Environmental Science & Technology

Article

Cite This: Environ. Sci. Technol. 2019, 53, 9203−9213

pubs.acs.org/est

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*[,†]

[†]Department of Toxicology, Oregon State University, Corvallis, Oregon 97331, United States

[‡]Department of Environmental Health Sciences, Columbia University, New York, New York 10032, United States

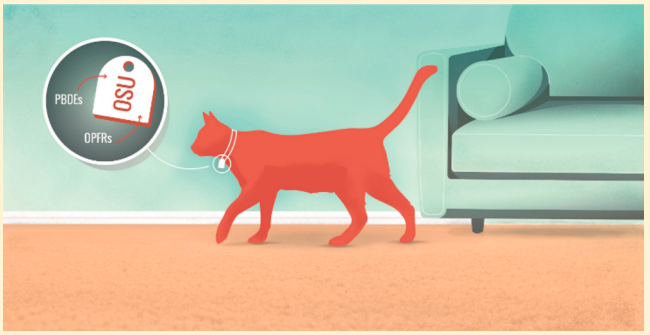
[§]Animal Endocrine Clinic, 21 West 100th Street, New York, New York 10025, United States

[∥]Carlson College of Veterinary Medicine, Oregon State University, Corvallis, Oregon 97331, United States

[⊥]New York Cat Hospital, 143 Freedom Place, New York, New York 10069, United States

Supporting Information

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 nonhyperthyroid cats, serum free thyroxine (fT_4), total T_4 (TT_4), 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 pet tags in comparison to nonhyperthyroid pet tags (adjusted odds ratio, $p < 0.07$; Mantel−Cox, $p < 0.02$). Higher TDCIPP concentrations were associated with air freshener use in comparison to no use ($p < 0.01$), residences built since 2005 compared to those pre-1989 ($p < 0.002$), and cats preferring to spend time on upholstered furniture in comparison to no preference ($p < 0.05$). Higher TDCIPP concentrations were associated with higher fT_4 and TT_4 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.



1. INTRODUCTION

Feline hyperthyroidism is the most commonly diagnosed endocrine-related disease among senior and geriatric housecats (≥10 years).[1] First clinically diagnosed in 1979, the prevalence of feline hyperthyroidism among US housecats 10 years or older has increased from 1 in 200 to 1 in 10 between 1980 and 2014.[2,3] Similar prevalence statistics are reported worldwide.[4−7] In North America, an estimated two million cats are currently diagnosed with hyperthyroidism.[3] 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.[3]

Domestic cats are the only nonhuman species frequently diagnosed with hyperthyroidism, known as toxic nodular goiter (TNG) in humans.[3] Feline hyperthyroidism and TNG result from excessive circulating concentrations of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3).[1,3] These progressive diseases, which also share clinical symptoms, exhibit adenomatous hyperplasias with autonomous cell growth and hormone secretion.[3,8] 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.[1] As with TNG,[9] feline hyperthyroidism does not develop due to dietary iodine deficiency alone.[1] However, iodine deficiency may function synergistically with other factors.[1,10] Reported risk factors for feline hyperthyroidism include increasing age,[5−7,11] canned cat food consumption,[2,4,7,11] and litter box use.[4,5]

Researchers have hypothesized that another risk factor for feline hyperthyroidism is household flame retardant (FR) exposures.[12−16] The hypothesis emerged because the earliest

Received: April 12, 2019
Revised: June 11, 2019
Accepted: June 12, 2019
Published: July 10, 2019

DOI: 10.1021/acs.est.9b02226
Environ. Sci. Technol. 2019, 53, 9203−9213

diagnoses coincided with the introduction of polybrominated diphenyl ethers (PBDEs) as FRs during the mid-1970s.[17] FRs are commonly used in textiles, polyurethane foam, plastics, and electronics to delay the ignition of a fire.[17−19] To meet flammability standards, PBDEs emerged as a major FR series with the common commercial mixtures of pentaBDE, octaBDE, and decaBDE.[17,18] 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.[18,20] The decaBDE mixture phaseout began in 2010, but PBDE detections continue in dust and biomonitoring samples.[21−23] Additionally, products containing PBDEs are infrequently replaced, such that PBDE exposures will likely continue despite the phaseouts.[17,18,24]

In response to the PBDE phaseout, organophosphate ester (OPE) production has increased over the past 10 years.[25] OPEs have been considered suitable alternatives to PBDEs for decades[25−27] and include analytes such as tris(1,3-dichloroisopropyl) phosphate (TDCIPP), tris(1-chloro-2-propyl) phosphate (TCIPP), tris(2-chloroethyl) phosphate (TCEP), and triphenyl phosphate (TPHP). Evidence suggests that both PBDEs[17,28] and OPEs[29−33] act as endocrine-disrupting chemicals (EDCs) with thyroid targets.

A fraction of household PBDEs and OPEs remain unbound and freely dissolved in the gas phase.[25,34,35] These biologically relevant, or bioavailable, FRs are significant for inhalation and dermal contact exposure routes.[35−38] In contrast, FRs bound to particulate matter (e.g., dust) are more significant for the ingestion pathway,[34] but all three exposure routes can lead to potential adverse health effects. Both cats[12−14] and young children[28,35] are hypothesized to experience FR exposures predominantly via dust ingestion and inhalation of gas-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 novel silicone passive sampling devices (PSDs). PSDs sequester unbound volatile and semivolatile organic compounds (VOCs, SVOCs) via diffusion because the PSD polymer mimics an organism's phospholipid membrane.[37−39] PSDs capture the bioavailable fraction of lipophilic organic chemicals, and researchers can quantify exposures. In comparison to active sampling devices, PSDs are lightweight, easy to use, and low cost.[39] Stationary PSDs underestimate individual exposures,[40] leading to an increased interest in personalized PSDs.

In 2014, silicone wristbands were first modified to function as personalized PSDs.[38−52] Worn against the skin, wristbands are capable of sequestering 1530 chemicals, including pesticides,[45−49] polycyclic aromatic hydrocarbons,[39,40,42,44] personal care products,[39,41,43−45] and FRs.[38,41,50−52] In Hammel et al. (n = 48),[51] 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. (n = 30),[52] BDE-47, -99, -100, and -153 concentrations were strongly correlated between serum and wristbands. Together, these studies suggest that wristbands can act as strong predictors of FR body burden.

In this study, silicone pet tags are introduced as a new configuration of personalized PSDs and compare bioavailable FR exposures between hyperthyroid and nonhyperthyroid 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 nonhyperthyroid 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. METHODS

2.1. Materials. Solvents were Optima grade and were purchased from Fisher Scientific (Pittsburgh, PA, USA). All analytical standards were purchased from Accustandard (New Haven, CT, USA) as single analyte or composite solutions. For the full list of individual FR analytes and extraction surrogates, see Table S1 in the Supporting Information. Prior to use, glassware was rinsed in a base bath, washed with detergent in an automatic dishwasher, rinsed with 18 MΩ cm water, and baked at >300 °C for 12 h. Airtight polytetrafluoroethylene (PTFE) storage bags and closures were purchased from Welch Fluorocarbon, Inc. (Dover, NH, USA).

