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Examination of Xylene Exposure in the U.S. Population Through Biomonitoring: NHANES 2005–2006, 2011–2016

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Abstract

Xylenes are aromatic hydrocarbons used for industrial applications such as the production of petrochemicals and plastics. Acute xylene exposures can negatively impact health through neurotoxicity and irritation of respiratory and dermal tissues. We quantified urinary biomarkers of xylene exposure [2-methylhippuric acid (2MHA) and a mixture of 3- and 4-methylhippuric acids (34MH)] in a representative sample of the U.S. population. Spot urine obtained during the National Health and Nutrition Examination Survey 2005–2006 and 2011–2016 was analyzed using ultra-high-performance liquid chromatography/tandem mass spectrometry. Exclusive smokers were distinguished from non-users using a combination of self-report and serum cotinine data. The median 2MHA and 34MH levels were higher for exclusive smokers (100 μg/g and 748 μg/g creatinine, respectively) than for non-users (27.4 μg/g and 168 μg/g creatinine, respectively). Participants who smoked cigarettes had significantly higher 2MHA and 34MH levels (p<0.0001) than unexposed participants. Smoking 1–10, 11–20, and >20 cigarettes per day (CPD) was significantly associated with 181%, 339% and 393% higher 2MHA levels, respectively. For 34MH, smoking 1–10, 11–20, and >20 CPD was significantly associated with 201%, 398%, and 471% higher 34MH levels, respectively. We confirm that tobacco smoke is a significant source of xylene exposure as measured by urinary 2MHA and 34MH levels.

Keywords

xylene; VOC metabolites; tobacco smoke exposure; biomonitoring; NHANES

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6. Declaration of interests

The authors declare that they have no conflict of interest.

1. Introduction

Xylenes are aromatic hydrocarbons commonly used for industrial applications due to their superior solvent properties (Angerer, 1979, Mohammadyan and Baharfar, 2015). They are synthetically derived from crude oil or coal tar and used in various commercial products such as petrochemicals, plastics, and paints. Additionally, other xylene sources in the environment include landfill gases, emissions from petroleum refineries, vehicle exhaust fumes, and tobacco smoke (Chambers, et al., 2011, Niaz, et al., 2015, Saliba, et al., 2017, Staszewska, et al., 2012). Xylene exists as three different positional isomers: *ortho*-, *meta*-, and *para*-xylene (*o*-xylene, *m*-xylene, and *p*-xylene). Throughout this report, the term xylene refers to a mixture of the three positional isomers unless otherwise stated.

Acute airborne xylene exposure events of ≥100 ppm have been noted to induce eye, nose, and throat irritation; narcosis; mild anemia; and liver enlargement in exposed individuals (Niaz, et al., 2015, Rajan, 2014). The Occupational Safety and Health Administration (OSHA) has designated a permissible exposure limit (PEL) of 100 ppm time-weighted average for general industry (OSHA, 2012). Acute exposures that exceed the PEL have been reported in the literature, typically occurring in workplace accidents or cases of intentional ingestion. These exposures have resulted in pulmonary congestion and edema, decreased urinary-clearance function, reduced muscular strength and coordination, depressed respiration, coma, and death (Agency for Toxic Substances and Disease Registry, 2007, Rajan, 2014). Exposure to xylene at low concentrations over extended periods has been evaluated, with exposed individuals developing nausea, gastrointestinal discomfort, vomiting, decreased grasping power, increased anxiety, and difficulties concentrating (Agency for Toxic Substances and Disease Registry, 2007, Rajan, 2014).

Exposure to xylene occurs primarily through dermal, oral, and respiratory pathways. Dermal absorption of liquid xylene has been shown to occur at a rate of 2 $\mu g/cm^2$/min, or approximately 12% of vapor xylene, which is absorbed by the lungs (Agency for Toxic Substances and Disease Registry, 2007, Engstrom, et al., 1977). Dermal exposure is likely to occur among those who work with xylene directly in occupational settings, such as painters, pesticide-manufacturing workers, medical-histology laboratory workers, polymer workers, and steelworkers (Angerer, 1979, Engstrom, et al., 1977, Lundberg and Sollenberg, 1986, Mohammadyan and Baharfar, 2015). Xylene ingestion may occur accidentally or intentionally in cases such as suicide and consumption of xylene-contaminated foods (Agency for Toxic Substances and Disease Registry, 2007, Niaz, et al., 2015). However, respiratory exposure is the most common xylene-exposure pathway, with pulmonary-retention efficiency of approximately 60% (Riihimäki and Savolainen, 1980). The lungs also provide an excretion route during periods of desaturation. Approximately 5% of retained xylene is excreted in exhaled breath unmodified (Sedivec and Flek, 1976).

Xylene is rapidly absorbed and metabolized in vitro. Nearly 95% of the metabolic products are generated through CYP450 2E1 liver microsomal enzyme oxidation of a methyl group to produce methylbenzoic acid. Methylbenzoic acid conjugates with glycine and produces methylhippuric acids, which are excreted in urine (Sedivec and Flek, 1976). The methylhippuric acid products are 2-methylhippuric acid (2MHA, *o*-xylene parent), 3-

methylhippuric acid (3MHA, *m*-xylene parent), and 4-methylhippuric acid (4MHA, *p*-xylene parent) (Ogata, et al., 1969, Sedivec and Flek, 1976).

