Polycyclic aromatic hydrocarbon metabolite levels and pediatric allergy and asthma in an inner-city cohort

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Abstract

Exposure to polycyclic aromatic hydrocarbons (PAH) has been associated with allergic sensitization and asthma. We hypothesized that increased urinary PAH metabolites are associated with allergy or asthma among children age 5 yrs in an inner-city birth cohort. As part of an ongoing prospective birth cohort under the auspices of the Columbia Center for Children's Environmental Health (CCCEH), urine was collected from 5-yr-old children (n = 222) of Dominican American and African American mothers in Northern Manhattan and South Bronx of New York City. Twenty-four PAH metabolites were measured in these specimens, and their levels (unadjusted and specific gravity corrected) were evaluated with IgE levels and asthma outcomes. Ten metabolites were detected in urine from all children. Concentrations ranged higher than those in representative samples of US children ages 6–11 in the National Health and Nutrition Examination Survey (NHANES). Among CCCEH children, compared with African Americans, the Dominican children had higher 2-hydroxynaphthalene but lower 9-hydroxyfluorene and 4-hydroxyphenanthrene concentrations. Increased 3-hydroxyfluorene and 3-hydroxyphenanthrene levels were associated with higher anti-mouse IgE levels (p < 0.05). These plus 2-hydroxynaphthalene, 2-hydroxyflourene and 1-hydroxyphenanthrene concentrations were associated with higher anti-mouse IgE levels on multivariate analyzes. Increased 2-hydroxyphenanthrene, 3-hydroxyphenanthrene and 4-hydroxyphenanthrene levels were associated with higher anti-cat IgE levels (p < 0.05) in univariate, but not multivariate, analyzes. Levels of PAH metabolites were not associated with respiratory symptoms. Measures of PAH metabolites suggest considerable exposure in an urban pediatric population, and possible associations with allergic sensitization to mouse.

Keywords

polycyclic aromatic hydrocarbons; inner-city asthma; allergen-specific IgE

Exposure to high levels of air pollution has been associated with decreased lung function, asthma, nasal symptoms, bronchitis and sensitization to inhalant allergens in both children and adults (1–5). These studies implicate traffic-related emissions, largely composed of diesel

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exhaust particles, trace metals, volatile organic compounds, nitrogen dioxide, particulate matter, and polycyclic aromatic hydrocarbons (PAH) in the development of respiratory symptoms, asthma or the onset of allergies.

Polycyclic aromatic hydrocarbon are produced during the incomplete combustion of organic material such as fuels, coal, wood, tobacco, and oil. Vehicle emissions are major sources of PAH in urban areas (6,7). Studies have shown that exposure to PAH is associated with adverse respiratory health outcomes. For example, our group reported that pre-natal exposure to Σ_8PAH (benz(a)anthracene, benzo(a)pyrene, 3) benzo(b)fluoranthene, benzo(g,h,i)perylene, benzo(k)fluoranthene, chrysene/isochrysene, dibenz (a,h)anthracene and indeno(1,2,3,c,d) pyrene) in the presence of post-natal exposure to environmental tobacco smoke (ETS), was associated with increased cough and wheeze at age 12 months, and breathing problems and reports of probable asthma at age 24 months (8). We also found that higher pre-natal exposure to PAH was associated with cough, wheezing and ear infections in infants in a Polish cohort (9). It has been suggested that PAH exposure may help drive proallergic immunoglobulin (Ig) E responses. For example, the PAH pyrene has been shown to enhance transcription of the T-cell interleukin (IL)-4 promoter (10). In mice, exposure to the PAH pyrene, anthracene, fluoranthene and benzo(a)pyrene upregulated anti-mountain cedar IgE production (11).

