**Evaluation of Tobacco Smoke and Diet as Sources of Exposure to Two Heterocyclic Aromatic Amines for the U.S. Population: NHANES 2013–2014**

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***Identifying Users of Combusted Tobacco and Non-Users of Tobacco***

Participants’ recent tobacco use was determined from self-report in response to an NHANES questionnaire (NHANES dataset: SMQRTU\_H). NHANES participants were not included in statistical analyses if they recently used smokeless tobacco or nicotine replacement therapy, as indicated by responding “yes” to question SMDANY (tobacco use within 5 days prior to NHANES physical examination) and “yes” to at least one of SMQ851, SMQ863, SMQ690D – SMQ690F, or SMQ690H –SMQ690J (smokeless tobacco and nicotine delivery products). Users of smokeless tobacco and nicotine replacement therapy would have adversely biased the results since use of these products are alternative sources of nicotine — and thereby its metabolite cotinine, which represents tobacco smoke exposure in the reported analyses) — but does not involve the combustion necessary for the formation of AαC and MeAαC. After excluding users of smokeless tobacco and nicotine replacement therapy, the remaining participants were identified as either exclusive users of combusted tobacco products (henceforth “exclusive smokers”) or non-users of any tobacco products. Participants who answered “yes” to SMDANY and “yes” to at least one of SMQ690A – SMQ690C and SMQ690G (cigarettes, pipes, cigars, hookahs/water pipes) were classified as exclusive smokers. Participants who answered “no” or were missing a response to SMDANY and had serum cotinine ≤10 ng/mL were classified as non-users of tobacco products. Serum cotinine concentrations exceeding 10 ng/mL is consistent with active use of combusted tobacco products, and was the basis for stratifying statistical analyses reported herein. In summary, the attrition of participants from statistical analysis is as follows: missing serum cotinine data (146 participants), use of smokeless tobacco and nicotine replacement therapy (135 participants), or missing data for other variables involved in regression models (532 participants). This attrition resulted in 1,792 study participants eligible for statistical analysis for AαC and 1,793 study participants for MeAαC. For the cigarettes smoked per day (CPD) regression model described below, 32 additional participants were excluded for missing CPD data leaving 1,760 study participants.

***Statistical Analysis***

NHANES recruits participants by using a multistage, probability sampling design. This complex design must be accounted for in order to estimate variances correctly and to achieve unbiased, nationally representative statistics. Robust estimation can be made by implementing survey sample weights (NHANES Special Sample weight; WTFSM) on each participant’s data and performing Taylor series linearization. This estimation approach was conducted in the statistical software applications SUDAAN®, Version 11.0.0 (Research Triangle Institute, Research Triangle Park, NC) and SAS® 9.4 (SAS Institute Inc. Cary, NC). Data from the NHANES 2013 – 2014 sampling cycle were analyzed with sample-weighted linear regression models that was stratified by tobacco use status (exclusive smokers vs. non-users). The distributions of urinary AαC and MeAαC measurements were strongly right-skewed, which would have adversely biased regression results. To improve their distributional symmetry, the urinary measurement data were transformed with the natural log for use as dependent variables in regression models. Parameters estimated from these models are reported herein, along with their 95 percent confidence intervals and *p*-values. The log-transformation of urinary concentration is interpretable as a scale of relative change, which may hinder interpretation of the parameter estimates. To minimize this difficulty, we also report the parameters transformed so that they represent the absolute change in biomarker concentration associated with an absolute increase in the *j*th predictor , as adapted from Rodríguez-Barranco, et al., 2017: . The sample-weighted geometric mean of biomarker concentration is represented by , which accompanies the tabulated regression results in their respective captions. The transformation of to herein assumes , so that represents the absolute change associated with a unit-increase in the predictor. The 95 percent confidence interval is: , where is the sample-weighted standard error of the parameter. The width of the may be slightly underestimated since GM is treated as a fixed quantity. In addition, and its are calculated at because it is where the regression parameters are estimated, owing to transformation of the dependent variable with the natural log, but and can be expected to vary at values different from the geometric mean. Statistical significance was set to α ≤ 0.05.

