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Characterization of US population levels of urinary methylcarbamoyl mercapturic acid, a metabolite of *N,N*-dimethylformamide and methyl isocyanate, in the National Health and Nutrition Examination Survey (NHANES) 2005–2006 and 2011–2016

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Abstract

Methylcarbamoyl mercapturic acid (MCAMA, N-acetyl-S-(N-methylcarbamoyl)-L-cysteine) is a urinary metabolite of *N,N*-dimethylformamide and methyl isocyanate, which are volatile organic compounds that are harmful to humans. *N,N*-dimethylformamide exposure causes liver damage, and methyl isocyanate inhalation damages the lining of the respiratory tract, which can increase risk of chronic obstructive pulmonary disease and asthma. This study characterizes urinary MCAMA levels in the US population and explores associations of MCAMA concentrations with select demographic and environmental factors. We used liquid chromatography tandem mass spectrometry to measure MCAMA in urine collected from study participants ≥ 12 years old (N = 8272) as part of the National Health and Nutrition Examination Survey 2005–2006 and 2011–2016. We produced multiple regression models with MCAMA concentrations as the dependent variable and sex, age, fasting time, race/ethnicity, diet, and cigarette smoking as independent variables. Cigarette smokers and nonsmokers had median urinary MCAMA concentrations of 517

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Author's contributions BMK wrote the final manuscript, and PB and DMC wrote the first draft of this paper. LZ and WZ performed statistical analysis of NHANES data using SAS, and generated figures with the data. VRDJ and BCB administered this project and supervised data collection. All authors edited and revised the manuscript.

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Competing interests The authors declare that they have no competing interests.

Ethical approval NHANES is conducted by the National Center for Health Statistics, U.S. Centers for Disease Control and Prevention (CDC). All protocols are approved by the NCHS Research Ethics Review Board ("NCHS Research Ethics Review Board (ERB) Approval," 2017).

Consent to participate All protocols include appropriate informed consent that is documented using protocols approved by the NCHS Research Ethics Review Board ("NCHS Research Ethics Review Board (ERB) Approval," 2017).

Consent to publish All protocols include appropriate informed consent that is documented using protocols approved by the NCHS Research Ethics Review Board ("NCHS Research Ethics Review Board (ERB) Approval," 2017).

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μg/g creatinine and 127 μg/g creatinine, respectively. Sample-weighted multiple regression analysis showed that MCAMA was positively associated with serum cotinine ($p < 0.0001$). Compared to non-exposed participants (serum cotinine ≤ 0.015 ng/mL), presumptive exposure to second-hand tobacco smoke (serum cotinine > 0.015–≤ 10 ng/mL and 0 cigarettes smoked per day) was associated with 20% higher MCAMA ($p < 0.0001$). Additionally, smoking 1–10 cigarettes per day was associated with 261% higher MCAMA ($p < 0.0001$), smoking 11–20 cigarettes per day was associated with 357% higher MCAMA ($p < 0.0001$), and smoking > 20 cigarettes per day was associated with 416% higher MCAMA ($p < 0.0001$). These findings underscore the strong association of tobacco smoke exposure with urinary MCAMA biomarker levels.

Keywords

N,N-Dimethylformamide; Methyl isocyanate; *N*-acetyl-*S*-(*N*-methylcarbamoyl)-L-cysteine; Methylcarbamoyl mercapturic acid; Tobacco smoke exposure; Volatile organic compounds

Introduction

Methylcarbamoyl mercapturic acid (MCAMA, *N*-acetyl-*S*-(*N*-methylcarbamoyl)-L-cysteine) is a nonspecific common urinary metabolite of methyl isocyanate (MIC) and *N,N*-dimethylformamide (DMF), which are volatile organic compounds that are harmful to humans. MIC is highly reactive and acutely toxic via inhalation (Singh and Ghosh 1987; Varma and Mulay 1993), and can cause pulmonary disease by damaging the cell lining of the respiratory tract resulting in fibrosis, degeneration, and obstruction of the respiratory airways (Mehta et al. 1990; Varma and Mulay 1993). Acute human MIC exposure occurred in 1984 due to a release of MIC from pesticide plant in Bhopal, India, which caused an estimated 15,000–20,000 premature deaths over the next two decades (Lucchini et al. 2017), and 200,000 cases of acute or chronic disease (Mehta et al. 1990) such as pulmonary fibrosis, bronchial asthma, chronic obstructive pulmonary disease (COPD), and emphysema (Mishra et al. 2009). Despite the dangers of isocyanates, they are still used in a variety of industrial applications, making them one of the most common causes of occupational asthma (Tan and Bernstein 2014). Additionally, MIC is believed to be present in tobacco smoke (Philippe and Honeycutt 1964), but MIC exposure from environmental sources such as tobacco smoke has yet to be fully characterized.

Similarly, DMF is present in trace amounts in tobacco leaves (Peng et al. 2004), but occupational exposure to DMF from other sources has been characterized more extensively than tobacco smoke. DMF has widespread industrial applications, and the USA produced or imported approximately 25,000 tons of DMF in 2000 (Li and Zeng 2019). Following exposure, DMF can be absorbed through the skin and/or lungs (Miyauchi et al. 2001; Mraz and Nohova 1992) and cause liver injury (He et al. 2010, 2015; Li and Zeng 2019; Luo et al. 2005; Qi et al. 2017; Wu et al. 2017), which may be due to metabolism of DMF to MIC. Biotransformation of DMF to MIC is thought to be hepatic (Gescher 1993; Hyland et al. 1992; Käfferlein and Angerer 2001); however, human metabolism of DMF to MIC has yet to be fully characterized, and other metabolic routes may exist. Once MIC is directly absorbed

or presumably made from DMF, it can form a glutathione conjugate which is further metabolized to MCAMA (Mráz et al. 2004; Slatter et al. 1991). While MCAMA concentrations immediately following occupational DMF exposure can vary with respect to environmental DMF (He et al. 2010; Kim et al. 2004; Miyauchi et al. 2014; Seitz et al. 2018), urinary MCAMA is correlated to repeated DMF exposure (Imbriani et al. 2002; Käfferlein et al. 2000; Seitz et al. 2018), which may be due to MCAMA's half-life of 16-23 hours (Casal Lareo and Perbellini 1995; Käfferlein et al. 2000; Mráz and Nohová 1992; Sakai et al. 1995), in comparison to DMF which has a half-life of only 5.1 h (Käfferlein et al. 2000). Thus, MCAMA may be advantageous for biomonitoring studies because it may detect human exposure to MIC or DMF over a larger timespan compared to their native compounds.

Population-based assessments of urinary MCAMA concentrations have shown that MCAMA is associated with race, demographics, and tobacco smoking. For example, characterization of MCAMA levels using the National Health and Nutrition Examination Survey (NHANES) has demonstrated that MCAMA is elevated among non-Hispanic whites compared to other racial groups, among females compared to males (Jain 2015), and among smokers compared to non-users (Jain 2015; Wei et al. 2016). Additionally, MCAMA concentrations are correlated with urinary cotinine, a tobacco-specific biomarker (Schettgen et al. 2008). However, despite these findings, a comprehensive multiple regression analysis that considers demographics, diet, tobacco smoke exposure, and body mass index (BMI) with respect to MCAMA levels in the US population using multiple NHANES cycles has yet to be completed.