Polycyclic aromatic hydrocarbons are metabolized to hydroxylated metabolites and excreted primarily as conjugates (12), which have been proposed as specific biomarkers of PAH exposure via inhalation of polluted air, intake of certain foods (e.g. charcoal broiled meats and other smoked foods), and absorption by the skin (i.e. from sources in soil, dirt)(12–14). Levels of 1-hydroxypyrene, the main pyrene metabolite, have been used as representative indicators of PAH exposure in various occupational settings [reviewed in (15)], but less so in non-occupationally exposed populations (13,16,17). In one, children living near a large industrial point source of PAH in Ukraine had higher levels of urinary 1-hydroxypyrene compared with children living farther away (16). A similar finding was repeated when levels of several hydroxyphenanthrene metabolites were measured from children living near industrial sites (18). Another study reported that levels of 1-hydroxypyrene were higher among a group of kindergarten children whose playground was located near high volumes of traffic in comparison with children whose playground was farther away (19). In a cohort of 75 children in Saudi Arabia, serum naphthalene and pyrene levels were elevated among asthmatic children, although covariates such as maternal history of asthma or allergy were not considered (20).

Recently, the U.S. Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey (NHANES) (1999–2000, 2001–02) provided comprehensive descriptions of reference ranges for a larger panel of PAH metabolites collected from a population of children and adults without suspected occupational exposures (21,22). Higher levels were detected among the children, suggesting that they may be at greater risk for adverse health effects. However, associations between this panel of PAH metabolite levels and asthma-related outcomes have not yet been evaluated.

The objectives of this study were to compare a suite of urinary PAH metabolite measurements with allergic outcomes and asthma in a pediatric inner-city cohort at age 5 yrs. Our approach was to study a subset of subjects from the Columbia Center for Children's Environmental Health (CCCEH), a longitudinal birth cohort assessing the effects of a variety of environmental exposures in Northern Manhattan and South Bronx in New York City on health outcomes. We hypothesized that increased urinary PAH metabolites are associated with allergy, asthma, or respiratory symptoms at age 5.

Materials and methods

As part of an ongoing longitudinal birth cohort study conducted under the auspices of the CCCEH, women ages 18–35, living in Northern Manhattan and the South Bronx, were enrolled during pregnancy (n = 725) from clinics affiliated with New York Presbyterian Hospital (Columbia campus) or Harlem Hospital as previously described (8,23). Non-smoking African American or Dominican women were recruited during late pregnancy between 1998 and 2006. Women were excluded if they reported a diagnosis of diabetes mellitus, hypertension, or human immunodeficiency virus infection, had their first prenatal visit after 20 wks gestation or resided in New York City for <1 yr before pregnancy. From this cohort, n = 222 children who had reached age 5 yrs from 22 February 2005 and 14 December 2007 were enrolled in this study. Informed consent was obtained from all participants in accordance with Columbia University's Institutional Review Board.

Questionnaires and urine collection

Questionnaires were administered to the mother prenatally, every 3 months through the child's age 2 yrs, and then every 6 months through age 5 yrs. Analyzes for this paper included data from the prenatal questionnaires, and from two questionnaires administered at age 5 yrs; the second one was coincident with the collection of urine. The pre-natal questionnaire was administered during the last trimester of pregnancy to determine maternal history of asthma, environmental exposures (such as traffic and pesticides) and demographic characteristics. Wheeze, asthma and other respiratory symptoms such as bronchitis, cough and ear infections of the children over the previous 3 months were assessed by the first age 5-yr questionnaire. The second 5-yr questionnaire was administered to assess current exposures to PAH, including questions on recent exposure to cigarette smoke, diet, and use of mothballs that may contain naphthalene within the last 2 days. Urine was collected, aliquotted, and frozen at −80°C prior to shipping to the Centers for Disease Control and Prevention on dry ice for analysis.

Measurement of polycyclic aromatic hydrocarbon metabolites

Each subject's sample was analyzed for a suite of 23 PAH metabolites as previously described (21,24). Analytical determination was conducted by using enzymatic deconjugation, followed by automated liquid-liquid extraction and quantified by gas chromatography/isotope dilution high-resolution mass spectrometry. The limit of detection (LOD) was defined as the higher of either the method blank LOD (three times standard deviation of method blanks after subtracting the average blank), or the instrument LOD (lowest point on the calibration curve having a signal >3 times the signal to noise ratio). Values at the LOD were recoded as half the LOD. To control for differences because of the dilution of the urine, specific gravity levels were measured in all samples using a handheld refractometer (Urine-Specific-Gravity-Refractometer-PAL-10-S-P14643C0; TAGO USA, Inc. Bellevue, WA 98005 USA), as recent data suggested that urinary creatinine may provide a biased estimate of dilution in asthmatics (25,26).