2.2. 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) were prepared as previously reported with minimal modifications.[44] Briefly, the tags were conditioned in a vacuum oven at 270−300 °C for 6 h at 0.1 Torr (Vacuum Oven, Blue-M, no. POM18VC, with Welch Duo-seal pump, no. 1405). Quality control (QC) samples were selected to evaluate for data quality objectives prior to storing the cat tags in sealed metal containers at 4 °C (see the Supporting Information). Pet tags were transferred to PTFE bags before deployment.

2.3. Cat Population and Recruitment. Cat recruitment (n = 78) occurred between December 2017 and October 2018 (Figure 1). 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). Nonhyperthyroid cats were recruited from the New York Cat Hospital ($n_{NY,nonhyperthyroid}$ = 16) and OSU's Animal Teaching Hospital ($n_{OR,nonhyperthyroid}$ = 23). For more details on cat recruitment, see the Supporting Information.

Figure 1. Study compared flame retardant exposures using silicone pet tags between hyperthyroid (n = 39) and nonhyperthyroid (n = 39) mature, senior, and geriatric cats (e.g., ≥7 years).

2.4. Flame Retardant Extraction and Analysis. The pet tags were cleaned, extracted, and analyzed as previously reported[39] (see the Supporting Information for details on

DOI: 10.1021/acs.est.9b02226
Environ. Sci. Technol. 2019, 53, 9203−9213

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 the Supporting Information and Table S2.

2.5. 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 half the LOD. All concentrations were converted to moles per gram of 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.[52]

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,[53] where covariates were included if they were associated with the independent variable at $p < 0.15$.

To confirm the significance of the adjusted odds ratios (OR), we performed two alternative analyses. A Kaplan−Meier procedure for censoring nondetected values compared hyperthyroid and nonhyperthyroid FR tag concentrations (Mantel−Cox χ^2).[54] Weighted quantile sum (WQS) regression for high-dimensional data sets assessed mixture effects in association with feline hyperthyroidism as the binary disease outcome (see the Supporting Information).[55−57] 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.[55−57] Chemical exposures occur as complex mixtures,[41] yielding high-dimensional data sets 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 data set.[56] Because the FR data set from this study demonstrated strong variable−variable correlations (Tables S2 and S3), WQS method application was appropriate as an alternative statistical approach. For the 21 FR components, the WQS method estimated a weighted linear index.[56,57] 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 OR, $p < 0.10$) 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 they were associated with the independent variable at $p < 0.15$.

3. RESULTS

3.1. Participant Population. Of the 78 tags distributed, all tags were worn for 7 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 multivariate linear models. All pet tags detected at least one FR above the LOQ. A summary of cat population demographics is given in Table 1.

Table 1. Population Demographics Reported between Hyperthyroid and Nonhyperthyroid Study Participants[a]

characteristic	hyperthyroid $n = 39$	nonhyperthyroid $n = 39$	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%)	
mean age ± SD (y)	13.1 ± 2.46	13.4 ± 2.22	0.591
mean weight ± SD (kg)	4.99 ± 1.46	4.85 ± 1.78	0.699
year adopted ± SD	2006 ± 4.12	2007 ± 4.22	0.511
time in residence ± SD (y)	7.50 ± 4.61	6.00 ± 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%)	

[a]Due to missing questionnaire answers, not all percentages add up to 100%.

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 OR values are shown in Table S3.

3.2. Flame Retardant Concentrations among Case-Control Cats. *3.2.1. OPEs.* All six OPEs were detected in at least one tag (Table 2). TPHP, TDCIPP, and TCIPP were detected in over 90% of pet tags in each group. TCEP and tri-*n*-butyl phosphate were detected over 50% of samples each, and tri-*n*-ethyl phosphate was detected in fewer than 50% of samples. For the Spearman correlation, we included all six OPEs for a total of 15 coefficients, 7 of which were significant (Table S4). This suggested that the OPEs were unlikely to originate from a common source.

TDCIPP concentrations were higher in hyperthyroid than in nonhyperthyroid tags (Table 2; adjusted OR, $p < 0.07$). The Mantel−Cox χ^2 value confirmed this result (Table 2 and Figure S1; 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

DOI: 10.1021/acs.est.9b02226
Environ. Sci. Technol. 2019, 53, 9203−9213

Table 2. Detection Frequencies, Summary Statistics, And Adjusted Odds Ratios for Flame Retardants Detected in at Least One Tag[a]

	detection frequency (% samples)		median (pmol/g tag)		geometric mean (pmol/g tag)						
target analyte	hyperthyroid	nonhyperthyroid	hyperthyroid	nonhyperthyroid	hyperthyroid	nonhyperthyroid	adjusted odds ratio (95% CI)	p value (odds ratio)	Mantel–Cox χ^2	p value (χ^2)	weighted quantile sum contribution
TNBP[b,c,d]	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[b,e,f]	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[b,d,g]	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[b,f,h,i]	100	94.9	1810	2410	2070	1860	1.01 (0.926, 1.11)	0.870	0.008	0.929	4.51×10^{-3}
TDCIPP[b,e,g,i]	94.9	97.4	113	114	146	126	1.37 (0.986, 2.26)	**0.060***	6.25	**0.012****	0.215
TPHP[b]	94.9	100	234	243	164	256	1.09 (0.427, 3.23)	0.840	0.596	0.440	1.67×10^{-8}
$\sum_6$OPEs[b,f,h,i]	*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 and BDE-33[h]	5.1	10.3	<LOD	<LOD	<LOD	<LOD	0.949 (0.810, 1.02)	0.186	2.60	0.107	0.035
BDE-47[h]	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[h]	10.3	10.3	<LOD	<LOD	<LOD	<LOD	0.975 (0.881, 1.02)	0.338	2.70	0.101	0.035
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[e,h]	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[h]	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[h]	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[h]	23.1	28.2	<LOD	<LOD	<LOD	1.14	0.955 (0.832, 1.01)	0.121	2.40	0.121	0.022
Σ_{36}BDEs[h]	*92.3*	*89.7*	*106*	*108*	*111*	*130*	*0.880 (0.585, 1.03)*	*0.142*	*1.14*	*0.285*	
EH-TBB[b,g,j]	7.7	17.9	<LOD	<LOD	<LOD	9.39	0.998 (0.993, 1.00)	0.142	0.073	0.787	0.035
$\sum_2$BFRs[b,g,j]	*7.7*	*17.9*	*<LOD*	*<LOD*	*<LOD*	*10.8*	*0.998 (0.993, 1.00)*	*0.142*	*0.073*	*0.787*	

[a]Mantel–Cox χ^2 values and WQS contributor weights are included as alternative analyses to confirm the adjusted odds ratio result.[54−58] Larger WQS index weights indicate a larger contribution to the mixture effect and a stronger association with feline hyperthyroidism. **Bold***: $p < 0.10$. **Bold****: $p < 0.05$. [b]Odds ratio calculated using nmol/g tag concentrations. [c]Covariates included age. [d]Covariates included breed. [e]Covariates included sampling season. [f]Covariates included years in current residence. [g]Covariates included year adopted. [h]Covariates included location. [i]Covariates included time spent outdoors. [j]Covariates included weight.

