Published in final edited form as:

Environ Res. 2015 July ; 140: 649–656. doi:10.1016/j.envres.2015.05.027.

Repeatedly High Polycyclic Aromatic Hydrocarbon Exposure and Cockroach Sensitization Among Inner-city Children

Kyung Hwa Jung^{a,*}, Stephanie Lovinsky-Desir^b, Matthew Perzanowski^c, Xinhua Liu^d, Christina Maher^a, Eric Gil^a, David Torrone^a, Andreas Sjodin^e, Zheng Li^e, Frederica P. Perera^c, and Rachel L. Miller^{a,c,f}

^aDivision of Pulmonary, Allergy and Critical Care of Medicine, Department of Medicine, College of Physicians and Surgeons, Columbia University, PH8E-101, 630 W. 168 St. New York, NY 10032, United States

^bDivision of Pediatric Pulmonary, Department of Pediatrics, College of Physicians and Surgeons, Columbia University, 3959 Broadway, CHC 7-745, New York, NY 10032, United States

^cMailman School of Public Health, Department of Environmental Health Sciences, Columbia University, 722 W. 168 St. New York, NY 10032, United States

^dMailman School of Public Health, Department of Biostatistics, Columbia University, 722 W. 168 St. New York, NY 10032, United States

^eCenters for Disease Control and Prevention, National Center for Environmental Health, Division of Laboratory Sciences, Organic Analytical Toxicology Branch, Atlanta, Georgia, United States

^fDivision of Pediatric Allergy, Immunology and Rheumatology, Department of Pediatrics, College of Physicians and Surgeons, Columbia University, PH8E-101, 630 W. 168 St. New York, New York, 10032, United States

Abstract

Background—Exposures to traffic-related air pollutants including polycyclic aromatic hydrocarbons (PAH) have been associated with the development and exacerbation of asthma. However, there is limited evidence on whether these pollutants are associated with the development of cockroach sensitization, a strong risk factor for urban asthma. We hypothesized that repeatedly high PAH exposure during childhood would be associated with increased risk of new cockroach sensitization.

Methods—As part of the research being conducted by the Columbia Center for Children's Environmental Health (CCCEH) birth cohort study in New York, a spot urine sample was

* **Corresponding author:** Kyung Hwa Jung, Ph.D., Department of Medicine, Columbia University College of Physicians and Surgeons, PH8E-101, 630 W. 168th St, New York, New York 10032, Tel: (212)-342-3317, Fax: (212)-305-2277, kj2237@cumc.columbia.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts of Interest Statement: None of the authors have financial relationships with a commercial entity that has an interest in the subject of this manuscript.

collected from children at age 5 years (2003–2008) and again at age 9–10 years (2008–2012; n=248) and analyzed for 10 PAH metabolites. Repeatedly high PAH (High-High) exposure was defined as measures above median for age 5 PAH metabolites at both time points. Child blood samples at age 5 and 9 years were analyzed for total, anti-cockroach, mouse, dust mite, cat and dog IgE. Relative risks (RR) were estimated with multivariable modified Poisson regression.

Results—Individual PAH metabolite levels, except for 1-naphthol (1-OH-NAP), increased by 10–60% from age 5 to age 9–10. The prevalence of cockroach sensitization increased from 17.6% (33/188) at age 5 to 33.0% (62/188) at 9 years ($p=0.001$). After controlling for potential covariates including cockroach sensitization at age 5 in regression analyses, positive associations were found between repeatedly high exposure (High-High) to 1-OH-NAP, 3-hydroxyphenanthrene (3-OH-PHEN), or 1-hydroxypyrene (1-OH-PYR) and cockroach sensitization at age 9 (p -values <0.05). Compared to Low-Low exposure, the relative risk (RR) [95% CI] with repeatedly high exposure was 1.83 [1.06–3.17] for 1-OH-NAP, 1.54 [1.06–2.23] for 3-OH-PHEN, and 1.59 [1.04–2.43] for 1-OH-PYR.

Conclusions—Repeatedly high levels of urinary PAH metabolites during childhood may increase likelihood of sensitization to cockroach allergen in urban inner-city children at age 9 years.

Keywords

Polycyclic aromatic hydrocarbons; urinary metabolites; cockroach IgE; childhood; inner-city

1. Introduction

Allergic sensitization is a key risk factor for the development of allergic diseases such as asthma, rhinitis, and eczema (Pawankar et al. 2011). In particular, sensitization to cockroach allergen combined with high allergen exposure is one of the strongest identified risk factors for more severe asthma in inner-city children (Rosenstreich et al. 1997; Togias et al. 2010). Similarly, our group at the Columbia Center for Children's Environmental Health (CCCEH) showed that early sensitization to cockroach and mouse allergens, pervasive urban environmental allergens, increased the risk of wheeze, rhinitis and atopic dermatitis among inner-city children aged 2 to 3 years (Chang et al. 2010; Donohue et al. 2008).

While many epidemiological studies have demonstrated that long-term exposure to traffic-related air pollution (e.g., particulate matter less than 2.5 μm ($\text{PM}_{2.5}$) and polycyclic aromatic hydrocarbons (PAH)) were associated with the increased risk of developing asthma and asthma-related symptoms in children (Gehring et al. 2010; Jung et al. 2012; McConnell et al. 2010), it is less clear whether traffic-related air pollutants contribute to the development of allergic sensitization given inconsistent results. For example, while few studies reported positive associations between long-term exposure to outdoor traffic-related air pollution (e.g., $\text{PM}_{2.5}$, $\text{PM}_{2.5}$ absorbance and NO_x) and allergic sensitization to outdoor allergens (i.e., pollen) (Morgenstern et al. 2008; Nordling et al. 2008), a meta-analysis on five European Birth prospective cohort studies (i.e., BAMSE-Sweden, LISAPlus and GINIplus-Germany, MASS-Great Britain, and PIAMA-The Netherlands) indicated that the long-term exposure to those air pollutants was not associated with the development of

allergic sensitization in children (Gruzieva et al. 2013). To date, most epidemiologic studies of air pollution and allergic sensitization have been extensively focused on outdoor air pollution from traffic sources. However, investigations on the effect of PAH, which are important constituents of traffic-related air pollution as well as indoor air pollution (Jung et al. 2010), on the development of allergic sensitization, are scarce.