Immunoglobin E

Blood was drawn at age 5 and serum was isolated, aliquotted, and stored at −80°C. Allergen-specific IgE (mouse, cockroach, cat, dog, and dust mite) and total IgE levels were measured by ImmunoCAP (Phadia Uppsala, Uppsala, Sweden) in duplicate, as described (27). Elevated allergen-specific IgE responses were defined as ≥0.35 IU/ml (Phadia Uppsala).

Statistical analysis

Hypothesis testing was preceded by descriptive statistics, including examination of frequency distributions and measures of central tendency and variation, simple correlations among

variables, and their variance–covariance matrices. Values were natural log transformed as needed to normalize the distributions and fulfill the requirements of the statistical tests performed. The main hypotheses use $p < 0.05$ and a two-tailed test for significance.

Fourteen of the 24 PAH metabolites were below the LOD in most urine samples, or with insufficient frequency to be included in further analyzes (footnote; Table 2). Urinary levels of the 10 highly detected metabolites were adjusted by specific gravity using a formula developed by Hauser et al. (28) for urinary metabolites of phthalates in an occupational setting, and adapted to a pediatric population (Table 2).

Geometric means for 10 PAH metabolites were calculated according to Grainger et al. (22). In some analyzes, levels from individual PAH metabolite levels were summed and then underwent natural log transformation. Statistical analyzes were conducted using uncorrected (fresh weight) and specific gravity-corrected PAH metabolite values. Initially, *t*-tests were conducted to compare the mean PAH levels (following natural log transformation) according to ethnicity, child sex, IgE positivity and/or the presence of respiratory symptoms or asthma. Logistic regression analyzes were conducted to evaluate whether the association detected between PAH metabolites and IgE in univariate analyzes remained significant after controlling for sex, ethnicity, maternal history of asthma, and exposure to ETS.

Results

Cohort characteristics

Our cohort consisted of children of mothers who are Dominican American (59.5%) and African American (40.5%). Approximately 21% reported a history of asthma. In the 48 h prior to collection of urine, approximately 24% of the children reportedly were exposed to ETS; approximately 12% of the children were exposed to their mothers' secondhand smoke. Over 15% of the children ate smoked meats prior to the measurement for PAH urinary metabolites (Table 1).

Polycyclic aromatic hydrocarbon metabolite levels

Widely varying levels of 10 PAH urinary metabolites was detected in all children as summarized in Table 2. Notably, several ethnic differences were apparent. Levels of 2-hydroxynaphthalene ranged higher in Dominican American when compared with African Americans, using t tests for both uncorrected and corrected data (specific gravity). In analyzes of metabolite levels corrected for specific gravity, levels of 9-hydroxyfluorene and 4-hydroxyphenanthrene ranged higher among African Americans. Concentrations (uncorrected) of the metabolites 1-hydroxypyrene, 1-hydroxynapthalene, and 2-hydroxynapthalene were higher in the CCCEH cohort when compared with the NHANES cohort, as defined by a geometric mean for CCCEH cohort that exceeds the upper 95% confidence interval (CI) for NHANES cohort (Table 2).

Polycyclic aromatic hydrocarbon metabolites, respiratory symptoms, and IgE production

To ascertain whether exposure to PAH, as determined by measurement of the metabolites in the urine, is associated with asthma or other respiratory symptoms, both individual metabolite levels and summed metabolite levels were compared (*t*-tests) with reported asthma, wheeze, cough, bronchitis, and ear infection. PAH metabolite levels were not associated with asthma or any of the respiratory symptoms assessed. Positive associations were not apparent when the data were stratified by race, sex and current ETS.