In this report, we used multiple regression models to determine the association between urinary MCAMA concentrations and age, sex, race, tobacco smoke exposure, diet, and BMI in the US population. We measured MCAMA concentrations in urine samples provided by participants in the 2005–2006, 2011–2012, 2013–2014, and 2015–2016 cycles of NHANES (National Center for Health Statistics 2020), and found statistically significant ($p < 0.05$) associations of MCAMA with respect to age, demographics, diet, BMI, and tobacco smoke, controlling for other variables.

Materials and methods

Study design

NHANES is a population-based survey designed to assess health and nutritional status through a cross-sectional observation of a complex, multistage probability sample representative of the civilian, non-institutionalized US population. The survey collects questionnaire data, physical examination data, and biological samples. NHANES is conducted by the National Center for Health Statistics, US Centers for Disease Control and Prevention (CDC). Use of NHANES data constitutes secondary data analysis and therefore exempts this protocol from CDC IRB approval.

Measurement of urinary MCAMA

We stored urine samples at − 70 °C. Urine specimens from NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016 were analyzed in 2014, 2013, 2018, and 2018, respectively (National Center for Health Statistics 2020). Prior to analysis, we thawed samples on a rack thawing station (BioMicroLab, Concord, CA) at room temperature and mixed using a rugged rotator (Glas-Col, Terre Haute, IN) for 15 min. We then prepared and analyzed the samples by high-performance liquid chromatography tandem mass spectrometry (LC-MS/MS), and quantified MCAMA using a stable isotope internal standard and standard curve as previously described (Alwis et al. 2012; Bagchi et al. 2018; Biren et al. 2020; Capella et al. 2019). We monitored mass-to-charge (m/z) transitions using scheduled multiple reaction monitoring at 219→162 for MCAMA and 223→166 for the internal standard $^{13}C_3$-^{15}N-MCAMA (Alwis et al. 2012). We made standard and internal standard solutions from neat MCAMA and $^{13}C_3$-^{15}N-MCAMA (Toronto Research Chemicals, North York, ON, Canada, cat. nos. A186625 and A186622, respectively) with water by o2si smart solutions® (Charleston, SC). We stored standards and internal standards in glass vials with screwcaps at − 70 °C. The LOD of MCAMA was 6.26 μg/L (Alwis et al. 2012).

Reported analytical results met the accuracy and precision specifications of the quality control/quality assurance program of the CDC National Center for Environmental Health, Division of Laboratory Sciences (Caudill et al. 2008). We imputed measurements below the limit-of-detection (LOD) by dividing the LOD by the square root of two (Hornung et al. 1990).

Statistical analysis

We evaluated statistical reliability to ensure all proportions follow the NCHS Data Presentation Standard. Our analysis considered the complex sampling of NHANES (i.e., we applied survey sample weights and used Taylor series linearization for variance estimation which respected strata and primary sampling units). We focused on study participants that were exclusive users of cigarette products (termed “exclusive cigarette smokers” in this report) and limited the source of tobacco smoke exposure to cigarette smoke. We excluded poly-users and smokers of cigars, cigarillos, hookahs, and pipes to standardize the quantity of tobacco smoke exposure among study participants. We also excluded non-combustible tobacco users to reduce the risk of biasing our estimations of the association between tobacco smoke exposure and MCAMA, as users of non-combustible tobacco products were expected to have elevated levels of cotinine but little change in MCAMA concentrations.

We summarized descriptive statistics and performed multiple regression analysis using two separate statistical models as previously described (Biren et al. 2020) using the SURVEYREG and SURVEYMEANS subroutines of SAS 9.4 (SAS Institutes, Cary, NC) with MCAMA as the dependent variable. One model was a sample-weighted regression model in which the samples were stratified by tobacco user group (exclusive cigarette smokers and nonsmokers, referred to as the “cotinine regression model”), and the other was an unstratified, weighted regression model with the self-reported average number of cigarettes smoked per day (CPD) over the 5 days preceding the NHANES physical exam

(referred to as the “CPD regression model”). We categorized age into the following ranges: 12–19, 20–39, 40–59, and ≥ 60 years. We included food intake at 24 h, and considered food intake as a continuous covariate; therefore, the association between food intake and MCAMA varies as the amount of food varies. In the cotinine regression model, exclusive cigarette smokers indicated “yes” to NHANES summary variable SMDANY (tobacco use within 5 days prior to NHANES physical examination based on responses from NHANES questions SMQ681, SMQ851, or SMQ863), “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 dissolvables), according to NHANES questionnaire data on recent tobacco use (NHANES dataset, SMQRTU), and had serum cotinine > 10 ng/mL. We identified participants as nonsmokers if they answered “no” to SMDANY and had serum cotinine ≤ 10 ng/mL. The serum cotinine threshold of > 10 ng/mL is consistent with active use of combusted cigarette products (Pirkle et al. 1996), and we combined this threshold with the self-report measure to create exclusive cigarette smokers and nonsmoker categories. We fit the cotinine regression model using the independent variables (e.g., cotinine, age, sex, race) for both exclusive cigarette smokers and nonsmokers. We retrieved a total of 10,961 samples from NHANES cycles 2005–2006, 2011–2012, 2013–2014, and 2015–2016, and excluded participants without sample weights ($N = 238$), participants with missing values for biomarker concentration and regression variables ($N = 1658$), and ineligible participants who did not belong to either the exclusive cigarette smoker or nonsmoker group ($N = 793$). After attrition, the final sample size for the statistical analysis was 8272 participants.

We used the CPD regression model to determine the association of urinary MCAMA concentrations with the frequency of cigarette smoking. In addition, we used serum cotinine to categorize non-smoking (0 CPD) participants as exposed to second-hand smoke. The CPD regression model was a sample-weighted regression model that used the variables common to our cotinine regression model. We classified cigarette smoke exposure as non-exposed to tobacco smoke (≤ 0.015 ng/mL serum cotinine, 0 CPD), presumptively exposed to second-hand tobacco smoke (> 0.015–≤ 10 ng/mL serum cotinine, 0 CPD), 1–10 CPD, 11–20 CPD, and > 20. The reference category was non-exposed participants. The CPD regression model comprised the same sample size as the cotinine regression model, but we excluded participants who could not be assigned to a CPD category, leaving 8197 participants.

We calculated the percent change in MCAMA associated with an independent categorical variable as previously described by using Eq. (1):

$$\%\,(\Delta\mathrm{MCAMA}) = (\text{exponentiated coefficient} - 1) \times 100 \tag{1}$$

We also calculated the % change in MCAMA associated with an increase of an independent continuous variable from zero to a percentile (median) by exponentiating the product of the estimated percentile value and coefficient, and treating the estimated percentile value as fixed, known values, not as estimates with quantified variability. This calculation can be expressed as Eq. (2):

$$\%\,(\Delta\mathrm{MCAMA}) = (e^{\text{percentile value} \times \text{coefficient}} - 1) \times 100 \quad (2)$$

Finally, we performed pairwise comparisons of least-square means using Bonferroni adjustment for subgroups of age and race/ethnicity separately in CPD regression model.

Results

Urinary MCAMA concentrations were above the limit of detection in 98.4, 99.9, 99.8, and 99.8% of all urine samples analyzed in the underlying target population from NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016 cycles, respectively. Table 1 shows the distributions of participants by age, sex, race/ethnic group, BMI, and NHANES cycle for 8272 participants. Table 2 shows the sample-weighted summary statistics for urinary MCAMA concentrations in this study. The median MCAMA concentrations in exclusive cigarette smokers and non-users were 517 μg/g and 127 μg/g creatinine, respectively.

