,3.12)	<0.001	0.961 (0.567,1.63)	0.879	2.59 (0.859,7.80)	0.089	1.72 (0.516,5.74)	0.366

Model A: no covariates

Model B: cholesterol as covariate

Model C: all covariates – cholesterol, age, breed, sampling season, years in current residence, year adopted, location, time spent outdoors, and weight

Table 2.4. Exponentiated beta (β) coefficients are shown for the multivariate linear model of $\log_{10}$ -transformed TDCIPP concentrations with household variables. Covariates include sampling season, adoption year, and whether the cat spent any time outdoors. The model was constructed using a stepwise variable selection procedure based on Akaike information criterion optimization. **Bold***: $p < 0.10$; **Bold****: $p < 0.05$.

Variable	10^{β}	95% CI	p-value
Household Cleaning			
Air freshener use			
Never	Reference		
Annual	0.653	0.330, 1.29	0.223
Seasonal	1.46	0.980, 2.19	0.066*
Monthly	1.97	1.22, 3.18	0.007**
Weekly+	1.61	1.18, 2.20	0.004**
Vacuum frequency			
0 times/month	Reference		
1-4 times/month	1.21	0.778, 1.88	0.402
5-8 times/month	0.982	0.607, 1.59	0.942
9+ times/month	1.06	0.646, 1.74	0.821
Residence			
Number of people	1.10	0.989, 1.22	0.085*
Residence built			
Prior to 1989	Reference		
1990-2004	1.25	0.888, 1.76	0.203
2005 to Present	2.05	1.34, 3.13	0.001**
Last purchase of upholstered furniture			
Prior to 2006	Reference		
2007-2012	2.14	1.26, 3.62	0.006**
2013-Present	1.19	0.718, 1.97	0.499
Feline Behaviors			
Any consumption of commercial dry food	2.77	1.71, 4.49	<0.001**
Preferred location in residence			
No preference	Reference		
Carpet/rug	0.590	0.265, 1.31	0.198
Cat bed/perch	0.849	0.645, 1.12	0.247
Furniture	1.45	1.02, 2.05	0.040**
Human bed	1.40	0.892, 2.21	0.146

Chapter 3 – Discovery of Firefighter Chemical Exposures using Military-Style Silicone
Dog Tags

Carolyn M. Poutasse, Walker S.C. Poston, Sara A. Jahnke, Christopher K. Haddock,
Lane G. Tidwell, Peter D. Hoffman, and Kim A. Anderson

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Radarweg 29

Amsterdam 1043 NX, Netherlands

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3.1 Abstract

Occupational chemical hazards in the fire service are hypothesized to play a role in increased cancer risk, but firefighter chemical exposure assessments are typically based on inexact surrogates. This study presents the military-style dog tag as a new configuration of silicone passive sampling device to sample individual firefighters' (n=56, n_{dogtags}=110) on- and off-duty exposures at one high and one low fire call volume department in the Kansas City, Missouri metropolitan area. Using a 65 PAH method (GC-MS/MS), the tags detected 45 unique PAHs, of which 18 were not previously identified as firefighting exposures. PAH concentrations were higher for on- compared to off-duty tags ($0.25 < \text{Cohen's } d \leq 0.80$) and for the high compared to the low fire call volume department ($0.25 \leq d < 0.70$). Using a 1530 analyte screening method (GC-MS), di-n-butyl phthalate, diisobutyl phthalate, guaiacol, and DEET were commonly detected analytes. The number of fire attacks a firefighter participated in was more strongly correlated with PAH concentrations than firefighter rank or years in the fire service. This suggested that quantitative data should be employed for firefighter exposure assessments, rather than surrogate measures. Because several detected analytes are listed as possible carcinogens, future firefighter exposure studies should consider evaluating complex mixtures to assess individual health risks.

3.2 Introduction

As essential components of the public safety net, career and volunteer firefighters must maintain a high fitness level to respond to emergencies in the communities they serve.¹¹⁴ Unfortunately, firefighters are suggested to have a relatively high incidence of negative health outcomes, including occupationally-related cancers.^{52, 115-117} Cohort and case-control studies have reported possible to probable associations between firefighting and the following cancers: non-Hodgkin's lymphoma, multiple myeloma, prostate, brain, bladder, buccal cavity, pharynx, intestine, kidney, liver, gall bladder, lung, mesothelioma, esophagus, skin, testicles, rectal, colon, stomach, leukemia, and melanoma.^{52, 115-119}

While estimated increased risk across cancers is ~10%, increased risk for some cancers (e.g. mesothelioma) can be up to 20%.⁵² The greater risks for incident cancers and cancer-related mortality among firefighters are hypothesized to be associated with occupational chemical exposures specific to the fire service.

During fire suppression activities, firefighters may be exposed to recognized or probable carcinogens, such as polycyclic aromatic hydrocarbons (PAHs), diesel fumes, and asbestos.^{52, 120-123} The International Agency for Research on Cancer (IARC) recently concluded firefighter occupational exposures ought to be classified as “possibly” carcinogenic to humans due to a limited number of studies and evidence.¹²¹ However, negative health endpoints beyond cancer also result from occupational exposures and should be included in firefighter exposure health studies. For instance, exposure to PAHs is associated with increased risks of cardiovascular disease and mortality from heart attack,¹²⁴ in addition to increasing blood pressure and heart rate, and accelerating the progression of atherosclerosis.^{116, 125, 126} Mechanistic and epidemiological evidence also associate PAH exposures with airway inflammation and asthma.¹²⁷ These studies can be best informed by a detailed characterization of chemical exposures that firefighters experience.

Currently, the assessment and characterization of firefighter exposures to potentially harmful chemicals are almost exclusively based on crude surrogate measures, including job title, department fire call volume, and career length in the fire service.^{52, 128, 129} Fire departments and stations may vary by the average number of fire calls per month, types of fires, maintenance of personal protective equipment (PPE), and frequency of situations involving hazardous materials.^{52, 120, 128, 129} Firefighters also may experience occupational exposures inside their fire departments due to cross-contamination of engine cabs and station quarters from contaminated PPE and diesel fumes.¹¹⁷ With potentially large variability between and within departments, such surrogate measures may produce biased risk estimates (e.g. overestimate or underestimate the exposure quantity and duration) and promote the need for quantitative measurements.

Two methodologies that attempt to overcome the shortcomings inherent in surrogate measures include active air samplers (AAS) and biological samples. Some studies have used AASs to assess firefighter chemical exposures, but the devices are costly, require electricity to function, and complicated to operate.¹³⁰ Because stationary samplers may underestimate individual exposures compared to personal samplers,^{38, 130} AAS backpacks are equipped with a battery pack and pump to continuously sample air and to assess personal chemical exposure.^{37, 121, 131} However, participants' compliance may be reduced due to concerns about safety and backpack weight.^{116, 132} To overcome compliance issues, some studies favor biological samples, such as blood or urine.^{124-126, 129} While biological samples integrate all routes of personal chemical exposures, they are subject to significant inter- and intra-individual variability.^{116, 127, 133} Additionally, neither technique adequately addresses exposures to currently unmonitored chemicals, which may be valuable to understand overall risks to firefighters.

Passive sampling devices (PSDs) can meet the need for a firefighter personal sampler that sequesters unmonitored chemicals. PSDs function by diffusing and concentrating the bioavailable, or gaseous phase, fraction of volatile and semi-volatile organic compounds (VOCs, SVOCs) into a hydrophobic polymer over time.^{3, 4, 18, 131} Although higher molecular weight SVOCs predominantly exist on surfaces and in dust,^{28, 91, 127, 134} a fraction of all SVOCs remain bioavailable in the gaseous phase.^{28, 91, 127, 133-135} The gaseous phase VOC and SVOC fractions are significant to human exposures and subsequent health effects via a combination of inhalation, dermal absorption, and limited ingestion.^{28, 92, 135-137} Estimates indicate that human uptake of SVOCs by skin absorption can be large, potentially equal to or exceeding intake through inhalation.²⁸ Furthermore, gaseous phase PAHs can account for up to 86% of the lifetime cancer risk (i.e. benzo[a]pyrene toxic equivalence factors),^{133, 138} and SVOC inhalation exposures during firefighting activities may increase due to high temperatures increasing the gaseous phase fraction.^{115, 127, 133} Quantifying the bioavailable SVOC fraction is critical for firefighter exposure assessments, and this need can be met using a new model of personal PSDs.

A recent advancement in PSDs is the personal silicone wristband, derived from commercially available wristbands.⁴ Silicone wristbands provide personal exposure assessments to partner with demographic data and health outcomes, leading to the inference of lifestyle and behaviors associated with chemical concentrations.^{12-18, 23, 36-38} To date, silicone PSDs have been used to measure PAH exposures with pregnant women and occupationally exposed roofers;^{4, 37} flame retardants with pre-school children, college students, and housecats;^{16, 17, 22, 36} and pesticides with farmers in developing countries and farmworker children in the US.^{13-15, 23} Because accurate measurements of chemical exposure are a critical component for estimating health effects, wristbands complemented current methods of personal chemical exposure in three separate studies. Hammel et al. 2016 compared wristbands with hand wipes and urine samples for organophosphate esters (OPEs), finding more significant correlations between the urinary metabolites and OPEs in wristbands than with hand wipes.³⁶ The follow-up study by Hammel et al. 2018 further correlated polybrominated diphenyl ether concentrations between wristbands and human serum.¹⁷ Similarly, Dixon et al. 2018 compared concentrations of PAHs in wristbands with AAS backpacks and urinary metabolites, finding more significant correlations between the corresponding urinary metabolites and PAHs in wristbands than with the backpack.³⁷ Because silicone PSDs can act as a biological mimic for human uptake, this study employed the military-style silicone dog tag as a new configuration, developed with the assistance of firefighter focus groups.

The first objective of this study was to evaluate the use and acceptability of the military-style dog tags as a new configuration of personalized silicone PSD. The remaining objectives were to investigate the effects of (1) on- versus off-duty time periods, (2) department fire call volume, and (3) firefighter rank on chemical exposures. Identification and quantification of bioavailable chemical exposures during firefighting activities can provide new opportunities to associate exposures to adverse health outcomes and to assess the effectiveness of innovative PPE to protect first responders and firefighters.

3.3 Materials and Methods

3.3.1 Materials

Optima-grade solvents were obtained from Fisher Scientific (Pittsburgh, PA, USA). Select analytical standards were purchased as single analytes or composite solutions from Accustandard (New Haven, CT), Sigma-Aldrich (St. Louis, MO), TCI America (Tokyo, Japan), SantaCruz Biotechnology (Dallas, TX), and Chiron (Trondheim, Norway). Before use, all laboratory equipment and glassware were washed in an automatic dishwasher with detergent, rinsed with 18 M Ω ·cm water, and baked at >300 °C for 12 h. Polytetrafluoroethylene (PTFE) storage bags and closures were purchased from Welch Fluorocarbon, Inc. (Dover, NH) for air-tight sampler storage and transport.

3.3.2 Silicone Dog Tag Preparation

The silicone dog tags (Figure 3.1; 6.0 cm long by 2.5 cm wide by 0.3 cm thick; ~5.4 g; <https://24hourwristbands.com>, Houston, TX, USA) were prepared as previously reported with minimal modifications.¹⁸ Briefly, the dog tags were vacuum oven conditioned at 300 °C for 12 h at 0.1 Torr (Vacuum Oven, Blue-M, model no. POM18VC, with Welch Duo-seal pump, model no. 1405). Quality control samples were selected to evaluate for data quality objectives prior to storing the dog tags in sealed metal containers at 4 °C (see Section 3.3.6). Dog tags were transferred to PTFE bags before and after deployment.

3.3.3 Firefighter Population and Recruitment

Participant informed consent was obtained in compliance with the procedures approved by the National Development and Research Institutes, Inc. (NDRI) Institutional Review Board (IRB00000634; Oregon State University (OSU) IRB Deferral 8313). Two fire departments in the Kansas City metropolitan area were selected based on the average monthly fire call volume, where “high volume” historically received over 12 fire calls per month and “low volume” fewer than 2 fire calls per month. To ensure the dog tags did not sample bioavailable SVOCs already embedded in current turnout gear, recruited

firefighters at each department ($n_{\text{lowvolume}}=29$; $n_{\text{highvolume}}=27$) were provided with new PPE: turnouts (GXTREME 3.0, Globe Manufacturing Company, LLC, Pittsfield, NH, USA) and hoods (Quest Particle Barrier Hoods, Quest Fire Apparel Inc., Saratoga Springs, NY, USA). After completing a survey on demographics, occupational history, and current exposures, recruited firefighters wore a dog tag on an elastic necklace during the next thirty on- and off-shift days, acting as their own control for non-occupational exposures. During fire calls, tags were worn over clothing but underneath their turnout gear. Sampling occurred from November 2018 to April 2019, and the number of fire attacks a firefighter participated in were recorded. The worn dog tags were returned to OSU, resealed in their respective PTFE bags.

3.3.4 Dog Tag Extractions

The dog tags underwent post-deployment cleaning to remove particulate matter with two rinses of 18 M Ω ·cm and one of isopropanol.⁴ The tags were then stored in amber glass jars at -20 °C until extraction, as previously described with minimal modifications.^{4, 18, 22, 23} Briefly, deuterated analytes were added as recovery surrogates, with respective average recoveries reported in Table B1. Dog tags were extracted with two 50 mL volumes of ethyl acetate at ambient temperature. Sample extracts were combined and reduced to one mL under nitrogen (Turbo-Vap L, Biotage, Charlotte, NC, USA; RapidVap, LabConco, Kansas City, MO, USA; N-EVAP 111, Organomation Associates, Berlin, MA, USA). Sample extracts were stored at 4 °C prior to additional cleanup by solid phase extraction (SPE).^{4, 16, 23} Sample aliquots of 100 μ L underwent SPE using acetonitrile (Cleanert S C18, Agela Technologies, Torrance, CA, USA), were solvent exchanged to iso-octane (OA-SYS N-EVAP 111, Organomation Associates, Berlin, MA, USA), and stored at 4 °C prior to instrument analysis.

3.3.5 Instrument Analysis

3.3.5.1 PAH Method

To investigate documented firefighter exposures, 63 parent and alkylated PAHs were quantitated using an Agilent (Santa Clara, CA) 7890 gas chromatograph (GC) with a 7000 triple quadrupole mass spectrometer (MS/MS).^{18, 24, 37, 38, 139, 140} The instrument parameters, analyte quantification, and target analyte list are given in Appendix B and Table B2, and target analyte concentrations were surrogate-corrected. PAHs were also included in the 1530 screening method.

3.3.5.2 1530 Screening Method

The analytical screen of 1530 chemicals using a 6890N GC with a 5975B Mass Selective Detector in full scan mode. The target list included 124 flame retardants, 185 industrial-related chemicals, 98 PAHs (data not shown), 773 pesticides, 76 personal care products (PCPs), 14 phthalates, and 260 polychlorinated biphenyls (PCBs), dioxins, and furans.^{19, 23} Details about the semi-quantitative method have been previously reported¹⁹ and the full analyte list is available online (<http://fses.oregonstate.edu/masv-analyte-list>). Instrument parameters and analyte semi-quantification are given in Appendix B.

3.3.6 Quality Assurance and Quality Control

Statistical analyses were performed using R free software (CRAN R Project version 3.5.2) and SAS statistical software (JMP Pro version 13.0.0; SAS Institute Inc., Cary, NC) for analytes detected in at least one tag. PAH concentrations were converted to moles per gram dog tag (mol/g tag), and analytes from the 1530 screening method were converted to moles per dog tag (mol/tag). Concentrations below the instrument limits of quantitation (LOQs) were substituted with a value equal to $LOQ/\sqrt{2}$ and below the instrument limits of detections (LODs) with $LOD/\sqrt{2}$. If target analyte concentrations were approximately log-normally distributed (Kolmogorov's test, $p < 0.05$), then a $\log_{10}$ -transformation was conducted, reassessed for normality, and applied to parametric statistical tests. As an alternative analysis, a modified Kaplan-Meier procedure for non-detected values was applied (Table B3, Table B6).