Univariate analyzes were conducted to determine whether exposure to PAH was associated with an increased risk for developing indoor allergen-specific IgE levels. Following adjustment

for specific gravity, significant positive associations with 3-hydroxyfluorene and 3-hydroxyphenanthrene levels and anti-mouse IgE antibodies were found. Significant positive associations with 2-hydroxyphenanthrene, 3-hydroxyphenanthrene and 4-hydroxyphenanthrene concentrations and anti-cat IgE antibodies also were found (Table 3). Most of the significant findings were detected in additional comparison with uncorrected metabolite levels (data not shown). In contrast, individual and summed PAH metabolite levels did not correlate with total IgE levels or the sum of all five allergen-specific (cockroach, mouse, dust mite, cat, and dog) IgE levels.

Analyzes performed within ethnicity showed that higher levels of 4-hydroxyphenanthrene were measured in association with higher levels of anti-cat IgE (mean 3.32 ± 0.09 vs. 3.97 ± 0.21 IU/ml, $p = 0.013$; specific gravity corrected; 3.52 ± 0.12 vs. 3.79 ± 0.38 IU/ml, $p = 0.010$; undiluted) only among Dominican Americans. No significant differences according to child sex, maternal history of asthma, or exposure to ETS for any of the allergen-specific IgE levels were detected in stratified analyzes, although the sample sizes were small.

Logistic regression modeling was conducted to determine odds ratios (OR) and 95% CI for predicting an elevated mouse IgE after controlling for sex, ethnicity, maternal history of asthma, and exposure to ETS. Higher levels of 2-hydroxynaphthalene, 2-hydroxyflourene, 3-hydroxyfluorene, 1-hydroxyphenanthrene, and 3-hydroxyphenanthrene were associated with mouse IgE ($n = 135$; specific gravity corrected: 2-hydroxynaphthalene: OR 1.92, 95% CI 0.99, 3.73, $p = 0.06$; 2-hydroxyflourene: OR 1.82, 95% CI 1.01, 3.28, $p = 0.045$, 3-hydroxyfluorene: OR 2.21, 95% CI 1.18, 4.19, $p = 0.01$; 1-hydroxyphenanthrene: OR 1.88, 95% CI 1.03, 3.49, $p = 0.04$; 3-hydroxyphenanthrene: OR=2.08, 95% CI 1.09, 4.00, $p = 0.03$; statistical significance confirmed using uncorrected values). Similar logistic modeling for predicting an elevated cat IgE after controlling for sex, ethnicity, maternal history of asthma, and exposure to ETS was conducted but significantly elevated OR were not detected. The OR for ethnicity was significant in analyzes examining the association between 1-hydroxynaphthalene levels and anti-cat IgE following correction by specific gravity (data not shown).

Discussion

Our objectives were to compare a suite of urinary PAH metabolite levels with asthma-related outcomes in a young pediatric inner-city cohort. We found that high levels of metabolites were detected and several ethnic differences in levels were apparent. Notably, levels in this Northern Manhattan and South Bronx cohort tend to run higher than those observed among slightly older children (ages 6–11) who were evaluated through NHANES, which is a nationally representative sample of the US population. In addition, while PAH metabolite levels were not associated with asthma or respiratory symptoms, positive associations with higher anti-mouse IgE, and possibly with anti-cat IgE levels, were found.

The mechanisms underlying the ethnic differences may be multifactorial. One explanation may be that air pollution exposure is relatively similar within neighborhoods that are more populated by one ethnic group compared with another. Alternate explanations may include ethnic or cultural differences in dietary preferences or other behaviors not measured in this study. Another possibility may relate to genetic factors that may impact the metabolism of these compounds. Some of these possibilities also were suggested by the NHANES reports. Many differences across Mexican Americans, non-Hispanic blacks and non-Hispanic whites were observed, depending on the individual PAH metabolite, but most commonly for 2-hydroxynaphthalene, 1-hydroxyphenanthrene, and 9-hydroxyphenanthrene (21). It is interesting that for 2-hydroxynaphthalene, considered a more specific indicator of exposure to airborne PAH exposure (29,30), levels were higher among Mexican Americans in the

NHANES study, and among Dominican Americans when compared with African Americans in the CCCEH cohort.