We also determined that MCAMA was associated with cigarette smoking and second-hand smoke exposure (serum cotinine > 0.015 to < 10 ng/mL) compared to non-exposed participants (serum cotinine ≤ 0.015 ng/mL) using a CPD regression model, which controls for urinary creatinine, age, sex, race/ethnic group, BMI, NHANES cycle, and diet (see the “Statistical analysis” section). Figure 1 shows the sample-weighted least-square means for each tobacco smoke exposure group, and Table 3 shows the exponentiated coefficient for each group in the CPD model, which we used to calculate the percent change in MCAMA associated with each variable, controlling for other variables in the model. As shown in Table 3, participants exposed to second-hand smoke had 21% higher MCAMA ($p < 0.0001$) compared to non-exposed participants. Furthermore, compared to non-exposed participants, smoking 1–10 CPD was associated with a 261% higher MCAMA ($p < 0.0001$), smoking 11–20 CPD was associated with a 357% higher MCAMA ($p < 0.0001$), and smoking > 20 CPD was associated with a 416% higher MCAMA ($p < 0.0001$). We also performed additional multiple regression analyses and calculated the percent change associated between each variable and MCAMA among exclusive cigarette smokers (Table 4) and nonsmokers (Table 5) using a cotinine regression model, which controls for the same variables as the CPD model, but adjusts for serum cotinine instead of CPD. We observed positive associations between MCAMA and serum cotinine among exclusive cigarette smokers (0.2% higher MCAMA per ng/mL cotinine, $p < 0.0001$) and nonsmokers (4% higher MCAMA per ng/mL cotinine, $p = 0.0002$).

We assessed the association between diet and MCAMA by modeling summed dietary consumption variables from the 24-h dietary recall questionnaire and calculating the association between MCAMA and the median consumption of each food group (Table S3) using Eq. (2). Coffee was the only dietary variable predictive of higher urinary MCAMA across all models, ranging from 1 to 8% higher at median consumption (~ 4 oz). Median fruit consumption was associated with lower MCAMA, but this association was not consistent across all models.

We also examined the relation between additional categorical variables (sex, race, age, BMI, and NHANES cycle) and urinary MCAMA in the three regression models, and the magnitude of these associations ranged from 41% lower to 31% higher MCAMA. Females had higher urinary MCAMA compared to males across all models. Whites had higher urinary MCAMA compared with most other race ethnicities across all models, and most of the least-square means of MCAMA concentrations across racial/ethnic groups in the CPD model (Table S1) were statistically significant when compared with one another (Table S2). Urinary MCAMA was also higher in higher age categories across all models. Furthermore, compared to the 2011–2020, urinary MCAMA was higher in the 2011–2012 NHANES cycle compared with most other cycles across all models.

Discussion

This report characterizes urinary MCAMA concentrations in a representative sample of the US population across four NHANES cycles. We detected MCAMA in more than 98% of samples analyzed, which is comparable to previous studies (De Jesús et al. 2020; Käfferlein and Angerer 1999; Wei et al. 2016). We found that higher urinary MCAMA was strongly associated with active smoking (CPD and serum cotinine), and, to a lesser degree, second-hand smoke exposure (serum cotinine). These findings underscore the importance of tobacco smoke as an exposure source that is associated with higher urinary MCAMA in the US population, and builds upon other analyses (Jain 2015; Lorkiewicz et al. 2018; Pluym et al. 2015; Schettgen et al. 2008; Wei et al. 2016). While previous studies found an association between MCAMA and tobacco smoking, our analyses better explore that relationship, including identifying an effect from secondhand smoke exposure and documenting the relation across four NHANES cycles.

The creatinine-adjusted urinary MCAMA concentrations in this study were approximately fourfold higher among exclusive cigarette smokers compared to non-users (517 μg/g and 127 μg/g creatinine, respectively), which is comparable to a recent analysis of data from the Population Assessment of Tobacco and Health study by our laboratory (De Jesús et al. 2020) and studies by other laboratories (Pluym et al. 2015; Wei et al. 2016). Two additional analyses have shown more modest differences in MCAMA concentrations between smokers and nonsmokers; however, these analyses may underestimate the association between cigarette smoke exposure and urinary MCAMA. Specifically, an analysis of MCAMA concentrations among NHANES 2011–2012 participants identified smokers using serum cotinine concentrations (≥ 10 ng/mL) (Jain 2015). In contrast, we categorized smokers using serum cotinine, smoking status, and cigarettes smoked per day, which allowed us to separate participants that were nonsmokers exposed to second-hand smoke and to exclude users of non-combustible tobacco products. In another study, participants did not smoke in the 48 h prior to specimen collection (Lorkiewicz et al. 2018), which may have decreased MCAMA concentrations among smokers.

Unlike previously published MCAMA studies, we also evaluated diet as a potential exposure source that would contribute to urinary MCAMA concentrations; however, the magnitudes of these associations between the median consumption of each dietary variable and MCAMA were relatively minor, and ranged from 1 to 8%. Coffee consumption was the only

dietary variable associated with higher urinary MCAMA across all models, perhaps because roasted coffee contains VOC that can be metabolized to MCAMA. Fruit consumption was a significant predictor of lower urinary MCAMA, but only in two of the three models. The association between MCAMA and fruit consumption may be due to fruit-induced metabolic changes such as altered expression cytochrome P450 enzyme 2E1 (Cyp2E1), the primary enzyme responsible for MCAMA formation from DMF (Hyland et al. 1992), and thus could impact the urinary concentrations MCAMA following DMF exposure.

We also observed associations between MCAMA and demographics in all statistical models, and these findings were consistent with previous studies (De Jesús et al. 2020; Jain 2015). Specifically, White participants had significantly higher urinary MCAMA compared to most other races/ethnicities, females had higher urinary MCAMA compared with males, and older participants had higher MCAMA concentrations compared to younger participants. These differences may be due to unassessed exposure sources, but may also be due to metabolic differences between demographics, such as Cyp2E1 activity being influenced by genetic polymorphisms (Nomiyama et al. 2001) and sex steroid hormones (Konstandi et al. 2013; Penaloza et al. 2014). However, no conclusive metabolic studies have characterized DMF/MIC metabolism with respect to age, sex, racial background, diet, tobacco smoke exposure, or Cyp2E1 activity. Additional variation between racial groups may occur due to a potential unknown endogenous source of MCAMA, which may explain the relatively high MCAMA detection rate among nonsmokers (Käfferlein and Angerer 1999). Finally, we used urinary creatinine concentrations to adjust for hydration; however, urinary creatinine excretion rate among males tends to be higher compared to females (James et al. 1988), and thus, the use of creatinine to adjust for variable hydration state may contribute to females appearing to have higher exposure.

We also observed that MCAMA was higher among participants in the 2011–2012 NHANES cycle compared to other NHANES cycles, which is consistent with observations of other VOC metabolites (Bagchi et al. 2018; Capella et al. 2019). However, the associations between MCAMA and NHANES cycle were not consistent across all regression models. Specifically, the association of MCAMA between NHANES 2011–2012 and the other NHANES cycles among nonsmokers was relatively minor (10%), and unlike the other regression models, MCAMA concentrations were not associated with all NHANES cycles. NHANES 2011–2012 cycle was the only NHANES cycle in which the urine specimens were analyzed within a year of specimen collection, and thus, the higher levels in this cycle might indicate instability of MCAMA in urines stored at − 70 °C for multiple years; however, our unpublished stability experiments indicate that MCAMA levels are stable in urine frozen at − 70 °C. Finally, the associations between MCAMA and NHANES cycle are unlikely to be due to analytical drift; our laboratory has an active QA/QC program, which includes internal and external proficiency testing across the time frame of these analyses.