PAH are a class of ubiquitous environmental pollutants produced during the incomplete combustion of organic materials. Urban children are exposed to high levels of lower-molecular-weight semivolatile PAH such as phenanthrene and pyrene from indoor sources (e.g., space heating, cooking, smoking, burning incense or candles) as well as higher-molecular weight nonvolatile PAH (e.g., benzo[a]pyrene) from outdoor traffic source (Jung et al. 2010). In addition to exposure during inhalation, children also may be exposed to PAH through ingestion of food containing PAH such as grilled and charred meats, and through dermal contact with PAH contaminated water or soil (ATSDR 1995). Hence, measures of urinary PAH metabolites indicate children's overall exposure levels that are integrated from inhaled, dietary, and dermal absorption.

The present study focused on the development of cockroach sensitization, in particular, because of substantially higher prevalence of cockroach sensitization in our inner-city cohort (17.6–33.0%) compared to nationally (Salo et al. 2014), and its large contribution to increased asthma morbidity and recurrent wheezing in children living in the US inner cities (De Vera et al. 2003; Wang et al. 2009). We previously reported that increased levels of PAH metabolites in single spot urine were associated with higher anti-mouse IgE among young inner-city children 5 years of age in cross-sectional analyses (Miller et al. 2010). Also, young children with higher prenatal exposure to PAH combined with prenatal cockroach allergen exposure had a greater risk of developing cockroach allergic sensitization at the ages of 5 to 7 years, compared to those with lower PAH exposure (Perzanowski et al. 2013). These results suggest that single measures of PAH exposure at either prenatal or age 5 may be associated with a greater likelihood of sensitization to mouse or cockroach allergens. Yet, to date, the prediction of repeated measures of exposure to PAH during early childhood and preadolescent period, that may represent long-term exposure in childhood, in the development of cockroach and other indoor allergen sensitization has not been addressed.

The goal of this study was to examine whether repeated measures of PAH exposure, at age 5 (early childhood) and again at age 9–10 years (preadolescent), is associated with the development of sensitization to cockroach allergens among inner-city children. We hypothesized that these surrogates for chronic PAH exposure would be associated with increased risk of new cockroach sensitization in this age group. Our approach was to examine data collected longitudinally from the CCCEH cohort at two ages during childhood (5, 9–10 years) when PAH exposure assessments and phenotypic outcomes were measured comprehensively.

2. Methods

2.1. Study population

A total of 727 nonsmoking, pregnant African American or Dominican women aged 18–35 living in Northern Manhattan and the South Bronx were enrolled between March 1998 and August 2006 and their children were followed prospectively (Miller et al. 2004; Perera et al. 2003). The mother of the child was compensated for study participation at both ages 5 and 9 years. Questionnaires were administered to the participants prenatally, every 3 months through age 2 years, subsequently every 6 months through age 5 years, and annually thereafter. Environmental tobacco smoke (ETS) exposure during pregnancy and cockroach or mouse allergen exposure were assessed by questionnaire. The study was approved by the Columbia University Institutional Review Board and written informed consent was obtained from all study participants. The Centers for Disease Control and Prevention (CDC) laboratory was determined not to be engaged in human subjects research since no personally identifiable information was made available to CDC researchers.

2.2. PAH assessment

Measures of PAH metabolites excreted in the urine, especially 1-hydroxypyrene (1-OH-PYR) the main metabolite of pyrene, have been used as a biomarker of PAH exposure from inhaled, dietary and dermal routes (Brant and Watson 2003; Li et al. 2010). A spot urine sample was collected from each child at clinic visits at age 5 years (2003–2008; n=434) and again at home visit at age 9–10 years (2008–2012; n=258). Samples were stored at –80°C until they were shipped frozen on dry ice to the CDC for PAH metabolite analysis. Of the 258 children with age 9–10 urinary sample, 248 children had age 5 urinary samples (Fig.1). The urinary concentrations of 10 PAH metabolites were measured at CDC using a method described in detail previously (Li et al. 2014). In brief, urine samples (1 mL) were first spiked with ¹³C-labeled internal standards, subjected to overnight enzymatic deconjugation, and followed by semi-automated liquid-liquid extraction. The sample extracts were thereafter evaporated, re-constituted, and derivatized to yield the trimethylsilyl derivatives of the OH-PAHs. Analytical measurement was performed by isotope dilution gas chromatography tandem mass spectrometry (GC-MS/MS). Each OH-PAH analyte had its own ¹³C-labeled internal standard used for quantification.

All OH-PAH analyses were subjected to a series of quality control and quality assurance checks as described elsewhere (Li et al., 2014). Two quality control materials (QCs)—QC High and QC Low—were prepared by spiking standard mixture into anonymous urine pools, and were analyzed along with each run of the urine samples. The coefficients of variation of the OH-PAH concentrations in the QC High and QC Low from 30 runs over a 3-month period were 4.7 %–13 %. The limits of detection for the analytical method ranged 1–18 ng/L, and the detection frequency ranged 68–100% for the 10 OH-PAHs in this study.

Specific gravity (SG) levels were measured using a handheld refractometer to permit adjustment for dilution of the urine. Urinary PAH metabolite concentrations were adjusted by specific gravity using a formula developed by Hauser et al. (2004) and adapted to a pediatric population, consistent with prior analyses (Hauser et al. 2004; Jung et al. 2014;

Miller et al. 2010). The ten metabolites of PAH monitored were: 1-naphthol (1-OH-NAP), 2-naphthol (2-OH-NAP), 2-hydroxyfluorene (2-OH-FLUO), 3-hydroxyfluorene (3-OH-FLUO), 9-hydroxyfluorene (9-OH-FLUO), 1-hydroxyphenanthrene (1-OH-PHEN), 2-hydroxyphenanthrene (2-OH-PHEN), 3-hydroxyphenanthrene (3-OH-PHEN), 4-hydroxyphenanthrene (4-OH-PHEN), and 1-OH-PYR.

2.3. Seroatopy

Serum samples were collected at age 5 (n=489) and 9 (n=229). Total and specific immunoglobulin (Ig) E to German cockroach, mouse, cat, dog, and *Dermatophagoides farinae* were measured from sera using Immunocap (Phadia, Uppsala, Sweden), as described (Donohue et al. 2008). All total and specific IgE were measured in duplicate; and the average values of two measures, after re-evaluating any out-of-range values, were used for analysis. Allergen-specific IgE levels of 0.35 IU/mL or greater were considered positive. Children with total IgE $\geq$ 80 IU/mL were considered seroatopic.