Exposure through diet is another potential source of AαC, especially when food is prepared at high temperature. Trained interviewers used structured questionnaires to collect food consumption information from NHANES participants. The interviewers used elaborate elicitation techniques — including food models and portion measurement guides — to translate a participant's recall of the type and amount of food consumed to a standardized encoding and amount [kg]. Dietary exposure was assessed based on the amount participants consumed within each U.S. Department of Agriculture (USDA) food group for the 24-hr period (midnight to midnight) preceding the dietary recall interview. The interviews were conducted in person on the same day that urine specimens were collected and as part of the physical examination. Data for the 24-hour recall period are publicly accessible in the NHANES Individual Foods – First Day file (NHANES dataset: DR1IFF\_H). These data comprise each item of food, beverage, or water reported consumed by the participant in the 24 hours preceding the NHANES physical examination, including the amount consumed. Each item was encoded with an eight-digit USDA food code that designates the item within standardized, hierarchical food groups, where the first digit represents one of nine major food groups, and each subsequent digit represents subgroups of increasing specificity (http://www.ars.usda.gov/ba/bhnrc/fsrg). Data for each item consumed by a participant were recorded in a separate record. The mass consumed in each food group was summed so that each participant was represented by a single record describing their intake of each food group in the previous 24 hours. Food groups were compiled by first apportioning each participant’s dietary intake over the nine major USDA food groups: milk products; meat, poultry, fish; eggs; legumes, nuts, seeds; grain products; fruits; vegetables; fats, oils, salad dressings; and sugars, sweets, beverages. For this report, two additional food subgroups were distinguished because of their potential for high AαC exposure arising from high temperature (i.e., broiling, baking, or frying) during preparation: high-temperature cooked beef and high-temperature cooked fish. Double counting was avoided by subtracting the amount consumed in each subgroup from the amount consumed in their respective food group. Supplementary Table S1 details the USDA food codes and logic for apportioning dietary intake.



**Supplementary Figure 1.** Chemical structures of A) 2-amino-9H-pyrido[2,3-b]indole (AαC) and B) 2-amino-3-methyl-9H-pyrido[2,3-b]indole (MeAαC). AαC is heterocyclic aromatic amine with exocyclic amine group; MeAαC is a methyl homolog of AαC.

|  |  |
| --- | --- |
| **Food Group** | **USDA Food Codes and Logic** |
| Milk and Milk Products | DR1IFDCD = 1 |
| Meat, Poultry, Fish and Mixtures | DR1IFDCD = 2 |
| Eggs | DR1IFDCD = 3 |
| Legumes, Nuts, and Seeds | DR1IFDCD = 4 |
| Grain Products | DR1IFDCD = 5 |
| Fruits | DR1IFDCD = 6 |
| Vegetables | DR1IFDCD = 7 |
| Fats, Oils, and Salad Dressings | DR1IFDCD = 8 |
| Sugars, Sweets, and Beverages | DR1IFDCD = 9 |
|  |  |
| High AaC Beef (boiled, baking, fried) [kg] | DR1IFDCD = 21101 (110,120,130), 21102 (110,120,130),  21103 (110,120,130), or 21003000  Then subtract total amount from DR1IFDCD = 2 |
| High AaC Fish (boiled, baking, fried) [kg] | DR1IFDCD = 26100, 26105, 26107, 26111, 26117,26119,26121, 26125, 26127, 26131, 26141, 26143, 26149, 26151  Then subtract total amount from DR1IFDCD = 2 |