All chemical categories (e.g. phthalates) and analytes detected in over 50% of the dog tags were investigated for concentration differences between duty shift days (paired t-test) and fire departments (t-test). A subset of chemical categories and analytes ($p < 0.10$) were selected for investigation with questionnaire variables. With concentration as the response variable, the multivariate regression models were constructed with all occupational-related variables (e.g. years in the fire service) and potential confounders (t-test or ANOVA, $p < 0.10$), using a stepwise selection procedure. The final adjusted models were determined using residual analyses, investigating influential observations, and evaluating goodness-of-fit with R-squared values.

3.4 Results and Discussion

3.4.1 Firefighter Compliance

Researchers recruited 56 firefighters between November 2018 and March 2019, for a total of 30 on- and off-duty days. All firefighters returned their on-duty tags ($n_{\text{on-duty}}=56$; 100% compliance), and all but two firefighters returned their off-duty tags ($n_{\text{off-duty}}=54$; 96% compliance). There were 16 dog tags returned to OSU with the PTFE bag partially sealed (85% compliance), which was included as a statistical confounder for select analytes (t-test, $p < 0.05$). All tags detected a minimum of 13 PAHs above the respective LOQs. A summary of firefighter population demographics is given in Table 3.1.

3.4.2 Chemical Detections

3.4.2.1 Chemical Detections: PAH Quantitative Method

Out of 110 dog tags, a total of 45 PAHs were detected at least once and 21 PAHs were detected in over 50% of the samples (Table B2, Figure B1A). No two dog tags had identical PAH exposure profiles, as visually represented in Figure 3.2A.

To the authors' knowledge, this study is the first to identify personal firefighter exposures to 18 unique PAHs (Figure 3.3, Table B2). Notably, five of these previously unidentified

PAHs were detected in over 75% of the dog tags (Table B2, Figure B1A). Although firefighter PAH exposures have been documented using PSDs, AASs, swatch samples, skin wipe samples, and dust samples,^{120, 122, 131, 141-148} these results indicate a need to explore exposures and toxicities beyond the EPA's 16 priority PAHs.¹⁴⁹

Table B3 compares on- and off-duty paired PAH tag concentrations (paired t-test) and low and high call volume department PAH tag concentrations (t-test). Figure 3.4A presents graphical representations of differences between paired duty status tags, while differences between fire departments are shown in Figures 3.4B.

The firefighter dog tags illustrated occupational PAH exposures, similar to a previous study where silicone wristbands were worn by roofers (n=8) applying hot mopping-grade asphalt (t=40 h).⁴ The roofer study used a 33 PAH method,¹⁵⁰ where 23 PAHs were detected. If the same 33 PAH method had been applied to the firefighter study, then 27 PAHs would have been detected, where the four additional target analytes were 9-methylanthracene, 3,6-dimethylphenanthrene, 6-methylchrysene, and indeno[1,2,3-c,d]pyrene. Indeno[1,2,3-c,d]pyrene is listed as an EPA priority PAH¹⁴⁹ and has been previously identified as a firefighter exposure. Because the silicone PSDs were worn for different lengths of time, direct concentration comparisons were not available. In both studies, samplers were worn underneath PPE, such that silicone PSDs could evaluate the PPE effectiveness when considering bioavailable PAH exposures.

3.4.2.2 Chemical Detections: 1530 Screening Method

Out of 110 dog tags, 101 unique chemicals were detected at least once (Figure 3.2B, Figure B2): 10 phthalates, 25 personal care products (PCPs), 19 PAHs, 15 pesticides, 22 industrial-related chemicals, nine flame retardants, and one PCB/dioxin/furan. No two dog tags had the same chemical exposure profile (Figure 3.2B), consistent with previous studies.^{15, 37}

The on-duty firefighter tags had a mean of 25.5 chemical detections, ranging from a minimum of 18 and a maximum of 35. This was a larger mean number of detections compared to the 20 mean detections from 262 silicone wristbands worn on three continents.²³ In North America alone (n=163), the mean number of total detections was 22.5, although these wristbands were worn during both occupational and non-occupational time periods and represent a wide demographic range.

Twenty-one target analytes were detected in over 50% of the samples, of which 11 were considered potential endocrine-disrupting chemicals (Table B5; <http://fses.oregonstate.edu/masv-analyte-list>, accessed August 2, 2019). Phthalates and PCPs were the most commonly detected categories and at the largest relative concentrations. This article does not examine PCP chemicals because of a focus on chemical exposures likely related to the occupation of firefighting. The 10 target analytes categorized as phthalates, industrial-related chemicals, and pesticides were selected for further investigation (Table B6). Table B6 includes comparisons of on- and off-duty paired tag concentrations (paired t-test) and of low and high call volume department tag concentrations (t-test). Figure 3.5A-D present graphical representations of both categorical and single analyte data. Differences between duty shift tags are shown in Figures 3.5A and 3.5B, while differences between fire departments are shown in Figures 3.5C and 3.5D.

3.4.3 Chemical Concentrations and Firefighter Variables: PAH Quantitative Method

Out of 21 PAHs displayed in Figure 3.4A, 20 demonstrated higher concentrations for on- compared to off-duty tags, of which 13 were statistically significant (Figure 3.4A, Table B3; paired t-test, $0.25 < \text{Cohen's } d \leq 0.70$, $p < 0.05$). Between fire departments, 15 of the 20 PAHs demonstrated higher concentrations at the high compared to low call volume department and seven were statistically significant (Figure 3.4B, Table B3; t-test, $d > 0.15$, $p < 0.05$).

If Table B3 indicated statistically significant differences, then multivariate models were constructed for those PAHs to investigate associations with variables in the questionnaire (Figure 3.6A-C, Table B4). A total of 19 PAHs were included in Figure 3.6A-C, with all 110 dog tag samples.

To our knowledge, this is the first paper to associate personalized firefighter bioavailable PAH exposures with questionnaire data. Generally, PAH concentrations were most strongly correlated with the number of fire attacks a firefighter participated in during the sampling period, compared to firefighter rank or number of years in the fire service (Figure 3.6A-C, Table B4). For instance, with every additional fire-related emergency, the median pyrene tag concentrations increased by 3% (95% CI: 1.01, 1.06). When examining the median number of fire calls per participant by department (low=7, high=13), this represented a difference of over 25% in pyrene concentrations by department. Although this trend was less pronounced for LMW PAHs, such as naphthalene, this correlation must be considered as chronic exposures and in the context of a firefighter's full career. Fire departments may wish to consider implementing additional decontamination procedures for especially active firefighters. For instance, field decontamination using wet soap, water, and scrubbing reduced PAH concentrations on used turnout jackets by a median of 85%,¹⁵¹ such that thorough decontamination procedures may help reduce personal PAH exposures. Researchers should also examine non-occupational sources of PAHs (e.g. fuels) when investigating firefighter exposures.

Compared to fire attack numbers, firefighter rank (Figure 3.6B, Table B4) was less positively correlated with PAH dog tag concentrations. Compared to captains and chiefs, operational firefighters generally experienced higher concentrations, although only four PAHs were statistically significant out of 19 PAHs investigated (Dunnett's, $p < 0.05$). Because captains and chiefs have more administrative roles than operational firefighters,¹⁵² they are less likely to enter a burning structure and therefore less likely to experience high PAH exposures during a fire event. The number of fire attacks and rank were not correlated (ANOVA, $p > 0.05$).

Similarly, years spent in the fire service (Figure 3.6C, Table B4) was less positively correlated with PAH concentrations than fire attack numbers. However, a small, non-significant trend was observed for 14 out of 19 PAHs, where an increasing number of years was correlated with increasing concentration. For instance, with every additional year in the fire service, anthracene concentrations increased by 3% (95% CI: 0.995, 1.08). This trend may be related to an increased willingness to take risks during a fire-related emergency. During a fire event, more experienced firefighters may spend more time on the fireground or within a burning structure, and therefore spend more time in locations with higher PAH concentrations, compared to less experienced firefighters. As a result, PAH exposures may inadvertently increase with the number of years spent in the fire service. The fire attacks numbers and fire service years were not correlated (ANOVA, $p > 0.05$). Because rank and fire service years were less predictive of PAH dog tag concentrations than fire attack numbers, quantitative data, should be employed for exposure assessments, rather than surrogate measures.

3.4.4 Chemical Concentrations and Firefighter Variables: 1530 Screening Method

If Table B6 indicated statistically significant differences between concentrations of on- and off-duty tags or the high and low call volume departments, then multivariate models were constructed for categorical and analyte data to investigate associations with variables in the questionnaire (Figure 3.7A-C, Table B7).

3.4.4.1 Phthalates

Summed phthalate concentrations were higher for on- compared to off-duty tags, as well as for di(2-ethylhexyl) phthalate (DEHP), diisobutyl phthalate (DIBP), di-n-butyl phthalate (DBP), and di-n-nonyl phthalate (DNNP) (Figure 3.5A, Figure 3.5B, Table B6; paired t-test, $d > 0.25$, $p < 0.05$). Diethyl phthalate (DEP) concentrations were lower in on- compared to off-duty tags (Figure 3.5B, Table B6; paired t-test, $d > 0.40$, $p < 0.05$).

Summed phthalate concentrations between call volume departments were comparable (Figure 3.5C, Table B6; t-test, $r < 0.10$, $p > 0.10$), but individual phthalate concentrations differed. Concentrations of butyl benzyl phthalate (BBP) and di-n-nonyl phthalate (DNNP) were lower at the high compared to low call volume department (Figure 3.5D, Table B6; t-test, $d > 0.40$, $p < 0.05$).

This is the first paper to associate individualized firefighter phthalate exposures with questionnaire data. No overall trends were observed for the number of fire attacks and firefighter rank (Figure 3.7A and 3.7B). However, phthalate concentrations were slightly higher with increasing years spent in the fire service (Figure 3.7C, Table B7), which was consistent with the PAH results (Figure 3.6C). Because of this consistency, we again suggest that this trend may be linked to an increased willingness to take risks during fire calls. Sources for phthalates include firefighter turnout gear, gloves, and hoods,^{122, 153} such that more experienced firefighters may spend more time in their turnout gear on the fireground than less experienced firefighters. Consequently, increasing years in the fire service may increase both phthalate and PAH exposures.

Phthalates have also been associated with a wide variety of consumer products, such as medical products and automotive parts.^{122, 154, 155} Manufacturers frequently add phthalates as plasticizers to increase longevity, although select phthalates are banned from use in childcare products in Europe due to health concerns.¹⁵⁵ The US EPA has classified multiple phthalates as probable carcinogens,^{123, 155, 156} prompting a need to consider phthalate exposures in conjunction with other possible carcinogens.

3.4.4.2 Industrial-Related

Summed industrial-related concentrations were higher for on- compared to off-duty tags, as well as guaiacol and benzothiazole concentrations (Figure 3.5A, Figure 3.5B, Table B6; paired t-test, $d > 0.55$, $p < 0.01$). Industrial-related concentrations were comparable between departments, although benzothiazole concentrations were statistically lower at the high call volume department (Figure 3.5D, Table B6; t-test, $r > 0.55$, $p < 0.01$). Because

the concentrations of only two target analytes from the industrial-related category (i.e. guaiacol and benzothiazole) were modeled with questionnaire data, overall trends were not examined.

To our knowledge, this is the first documented occurrence of bioavailable guaiacol and benzothiazole exposures among structural firefighters. Guaiacol, a major component of wood smoke and creosote,¹⁵⁷ is categorized as a probable human carcinogen by IARC.¹⁵⁸ Among wildland firefighters, urinary metabolites of guaiacol have been documented¹⁵⁹ and guaiacol has been recommended as a measure of wood smoke exposure. Although the number of fire attacks and years in the fire service were not statistically associated with tag concentrations (Figure 3.7A, Figure 3.7B), guaiacol concentrations were higher from dog tags worn by captains compared to operational firefighters (Figure 3.7B, Table B7).

Benzothiazole and its derivatives are typically manufactured for a variety of industrial applications, such as corrosion inhibitors to increase product performance and as azo dyes for consumer products.^{160, 161} Benzothiazole also occurs naturally as a volatile organic constituent in black tea leaves¹⁶² and a flavor compound by fungi.¹⁶³ Interestingly, derivatives of benzothiazole (e.g. 2-arylbenzothiazole) are used as a basis for various pharmacological agents and have emerged as promising anti-cancer therapeutics in drug discovery.¹⁶⁴ With this background information, the frequent detection of benzothiazole (n=81 dog tags, 74%) served as a reminder that chemical exposures may not necessarily lead to adverse health outcomes and that individual mixture components of complex firefighter chemical exposures may have significant toxicological implications (see Section 3.4.5). Although the number of fire attacks and years in the fire service were not significant variables (Figure 3.7A and 3.7B), higher median benzothiazole concentrations were associated with dog tags worn by operational firefighters compared to captains and chiefs (Figure 3.7B, Table B7).

3.4.4.3 Pesticides

Summed pesticide concentrations were similar between on- and off-duty tags (Figure 3.5A, Table B6), but N,N-diethyl-m-toluamide concentrations were higher for on- compared to off-duty dog tags (Figure 3.5B, Table B6; paired t-test, $d > 0.25$, $p < 0.05$). Combined pesticide concentrations were higher at the high compared to low call volume department, potentially driven by N,N-diethyl-m-toluamide concentrations (Figure 3.5C, Figure 3.5D, Table B6, t-test, $d > 0.35$, $p < 0.05$).

N,N-diethyl-m-toluamide is commonly known as the insect repellent DEET, and the number of fire attacks was statistically associated with increasing concentrations (Figure 3.7A; 6%, 95% CI: 1.01, 1.12). DEET may be commonly present at building or car fires, even during winter months. Although DEET is not currently classifiable as a human carcinogen according to the US EPA,¹⁶⁵ future cancer risk assessments of firefighter chemical exposures may need to consider the mixture effects of personal pesticide use with occupational chemicals.

3.4.5 Toxicological Implications

As demonstrated in this study, firefighters are exposed to complex chemical mixtures while both on- and off-duty; however, toxicological studies and cancer risk assessments typically focus on single chemicals.^{53, 166} Compared to single component toxicological tests, chemicals may have different toxicities in a mixture, which could result in additive, synergistic, or antagonistic effects.⁵³ When evaluating chemicals individually, researchers may inadvertently over- or underestimate firefighter health risks.^{167, 168} Real-world individualized chemical mixtures may inform toxicological experiments and provide a broader context for future firefighter risk assessments.

3.4.6 Limitations

There were several limitations associated with this study. First, the firefighters were non-random recruitments and not necessarily representative of the wider US firefighter population. Second, the small sample size limited the ability to assess for potential

confounders. Third, firefighters did not keep daily logs of their activities and potential exposures during the study period. However, given the evidence presented in this study, daily logs and personal diaries are less useful than quantitative data for exposure assessments. Fourth, the silicone dog tags sample both SVOCs and VOCs in the bioavailable phase, which combines inhalation, dermal, and some ingestion exposure pathways. The chemical exposures associated with a specific exposure pathway cannot currently be isolated with this study design.

3.5 Conclusions

This is the first study to apply military-style silicone dog tags as a personal PSDs to investigate occupational and non-occupational firefighter bioavailable chemical exposures at multiple fire departments. The dog tags detected 18 PAHs that had not previously been known as firefighter exposures, and several commonly detected analytes besides PAHs (e.g. phthalates, DEHP) are currently classified as possible carcinogens. When detected, the majority of chemicals had higher tag concentrations when worn on- compared to off-duty and from the high compared to the low call volume department. The number of fire attacks were positively associated with increasing PAH dog tag concentrations, demonstrating that quantitative data provides a more accurate picture of firefighter exposures compared to crude surrogate measurements. For future cancer risk assessments, researchers ought to consider the complexity of firefighter chemical exposures, as demonstrated in this study, to fully evaluate occupational health risks.



Figure 3.1. Silicone dog tags were worn around the neck underneath firefighting personal protective equipment.