2.4. Cockroach allergen exposure

Cockroach allergen exposure was assessed by questionnaires administered to the mother by asking “How often do you see cockroaches in your home/apartment” at child’s ages 5 and 9 years. They were given five choices of answers as follows: Never, rarely, less than weekly, weekly, and daily. Children were considered to be exposed to cockroach allergen if they reported cockroaches seen at least weekly.

2.5. Statistical analysis

Analyses were restricted to children who had completed PAH metabolite and cockroach IgE levels measured at both 5 and 9 years, with a final sample size of 188 (Fig. 1). Proportion was calculated for categorical characteristics of the samples included and excluded from the current analysis. Chi-square test was used to detect difference in the proportions between the two samples. Spearman correlation coefficient was calculated for correlation in PAH metabolites between measures at ages 5 and 9–10 while McNemar test was used to detect differences between paired proportions at the two ages. The change in proportion of variables of interest from age 5 to age 9–10 was examined by a model for binary repeated measures. To obtain a measure for exposure pattern in each individual PAH compound, we first dichotomized the SG adjusted urinary PAH metabolites (ages 5 and 9–10) at their median values of age 5 measures. Then we categorized the repeated measures of PAH metabolites for each child into four groups (age 5-age 9–10: High-High [repeatedly high], High-Low, Low-High vs. Low-Low [reference]) for each individual PAH compound. To assess the associations between the composed variables for the repeated PAH measures at ages 5 and 9–10 and allergic sensitization at age 9, we used a modified Poisson regression for the dichotomous outcome (yes vs. no cockroach sensitization at age 9), with and without controlling for potential confounding factors of sex, race/ethnicity, maternal asthma, prenatal ETS exposure, cockroach allergen exposure (either at age 5 or 9) and cockroach sensitization at age 5. To aid interpretation of result, we derived relative risk (RR) along with 95% confidence interval (CI) from the estimated models fit to the data.

Data analysis was conducted with SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). All tests were two-sided with significance level of 0.05.

3. Results

3.1. Cohort characteristics

Table 1 shows that children included in analyses did not differ in the variables from the CCCEH children who were excluded from the analysis due to missing data, except that they had a higher proportion of African Americans and a slightly higher proportion of common mouse sightings at both ages. Among those included, 37.7% reported cockroach sightings at least weekly at age 5 with a lower rate at age 9 (19.3%) (McNemar test: $p < 0.001$). The prevalence of cockroach sensitization was higher in boys than in girls at both ages (19/87 [21.8%] vs. 14/101 [13.9%] at age 5 and 34/87 [39.1%] vs. 28/101 [27.7%]) while not statistically significant (χ^2 test, $ps = 0.10$).

3.2. PAH metabolites

Levels of 10 urinary PAH metabolites at ages 5 and 9–10, in comparison with those in representative samples of US children ages 6–11 in the National Health and Nutrition Examination Survey (NHANES), are shown in Table 2. Naphthol isomers (i.e., 1-OH-NAP and 2-OH-NAP) were the most abundant compounds among the measured individual PAH metabolites (>80% of total sum of 10 PAH at both ages). Geometric mean concentrations (fresh weight; not specific gravity adjusted) of the metabolites were 1.0–2.5 times higher in the CCCEH cohort when compared with the NHANES cohort (fresh weight) (Table 2).

3.3. Repeated PAH metabolites and cockroach sensitization

Individual PAH metabolite levels, except for 1-OH-NAP, increased by 10–60% from age 5 to age 9–10 (Table 2, SG adjusted). The concentrations of PAH metabolites, except for 1-OH-NAP, were correlated between ages 5 and 9–10 years with Spearman correlation ranging between 0.17 and 0.39 (Table 2). The prevalence of cockroach sensitization significantly increased between age 5 (33/188 [17.6%]) and 9 years (62/188 [33.0%]) (Table 3, McNemar test: $p = 0.001$). Similar trends were observed for any specific or positive total IgE (total IgE ≥ 80 IU/mL) (Table 3). In models without covariate adjustment, neither repeatedly high PAH metabolites (High-High) nor other exposure groups (High-Low or Low-High) were at significantly increased risk of cockroach sensitization at age 9, when compared to the reference group (data not shown).

After controlling for covariates, the models revealed a statistically significant increase in the risk of cockroach sensitization at age 9 with the repeatedly High-High 3-OH-PHEN compared to the reference group (Table 4 and Fig. 2, RR [95% CI]; 1.54 [1.06–2.23]). However, there were no significant risk increases in the risk of cockroach sensitization associated with the groups of either High-Low or Low-High 3-OH-PHEN, compared to a reference group. Similarly, compared to the Low-Low exposure group, High-High 1-OH-NAP and 1-OH-PYR increased risk of cockroach sensitization at age 9 (Table 4 and Fig. 2, RR [95% CI]; 1.83 [1.06–3.17] for 1-OH-NAP and 1.59 [1.04–2.43] for 1-OH-PYR). Mouse sensitization also increased from 9.6% at age 5 to 14% at age 9–10 years (McNemar test:

p=0.194), but the risk of mouse sensitization was not associated with PAH exposure variables in the analysis with and without covariate adjustment (data not shown). Similarly, neither total nor any positive indoor allergen-specific IgE were associated with PAH measures (data not shown).

4. Discussion

In this prospective birth cohort, we found that repeatedly high levels of PAH metabolites during childhood were associated with new sensitization to cockroach at age 9 years. To our knowledge, this is the first study to report an association between measures of PAH exposure over childhood and the development of new cockroach sensitization in urban children. These findings are important given the wealth of data demonstrating that cockroach sensitization is common and associated with developing or exacerbating pediatric asthma (Donohue et al. 2008; Rosenstreich et al. 1997; Togias et al. 2010).

The strengths of the study include the longitudinal study design that includes repeat measures of PAH metabolites and cockroach IgE levels. The results from multi-level PAH analysis revealed that repeatedly high exposure to PAHs (High-High) during childhood, but not other exposure categories (High-Low or Low-High), were associated with the development of cockroach sensitization. These results are consistent with other reports that early life exposure to cockroach allergen (e.g., Bla g 1 and Bla g 2) and during early childhood has been associated with cockroach sensitization (Huss et al. 2001; Perzanowski et al. 2013). Another strength was our ability to control for reported cockroach allergen exposure, previously correlated with cockroach allergen (Bla g 2) levels in dust samples (Rauh et al. 2002), to discern the independent association of PAHs on cockroach sensitization.