**Supplementary table 1. USDA food codes and logic defining evaluated food groups**

| **Predictor** | **Level** | **GM [95%CI]** | **10th %ile** | **25th %ile** | **50th %ile** | **75th %ile** | **90th %ile** | **95th %ile** | **Sample Size** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| All |  | 14.30 [10.79, 17.81] | 0.87 | 4.49 | 19.97 | 60.61 | 108.1 | 170.0 | 1,002 |
| Age | 18 – 39 | 11.18 [8.69, 13.67] | 0.91 | 3.69 | 11.71 | 40.10 | 91.16 | 130.7 | 418 |
| Age | 40 – 59 | 17.72 [10.40, 25.04] | 0.70 | 6.73 | 32.89 | 68.94 | 128.1 | 177.1 | 401 |
| Age | ≥60 | 17.72 [3.40, 32.03] | 0.50 | 6.96 | 22.91 | 82.26 | 138.1 | 239.3 | 183 |
| BMI | Healthy Weight | 20.73 [15.10, 26.36] | 2.11 | 7.56 | 23.39 | 67.80 | 125.8 | 195.7 | 321 |
| BMI | Overweight/Obese | 11.85 [8.06, 15.65] | 0.63 | 2.62 | 18.22 | 56.71 | 101.3 | 157.8 | 641 |
| BMI | Underweight | 45.35 [20.26, 70.44] | 7.87 | 16.15 | 64.83 | 106.4 | 138.4 | 151.7 | 28 |
| PIR | No | 11.70 [8.14, 15.27] | 0.67 | 3.03 | 15.83 | 53.81 | 95.46 | 146.1 | 584 |
| PIR | Yes | 26.74 [16.59, 36.90] | 1.87 | 12.78 | 34.67 | 88.41 | 162.3 | 196.5 | 345 |
| Race | Mexican American | 5.19 [3.39, 6.98] | 0.54 | 1.60 | 4.48 | 15.47 | 63.50 | 85.11 | 70 |
| Race | Non-Hispanic Black | 17.55 [13.61, 21.48] | 2.15 | 8.92 | 24.14 | 50.72 | 80.50 | 119.7 | 251 |
| Race | Non-Hispanic White | 15.65 [10.17, 21.13] | 0.86 | 4.75 | 21.23 | 68.08 | 128.0 | 197.2 | 523 |
| Race | Other Hispanic | 19.98 [6.48, 33.47] | 1.64 | 9.72 | 24.20 | 57.05 | 86.63 | 119.9 | 60 |
| Race | Other/Multi-Racial | 7.43 [3.56, 11.30] | 0.21 | 0.92 | 11.41 | 42.78 | 76.42 | 97.50 | 98 |
| Sex | Female | 23.38 [15.83, 30.92] | 1.85 | 10.42 | 31.71 | 79.16 | 144.9 | 175.6 | 437 |
| Sex | Male | 9.99 [7.23, 12.74] | 0.59 | 2.34 | 14.94 | 43.14 | 93.77 | 150.9 | 565 |

**Supplementary table 2. Geometric means and selected percentiles of urinary AαC concentrations (ng/g) for U.S. population with Serum Cotinine >=10 ng/mL.**

| **Predictor** | **Level** | **GM [95%CI]** | **10th %ile** | **25th %ile** | **50th %ile** | **75th %ile** | **90th %ile** | **95th %ile** | **Sample Size** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| All |  | 0.92 [0.84, 1.00] | 0.29 | 0.46 | 0.82 | 1.51 | 3.19 | 5.80 | 1,327 |
| Age | 18 – 39 | 0.92 [0.79, 1.04] | 0.27 | 0.45 | 0.80 | 1.54 | 3.03 | 5.51 | 479 |
| Age | 40 – 59 | 0.99 [0.84, 1.14] | 0.31 | 0.46 | 0.83 | 1.57 | 4.41 | 7.34 | 418 |
| Age | ≥60 | 0.85 [0.73, 0.97] | 0.30 | 0.46 | 0.79 | 1.29 | 2.58 | 3.75 | 430 |
| BMI | Healthy Weight | 1.06 [0.94, 1.19] | 0.34 | 0.56 | 0.96 | 1.72 | 3.77 | 5.63 | 392 |
| BMI | Overweight/Obese | 0.86 [0.77, 0.95] | 0.27 | 0.43 | 0.75 | 1.37 | 3.11 | 5.94 | 908 |
| BMI | Underweight | 1.40 [0.18, 2.63] | 0.36 | 0.50 | 1.40 | 2.18 | 2.86 | 11.4 | 17 |
| PIR | No | 0.92 [0.83, 1.02] | 0.29 | 0.46 | 0.80 | 1.52 | 3.39 | 6.04 | 995 |
| PIR | Yes | 0.80 [0.66, 0.94] | 0.27 | 0.41 | 0.70 | 1.39 | 2.45 | 4.30 | 236 |
| Race | Mexican American | 0.98 [0.84, 1.11] | 0.30 | 0.49 | 0.88 | 1.58 | 3.12 | 5.79 | 244 |
| Race | Non-Hispanic Black | 0.56 [0.51, 0.62] | 0.22 | 0.31 | 0.46 | 0.91 | 1.47 | 3.17 | 217 |
| Race | Non-Hispanic White | 0.96 [0.85, 1.08] | 0.31 | 0.49 | 0.85 | 1.55 | 3.65 | 6.10 | 528 |
| Race | Other Hispanic | 0.95 [0.69, 1.20] | 0.27 | 0.46 | 0.80 | 1.76 | 3.79 | 6.48 | 136 |
| Race | Other/Multi-Racial | 0.98 [0.84, 1.11] | 0.40 | 0.55 | 0.79 | 1.58 | 2.70 | 3.93 | 202 |
| Sex | Female | 1.02 [0.90, 1.13] | 0.32 | 0.54 | 0.87 | 1.69 | 3.40 | 5.95 | 729 |
| Sex | Male | 0.82 [0.75, 0.88] | 0.26 | 0.40 | 0.70 | 1.33 | 3.06 | 5.44 | 598 |