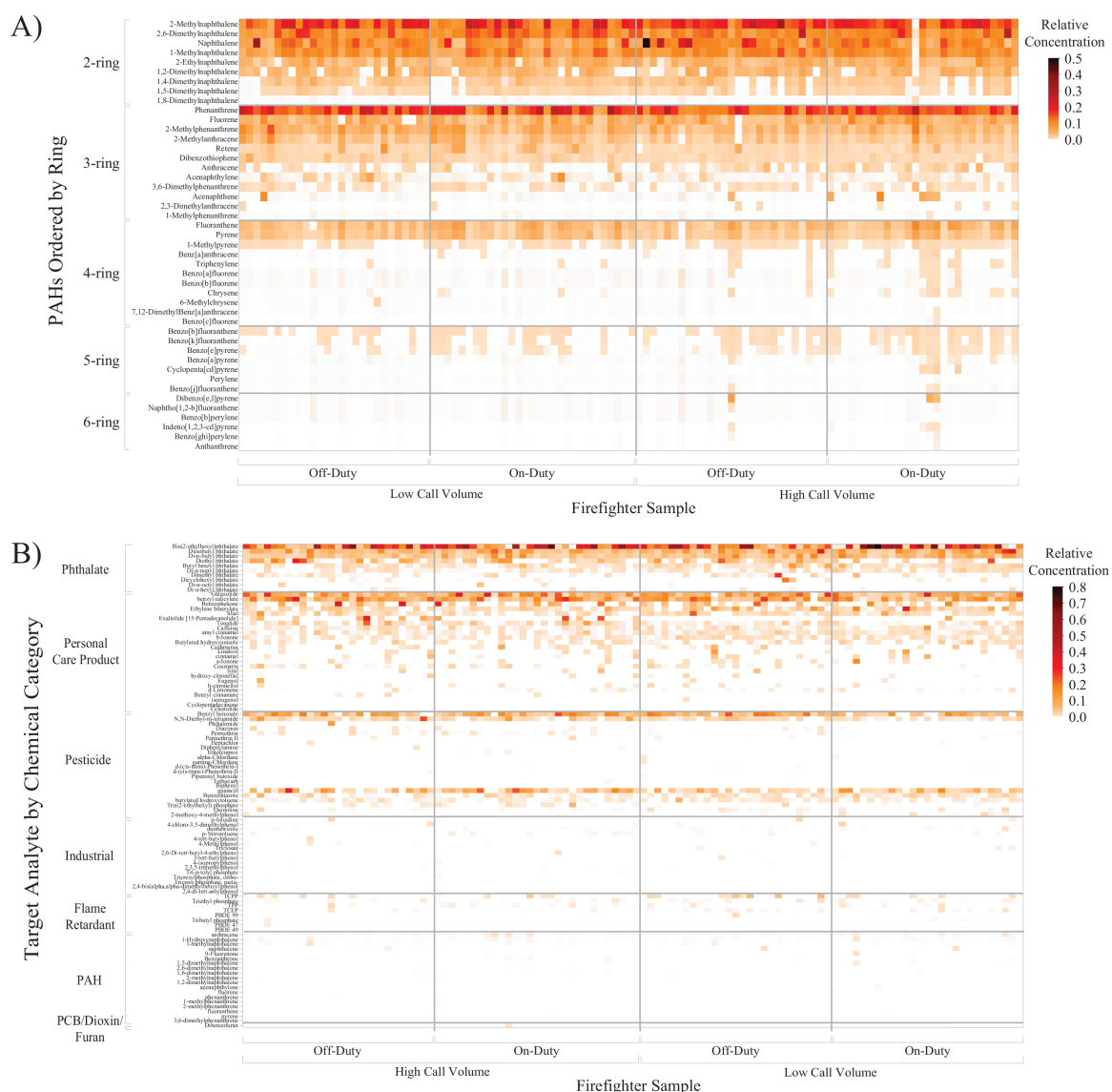


Figure 3.2. The heat maps display each firefighter dog tag sample by fire department and by duty shift in conjunction with their exposure profiles for the A) PAH method and B) 1530 screening method. PAHs were grouped by the number of fused aromatic rings (e.g. benzene), and the screening method analytes were grouped by chemical category. No two tags had the same chemical exposure profile.

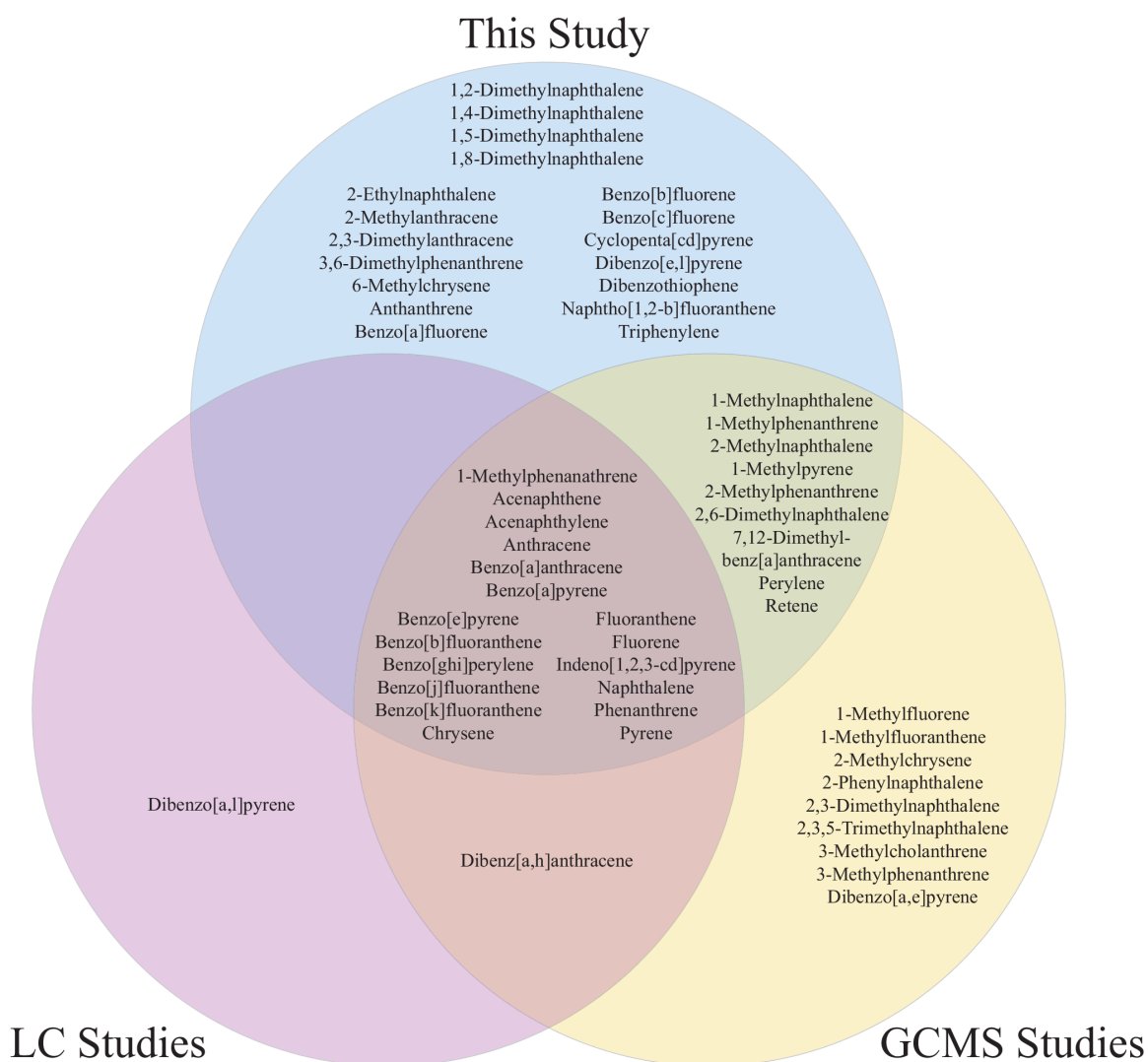


Figure 3.3. The dog tag samples identified 18 PAHs previously unassociated with firefighting using gas chromatography triple quadrupole mass spectrometry¹⁴⁰ compared to earlier studies examining personal firefighter exposures. Studies using gas chromatography mass spectrometry (GC-MS) included Alexander and Baxter 2014, Fabian et al. 2011, Shen et al. 2018, Sjostrom et al. 2019, Stec et al. 2018, Strandberg et al. 2018, and Wingfors et al. 2018.^{120, 122, 131, 143, 145, 147, 169} Studies using liquid chromatography (LC) included Fent et al. 2014, Fent et al. 2018, and Oliveira et al. 2017.^{141, 142, 146}

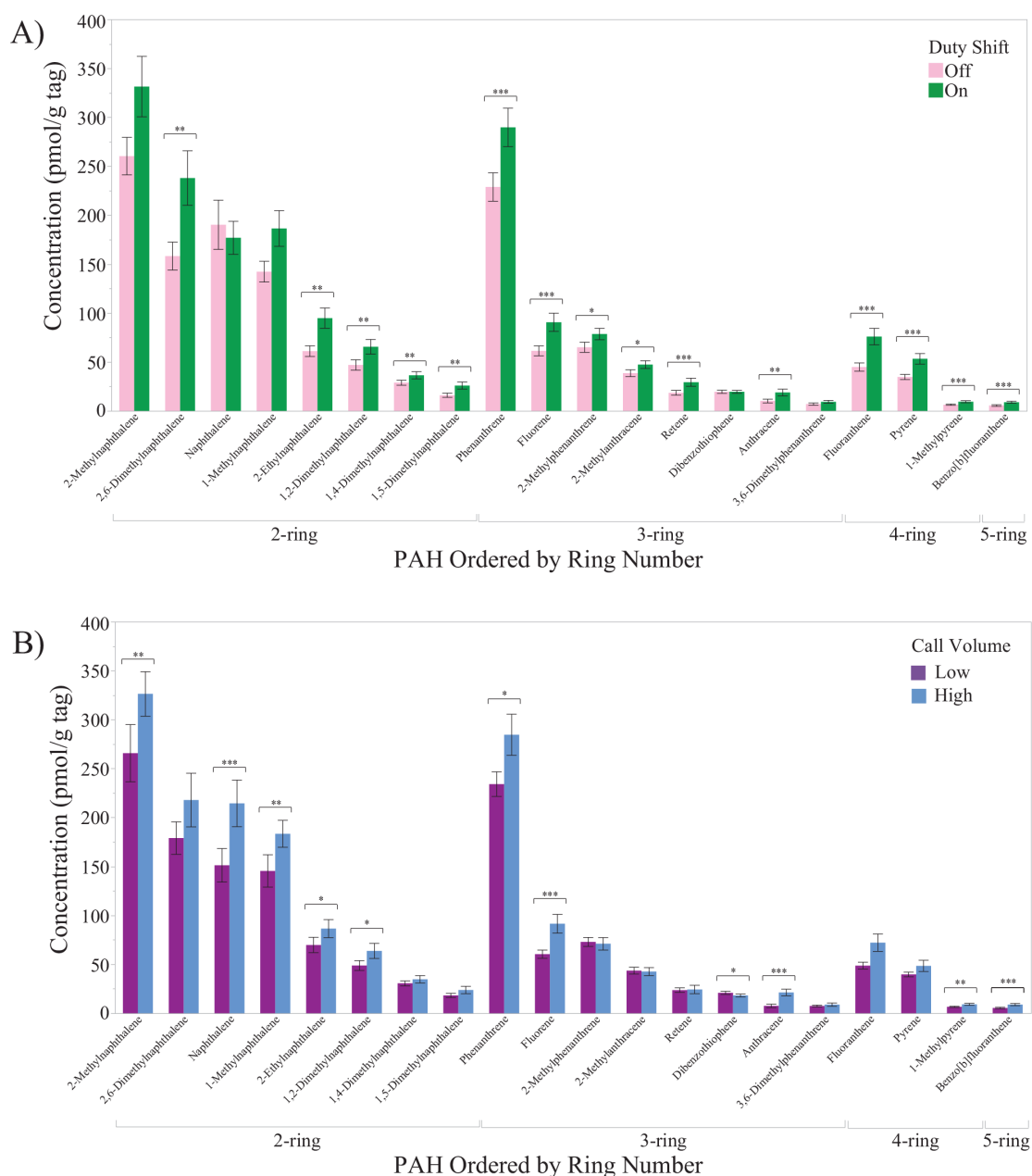


Figure 3.4. Bar graphs compare the PAH concentrations between (A) on- and off-duty paired dog tags and (B) high and low call volume departments. Generally, occupational PAH concentrations were higher than non-occupational concentrations, and higher at the high compared to the low call volume department. **Bold***: $p < 0.10$. **Bold****: $p < 0.05$. **Bold*****: $p < 0.01$ (2-sided p-value).

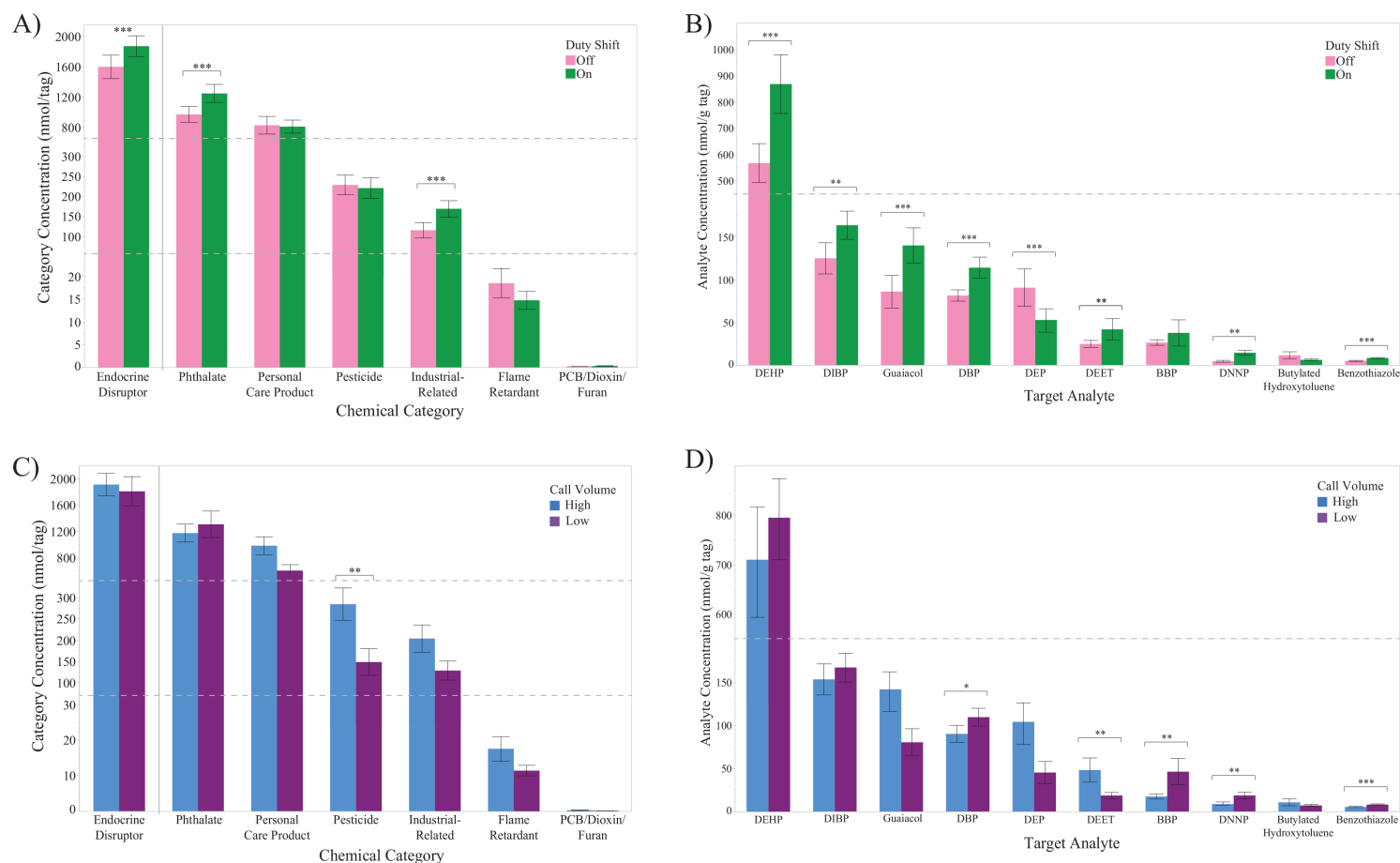


Figure 3.5. Bar graphs compare the chemical concentrations (A, B) between on- and off-duty paired dog tags and (C, D) between high and low call volume departments. The (A,C) summed chemical categories and (B,D) target analytes are shown. **Bold***: $p < 0.10$. **Bold****: $p < 0.05$. **Bold*****: $p < 0.01$ (two-sided p-value). Abbreviations: DEHP – di(2-ethylhexyl) phthalate, DIBP – diisobutyl phthalate, DBP – di-n-butyl phthalate, DEP – diethyl phthalate, DEET – N,N-diethyl-m-toluamide, BBP – butyl benzyl phthalate, DNNP – di-n-nonyl phthalate.