We used urinary PAH metabolites as our exposure metrics. The levels of PAH metabolites significantly increased from age 5 to age 9–10 with minimal correlations with each other, suggesting increases in levels inhaled and ingested over time. Supporting the former explanation, we recently found a significant increase in residential indoor PAH levels between age 5–6 and 9–10, possibly due to increased use of gas stoves for cooking and residential burning of more contaminated dirty heating oil (Jung et al. 2014). However, given the minimal correlation of airborne pyrene with 1-OH-PYR previously observed in our CCCEH cohort at age 9–10 (Jung et al. 2014), dietary intake also may have contributed to the increased levels. For example, more frequent consumption of high-PAH containing foods, such as grilled/smoked foods, may occur with childhood aging and may contribute to an elevation in 1-OH-PYR levels over time (Gidding et al. 2005; Kudlová and Schneidrová 2012). To distinguish further the impact of airborne versus urinary PAH on cockroach sensitization, additional exploratory models replaced 1-OH-PYR with airborne pyrene measures. Despite the small sample size (n=104), repeatedly high levels of airborne pyrene also appeared associated with cockroach sensitization at age 9 (median=1.01 ng/m³, RR [95% CI]; 1.67 [0.98–2.86], p=0.06). Collectively, these data suggest that the effect of PAH on cockroach sensitization may occur through the airways while the contribution of ingested PAHs to the development of cockroach sensitization also should be considered.

Unlike this study that focuses on measures of PAH over time specifically, previous studies with outdoor ambient monitoring were unable to detect significant positive associations between traffic-related air pollutants (e.g., PM_{2.5}, PM_{2.5} absorbance and NO_x) and sensitization to inhalant allergens (Brauer et al. 2007; Gehring et al. 2010; Gruzieva et al. 2013), except for a few that focused on outdoor pollens (Morgenstern et al. 2008; Wyler et al. 2000). The present association with PAH also differs from what we showed previously in this cohort when we used concurrent proximity to highway, a proxy for any outdoor traffic-related air pollution exposure at the earlier ages between 2 and 5 years (Patel et al. 2011). In that study, concurrent proximity to highway was associated with total IgE, but not with any indoor allergen-specific IgE at the earlier ages (i.e., German cockroach, cat, mouse, dog, and *Dermatophagoides farinae*) between 2 and 5 years (Patel et al. 2011). Given positive associations exclusively with outdoor pollens observed in other cohorts, increase in total IgE could be due to elevation in outdoor pollen IgE levels. Yet this association with indoor allergen sensitization and PAH metabolites now observed seems to be consistent with our previously reported positive associations between PAH levels measured in single spot urine and mouse sensitization at age 5 (Miller et al. 2010). Hence, the current study finding provides further evidence that chronic exposure to PAH specifically during childhood may increase risk of developing cockroach sensitization.

While the mechanism underlying the relationship between cockroach allergen exposure and sensitization may not be clear, one could postulate that exposure to cockroach and other indoor allergens results in increased antigen presentation leading to the development of an allergic immune response. For example, enhanced cockroach-derived protease activity may upregulate protease-activated receptor-2 leading to greater penetration of allergen proteins into human airway epithelial cells and epidermis (Hong et al. 2004; Jeong et al. 2008). Alternately, indoor airborne particles may not only contain gaseous/particulate pollutants such as PAH but also can carry indoor allergens derived from mouse or cockroach to enhance the likelihood of indoor allergen sensitization (Platts-Mills et al. 1986).

Previous experimental studies also have demonstrated that PAH exposure in particular may induce allergic sensitization. For example, exposure to phenanthrene has been shown to increase IgE production in vitro (Tsien et al. 1997) and act in vivo as an adjuvant for development of total and ragweed-specific IgE in the human respiratory mucosa (Saxon and Diaz-Sanchez 2000). Also, there is evidence that exposure to pyrene can induce production of proallergic cytokine IL-4 in primary human T cells (Bömmel et al. 2000). Similarly, administration of several metabolites of benzo(a)pyrene (BaP) such as BaP-Quinones also enhanced IgE-mediated IL-4 production in human basophils (Kepley et al. 2003). Nevertheless, there are no reported experimental models of chronic and repeated PAH measures and sensitization to cockroach allergen specifically.

Our earlier cross-sectional report on positive associations of PAH metabolite levels with mouse IgE at age 5 (Miller et al. 2010) were not seen in our present prospective longitudinal study, with outcomes measured at age 9. Possible explanations may include differences in study design (cross-sectional vs longitudinal), timing of greater PAH exposure (age 5 vs age 9–10), as well as measures of different duration of exposure (single time vs repeated measures over time). Given the previously observed association between PAH exposure and

mouse IgE at age 5, we repeated the same statistical analyses, but restricted to those included for the present study and positive associations were not found. The previously observed associations were driven by children who were excluded from the present study due to missing age 9 measures, limiting the model. Despite similarities in most major demographic characteristics between the two included/excluded groups, a selection bias may have been introduced.

This study had several limitations. The sample size was small because only a subset of children completed age 9–10 urine collections. Second, we combined reported cockroach allergen exposure either at age 5 or 9 to maximize the sample size and statistical power, although allergen exposure at different ages could be potentially independent predictor for allergic sensitization (Perzanowski et al. 2013). However, 66% of subjects reported the same response to cockroach sightings between two age points. Further, the main results remained the same, even after controlling for reported cockroach allergen exposure at each age separately. Third, twenty five percent (47/188) of age 9–10 PAH metabolites were measured after age 9 serum collections while seventy five percent of them were measured prior to the serum collections. To minimize this limitation, we further controlled for age-related differences in PAH exposure assessment in the model; results remained the same (data not shown). Fourth, we were not able to capture cockroach allergen exposure at school that also has been shown to be an important source of cockroach and mouse allergen exposures (Huffaker and Phipatanakul 2014). Lastly, the half-lives of PAH metabolites are relatively short: following dietary exposure (2.5–6.1 h) (Li et al. 2012) and inhalation exposure (6–35 h) (Jongeneelen et al. 1990), reflecting short-term exposure. Nevertheless, a study of repeat measures of PAH metabolites during an 8-consecutive days reported that 1-OH-PYR has relatively high reproducibility and lower within-subject variability over time (e.g., intraclass correlation coefficients (ICC) of 1-OH-PYR=0.55–0.76) (Li et al. 2009). Given observed significant correlations between age 5 and age 9–10 PAH metabolite levels ($\rho=0.17$ – 0.39 ; $p<0.001$ except for 1-OH-NAP), the use of PAH measures from repeat spot urine samples likely reflects chronic exposure.