This study has several limitations. Urinary MCAMA is a nonselective exposure biomarker because it is a metabolite of multiple exogenous chemicals, including DMF and MIC. MCAMA was measured in a single spot urine that integrated exposure over a relatively short period of time, and thus, the association between MCAMA and different exposure sources was also blurred by varying time of last exposure. Lastly, we adjusted for variable hydration

through urinary creatinine; however, creatinine excretion rate can also be influenced by other factors such as diet and creatine supplementation. Despite these weaknesses, this report provides the most comprehensive analysis of MCAMA concentrations in the US population to date and will serve as a reference for future biomonitoring studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Alwis KU, Blount BC, Britt AS, Patel D, Ashley DL (2012) Simultaneous analysis of 28 urinary VOC metabolites using ultra high performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry (UPLC-ESI/MSMS). Anal Chim Acta 750:152–160. 10.1016/J.ACA.2012.04.009 [PubMed: 23062436]

Bagchi P, Geldner N, DeCastro BR, De Jesús VR, Park SK, Blount BC (2018) Crotonaldehyde exposure in U.S. tobacco smokers and nonsmokers: NHANES 2005–2006 and 2011–2012. Environ Res 163:1–9. 10.1016/J.ENVRES.2018.01.033 [PubMed: 29407484]

Biren C, Zhang L, Bhandari D, Blount BC, De Jesús VR (2020) Isoprene exposure in the United States based on urinary IPM3: NHANES 2015–2016. Environ Sci Technol 54:2370–2378. 10.1021/acs.est.9b06587 [PubMed: 31961658]

Capella KM, Roland K, Geldner N, Rey deCastro B, De Jesús VR, van Bemmel D, Blount BC (2019) Ethylbenzene and styrene exposure in the United States based on urinary mandelic acid and phenylglyoxylic acid: NHANES 2005–2006 and 2011–2012. Environ Res 171:101–110. 10.1016/J.ENVRES.2019.01.018 [PubMed: 30660916]

Casal Lareo A, Perbellini L (1995) Biological monitoring of workers exposed to N-N-dimethylformamide - II. Dimethylformamide and its metabolites in urine of exposed workers. Int Arch Occup Environ Health 67:47–52. 10.1007/BF00383132 [PubMed: 7622279]

Caudill SP, Schleicher RL, Pirkle JL (2008) Multi-rule quality control for the age-related eye disease study. Stat Med 27:4094–4106. 10.1002/sim.3222 [PubMed: 18344178]

De Jesús VR, Bhandari D, Zhang L, Reese C, Capella K, Tevis D, Zhu W, Del Valle-Pinero AY, Lagaud G, Chang JT, van Bemmel D, Kimmel HL, Sharma E, Goniewicz ML, Hyland A, Blount BC (2020) Urinary biomarkers of exposure to volatile organic compounds from the population assessment of tobacco and health study wave 1 (2013–2014). Int J Environ Res Public Health 17:1–12. 10.3390/ijerph17155408

Gescher A (1993) Metabolism of N,N-dimethylformamide: key to the understanding of its toxicity. Chem Res Toxicol 6:246–251. 10.1021/tx00033a001

He J, Wang P, Zhu JQ, Wu G, Ji JM, Xue Y (2010) Role of urinary biomarkers of N,N-dimethylformamide in the early detection of hepatic injury among occupational exposed workers. Int Arch Occup Environ Health 83:399–406. 10.1007/s00420-010-0520-8 [PubMed: 20151308]

He J, Liu J, Kong Y, Yang W, Zhang Z (2015) Serum activities of liver enzymes in workers exposed to sub-TLV levels of dimethylformamide. Int J Occup Med Environ Health 28:395–398. 10.13075/ijomeh.1896.00086 [PubMed: 26182934]

Hornung RW, Reed LD, Hornung RW, Reed LD (1990) Estimation of average concentration in the presence of nondetectable values. Appl Occup Environ Hyg 5:46–51. 10.1080/1047322X.1990.10389587

Hyland R, Gescher A, Thummel K, Schiller C, Jheeta P, Mynett K, Smith AW, Mráz J (1992) Metabolic oxidation and toxification of n-methylformamide catalyzed by the cytochrome P450 isoenzyme CYP2E1. Mol Pharmacol 41:259–266 [PubMed: 1538706]

Imbriani M, Maestri L, Marraccini P, Saretto G, Alessio A, Negri S, Ghittori S (2002) Urinary determination of N-acetyl-S-(N-methylcarbomyl)cysteine and N-methylformamide in workers exposed to N,N-dimethylformamide. Int Arch Occup Environ Health 75:445–452. 10.1007/s00420-002-0335-3 [PubMed: 12172890]

Jain RB (2015) Distributions of selected urinary metabolites of volatile organic compounds by age, gender, race/ethnicity, and smoking status in a representative sample of U.S. adults. Environ Toxicol Pharmacol 40:471–479. 10.1016/J.ETAP.2015.07.018 [PubMed: 26282484]

James GD, Sealey JE, Alderman M, Ljungman S, Mueller FB, Pecker MS, Laragh JH (1988) A longitudinal study of urinary creatinine and creatinine clearance in normal subjects. Am J Hypertens 1:124–131. 10.1093/ajh/1.2.124 [PubMed: 3401350]

Käfferlein HU, Angerer J (1999) Determination of N-acetyl-S-(N-methylcarbamoyl)cysteine (AMCC) in the general population using gas chromatography-mass spectrometry. J Environ Monit 1:465–469 [PubMed: 11529165]

Käfferlein HU, Angerer J (2001) N-methylcarbamoylated valine of hemoglobin in humans after exposure to N,N-dimethylformamide: evidence for the formation of methyl isocyanate? Chem Res Toxicol 14:833–840. 10.1021/tx000230r [PubMed: 11453729]

Käfferlein HU, Göen T, Müller J, Wrbitzky R, Angerer J (2000) Biological monitoring of workers exposed to N,N-dimethylformamide in the synthetic fibre industry. Int Arch Occup Environ Health 73:113–120. 10.1007/s004200050016 [PubMed: 10741509]

Kim HA, Kim K, Heo Y, Lee SH, Choi HC (2004) Biological monitoring of workers exposed to N,N-dimethylformamide in synthetic leather manufacturing factories in Korea. Int Arch Occup Environ Health 77:108–112. 10.1007/s00420-003-0474-1 [PubMed: 14663587]

Konstandi M, Cheng J, Gonzalez FJ (2013) Sex steroid hormones regulate constitutive expression of Cyp2e1 in female mouse liver. Am J Physiol Endocrinol Metab 304:E1118–E1128. 10.1152/ajpendo.00585.2012 [PubMed: 23548611]

Li M-J, Zeng T (2019) The deleterious effects of N,N-dimethylformamide on liver: a mini-review. Chem Biol Interact 298:129–136. 10.1016/J.CBI.2018.12.011 [PubMed: 30576622]

Lorkiewicz P, Riggs DW, Keith RJ, Conklin DJ, Xie Z, Sutaria S, Lynch B, Srivastava S, Bhatnagar A (2018) Comparison of urinary biomarkers of exposure in humans using electronic cigarettes, combustible cigarettes, and smokeless tobacco. Nicotine Tob Res 21:1–11. 10.1093/ntr/nty089