Studies have shown that tobacco smoke is a common source of xylene, and among smokers it is the principal exposure source of xylene (Chambers, et al., 2006, Chambers, et al., 2011, Pazo, et al., 2016). Comparisons of blood-xylene levels among tobacco smokers and non-smokers show that the former have higher levels compared to non-users (Chambers, et al., 2011). However, exposure to xylene [and other volatile organic compounds (VOCs)] can also be assessed by measuring their metabolites in urine. While measuring VOCs in blood provides a direct assessment of VOC burden *in vivo* (Chambers, et al., 2006), urinary biomarkers of VOC exposure have a longer biological half-life than VOCs in blood, and are more stable during storage and handling (Boyle, et al., 2016). VOC metabolites in urine have been examined in the U.S. population through the National Health and Nutrition Examination Survey (NHANES) since 2005 (Bagchi, et al., 2018, U.S. Centers for Disease Control and Prevention). We evaluated xylene exposure by quantifying 2MHA and a mixture of 3MHA and 4MHA (34MH). Another metabolic product, dimethylphenyl mercapturic acid (DPMA), was also reported to be a marker for xylene exposure, but it is formed at a ratio of only 0.0003% of 2MHA and 34MH levels (Gonzalez-Reche, et al., 2003). Finally, we examined the influence of demographic variables (e.g., age, sex, and race/Hispanic origin) on 2MHA and 34MH concentrations through the use of regression models.

2. Materials and methods

2.1 Study design

NHANES is a population-based survey conducted by the National Center for Health Statistics (NCHS) of the U.S. Centers for Disease Control and Prevention (CDC). The survey is designed to assess health and nutritional status through a cross-sectional observation of a complex, multistage probability-sample representative of the civilian, non-institutionalized population. A total of 3,545 participants age 12 years and older for NHANES 2005 – 2006 (one-half subset) and 7,461 participants age 6 years and older for NHANES 2011 – 2012, 2013 – 2014 and 2015 – 2016 survey cycles (one-third subset, including all 3–5-year-old participants from 2015 – 2016) were eligible for measurements of urinary VOCs including those investigated in this study. Samples with incomplete data for analytical variables or ineligible criteria were excluded (see statistical analysis section).

2.2 Laboratory method

We measured 2MHA and 34MH in urine samples using ultra-high-performance liquid chromatography (Classic Acquity; Waters Inc., Milford, MA) in combination with electrospray ionization tandem mass spectrometry (Sciex 5500 Triple Quad; Foster City, CA) as described previously (Alwis, et al., 2012, Bagchi, et al., 2018, Capella, et al., 2019). Of note, 3MHA and 4MHA are not baseline-separated chromatographically and are reported as the summed product 34MH. We monitored 2MHA and 34MH as follows: *m/z* 192→148 (quantitation ion) and *m/z* 192→91 (confirmation ion). We used 2MHA-d_7 and 34MH-d_7 as their respective internal standards, which were monitored at *m/z* 199→155. The limits of detection (LOD) for 2MHA and 34MH were 5.00 and 8.00 ng/mL, respectively.

2.3 Statistical analysis

Since NHANES participants are recruited through multistage probability sampling, it is necessary to account for this complex design to estimate variances properly and to produce unbiased, nationally representative statistics. Robust estimation can be accomplished by applying survey stratification, cluster information, and sample weights to each participant's data and using Taylor series linearization to produce variance estimates. To adjust for the number of NHANES cycles, we divided the subsample weights WTSVOC2Y for 2005–2006 and WTFSM for 2011–2012, 2013–2014, and 2015–2016 by four. We used this estimation approach as implemented in the SURVEYFREQ, SURVEYMEANS, and SURVEYREG subroutines of the SAS statistical software application version 9.4 (SAS Institute, Cary, NC) (Capella, et al., 2019).

To study the relationship between 2MHA/34MH and demographic covariates within specific subpopulations defined by tobacco product use, we developed sample-weighted linear regression models stratified by tobacco use status (exclusive smokers of combusted tobacco products vs. non-users) using data from the NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016 survey cycles. The dependent variables were urinary 2MHA and 34MH concentrations (ng/mL) and the independent variables were age, sex, race/Hispanic origin, poverty level (impoverishment), weight status (body mass index, BMI), fasting time, serum-cotinine level, 24-hour dietary recall, and NHANES cycle, as previously described (Bagchi, et al., 2018, Biren, et al., 2020, Espenship, et al., 2019). Because the distribution of measurements was strongly right-skewed, urinary 2MHA and 34MH concentration data were transformed with the natural log for regression analysis. NHANES cycle, fasting time, creatinine level, and demographic covariates were included in the model *a priori*. We report coefficients from these models, along with their 95% confidence intervals and *p*-values as described previously (Biren, et al., 2020). Statistical significance level was set to $\alpha = 0.05$. An evaluation of statistical reliability was performed and found all proportions followed the NCHS Data Presentation Standard.

Study participants were identified as exclusive daily users of cigarette products (exclusive smokers) if they responded "yes" to NHANES question SMDANY (tobacco use within five days prior to NHANES physical examination), "yes" to SMQ690a (cigarette use), "no" to SMQ690b-SMQ690J (use of pipes, cigars, chewing tobacco, snuff, patch/gum, hookah/water pipes, e-cigarettes, snus, and dissolvable tobacco), according to NHANES questionnaire data on recent tobacco use (NHANES dataset: SMQRTU_I), and had serum cotinine >10 ng/mL. Participants were identified as non-users if they had serum cotinine ≤10 ng/mL. The serum cotinine threshold of >10 ng/mL has been identified as consistent with the active use of traditional cigarette products (Pirkle, et al., 1996) and was used to stratify self-identified exclusive smokers and non-users.

To explore the association between urinary biomarker concentrations and the frequency of cigarette smoking, we ran a regression model with the self-reported average number of cigarettes smoked per day (CPD) over the five days preceding the NHANES physical exam. This sample-weighted CPD regression model was non-stratified using the same predictors as the stratified regression model. The tobacco-smoke exposure variable was classified as ≤0.015 ng/mL serum cotinine (non-exposed to tobacco smoke); >0.015 – ≤10 ng/mL serum

cotinine; and 1–10, 11–20, and >20 CPD, where the reference category was non-exposed participants. The CPD regression model comprised the same sample size as the stratified regression model but excluded participants who could not be assigned to a CPD category, leaving 7,697 participants.

We measured the Pearson correlation coefficients between urinary xylene metabolites 2MHA, 34MH, and blood xylene levels VOX (*o*-xylene) and VXY (*m*-/*p*-xylene), in addition to stratification by serum cotinine level. Blood-xylene data were obtained from NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016 cycles. Urinary and blood data sets were paired by unique identification numbers to ensure that both specimens came from the same individual. Pearson correlation coefficients were calculated from the natural log-transformed data. Urinary data were creatinine-ratioed before natural log transformation.