5. Conclusion

Levels of PAH metabolites among the CCCEH children that live in New York City are substantially higher than US national reference values suggesting possible greater risk for PAH-associated diseases. Here we report that repeated high measures of PAH exposure at two ages increased the risk of developing sensitization to cockroach allergen in children between the ages of 5 and 9 years. To our knowledge, this is the first report on the incidence of allergen-specific sensitization associated with presumably repeated high PAH exposure during childhood. Our findings offer further evidence that early childhood and preadolescent period are important time windows of exposure for the development of sensitization to cockroach allergen, consistent with reports about other allergens (e.g., *Alternaria*, Bermuda grass, careless weed and olive, mesquite and mulberry tree allergens) (Stern et al. 2004). Given the well-established link between cockroach sensitization and the risk of asthma (Rosenstreich et al. 1997; Togias et al. 2010), reduction in PAH exposure by altering a high PAH diet and by reducing the sources of ambient PAH (e.g., ETS exposure, gas cooking, heating oil combustion, and traffic emission) could reduce cockroach sensitization and thus

prevent adverse respiratory outcomes during childhood especially in urban inner-city communities.

Acknowledgements

This work was supported by NIH (R01ES013163, P50ES015905, P01ES09600, R01ES08977, P30ES09089), and by US. Environmental Protection Agency (US EPA grants RD832096, R827027, RD832141, RD834509). Its contents are solely the responsibility of the grantee and do not necessarily represent the official views of the US EPA. Further, the US EPA does not endorse the purchase of any commercial products or services mentioned in the publication and also supported by the Educational Foundation of America, the John & Wendy Neu Family Foundation, the New York Community Trust, and the Trustees of the Blanchette Hooker Rockefeller Fund. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Abbreviations

BC	Black Carbon
CCCEH	Columbia Center for Children's Environmental Health
DEP	Diesel Exhaust Particle
EC	Elemental Carbon
ETS	Environmental Tobacco Smoke
IgE	Immunoglobulin E
NYC	New York City
OR	Odds Ratio
PAH	Polycyclic Aromatic Hydrocarbons
PM	Particulate Matter
RR	Relative Risk
1-OH-NAP	1-Naphthol
2-OH-NAP	2-Naphthol
2-OH-FLUO	2-hydroxyfluorene
3-OH-FLUO	3-hydroxyfluorene
9-OH-FLUO	9-hydroxyfluorene
1-OH-PHEN	1-hydroxyphenanthrene
2 -OH-PHEN	2-hydroxyphenanthrene
3-OH-PHEN	3-hydroxyphenanthrene
4-OH-PHEN	4-hydroxyphenanthrene
1-OH-PYR	1-hydroxypyrene
SG	Specific Gravity

References

- ATSDR. Toxicological profile for polycyclic aromatic hydrocarbons(pahs). 1995
- Bömmel H, Li-Weber M, Serfling E, Duschl A. The environmental pollutant pyrene induces the production of il-4. *Journal of allergy and clinical immunology*. 2000; 105:796–802. [PubMed: 10756232]
- Brant HCA, Watson WP. Monitoring human occupational and environmental exposures to polycyclic aromatic compounds. *Annals of Occupational Hygiene*. 2003; 47:349–378. [PubMed: 12855487]
- Brauer M, Hoek G, Smit H, De Jongste J, Gerritsen J, Postma DS, et al. Air pollution and development of asthma, allergy and infections in a birth cohort. *European Respiratory Journal*. 2007; 29:879. [PubMed: 17251230]
- Chang C, Gauvey-Kern K, Johnson A, Kelvin EA, Chew GL, Perera F, et al. Cord blood versus age 5 mononuclear cell proliferation on ige and asthma. *Clinical and Molecular Allergy*. 2010; 8:11. [PubMed: 20684781]
- De Vera MJ, Drapkin S, Moy JN. Association of recurrent wheezing with sensitivity to cockroach allergen in inner-city children. *Annals of Allergy, Asthma & Immunology*. 2003; 91:455–459.
- Donohue KM, Al-alem U, Perzanowski MS, Chew GL, Johnson A, Divjan A, et al. Anti-cockroach and anti-mouse ige are associated with early wheeze and atopy in an inner-city birth cohort. *The Journal of Allergy and Clinical Immunology*. 2008; 122:914. [PubMed: 19000580]
- Gehring U, Wijga AH, Brauer M, Fischer P, de Jongste JC, Kerkhof M, et al. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *American journal of respiratory and critical care medicine*. 2010; 181:596–603. [PubMed: 19965811]
- Gidding SS, Dennison BA, Birch LL, Daniels SR, Gilman MW, Lichtenstein AH, et al. Dietary recommendations for children and adolescents. *Circulation*. 2005; 112:2061–2075. [PubMed: 16186441]
- Gruzdeva O, Gehring U, Aalberse R, Agius R, Beelen R, Behrendt H, et al. Meta-analysis of air pollution exposure association with allergic sensitization in european birth cohorts. *Journal of Allergy and Clinical Immunology*. 2013
- Hauser R, Meeker JD, Park S, Silva MJ, Calafat AM. Temporal variability of urinary phthalate metabolite levels in men of reproductive age. *Environmental health perspectives*. 2004; 112:1734. [PubMed: 15579421]
- Hong JH, Lee S-I, Kim K-E, Yong T-S, Seo JT, Sohn MH, et al. German cockroach extract activates protease-activated receptor 2 in human airway epithelial cells. *Journal of Allergy and Clinical Immunology*. 2004; 113:315–319. [PubMed: 14767448]
- Huffaker M, Phipatanakul W. Introducing an environmental assessment and intervention program in inner-city schools. *Journal of Allergy and Clinical Immunology*. 2014; 134:1232–1237. [PubMed: 25441649]
- Huss K, Adkinson NF Jr, Eggleston PA, Dawson C, Van Natta ML, Hamilton RG. House dust mite and cockroach exposure are strong risk factors for positive allergy skin test responses in the childhood asthma management program*. *Journal of allergy and clinical immunology*. 2001; 107:48–54. [PubMed: 11149990]
- Jeong SK, Kim HJ, Youm J-K, Ahn SK, Choi EH, Sohn MH, et al. Mite and cockroach allergens activate protease-activated receptor 2 and delay epidermal permeability barrier recovery. *Journal of Investigative Dermatology*. 2008; 128:1930–1939. [PubMed: 18305573]
- Jongeneelen F, van Leeuwen FE, Oosterink S, Anzion R, Van der Loop F, Bos R, et al. Ambient and biological monitoring of cokeoven workers: Determinants of the internal dose of polycyclic aromatic hydrocarbons. *British journal of industrial medicine*. 1990; 47:454–461. [PubMed: 2383514]
- Jung KH, Patel MM, Moors K, Kinney PL, Chillrud SN, Whyatt R, et al. Effects of heating season on residential indoor and outdoor polycyclic aromatic hydrocarbons, black carbon, and particulate matter in an urban birth cohort. *Atmospheric Environment*. 2010; 44:4545–4552. [PubMed: 20938487]