Lucchini RG, Hashim D, Acquilla S, Basanets A, Bertazzi PA, Bushmanov A, Crane M, Harrison DJ, Holden W, Landrigan PJ, Luft BJ, Mocarelli P, Mazitova N, Melius J, Moline JM, Mori K, Prezant D, Reibman J, Reissman DB, Stazharau A, Takahashi K, Udasin IG, Todd AC (2017) A comparative assessment of major international disasters: the need for exposure assessment, systematic emergency preparedness, and lifetime health care. BMC Public Health 17:1–12. 10.1186/s12889-016-3939-3 [PubMed: 28049454]

Luo JC, Cheng TJ, Kuo HW, Chang MJW (2005) Abnormal liver function associated with occupational exposure to dimethylformamide and glutathione S-transferase polymorphisms. Biomarkers 10:464–474. 10.1080/13547500500333648 [PubMed: 16308270]

Mehta PS, Mehta AS, Mehta SJ, Makhijani AB (1990) Bhopal tragedy's health effects: a review of methyl isocyanate toxicity. JAMA 264:74–75. 10.1007/978-1-4020-9160-5_183

Mishra PK, Samarth RM, Pathak N, Jain SK, Banerjee S, Maudar KK (2009) Bhopal gas tragedy: review of clinical and experimental findings after 25 years. Int J Occup Med Environ Health 22:193–202. 10.2478/v10001-009-0028-1 [PubMed: 19819837]

Miyauchi H, Tanaka S, Nomiyama T, Seki Y, Imamiya S, Kazuyuki O (2001) N,N-Dimethylformamide (DMF) vapor absorption through the skin in workers. J Occup Health 43:92–94. 10.1539/joh.43.92

Miyauchi H, Tsuda Y, Minozoe A, Tanaka S, Arito H, Tsukahara T, Nomiyama T (2014) Occupational exposure to N,N-dimethylformamide in the summer and winter. Ind Health 52:512–520. 10.2486/indhealth.2014-0070 [PubMed: 25224331]

Mraz J, Nohova H (1992) Percutaneous absorption of N,N-dimethylformamide in humans. Int Arch Occup Environ Health 64:79–83. 10.1007/BF00381473 [PubMed: 1399027]

Mráz J, Nohová H (1992) Absorption, metabolism and elimination of N,N-dimethylformamide in humans. Int Arch Occup Environ Health 64:85–92. 10.1007/BF00381474 [PubMed: 1399028]

Mráz J, Šimek P, Chvalová D, Nohová H, Šmigolová P (2004) Studies on the methyl isocyanate adducts with globin. Chem Biol Interact 148:1–10. 10.1016/J.CBI.2003.06.003 [PubMed: 15223351]

National Center for Health Statistics (2020) NHANES questionnaires, datasets, and related documentation [WWW Document]. Natl. Heal. Nutr. Exam. Surv URL https://wwwn.cdc.gov/nchs/nhanes/

NCHS Research Ethics Review Board (ERB) Approval [WWW Document] (2017) Natl. Cent. Heal. Stat. Centers Dis. Control Prev

Nomiyama T, Nakashima H, Sano Y, Chen LL, Tanaka S, Miyauchi H, Yamauchi T, Sakurai H, Omae K (2001) Does the polymorphism of cytochrome P-450 2E1 affect the metabolism of N,N-dimethylformamide? Comparison of the half-lives of urinary N-methylformamide. Arch Toxicol 74:755–759. 10.1007/s002040000197 [PubMed: 11305777]

Penaloza CG, Estevez B, Han DM, Norouzi M, Lockshin RA, Zakeri Z (2014) Sex-dependent regulation of cytochrome P450 family members Cyp1a1, Cyp2e1, and Cyp7b1 by methylation of DNA. FASEB J 28:966–977. 10.1096/fj.13-233320 [PubMed: 24161885]

Peng F, Sheng L, Liu B, Tong H, Liu S (2004) Comparison of different extraction methods: steam distillation, simultaneous distillation and extraction and headspace co-distillation, used for the analysis of the volatile components in aged flue-cured tobacco leaves. J Chromatogr A 1040:1–17. 10.1016/j.chroma.2004.03.057 [PubMed: 15248421]

Philippe RJ, Honeycutt RG (1964) Methyl isocyanate in cigarette smoke and its retention by an adsorption-type filter. Liggett Myers Tob. Co

Pirkle JL, Flegal KM, Bernert JT, Debra J (1996) Exposure of the US population to environmental tobacco smoke: the Third National Health and Nutrition Examination Survey, 1988 to 1991. JAMA 114:1233–1240. 10.1289/ehp.8850

Pluym N, Gilch G, Scherer G, Scherer M (2015) Analysis of 18 urinary mercapturic acids by two high-throughput multiplex-LC-MS/MS methods. Anal Bioanal Chem 407:5463–5476. 10.1007/s00216-015-8719-x [PubMed: 25935678]

Qi C, Gu Y, Sun Q, Gu H, Xu B, Gu Q, Xiao J, Lian Y (2017) Low-dose N,N-Dimethylformamide exposure and liver injuries in a cohort of Chinese leather industry workers. J Occup Environ Med 59:434–439. 10.1097/JOM.0000000000000983 [PubMed: 28368964]

Sakai T, Kageyama H, Araki T, Yosida T, Kuribayashi T, Masuyama Y (1995) Biological monitoring of workers exposed to N,N-dimethylformamide by determination of the urinary metabolites, N-methylformamide and N-acetyl-S-(N-methylcarbamoyl) cysteine. Int Arch Occup Environ Health 67:125–129. 10.1007/BF00572236 [PubMed: 7672856]

Schettgen T, Musiol A, Kraus T (2008) Simultaneous determination of mercapturic acids derived from ethylene oxide (HEMA), propylene oxide (2-HPMA), acrolein (3-HPMA), acrylamide (AAMA) and N,N-dimethylformamide (AMCC) in human urine using liquid chromatography/tandem mass spectrometry. Rapid Commun Mass Spectrom 22:2629–2638. 10.1002/rcm.3659 [PubMed: 18666198]

Seitz M, Kilo S, Eckert E, Müller J, Drexler H, Göen T (2018) Validity of different biomonitoring parameters for the assessment of occupational exposure to N,N-dimethylformamide (DMF). Arch Toxicol 92:2183–2193. 10.1007/s00204-018-2219-7 [PubMed: 29748790]

Singh MP, Ghosh S (1987) Bhopal gas tragedy: model simulation of the dispersion scenario. J Hazard Mater 17:1–22. 10.1016/0304-3894(87)85039-2

Slatter JG, Rashed MS, Pearson PG, Han DH, Baillie TA (1991) Biotransformation of methyl isocyanate in the rat. Evidence for glutathione conjugation as a major pathway of metabolism and

implications for isocyanate-mediated toxicities. Chem Res Toxicol 4:157–161. 10.1021/tx00020a006 [PubMed: 1782345]

Tan J, Bernstein JA (2014) Occupational asthma: an overview. Curr Allergy Asthma Rep 14:1–7. 10.1007/s11882-014-0431-y

Varma DR, Mulay S (1993) The bhopal accident and methyl isocyanate toxicity. J Toxicol Environ Health:513–529. 10.1016/B978-012088523-7/50008-9 [PubMed: 8277516]

