Environmental Science & Technology Letters

Letter

pubs.acs.org/journal/estlcu

Temporal Trends in Exposure to Organophosphate Flame Retardants in the United States

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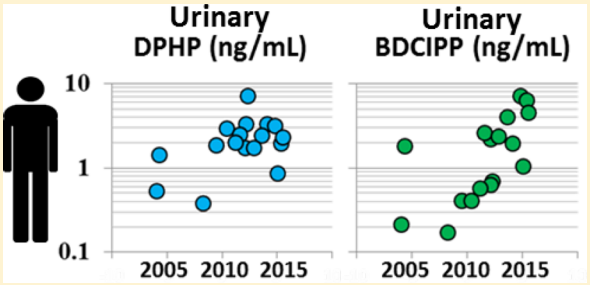
Supporting Information

ABSTRACT: During the past decade, use of organophosphate compounds as flame retardants and plasticizers has increased. Numerous studies investigating biomarkers (i.e., urinary metabolites) demonstrate ubiquitous human exposure and suggest that human exposure may be increasing. To formally assess temporal trends, we combined data from 14 U.S. epidemiologic studies for which our laboratory group previously assessed exposure to two commonly used organophosphate compounds, tris(1,3-dichloro-2-propyl) phosphate (TDCIPP) and triphenyl phosphate (TPHP). Using individual-level data and samples collected between 2002 and 2015, we assessed temporal and seasonal trends in urinary bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) and diphenyl phosphate (DPHP), the metabolites of TDCIPP and TPHP, respectively. Data suggest that BDCIPP concentrations have increased dramatically since 2002. Samples collected in 2014 and 2015 had BDCIPP concentrations that were more than 15 times higher than those collected in 2002 and 2003 (10^{β} = 16.5; 95% confidence interval from 9.64 to 28.3). Our results also demonstrate significant increases in DPHP levels; however, increases were much smaller than for BDCIPP. Additionally, results suggest that exposure varies seasonally, with significantly higher levels of exposure in summer for both TDCIPP and TPHP. Given these increases, more research is needed to determine whether the levels of exposure experienced by the general population are related to adverse health outcomes.



INTRODUCTION

Polybrominated diphenyl ethers (PBDEs) were once among the most widely used flame retardant chemicals applied to consumer products; however, concern over their persistence and toxicity led to their phase-out beginning in the early 2000s. Since then, the chemical flame retardant industry has moved toward replacements.[1−5] One class of alternatives consists of the organophosphate flame retardants (PFRs), which include chlorinated alkyl phosphates [e.g., tris(1,3-dichloro-2-propyl) phosphate (TDCIPP)] and nonhalogenated aryl phosphates [e.g., triphenyl phosphate (TPHP)]. Data suggest that PFR use increased after the PBDE phase-out, and they are now among the most commonly detected flame retardants in furniture and

Received: December 27, 2016
Revised: January 26, 2017
Accepted: January 27, 2017
Published: February 8, 2017

DOI: 10.1021/acs.estlett.6b00475
Environ. Sci. Technol. Lett. 2017, 4, 112−118

Table 1. Characteristics of Included Cohorts and Their Participants in the United States