DOI: 10.1021/acs.est.9b02226
Environ. Sci. Technol. 2019, 53, 9203−9213

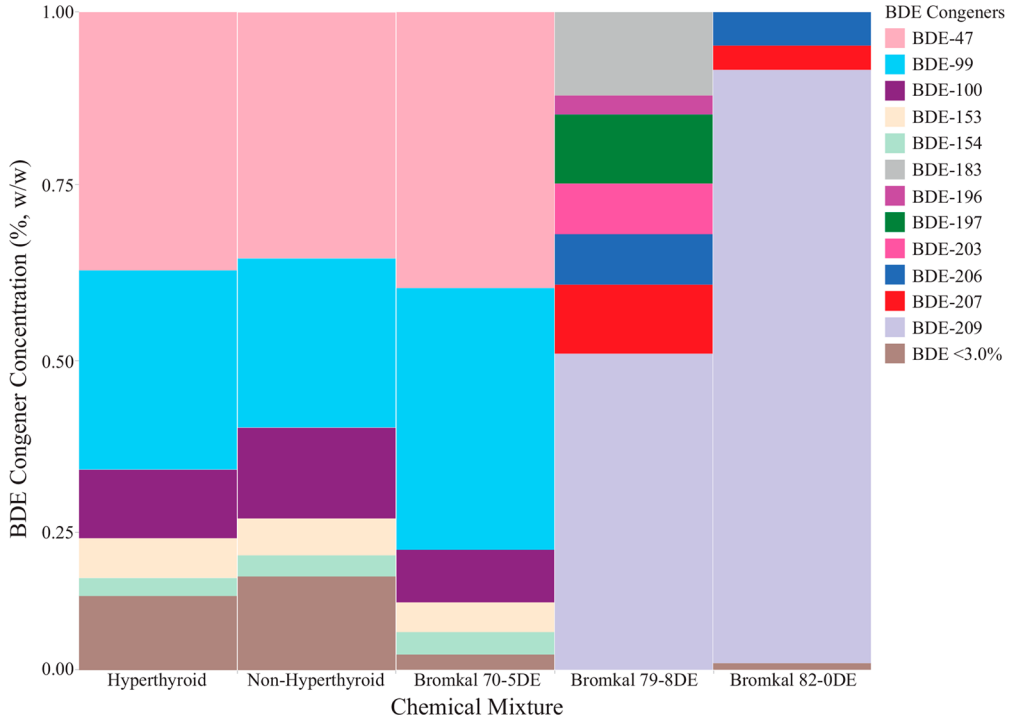


Figure 2. Mean PBDE congener profiles identified from hyperthyroid and nonhyperthyroid tags in comparison to three commercial PBDE mixtures, known as the Bromkal formulation series.[59] The pentaBDE mixture (Bromkal 70-5DE) matched the pet tag congener profiles more closely than the octaBDE (Bromkal 79-8DE) and decaBDE (Bromkal 82-0DE) mixtures.

the disease outcome (β = 0.07; p > 0.90). The remaining five OPE concentrations and $\sum_6$OPEs demonstrated no difference between hyperthyroid and nonhyperthyroid tags (Table 2; adjusted OR, p > 0.10; Mantel−Cox, p > 0.10). This result suggested that, in addition to TDCIPP, hyperthyroid and nonhyperthyroid cats experience similar OPE exposures.

3.2.2. PBDEs. Out of 36 PBDEs in the analytical method, 15 congeners were detected in at least one pet tag (Table 2). Low molecular weight (LMW) congeners (e.g., 1−5 bromines) were more frequently detected in comparison to high molecular weight (HMW) congeners (e.g., 6−10 bromines).

PBDE congeners were detected with similar frequency between hyperthyroid and nonhyperthyroid tags (Table 2). BDE-47 was the most frequently detected congener (>80%) in both hyperthyroid and nonhyperthyroid 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 and -33, -8, -12, and -25 were detected in <25% of samples. The PBDE congener concentrations and $\sum_{36}$PBDEs demonstrated no difference between hyperthyroid and nonhyperthyroid tags (Table 2; adjusted OR, p > 0.10; Mantel−Cox, p > 0.10). This result suggested that hyperthyroid and nonhyperthyroid cats experience similar PBDE exposures.

For the Spearman correlation, we included the 6 most frequently detected PBDE congeners for a total of 15 coefficients, all of which were statistically significant (Table S5). In contrast to 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 formulations[59] used to treat a wide variety of consumer products prior to the phaseouts.[17,18] The Bromkal congener compositions were compared to the mean hyperthyroid and nonhyperthyroid congener profiles from this study (Figure 2).[59]

3.2.3. 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 in comparison to nonhyperthyroid tags. Neither EH-TBB nor $\sum_2$BFR concentrations were different between the hyperthyroid and nonhyperthyroid cat tags (Table 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.

3.3. Thyroid Hormone Concentrations. We investigated serum thyroid profile results from nonhyperthyroid cats (n = 39) to assess correlations between FR concentrations and thyroid function. Only nonhyperthyroid cats were included in this analysis due to potential bias from hyperthyroid cat weight loss (see section 4.4). Summary statistics for free T_4 (fT_4), total T_4 (TT_4), total T_3 (TT_3), and thyroid-stimulating hormone are reported in Table S1.

Multivariate associations between $\log_{10}$-transformed concentrations of OPEs and thyroid hormones (Table 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. In comparison 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 3; p < 0.002, p < 0.03) and TCIPP was negatively associated (Table 3; p < 0.001). For TT_4, TDCIPP and TCEP were positively associated (Table 3; p < 0.01, p < 0.002), with similar results for TT_3 (Table 3; p < 0.10, p < 0.002).

DOI: 10.1021/acs.est.9b02226
Environ. Sci. Technol. 2019, 53, 9203−9213

Table 3. Exponentiated β Coefficients for the Multivariate Linear Models of $\log_{10}$-Transformed OPE and Thyroid Hormone Concentrations[a]

hormone and model	TNBP		TNEP		TCEP		TCIPP		TDCIPP		TPHP	
	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 (μg/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

[a]The model was constructed using a stepwise variable selection procedure based on Akaike information criterion optimization. **Bold***: $p < 0.05$. 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.

3.4. 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 4). Reference groups are indicated in the effect estimate column (10^{β}). For instance, the median TDCIPP pet tag concentrations in homes with weekly air freshener use was 61% higher in comparison 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 in comparison to those built prior to 1989 ($p < 0.002$) and residences containing upholstered furniture purchased between 2007 and 2012 in comparison 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

Table 4. Exponentiated β Coefficients for the Multivariate Linear Model of $\log_{10}$-Transformed TDCIPP Concentrations with Household Variables[a]

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			
no. 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 to 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

[a]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****: $p < 0.05$.