Higher PAH metabolite levels detected in the CCCEH cohort, when compared with the NHANES cohort, likely reflect differences attributable to the ubiquitous traffic-related and other sources of air pollution in the urban environment of the CCCEH cohort. The alternate explanation relates to the slightly younger age at time of assessment for the CCCEH children, when some PAH metabolite levels (e.g., 1-hydroxypryene, 1-hydroxyphenenthrene, 3-hydroxyphenenth-rene, 2-hydroxyfluorene, and 3-hydroxyfluorene) tend to run higher (21), presumably because of age-related differences in the ability to metabolize these products. In support of the later possibility, higher metabolite levels among children younger than 6 yrs old were detected in a German cohort study (31). These findings also could reflect differences in dietary intake (32). Regardless, they may be indicators of greater potential risk for the later development of PAH-associated diseases.

The associations between PAH metabolite levels and anti-mouse IgE levels complements other studies that suggest exposure to trafic-related air pollution may upregulate allergic immune responses (4,33,34). The evidence that PAH specifically may help drive allergy comes from *in vitro* studies that demonstrated that diesel-derived PAH-enhanced IgE production by tonsillar B cells (35). Exposure to pyrene has been associated with upregulation of the IL-4 promoter (10). In addition, pyrene, benzo(a)-pyrene, anthracene, phenanthrene, and flouranthene have been shown to increase IgE production, T helper 2 cytokine production, and mucosal inflammation in adult humans and animals challenged by allergens (11,36,37). One could speculate that the association between PAH metabolite levels with allergens derived from mice raises the possibility that the PAH-mediated upregulation of allergy may be more likely to occur in association with mammalian proteins compared with those derived from cockroach and other arthropods. Curiously, children of dog owners were more likely to experience bronchitic symptoms following exposure to particulate matter and other air pollutants than children living with a cat or no pets at all (38), also suggesting that exposure to mammalian proteins could enhance the immune response to air pollution exposure.

A few studies have suggested that exposure to PAH may be associated with asthma-related symptoms (8,9), unlike in the analyzes reported here. Explanations may include the possibility that PAH, like diesel, may be more associated with acute asthma exacerbations than asthma development, and that our questionnaires that surveyed symptoms over the last 3 months were not sufficiently sensitive to distinguish very recent wheeze. Alternately, insufficient statistical power, particular for assessing infrequent outcomes of ear infection and bronchitis, may explain this negative finding.

Several limitations should be acknowledged. The half-lives of PAH metabolites may be as short as 6–35 h (39). and variations in exposure across time may be large. Other pathways for degradation, including excretion in the feces may have contributed (40). We also cannot rule out that these findings may be related to the large number of multiple comparisons or unmeasured covariates.

In conclusion, levels of metabolites to PAH are elevated in this young inner-city cohort, compared with US national reference values. An association with anti-mouse IgE production was detected. Additional interventions against exposure to PAH emissions, including those from secondhand smoke and traffic, are warranted to facilitate diminished risk of adverse health effects for susceptible young children.

Acknowledgments

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Table 1

Cohort characteristics

Characteristics	% (n/total)[*]
Mother's ethnicity[†]	
Dominican	59.5 (132/222)
African American	40.5 (90/222)
Mothers with history of asthma[†]	21.0 (37/176)
Father's ethnicity[†]	
Dominican	52.9 (117/221)
African American	30.3 (67/221)
Other	16.7 (37/221)
Child's sex	
Male	53.6 (119/222)
Female	46.4 (103/222)
Maternal education (with 12th grade education)[†]	16.2 (36/222)
Mothers currently receiving public assistance[†]	49.8 (108/217)
Mothers currently receiving Medicaid[†]	69.0 (149/216)
Mothers smoked cigarettes in the last 2 days[‡]	11.9 (25/210)
Child around any smoker in last 2 days[‡]	23.9 (39/209)
Child ate in last 2 days[‡]	
Smoked meats	15.2 (32/210)
Smoked nuts	1.9 (4/210)
Smoked fish	0.5 (1/210)
Charbroiled hamburgers	9.0 (19/210)
Mothballs used in the home in the last year[‡]	0.9 (2/210)

[*] Data were missing from questionnaires where noted.

[†] Data obtained at enrollment of mothers.

[‡] Data obtained at age 5 yr at time of urine collection.