year of sample collection	state (n)	SG-corrected GM DPHP (ng/mL)	SG-corrected GM BDCIPP (ng/mL)	mean age (standard deviation)	percent male	percent females pregnant	analysis date	analysis method	ref
adults	**combined (741)**	**1.5**	**1.3**	**32.3 (9.3)**	**26.3**	**48.0**			
2002–2005	North Carolina (347)[a]	1.4	1.8	29.6 (5.1)	0.0	100.0	09/2015 10/2015 01/2016	enzyme digestion, SPE, isotope dilution, LC–ESI-MS/MS	17
2002–2007	Massachusetts (45)	0.3	0.1	36.6 (4.3)	100.0	–	11/2011	SPE, isotope dilution, LC–APCI-MS/MS	20
2009	Massachusetts (29)	1.8[b]	0.4	46.1 (13.9)	17.2	0.0	07/2012	SPE, isotope dilution, LC–APCI-MS/MS	21
2011	North Carolina (9)	3.0	0.4	34.9 (7.4)	44.4	0.0	03/2011	SPE, isotope dilution, LC–APCI-MS/MS	11
2011	Massachusetts (46)[c]	1.7	0.5	39.8 (12.1)	55.3	4.8	01/2014	SPE, isotope dilution, LC–APCI-MS/MS	29
2011–2012	North Carolina (8)	1.9	1.3	–[d]	0.0	100.0	12/2012	SPE, isotope dilution, LC–APCI-MS/MS	18
2011–2012	North Carolina (64)	1.8	0.8	42.6 (12.6)[e]	46.9	0.0	07/2013	SPE, isotope dilution, LC–APCI-MS/MS	19
2012	New Hampshire (11)	7.1	0.7	20.1 (1.1)	0.0	0.0	01/2013	SPE, isotope dilution, LC–APCI-MS/MS	22
2012–2013	North Carolina (69)	1.7	2.3	25.9 (5.1)	100.0	–	03/2014	SPE, isotope dilution, LC–ESI-MS/MS	23
2013–2014	New Jersey (18)	1.9	2.4	39.7 (5.0)[f]	0.0	0.0	03/2014	SPE, isotope dilution, LC–ESI-MS/MS	14
2014–2015	North Carolina (27)	1.7	1.3	22.3 (3.2)	3.7	0.0	04/2014 03/2015	SPE, isotope dilution, LC–ESI-MS/MS	6
2015	California (28)	1.2	3.3	37.2 (3.8)	0.0	0.0	11/2015	enzyme digestion, SPE, isotope dilution, LC–ESI-MS/MS	15
2015	North Carolina (40)	2.4	4.7	29.8 (8.5)	37.5	0.0	09/2015	enzyme digestion, SPE, isotope dilution, LC–ESI-MS/MS	24
children	**combined (116)**	**2.9**	**6.1**	**2.8 (2.2)**	**53.4**	–			
2011	Massachusetts (14)	2.0	1.0	6.3 (2.2)	50.0	–	01/2014	SPE, isotope dilution, LC–APCI-MS/MS	29
2013–2014	New Jersey (26)	3.0	5.6	3.2 (0.9)[g]	47.8	–	03/2014	SPE, isotope dilution, LC–ESI-MS/MS	14
2014–2015	North Carolina (43)	3.2	7.3	0.7 (0.4)	63.8	–	04/2015	SPE, isotope dilution, LC–APCI-MS/MS	16
2015	California (33)	2.9	10.9	3.7 (1.5)	53.1	–	11/2015	enzyme digestion, SPE, isotope dilution, LC–ESI-MS/MS	15

[a]Two participants from the original cohort (n = 349) who were <18 years of age were excluded from analyses. [b]DPHP data not previously reported and provided by author. [c]One participant in the original cohort had very dilute urine and was excluded from analyses. [d]Individual participant ages were not collected and were imputed as 32 years for further statistical analyses. [e]The participant age was missing for 11 participants and was imputed as a random number within one standard deviation of the cohort mean for further statistical analyses. [f]The participant age was missing for two participants and was imputed as a random number within one standard deviation of the cohort mean for further statistical analyses. [g]The participant age and sex were missing for four participants and were imputed as a random number within one standard deviation of the cohort mean for age, or randomly for sex.

DOI: 10.1021/acs.estlett.6b00475
Environ. Sci. Technol. Lett. 2017, 4, 112–118

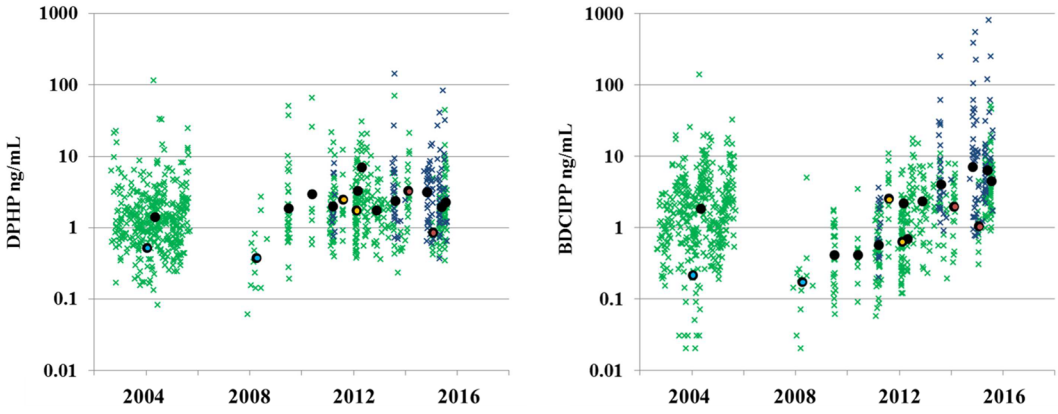


Figure 1. Urinary PFR metabolite levels by year. Individual participant values are shown for adults (green) and children (blue). Black dots indicate the geometric mean in each cohort [two geometric means are shown for refs 20 (blue fill), 19 (yellow fill), and 6 (red fill) because samples were collected over two sampling campaigns with different participants].