- Jung KH, Hsu SI, Yan B, Moors K, Chillrud SN, Ross J, et al. Childhood exposure to fine particulate matter and black carbon and the development of new wheeze between ages 5 and 7 in an urban prospective cohort. *Environment International*. 2012; 45:44–50. [PubMed: 22572116]
- Jung KH, Liu B, Lovinsky-Desir S, Yan B, Camann D, Sjodin A, et al. Time trends of polycyclic aromatic hydrocarbon exposure in new york city from 2001 to 2012: Assessed by repeat air and urine samples. *Environmental research*. 2014; 131:95–103. [PubMed: 24709094]
- Kepley CL, Lauer FT, Oliver JM, Burchiel SW. Environmental polycyclic aromatic hydrocarbons, benzo (a) pyrene (bap) and bap-quinones, enhance ige-mediated histamine release and il-4 production in human basophils. *Clinical Immunology*. 2003; 107:10–19. [PubMed: 12738245]
- Kudlová E, Schneidrová D. Dietary patterns and their changes in early childhood. *Cent Eur J Public Health*. 2012; 20:126–134. [PubMed: 22966737]
- Li Z, Romanoff LC, Lewin MD, Porter EN, Trinidad DA, Needham LL, et al. Variability of urinary concentrations of polycyclic aromatic hydrocarbon metabolite in general population and comparison of spot, first-morning, and 24-h void sampling. *Journal of Exposure Science and Environmental Epidemiology*. 2009; 20:526–535. [PubMed: 19707251]
- Li Z, Mulholland JA, Romanoff LC, Pittman EN, Trinidad DA, Lewin MD, et al. Assessment of non-occupational exposure to polycyclic aromatic hydrocarbons through personal air sampling and urinary biomonitoring. *Journal of Environmental Monitoring*. 2010; 12:1110–1118. [PubMed: 21491629]
- Li Z, Romanoff L, Bartell S, Pittman EN, Trinidad DA, McClean M, et al. Excretion profiles and half-lives of ten urinary polycyclic aromatic hydrocarbon metabolites after dietary exposure. *Chemical research in toxicology*. 2012; 25:1452–1461. [PubMed: 22663094]
- Li Z, Romanoff LC, Trinidad DA, Pittman EN, Hilton D, Hubbard K, et al. Quantification of 21 metabolites of methylnaphthalenes and polycyclic aromatic hydrocarbons in human urine. *Analytical and bioanalytical chemistry*. 2014; 406:3119–3129. [PubMed: 24714969]
- McConnell R, Islam T, Shankardass K, Jerrett M, Lurmann F, Gilliland F, et al. Childhood incident asthma and traffic-related air pollution at home and school. *Environmental health perspectives*. 2010:1021–1026. [PubMed: 20371422]
- Miller R, Garfinkel R, Lendor C, Hoepner L, Li Z, Romanoff L, et al. Polycyclic aromatic hydrocarbon metabolite levels and pediatric allergy and asthma in an inner city cohort. *Pediatric Allergy and Immunology*. 2010; 21:260–267. [PubMed: 20003063]
- Miller RL, Garfinkel R, Horton M, Camann D, Perera FP, Whyatt RM, et al. Polycyclic aromatic hydrocarbons, environmental tobacco smoke, and respiratory symptoms in an inner-city birth cohort. *Chest*. 2004; 126:1071–1078. [PubMed: 15486366]
- Morgenstern V, Zutavern A, Cyrys J, Brockow I, Koletzko S, Kramer U, et al. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. *Am J Respir Crit Care Med*. 2008; 177:1331–1337. [PubMed: 18337595]
- Nordling E, Berglind N, Melén E, Emenius G, Hallberg J, Nyberg F, et al. Traffic-related air pollution and childhood respiratory symptoms, function and allergies. *Epidemiology*. 2008; 19:401. [PubMed: 18379426]
- Patel MM, Quinn JW, Jung KH, Hoepner L, Diaz D, Perzanowski M, et al. Traffic density and stationary sources of air pollution associated with wheeze, asthma, and immunoglobulin e from birth to age 5 years among new york city children. *Environmental Research*. 2011
- Pawankar, R.; Canonica, G.; Holgate, S.; Lockey, R. Wao white book on allergy. Milwaukee, WI: World Allergy Organization; 2011. p. 1-216.
- Perera FP, Rauh V, Tsai WY, Kinney P, Camann D, Barr D, et al. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. *Environmental health perspectives*. 2003; 111:201. [PubMed: 12573906]
- Perzanowski MS, Chew GL, Divjan A, Jung KH, Ridder R, Tang D, et al. Early-life cockroach allergen and polycyclic aromatic hydrocarbon exposures predict cockroach sensitization among inner-city children. *Journal of allergy and clinical immunology*. 2013
- Platts-Mills TA, Heymann PW, Longbottom JL, Wilkins SR. Airborne allergens associated with asthma: Particle sizes carrying dust mite and rat allergens measured with a cascade impactor. *Journal of allergy and clinical immunology*. 1986; 77:850–857. [PubMed: 3711552]