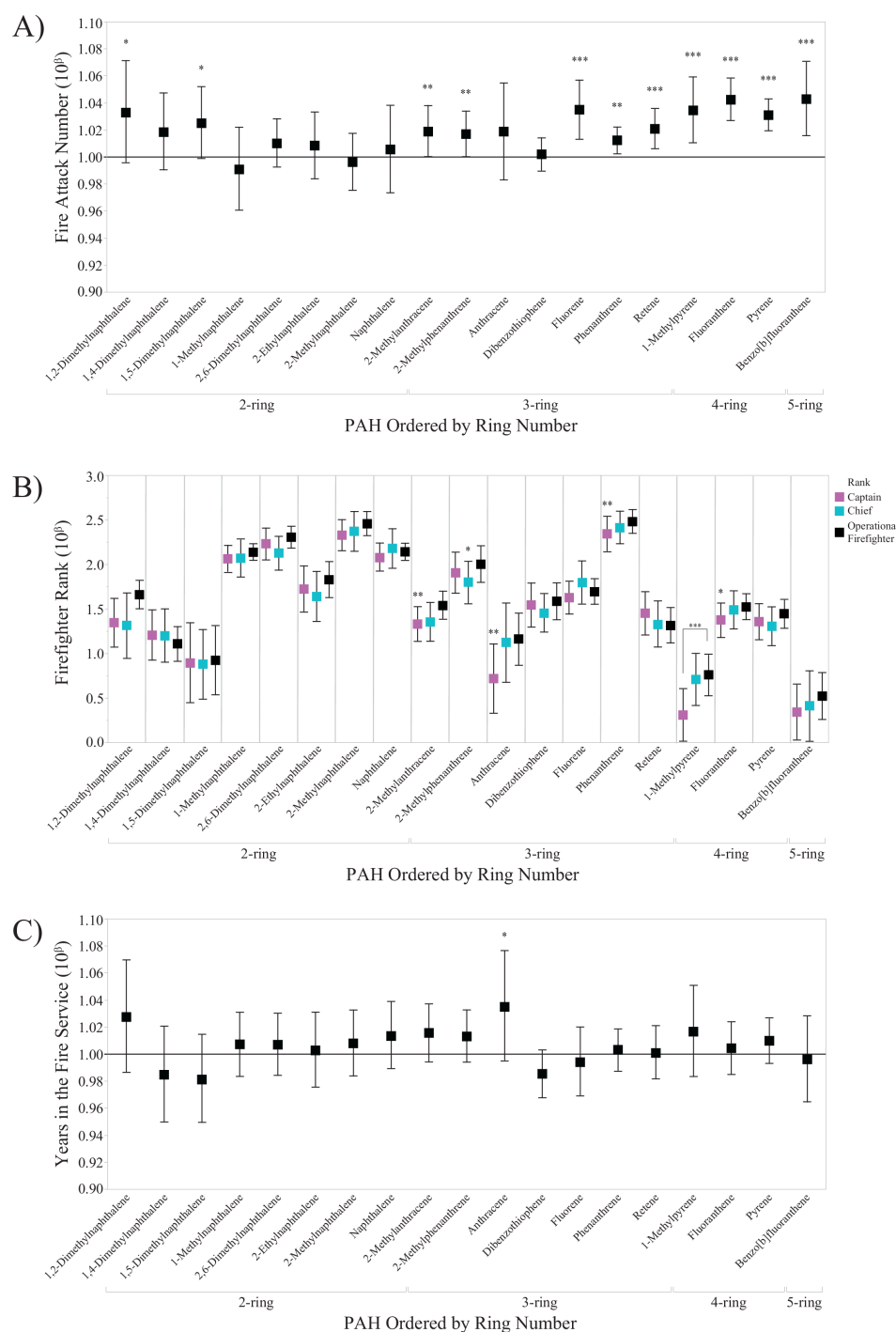


Figure 3.6. Exponentiated β parameter coefficients from the 19 PAH models are shown for occupation-related variables of A) number of fire attacks during the sampling period, B) firefighter rank, and C) years spent in the fire service. In Figures 3.6A and 3.6C, a positive change in PAH concentration was represented by the solid line at $10^0=1.0$. **Bold***: $p<0.10$. **Bold****: $p<0.05$. **Bold*****: $p<0.01$.

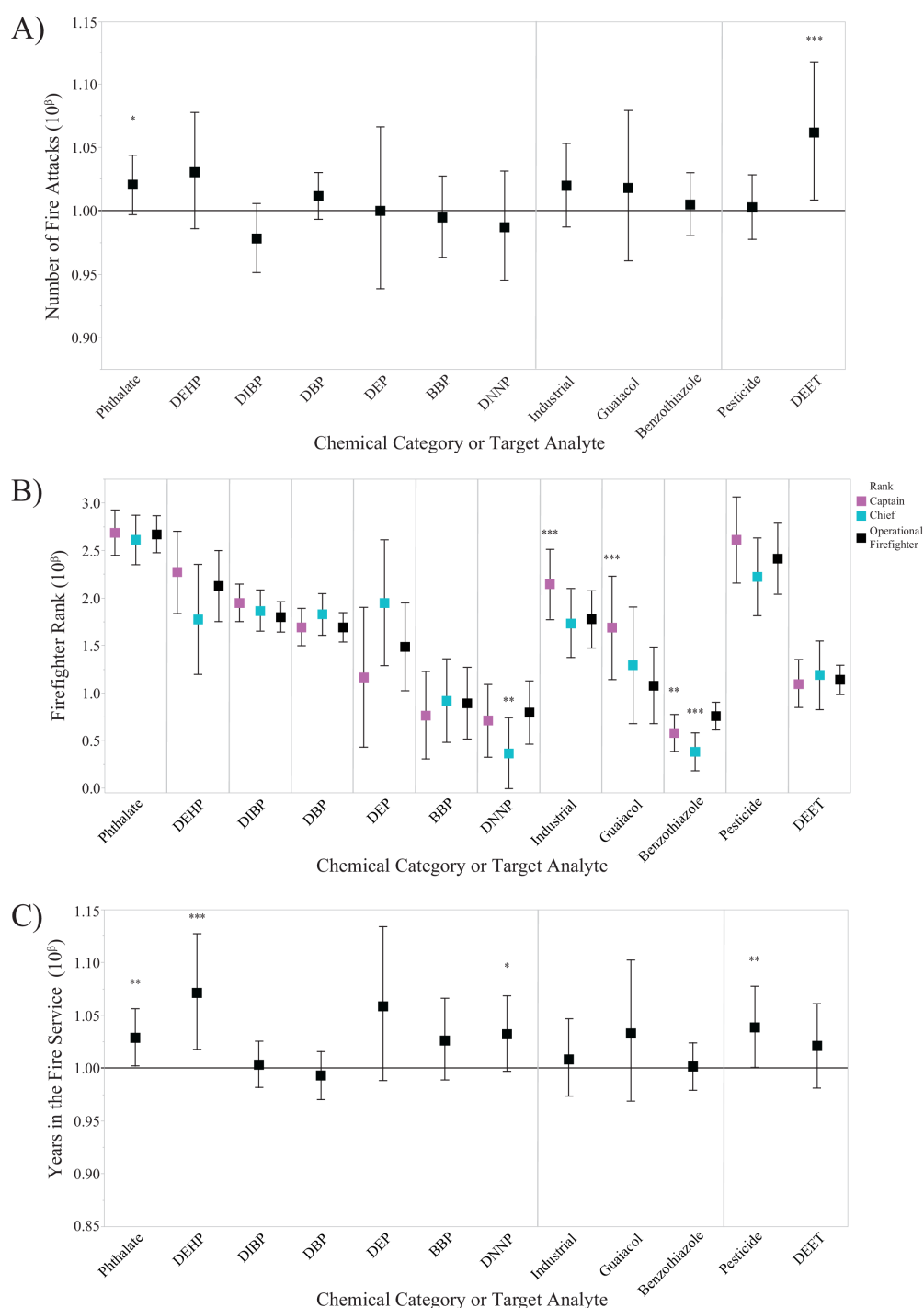


Figure 3.7. Exponentiated β parameter coefficients from the 12 screening method models are shown for occupation-related variables of A) number of fire attacks during the sampling period, B) firefighter rank, and C) years spent in the fire service. In Figures 3.7A and 3.7C, a positive change in chemical concentration was represented by the solid line at $10^6=1.0$. **Bold***: $p<0.10$. **Bold****: $p<0.05$. **Bold*****: $p<0.01$.

Table 3.1. Firefighter demographics are presented for the high and low call volume departments. The term “operational firefighter” includes firefighters, paramedics, drivers/operators/engineers, and individuals with multiple ranks. Due to rounding, not all percentages total 100.

Firefighter Variable	High	Low
Age	37.4±7.98	38.8±7.09
Years in fire service	13.7±9.72	13.4±6.83
Rank		
Operational firefighter	18 (62%)	17 (63%)
Captain	7 (24%)	7 (26%)
Chief	4 (14%)	3 (11%)
Education		
High school graduate	1 (3%)	1 (4%)
College classes	23 (79%)	16 (59%)
College graduate	4 (14%)	10 (37%)
Advanced degree	1 (3%)	0 (0%)
Minority		
Caucasian male	26 (90%)	26 (96%)
Not a Caucasian male	3 (10%)	1 (4%)

Chapter 4 – Conclusion

This dissertation introduced new configurations of silicone PSDs, beyond silicone wristbands, for assessing personal exposures to chemical mixtures. In Chapter 1, we reviewed the attributes, current studies, and potential future applications of silicone wristbands. Participants in exposure science studies can easily wear wristbands, which sample a wide range of bioavailable organic chemicals in their everyday environment. However, depending upon the study design and participant, there is increasing interest in developing silicone PSDs beyond the wristband to sample personal chemical exposures. We developed the silicone pet tag to be worn on a companion animal's collar (Figure 2.1) and the military-style silicone dog tag to be worn as a necklace (Figure 3.1).

With silicone PSDs, researchers can associate chemical concentrations with disease endpoints in animal surrogate and human population studies. In Chapter 2, we developed the silicone pet tag and compared flame retardant concentrations between hyperthyroid and non-hyperthyroid cats. Pet tags worn by hyperthyroid cats had higher concentrations of TDCIPP, and thyroid hormone blood concentrations from healthy cats were positively correlated with TDCIPP concentrations. Despite the small sample size and limited extrapolation to the larger feline population, these results provided the first evidence that TDCIPP exposures may be associated with the onset of feline hyperthyroidism. These results indicated that silicone PSDs can examine chemical exposures in complex epidemiological studies, with a focus on disease endpoints. Notably, the TDCIPP mechanism of action within the thyroid system remains unknown,⁸⁶ although some researchers have suggested the downregulation of messenger RNA expression and ribosome protein genes along the hypothalamic-pituitary-thyroid axis may play a role in TDCIPP-induced phenotypic changes.⁹⁰

Although TDCIPP has been previously implicated as an EDC with thyroid targets,⁸⁶⁻⁸⁹ future studies would benefit from conducting additional bloodwork analyses and correlating flame retardant concentrations between blood and silicone pet tags. Chemical

concentrations from silicone wristbands are indicative of body burden,^{17, 36, 37} but we have yet to demonstrate this in cats. An additional area of future study includes pairing human and companion animal silicone PSDs to explore the chemical concentration correlations between cats, human adults, and children. Such data would help determine whether household exposures are more similar between cats and children⁷² or between cats and adults, and whether cats are an appropriate surrogate animal model for chemical exposures in the home environment.

Chapter 2 focused on flame retardant exposures, but screening the silicone pet tags for other potential EDC exposures could provide further insight into chemical mixture complexity. Because EDCs span multiple chemical classes and have the potential to induce significant health effects via hormone disruption, researchers need to characterize common EDC mixtures, including those frequently present at low concentrations.²³ Potential EDCs, such as phthalates¹⁷⁰ and personal care products,²³ have different mechanisms of action, such that mixture components may interact and lead to antagonistic, additive, or synergistic effects in the thyroid system.⁵³ Investigating the silicone pet tags for other EDCs may lead to a representative household EDC mixture for future toxicological experiments.

Researchers can also quantify exposure differences between individuals in high-intensity occupational settings using chemical concentrations from silicone PSDs. In Chapter 3, we compared silicone dog tag chemical concentrations from firefighter participants, comparing concentrations between on- and off-duty time periods and between low and high call volume departments. The dog tags, developed with the assistance of the firefighter focus groups, were analyzed using the 65 PAH method and the 1530 semi-quantitative target analyte screening method as an exploratory analysis. With the silicone dog tags, we identified 18 unique PAHs that had been previously unidentified as firefighting exposures. Chemical concentrations were higher in the on- compared to the off-duty dog tags and in the high compared to the low call volume department dog tags. PAH concentrations were most strongly correlated with the number of fire attacks a

firefighter participated in during the sampling period, compared to firefighter rank and years in the fire service. Collectively, these results indicated that quantitative data should be utilized over surrogate measurements, such as job descriptions, for future firefighter exposure assessments. Although each dog tag exposure profile was unique, researchers may be able to simplify these results and develop a representative firefighter occupational exposure mixture for toxicological experiments.

A possible future study to investigate firefighter chemical exposures combines both silicone pet tags and military-style silicone dog tags: paired samplers worn by human fire investigators and arson dogs, or accelerant detector canines. Although a firefighter cohort study would provide the most data investigating disease endpoints with chemical exposures, the average firefighter career can last over 20 years. This may lead to extensive study costs and project management turnover. By comparison, dogs can live up to 15 years but may only work 10 years in the canine unit before retirement.¹⁷¹ Fire departments responding to a minimum of 50 structural fires per year can apply to the State Farm Arson Dog Program.¹⁷² Furthermore, arson dogs have been diagnosed with various types of cancer,¹⁷³ potentially enabling the canine units to act as animal surrogates for human firefighters in a future cohort study.

For both Chapters 2 and 3, participants were given the option to have their silicone PSD chemical results returned to them. In the report-back, we included the overall study goals, major results, comparisons with other study volunteers, and suggestions for reducing exposures. Although based on a vetted report-back format, the cat and firefighter reports were original creations and were well received by the participants. Returning the chemical results opened opportunities for further dialogue on scientific studies and methods to reduce chemical exposures.

Ongoing and future studies with silicone PSDs will continue to advance the fields of exposure science and epidemiology, building off of results from the 28 studies currently published (Figure 4.1). Ongoing studies include repeat silicone wristband measurements

by individuals impacted by Hurricane Harvey,⁵⁶ as well as paired wristband, respiratory, and location data for individuals diagnosed with asthma.⁵⁰ Such research enable scientists to investigate the intersection between chemical exposures and disease outcomes. There is also enormous potential to include wristbands in future health intervention studies and to determine what behavioral changes (e.g. air freshener use)²² are most strongly associated with chemical concentrations. As accessible scientific technologies, silicone wristbands and silicone PSDs can translate complex chemical exposure data for communities, stakeholders, and regulators. With the assistance of participant contributions and public discourse, silicone PSDs can effectively contribute to the efforts of science supporting society.