electronics.[1−5] Additionally, PFRs are used in other products. For example, TPHP is used as a plasticizer and is found in a variety of applications (e.g., nail polish[6]). Like PBDEs, PFRs are additives that are not chemically bound to products. Consequently, they migrate into indoor air and dust, where they are ubiquitously detected.[7−10]

In humans, PFRs are thought to be rapidly metabolized and excreted in urine ($t_{1/2}$ of approximately hours). PFR metabolites are used as exposure biomarkers and have been detected in urine samples from people living around the world.[6,11−27] Although data suggest PFR exposure is widespread and potentially increasing, past studies have been limited in their ability to assess exposure trends because they have generally been conducted over relatively short periods. In addition, comparisons of metabolite concentrations across studies have been limited by differences in cohort composition and potential interlab variability.[28] However, by compiling individual-level data from 14 U.S.-based epidemiologic studies conducted by our laboratory in 2002−2015, we are able to more thoroughly evaluate temporal trends in urinary PFR metabolite concentrations. Here, we assess temporal trends in metabolites of TDCIPP and TPHP, bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) and diphenyl phosphate (DPHP), respectively.

MATERIALS AND METHODS

Study Populations. Data were compiled from epidemiologic studies for which our laboratory group previously measured urinary PFR metabolites [857 individuals (Table 1)].[6,11,14−24,29] Descriptive studies were reported previously and are not discussed in detail here. Briefly, urine samples were collected in 2002−2015 and analyzed in 2009−2016. Individual studies were primarily located in North Carolina or the Northeastern United States, with the exception of one California cohort. Several studies included measurements of the same individuals at multiple time points; however, because measurements were generally closely spaced (i.e., days to weeks apart), we included a single measurement per participant, selected as the first urine sample,[18,19] or the last for the FLaRE study that included only children at the final assessment.[29] In addition, two studies were designed to assess contributions of specific exposure sources (fingernail polish and gymnastics practice).[6,22] From these studies, we selected the measurements intended to represent background exposure. All protocols were reviewed and approved by the relevant Institution Review Boards.

Urine Analysis. Extraction and analysis procedures for BDCIPP and DPHP have been described previously.[11,14,15] Briefly, samples were extracted and cleaned with solid-phase extraction (SPE) techniques (Table 1), using identical columns and sorbent material (Strata-X-AW). Some studies included an enzyme digestion step prior to SPE for analysis of BCIPHIPP sulfate and glucuronide conjugates, but this is not expected to bias DPHP and BDCIPP concentrations because they have no known conjugated metabolites.[30] In all studies, deuterium-labeled standards of DPHP and BDCIPP were used for quantification by spiking prior to SPE, and recoveries of internal standards through the extraction process were quantified using ^{13}C-labeled DPHP. All samples were analyzed using liquid chromatography and tandem mass spectrometry (LC−MS/MS), although ionization techniques differed between studies, either atmospheric pressure chemical ionization or electrospray ionization. All studies employed thorough QA/QC programs with laboratory blanks and duplicates. Specific gravity was also measured in samples prior to analysis using a digital hand-held refractometer (Atago).

Covariate Data. Although included studies varied in terms of collected covariates, all recorded the date that samples were collected. Individual participant ages were available for 97.1% of participants. If missing, age was imputed as a random number within one standard deviation of the study mean. However, eight women from ref 18 were assigned 32 years of age as they were missing data on age but were known to be pregnant. Sex was available for 99.5% of participants and was randomly imputed for the four participants for which it was missing. Pregnancy status was confirmed for many female participants;[17,18,29] however, if pregnancy status was not obtained, we assumed they were not pregnant. While the majority of urine samples were spot urines, 40 were first-morning voids and eight were 24 h collections.