- Rauh VA, Chew GR, Garfinkel RS. Deteriorated housing contributes to high cockroach allergen levels in inner-city households. *Environmental Health Perspectives*. 2002; 110:323. [PubMed: 11929744]
- Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *New England Journal of Medicine*. 1997; 336:1356–1363. [PubMed: 9134876]
- Salo PM, Arbes SJ Jr, Jaramillo R, Calatroni A, Weir CH, Sever ML, et al. Prevalence of allergic sensitization in the united states: Results from the national health and nutrition examination survey (nhanes) 2005-2006. *Journal of Allergy and Clinical Immunology*. 2014
- Saxon A, Diaz-Sanchez D. Diesel exhaust as a model xenobiotic in allergic inflammation. *Immunopharmacology*. 2000; 48:325–327. [PubMed: 10960677]
- Stern D, Lohman I, Wright A, Taussig L, Martinez F, Halonen M. Dynamic changes in sensitization to specific aeroallergens in children raised in a desert environment. *Clinical & Experimental Allergy*. 2004; 34:1563–1669. [PubMed: 15479271]
- Togias A, Fenton MJ, Gergen PJ, Rotrosen D, Fauci AS. Asthma in the inner city: The perspective of the national institute of allergy and infectious diseases. *Journal of Allergy and Clinical Immunology*. 2010; 125:540–544. [PubMed: 20226290]
- Tsien A, Diaz-Sanchez D, Ma J, Saxon A. The organic component of diesel exhaust particles and phenanthrene, a major polyaromatic hydrocarbon constituent, enhances ige production by ige-secreting ebv-transformed human b cellsin vitro* 1. *Toxicology and applied pharmacology*. 1997; 142:256–263. [PubMed: 9070347]
- Wang J, Visness C, Calatroni A, Gergen P, Mitchell H, Sampson H. Effect of environmental allergen sensitization on asthma morbidity in inner-city asthmatic children. *Clinical & Experimental Allergy*. 2009; 39:1381–1389. [PubMed: 19489919]
- Wyler C, Braun-Fahrlander C, Kunzli N, Schindler C, Ackermann-Liebrich U, Perruchoud AP, et al. Exposure to motor vehicle traffic and allergic sensitization. *Epidemiology*. 2000; 11:450–456. [PubMed: 10874554]

Fig. 1.
Schema of study data structure.

Fig. 2.

Relationship of elevated levels of (a) 1-OH-NAP and (b) 3-OH-PHEN at ages 5 and 9–10 with cockroach sensitization at 9 years of age (N=188).

Relative risk estimates of cockroach sensitization associated with each combination of age 5 and age 9–10 years urinary PAH metabolite levels (Low-High, High-Low, and High-High vs Low-Low), adjusting for ethnicity, sex, maternal asthma, prenatal ETS, the report of

cockroach sightings common either at age 5 or 9, and cockroach sensitization at age 5; *p-value <0.05; 1-naphthol (1-OH-NAP), 3-hydroxyphenanthrene (3-OH-PHEN).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1Demographic characteristic of the study cohort [no. (%)]^a

Characteristic	<u>Subjects included^b</u>	<u>Subjects excluded^c</u>
	<u>N=188</u>	<u>N=539</u>
	<u>N/total (%)</u>	<u>N/total [%]</u>
Maternal ethnicity		
-Dominican	103/188 (54.8)	370/539 (68.6)
-African American	85/188 (45.2)*	169/539 (31.4)
Girls	101/188 (53.7)	275/539 (51.0)
Maternal high school or greater degree	111/183 (60.7)	345/530 (65.1)
Maternal asthma (+)	43/188 (22.9)	120/539 (22.3)
Prenatal ETS exposure ^d (+)	72/188 (38.3)	174/529 (32.9)
At age 5: Smoker in home ^e	32/186 (17.2)	66/362 (18.2)
Cockroach sightings ^f	69/183 (37.7)	126/361 (34.9)
Mouse sightings ^f	45/185 (24.3)*	59/364 (16.2)
At age 9: Smoker in home ^e	25/188 (13.3)	30/232 (12.9)
Cockroach sightings ^f	36/187 (19.3)	45/232 (19.4)
Mouse sightings ^f	29/188 (15.4)	27/231 (11.7)

^a None of the demographics differed significantly between the children included when compared to those excluded ($p>0.05$), with the exception of a higher prevalence of African American and mouse sightings common;

* $p<0.05$.

^b Includes all participants who had urine samples collected for PAH metabolites and cockroach serum IgE analyzed at ages 5 and 9 years.

^c Due to missing data. N=479 CCCEH subjects did not have urine samples collected either at age 5 or 9, n=27 had no cockroach IgE at age 5, n=31 had no cockroach IgE at age 9, n=2 had missing covariates.

^d Prenatal ETS exposure was defined as the report of any smoker in the house during pregnancy.

^e Responded "yes" when asked about the presence of any smoker in home.

^f Cockroaches or mice seen at least weekly (weekly and daily basis) versus never, rarely or less than weekly.

Table 2
Geometric mean levels of PAH metabolites (95% confidence interval of geometric mean; ng/l of urine, n=188)

PAH metabolites	S.G. Adjustment	CCCEH		NHANES ^c Age 6–11 yrs	Ratio (CCCEH/NHANES) ^d		Correlations between age 5 and 9 PAH ^e
		Age 5 ^a	Age 9 ^b		Age 5	Age 9	
1-OH-NAP	Unadjusted	2330 (1930–2813)	1444 (1221–1707)	1540 (1360–1750)	1.5	0.9	-
	Adjusted	2792 (2324–3355)	1642 (1410–1911) ^{***}	-	-	-	0.10
2-OH-NAP	Unadjusted	3460 (3020–3964)	5251 (4580–6020)	2110 (1800–2470)	1.6	2.5	-
	Adjusted	4126 (3623–4699)	6042 (5355–6817) ^{***}	-	-	-	0.28 ^{***}
2-OH-FLUO	Unadjusted	262 (232–294)	338 (301–380)	209 (183–239)	1.3	1.6	-
	Adjusted	308 (275–344)	388 (353–426) ^{**}	-	-	-	0.24 ^{***}
3-OH-FLUO	Unadjusted	108 (96–122)	129 (114–145)	89 (77–103)	1.2	1.4	-
	Adjusted	128 (114–143)	147 (133–163)	-	-	-	0.25 ^{***}
9-OH-FLUO	Unadjusted	244 (218–273)	398 (352–449)	209 (184–238)	1.2	1.9	-
	Adjusted	289 (260–321)	453 (408–502) ^{***}	-	-	-	0.18 [*]
1-OH-PHEN	Unadjusted	143 (127–160)	171 (151–193)	138 (124–154)	1.0	1.2	-
	Adjusted	168 (151–187)	195 (176–216) [*]	-	-	-	0.33 ^{***}
2-OH-PHEN	Unadjusted	44 (39–50)	69 (60–78)	45 (40–51)	1.0	1.5	-
	Adjusted	52 (46–58)	79 (70–89) ^{***}	-	-	-	0.28 ^{***}
3-OH-PHEN	Unadjusted	136 (121–152)	155 (136–176)	116 (100–134)	1.2	1.3	-