DOI: 10.1021/acs.est.9b02226
Environ. Sci. Technol. 2019, 53, 9203−9213

sleep on furniture compared to cats with no location preference ($p < 0.05$).

3.5. Intrahousehold 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/nonhyperthyroid cats and two pairs of two nonhyperthyroid cats living in the same household. All FR concentrations were normalized using log K_{oa} values to account for variable FR−silicone affinity.[52] Each pet tag FR profile was unique, regardless of the shared household environment (Figure 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 1−6 h/day on upholstered furniture. Consistent with the results in Table 4, this suggested an association between elevated TDCIPP exposures and increased time spent on upholstered furniture ($p < 0.05$).

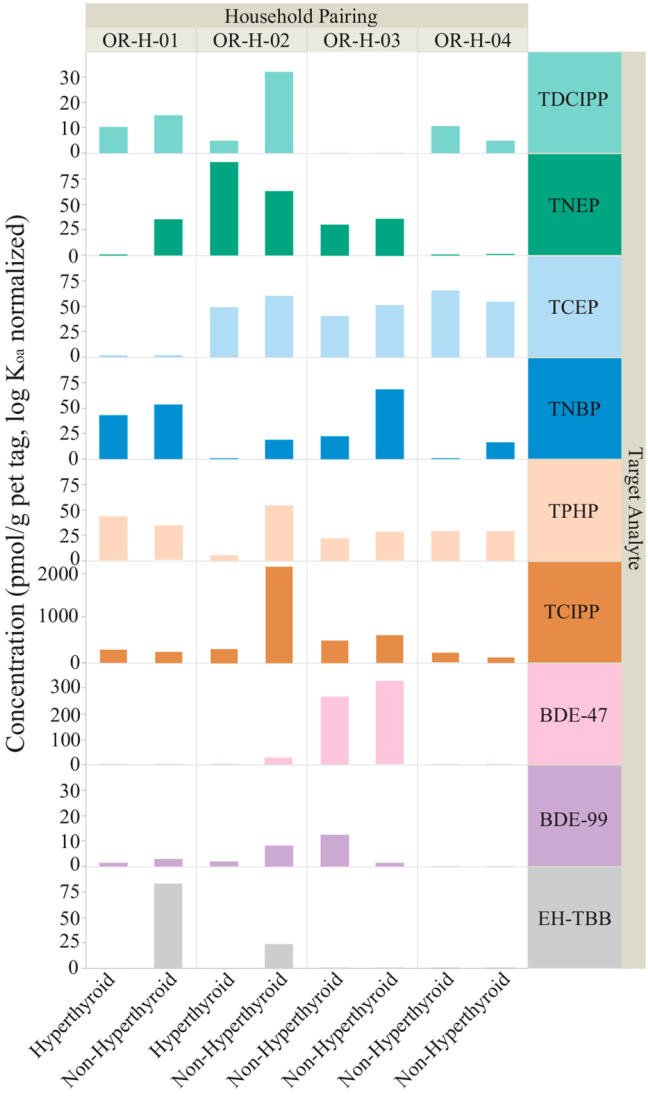


Figure 3. FR profiles from four pairs of cats living in the same household compared to identify individual variations. The FR profiles between nonhyperthyroid cats in a household (OR-H-03, OR-H-04) were visually more similar than profiles between a hyperthyroid and nonhyperthyroid cat (OR-H-01, OR-H-02). Each individual FR profile was unique, indicative of the sampler sensitivity to individual feline behaviors.

4. DISCUSSION

4.1. 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 in monitoring companion animal chemical exposures.

4.2. TDCIPP. *4.2.1. This Study.* To our knowledge, this is the first study to investigate bioavailable household OPE exposures between hyperthyroid and nonhyperthyroid cats. Of the OPEs, PBDEs, and BFRs detected, TDCIPP concentrations were higher in pet tags from hyperthyroid in comparison to nonhyperthyroid cats (Table 2; adjusted odds ratio, $p < 0.07$; Mantel−Cox, $p < 0.02$). In Table 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 nonhyperthyroid cats. TDCIPP also had the largest 10^{β} coefficients, and therefore affected fT_4, TT_4, and TT_3 more strongly, in comparison to other OPEs in Table 3. This result was further suggestive of a link between TDCIPP exposure and thyroid function. In combination 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.

4.2.2. Background. Prior to the earliest diagnoses of feline hyperthyroidism, manufacturers introduced TDCIPP as a household FR.[26,29,60] Known as Fyrol FR2,[19,26,61] TDCIPP was initially applied to children's sleepwear to meet US flammability standards in the mid-1970s. Concerns of mutagenicity[26,62] led to its discontinuation from sleepwear products in May 1977.[29,61] However, TDCIPP use continued in other consumer products, particularly upholstered furniture containing polyurethane foam.[29,63,64] Annual US demand for TDCIPP expanded from an estimated 450 tons in 1997 to 22700 tons in 2006.[25,33] TDCIPP use has continued to grow in the past decade with the subsequent PBDE phaseout.[23,63,64]

Additionally, a growing body of evidence has implicated TDCIPP as an EDC with thyroid targets.[25,29−31] TDCIPP exposures have been correlated with altered thyroid hormone levels in human men,[65] as well as suspected neurotoxicity, developmental toxicity, and hepatotoxicity in various model organisms.[25,31] Although TDCIPP mechanisms of action remain unknown, there is interest in the downregulation of mRNA expression and ribosome protein genes along the hypothalamic−pituitary−thyroid axis.[31−33] 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).[33] With historic TDCIPP use and exposure differences observed in this study, evidence of EDC 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,[27] can potentially be monitored using cats as sentinels.[66,67] Such TDCIPP and other chemical exposure data may be particularly useful in

DOI: 10.1021/acs.est.9b02226
Environ. Sci. Technol. 2019, 53, 9203−9213

homes with either a cat at risk of developing feline hyperthyroidism and/or a human at risk of developing TNG.

4.2.3. Household and Behavioral Variables. Associations between TDCIPP pet tag concentrations and household and behavioral variables suggested preventative health interventions that could be implemented to reduce TDCIPP exposures (Table 4). With cleaning-related variables, elevated TDCIPP concentrations with air freshener use may indicate OPE applications beyond flame retarding (e.g., plasticizers, antifoaming agents).[25,27,39] For instance, OPE use as antifoaming agents[27,39] 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.[38] 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.[25]

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,[1,2,5,36] and warrants further study. TDCIPP concentrations were also positively associated with cats that preferred to sleep on furniture ($p < 0.05$) in comparison to cats with no location preference, a result attributable to high flammability standards for human consumer products.[63]

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.