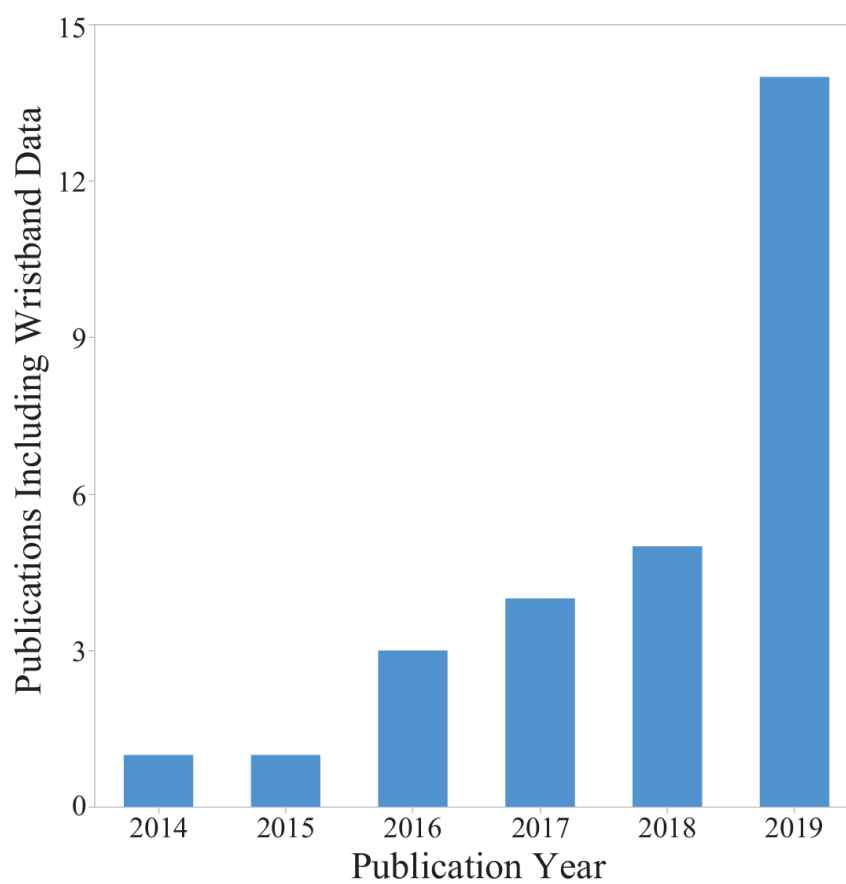


Figure 4.1. Between 2014 and 2019, the number of publications including silicone wristband and silicone PSDs data has increased.

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Appendices

Appendix A: Supporting Information to Chapter 2 – Silicone Pet Tags Associate Tris(1,3-Dichloro-2-Isopropyl) Phosphate Exposures with Feline Hyperthyroidism

Cat Recruitment

As stipulated by the inclusion criteria, all cats were over seven years old. Cat owners completed a consent form and three-page questionnaire about their cat's home environment. If multiple cats were recruited from the same home (n=10), owners completed a consent form and questionnaire for each cat individually.

The diagnosis of hyperthyroidism (n=39) was established on the basis of clinical signs consistent with the disease (e.g. weight loss despite good appetite), a palpable thyroid nodule on physical examination, high basal total thyroxine (TT₄) and free T₄ (fT₄) concentrations, and a good clinical response to treatment for hyperthyroidism. Hyperthyroid cats who had recently undergone treatment with radioiodine or were currently undergoing anti-thyroid drug treatment were eligible.

Non-hyperthyroid, or euthyroid, cats (n=39) were considered healthy on the basis of history, physical examination findings (e.g. lack of palpable thyroid tumors), and results of routine laboratory examinations (e.g. serum biochemical analysis) and serum thyroid profile. The serum thyroid profile included concentrations of fT₄, TT₄, total triiodothyronine (TT₃), and thyroid-stimulating hormone (TSH).

If an enrolled cat did not regularly wear a collar, researchers provided a complimentary collar. Cats wore the pet tag for seven days before the owner removed the tag from the collar, resealed it in the PTFE bag, and returned it to the study coordinator.^{16, 18}

Serum Thyroid Hormone Panel

Non-hyperthyroid cats were required to undergo a serum thyroid panel of tests, including free thyroxine (fT₄), TT₄, TT₃, and TSH, to assess his or her thyroid status and to determine eligibility for this study. After the cat owner completed the consent form and

questionnaire, the recruiting veterinarian examined the cat for clinical findings of feline hyperthyroidism (e.g. palpable goiter). If no clinical features of feline hyperthyroidism were detected, then the veterinarian drew two to three mL of blood, and the sample was shipped to IDEXX Laboratories for the analysis of serum fT₄, TT₄, TT₃, and TSH, conducted by assays validated for cats as previously reported.¹⁷⁴⁻¹⁷⁶ If fT₄ and TT₄ concentrations were within the respective reference intervals (Table A2), then the cat was eligible to be a non-hyperthyroid participant for the study.

Flame Retardant Extraction

The pet tags underwent post-deployment cleaning to remove particulate matter with two rinses of 18 MΩ·cm water and one of isopropanol.¹⁶ The tags were stored in amber glass jars at -20 °C, and then extracted and analyzed as previously reported.^{4, 16} Briefly, FBDE-118 and 2-bromobiphenyl were added as a recovery surrogates, with respective average recoveries of 91±18% (median=92%) and 90±19% (median=91%). Pet tags were extracted with two 100 mL volumes of ethyl acetate at ambient temperature. Sample extracts were combined and quantitatively reduced to one mL under nitrogen (Turbo-Vap L, Biotage, Charlotte, NC, USA; RapidVap, LabConco, Kansas City, MO, USA; N-EVAP 111, Organomation Associates, Berlin, MA, USA). Sample extracts were stored at 4 °C prior to instrument analysis.

The sample extract aliquots were combined with FBDE-126 as the internal standard. Targeted analysis of 44 FRs occurred using an Agilent 7890A gas chromatograph coupled with an Agilent 5975C mass spectrometer (Santa Clara, CA). The gas chromatograph was operated in electron impact mode (70 eV) and select ion monitoring.

Instrument Parameters

The instrument parameters were configured as previously reported.¹⁶ Briefly, an Agilent 7890A gas chromatograph was coupled with an Agilent 5975C mass spectrometer (Santa Clara, CA) for analysis of 44 flame retardant analytes. An Agilent DB-5MS column (30

m × 0.25 mm × 0.25 µm) was operated in electron impact mode (70 eV) and select ion monitoring. Samples were loaded using an Agilent 2 mm dimpled liner and pulsed splitless injection. The temperatures of the MS source, quadrupole, and detector transfer line were set to 250 °C, 150 °C, and 300 °C respectively. The pulse pressure was 30 psi (0.5 min) at a 3 mL/min purge and a 35 mL/min purge after 1 minute. The temperature profile started at 90 °C (1.25 min), ramped to 240 °C (10 °C/min), ramped to 310 °C (20 °C/min), and held at 310 °C (10 min).

The limits of detection (LODs) and limits of quantitation (LOQs) were determined as previously reported.¹⁶ Briefly, for each analyte, the lowest standard with a 15:1 signal-to-noise ratio was run seven times. The resulting standard deviation was used to calculate a 99% confidence interval with the Student's *t*-value and appropriate degree of freedom. LOQs were five times higher than the LODs. The method LODs and LOQs for all analytes, surrogate standards, and internal standard are reported in Table A1.

Quality Control

To ensure pet tags met the data quality objectives, QC samples^{18, 177} accounted for 47% of the total samples analyzed. QC samples included cat tag conditioning verifications (n=4), trip blanks (n=1), laboratory control blanks (n=4), sample duplicates (n=1), sample overspikes (n=2), instrument solvent blanks (n=43), and continuing calibration verifications (n=13). All target analytes were below their respective LODs in all blank QC. All calibration verifications were within data quality objectives at ±30% of the true value for 70% of the target analytes.

A “cat collar” QC sample was included because two pet tags were returned with the collars still attached. Only TCIPP was detected in this QC, below the LOQ. Because the TCIPP LOQ was over 10-fold lower than either pet tag TCIPP concentration, no correction was made to the samplers returned with the collars.

Particulate-Bound Fraction

A measure of bioavailability is the octanol-air partition coefficients (K_{oa}) of individual chemicals.¹⁷ Because LMW PBDE congeners have lower log K_{oa} values (e.g. 3 to 13),¹⁸ they partition more readily into the air than particulate matter.^{28, 91} Consequently, the LMW congeners also partition more readily into the silicone pet tags than particulate matter. In contrast, HMW PBDE congeners have higher log K_{oa} values and are more frequently detected in house dust than in air.

For this study, any particulate matter on the silicone pet tags was removed during the post-deployment cleaning process.¹⁸ Some previous studies did not include this step prior to laboratory extractions.¹⁷ In general, particulate-bound FRs are “biologically unavailable” for uptake by silicone PSDs.³ Washing the samplers prior to extraction enabled this study to focus only on FRs sequestered by the polymer matrix.

Table A1. Target analytes, CAS numbers, and method limits of detection and quantification are reported for the flame retardant method. LOD – Limit of detection; LOQ – Limit of quantitation; SS – Surrogate standard; IS – Internal standard; N/A – Not applicable.

Target Analyte	Abbreviation	CAS	MW	Method LOD (pmol/g) ^a	Method LOQ (pmol/g)
<i>Polybrominated diphenyl ethers</i>					
2-bromodiphenyl ether	BDE-1	7025-06-1	249.1	3.01	15.1
3-bromodiphenyl ether	BDE-2	6976-00-2	249.1	2.46	12.3
4-bromodiphenyl ether	BDE-3	101-55-3	249.1	2.76	13.8
2,4-dibromodiphenyl ether	BDE-7	53592-10-2	328.0	1.76	8.81
2,4'-dibromodiphenyl ether	BDE-8	49602-91-7	328.0	1.70	8.51
3,2'-dibromodiphenyl ether	BDE-10	2050-47-7	328.0	2.16	10.8
3,3'-dibromodiphenyl ether	BDE-11	6903-63-5	328.0	1.83	9.15
3,4-dibromodiphenyl ether	BDE-12	189084-59-1	328.0	1.80	8.99
3,4'-dibromodiphenyl ether	BDE-13	57186-90-0	328.0	1.19	5.91
4,4'-dibromodiphenyl ether	BDE-15	2050-47-7	328.0	1.05	5.24
2,2',4-tribromodiphenyl ether	BDE-17	147217-75-2	406.9	1.51	7.52
2,3',4-tribromodiphenyl ether	BDE-25	147217-77-4	406.9	1.12	5.58
2,4,4'-tribromodiphenyl ether & 2',3,4-tribromodiphenyl ether	BDE-28 & BDE-33	41318-75-6 & 337513-67-4	406.9	1.02	5.11
2,4,6-tribromodiphenyl ether	BDE-30	49690-94-0	406.9	1.39	6.96
2,4',6-tribromodiphenyl ether	BDE-32	189084-60-4	406.9	1.52	7.62
3,3',4-tribromodiphenyl ether	BDE-35	147217-80-9	406.9	2.90	14.5
3,4,4'-tribromodiphenyl ether	BDE-37	147217-81-0	406.9	0.654	3.27
2,2',4,4'-tetrabromodiphenyl ether	BDE-47	5436-43-1	485.8	1.59	7.93
2,2',4,5'-tetrabromodiphenyl ether	BDE-49	243982-82-3	485.8	1.46	7.29
2,3',4,4'-tetrabromodiphenyl ether	BDE-66	189084-61-5	485.8	1.94	9.70
2,3',4',6-tetrabromodiphenyl ether	BDE-71	189084-62-6	485.8	1.04	5.23
2,4,4',6-tetrabromodiphenyl ether	BDE-75	189084-63-7	485.8	1.43	7.14
3,3',4,4'-tetrabromodiphenyl ether	BDE-77	93703-48-1	485.8	0.642	3.21
2,2',4,4',5-pentabromodiphenyl ether	BDE-99	60348-60-9	564.7	1.52	7.61
2,2',4,4',6-pentabromodiphenyl ether	BDE-100	189084-64-8	564.7	1.57	7.84
2,3,4,5,6-pentabromodiphenyl ether	BDE-116	189084-65-9	564.7	1.42	7.10
2,3',4,4',5-pentabromodiphenyl ether	BDE-118	446254-80-4	564.7	1.51	7.54

Table A1. Flame retardant method (Continued)

Target Analyte	Abbreviation	CAS	MW	Method LOD (pmol/g) ^a	Method LOQ (pmol/g)
<i>Polybrominated diphenyl ethers</i>					
2,3',4,4',6-pentabromodiphenyl ether	BDE-119	189084-66-0	564.7	1.08	5.38
2,2',3,4,4',5'-hexabromodiphenyl ether	BDE-138	182677-30-1	643.6	1.17	5.87
2,2',4,4',5,5'-hexabromodiphenyl ether	BDE-153	68631-49-2	643.6	0.766	3.82
2,2',4,4',5,6'-hexabromodiphenyl ether	BDE-154	207122-15-4	643.6	0.928	4.63
2,3,4,4',5,6-hexabromodiphenyl ether	BDE-166	189084-58-0	643.6	0.771	3.85
2,2',3,4,4',5,6-heptabromodiphenyl ether	BDE-181	189084-67-1	715.5	12.5	62.8
2,2',3,4,4',5',6-heptabromodiphenyl ether	BDE-183	207122-16-5	715.5	10.8	53.9
2,3,3',4,4',5,6-heptabromodiphenyl ether	BDE-190	189084-68-2	715.5	7.10	35.5
<i>Organophosphate flame retardants</i>					
Tri-n-butyl phosphate	TNBP	126-73-8	266.3	4.43	22.3
Tri-n-ethyl phosphate	TNEP	78-40-0	182.2	10.8	53.9
Triphenyl phosphate	TPHP	115-86-6	326.3	1.31	6.53
Tris(2-chloroethyl) phosphate	TCEP	115-96-8	285.5	20.4	102
Tris(1-chloro-2-isopropyl) phosphate	TCIPP	13674-84-5	327.6	27.7	139
Tris(1,3-dichloro-2-isopropyl) phosphate	TDCIPP	13674-87-8	427.9	20.8	104
<i>Brominated flame retardants</i>					
2-ethylhexyl-2,3,4,5-tetrabromobenzoate	EH-TBB	183658-27-7	549.9	8.37	41.8
Di(2-ethylhexyl)tetrabromophthalate	TBPH	26040-51-7	706.1	1.46	7.29
<i>Reference Standards</i>					
2-Bromobiphenyl	2-BBP (SS)	2052-07-5	233.1	3.54	17.7
5'-Fluoro-3,3',4,4',5-pentabromodiphenyl ether	FBDE-126 (IS)	N/A	583.7	N/A	N/A
5'-Fluoro-2,3',4,4',5-pentabromodiphenyl ether	FBDE-118 (SS)	N/A	583.7	1.78	8.89

Table A2. Reference ranges and summary statistics are reported for hormones included in the serum thyroid profile for the 39 non-hyperthyroid cats recruited for the study. Out of free thyroxine (fT₄), total T₄ (TT₄), total triiodothyronine (TT₃), and thyroid-stimulating hormone (TSH) concentrations, a cat was eligible to be a non-hyperthyroid participant if the fT₄ and TT₄ concentrations were within the respective reference intervals.

Thyroid Hormone	Reference Range	Geometric Mean	Standard Deviation	Median	This Study Range
fT ₄ (ng/dL)	0.7-2.6	1.15	0.41	1.10	0.50-2.10
TT ₄ (ug/dL)	0.8-4.7	2.27	0.47	2.20	1.70-3.50
TT ₃ (ng/dL)	52-182	34.0	7.12	35.0	4.1-48.0
TSH (ng/mL)	0.05-0.42	0.04	0.07	0.05	0.01-0.41

Table A3. Spearman's rho correlation coefficients are reported for OPEs detected in over 10% of pet tag samples (n=78). Correlation coefficients were calculated from concentrations in units of picomole of target analyte per gram of pet tag.