**Supplementary table 3. Geometric means and selected percentiles of urinary AαC concentrations (ng/g) for U.S. population with serum cotinine <10 ng/mL.**

| **Predictor** | **Level** | **GM [95%CI]** | **10th %ile** | **25th %ile** | **50th %ile** | **75th %ile** | **90th %ile** | **95th %ile** | **Sample Size** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| All |  | - | 0.13 | 0.23 | 0.79 | 3.03 | 7.41 | 9.99 | 1,004 |
| Age | 18 – 39 | - | 0.11 | 0.21 | 0.59 | 2.21 | 5.95 | 8.04 | 419 |
| Age | 40 – 59 | - | 0.14 | 0.30 | 1.25 | 4.24 | 7.98 | 10.30 | 401 |
| Age | ≥60 | - | 0.18 | 0.23 | 1.05 | 4.55 | 9.95 | 17.76 | 184 |
| BMI | Healthy Weight | - | 0.15 | 0.24 | 1.36 | 4.21 | 8.33 | 11.39 | 323 |
| BMI | Overweight/Obese | - | 0.12 | 0.22 | 0.66 | 2.54 | 6.96 | 9.65 | 640 |
| BMI | Underweight | - | 0.21 | 0.57 | 4.97 | 7.70 | 7.99 | N/A | 29 |
| PIR | No | - | 0.12 | 0.20 | 0.64 | 2.45 | 6.39 | 9.37 | 584 |
| PIR | Yes | - | 0.18 | 0.37 | 1.49 | 5.21 | 9.56 | 11.47 | 346 |
| Race | Mexican American | - | 0.11 | 0.15 | 0.21 | 0.59 | 3.45 | 4.79 | 70 |
| Race | Non-Hispanic Black | - | 0.12 | 0.28 | 1.19 | 2.98 | 6.48 | 9.30 | 251 |
| Race | Non-Hispanic White | - | 0.15 | 0.24 | 0.79 | 3.50 | 8.05 | 11.51 | 526 |
| Race | Other Hispanic | - | 0.07 | 0.37 | 1.26 | 3.22 | 7.77 | 9.47 | 59 |
| Race | Other/Multi-Racial | - | 0.11 | 0.14 | 0.49 | 2.34 | 3.85 | 6.42 | 98 |
| Sex | Female | - | 0.13 | 0.24 | 1.21 | 4.19 | 7.94 | 10.29 | 440 |
| Sex | Male | - | 0.13 | 0.22 | 0.59 | 2.44 | 6.47 | 9.67 | 564 |

N/A: not sufficient participants for calculation

-: Geometric means were not calculated because of low detection rate of MeAαC in NHANES 2013–2014 participants (30.9%)

Reference: CDC, 2009. Fourth National Report on Human Exposure to Environmental Chemicals. Available: https://www.cdc.gov/exposurereport/pdf/fourthreport.pdf