Statistical Analysis. Previous publications from each study demonstrate frequent detection of BDCIPP and DPHP. If a particular metabolite was not detected, we imputed the concentration as the method detection limit divided by 2. We visually assessed plots of metabolite concentrations over time (Figure 1) and evaluated the shape of potential relationships using smoothing. On the basis of plot and smoothing results, which suggested that relationships between the date of

DOI: 10.1021/acs.estlett.6b00475
Environ. Sci. Technol. Lett. 2017, 4, 112−118

Table 2. Regression Analyses with Year (two-year categories) and Season (four categories) of Sample Collection as a Predictor of Urinary PFR Metabolite Levels[a]

		BDCIPP		DPHP	
	no.	10^{β} (95% CI)	p value	10^{β} (95% CI)	p value
adults (≥18 years of age)					
2002–2003	132	reference	–	reference	–
2004–2005	248	1.22 (0.98, 1.52)	0.08	1.02 (0.83, 1.26)	0.83
2006–2007	1	–	–	–	–
2008–2009	40	0.81 (0.50, 1.31)	0.39	1.56 (0.99, 2.47)	0.06
2010–2011	67	2.41 (1.57, 3.70)	<0.0001	2.98 (1.99, 4.46)	<0.0001
2012–2013	157	6.86 (4.66, 10.1)	<0.0001	2.94 (2.04, 4.23)	<0.0001
2014–2015	96	16.5 (9.64, 28.3)	<0.0001	1.93 (1.16, 3.20)	0.01
winter	206	reference	–	reference	–
spring	185	2.06 (1.67, 2.53)	<0.0001	0.99 (0.81, 1.20)	0.90
summer	238	4.13 (3.39, 5.04)	<0.0001	1.54 (1.27, 1.85)	<0.0001
fall	112	1.77 (1.38, 2.26)	<0.0001	0.97 (0.77, 1.23)	0.82
children (≤10 years of age)					
2010–2011	14	reference	–	reference	–
2012–2013	25	1.02 (0.28, 3.69)	0.98	0.65 (0.26, 1.60)	0.34
2014–2015	77	3.90 (1.36, 11.1)	0.01	0.74 (0.35, 1.54)	0.41
winter	23	reference	–	reference	–
spring	39	2.28 (0.88, 5.91)	0.09	1.70 (0.87, 3.34)	0.12
summer	32	8.48 (3.16, 22.8)	<0.0001	2.34 (1.16, 4.69)	0.02
fall	22	3.03 (1.32, 6.96)	0.009	0.72 (0.40, 1.29)	0.27

[a]Exponentiated β coefficients represent the multiplicative change in metabolite concentrations relative to the reference group. Analyses stratified by age and adjusted for sex (male, nonpregnant female, and pregnant female), age (continuous), year of collection, and season of collection.

collection and metabolite levels were nonlinear, collection times were categorized into 2 year periods for analyses. Metabolite concentrations were not normally distributed and were log-transformed in regression analyses. β coefficients from these models were exponentiated for interpretation and represent the multiplicative change in metabolite concentration. Analyses were adjusted for age (continuous), sex (male, nonpregnant female, and pregnant female), and season of collection, factors that previous research suggests may be related to PFR metabolite concentrations.[12,17,19] We also considered potential confounding by the number of years a sample had been stored prior to analysis; however, storage time (continuous) was strongly collinear with collection date as older samples tended to be stored longer than newer samples before analysis. To address this issue, we dichotomized storage time at 1 year. The dichotomized storage time was not associated with urinary metabolite concentrations and was excluded from the final adjustment set. Although we do not expect the enzyme digestion step or the differing ionization techniques to impact BDCIPP and DPHP levels, we considered potential confounding by the analysis method. The method was not associated with urinary metabolite concentrations and was dropped from analyses. Because previous results suggest that children have greater exposure to PFRs than adults do,[12,14−16,25] and children were concentrated in later years of sample collection, we conducted analyses separately for children (≤10 years of age) and adults (≥18 years of age). To account for urine dilution, we present results using specific gravity-corrected urine concentrations;[31] however, uncorrected analyses produced nearly identical results (not shown). Statistical analyses were conducted in SAS version 9.4.

