Environmental Pollution xxx (2017) 1–7

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Distribution and predictors of urinary polycyclic aromatic hydrocarbon metabolites in two pregnancy cohort studies☆

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ARTICLE INFO

Article history:
Received 3 August 2017
Received in revised form
25 September 2017
Accepted 26 September 2017
Available online xxx

Keywords:
Pregnancy
Polycyclic aromatic hydrocarbons
Exposure assessment

ABSTRACT

Pregnant women and their fetuses represent susceptible populations to environmental contaminants. Exposure to polycyclic aromatic hydrocarbons (PAHs) among pregnant women may contribute to adverse birth outcomes such as preterm birth. Multiple previous studies have assessed airborne sources of PAHs among pregnant women but few have measured urinary PAH metabolites which can capture total exposure through multiple routes. The aim of this study was to bridge this knowledge gap by assessing longitudinal urinary PAH metabolite concentrations over two time points in pregnancy cohorts in Boston (N = 200) and Puerto Rico (N = 50) to better understand exposure distributions throughout pregnancy and how they relate to demographic factors. Urine samples were analyzed for 1-NAP, 2-NAP, 2-FLU, 1-PHE, 2,3-PHE, 4-PHE, 9-PHE, and 1-PYR. Concentrations of 2-NAP, 1-PYR, and 4-PHE were higher in Puerto Rico, while all other metabolites were present in higher concentrations in Boston. In Puerto Rico, intraclass correlation coefficients (ICC) were weak to moderate, ranging from 0.06 to 0.42. PAH metabolite concentrations were significantly higher among younger, heavier (except 1-NAP and 9-PHE), and less educated individuals in Boston only. Consistent significant associations between PAH concentrations and measured covariates were not found in Puerto Rico. Our results suggest that potentially important differences in PAH exposure exist between these two populations. Additionally, our results indicate that multiple urinary measurements are required to accurately assess PAH exposure throughout pregnancy.

1. Introduction

Polycyclic aromatic hydrocarbons are compounds that are released as byproducts of incomplete combustion reactions. Outdoor air can be contaminated with PAHs from industrial combustion, wood fires, automobile exhaust, and asphalt (Agency for Toxic Substances and Disease Registry, 1995), while indoor air contamination can also occur through home heating and cooking emissions (Lewtas, 2007). Numerous PAHs have been classified as carcinogens by the International Agency for Research on Cancer (IARC (International Agency for Research on Cancer), 2010). Human exposure occurs via inhalation of indoor or outdoor air, ingestion of food, particularly grilled or smoked meats (Agency for Toxic Substances and Disease Registry, 1995), and exposure to tobacco smoke (Aquilina et al., 2010). Once in the body, PAH parent compounds undergo metabolic biotransformation resulting in hydroxylated metabolites which are then excreted in urine (Ramesh et al., 2004). Despite evidence of adverse health effects caused by PAHs, exposure is still widespread. Parent PAH compounds have previously been detected in studies worldwide assessing ambient (Jung et al., 2014) and personal (Tonne et al., 2004) air. Urinary

☆ This paper has been recommended for acceptance by David Carpenter.

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https://doi.org/10.1016/j.envpol.2017.09.087
0269-7491/

metabolites (CDC, 2015; Urbancova et al., 2017) and DNA-adducts in blood and tissue (Perera et al., 2005a; Whyatt et al., 1998) have also been found. A positive association between PAH exposure and oxidative stress and indicators of cardiovascular disease morbidity and mortality has been demonstrated among occupationally exposed individuals (Brucker et al., 2014; Burstyn et al., 2005; Jeng et al., 2011; Wang et al., 2016). Although fewer in number, studies conducted among non-occupationally exposed populations have shown that urinary biomarkers of PAH exposure are positively associated with increased serum CRP levels and total white blood cells counts (Alshaarawy et al., 2013), as well as childhood obesity (Scinicariello and Buser, 2014).

Pregnant women and the developing fetus are particularly sensitive to environmental exposures. Birth weight and birth size have been shown to be associated with PAH levels measured via dietary, personal and ambient air, and occupational exposures, as well as PAH-DNA adducts (Choi et al., 2006, 2012; Dejmek et al., 2000; Duarte-Salles et al., 2013; Jedrychowski et al., 2012; Langlois et al., 2014; Perera et al., 2005b; Tang et al., 2006). Developmental abnormalities including cephalization index (Polanska et al., 2014a), premature fusion of skull sutures (O'Brien et al., 2016), neural tube defects (Yi et al., 2015), and spina bifida (Langlois et al., 2012) have also been observed following *in utero* exposure to PAHs. A limited number of studies have shown pregnant mothers to be at increased risk of preterm birth when exposed to PAHs, but these and the previously mentioned pregnancy studies are limited by small sample size and number of cases (Choi et al., 2008; Guo et al., 2012; Singh et al., 2008), or by utilizing only outdoor air monitoring data for exposure assessment and ignoring dietary and indoor air exposures (Padula et al., 2014; Vassilev et al., 2001; Wilhelm et al., 2011).