Reported analytical results met the accuracy and precision specifications of the quality control/quality assurance program of the Division of Laboratory Sciences in the CDC National Center for Environmental Health. Measurements below the LOD were substituted with the quotient of the LOD divided by the square root of two (Hornung and Reed, 1990).

3. Results

We examined the detection rate of each metabolite to determine whether it was sufficient for robust statistical analysis. We detected 2MHA and 34MH in 94.3% and 99.6%, respectively, of all urine samples analyzed from NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016 cycles. Urinary DPMA levels were excluded from regression analyses and descriptive statistical models due to its low detection rate of 0.35% over four cycles. Sample-weighted demographic distributions across all survey cycles are presented in Table 1. Creatinine-ratioed median concentrations of 2MHA and 34MH for exclusive smokers were 100 μg/g and 748 μg/g creatinine, respectively. Moreover, creatinine-ratioed median concentrations of 2MHA and 34MH for non-users were 27.4 μg/g and 168 μg/g creatinine, respectively. Detailed median and selected percentiles of 2MHA and 34MH by smoking status are presented in Tables 2A and 2B.

We conducted multiple regression analysis on exclusive smokers (serum cotinine ≥10 ng/mL) for 2MHA and 34MH (Tables 3A and 3B). Likewise, multiple regression analysis was conducted on non-users (serum cotinine ≤10 ng/mL) for both 2MHA and 34MH (Tables 4A and 4B). The same set of demographic variables were evaluated. We found that, among exclusive smokers, serum cotinine was positively associated with both urinary 2MHA and 34MH ($p<0.0001$), and increase of serum cotinine from zero to the observed median of 212 ng/mL was associated with 75% and 80%, respectively, increase in urinary 2MHA and 34MH, controlling for other variables. (These percentage increases were obtained as multiplication of the specified increase in serum cotinine with the estimated regression coefficient, e.g., 75% = (exp(2.65E-03*212)-1)*100 for 2MHA.) Furthermore, among non-users, serum cotinine also is positively associated with urinary 2MHA and 34MH ($p=0.0414$ and 0.0091, respectively), and increase of serum cotinine from zero to the observed median of 0.019 ng/mL is associated with 0.08% and 0.09%, respectively, increase in urinary 2MHA and 34MH, controlling for other variables. Additionally, we did not find 24-hour dietary

recall to be significantly associated with 2MHA and 34MH and thus excluded it from our regression models.

Sample-weighted geometric least-square means of urinary 2MHA and 34MH for self-reported CPD are shown in Figure 1, ratioed for urinary creatinine, sex, age, race/Hispanic origin, and weight status. In the model, 2MHA and 34MH concentrations increased with respect to increasing CPD (Tables 5A and 5B). All participants who smoked cigarettes had significantly higher 2MHA and 34MH levels ($p< 0.0001$) than unexposed participants (serum cotinine ≤ 0.015 ng/mL). When compared with the reference group (serum cotinine ≤ 0.015 ng/mL) and controlling for confounders, smoking 1–10, 11–20, and >20 CPD was significantly associated with 181%, 339%, and 393% higher 2MHA levels ($p<0.0001$), respectively. For 34MH, smoking 1–10, 11–20, and >20 CPD was significantly associated with 201%, 398%, and 471% higher 34MH levels ($p<0.0001$), respectively.

We evaluated the Pearson correlation of xylene metabolites in comparison to the blood level of the parent compound for that specific xylene isomer (Table 6). Strong correlations were observed among exclusive smokers' blood levels of the parent compound (VOX and VXY) and their creatinine-ratioed urinary metabolites (2MHA and 34MH, respectively). Among exclusive smokers, 2MHA exhibited a good correlation with *o*-xylene in blood (VOX, 0.53); 34MH showed a good correlation with *m*-/*p*-xylene in blood (VXY, 0.61).

Our analysis revealed associations of 2MHA and 34MHA with various demographic variables, albeit at lower magnitude and/or inconsistently across multiple models. Specifically, we observed an increase in the median concentrations of 2MHA and 34MH with increased age among exclusive smokers but not among non-users. Additionally, females who are exclusive smokers had higher urinary 2MHA and 34MH levels than males (5% and 10%, respectively), but this finding was statistically significant only for 34MH. Using participants aged 20–39 years as the reference, older adult exclusive smokers (age 40–59 years) had higher 2MHA and 34MH concentrations (21% and 28%, respectively; $p<0.0001$). Compared with non-Hispanic Whites, individuals identifying as non-Hispanic Black, Hispanic and Other Race/Multi-Racial had lower 2MHA and 34MH among both exclusive smokers and non-users, with statistically significant *p*-values for all exclusive smoker classifications and non-user, non-Hispanic Blacks.

4. Discussion

This report provides the first biomonitoring evaluation of xylene exposure across a representative sample of the U.S. population. The overall detection rates for 2MHA and 34MH were 94.3% and 99.6% on average across the four NHANES survey cycles, respectively. These detect rates are higher than those observed for their parent compounds in blood over the same cycles (*o*-xylene, 42.3%; *m*-/*p*-xylene, 76.3%), which may be due to the longer physiological half-lives of urinary metabolites compared with their intact parent VOCs. In addition, the detection rate for urinary DPMA was <1% over four NHANES cycles, suggesting that DPMA may not be a suitable biomarker of non-occupational xylene exposure. The high detection rates found for 2MHA and 34MH may be attributed to the ubiquitous presence of xylene in the environment. Ambient air xylene concentration is

approximately 0.23 ppb, with suburban areas at 0.69 ppb and urban areas as high as 1,789 ppb (Agency for Toxic Substances and Disease Registry, 2007). Additionally, indoor xylene exposure can be high due to the presence of adhesives, paints, and carpets in indoor environments (Agency for Toxic Substances and Disease Registry, 2007).