Wei B, Alwis KU, Li Z, Wang L, Valentin-Blasini L, Sosnoff CS, Xia Y, Conway KP, Blount BC (2016) Urinary concentrations of PAH and VOC metabolites in marijuana users. Environ Int 88:1–8. 10.1016/J.ENVINT.2015.12.003 [PubMed: 26690539]

Wu Z, Liu Q, Wang C, Xu B, Guan M, Ye M, Jiang H, Zheng M, Zhang M, Zhao W, Jiang X, Leng S, Cheng J (2017) A comparative benchmark dose study for N, N-dimethylformamide induced liver injury in a Chinese occupational cohort. Toxicol Sci 158:140–150. 10.1093/toxsci/kfx076 [PubMed: 28505332]

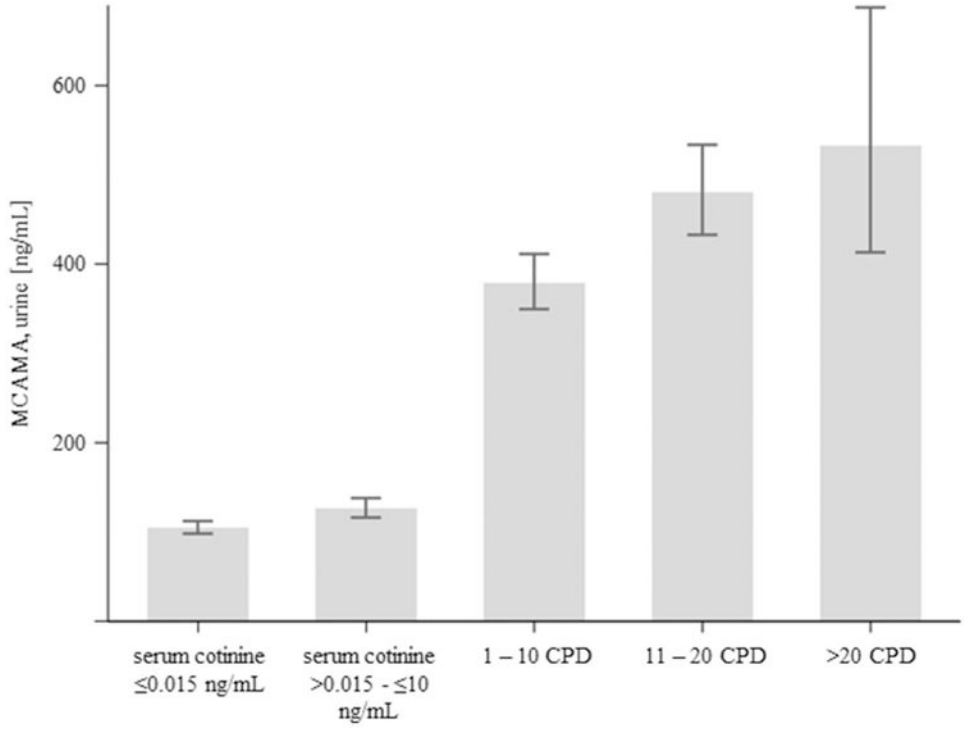

Fig. 1.

Least-square means of urinary MCAMA concentrations for different cigarettes per day (CPD) categories, adjusted for all other regression variables (e.g., age, sex, and race/ethnicity)

Table 1

Distributions of study participants by age, sex, race/ethnic group, BMI, and NHANES cycle for NHANES 2005—2006, 2011— 2012, 2013— 2014, and 2015— 2016 (N = 8,272)[1]

Variable	*N*[2], exclusive cigarette smokers	Percent (SE)[3], exclusive cigarette smokers	*N*[2], nonsmokers	Percent (SE)[3], nonsmokers
Sex				
Male	1336	52.51 (1.28)	2686	45.41 (0.80)
Female	1027	47.49 (1.28)	3223	54.59 (0.80)
Age				
12–19	84	2.43 (0.33)	891	5.29 (0.39)
20–39	868	41.08 (1.59)	1775	32.92 (1.07)
40–59	910	40.57 (1.64)	1559	34.65 (0.99)
≥ 60	501	15.92 (1.00)	1684	27.15 (1.10)
Race/ethnicity				
Non-Hispanic White	1130	69.51 (2.37)	2250	67.10 (1.89)
Non-Hispanic Black	640	13.95 (1.46)	1251	9.66 (0.97)
Mexican American	220	6.16 (0.87)	1224	9.56 (1.05)
Other Hisp. or other/multi-race	373	10.38 (1.02)	1184	13.68 (0.84)
BMI				
Healthy weight	794	35.01 (1.40)	1872	30.05 (1.04)
Overweight/obesity	1500	62.14 (1.36)	3958	68.89 (1.08)
Underweight	69	2.85 (0.46)	79	1.06 (0.15)
NHANES cycle				
2005–2006	469	31.02 (2.26)	2356	25.49 (1.62)
2011–2012	653	25.03 (1.85)	1116	24.28 (1.54)
2013–2014	656	21.55 (1.43)	1223	24.79 (1.35)
2015–2016	585	22.40 (1.39)	1214	25.44 (1.66)

[1] Same data as in stratified cotinine regression models

[2] Not sample-weighted

[3] Sample-weighted

Table 2

Median sample-weighted urinary MCAMA concentrations in μg/g creatinine (25th percentile, 75th percentile) from NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016 (N = 8272)[1]

Variable	Exclusive cigarette smokers	Nonsmokers
All	517 (298, 803)	127 (72.7, 204)
Sex		
Male	438 (253, 650)	115 (66.3, 179)
Female	614 (380, 999)	141 (77.9, 231)
Age		
12–19	270 (172, 370)	64.9 (47.5, 98.7)
20–39	380 (219, 563)	101 (60.8, 160)
40–59	634 (427, 983)	142 (85.4, 229)
≥ 60	654 (455, 1.01E+03)	162 (96.3, 246)
Race/ethnicity		
Non-Hispanic White	581 (389, 907)	146 (83.5, 226)
Non-Hispanic Black	288 (199, 455)	73.5 (48.4, 113)
Mexican American	241 (171, 459)	107 (65.5, 160)
Other Hisp. or other/multi-race	480 (272, 754)	110 (65.1, 179)
BMI		
Healthy weight	533 (316, 875)	123 (67.6, 204)
Overweight/obesity	491 (290, 766)	129 (75.1, 203)
Underweight	586 (401, 817)	88.2 (62.4, 296)
NHANES cycle		
2005–2006	469 (266, 777)	105 (60.4, 179)
2011–2012	604 (396, 889)	144 (85.7, 234)
2013–2014	514 (293, 821)	130 (72.6, 222)
2015–2016	472 (279, 709)	128 (77.7, 196)

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

Table 3

Coefficients (95% confidence interval, CI) and exponentiated coefficients (95% CI) from multivariate analysis of urinary MCAMA (ng/mL) from NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016 using the CPD regression model (*N* = 8197)