Table 2

Polycyclic aromatic hydrocarbons (PAH) metabolite levels (geometric mean 95% confidence interval; ng/l of urine)

Metabolite	Ethnicity/gender	CCCEH age 5 yrs		NHANES age 6–11 yrs<
		Specific gravity corrected[*]	Uncorrected	
1-Hydroxypyrene	Dominican	155 (133–182)	141 (122–164)	60 (53–68)
	African American	169 (136–210)	145 (115–181)	
	Female	167 (141–197)	143 (121–170)	
	Male	153 (125–187)	141 (117–172)	
1-Hydroxynaphthalene	Dominican	2539 (199–3225)	2314 (1816–2949)	1430 (1170–1730)
	African American	3569 (2613–4874)	2968 (2179–4044)	
	Female	3327 (2570–4306)	2757 (2116–3592)	
	Male	2490 (1875–3306)	2345 (1779–3091)	
2-Hydroxynaphthalene	Dominican	4675 (3943–5543)	4266 (3622–5024)	1690 (1560–1840)
	African American	3262 (2741–3882)	2719 (2246–3292)	
	Female	4333 (3679–5103)	3593 (3042–4245)	
	Male	3752 (3096–4546)	3498 (2870–4263)	
2-Hydroxyfluorene	Dominican	269 (232–314)	246 (212–284)	246 (219–277)
	African American	321 (261–393)	267 (214–331)	
	Female	289 (246–340)	240 (203–283)	
	Male	290 (240–350)	273 (227–328)	
3-Hydroxyfluorene	Dominican	110 (94–128)	100 (86–116)	106 (95–119)
	African American	141 (114–173)	117 (93–147)	
	Female	120 (101–141)	99 (82–120)	
	Male	124 (102–150)	116 (97–139)	
9-Hydroxyfluorene	Dominican	235 (204–271)	214 (187–246)	169 (142–201)
	African American	311 (54–1801)	258 (216–308)	
	Female	268 (233–309)	221 (192–255)	
	Male	257 (215–308)	242 (204–287)	
1-Hydroxyphenanthrene	Dominican	166 (144–191)	151 (131–174)	119 (104–137)
	African American	166 (138–203)	137 (111–170)	
	Female	165 (141–192)	137 (116–161)	
	Male	167 (139–201)	157 (131–188)	
2-Hydroxyphenanthrene	Dominican	49 (42–58)	45 (39–52)	41 (34–48)
	African American	58 (47–71)	48 (39–59)	
	Female	54 (46–62)	44 (38–52)	
	Male	52 (43–63)	48 (40–59)	
3-Hydroxyphenanthrene	Dominican	152 (131–175)	138 (120–159)	105 (91–122)
	African American	185 (150–228)	153 (124–189)	
	Female	164 (142–190)	136 (117–159)	
	Male	164 (134–200)	153 (127–185)	
4-Hydroxyphenanthrene	Dominican	32 (28–38)	29 (25–35)	35 (24–49)
	African American	46 (37–58)	38 (30–48)	

| Metabolite | Ethnicity/gender | CCCEH age 5 yrs | | NHANES age 6–11 yrs< |
		Specific gravity corrected[*]	Uncorrected	
	Female	36 (30–43)	30 (25–35)	
	Male	39 (32–48)	37 (30–45)	

Based on NHANES data for years 2001–02 n = 2748 participants. The following metabolites were below LOD: 9-hydroxyphenanthrene, 1-hydroxybenzo (c) phenanthrene, 2-hydroxybenzo (c) phenanthrene, 3-hydroxybenzo (c) phenanthrene, 1-hydroxybenz (a)anthracene, 3-hydroxybenz (a)anthracene, 9-hydroxybenz (a) anthracene, 1-hydroxychrysene, 2-hydroxychrysene, 3-hydroxychrysene, 4-hydroxychrysene, 6-hydroxychrysene, 3-hydroxybenzo (a)pyrene, 7-hydroxybenzo (a)pyrene.

[*] Above data adjusted for specific gravity using the following formula PAHc = PAH × [(1.019 − 1)/(SG − 1)], where constant refers to median specific gravity measure observed in the cohort.

[†] These data as presented are not stratified according to ethnicity or sex.