PAH metabolites	S.G. Adjustment	CCCEH		NHANES ^c Age 6–11 yrs	Ratio (CCCEH/NHANES) ^d		Correlations between age 5 and 9 PAH ^e
		Age 5 ^a	Age 9 ^b		Age 5	Age 9	
4-OH-PHEN	Adjusted	159 (143–178)	178 (160–197)	-	-	-	0.28***
	Unadjusted	31 (27–36)	35 (30–40)	25 (22–28)	1.2	1.4	-
	Adjusted	37 (32–42)	40 (35–45)	-	-	-	0.17*
1-OH-PYR	Unadjusted	142 (124–162)	230 (201–264)	112 (97–130)	1.3	2.1	-
	Adjusted	166 (147–188)	263 (235–296)***	-	-	-	0.39***

^a Variable adjusted for specific gravity (SG) using the formula: $\text{PAH} \times [(1.0194 - 1) / (\text{SG} - 1)]$, where constant refers to median specific gravity measured at age 5.

^b Variable adjusted for specific gravity using the formula: $\text{PAH} \times [(1.0232 - 1) / (\text{SG} - 1)]$, where constant refers to median specific gravity measured at age 9–10. Wilcoxon Signed Rank Test for differences between age 5 and age 9–10 PAH metabolite levels: *p<0.05; **p 0.01; ***p-value 0.001.

^c 2003–2004 NHANES data presented in fresh weight PAH metabolite levels (n=338).

^d CCCEH/NHANES is the ratio of the geometric mean levels of fresh weight PAH metabolites measured among CCCEH children at ages 5 or 9–10 years to NHANES data (2003–2004) collected among children ages 6–11 years.

^e Spearman correlation coefficient (r) presented: *p <0.05; **p 0.01; ***p 0.001.

Table 3

Prevalence of cockroach sensitization at ages 5 and 9 years

Sensitization	Age 5	Age 9	McNemar's test
	N/total (%)	N/total (%)	p-value
Seroatopic ^a	51/169 (30.2%)	72/149 (48.3%)	<0.001
Any specific indoor IgE ^b	55/188 (29.3%)	81/188 (43.1%)	<0.001
Cockroach IgE ^c	33/188 (17.6%)	62/188 (33.0%)	<0.001
Mouse IgE ^c	18/188 (9.6%)	23/164 (14.0%)	0.146

^aTotal IgE ≥ 80 IU/mL^bChildren with a specific IgE >0.35 IU/mL to any of five indoor allergens tested (e.g., German cockroach, cat, mouse, dog, and *Dermatophagoides farina*).^cPositive IgE ≥ 0.35 IU/mL

Table 4

PAH metabolites at ages 5 and 9/10 and cockroach sensitization at 9 years of age (n=188)

PAH metabolites	Median ^b ng/l	Covariate-adjusted relative risk, RR _{adj} (95% CI) ^a			
		Low-Low (Reference)	High-High	High-Low	Low-High
1-OH-NAP	2230	1	1.83 (1.06–3.17)	0.96 (0.61–1.48)	0.80 (0.53–1.21)
2-OH-NAP	3821	1	0.89 (0.61–1.32)	0.88 (0.52–1.50)	1.29 (0.84–1.97)
2-OH-FLUO	295	1	1.06 (0.71–1.61)	1.05 (0.67–1.66)	0.84 (0.54–1.29)
3-OH-FLUO	115	1	1.08 (0.74–1.57)	0.74 (0.44–1.24)	0.80 (0.51–1.26)
9-OH-FLUO	272	1	1.19 (0.75–1.88)	1.41 (0.81–2.46)	0.95 (0.58–1.54)
1-OH-PHEN	163	1	1.26 (0.86–1.86)	1.17 (0.76–1.80)	1.00 (0.63–1.57)
2-OH-PHEN	49	1	1.23 (0.80–1.90)	1.03 (0.59–1.77)	1.16 (0.73–1.84)
3-OH-PHEN	150	1	1.54* (1.06–2.23)	1.20 (0.77–1.88)	1.13 (0.72–1.77)
4-OH-PHEN	36	1	1.32 (0.78–2.23)	1.46 (0.91–2.34)	1.43 (0.88–2.33)
1-OH-PYR	160	1	1.59* (1.04–2.43)	1.39 (0.73–2.66)	1.50 (0.98–2.28)
Prevalence, n (%)					
Total n		Low-Low	High-High	High-Low	Low-High
1-OH-NAP	188	68 (36.2)	27 (14.4)	66 (35.1)	27 (14.4)
2-OH-NAP	188	44 (23.4)	74 (39.4)	20 (10.6)	50 (26.6)
2-OH-FLUO	188	41 (21.8)	61 (32.4)	33 (17.6)	53 (28.2)
3-OH-FLUO	188	47 (25.0)	62 (33.0)	32 (17.0)	47 (25.0)
9-OH-FLUO	188	35 (18.6)	75 (39.9)	19 (10.1)	59 (31.4)
1-OH-PHEN	188	56 (29.8)	62 (33.0)	32 (17.0)	38 (20.2)
2-OH-PHEN	188	38 (20.2)	76 (40.4)	18 (9.6)	56 (29.8)
3-OH-PHEN	188	58 (30.9)	59 (31.4)	35 (18.6)	36 (19.1)
4-OH-PHEN	188	53 (28.2)	48 (25.5)	46 (24.5)	41 (21.8)
1-OH-PYR	188	35 (18.6)	79 (42.0)	15 (8.0)	59 (31.4)

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

^dModel adjusted for ethnicity, sex, maternal asthma, prenatal ETS, the report of cockroach sightings common either at age 5 or 9, and cockroach sensitization at age 5; $p < 0.05$.

^eThe median level of individual S.G. adjusted PAH metabolites at age 5 was used to obtain a measure of high/low exposure at ages 5 and 9–10 years.