4.3. PBDEs. *4.3.1. Congeners.* Similarities between the pet tags and the pentaBDE mixture (Figure 2) suggested that hyperthyroid and nonhyperthyroid cats experience similar PBDE exposures and that bioavailable PBDE exposures are not associated with feline hyperthyroidism. Both hyperthyroid and nonhyperthyroid pet tag profiles closely matched the pentaBDE mixture (Bromkal 70-5DE), in comparison to the octaBDE (Bromkal 79-8DE) and decaBDE (Bromkal 82-0DE) mixtures.[59] 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).[14,16] Although hyperthyroid and nonhyperthyroid pet tags demonstrated similar PBDE exposures 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.

4.3.2. Previous Literature. Previous studies on feline PBDE exposures included samples of cat serum,[12−16,67−71] household dust,[13,14,16,69] and commercial cat food.[12−14,68] However, only three publications have positively associated hyperthyroidism diagnoses, serum PBDE concentrations, and dust PBDE concentrations.[14−16]

The strongest evidence for a link between PBDE exposures and feline hyperthyroidism came from Guo et al., a longitudinal case-control study ($n_{total} = 22$), where the median serum concentrations of 19 PBDE congeners were higher in hyperthyroid than in nonhyperthyroid cats.[15] Separately, Engdahl et al. demonstrated a significant association between dust and serum PBDE concentrations in homes with nonhyperthyroid cats ($n_{total} = 17$), but this was solely applicable for BDE-47, -99, and -153.[16] To date, studies have only examined dust ingestion as the primary FR exposure route for indoor cats.[14−16]

4.4. 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,[20,72] but over 90% of hyperthyroid cats experience moderate to extreme weight loss prior to treatment.[73] Weight loss introduces potential overestimation bias into serum PBDE concentrations for hyperthyroid cats because PBDEs stored in fat can be released into serum.[17] In contrast, the silicone pet tags effectively avoid bias resulting from weight loss while still indicative of body burden.[42,51,52] Silicone pet tags may serve as a supplement to cat serum samples for future studies.

4.5. Intrahousehold Variations. Each pet tag featured unique FR exposures for each cat in a shared household (Figure 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 1−6 h/day on upholstered furniture, consistent with results from Table 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 intrahousehold comparisons provide future opportunities to explore other feline chemical exposures, particularly additional EDCs with thyroid targets. As seen in Figure 3, among the hyperthyroid/nonhyperthyroid pairs, the nonhyperthyroid pet tags featured higher concentrations of TDCIPP, TNBP, and EH-TBB. Other potential EDCs, such as phthalates,[41] were not captured by the FR analytical method, and such data may provide insight into additional household chemical exposures.

4.6. Study Limitations. There were several limitations to this study. First, the study population was composed of nonrandom recruitments and may not be representative of the wider US 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.[39] 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.[74] 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).

DOI: 10.1021/acs.est.9b02226
Environ. Sci. Technol. 2019, 53, 9203−9213

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 nonhyperthyroid 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.9b02226.

Explanatory paragraphs and figures and tables as detailed in the text (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*K.A.A.: tel, (541) 737-8501; e-mail, kim.anderson@oregonstate.edu.

ORCID

Carolyn M. Poutasse: 0000-0001-7128-044X

Kim A. Anderson: 0000-0002-5258-2925

Present Address

#D.G.: Pure Paws Veterinary Clinic, 944 Fulton St., Brooklyn, NY 11238, United States

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding

Funding was provided by a National Institute of Environmental Health Science Toxicology Training Grant (Grant T32ES007060-37) and the Food Safety and Environmental Stewardship Laboratory.

Notes

The authors declare the following competing financial interest(s): Kim A. Anderson, an author of this research, discloses a financial interest in MyExposome, Inc., which is marketing products related to the research being reported. The terms of this arrangement have been reviewed and approved by OSU in accordance with its policy on research conflicts of interest. The authors have no other disclosures.

■ ACKNOWLEDGMENTS

I give special thanks to the cat owners and their cats for their assistance in this research. Special thanks is also given to the Institutional Animal Care and Use Committees, the OSU Superfund Research Program Core D for chemistry support, and the veterinary clinicians, Richard Scott, Peter Hoffman, Clarisa Caballero-Ignacio, Holly Dixon, Michael Barton, Diana Rohlman, Amberlie Barnard, Jarvis Barnard, Elizabeth Gibson, Whitney Cowell, Anne Bozack, Courtney Barden, Candace Remcho, and Piper Poutasse.

■ ABBREVIATIONS

ACUP, animal care and use protocol; EH-TBB, 2-ethylhexyl-2,3,4,5-tetrabromobenzoate; FR, flame retardant; LOD, limit of detection; LOQ, limit of quantitation; OPE, organophosphate ester; PBDE, polybrominated diphenyl ether; PSD, passive sampling device; PTFE, polytetrafluoroethylene; TNG, toxic nodular goiter; TCEP, tris(2-chloroethyl) phosphate; TCIPP, tris(1-chloro-2-propyl) phosphate; TDCIPP, tris(1,3-dichloroisopropyl) phosphate; TPHP, triphenyl phosphate; SVOC, semivolatile organic compound; VOC, volatile organic compound

■ REFERENCES

(1) Peterson, M. What's Causing This Epidemic of Thyroid Disease and Can We Prevent It? *J. Feline Med. Surg.* **2012**, *14* (11), 804−818.

(2) Scarlett, J. M.; Moise, N. S.; Rayl, J. Feline Hyperthyroidism - a Descriptive and Case-Control Study. *Prev. Vet. Med.* **1988**, *6* (4), 295−309.

(3) Peterson, M. E. Feline Hyperthyroidism: An Animal Model for Toxic Nodular Goiter. *J. Endocrinol.* **2014**, *223* (2), T97−T114.

(4) Kass, P. H.; Peterson, M. E.; Levy, J.; James, K.; Becker, D. V.; Cowgill, L. Evaluation of Environmental, Nutritional, and Host Factors in Cats with Hyperthyroidism. *J. Vet. Intern. Med.* **1999**, *13* (4), 323−329.

(5) Wakeling, J.; Everard, A.; Brodbelt, D.; Elliott, J.; Syme, H. Risk Factors for Feline Hyperthyroidism in the UK. *J. Small Anim. Pract.* **2009**, *50* (8), 406−414.

(6) Bree, L.; Gallagher, B. A.; Shiel, R. E.; Mooney, C. T. Prevalence and Risk Factors for Hyperthyroidism in Irish Cats from the Greater Dublin Area. *Irish Vet. J.* **2018**, *71*, 10.

(7) McLean, J. L.; Lobetti, R. G.; Mooney, C. T.; Thompson, P. N.; Schoeman, J. P. Prevalence of and Risk Factors for Feline Hyperthyroidism in South Africa. *J. Feline Med. Surg.* **2017**, *19* (10), 1103−1109.

(8) Peterson, M. E.; Ward, C. R. Etiopathologic Findings of Hyperthyroidism in Cats. *Vet. Clin. N. Am.* **2007**, *37* (4), 633.