**Supplementary table 4. Geometric means and selected percentiles of urinary MeAαC concentrations (ng/g) for U.S. population with serum cotinine >=10 ng/mL.**

| **Predictor** | **Level** | **GM [95%CI]** | **10th %ile** | **25th %ile** | **50th %ile** | **75th %ile** | **90th %ile** | **95th %ile** | **Sample Size** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| All |  | - | 0.12 | 0.16 | 0.27 | 0.49 | 0.84 | 1.20 | 1,327 |
| Age | 18 – 39 | - | 0.11 | 0.15 | 0.23 | 0.45 | 0.72 | 0.95 | 480 |
| Age | 40 – 59 | - | 0.12 | 0.17 | 0.29 | 0.52 | 0.92 | 1.28 | 418 |
| Age | ≥60 | - | 0.13 | 0.18 | 0.29 | 0.53 | 0.92 | 1.30 | 429 |
| BMI | Healthy Weight | - | 0.13 | 0.20 | 0.37 | 0.58 | 0.97 | 1.41 | 392 |
| BMI | Overweight/Obese | - | 0.12 | 0.15 | 0.24 | 0.45 | 0.76 | 1.11 | 907 |
| BMI | Underweight | - | 0.17 | 0.23 | 0.54 | 1.11 | 1.25 | 1.42 | 17 |
| PIR | No | - | 0.12 | 0.17 | 0.27 | 0.51 | 0.87 | 1.22 | 995 |
| PIR | Yes | - | 0.11 | 0.15 | 0.23 | 0.39 | 0.70 | 0.97 | 237 |
| Race | Mexican American | - | 0.13 | 0.16 | 0.26 | 0.49 | 0.78 | 0.92 | 244 |
| Race | Non-Hispanic Black | - | 0.10 | 0.13 | 0.18 | 0.24 | 0.43 | 0.58 | 217 |
| Race | Non-Hispanic White | - | 0.12 | 0.17 | 0.29 | 0.53 | 0.95 | 1.28 | 528 |
| Race | Other Hispanic | - | 0.12 | 0.15 | 0.24 | 0.39 | 0.64 | 0.89 | 136 |
| Race | Other/Multi-Racial | - | 0.15 | 0.21 | 0.36 | 0.58 | 0.91 | 1.32 | 202 |
| Sex | Female | - | 0.14 | 0.20 | 0.35 | 0.60 | 1.01 | 1.28 | 728 |
| Sex | Male | - | 0.11 | 0.14 | 0.21 | 0.40 | 0.63 | 0.86 | 599 |

-: Geometric means were not calculated because of low detection rate of MeAαC in NHANES 2013–2014 participants (30.9%) (CDC, 2009)

Reference: CDC, 2009. Fourth National Report on Human Exposure to Environmental Chemicals. Available: https://www.cdc.gov/exposurereport/pdf/fourthreport.pdf

**Supplementary table 5. Geometric means and selected percentiles of urinary MeAαC concentrations (ng/g) for U.S. population with serum cotinine <10 ng/mL.**