		TPHP	TCIPP	TDCIPP	TNBP	TCEP	TNEP
TPHP	r _s	1	0.461	0.305	0.296	0.238	0.131
	p-value	--	<0.001*	0.007*	0.009*	0.036*	0.253
TCIPP	r _s		1	0.394	0.111	0.082	0.263
	p-value		--	<0.001*	0.335	0.478	0.020*
TDCIPP	r _s			1	-0.053	0.271	0.155
	p-value			--	0.648	0.016*	0.176
TNBP	r _s				1	0.129	0.033
	p-value				--	0.259	0.773
TCEP	r _s					1	0.047
	p-value					--	0.684
TNEP	r _s						1
	p-value						--

Bold*: p<0.05

Table A4. Spearman's correlation coefficients are reported for PBDE congeners detected in over 10% of pet tag samples (n=78). Correlation coefficients were calculated from concentrations in units of picomole of target analyte per gram of pet tag.

		BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-49
BDE-47	r_s	1	0.577	0.491	0.519	0.592	0.462
	p-value	--	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
BDE-99	r_s		1	0.542	0.632	0.675	0.439
	p-value		--	<0.001*	<0.001*	<0.001*	<0.001*
BDE-100	r_s			1	0.620	0.537	0.426
	p-value			--	<0.001*	<0.001*	<0.001*
BDE-153	r_s				1	0.830	0.445
	p-value				--	<0.001*	<0.001*
BDE-154	r_s					1	0.543
	p-value					--	<0.001*
BDE-49	r_s						1
	p-value						--

Bold*: $p < 0.05$

Table A5. Unadjusted odds ratios are reported for flame retardants detected in at least one pet tag.

Target Analyte	Unadjusted Odds Ratio (95% CI)	P-value (odds ratio)
TNBP ^a	1.61 (0.313, 8.29)	0.566
TNEP ^a	0.852 (0.117, 6.23)	0.874
TCEP ^a	0.278 (0.027, 2.91)	0.279
TCIPP ^a	1.03 (0.952, 1.12)	0.409
TDCIPP ^a	1.36 (0.923, 2.02)	0.059*
TPHP ^a	1.09 (0.469, 2.53)	0.840
Σ_6OPEs^a	<i>1.03 (0.955, 1.12)</i>	<i>0.415</i>
BDE-8	--	--
BDE-12	--	--
BDE-15	--	--
BDE-17	--	--
BDE-25	--	--
BDE-28& BDE-33	0.390 (0.076, 1.99)	0.258
BDE-47	0.940 (0.447, 1.98)	0.870
BDE-49	0.702 (0.177, 2.78)	0.614
BDE-66	0.759 (0.045, 12.7)	0.848
BDE-99	0.987 (0.508, 1.92)	0.970
BDE-100	0.641 (0.329, 1.25)	0.190
BDE-138	--	--
BDE-153	0.689 (0.291, 1.63)	0.396
BDE-154	0.501 (0.156, 1.61)	0.246
$\Sigma_{36}BDEs$	<i>0.859 (0.564, 1.01)</i>	<i>0.326</i>
EH-TBB ^a	0.489 (0.061, 3.93)	0.492
Σ_2BFRs^a	<i>0.490 (0.061, 3.93)</i>	<i>0.492</i>

Bold*: p<0.10

^aOdds ratio calculated using nmol/g tag concentrations

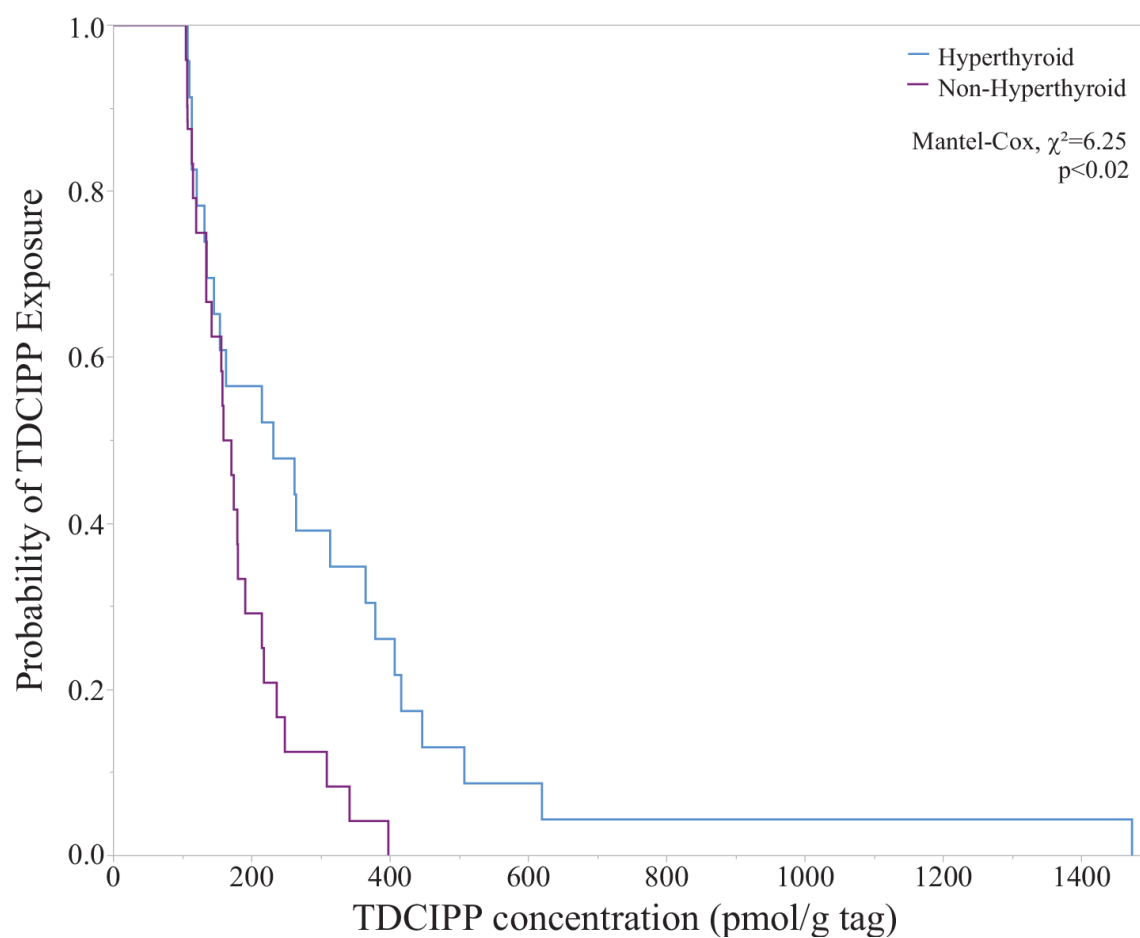


Figure A1. The Mantel-Cox non-parametric test for comparing survival curves indicated that hyperthyroid and non-hyperthyroid TDCIPP tag concentrations were statistically different.



Figure A2. Cat owners appreciated the opportunity to share photos of their cats participating in the study.

Appendix B: Supporting Information to Chapter 3 - Discovery of Firefighter Chemical Exposures using Military-Style Silicone Dog Tags

Firefighter Recruitment

As stipulated by the sampling procedures (NDRI IRB00000634, OSU IRB Deferral 8313), we used a purposeful sampling of heterogeneous instances strategy to select two career departments, Raytown Fire Protection District and Southern Platte Fire Protection District, one with a high fire call volume (>12/month) and one with a low fire call volume (<2/month) based on their historical fire call records. Both departments were otherwise comparable with respect to the number of stations, operational personnel, number of shifts and days worked per month, and community size that they serve. All operational firefighters who were available during the recruitment period were solicited. We recruited >90% of available firefighters for this study. All firefighters were fitted for new turnout gear and particle barrier hoods as a part of this study. Firefighters completed a consent form and five-page baseline questionnaire about their demographics and suspected exposures.

Instrument Parameters: GC-MS/MS

A sample was loaded using an Agilent 4 mm liner and injected in pulsed splitless mode (320 °C, 35 psi pulse pressure, 25 mL/min purge after 0.7 minutes) onto an Agilent Select PAH column (30 m × 0.25 mm × 0.15 µm) with helium carrier gas (2 mL/min). The temperatures of the source and mass detector transfer line were set to 340 °C, 320 °C, and 300 °C respectively. The temperature profile started at 60 °C (1 min), then ramped to 180 °C (40 °C/min), 230 °C (3°C/min), 280 °C (1.5 °C/min), hold for 10 min, then ramped to 298 °C (6 °C/min), 350 °C (16 °C/min), and finally held at 350 °C for 4 min.¹⁴⁰

Analyte Quantification: PAH Quantitative Method

Target analyte data from GC-MS/MS was analyzed using MassHunter Quantitative Analysis v.B.06.00 SP1 build 6.0.388.1 (Agilent Corp. Wilmington, DE) software. Extraction surrogates (Table B1) were quantified relative to the internal standard (perylene_{d12}), and target analytes were quantified relative to the most appropriate surrogate (e.g. retention time). Positive analyte identification was based on retention time, peak shape, and the presence of at least one qualifier ion within $\pm 30\%$ of the expected value. PAH quantification occurred using an internal standard calibration with 7-9 point calibration curves (1 to 10,000 pg/uL) and coefficients of determination of >0.99 . Limits of detection (LODs) were determined by running the 1 pg/uL standard seven times to calculate the standard deviation and 99% confidence interval with the Student's *t*-value. The limits of quantification (LOQs) were five times higher than the LODs.¹⁴⁰ During the PAH method, the laboratory processing blanks quantified 1,2-dimethylnaphthalene, 1-methylnaphthalene, 2,6-dimethylnaphthalene, 2-ethylnaphthalene, 2-methylnaphthalene, and naphthalene. The laboratory processing blanks were used for laboratory background correction prior to statistical analyses.

Instrument Parameters: GC-MS

An Agilent DB-5MS column (30 m $\times$ 0.25 mm $\times$ 0.25 μ m) was operated in electron impact mode (70 eV) and the inlet pressure was locked to the retention time of chlorpyrifos (19.20 $\pm$ 0.20 min). Samples were loaded using an Agilent 4 mm liner and pulsed splitless injection. The temperatures of the MS source and quadrupole, and detector transfer line were set to 150 °C and 300 °C respectively. The pulse pressure was 25 psi (0.5 min) at a 3 mL/min purge and a 20 mL/min purge after 0.45 minutes. The temperature profile started at 70 °C, then ramped to 200 °C, 280 °C, and 310 °C, and finally held at 325 °C.¹⁹

Analyte Quantification: 1530 Screening Method

As a high-throughput screen, the method used an automated mass spectral deconvolution and identification system (AMDIS v. 2.66, National Institute of Standards and Technology) coupled with deconvolution reporting software (DRS, Agilent). Target analyte quantified by AMDIS ($\geq 60\%$ library match) were manually reviewed to remove false positives. Positive analyte identification was based on previously reported data quality objectives to reduce false positives: retention time shifts ± 0.75 min, peak responses greater than 3:1 signal-to-noise ratio, and at least one qualifier ion within the expected ratio with the quantifier ion.^{19, 23} During the 1530 screening method, the laboratory processing blanks quantified 2,4-di-tert-butylphenol, 2,4-bis(alpha,alpha-dimethylbenzyl) phenol, di(2-ethylhexyl) phthalate (DEHP), and di-n-octyl phthalate. Again, the laboratory processing blanks were used for background subtraction before statistical analyses.

Table B1. Deuterated extraction surrogates were applied to all dog tag samples, and percent recoveries are reported (mean, median, standard deviation). The screening method calculated the surrogate concentrations to within a factor of 2.5 of the true value.¹⁹

Extraction Surrogate	1530 Screening Method			PAH Quantitative Method		
	Median	Mean	Standard Deviation	Median	Mean	Standard Deviation
Acenaphthylene-d8	162	157	28	72	72	13
Benzo[a]pyrene-d12	148	136	48	108	109	15
Benzo[ghi]perylene-d12	130	120	33	117	117	16
Chrysene-d12	260	252	51	99	97	19
Fluoranthene-d10	240	244	62	97	99	19
Naphthalene-d8	110	106	29	40	40	11
PCB 100	140	135	56	--	--	--
PCB 209	124	110	29	--	--	--
Phenanthrene-d10	200	202	38	97	99	19
Tetrachloro-meta-xylene	92	92	24	--	--	--
9-Fluorenone-d8	360	361	91	--	--	--

Table B2. The PAH analytical method included 65 target analytes, for which the CAS number, molecular weight (MW), instrument limits of detection (LOD) and quantitation (LOQ), detection frequency, and summary statistics (pmol/tag) are provided. Highlighted analytes indicate the 18 PAHs (Figure 3.3) which were first identified as firefighter exposures in this study.

Target Analyte	MW (g/mole)	CAS Number	Instru. LOD (pmol/g tag)	Instru. LOQ (pmol/g tag)	Detection Frequency (% of 110 dog tags)	Median	Mean	Standard Deviation	Range
Naphthalene	128.17	91-20-3	1.50	7.51	99%	153	184	156	<LOD-1260
2-Methylnaphthalene	142.20	91-57-6	0.912	4.56	99%	265	297	194	<LOD-907
1-Methylnaphthalene	142.20	90-12-0	0.365	1.81	99%	146	165	113	<LOD-568
2-Ethylnaphthalene	156.09	939-27-5	1.15	5.74	96%	56.7	78.5	63.6	<LOQ-386
2,6-Dimethylnaphthalene	156.22	581-42-0	1.06	5.25	100%	157	199	169	<LOQ-1310
1,3- and 1,6-Dimethylnaphthalene	--	575-41-7 and 575-43-9	0.960	4.80	0.0%	--	--	--	--
1,4-Dimethylnaphthalene	156.22	571-58-4	1.47	7.37	81%	31.0	33.0	24.0	<LOD-141
1,5-Dimethylnaphthalene	156.22	571-61-9	1.41	7.03	79%	15.2	21.4	22.8	<LOD-149
1,2-Dimethylnaphthalene	156.22	573-98-8	1.11	5.57	81%	50.8	56.7	48.6	<LOD-350
1,8-Dimethylnaphthalene	156.22	569-41-5	0.984	4.92	0.9%	<LOD	<LOQ	<LOD	<LOD-8.02
2,6-Diethylnaphthalene	184.27	59919-41-4	0.814	4.08	0.0%	--	--	--	--
Acenaphthylene	152.19	208-96-8	2.84	14.2	25%	<LOD	<LOQ	22.4	<LOD-173
Acenaphthene	154.20	83-32-9	1.29	6.43	6.4%	<LOD	14.4	64.7	<LOD-596
Fluorene	166.22	86-73-7	0.880	4.42	96%	67.8	76.5	57.4	<LOD-513
Dibenzothiophene	184.26	132-65-0	0.241	1.21	99%	17.2	19.7	11.4	<LOD-67.6
Phenanthrene	178.23	85-01-8	0.478	2.40	100%	235	260	131	37.5-773
Anthracene	178.23	120-12-7	1.09	5.43	50%	<LOQ	14.9	21.0	<LOD-120
2-Methylphenanthrene	192.25	2531-84-2	0.376	1.86	99%	62.3	72.2	41.3	<LOD-222
2-Methylanthracene	192.25	613-12-7	0.453	2.27	98%	35.9	43.3	28.0	<LOD-148
1-Methylphenanthrene	192.25	832-69-9	1.02	5.12	0.9%	<LOD	<LOQ	<LOD	<LOD-10.9
9-Methylanthracene	192.25	779-02-2	0.838	4.21	0.0%	--	--	--	--
3,6-Dimethylphenanthrene	206.28	1576-67-6	0.377	1.87	67%	5.55	8.42	10.2	<LOD-60.6
2,3-Dimethylanthracene	206.28	613-06-9	0.305	2.44	7.3%	<LOD	<LOQ	4.90	<LOD-33.3
Fluoranthene	202.26	206-44-0	0.490	1.57	98%	46.3	60.9	51.9	<LOD-428
9,10-Dimethylanthracene	206.28	781-43-1	0.763	3.80	0.0%	--	--	--	--

Table B2. The PAH analytical method (Continued)