The sample-weighted multiple linear regression models reveal that the median serum cotinine for exclusive smokers was significantly associated with 75% and 80% higher urinary 2MHA and 34MH levels, respectively ($p<0.0001$), controlling for confounding variables. For non-users, the median serum cotinine was significantly associated with 0.08% and 0.09% higher 2MHA and 34MH levels, respectively. Similarly, smoking more cigarettes per day was associated with increased urinary 2MHA and 34MH in a dose-response pattern (Figure 1). Results from both the serum cotinine and the tobacco-smoke exposure (CPD) models further indicate that tobacco smoke is a major source of xylene exposure for the general U.S. population, even as second-hand exposure (as shown in the serum cotinine model for non-users). In addition, sample-weighted geometric least-square means of urinary 2MHA and 34MH for self-reported CPD (Figure 1; Tables 5A, 5B), adjusted for confounders, show that their concentrations increase with respect to increasing CPD. All participants who smoked cigarettes had significantly higher 2MHA and 34MH levels than non-users, although the toxicological significance of these levels of xylene exposure is unknown.

Demographic variables were also evaluated for association with urinary 2MHA and 34MH in the sample-weighted multiple linear regression models. Of note, females had higher 2MHA and 34MH than males. An explanation could be the effect of creatinine adjustments. While urinary creatinine excretion is relatively consistent in an individual, the amount excreted can vary significantly between individuals, based on lean body mass and a variety of genetic and physiological factors. Creatinine production is higher in people with more muscle mass and tends to be higher in males compared with females and higher in non-Hispanic blacks compared with other races (Barr, et al., 2005). Another possible reason for the difference in xylene metabolites between racial groups could be related to polymorphisms of cytochrome P450 2E1. Some polymorphisms of this enzyme have different activity rates, leading to varying toxicokinetic profiles among different racial groups (Droz, et al., 1997, Inoue, 1986). Nevertheless, the contribution of these demographic variables to 2MHA and 34MH levels are approximately an order of magnitude less than from smoking a pack of cigarettes per day.

Our analysis also showed strong correlations among previously reported blood levels of the parent compounds (*o*-xylene and *m/p*-xylene, Table 6) and their urinary metabolites (2MHA, 34MH, respectively) in biological samples collected during the same mobile exam center visit. Among exclusive smokers, creatinine-ratioed 2MHA exhibited a good correlation with *o*-xylene in blood (VOX, 0.53) and creatinine-ratioed 34MH also showed a good correlation with *m*/*p*-xylene in blood (VXY, 0.61). Both VOX and VXY were strongly correlated among exclusive smokers and non-users. These findings illustrate the complementary nature of parent VOC and VOC-metabolite analysis when assessing xylene exposure through biomonitoring.

5. Conclusion

Our data show that 2MHA and 34MH are significantly higher among exclusive smokers compared to non-users. Serum-cotinine levels and higher CPD smoking rates were significantly with higher 2MHA and 34MH levels. Moreover, blood xylene levels were shown to be correlated with 2MHA and 34MH concentrations, further establishing the suitability of using urinary metabolites to evaluate xylene exposure. Smoking >20 CPD was associated with markedly higher 2MHA (393%) and 34MH (471%) levels. Our findings suggest that tobacco smoke is a major source of xylene exposure in the U.S. population. Future studies of background xylene exposures are necessary to continue the evaluation of xylene exposure trends for the U.S. population as smoking prevalence and regulations change.

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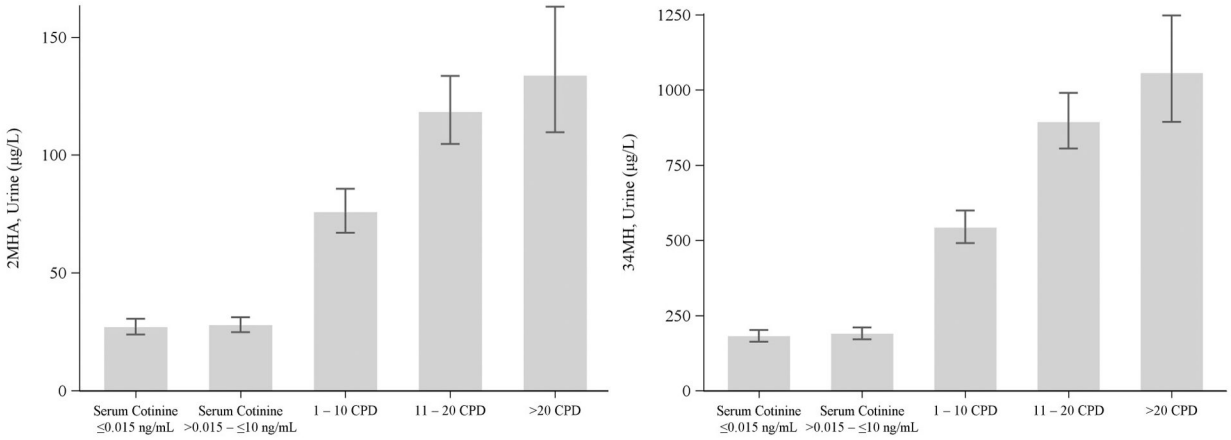

Figure 1.

Sample-weighted geometric least-square means [95% confidence intervals] of 2MHA and 34MH concentrations (µg/L) for each CPD category (N=7,697)

Table 1.