Variable	Coefficient (95% CI)[1]	Exponentiated coefficient (95% CI)[2]	p value	% (Δ MCAMA)[3]
Tobacco smoke exposure				
≤ 0.015 ng/mL cotinine, serum	Reference	Reference		Reference
> 0.015–≤ 10 ng/mL cotinine, serum	0.1940 (0.1400, 0.2479)	1.21 (1.15, 1.28)	< 0.0001	21% higher
1–10 CPD	1.2823 (1.2182, 1.3464)	3.61 (3.38, 3.84)	< 0.0001	261% higher
11–20 CPD	1.5204 (1.4226, 1.6182)	4.57 (4.15, 5.04)	< 0.0001	357% higher
> 20 CPD	1.6400 (1.3782, 1.9018)	5.16 (3.97, 6.70)	< 0.0001	416% higher
Creatinine, urine (g/L)[2]	0.8062 (0.7592, 0.8531)	2.24 (2.14, 2.35)	< 0.0001	124% higher per g/L creatinine
Fasting time (HH.00)	0.0074 (0.0033, 0.0115)	1.01 (1.00, 1.01)	0.0006	1% higher per hour
Sex				
Male	Reference	Reference		Reference
Female	0.1655 (0.1143, 0.2168)	1.18 (1.12, 1.24)	< 0.0001	18% higher
Age				
12–19	− 0.3048 (− 0.3968, − 0.2128)	0.737 (0.672, 0.808)	< 0.0001	26% lower
20–39	Reference	Reference		Reference
40–59	0.2289 (0.1728, 0.2850)	1.26 (1.19, 1.33)	< 0.0001	26% higher
≥ 60	0.2834 (0.2180, 0.3488)	1.33 (1.24, 1.42)	< 0.0001	33% higher
Race/ethnicity				
Non-Hispanic White	Reference	Reference		Reference
Non-Hispanic Black	− 0.3705 (− 0.4333, − 0.3077)	0.690 (0.648, 0.735)	<0.0001	31% lower
Mexican American	− 0.0887 (− 0.1534, − 0.0241)	0.915 (0.858, 0.976)	0.0079	8.5% lower
Other Hisp. or other/multi-race	− 0.1408 (− 0.2132, − 0.0684)	0.869 (0.808, 0.934)	0.0002	13% lower
BMI				
Underweight	0.2317 (0.0280, 0.4353)	1.26 (1.03, 1.55)	0.0264	26% higher
Healthy weight	Reference	Reference		Reference
Overweight/obesity	− 0.0069 (− 0.0651, 0.0513)	0.993 (0.937, 1.05)	0.8132	N.S.
NHANES cycle				

Variable	Coefficient (95% CI)[1]	Exponentiated coefficient (95% CI)[2]	p value	% (Δ MCAMA)[3]
2005–2006	− 0.2517 (− 0.3347, − 0.1687)	0.777 (0.716, 0.845)	< 0.0001	22% lower
2011–2012	Reference	Reference		Reference
2013–2014	− 0.2166 (− 0.3275, − 0.1057)	0.805 (0.721, 0.900)	0.0002	20% lower
2015–2016	− 0.2201 (− 0.2944, − 0.1458)	0.802 (0.745, 0.864)	< 0.0001	20% lower
Food consumed (kg)				
Milk products	− 0.0418 (− 0.1299, 0.0464)	0.959 (0.878, 1.05)	0.347	N.S.
Meat, poultry	− 0.0658 (− 0.1791, 0.0476)	0.936 (0.836, 1.05)	0.2507	N.S.
Eggs	0.0888 (− 0.2796, 0.4572)	1.09 (0.756, 1.58)	0.6316	N.S.
Legumes, nuts, seeds	− 0.0030 (− 0.2198, 0.2138)	0.997 (0.803, 1.24)	0.9778	N.S.
Grain products	− 0.0386 (− 0.1299, 0.0527)	0.962 (0.878, 1.05)	0.4013	N.S.
Fruits	− 0.2833 (− 0.3812, − 0.1854)	0.753 (0.683, 0.831)	< 0.0001	5% lower
Vegetables	− 0.0944 (− 0.2313, 0.0425)	0.910 (0.794, 1.04)	0.1731	N.S.
Fats, oils, salad dressings	0.4118 (− 0.7916, 1.6153)	1.51 (0.453, 5.03)	0.4965	N.S.
Sugars, sweets, beverages	− 0.0106 (− 0.0282, 0.0070)	0.989 (0.972, 1.01)	0.234	N.S.
Smoked meat, poultry, fish	0.5507 (− 0.8273, 1.9288)	1.73 (0.437, 6.88)	0.4274	N.S.
Cruciferous vegetables	− 0.6681 (− 1.2979, − 0.0383)	0.513 (0.273, 0.962)	0.038	0%
Coffee	0.4736 (0.4076, 0.5396)	1.61 (1.50, 1.72)	< 0.0001	5.8% higher
Intercept	3.6928 (3.5696, 3.8160)	40.2 (35.5, 45.4)	N/A	N/A

N.S. not significant

[1] MCAMA concentration was natural log-transformed for the regression model

[2] Urinary creatinine concentration reported in g/L so that its coefficient simplifies to a more interpretable scale

[3] % (Δ MCAMA) for each food group was calculated from median consumption

Table 4

Coefficients (95% confidence interval, CI) and exponentiated coefficients (95% CI) from multivariate analysis of urinary MCAMA (ng/mL) among exclusive cigarette smokers from NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016 using the cotinine regression model (see the "Materials and methods" section, $N = 2363$)

Variable	Coefficient (95%CI)[1]	Exponentiated coefficient (95% CI)[2]	*p* value	% (Δ MCAMA)[3]
Creatinine, urine (g/L)[2]	0.7482 (0.6968, 0.7996)	2.11 (2.01, 2.22)	< 0.0001	111% higher per g/L creatinine
Fasting time (HH.00)	0.0023 (− 0.0038, 0.0084)	1.00 (0.996, 1.01)	0.4565	N.S.
Cotinine, serum (ng/mL)	0.0024 (0.0021, 0.0028)	1.002 (1.00, 1.00)	< 0.0001	0.2% higher per ng/mL cotinine
Sex				
Male	Reference	Reference		Reference
Female	0.2668 (0.1935, 0.3402)	1.31 (1.21, 1.41)	< 0.0001	31% higher
Age				
12–19	− 0.2076 (− 0.4175, 0.0023)	0.813 (0.659, 1.00)	0.0525	N.S.
20–39	Reference	Reference		Reference
40–59	0.3225 (0.2531, 0.3918)	1.38 (1.29, 1.48)	< 0.0001	38% higher
≥ 60	0.3301 (0.2368, 0.4234)	1.39 (1.27, 1.53)	< 0.0001	39% higher
Race/ethnicity				
Non-Hispanic White	Reference	Reference		Reference
Non-Hispanic Black	− 0.5246 (− 0.5967, − 0.4526)	0.592 (0.551, 0.636)	< 0.0001	41% lower
Mexican American	− 0.2529 (− 0.3724, − 0.1334)	0.777 (0.689, 0.875)	< 0.0001	22% lower
Other Hisp. or other/multi-race	− 0.0772 (− 0.1777, 0.0232)	0.926 (0.837, 1.02)	0.1295	N.S.
BMI				
Underweight	0.0687 (− 0.0890, 0.2263)	1.07 (0.915, 1.25)	0.3872	N.S.
Healthy weight	Reference	Reference		Reference
Overweight/obesity	0.0502 (− 0.0250, 0.1254)	1.05 (0.975, 1.13)	0.187	N.S.
NHANES cycle				
2005–2006	− 0.1017 (− 0.1965, − 0.0070)	0.903 (0.822, 0.993)	0.0358	10% lower
2011–2012	Reference	Reference		Reference
2013–2014	− 0.1098 (− 0.2619, 0.0423)	0.896 (0.770, 1.04)	0.154	N.S.
2015–2016	− 0.1046 (− 0.2015, − 0.0077)	0.901 (0.818, 0.992)	0.0349	10% lower