Target Analyte	MW (g/mole)	CAS Number	Instru. LOD (pmol/g tag)	Instru. LOQ (pmol/g tag)	Detection Frequency (% of 110 dog tags)	Median	Mean	Standard Deviation	Range
Pyrene	202.25	129-00-0	0.385	1.91	99%	35.8	44.4	33.1	<LOD-292
Retene	234.33	483-65-8	0.664	3.31	99%	17.1	24.2	25.8	<LOD-223
Benzo[a]fluorene	216.23	238-84-6	1.43	4.28	7.3%	<LOD	<LOQ	<LOQ	<LOD-35.2
Benzo[b]fluorene	216.23	243-17-4	1.43	4.28	3.6%	<LOD	<LOQ	4.55	<LOD-35.7
Benzo[c]fluorene	216.23	205-12-9	0.257	1.28	3.6%	<LOD	<LOQ	1.75	<LOD-18.4
1-Methylpyrene	216.28	2381-21-7	0.325	1.63	72%	8.66	8.12	6.73	<LOD-43.2
Benz[a]anthracene	228.29	56-55-3	0.608	3.06	12%	<LOD	3.14	8.84	<LOD-72.5
Cyclopenta[c,d]pyrene	229.27	27208-37-3	0.434	2.19	3.6%	<LOD	<LOQ	10.1	<LOD-96.3
Triphenylene	228.29	217-59-4	0.333	1.65	15%	<LOD	2.41	5.11	<LOD-26.5
Chrysene	228.28	218-01-9	0.406	2.02	17%	<LOD	2.36	7.21	<LOD-62.0
6-Methylchrysene	242.31	1705-85-7	0.680	3.39	0.9%	<LOD	<LOQ	<LOQ	<LOD-14.6
5-Methylchrysene	242.31	3697-24-3	1.28	3.82	0.0%	--	--	--	--
Benzo[b]fluoranthene	252.30	205-99-2	0.272	1.36	63%	8.39	7.47	7.14	<LOD-42.2
7,12-Dimethylbenz[a]anthracene	256.34	57-97-6	0.679	3.40	0.9%	<LOD	<LOQ	<LOQ	<LOD-16.8
Benzo[k]fluoranthene	252.30	207-08-9	0.389	1.93	40%	<LOD	5.17	6.17	<LOD-26.1
Benzo[j]fluoranthene	252.30	205-82-3	0.411	2.05	11%	<LOD	<LOQ	2.54	<LOD-24.1
Benz[j] and [e]aceanthrylene	--	202-33-5 and 199-54-2	1.23	3.67	0.0%	--	--	--	--
Benzo[e]pyrene	252.30	192-97-2	0.521	2.59	45%	<LOD	3.72	5.14	<LOD-33.0
Benzo[a]pyrene	252.30	50-32-8	0.866	4.33	13%	<LOQ	<LOQ	<LOQ	<LOD-42.2
Perylene	252.32	198-55-0	0.730	3.67	1.8%	<LOD	<LOQ	<LOD	<LOD-7.60
Indeno[1,2,3-c,d]pyrene	276.33	193-39-5	0.174	0.885	4.5%	<LOD	<LOQ	2.52	<LOD-21.8
Dibenzo[a,h]pyrene	278.35	53-70-3	0.679	3.40	0.0%	--	--	--	--
Picene	278.35	213-46-7	0.492	2.47	0.0%	--	--	--	--
Benzo[ghi]perylene	276.33	191-24-2	0.228	1.15	2.7%	<LOD	0.378	<LOQ	<LOD-10.8
Anthanthrene	276.33	191-26-4	0.221	1.11	0.9%	<LOD	<LOQ	<LOQ	<LOD-9.69
Naphtho[1,2-b]fluoranthene	302.36	5385-22-8	1.02	1.02	1.8%	<LOD	1.15	<LOD	<LOD-8.81
Naphtho[2,3-j] and [1,2-k]fluoranthene	--	205-83-4 and 238-04-0	1.02	1.02	0.0%	--	--	--	--

Table B2. The PAH analytical method (Continued)

Target Analyte	MW (g/mole)	CAS Number	Instru. LOD (pmol/g tag)	Instru. LOQ (pmol/g tag)	Detection Frequency (% of 110 dog tags)	Median	Mean	Standard Deviation	Range
Dibenzo[a,e]fluoranthene	302.37	5385-75-1	0.288	1.45	0.0%	--	--	--	--
Dibenzo[a,l]pyrene	302.37	191-30-0	0.294	1.48	0.0%	--	--	--	--
Naphtho[2,3-k]fluoranthene	302.37	207-18-1	1.02	1.02	0.0%	--	--	--	--
Naphtho[2,3-e]pyrene	302.37	193-09-9	1.02	1.02	0.0%	--	--	--	--
Dibenzo[a,e]pyrene	302.37	192-65-4	3.944	19.7	0.0%	--	--	--	--
Coronene	300.35	191-07-1	0.432	2.15	0.0%	--	--	--	--
Dibenzo[e,l]pyrene	302.36	192-51-8	1.02	1.02	2.7%	<LOD	5.86	28.9	<LOD-180
Naphtho[2,3-a]pyrene	302.36	196-42-9	1.02	1.02	0.0%	--	--	--	--
Benzo[b]perylene	302.36	197-70-6	1.02	1.02	0.0%	--	--	--	--
Dibenzo[a,i]pyrene	302.36	189-55-9	0.870	4.35	0.0%	--	--	--	--
Dibenzo[a,h]pyrene	302.36	189-64-0	0.318	1.59	0.0%	--	--	--	--

Table B3. For PAHs detected in at least 50% of the dog tags, the effect sizes from the parametric statistical tests are presented, in order of detection frequency and the number of aromatic rings. Positive effect sizes^a indicated that tags had higher concentrations from on-duty compared to off-duty shifts (paired t-test)^b and from high compared to low call volume department (two-sided t-test)^b. Higher Mantel-Cox χ^2 test statistics indicated that tag concentrations between fire departments were different.

PAH Target Analyte		Between Duty Shift		Between Call Volume		
		Median (pmol/g tag)		Cohen's d, paired t-test	Cohen's d, t-test	Mantel-Cox χ^2
		On-Duty	Off-duty			
2-ring	2,6-Dimethylnaphthalene	176	139	0.351**	0.177	2.52
	High Call Volume	197	153			
	Low Call Volume	139	127			
	Naphthalene	153	157	-0.147	0.511***	4.00**
	High Call Volume	184	185			
	Low Call Volume	81.8	123			
	2-Methylnaphthalene	288	254	0.068	0.364**	0.140
	High Call Volume	336	278			
	Low Call Volume	168	223			
	1-Methylnaphthalene	152	135	0.089	0.395**	3.36*
	High Call Volume	179	145			
	Low Call Volume	84.2	117			
	2-Ethylnaphthalene	69.1	53.7	0.305**	0.295*	1.60
	High Call Volume	84.7	59.0			
	Low Call Volume	51.7	50.8			
	1,4-Dimethylnaphthalene	35.1	28.2	0.318**	0.173	2.86*
	High Call Volume	37.5	30.3			
	Low Call Volume	27.2	27.6			
	1,2-Dimethylnaphthalene	54.2	47.6	0.314**	0.307*	2.36
	High Call Volume	65.5	51.0			
	Low Call Volume	51.1	44.6			
	1,5-Dimethylnaphthalene	20.4	12.9	0.359**	0.029	3.98**
	High Call Volume	25.2	11.4			
	Low Call Volume	15.2	13.02			
3-ring	Phenanthrene	262	202	0.417***	0.259*	5.19**
	High Call Volume	285	196			
	Low Call Volume	221	229			
	Dibenzothiophene	17.6	17.2	0.002	-0.267*	0.877
	High Call Volume	18.7	15.1			
	Low Call Volume	17.0	20.5			
	2-Methylphenanthrene	70.4	58.2	0.264*	-0.238	0.002
	High Call Volume	67.0	48.0			
	Low Call Volume	79.7	62.9			
	Retene	20.8	14.9	0.749***	-0.150	0.466
	High Call Volume	18.0	13.8			
	Low Call Volume	22.7	16.3			
	2-Methylanthracene	42.9	32.3	0.263*	-0.163	0.052
	High Call Volume	38.5	28.4			
	Low Call Volume	44.8	33.3			

Table B3. PAH effect sizes (Continued)

PAH Target Analyte		Between Duty Shift		Between Call Volume		
		Median (pmol/g tag)		Cohen's d, paired t-test	Cohen's d, t-test	Mantel- Cox χ^2
		On-Duty	Off-duty			
3-ring	Fluorene	75.6	52.5	0.477***	0.485***	10.7***
	High Call Volume	97.2	55.6			
	Low Call Volume	62.2	51.7			
	3,6-Dimethylphenanthrene	6.25	5.02	0.156	-0.016	0.696
	High Call Volume	5.59	5.35			
	Low Call Volume	6.77	4.86			
	Anthracene	7.20	<LOD	0.278**	0.684***	8.09***
	High Call Volume	21.1	<LOQ			
	Low Call Volume	<LOD	<LOD			
4-ring	Pyrene	45.7	30.9	0.626***	0.040	2.76*
	High Call Volume	45.5	31.2			
	Low Call Volume	46.0	30.4			
	Fluoranthene	64.5	38.3	0.686***	0.243	7.69***
	High Call Volume	65.3	39.6			
	Low Call Volume	57.8	38.0			
	1-Methylpyrene	9.86	8.06	0.515***	0.367**	2.12
	High Call Volume	10.1	8.33			
	Low Call Volume	9.47	8.02			
5-ring	Benzo[b]fluoranthene	9.77	7.48	0.585***	0.480***	4.31**
	High Call Volume	10.5	7.98			
	Low Call Volume	9.44	7.13			

^aEffect sizes: large $\geq$ 0.50, medium $\geq$ 0.30, small $\geq$ 0.10

^b**Bold***: p<0.10. **Bold****: p<0.05. **Bold*****: p<0.01 (two-sided p-value)

Table B4. Multivariate models were constructed for PAHs and questionnaire variables, with PAH concentration as the response variable, if parametric tests indicated statistically significant differences (Table B3). Only variables relating to occupational exposures (number of fire attacks, rank, and years in the fire service) are displayed. The exponentiated parameters for captain and chief were compared to operational firefighters as the reference group.

PAH		Number of Fire Attacks	Firefighter Rank			Years in the Fire Service
		Concentration change/fire (95% CI)	Captain (10 ^β)	Chief (10 ^β)	Operational Firefighter (10 ^β)	Concentration change/year (95% CI)
2-ring	1,2-Dimethylnaphthalene	1.03* (0.991, 1.07)	1.35 (1.07, 1.62)	1.31 (0.945, 1.68)	1.66 (1.50, 1.82)	1.03 (0.987, 1.07)
	1,4-Dimethylnaphthalene ^{a,b}	1.02 (0.991, 1.05)	1.21 (0.927, 1.49)	1.20 (0.903, 1.50)	1.11 (0.913, 1.30)	0.985 (0.950, 1.02)
	1,5-Dimethylnaphthalene ^{a-d}	1.03* (0.999, 1.05)	0.897 (0.448, 1.35)	0.879 (0.538, 1.31)	0.926 (0.537, 1.31)	0.982 (0.950, 1.01)
	1-Methylnaphthalene	0.991 (0.961, 1.02)	2.06 (1.91, 2.21)	2.07 (1.86, 2.29)	2.14 (2.05, 2.23)	1.01 (0.984, 1.03)
	2,6-Dimethylnaphthalene ^{a,b}	1.01 (0.993, 1.04)	2.23 (2.05, 2.41)	2.13 (1.94, 2.32)	2.31 (2.18, 2.43)	1.01 (0.984, 1.03)
	2-Ethylnaphthalene ^e	1.01 (0.984, 1.03)	1.72 (1.47, 1.98)	1.64 (1.36, 1.92)	1.83 (1.63, 2.03)	1.00 (0.976, 1.03)
	2-Methylnaphthalene ^{f,g}	0.996 (0.975, 1.02)	2.33 (2.15, 2.50)	2.37 (2.15, 2.60)	2.46 (2.32, 2.60)	1.01 (0.984, 1.03)
	Naphthalene	1.01 (0.974, 1.04)	2.08 (1.93, 2.24)	2.18 (1.96, 2.40)	2.14 (2.05, 2.24)	1.01 (0.989, 1.04)
3-ring	2-Methylanthracene ^{h,i}	1.02** (1.00, 1.04)	1.33** (1.14, 1.53)	1.36 (1.14, 1.57)	1.54 (1.39, 1.70)	1.02 (0.994, 1.04)
	2-Methylphenanthrene ^{c,h,i}	1.02** (1.00, 1.04)	1.91 (1.68, 2.14)	1.80* (1.56, 2.04)	2.00 (1.80, 2.21)	1.01 (0.994, 1.03)
	Anthracene ^d	1.02 (0.983, 1.05)	0.719** (0.330, 1.11)	1.12 (0.678, 1.57)	1.16 (0.869, 1.45)	1.03* (0.995, 1.08)
	Dibenzothiophene ^{a,c,h,i,j}	1.00 (0.990, 1.01)	1.54 (1.30, 1.79)	1.46 (1.24, 1.67)	1.59 (1.38, 1.79)	0.985 (0.968, 1.00)
	Fluorene ^{b,f,g}	1.03*** (1.01, 1.06)	1.63 (1.44, 1.81)	1.80 (1.55, 2.04)	1.70 (1.55, 1.84)	0.994 (0.969, 1.02)
	Phenanthrene ^{a,h-k}	1.01** (1.00, 1.02)	2.34** (2.14, 2.54)	2.42 (2.23, 2.60)	2.48 (2.35, 2.62)	1.00 (0.987, 1.02)
	Retene ^{b-d,h,j}	1.02*** (1.01, 1.04)	1.45 (1.21, 1.69)	1.33 (1.07, 1.59)	1.32 (1.12, 1.52)	1.00 (0.982, 1.02)

Bold*: p<0.10. **Bold****: p<0.05. **Bold*****: p<0.01.

Covariates (t-test or ANOVA, p<0.10) included were ^amarital status, ^bincome, ^cregular cigarette or cigar use, ^dfrequently grilling meat, ^eeducation level, ^fregular use of snuff or dip, ^gregular use of cleaning supplies or disinfectants, ^hregular exposure to secondhand smoke, ⁱliving close to an agricultural area, ^jhaving a fireplace in the home, and ^kliving close to a highway.

Table B6. PAH multivariate models with questionnaire variables (Continued)

PAH		Number of Fire Attacks	Firefighter Rank			Years in the Fire Service
		Concentration change/fire (95% CI)	Captain (10 ^β)	Chief (10 ^β)	Operational Firefighter (10 ^β)	Concentration change/year (95% CI)
4-ring	1-Methylpyrene ^{a,h,j}	1.03*** (1.01, 1.06)	0.311*** (0.016, 0.607)	0.709 (0.417, 1.00)	0.759 (0.527, 0.992)	1.02 (0.983, 1.05)
	Fluoranthene ^{d,f,h,j}	1.04*** (1.02, 1.04)	1.37* (1.18, 1.57)	1.49 (1.28, 1.70)	1.53 (1.38, 1.67)	1.00 (0.993, 1.03)
	Pyrene ^{a,c,d,j}	1.03*** (1.01, 1.06)	1.36 (1.15, 1.56)	1.31 (1.09, 1.52)	1.45 (1.28, 1.61)	1.01 (0.993, 1.03)
5	Benzo[b]fluoranthene ^{b,c,f,h}	1.04*** (1.02, 1.07)	0.344 (0.029, 0.658)	0.410 (0.015, 0.806)	0.524 (0.261, 0.787)	0.996 (0.965, 1.03)

Bold*: p<0.10. **Bold**:** p<0.05. **Bold***:** p<0.01.

Covariates (t-test or ANOVA, p<0.10) included were ^amarital status, ^bincome, ^cregular cigarette or cigar use, ^dfrequently grilling meat, ^eeducation level, ^fregular use of snuff or dip, ^gregular use of cleaning supplies or disinfectants, ^hregular exposure to secondhand smoke, ⁱliving close to an agricultural area, ^jhaving a fireplace in the home, and ^kliving close to a highway.