| **Predictor** | **Level** | **Slope [95% CI]1** | **p-Value** | **𝚫Y [95% CI]2** |
| --- | --- | --- | --- | --- |
| Creatinine [g/ml] | Slope | 295 [210, 379] | <.0001 | 1.14E+128 [1.45E+94, 8.91E+161] |
| Fasting Time [HH.00] | Slope | -0.0191 [-0.0289, -9.29E-03] | 0.0009 | -0.0249 [-0.0365, -0.0132] |
| Tobacco Smoke Exposure | ≤0.05 ng/mL Cotinine, Serum | Ref. | . | Ref. |
| Tobacco Smoke Exposure | >0.05 – ≤10 ng/mL Cotinine, Serum | 0.289 [0.0883, 0.489] | 0.008 | 0.440 [0.145, 0.796] |
| Tobacco Smoke Exposure | 1 – 10 CPD (0.5 pack) | 2.94 [2.70, 3.18] | <.0001 | 23.6 [18.7, 29.6] |
| Tobacco Smoke Exposure | 11 – 20 CPD (1 pack) | 3.92 [3.75, 4.09] | <.0001 | 65.0 [55.6, 75.9] |
| Tobacco Smoke Exposure | >20 CPD (>1 pack) | 4.46 [3.93, 5.00] | <.0001 | 113 [68.6, 185] |
| Sex | Male | Ref. | . | Ref. |
| Sex | Female | 5.20E-03 [-0.0945, 0.105] | 0.91 | 6.86E-03 [-0.109, 0.134] |
| Age | 18 – 39 | -0.0130 [-0.176, 0.150] | 0.87 | -0.0170 [-0.197, 0.192] |
| Age | 40 – 59 | Ref. | . | Ref. |
| Age | ≥60 | -0.107 [-0.288, 0.0737] | 0.23 | -0.134 [-0.315, 0.0802] |
| Race/Ethnicity | Non-Hispanic White | Ref. | . | Ref. |
| Race/Ethnicity | Non-Hispanic Black | -0.169 [-0.351, 0.0141] | 0.07 | -0.204 [-0.376, -7.63E-04] |
| Race/Ethnicity | Mexican American | -0.0385 [-0.298, 0.221] | 0.76 | -0.0497 [-0.319, 0.292] |
| Race/Ethnicity | Other Hispanic | -4.08E-03 [-0.232, 0.224] | 0.97 | -5.36E-03 [-0.253, 0.300] |
| Race/Ethnicity | Other/Multi-Racial | -0.148 [-0.277, -0.0196] | 0.03 | -0.181 [-0.308, -0.0388] |
| BMI | Underweight | 0.0652 [-0.292, 0.422] | 0.70 | 0.0886 [-0.304, 0.634] |
| BMI | Healthy Weight | Ref. | . | Ref. |
| BMI | Overweight/Obese | -0.0476 [-0.222, 0.127] | 0.57 | -0.0611 [-0.247, 0.157] |
| Impoverished | No | Ref. | . | Ref. |
| Impoverished | Yes | 0.100 [-0.0192, 0.220] | 0.09 | 0.139 [-0.0126, 0.308] |
| Food Consumed [kg/d] | Milk Products | -0.116 [-0.263, 0.0324] | 0.12 | -0.144 [-0.293, 0.0272] |
| Food Consumed [kg/d] | Meat, Poultry | 0.218 [-0.140, 0.575] | 0.21 | 0.320 [-0.138, 0.957] |
| Food Consumed [kg/d] | Eggs | 0.0792 [-0.518, 0.677] | 0.78 | 0.108 [-0.493, 1.15] |
| Food Consumed [kg/d] | Legumes, Nuts, Seeds | -0.0658 [-0.983, 0.851] | 0.88 | -0.0838 [-0.785, 1.55] |
| Food Consumed [kg/d] | Grain Products | -0.176 [-0.422, 0.0704] | 0.15 | -0.212 [-0.435, 0.0683] |
| Food Consumed [kg/d] | Fruits | -0.0700 [-0.302, 0.162] | 0.53 | -0.0889 [-0.325, 0.203] |
| Food Consumed [kg/d] | Vegetables | -0.401 [-0.799, -1.98E-03] | 0.049 | -0.434 [-0.705, -0.0440] |
| Food Consumed [kg/d] | Fats, Oils, Salad Dressings | 1.14 [-0.605, 2.89] | 0.18 | 2.80 [-0.488, 19.2] |
| Food Consumed [kg/d] | Sugars, Sweets, Beverages | 0.0160 [-0.0209, 0.0528] | 0.37 | 0.0212 [-0.0233, 0.0672] |
| Food Consumed [kg/d] | High AaC Beef | 2.61 [0.363, 4.87] | 0.03 | 16.7 [0.950, 141] |
| Food Consumed [kg/d] | High AaC Fish | -0.487 [-0.953, -0.0212] | 0.04 | -0.507 [-0.789, -0.0749] |
|  |  |  |  |  |

1. The dependent variable, biomarker concentration, was natural log-transformed for the regression model.

2. ∆Y is the expected change in biomarker concentration in pg/mL associated with a unit-increase in the predictor, controlling for other predictors in the model and calculated at the overall geometric mean.

**Supplementary table 6. Sample weighted multiple regression results for urinary AαC concentrations [pg/mL] in NHANES 2013-2014 (N = 1,760). The geometric mean of urinary AαC used for computing is 1.32 pg/mL.**