(9) Derwahl, M.; Studer, H. Nodular Goiter and Goiter Nodules: Where Iodine Deficiency Falls Short of Explaining the Facts. *Exp. Clin. Endocrinol. Diabetes* **2001**, *109* (5), 250−60.

(10) Edinboro, C. H.; Scott-Moncrieff, J. C.; Glickman, L. T. Feline Hyperthyroidism: Potential Relationship with Iodine Supplement Requirements of Commercial Cat Foods. *J. Feline Med. Surg.* **2010**, *12* (9), 672−679.

(11) Martin, K. M.; Rossing, M. A.; Ryland, L. M.; DiGiacomo, R. F.; Freitag, W. A. Evaluation of Dietary and Environmental Risk Factors for Hyperthyroidism in Cats. *J. Am. Vet. Med. Assoc.* **2000**, *217* (6), 853−856.

(12) Dye, J. A.; Venier, M.; Zhu, L.; Ward, C. R.; Hites, R. A.; Birnbaum, L. S. Elevated PBDE Levels in Pet Cats: Sentinels for Humans? *Environ. Sci. Technol.* **2007**, *41* (18), 6350−6356.

(13) Mensching, D. A.; Slater, M.; Scott, J. W.; Ferguson, D. C.; Beasley, V. R. The Feline Thyroid Gland: A Model for Endocrine Disruption by Polybrominated Diphenyl Ethers (PBDEs)? *J. Toxicol. Environ. Health, Part A* **2012**, *75* (4), 201−12.

(14) Norrgran, J.; Jones, B.; Bignert, A.; Athanassiadis, I.; Bergman, A. Higher PBDE Serum Concentrations May Be Associated with Feline Hyperthyroidism in Swedish Cats. *Environ. Sci. Technol.* **2015**, *49* (8), 5107−14.

(15) Guo, W. H.; Gardner, S.; Yen, S. M.; Petreas, M.; Park, J. S. Temporal Changes of PBDE Levels in California House Cats and a Link to Cat Hyperthyroidism. *Environ. Sci. Technol.* **2016**, *50* (3), 1510−1518.

(16) Norrgran Engdahl, J.; Bignert, A.; Jones, B.; Athanassiadis, I.; Bergman, A.; Weiss, J. M. Cats' Internal Exposure to Selected Brominated Flame Retardants and Organochlorines Correlated to House Dust and Cat Food. *Environ. Sci. Technol.* **2017**, *51* (5), 3012−3020.

(17) Birnbaum, L. S.; Staskal, D. F. Brominated Flame Retardants: Cause for Concern? *Environ. Health Perspect.* **2004**, *112* (1), 9−17.

(18) US EPA *Polybrominated Diphenyl Ethers (PBDEs): Action Plan*, 2009.