We conducted sensitivity analyses to determine the robustness of results to assumptions about cohort composition, sample type, and analysis. To evaluate the impact of including participants with missing data, we conducted analyses restricted to participants with complete data. In addition, we conducted analyses including only spot urine samples. Results were indistinguishable from those using all data. Additionally, our final data set contained a number of pregnant women, particularly the 2002–2005 set. To ensure that temporal patterns were not driven by time-dependent differences in the types of participants included (e.g., pregnant women), we conducted secondary analyses excluding pregnant women. Finally, data were collected in several different geographic regions, including California, where exposure may be higher because of stronger flammability standards. We additionally conducted analyses excluding California participants.

RESULTS AND DISCUSSION

Thirteen studies included adults who ranged in age from 18 to 67 years [n = 741; mean age of 32.3 ± 9.3 years (Table 1)]. Three of these studies included children, and one additional study focused exclusively on children [n = 116; mean age of 2.8 ± 2.2 years (Table 1)]. Among adults, 73.7% of participants were female, and of those, 65.5% were pregnant. Children were more evenly distributed by sex than adults (53.4% male).

BDCIPP and DPHP were detectable in >83% of samples from each study and were detected overall in 96 and 91% of samples, respectively. Individual study participants' metabolite concentrations are shown in Figure 1 along with geometric mean metabolite concentrations for each study. As reported previously, samples from children tended to have metabolite concentrations higher than the concentrations of those from adults, particularly for BDCIPP, a finding highlighted in many studies.[12,14−16,25] BDCIPP and DPHP levels also tended to be higher among pregnant women, suggesting differences in metabolism and excretion or exposure behavior patterns during pregnancy.

Our results suggest that urinary BDCIPP levels have increased dramatically in recent years (Table 2). Among adults,

DOI: 10.1021/acs.estlett.6b00475
Environ. Sci. Technol. Lett. 2017, 4, 112−118

samples collected in 2014 and 2015 had BDCIPP concentrations that were 16.5 times those in urine samples collected in 2002 and 2003 [95% confidence interval (CI) from 9.64 to 28.3 (Table 2)]. Although the range of collection dates was narrower, samples from children displayed similar trends; children providing samples in 2014 and 2015 had urinary BDCIPP concentrations that were 3.90 times those in samples collected in 2010 and 2011 [95% CI from 1.36 to 11.1 (Table 2)]. Time trends were similar and slightly stronger when we excluded pregnant women (Table S1). When we excluded California participants, patterns of association remained very similar (Table S2).

Previous research demonstrates that TDCIPP is commonly used in residential furniture and is widely detected in indoor environments; however, there have been few evaluations of temporal trends in different matrices.[3,8] In a small California house dust assessment, TDCIPP levels were stable between 2006 and 2011.[9] Interestingly, we saw the largest increases in urinary BDCIPP after this period. Additional data investigating the presence of TDCIPP in residential furniture suggest that use may have increased after the Penta-BDE phase-out but has declined since 2014.[3] It will take several more years of data collection to determine if these decreases will impact exposure.

Urinary DPHP concentrations were significantly higher for samples collected in 2010−2015 compared to samples collected in 2002 and 2003. For example, samples collected in 2010 and 2011 had urinary DPHP concentrations 2.98 times those of samples collected in 2002 and 2003 [95% CI from 1.99 to 4.46 (Table 2)]. Although concentrations were also significantly higher in 2014 and 2015, the magnitude of the effect (i.e., OR = 1.93) was smaller than the effect estimates for 2010 and 2011 or 2012 and 2013, suggesting exposure may have peaked during this period and could be in decline. We observed no trends in DPHP concentrations among children; however, children's samples were collected over a period narrower than that of adults (Table 2). Excluding pregnant women and California participants had little impact on results (Tables S1 and S2).