Table 3

Comparison of mean polycyclic aromatic hydrocarbons (PAH) levels with allergen-specific IgE positivity (specific gravity corrected[†])

PAH metabolite	IgE positivity (<, >0.35 IU/ml)	Mean Log PAH levels (ng/l) s.e.				
		Mouse n = 169	Cockroach n = 169	Dust mite n = 168	Cat n = 183	Dog n = 182
1-Hydroxypyrene	−	4.97 ± 0.07	5.03 ± 0.08	5.01 ± 0.07	4.97 ± 0.07	5.01 ± 0.07
	+	5.26 ± 0.28	4.97 ± 0.15	4.99 ± 0.31	5.15 ± 0.18	4.89 ± 0.23
1-Hydroxynaphthalene	−	7.90 ± 0.12	8.00 ± 0.13	7.90 ± 0.11	8.08 ± 0.12	8.01 ± 0.11
	+	7.81 ± 0.31	7.49 ± 0.18	7.88 ± 0.33	7.39 ± 0.17	7.53 ± 0.19
2-Hydroxynaphthalene	−	8.23 ± 0.08	8.24 ± 0.08	8.27 ± 0.08	8.27 ± 0.07	8.29 ± 0.07
	+	8.65 ± 0.19	8.43 ± 0.13	8.36 ± 0.23	8.37 ± 0.17	8.17 ± 0.21
2-Hydroxyfluorene	−	5.57 ± 0.07	5.64 ± 0.08	5.63 ± 0.07	5.57 ± 0.07	5.61 ± 0.06
	+	6.07 ± 0.23	5.58 ± 0.13	5.63 ± 0.26	5.77 ± 0.14	5.48 ± 0.17
3-Hydroxyfluorene	−	4.66 ± 0.07*	4.75 ± 0.08	4.73 ± 0.07	4.69 ± 0.07	4.72 ± 0.07
	+	5.31 ± 0.23*	4.68 ± 0.14	4.70 ± 0.30	4.92 ± 0.14	4.68 ± 0.18
9-Hydroxyfluorene	−	5.52 ± 0.06	5.53 ± 0.07	5.53 ± 0.06	5.50 ± 0.06	5.52 ± 0.06
	+	5.72 ± 0.24	5.63 ± 0.15	5.74 ± 0.27	5.77 ± 0.17	5.71 ± 0.17
1-Hydroxyphenanthrene	−	5.00 ± 0.07	5.04 ± 0.07	5.05 ± 0.07	5.02 ± 0.06	5.07 ± 0.06
	+	5.47 ± 0.25	5.12 ± 0.16	5.06 ± 0.31	5.29 ± 0.17	4.86 ± 0.17
2-Hydroxyphenanthrene	−	3.84 ± 0.07	3.89 ± 0.08	3.90 ± 0.07	3.84 ± 0.07*	3.89 ± 0.07
	+	4.36 ± 0.26	3.93 ± 0.15	3.76 ± 0.33	4.17 ± 0.15*	3.79 ± 0.16
3-Hydroxyphenanthrene	−	4.97 ± 0.07*	5.02 ± 0.07	5.03 ± 0.06	4.99 ± 0.07*	5.04 ± 0.07
	+	5.49 ± 0.24*	5.12 ± 0.15	5.03 ± 0.32	5.32 ± 0.15*	5.00 ± 0.17
4-Hydroxyphenanthrene	−	3.52 ± 0.08	3.54 ± 0.08	3.56 ± 0.08	3.48 ± 0.08*	3.54 ± 0.08
	+	4.00 ± 0.32	3.72 ± 0.15	3.76 ± 0.36	3.97 ± 0.21*	3.74 ± 0.25
Sum of metabolites	−	9.14 ± 0.08	9.18 ± 0.09	9.17 ± 0.08	9.22 ± 0.08	9.22 ± 0.08
	+	9.35 ± 0.19	9.09 ± 0.12	9.18 ± 0.23	9.05 ± 0.12	8.88 ± 0.15

*
p < 0.05 Two-tailed, t-test of natural log transformed data.

[†]
Above data adjusted for specific gravity using the following formula PAHc = PAH × [(1.019−1)/(SG − 1)], where constant refers to median specific gravity measure observed in the cohort.