Study demographics and distributions for NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016 (N=7,803)[1]

Predictor	Level	N[2], Exclusive Smokers	Percent (SE)[3], Exclusive Smokers	N[2], Non-Users	Percent (SE)[3], Non-Users
Sex	Male	1,383	54.62 (1.12)	2,475	45.76 (0.87)
	Female	1,000	45.38 (1.12)	2,945	54.24 (0.87)
Age	12 – 19	107	2.82 (0.34)	834	5.42 (0.41)
	20 – 39	891	41.22 (1.55)	1,639	32.93 (1.17)
	40 – 59	903	39.95 (1.51)	1,411	34.78 (1.02)
	≥60	482	16.01 (0.98)	1,536	26.86 (1.16)
Race/Hispanic Origin	Non-Hispanic White	1,132	68.88 (2.20)	2,132	68.50 (1.84)
	Non-Hispanic Black	696	15.50 (1.50)	1,154	9.56 (0.95)
	Hispanic	355	9.24 (1.06)	1,532	14.76 (1.27)
	Other Race/Multi-Racial	200	6.38 (0.76)	602	7.18 (0.54)
Weight Status	Healthy Weight	804	34.68 (1.58)	1,722	29.80 (1.12)
	Overweight/Obesity	1,515	62.55 (1.52)	3,628	69.20 (1.15)
	Underweight	64	2.77 (0.48)	70	1.00 (0.15)
Impoverishment	No	1,583	76.36 (1.46)	4,378	88.65 (0.82)
	Yes	800	23.64 (1.46)	1,042	11.35 (0.82)
NHANES Cycle	2005 – 2006	487	30.10 (2.15)	2,263	26.77 (1.73)
	2011 – 2012	648	24.96 (1.97)	1,025	24.54 (1.68)
	2013 – 2014	630	21.85 (1.50)	1,015	22.93 (1.44)
	2015 – 2016	618	23.09 (1.40)	1,117	25.76 (1.75)

[1]Same data as in stratified serum-cotinine regression models

[2]Not sample-weighted

[3]Standard error [(SE), (sample-weighted)]. The percentages were calculated as weighted percent of exclusive smokers or weighted percent of non-users.

Table 2A.

2MHA Values [μg/g creatinine] and median [25th ,75th percentiles] by smoking status (N=7,803)[1]

Predictor	Level	Exclusive Smokers	Non-Users
	All	100 [55.0, 173]	27.4 [13.8, 58.9]
Sex	Male	91.4 [49.3, 155]	26.4 [13.0, 56.0]
	Female	114 [62.0, 193]	28.0 [14.2, 61.4]
Age	12 – 19	57.8 [28.9, 128]	25.7 [12.7, 63.1]
	20 – 39	77.3 [43.3, 133]	26.1 [13.9, 56.6]
	40 – 59	125 [67.8, 214]	28.3 [14.2, 59.9]
	≥60	115 [72.1, 178]	28.0 [13.5, 60.6]
Race/Hispanic Origin	Non-Hispanic White	117 [64.5, 197]	29.9 [14.3, 63.4]
	Non-Hispanic Black	68.7 [36.4, 112]	18.6 [10.4, 37.1]
	Hispanic	70.6 [38.1, 123]	24.6 [14.4, 52.1]
	Other Race/Multi-Racial	81.5 [47.9, 146]	26.8 [13.6, 55.3]
Weight Status	Healthy Weight	115 [60.1, 199]	29.1 [14.9, 64.9]
	Overweight/Obesity	93.5 [51.6, 152]	26.7 [13.2, 56.6]
	Underweight	95.7 [49.7, 210]	35.8 [13.8, 87.9]
Impoverishment	No	100 [53.7, 175]	28.2 [14.0, 60.3]
	Yes	100 [59.0, 167]	21.3 [12.5, 49.4]
NHANES Cycle	2005 – 2006	80.5 [47.4, 133]	25.5 [13.6, 53.7]
	2011 – 2012	125 [61.0, 204]	28.5 [14.6, 60.6]
	2013 – 2014	101 [50.2, 170]	27.6 [13.6, 59.9]
	2015 – 2016	109 [62.7, 181]	28.2 [13.7, 60.3]

[1]Same data as in stratified serum cotinine regression models

Table 2B.

34MH Values [μg/g creatinine] and median [25th, 75th percentiles] by smoking status (N=7,803)[1]

Predictor	Level	Exclusive Smokers	Non-Users
	All	748 [439, 1.20E+03]	168 [96.3, 382]
Sex	Male	687 [402, 1.08E+03]	164 [90.5, 348]
	Female	827 [492, 1.36E+03]	171 [101, 407]
Age	12 – 19	393 [241, 744]	171 [100, 363]
	20 – 39	571 [348, 972]	149 [88.1, 347]
	40 – 59	906 [559, 1.38E+03]	171 [95.4, 386]
	≥60	851 [574, 1.35E+03]	180 [108, 414]
Race/Hispanic Origin	Non-Hispanic White	855 [510, 1.32E+03]	184 [107, 407]
	Non-Hispanic Black	517 [298, 780]	118 [73.4, 256]
	Hispanic	491 [268, 832]	140 [90.5, 338]
	Other Race/Multi-Racial	754 [374, 1.22E+03]	143 [78.3, 309]
Weight Status	Healthy Weight	852 [479, 1.34E+03]	171 [100, 406]
	Overweight/Obesity	707 [427, 1.08E+03]	166 [93.7, 365]
	Underweight	693 [395, 1.27E+03]	254 [137, 592]
Impoverishment	No	753 [438, 1.20E+03]	171 [97.6, 387]
	Yes	721 [440, 1.21E+03]	140 [88.0, 310]
NHANES Cycle	2005 – 2006	676 [424, 1.11E+03]	171 [109, 321]
	2011 – 2012	854 [492, 1.35E+03]	166 [98.3, 405]
	2013 – 2014	713 [398, 1.21E+03]	169 [90.2, 431]
	2015 – 2016	728 [459, 1.17E+03]	165 [86.8, 380]

[1]Same data as in stratified serum cotinine regression models

Table 3A.