Our results showing increases in DPHP are consistent with a small study showing TPHP increases in household dust between 2006 and 2011.[9] Although long-term human exposure trends have not been assessed previously, to the best of our knowledge, short-term trends were recently evaluated in pooled samples from Chinese adults.[32] Ma et al. reported no change in TPHP concentrations between samples collected in 2011 and 2015 in China, suggesting that exposure levels were relatively constant during this period.[32] Our results suggest that TPHP exposure may have started to decrease post-2011, suggesting that TPHP use as a flame retardant or in other applications could be decreasing. Although urinary DPHP is thought to be an indicator of TPHP exposure, other compounds may be metabolized to DPHP and DPHP itself may be used in consumer products.[33]

A seasonal trend was observed in urinary BDCIPP; concentrations were significantly higher in spring, summer, and fall than in winter. For example, BDCIPP concentrations were 4.13 times as high in summer as in winter [95% CI from 3.39 to 5.04 (Table 2)]. DPHP concentrations were also higher in summer but to a lesser degree [$10^{\beta} = 1.54$; 95% CI from 1.27 to 1.85 (Table 2)] and were not statistically different in spring and fall versus winter. Cumulatively, these findings suggest that PFR exposure could be temperature-dependent. Indoor temperatures are generally more stable, suggesting that outdoor air or other microenvironments could be more important drivers of exposure than previously thought. TDCIPP is commonly used in automobiles,[34] so it is possible that temperature fluctuations in automobiles (e.g., from sitting in the sun) are driving seasonal exposure differences. Alternatively, seasonal behavior changes could explain patterns (e.g., differences in time spent indoors or changes in ventilation). Regardless of the underlying reason, our results suggest the season of collection could be an important factor to consider in epidemiologic studies relying on single urine samples to assess long-term exposure.

Our results represent the first long-term assessment of human PFR exposure and have the advantage of including numerous measurements conducted by the same laboratory. However, our results should be interpreted in the context of several important limitations. First, data were collected for research of various, unrelated hypotheses; therefore, the study populations included are not representative of the general population. A randomly selected population with longitudinal follow-up would provide a stronger resource for evaluating trends. Several other groups have measured urinary PFR metabolites in different parts of the world.[12,13,25−27] With the exception of samples from Australia, which had substantially higher DPHP levels,[12] observed concentrations were similar or slightly lower than those analyzed by our group in U.S. studies for the time period under evaluation. We analyzed samples at different points in time with variable storage times and conditions. We did not find associations between concentration and storage times greater than or less than 1 year; however, we were unable to evaluate differences with finer granularity because of collinearity between storage time and collection date. It is possible that samples could degrade over time and potentially impact concentrations; however, this seems unlikely to explain the patterns we observed because we do not see patterns of decrease in analyses with SRM 3673, which we have analyzed numerous times, with variable storage durations. Storage containers were also different across studies; however, it is unlikely that storage method (i.e., glass or plastic) influenced our results, as recent work by Carignan et al. indicates little impact on metabolite concentration.[35] Additionally, our analyses primarily relied on spot urine samples. While previous research suggests that spot urine samples are reliable estimates of exposure over time, they are likely subject to greater variation in individual PFR concentrations than first-morning voids or 24 h urine collections because of the rapid metabolism of PFRs.[18,19] This may explain some of the variability in metabolite concentrations observed. Using individual average urine concentrations rather than spot urine measures would reduce observed scatter in the data. However, we feel that it is unlikely that our use of spot urine samples in this analysis is driving the observed trends. Finally, it is possible that residual confounding may influence the observed differences (e.g., body mass index and behavioral characteristics) but would have to be very strong to explain the entirety of observed trends.

TDCIPP exposure, as indicated by urinary BDCIPP levels, appears to have increased over the past 15 years. Similarly, our data suggest that TPHP exposure also may have increased 2002 to 2011 but may have leveled off or decreased since 2011. Additional data are urgently needed to determine whether levels of exposure experienced by the general population are related to adverse health outcomes.

DOI: 10.1021/acs.estlett.6b00475
Environ. Sci. Technol. Lett. 2017, 4, 112−118

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.estlett.6b00475.

One table that presents results restricted to nonpregnant adults and one table that presents results restricted to participants not living in the state of California at the time of sample collection (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Portions of this work were funded by the National Institute of Environmental Health Sciences (R01 ES016099 to H.M.S., R21 ES023904 to J.L.D., P01 ES022831 to S.K.M., R01 ES009718 and ES022955 to R.H., T32 ES014562 and R01 ES015829 supporting E.V.P., T32 ES007069 and T32 ES014562 supporting C.C., and R01 ES015829 to T.F.W.), by the U.S. Environmental Protection Agency (RD-83543701 to S.K.M.), and by a Health and the Environment award from the Duke University School of Medicine and the Duke Nicholas School of the Environment to S.K.M. and H.M.S.

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DOI: 10.1021/acs.estlett.6b00475
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