Variable	Coefficient (95%CI)[1]	Exponentiated coefficient (95% CI)[2]	*p* value	% (Δ MCAMA)[3]
Food consumed (kg)				
Milk products	− 0.0369 (− 0.1450, 0.0713)	0.964 (0.865, 1.07)	0.4983	N.S.
Meat, poultry, fish	− 0.0257 (− 0.1936, 0.1422)	0.975 (0.824, 1.15)	0.7607	N.S.
Eggs	0.2317 (− 0.3755, 0.8388)	1.26 (0.687, 2.31)	0.4485	N.S.
Legumes, nuts, seeds	− 0.0362 (− 0.4159, 0.3435)	0.964 (0.660, 1.41)	0.8495	N.S.
Grain products	0.0343 (− 0.0776, 0.1462)	1.03 (0.925, 1.16)	0.5422	N.S.
Fruits	− 0.1146 (− 0.2629, 0.0336)	0.892 (0.769, 1.03)	0.1272	N.S.
Vegetables	0.0052 (− 0.1732, 0.1837)	1.01 (0.841, 1.20)	0.9536	N.S.
Fats, oils, salad dressings	− 0.0768 (− 1.7153, 1.5617)	0.926 (0.180, 4.77)	0.9256	N.S.
Sugars, sweets, beverages	− 0.0137 (− 0.0360, 0.0087)	0.986 (0.965, 1.01)	0.2259	N.S.
Smoked meat, poultry, fish	1.5529 (− 5.1958, 8.3016)	4.72 (5.54E−03, 4.03E+03)	0.6472	N.S.
Cruciferous vegetables	− 0.4866 (− 1.1906, 0.2175)	0.615 (0.304, 1.24)	0.1721	N.S.
Coffee	0.0956 (0.0573, 0.1340)	1.10 (1.06, 1.14)	< 0.0001	1.1% higher
Intercept	4.4659 (4.2367, 4.6951)	87.0 (69.2, 109)	N/A	N/A

N.S. not significant

[1] MCAMA concentration was natural log-transformed for the regression model

[2] Urinary creatinine concentration reported in g/L so that its coefficient simplifies to a more interpretable scale

[3] % (Δ MCAMA) for each food group was calculated from median consumption

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Table 5

Coefficients (95% confidence interval, CI) and exponentiated coefficients (95% CI) from multivariate analysis of urinary MCAMA (ng/mL) among nonsmokers from NHANES 2005–2006, 2011–2012, 2013–2014, and 2015–2016 using the cotinine regression model (see the "Materials and methods" section, $N = 5909$)

Level	Coefficient (95% CI)[1]	Exponentiated coefficient (95% CI)[2]	*p* value	% (Δ MCAMA)[3]
Creatinine, urine (g/L)[2]	0.8257 (0.7722, 0.8792)	2.28 (2.16, 2.41)	< 0.0001	128% higher per g/L cotinine
Fasting time (HH.00)	0.0082 (0.0033, 0.0132)	1.01 (1.00, 1.01)	0.0015	1% higher per hour fasting
Cotinine, serum (ng/mL)	0.0359 (0.0181, 0.0537)	1.04 (1.02, 1.06)	0.0002	4% higher per ng/mL cotinine
Sex				
Male	Reference	Reference		Reference
Female	0.1546 (0.0962, 0.2129)	1.17 (1.10, 1.24)	< 0.0001	17% higher
Age				
12–19	− 0.2007 (− 0.2849, − 0.1165)	0.818 (0.752, 0.890)	< 0.0001	18% lower
20–39	Reference	Reference		Reference
40–59	0.2049 (0.1402, 0.2696)	1.23 (1.15, 1.31)	< 0.0001	23% higher
≥ 60	0.2965 (0.2228, 0.3701)	1.35 (1.25, 1.45)	< 0.0001	35% higher
Race/ethnicity				
Non-Hispanic White	Reference	Reference		
Non-Hispanic Black	− 0.3913 (− 0.4600, − 0.3226)	0.676 (0.631, 0.724)	< 0.0001	32% lower
Mexican American	− 0.0567 (− 0.1259, 0.0125)	0.945 (0.882, 1.01)	0.1067	N.S.
Other Hisp. or other/multi-race	− 0.1252 (− 0.1970, − 0.0533)	0.882 (0.821, 0.948)	0.0009	12% lower
BMI				
Underweight	0.1009 (− 0.1569, 0.3587)	1.11 (0.855, 1.43)	0.437	N.S.
Healthy weight	Reference	Reference	.	Reference
Overweight/obesity	0.0267 (− 0.0368, 0.0903)	1.03 (0.964, 1.09)	0.4039	N.S.
NHANES cycle				
2005–2006	− 0.2509 (− 0.3278, − 0.1740)	0.778 (0.720, 0.840)	< 0.0001	22% lower
2011–2012	Reference	Reference		
2013–2014	− 0.0999 (− 0.2050, 0.0052)	0.905 (0.815, 1.01)	0.062	10% lower
2015–2016	− 0.1188 (− 0.1859, − 0.0518)	0.888 (0.830, 0.950)	0.0008	11% lower
Food consumed (kg)				

Level	Coefficient (95% CI)[1]	Exponentiated coefficient (95% CI)[2]	*p* value	% (Δ MCAMA)[3]
Milk products	− 0.0455 (− 0.1385, 0.0475)	0.956 (0.871, 1.05)	0.3321	N.S.
Meat, poultry, fish	− 0.0539 (− 0.1714, 0.0637)	0.948 (0.842, 1.07)	0.3635	N.S.
Eggs	0.0795 (− 0.3053, 0.4643)	1.08 (0.737, 1.59)	0.681	N.S.
Legumes, nuts, seeds	0.0040 (− 0.2301, 0.2380)	1.00 (0.794, 1.27)	0.9732	N.S.
Grain products	− 0.0261 (− 0.1368, 0.0846)	0.974 (0.872, 1.09)	0.639	N.S.
Fruits	− 0.2509 (− 0.3648, − 0.1369)	0.778 (0.694, 0.872)	< 0.0001	1.2% lower
Vegetables	− 0.0925 (− 0.2425, 0.0574)	0.912 (0.785, 1.06)	0.2221	N.S.
Fats, oils, salad dressings	0.4963 (− 0.8879, 1.8804)	1.64 (0.412, 6.56)	0.4763	N.S.
Sugars, sweets, beverages	− 0.0209 (− 0.0433, 0.0016)	0.979 (0.958, 1.00)	0.0676	N.S.
Smoked meat, poultry, fish	2.5100 (− 0.1859, 5.2058)	12.3 (0.830, 182)	0.0675	N.S.
Cruciferous vegetables	− 0.5459 (− 1.1915, 0.0996)	0.579 (0.304, 1.10)	0.096	N.S.
Coffee	0.6288 (0.5316, 0.7260)	1.88 (1.70, 2.07)	< 0.0001	8% higher
Intercept	3.5618 (3.4138, 3.7097)	35.2 (30.4, 40.8)	N/A	N/A

N.S. not significant

[1] MCAMA concentration was natural log-transformed for the regression model

[2] Urinary creatinine concentration reported in g/L so that its coefficient simplifies to a more interpretable scale

[3] % (Δ MCAMA) for each food group was calculated from median consumption