Urinary 2MHA (ng/mL) in exclusive smokers (N=2,383): Sample-weighted multiple linear regression model among NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016

Predictor	Level	Coefficient [95% CI][1]	Exponential Coefficient [95%CI][1]	p-Value
Intercept	Intercept	3.34 [3.13, 3.54]		
Creatinine, Urine [g/L][2]	Coefficient	0.548 [0.485, 0.612]	1.73 [1.63, 1.84]	<0.0001
Cotinine, Serum [ng/mL]	Coefficient	2.65E-03 [2.31E-03, 3.00E-03]	1.00 [1.00, 1.00]	<0.0001
Sex	Male	Ref.	Ref.	
	Female	0.0517 [−0.0434, 0.147]	1.05 [0.959, 1.16]	0.2815
Age	12 – 19	−0.0563 [−0.341, 0.228]	0.945 [0.715, 1.25]	0.6942
	20 – 39	Ref.	Ref.	
	40 – 59	0.193 [0.109, 0.276]	1.21 [1.12, 1.32]	<0.0001
	≥60	0.0986 [−0.0227, 0.220]	1.10 [0.980, 1.24]	0.1093
Race/Hispanic Origin	Non-Hispanic White	Ref.	Ref.	
	Non-Hispanic Black	−0.404 [−0.505, −0.302]	0.668 [0.604, 0.738]	<0.0001
	Hispanic	−0.187 [−0.302, −0.0730]	0.829 [0.741, 0.928]	0.0017
	Other Race/Multi-Racial	−0.204 [−0.342, −0.0657]	0.816 [0.712, 0.934]	0.0045
Weight Status	Underweight	0.0129 [−0.208, 0.234]	1.01 [0.816, 1.26]	0.9073
	Healthy Weight	Ref.	Ref.	
	Overweight/Obese	−0.0158 [−0.113, 0.0818]	0.984 [0.895, 1.08]	0.7478
Impoverished	No	Ref.	Ref.	
	Yes	0.0565 [−0.0300, 0.143]	1.06 [0.972, 1.15]	0.1967
NHANES Cycle	2005 – 2006	−0.215 [−0.318, −0.112]	0.807 [0.729, 0.893]	<0.0001
	2011 – 2012	Ref.	Ref.	
	2013 – 2014	−0.233 [−0.418, −0.0494]	0.792 [0.661, 0.948]	0.0138
	2015 – 2016	0.0628 [−0.0415, 0.167]	1.06 [0.961, 1.18]	0.2331

[1]The dependent variable, biomarker concentration, was natural log-transformed for the regression model and back-transformed for interpretation.

[2]Although urinary creatinine concentration is usually reported in mg/dL, here this concentration is in g/L so that its coefficient simplifies to the more readily interpretable scale.

Table 3B.

Urinary 34MH (ng/mL) in exclusive smokers (N=2,383): Sample-weighted multiple linear regression model among NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016

Predictor	Level	Coefficient [95% CI][1]	Exponential Coefficient [95%CI][1]	p-Value
Intercept	Intercept	4.99 [4.78, 5.21]		
Creatinine, Urine [g/L][2]	Coefficient	0.691 [0.631, 0.751]	2.00 [1.88, 2.12]	<0.0001
Cotinine, Serum [ng/mL]	Coefficient	2.77E-03 [2.43E-03, 3.12E-03]	1.00 [1.00, 1.00]	<0.0001
Sex	Male	Ref.	Ref.	
	Female	0.0944 [4.42E-03, 0.184]	1.10 [1.01, 1.20]	0.0401
Age	12 – 19	−0.194 [−0.440, 0.0514]	0.823 [0.647, 1.05]	0.1190
	20 – 39	Ref.	Ref.	
	40 – 59	0.248 [0.168, 0.329]	1.28 [1.18, 1.39]	<0.0001
	≥60	0.215 [0.0906, 0.338]	1.24 [1.10, 1.40]	0.0010
Race/Hispanic Origin	Non-Hispanic White	Ref.	Ref.	
	Non-Hispanic Black	−0.456 [−0.560, −0.352]	0.634 [0.573, 0.702]	<0.0001
	Hispanic	−0.251 [−0.373, −0.130]	0.778 [0.690, 0.876]	0.0001
	Other Race/Multi-Racial	−0.128 [−0.322, 0.0661]	0.880 [0.727, 1.06]	0.1924
Weight Status	Underweight	−0.0290 [−0.257, 0.199]	0.971 [0.777, 1.22]	0.8007
	Healthy Weight	Ref.	Ref.	
	Overweight/Obese	6.40E-03 [−0.0938, 0.107]	1.01 [0.912, 1.11]	0.8989
Impoverished	No	Ref.	Ref.	
	Yes	0.0793 [−6.07E-03, 0.165]	1.08 [0.996, 1.18]	0.0681
NHANES Cycle	2005 – 2006	−3.06E-03 [−0.0921, 0.0860]	0.997 [0.914, 1.09]	0.9454
	2011 – 2012	Ref.	Ref.	
	2013 – 2014	−0.194 [−0.356, −0.0322]	0.823 [0.703, 0.965]	0.0196
	2015 – 2016	0.0551 [−0.0765, 0.187]	1.06 [0.929, 1.20]	0.4061

[1]The dependent variable, biomarker concentration, was natural log-transformed for the regression model and back-transformed for interpretation.

[2]Although urinary creatinine concentration is usually reported in mg/dL, here this concentration is in g/L so that its coefficient simplifies to the more readily interpretable scale.

Table 4A.

Urinary 2MHA (ng/mL) in non-users (N=5,420): Sample-weighted multiple linear regression model among NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016