The aim of this study was to evaluate and compare urinary PAH biomarker distributions among ongoing pregnancy cohorts in Boston and Puerto Rico, as well as with those reported in the US National Health and Nutrition Examination Survey (NHANES). We also set out to assess temporal variability of PAH concentrations measured in repeated urine samples collected from the same women at two time points during pregnancy, as well as demographic predictors of urinary PAH concentrations in these cohorts. Results of this study can be used to inform the most appropriate and efficient exposure assessment strategies in the design of future studies investigating the association between PAH exposure and adverse pregnancy outcomes.

2. Materials and methods

2.1. Study populations

2.1.1. Boston population

Beginning in 2006, women were recruited at their initial prenatal visit at Brigham and Women's Hospital (BWH) in Boston, MA, as part of the ongoing LIFECODES longitudinal cohort study. Inclusion criteria were: 1) recruitment prior to 15 weeks gestation; 2) maternal age >18; and 3) intention to deliver at BWH. As part of the study design, women provide urine samples for biomarker assessment at four visits during pregnancy (approximately 10, 18, 26, and 35 weeks gestation) which are stored for future biomarker assessment. From the women who delivered between 2006 and 2008 we selected 130 cases of preterm birth (delivery <37 weeks gestation) as well as 352 random controls, with the intention of examining maternal exposure to phthalates during pregnancy in relation to preterm birth (Ferguson et al., 2014). Pregnant mothers from this case-control population were median 33 years of age, primarily white (59%), did not use tobacco products during pregnancy (92.3%), and were of high socioeconomic status (80% with private rather than public health insurance providers) (Ferguson et al., 2014). In this exploratory analysis of PAH exposure, we selected 200 urine samples from the third study visit (median gestational age 26 weeks) for measurement. Half of the samples were from mothers who delivered preterm and half were from term mothers. Throughout analyses within this population, we did not stratify based on case/control status as no differences were observed in this small subset (data not shown).

2.1.2. Puerto Rico population

The Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) study is a birth cohort study designed to investigate the relationship between environmental contaminant exposures and preterm birth on the island of Puerto Rico (Meeker et al., 2013). Recruitment began in 2010 and inclusion criteria were as follows: 1) maternal age 18–40 years; 2) residence within the study area (Northern karst region of Puerto Rico); 3) no use of contraceptives three months prior to pregnancy; 4) no use of *in vitro* fertilization for the present pregnancy; and 5) no known medical complications (Meeker et al., 2013). As part of the study protocol, participants provide urine samples at three visits in pregnancy. Mothers in this population are also largely non-smokers (97%), but are slightly younger than those from the Boston population (median age 27 years) and of lower socioeconomic status (44% household income <$20,000 per year) (Meeker et al., 2013). For the purposes of this study, we selected 50 participants who had urine samples stored from visits 1 and 3 for analysis of PAH metabolites (n = 100 samples total).

2.1.3. NHANES population

In order to compare PAH concentrations from these study populations with those observed in the general US populations, we examined biomarker data from the National Health and Nutrition Examination Survey from 2011 to 2012 (Centers for Disease Control and Prevention, 2015). Using information from the demographic questionnaire, we restricted our analyses to female participants who were 18–40 years of age. For all analyses we included appropriate weights to account for the survey design, as described in detail on the NHANES website (Centers for Disease Control and Prevention, 2013b).

2.2. Urinary PAH metabolite measurement

For the Boston and Puerto Rico populations, urinary PAH metabolites were measured by isotope dilution-liquid chromatography with tandem mass spectrometry (LCMS) at NSF International (Ann Arbor, MI, USA). The parent PAH compounds, metabolites

Table 1
Polycyclic aromatic hydrocarbons (PAH), urinary metabolites, abbreviations, and assay limits of detection at NSF International and CDC (ng/L).

PAH	Urinary metabolite	Abbreviation	NSF LOD	CDC LOD[a]
Napthalene	1-hydroxynapthalene	1-NAP	50	44
	2-hydroxynapthalene	2-NAP	50	42
Fluorene	2-hydroxyfluorene	2-FLU	10	10
Phenanthrene	1-hydroxyphenanthrene	1-PHE	10	10
	2-hydroxyphenanthrene	2&3-PHE	10[b]	10
	3-hydroxyphenanthrene			10
	4-hydroxyphenanthrene	4-PHE	10	10
	9-hydroxyphenanthrene	9-PHE	10	–
Pyrene	1-hydroxypyrene	1-PYR	10	10

Abbreviations: NSF, NSF International, Ann Arbor, MI, USA; CDC, Centers for Disease Control and Prevention, Atlanta, GA, USA; LOD, limit of detection. Adapted from: http://www.cdc.gov/biomonitoring/Naphthalene_BiomonitoringSummary.html.

[a] From NHANES 2011–2012.

[b] 2-OH-PHE and 3-OH-PHE quantitated together by NSF.

Please cite this article in press as: Cathey, A., et al., Distribution and predictors of urinary polycyclic aromatic hydrocarbon metabolites in two pregnancy cohort studies, Environmental Pollution (2017), https://doi.org/10.1016/j.envpol.2017.09.087