DOI: 10.1021/acs.est.9b02226
Environ. Sci. Technol. 2019, 53, 9203−9213

(19) Sanders, H. J. Flame Retardants. *Chem. Eng. News* **1978**, *56* (17), 22−36.
(20) Kim, Y. R.; Harden, F. A.; Toms, L. M. L.; Norman, R. E. Health Consequences of Exposure to Brominated Flame Retardants: A Systematic Review. *Chemosphere* **2014**, *106*, 1−19.
(21) Allen, J. G.; McClean, M. D.; Stapleton, H. M.; Webster, T. F. Critical Factors in Assessing Exposure to PBDEs Via House Dust. *Environ. Int.* **2008**, *34* (8), 1085−1091.
(22) Dodson, R. E.; Perovich, L. J.; Covaci, A.; Van den Eede, N.; Ionas, A. C.; Dirtu, A. C.; Brody, J. G.; Rudel, R. A. After the PBDE Phase-Out: A Broad Suite of Flame Retardants in Repeat House Dust Samples from California. *Environ. Sci. Technol.* **2012**, *46* (24), 13056−13066.
(23) Hammel, S. C.; Hoffman, K.; Lorenzo, A. M.; Chen, A.; Phillips, A. L.; Butt, C. M.; Sosa, J. A.; Webster, T. F.; Stapleton, H. M. Associations between Flame Retardant Applications in Furniture Foam, House Dust Levels, and Residents' Serum Levels. *Environ. Int.* **2017**, *107*, 181−189.
(24) Sjodin, A.; Jones, R. S.; Caudill, S. P.; Wong, L. Y.; Turner, W. E.; Calafat, A. M. Polybrominated Diphenyl Ethers, Polychlorinated Biphenyls, and Persistent Pesticides in Serum from the National Health and Nutrition Examination Survey: 2003−2008. *Environ. Sci. Technol.* **2014**, *48* (1), 753−60.
(25) van der Veen, I.; de Boer, J. Phosphorus Flame Retardants: Properties, Production, Environmental Occurrence, Toxicity and Analysis. *Chemosphere* **2012**, *88* (10), 1119−1153.
(26) Gold, M. D.; Blum, A.; Ames, B. N. Another Flame Retardant, Tris-(1,3-Dichloro-2-Propyl)-Phosphate, and Its Expected Metabolites Are Mutagens. *Science* **1978**, *200* (4343), 785−787.
(27) Ospina, M.; Jayatilaka, N. K.; Wong, L. Y.; Restrepo, P.; Calafat, A. M. Exposure to Organophosphate Flame Retardant Chemicals in the U.S. General Population: Data from the 2013−2014 National Health and Nutrition Examination Survey. *Environ. Int.* **2018**, *110*, 32−41.
(28) Darnerud, P. Toxic Effects of Brominated Flame Retardants in Man and in Wildlife. *Environ. Int.* **2003**, *29* (6), 841−853.
(29) Dishaw, L. V.; Macaulay, L. J.; Roberts, S. C.; Stapleton, H. M. Exposures, Mechanisms, and Impacts of Endocrine-Active Flame Retardants. *Curr. Opin. Pharmacol.* **2014**, *19*, 125−133.
(30) Kojima, H.; Takeuchi, S.; Itoh, T.; Iida, M.; Kobayashi, S.; Yoshida, T. Vitro Endocrine Disruption Potential of Organophosphate Flame Retardants Via Human Nuclear Receptors. *Toxicology* **2013**, *314* (1), 76−83.
(31) Farhat, A.; Crump, D.; Chiu, S.; Williams, K. L.; Letcher, R. J.; Gauthier, L. T.; Kennedy, S. W. Ovo Effects of Two Organophosphate Flame Retardants-TCPP and TDCPP-on Pipping Success, Development, mRNA Expression, and Thyroid Hormone Levels in Chicken Embryos. *Toxicol. Sci.* **2013**, *134* (1), 92−102.
(32) Wang, Q.; Liang, K.; Liu, J.; Yang, L.; Guo, Y.; Liu, C.; Zhou, B. Exposure of Zebrafish Embryos/Larvae to TDCPP Alters Concentrations of Thyroid Hormones and Transcriptions of Genes Involved in the Hypothalamic-Pituitary-Thyroid Axis. *Aquat. Toxicol.* **2013**, *126*, 207−13.
(33) Li, J.; Giesy, J. P.; Yu, L.; Li, G.; Liu, C. Effects of Tris(1,3-Dichloro-2-Propyl) Phosphate (Tdcpp) in Tetrahymena Thermophila: Targeting the Ribosome. *Sci. Rep.* **2015**, *5*, 10562.
(34) Liagkouridis, L.; Cousins, A. P.; Cousins, I. T. Physical-Chemical Properties and Evaluative Fate Modelling of 'Emerging' and 'Novel' Brominated and Organophosphorus Flame Retardants in the Indoor and Outdoor Environment. *Sci. Total Environ.* **2015**, *524*, 416−426.
(35) Lorber, M. Exposure of Americans to Polybrominated Diphenyl Ethers. *J. Exposure Sci. Environ. Epidemiol.* **2008**, *18* (1), 2−19.
(36) Weschler, C. J.; Nazaroff, W. W. SVOC Exposure Indoors: Fresh Look at Dermal Pathways. *Indoor Air* **2012**, *22* (5), 356−377.
(37) Anderson, K.; Hillwalker, W. Bioavailability. In *Ecotoxicology*; Jorgensen, S. E., Fath, B. D., Eds.; Elsevier: Oxford, 2008; Vol. *1*, pp 348−357.
(38) Kile, M. L.; Scott, R. P.; O'Connell, S. G.; Lipscomb, S.; MacDonald, M.; McClelland, M.; Anderson, K. A. Using Silicone Wristbands to Evaluate Preschool Children's Exposure to Flame Retardants. *Environ. Res.* **2016**, *147*, 365−372.
(39) O'Connell, S. G.; Kincl, L. D.; Anderson, K. A. Silicone Wristbands as Personal Passive Samplers. *Environ. Sci. Technol.* **2014**, *48* (6), 3327−3335.
(40) Paulik, L. B.; Hobbie, K. A.; Rohlman, D.; Smith, B. W.; Scott, R. P.; Kincl, L.; Haynes, E. N.; Anderson, K. A. Environmental and Individual PAH Exposures near Rural Natural Gas Extraction. *Environ. Pollut.* **2018**, *241*, 397−405.
(41) Dixon, H. M.; Armstrong, G.; Barton, M.; Bergmann, A. J.; Bondy, M.; Halbleib, M. L.; Hamilton, W.; Haynes, E.; Herbstman, J.; Hoffman, P.; Jepson, P.; Kile, M. L.; Kincl, L.; Laurienti, P. J.; North, P.; Paulik, L. B.; Petrosino, J.; Points, G. L.; Poutasse, C. M.; Rohlman, D.; Scott, R. P.; Smith, B.; Tidwell, L. G.; Walker, C.; Waters, K. M.; Anderson, K. A. Discovery of Common Chemical Exposures across Three Continents Using Silicone Wristbands. *R. Soc. Open Sci.* **2019**, *6* (2), 181836.
(42) Dixon, H. M.; Scott, R. P.; Holmes, D.; Calero, L.; Kincl, L. D.; Waters, K. M.; Camann, D. E.; Calafat, A. M.; Herbstman, J. B.; Anderson, K. A. Silicone Wristbands Compared with Traditional Polycyclic Aromatic Hydrocarbon Exposure Assessment Methods. *Anal. Bioanal. Chem.* **2018**, *410* (13), 3059−3071.
(43) Bergmann, A. J.; Points, G. L.; Scott, R. P.; Wilson, G.; Anderson, K. A. Development of Quantitative Screen for 1550 Chemicals with GC-MS. *Anal. Bioanal. Chem.* **2018**, *410* (13), 3101−3110.
(44) Anderson, K. A.; Points, G. L., III; Donald, C. E.; Dixon, H. M.; Scott, R. P.; Wilson, G.; Tidwell, L. G.; Hoffman, P. D.; Herbstman, J. B.; O'Connell, S. G. Preparation and Performance Features of Wristband Samplers and Considerations for Chemical Exposure Assessment. *J. Exposure Sci. Environ. Epidemiol.* **2017**, *27* (6), 551.
(45) Bergmann, A. J.; North, P. E.; Vasquez, L.; Bello, H.; Ruiz, M. d. C. G.; Anderson, K. A. Multi-Class Chemical Exposure in Rural Peru Using Silicone Wristbands. *J. Exposure Sci. Environ. Epidemiol.* **2017**, *27* (6), 560.
(46) Donald, C. E.; Scott, R. P.; Blaustein, K. L.; Halbleib, M. L.; Sarr, M.; Jepson, P. C.; Anderson, K. A. Silicone Wristbands Detect Individuals' Pesticide Exposures in West Africa. *R. Soc. Open Sci.* **2016**, *3* (8), 160433.
(47) Vidi, P. A.; Anderson, K. A.; Chen, H. Y.; Anderson, R.; Salvador-Moreno, N.; Mora, D. C.; Poutasse, C.; Laurienti, P. J.; Daniel, S. S.; Arcury, T. A. Personal Samplers of Bioavailable Pesticides Integrated with a Hair Follicle Assay of DNA Damage to Assess Environmental Exposures and Their Associated Risks in Children. *Mutat. Res., Genet. Toxicol. Environ. Mutagen.* **2017**, *822*, 27−33.
(48) Aerts, R.; Joly, L.; Szternfeld, P.; Tsilikas, K.; De Cremer, K.; Castelain, P.; Aerts, J. M.; Van Orshoven, J.; Somers, B.; Hendrickx, M.; Andjelkovic, M.; Van Nieuwenhuyse, A. Silicone Wristband Passive Samplers Yield Highly Individualized Pesticide Residue Exposure Profiles. *Environ. Sci. Technol.* **2018**, *52* (1), 298−307.
(49) Harley, K. G.; Parra, K. L.; Camacho, J.; Bradman, A.; Nolan, J. E.; Lessard, C.; Anderson, K. A.; Poutasse, C. M.; Scott, R. P.; Lazaro, G. Determinants of Pesticide Concentrations in Silicone Wristbands Worn by Latina Adolescent Girls in a California Farmworker Community: The COSECHA Youth Participatory Action Study. *Sci. Total Environ.* **2019**, *652*, 1022−1029.
(50) Lipscomb, S. T.; McClelland, M. M.; MacDonald, M.; Cardenas, A.; Anderson, K. A.; Kile, M. L. Cross-Sectional Study of Social Behaviors in Preschool Children and Exposure to Flame Retardants. *Environ. Health* **2017**, *16*, 10.
(51) Hammel, S. C.; Hoffman, K.; Webster, T. F.; Anderson, K. A.; Stapleton, H. M. Measuring Personal Exposure to Organophosphate Flame Retardants Using Silicone Wristbands and Hand Wipes. *Environ. Sci. Technol.* **2016**, *50* (8), 4483−91.
(52) Hammel, S. C.; Phillips, A. L.; Hoffman, K.; Stapleton, H. M. Evaluating the Use of Silicone Wristbands to Measure Personal