Predictor	Level	Coefficient [95% CI][1]	Exponential Coefficient [95%CI][1]	p-Value
Intercept	Intercept	2.63 [2.48, 2.78]		
Creatinine, Urine [g/L][2]	Coefficient	0.648 [0.583, 0.713]	1.91 [1.79, 2.04]	<0.0001
Cotinine, Serum [ng/mL]	Coefficient	0.0411 [1.22E-03, 0.0809]	1.04 [1.00, 1.08]	<0.0001
Sex	Male	Ref.	Ref.	
	Female	−0.0385 [−0.128, 0.0509]	0.962 [0.881, 1.05]	0.3931
Age	12 – 19	0.0692 [−0.0543, 0.193]	1.07 [0.949, 1.21]	0.2672
	20 – 39	Ref.	Ref.	
	40 – 59	0.0345 [−0.0606, 0.130]	1.04 [0.943, 1.14]	0.4711
	≥60	−0.0135 [−0.127, 0.100]	0.987 [0.882, 1.10]	0.8141
Race/Hispanic Origin	Non-Hispanic White	Ref.	Ref.	
	Non-Hispanic Black	−0.286 [−0.375, −0.198]	0.751 [0.689, 0.819]	<0.0001
	Hispanic	−0.0213 [−0.116, 0.0738]	0.979 [0.892, 1.07]	0.6558
	Other Race/Multi-Racial	−0.135 [−0.296, 0.0261]	0.874 [0.746, 1.02]	0.0991
Weight Status	Underweight	0.207 [−0.230, 0.644]	1.23 [0.802, 1.89]	0.3463
	Healthy Weight	Ref.	Ref.	
	Overweight/Obese	−0.0427 [−0.139, 0.0534]	0.958 [0.872, 1.05]	0.3780
Impoverished	No	Ref.	Ref.	
	Yes	−0.0905 [−0.191, 0.0101]	0.913 [0.828, 1.01]	0.0771
NHANES Cycle	2005 – 2006	−0.0513 [−0.214, 0.111]	0.950 [0.810, 1.11]	0.5301
	2011 – 2012	Ref.	Ref.	
	2013 – 2014	−0.0900 [−0.268, 0.0877]	0.914 [0.768, 1.09]	0.3153
	2015 – 2016	−0.0319 [−0.204, 0.140]	0.969 [0.819, 1.15]	0.7115

[1]The dependent variable, biomarker concentration, was natural log-transformed for the regression model and back-transformed for interpretation.

[2]Although urinary creatinine concentration is usually reported in mg/dL, here this concentration is in g/L so that its coefficient simplifies to the more readily interpretable scale.

Table 4B.

Urinary 34MH (ng/mL) in non-users (N=5,420): Sample-weighted multiple linear regression model among NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016

Predictor	Level	Coefficient [95% CI][1]	Exponential Coefficient [95%CI][1]	p-Value
Intercept	Intercept	4.15 [4.01, 4.29]		
Creatinine, Urine [g/L][2]	Coefficient	0.864 [0.797, 0.931]	2.37 [2.22, 2.53]	<0.0001
Cotinine, Serum [ng/mL]	Coefficient	0.0478 [0.0101, 0.0856]	1.05 [1.01, 1.09]	0.0139
Sex	Male	Ref.	Ref.	
	Female	0.0575 [−0.0204, 0.135]	1.06 [0.981, 1.14]	0.1452
Age	12 – 19	0.0970 [−0.0216, 0.216]	1.10 [0.981, 1.24]	0.1070
	20 – 39	Ref.	Ref.	
	40 – 59	0.118 [0.0104, 0.227]	1.13 [1.01, 1.25]	0.0322
	≥60	0.192 [0.0821, 0.302]	1.21 [1.09, 1.35]	0.0009
Race/Hispanic Origin	Non-Hispanic White	Ref.	Ref.	
	Non-Hispanic Black	−0.358 [−0.448, −0.268]	0.699 [0.640, 0.763]	<0.0001
	Hispanic	−0.0755 [−0.173, 0.0217]	0.927 [0.843, 1.02]	0.1257
	Other Race/Multi-Racial	−0.266 [−0.437, −0.0948]	0.766 [0.648, 0.907]	0.0029
Weight Status	Underweight	0.388 [0.0414, 0.734]	1.47 [1.05, 2.07]	0.0288
	Healthy Weight	Ref.	Ref.	
	Overweight/Obese	−0.0308 [−0.125, 0.0637]	0.970 [0.884, 1.06]	0.5168
Impoverished	No	Ref.	Ref.	
	Yes	−0.0648 [−0.171, 0.0417]	0.937 [0.844, 1.04]	0.2283
NHANES Cycle	2005 – 2006	3.09E-03 [−0.101, 0.107]	1.00 [0.906, 1.11]	0.9529
	2011 – 2012	Ref.	Ref.	
	2013 – 2014	−0.0421 [−0.189, 0.105]	0.959 [0.830, 1.11]	0.5683
	2015 – 2016	−0.0705 [−0.203, 0.0623]	0.932 [0.818, 1.06]	0.2926

[1]The dependent variable, biomarker concentration, was natural log-transformed for the regression model and back-transformed for interpretation.

[2]Although urinary creatinine concentration is usually reported in mg/dL, here this concentration is in g/L so that its coefficient simplifies to the more readily interpretable scale.

Table 5A.

Urinary 2MHA (ng/mL) (N=7,697): Sample-weighted multiple linear regression model among NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016

Predictor	Level	Coefficient [95% CI][1]	Exponential Coefficient [95%CI][1]	p-Value
Intercept	Intercept	2.6346 [2.4903, 2.7789]		
Tobacco Smoke Exposure	≤0.015 ng/mL Serum Cotinine	Ref.	Ref.	
	>0.015 – ≤10 ng/mL Serum Cotinine	0.0318 [−0.0683, 0.1319]	1.03 [0.936, 1.14]	0.5276
	1 – 10 CPD	1.0334 [0.9345, 1.1324]	2.81 [2.55, 3.10]	<0.0001
	11 – 20 CPD	1.4797 [1.3636, 1.5959]	4.39 [3.92, 4.92]	<0.0001
	>20 CPD	1.5960 [1.3792, 1.8128]	4.93 [3.99, 6.10]	<0.0001
Creatinine, Urine [g/L][2]	Slope	0.6258 [0.5785, 0.6731]	1.87 [1.78, 1.96]	<0.0001
Sex	Male	Ref.	Ref.	
	Female	−0.0161 [−0.0987, 0.0665]	0.984 [0.908, 1.07]	0.6983
Age	12 – 19	0.0835 [−0.0267, 0.1937]	1.09 [0.976, 1.21]	0.1348
	20 – 39	Ref.	Ref.	
	40 – 59	0.0762 [0.0022, 0.1501]	1.08 [1.00, 1.16]	0.0436
	≥60	0.0063 [−0.0907, 0.1033]	1.01 [0.915, 1.11]	0.8967
Race/Hispanic Origin	Non-Hispanic White	Ref.	Ref.	
	Non-Hispanic Black	−0.2672 [−0.3399, −0.1946]	0.765 [0.713, 0.822]	<0.0001
	Hispanic	−0.0511 [−0.1334, 0.0311]	0.950 [0.877, 1.03]	0.2185
	Other Race/Multi-Racial	−0.1579 [−0.2907, −0.0252]	0.854 [0.750, 0.973]	0.0205
Weight Status	Underweight	0.1744 [−0.1133, 0.4621]	1.19 [0.898, 1.58]	0.2303
	Healthy Weight	Ref.	Ref.	
	Overweight/Obese	−0.0536 [−0.1406, 0.0335]	0.948 [0.870, 1.03]	0.2232
Impoverished	No	Ref.	Ref.	
	Yes	−0.0335 [−0.1118, 0.0448]	0.967 [0.896, 1.04]	0.3960
NHANES Cycle	2005 – 2006	−0.1087 [−0.2471, 0.0297]	0.897 [0.783, 1.03]	0.1215
	2011 – 2012	Ref.	Ref.	
	2013 – 2014	−0.1059 [−0.2627, 0.0509]	0.899 [0.771, 1.05]	0.1818
	2015 – 2016	−0.0174 [−0.1634, 0.1287]	0.983 [0.852, 1.13]	0.8129