Table B5. The 21 target analytes detected in over 50% of the 110 dog tags are reported, with the analyte name, primary chemical category, endocrine disruptor status, detection frequency, and summary statistics (nmol/tag) are presented.

Target Analyte	Abbreviation	Primary Chemical Category	Potential Endocrine Disruptor	Detection Frequency (%)	Median	Mean	Standard Deviation	Range
Di-n-butyl phthalate	DBP	Phthalate	Yes	100%	82.0	101	82.9	4.40-512
Diisobutyl phthalate	DIBP	Phthalate	Yes	100%	116	157	127	7.69-586
Di(2-ethylhexyl) phthalate	DEHP	Phthalate	Yes	99%	413	740	736	<0.384-3190
Galaxolide	--	PCP	Yes	98%	153	251	239	<0.387-799
Benzyl salicylate	--	PCP	Yes	97%	169	228	253	<0.438-1690
1-methylnaphthalene	--	PAH	No	90%	0.524	0.682	0.484	<0.352-2.54
Benzyl benzoate	--	Pesticide	No	89%	122	178	169	<1.40-759
Tonalide	--	PCP	No	89%	6.00	32.1	68.1	<0.387-474
Butyl benzyl phthalate	BBP	Phthalate	Yes	86%	12.5	30.7	79.7	<0.640-618
Amyl cinnamal	--	PCP	No	84%	7.33	14.5	21.0	<0.989-112
B-Ionone	--	PCP	No	84%	5.69	12.6	22.6	<0.520-167
Guaiacol	--	Industrial-related	No	83%	60.6	111	148	<1.45-13.6
N,n-diethyl-m-toluamide	DEET	Pesticide	No	83%	15.3	35.3	77.3	<0.784-687
Benzophenone	--	PCP	Yes	80%	23.9	39.2	52.6	<0.549-351
Di-n-nonyl phthalate	DNNP	Phthalate	Yes	80%	7.05	13.8	21.8	<0.358-137
Lilial	--	PCP	Yes	79%	11.5	31.5	80.7	<0.979-708
Butylated hydroxytoluene	BHT	Industrial-related	Yes	75%	5.60	8.86	21.4	<0.454-218
Benzothiazole	--	Industrial-related	No	74%	5.88	6.80	5.40	<1.11-22.6
Butylated hydroxyanisole	BHA	Industrial-related	Yes	74%	8.87	10.5	12.4	<0.828-96.3
Diethyl phthalate	DEP	Phthalate	Yes	60%	22.7	72.4	145	<0.297-830
Anthracene	--	PAH	No	52%	0.390	1.01	1.03	<0.610-4.76

Table B6. For target analytes (frequency detection>50%), the effect sizes from the parametric statistical tests are presented. Positive effect sizes^a indicated that tags had higher concentrations from on-duty compared to off-duty shifts (paired t-test)^b and from high compared to low call volume department (t-test)^b. Higher Mantel-Cox χ^2 test statistics indicated that tag concentrations between fire departments were different.

Chemical	Between Duty Shift		Between Call Volume		
	Median (nmol/tag)		Cohen's d, paired t-test	Cohen's d, t-test	Mantel-Cox χ^2
	On-Duty	Off-duty			
Phthalate	1130	790	0.413***	-0.042	0.881
High Call Volume	1140	820			
Low Call Volume	932	689			
DBP	86.0	76.1	0.411***	-0.366*	3.86**
High Call Volume	73.5	70.4			
Low Call Volume	112	86.1			
DIBP	126	109	0.334**	-0.106	0.226
High Call Volume	129	107			
Low Call Volume	123	120			
DEHP	710	359	0.404***	-0.107	1.25
High Call Volume	717	382			
Low Call Volume	434	281			
BBP	14.2	11.1	0.110	-0.416**	2.23
High Call Volume	12.0	9.55			
Low Call Volume	25.8	11.4			
DNNP	8.26	6.33	0.306**	-0.433**	4.16**
High Call Volume	5.04	4.23			
Low Call Volume	12.9	6.41			
DEP	<LOQ	33.6	-0.479***	0.346	3.05*
High Call Volume	27.8	23.2			
Low Call Volume	<LOQ	35.8			
Industrial-related	109	58.6	0.744***	0.263	3.03*
High Call Volume	162	57.8			
Low Call Volume	102	61.3			
Guaiacol	77.9	30.2	0.714***	0.186	7.39***
High Call Volume	131	28.7			
Low Call Volume	67.2	35.2			
Butylated hydroxytoluene	5.23	5.94	-0.173	0.056	2.85*
High Call Volume	5.59	4.91			
Low Call Volume	4.74	6.19			
Benzothiazole	7.20	4.15	0.581***	-0.578***	1.50
High Call Volume	6.01	2.81			
Low Call Volume	10.5	4.59			
Pesticide	137	176	-0.026	0.378**	1.64
High Call Volume	242	181			
Low Call Volume	86.1	172			
DEET	20.5	10.2	0.276**	0.482**	6.39**
High Call Volume	22.7	16.1			
Low Call Volume	17.0	6.84			

Effect sizes: large $\geq$ 0.50, medium $\geq$ 0.30, small $\geq$ 0.10; **Bold***: $p<0.10$. **Bold****: $p<0.05$. **Bold*****: $p<0.01$

Table B7. Multivariate models were constructed for chemical categories or target analytes (screening method) and questionnaire variables, if non-parametric tests indicated statistically significant differences (Table B6). Only variables relating to occupational exposures (number of fire attacks, rank, and years in the fire service) are displayed. The exponentiated parameters for captain and chief were compared to operational firefighters as the reference group.

Chemical Category or Target Analyte	Number of Fire Attacks	Firefighter Rank			Years in the Fire Service
	Concentration change/fire (95% CI)	Captain (10 ^β)	Chief (10 ^β)	Operational Firefighter (10 ^β)	Concentration change/year (95% CI)
Phthalates ^{a,b}	1.02* (0.997, 1.04)	2.69 (2.45, 2.93)	2.61 (2.35, 2.87)	2.67 (2.48, 2.87)	1.03** (1.00, 1.06)
DEHP ^{a,c}	1.03 (0.986, 1.08)	2.27 (1.84, 2.70)	1.77 (1.20, 2.35)	2.13 (1.75, 2.50)	1.07*** (1.02, 1.13)
DIBP ^a	0.978 (0.951, 1.01)	1.95 (1.75, 2.15)	1.87 (1.65, 2.08)	1.80 (1.64, 1.96)	1.00 (0.982, 1.03)
DBP ^{a,d,e}	1.01 (0.993, 1.03)	1.70 (1.50, 1.89)	1.83 (1.61, 2.05)	1.69 (1.54, 1.85)	0.993 (0.970, 1.02)
DEP ^{a,b,d,f,g}	1.01 (0.993, 1.04)	1.17 (0.431, 1.90)	1.95 (1.29, 2.61)	1.49 (1.02, 1.95)	1.06 (0.988, 1.13)
BBP ^{a,e,h}	0.995 (0.963, 1.03)	0.767 (0.307, 1.23)	0.921 (0.482, 1.36)	0.894 (0.517, 1.27)	1.03 (0.989, 1.07)
DNNP ^{a,c,h}	0.987 (0.945, 1.03)	0.708 (0.325, 1.09)	0.306** (-0.128, 0.741)	0.795 (0.462, 1.13)	1.03* (0.997, 1.07)
Industrial-Related ^{a,b,d,h}	1.02 (0.987, 1.04)	2.14*** (1.77, 2.51)	1.74 (1.37, 2.10)	1.77 (1.47, 2.08)	1.01 (0.974, 1.05)
Guaiacol ^{a,d}	1.02 (0.961, 1.08)	1.69*** (1.14, 2.23)	1.29 (0.679, 1.91)	1.08 (0.678, 1.48)	1.03 (0.969, 1.10)
Benzothiazole ^{f,g}	1.01 (0.981, 1.03)	0.581** (0.387, 0.775)	0.382*** (0.183, 0.581)	0.758 (0.612, 0.903)	1.00 (0.979, 1.02)
Pesticides ^{a,c,g}	1.00 (0.978, 1.03)	2.61 (2.16, 3.06)	2.22 (1.81, 2.63)	2.41 (2.04, 2.79)	1.04** (1.00, 1.08)
DEET	1.06** (1.01, 1.12)	1.10 (0.849, 1.35)	1.19 (0.825, 1.55)	1.14 (0.984, 1.29)	1.02 (0.981, 1.06)

Bold*: p<0.10. **Bold**:** p<0.05. **Bold***:** p<0.01.

Covariates (t-test or ANOVA, p<0.05) included were ^aexposure to secondhand smoke, ^bliving close to a highway, ^cregular use of cigarettes or cigars, ^dhaving a fireplace in the home, ^etraveling more than three hours for work, ^fmarital status, ^gincome, and ^heducation.

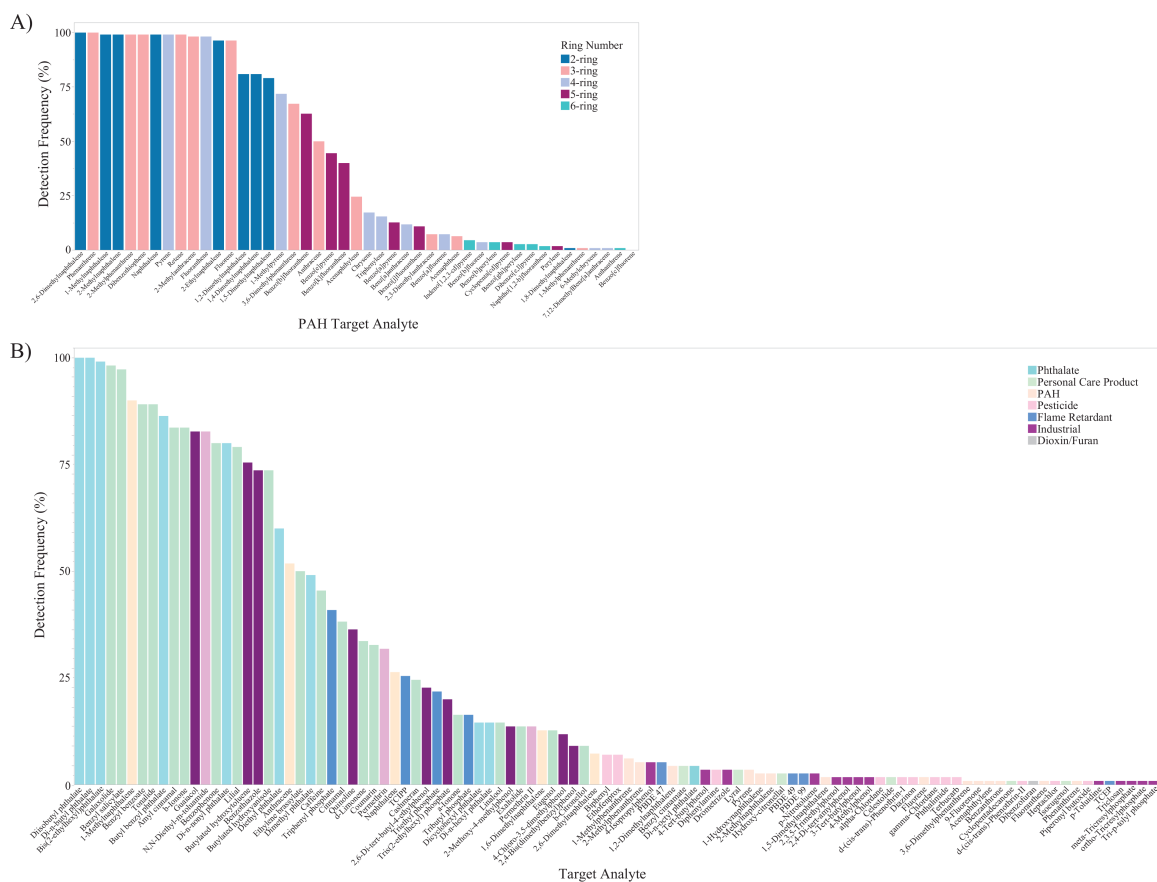


Figure B1. The target analytes detected are shown in order of frequency and by chemical class for the A) 65 PAH method and B) 1530 screening method.

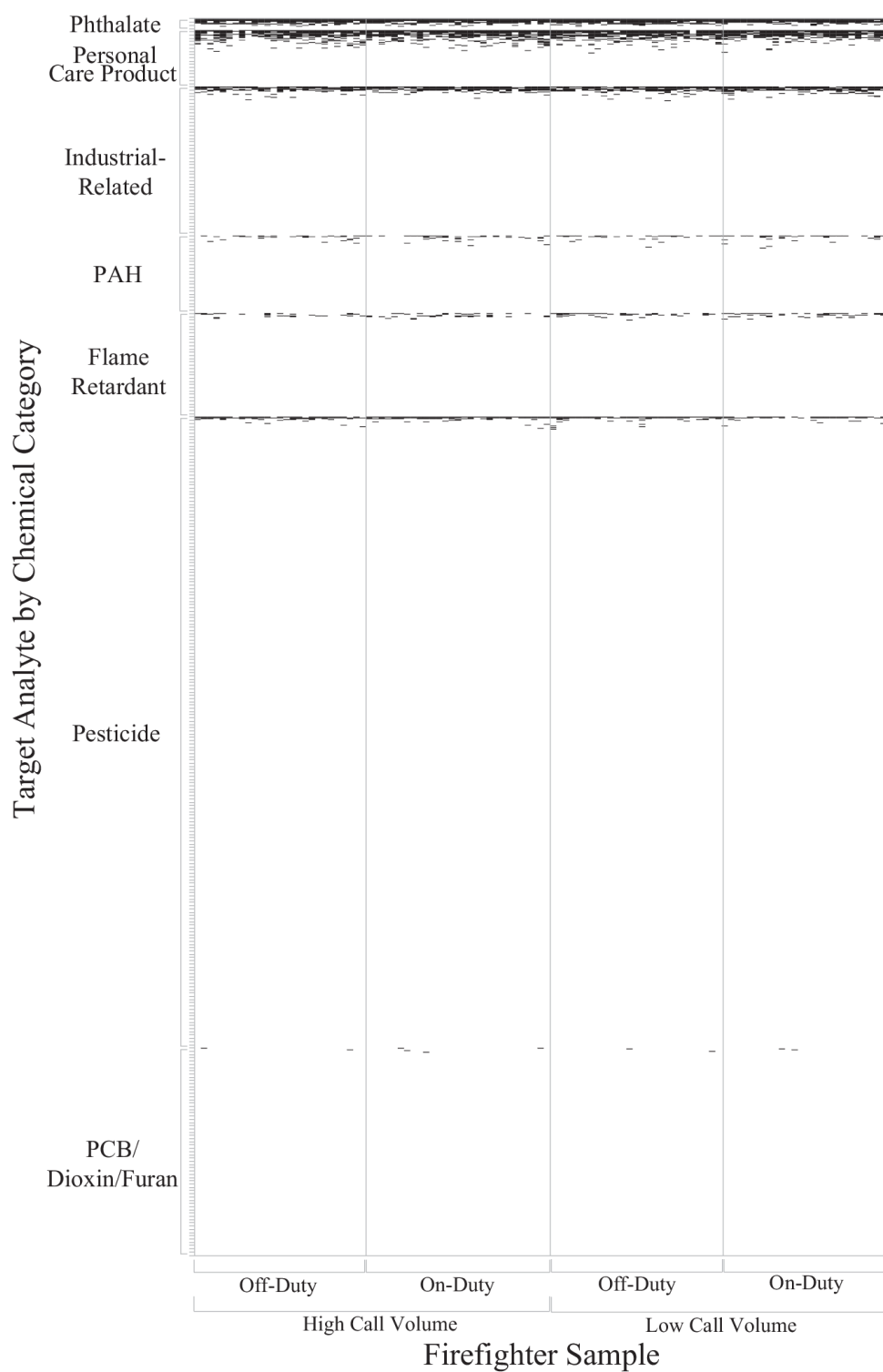


Figure B2. A heat map for the presence-absence of the 1530 target analytes in the 110 dog tags is presented. Firefighter tags were organized by fire department and duty shift.