DOI: 10.1021/acs.est.9b02226
Environ. Sci. Technol. 2019, 53, 9203−9213

Exposure to Brominated Flame Retardants. *Environ. Sci. Technol.* **2018**, *52* (20), 11875−11885.
(53) Breslow, N. E.; Day, N. E. *Statistical Methods in Cancer Research*; Distributed for IARC by WHO: Geneva, Switzerland, 1980; Vol. *1*, The Analysis of Case-Control Studies.
(54) Helsel, D. R. *Nondetects and Data Analysis. Statistics for Censored Environmental Data*; Wiley-Interscience: 2005.
(55) Carrico, C.; Gennings, C.; Wheeler, D. C.; Factor-Litvak, P. Characterization of Weighted Quantile Sum Regression for Highly Correlated Data in a Risk Analysis Setting. *J. Agric Biol. Environ. Stat* **2015**, *20* (1), 100−120.
(56) Czarnota, J.; Gennings, C.; Wheeler, D. C. Assessment of Weighted Quantile Sum Regression for Modeling Chemical Mixtures and Cancer Risk. *Cancer Inf.* **2015**, *14s2*, CIN.S17295.
(57) Czarnota, J.; Gennings, C.; Colt, J. S.; De Roos, A. J.; Cerhan, J. R.; Severson, R. K.; Hartge, P.; Ward, M. H.; Wheeler, D. C. Analysis of Environmental Chemical Mixtures and Non-Hodgkin Lymphoma Risk in the NCI-SEER NHL Study. *Environ. Health Perspect.* **2015**, *123* (10), 965−70.
(58) Helsel, D. R. More Than Obvious: Better Methods for Interpreting Nondetect Data. *Environ. Sci. Technol.* **2005**, *39*, 419A.
(59) La Guardia, M. J.; Hale, R. C.; Harvey, E. Detailed Polybrominated Diphenyl Ether (PBDE) Congener Composition of the Widely Used Penta-, Octa-, and Deca-PBDE Technical Flame-Retardant Mixtures. *Environ. Sci. Technol.* **2006**, *40* (20), 6247−6254.
(60) Council, N. R. *Toxicological Risks of Selected Flame Retardant Chemicals*; National Academies Press: 2000.
(61) Brozan, N. Another Nightwear Chemical Causes a Safety Controversy. *NY Times* 10/15/1977, **1977**.
(62) WHO *Environmental Health Criteria 209, Flame Retardants: Tris (Chloropropyl) Phosphate and Tris (2-Chloroethyl) Phosphate*; World Health Organisation: Geneva, Switzerland, 1998.
(63) Dodson, R. E.; Rodgers, K. M.; Carey, G.; Cedeno Laurent, J. G.; Covaci, A.; Poma, G.; Malarvannan, G.; Spengler, J. D.; Rudel, R. A.; Allen, J. G. Flame Retardant Chemicals in College Dormitories: Flammability Standards Influence Dust Concentrations. *Environ. Sci. Technol.* **2017**, *51* (9), 4860−4869.
(64) Stapleton, H. M.; Sharma, S.; Getzinger, G.; Ferguson, P. L.; Gabriel, M.; Webster, T. F.; Blum, A. Novel and High Volume Use Flame Retardants in US Couches Reflective of the 2005 PentaBDE Phase Out. *Environ. Sci. Technol.* **2012**, *46* (24), 13432−13439.
(65) McGee, S. P.; Cooper, E. M.; Stapleton, H. M.; Volz, D. C. Early Zebrafish Embryogenesis Is Susceptible to Developmental TDCPP Exposure. *Environ. Health Perspect.* **2012**, *120* (11), 1585.
(66) Henriquez-Hernandez, L. A.; Carreton, E.; Camacho, M.; Montoya-Alonso, J. A.; Boada, L. D.; Bernal Martin, V.; Falcon Cordon, Y.; Falcon Cordon, S.; Zumbado, M.; Luzardo, O. P. Potential Role of Pet Cats as a Sentinel Species for Human Exposure to Flame Retardants. *Frontiers in veterinary science* **2017**, *4*, 79.
(67) Walter, K. M.; Lin, Y. P.; Kass, P. H.; Puschner, B. Association of Polybrominated Diphenyl Ethers (PBDEs) and Polychlorinated Biphenyls (PCBs) with Hyperthyroidism in Domestic Felines, Sentinels for Thyroid Hormone Disruption. *BMC Vet. Res.* **2017**, *13*, 120.
(68) Mizukawa, H.; Nomiyama, K.; Nakatsu, S.; Iwata, H.; Yoo, J.; Kubota, A.; Yamamoto, M.; Ishizuka, M.; Ikenaka, Y.; Nakayama, S. M.; Kunisue, T.; Tanabe, S. Organohalogen Compounds in Pet Dog and Cat: Do Pets Biotransform Natural Brominated Products in Food to Harmful Hydroxlated Substances? *Environ. Sci. Technol.* **2016**, *50* (1), 444−52.
(69) Chow, K.; Hearn, L. K.; Zuber, M.; Beatty, J. A.; Mueller, J. F.; Barrs, V. R. Evaluation of Polybrominated Diphenyl Ethers (PBDEs) in Matched Cat Sera and House Dust Samples: Investigation of a Potential Link between PBDEs and Spontaneous Feline Hyperthyroidism. *Environ. Res.* **2015**, *136*, 173−179.
(70) Norrgran, J.; Jones, B.; Lindquist, N. G.; Bergman, A. Decabromobiphenyl, Polybrominated Diphenyl Ethers, and Brominated Phenolic Compounds in Serum of Cats Diagnosed with the Endocrine Disease Feline Hyperthyroidism. *Arch. Environ. Contam. Toxicol.* **2012**, *63* (1), 161−8.
(71) Guo, W. H.; Park, J. S.; Wang, Y. Z.; Gardner, S.; Baek, C.; Petreas, M.; Hooper, K. High Polybrominated Diphenyl Ether Levels in California House Cats: House Dust a Primary Source? *Environ. Toxicol. Chem.* **2012**, *31* (2), 301−306.
(72) Herbstman, J. B.; Sjodin, A.; Kurzon, M.; Lederman, S. A.; Jones, R. S.; Rauh, V.; Needham, L. L.; Tang, D.; Niedzwiecki, M.; Wang, R. Y.; Perera, F. Prenatal Exposure to PBDEs and Neurodevelopment. *Environ. Health Perspect.* **2010**, *118* (5), 712−9.
(73) Mooney, C. T.; Peterson, M. E. *BSAVA Manual of Canine and Feline Endocrinology*; British Small Animal Veterinary Association: 2004.
(74) Booij, K.; Smedes, F.; Van Weerlee, E. M. Spiking of Performance Reference Compounds in Low Density Polyethylene and Silicone Passive Water Samplers. *Chemosphere* **2002**, *46* (8), 1157−1161.

DOI: 10.1021/acs.est.9b02226
Environ. Sci. Technol. 2019, 53, 9203−9213