[1]The dependent variable, biomarker concentration, was natural log-transformed for the regression model and back-transformed for interpretation.

[2]Urinary creatinine concentration is usually reported in mg/dL, but here this concentration is in g/L so that its coefficient simplifies to the more readily interpretable scale.

Table 5B.

Urinary 34MH (ng/mL) (N=7,697): Sample-weighted multiple linear regression model among NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016

Predictor	Level	Coefficient [95% CI][1]	Exponential Coefficient [95%CI][1]	p-Value
Intercept	Intercept	4.1729 [4.0361, 4.3098]		
Tobacco Smoke Exposure	≤0.015 ng/mL Serum Cotinine	Ref.	Ref.	
	>0.015 – ≤10 ng/mL Serum Cotinine	0.0476 [−0.0389, 0.1342]	1.05 [0.963, 1.14]	0.2753
	1 – 10 CPD	1.1005 [1.0181, 1.1830]	3.01 [2.77, 3.26]	<0.0001
	11 – 20 CPD	1.6061 [1.4963, 1.7160]	4.98 [4.47, 5.55]	<0.0001
	>20 CPD	1.7430 [1.5730, 1.9129]	5.71 [4.84, 6.75]	<0.0001
Creatinine, Urine [g/L][2]	Slope	0.8248 [0.7747, 0.8749]	2.28 [2.17, 2.40]	<0.0001
Sex	Male	Ref.	Ref.	
	Female	0.0667 [−0.0018, 0.1352]	1.07 [0.999, 1.14]	0.0563
Age	12 – 19	0.0860 [−0.0139, 0.1859]	1.09 [0.988, 1.20]	0.0901
	20 – 39	Ref.	Ref.	
	40 – 59	0.1514 [0.0647, 0.2382]	1.16 [1.07, 1.27]	0.0009
	≥60	0.1968 [0.1051, 0.2884]	1.22 [1.11, 1.33]	<0.0001
Race/Hispanic Origin	Non-Hispanic White	Ref.	Ref.	
	Non-Hispanic Black	−0.3342 [−0.4034, −0.2649]	0.716 [0.669, 0.766]	<0.0001
	Hispanic	−0.1046 [−0.1897, −0.0196]	0.901 [0.829, 0.979]	0.0167
	Other Race/Multi-Racial	−0.2595 [−0.4033, −0.1157]	0.771 [0.670, 0.888]	0.0006
Weight Status	Underweight	0.2623 [0.0123, 0.5122]	1.30 [1.02, 1.66]	0.0400
	Healthy Weight	Ref.	Ref.	
	Overweight/Obese	−0.0411 [−0.1239, 0.0418]	0.960 [0.885, 1.04]	0.3259
Impoverished	No	Ref.	Ref.	
	Yes	−0.0170 [−0.0949, 0.0610]	0.983 [0.911, 1.06]	0.6647
NHANES Cycle	2005 – 2006	−0.0217 [−0.1139, 0.0705]	0.978 [0.894, 1.07]	0.6392
	2011 – 2012	Ref.	Ref.	
	2013 – 2014	−0.0580 [−0.1856, 0.0696]	0.944 [0.833, 1.07]	0.3673
	2015 – 2016	−0.0481 [−0.1629, 0.0667]	0.953 [0.852, 1.07]	0.4056

[1]The dependent variable, biomarker concentration, was natural log-transformed for the regression model and back-transformed for interpretation.

[2]Urinary creatinine concentration is usually reported in mg/dL, but here this concentration is in g/L so that its coefficient simplifies to the more readily interpretable scale.

Table 6.

Correlation (variance) matrix of urinary creatinine-ratioed 2MHA and 34MHA versus blood xylene levels (VOX, VXY) among NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016 (N=7,853)

Biomarker	Exclusive Smokers (N=2,152)				Non-Users (N=5,701)			
	2MHA	34MH	VOX	VXY	2MHA	34MH	VOX	VXY
2MHA	1	0.87 (0.01)	0.56 (0.04)	0.61 (0.03)	1	0.77 (0.01)	0.35 (0.03)	0.38 (0.03)
34MH	0.87 (0.01)	1	0.59 (0.04)	0.64 (0.03)	0.77(0.01)	1	0.34 (0.03)	0.37 (0.03)
VOX	0.56 (0.04)	0.59 (0.04)	1	0.93 (0.01)	0.35 (0.03)	0.34(0.03)	1	0.83 (0.01)
VXY	0.61 (0.03)	0.64 (0.03)	0.93 (0.01)	1	0.38 (0.03)	0.37 (0.03)	0.83 (0.01)	1