Jain, *Cogent Environmental Science* (2016), 2: 1259880
http://dx.doi.org/10.1080/23311843.2016.1259880

cogent environmental science

ENVIRONMENTAL CHEMISTRY, POLLUTION & WASTE MANAGEMENT | RESEARCH ARTICLE

An improved approach to report creatinine-corrected analyte concentrations in urine

Ram B. Jain[1]*

Received: 02 April 2016
Accepted: 07 November 2016
First Published: 14 November 2016

*Corresponding author: 2959 Estate View Court, Dacula, GA, USA
E-mail: Jain.ram.b@gmail.com

Reviewing editor:
Lian Pin Koh, University of Adelaide, Australia

Additional information is available at the end of the article

Abstract: Traditionally, urinary analyte concentrations (UAC_{Obs}) are divided by the observed urine creatinine (UCR_{Obs}) concentrations to allow for hydration correction. However, this method ignores the variability in the levels of urine creatinine due to such factors as age, gender, race/ethnicity, and others. Consequently, a method to develop a correction factor that incorporates adjustment due to most, if not all the factors that may affect urine creatinine concentrations was developed. This correction factor is applied to UCR_{Obs} to determine UCR_{Corr}, which can then be used in place of UCR_{Obs} to compute modified creatinine-corrected analyte concentration as UAC_{Obs}/UCR_{Corr} instead of UAC_{Obs}/UCR_{Obs}. For this study, data for urine creatinine from National Health and Nutrition Examination Survey (NHANES) for 2007–2010 were used to develop this correction factor to account for variability in urine creatinine due to age, race/ethnicity, gender, and body mass index. For each participant, correction factor β and its standard error for each of the 64 categories of age-race/ethnicity-gender were computed. In order to compute creatinine-corrected analyte concentration, observed analyte concentration was divided by the corrected value of observed urine creatinine whereas the corrected value of urine creatinine was the observed value minus the correction factor. Correction factor for each participant was a random number drawn from the normal distribution with mean β and standard deviation SE. The proposed methodology was applied to the 2009–2010

ABOUT THE AUTHOR

Ram B. Jain has been involved in Environmental Science research since 2002. He is currently retired but continues to indulge in research work using data from National Health and Nutrition Examination Survey in his spare time. He has published over 70 papers in various journals. His most recent publications appeared in Environmental Science and Pollution Research, Biomarkers, Journal of Chemistry, and Journal of Environmental and Health Sciences.

PUBLIC INTEREST STATEMENT

Urine is the preferred matrix in which to measure the concentration of many environmental toxicants. Measured concentration of toxicants in urine may, however, be affected by how diluted the urine sample may be. In order to nullify the effect of urinary dilution, toxicant concentrations in urine are usually reported as per unit weight of creatinine present in the urine. This method of reporting toxicant concentrations in urine ignores the "natural" variability in urinary creatinine concentrations due to age, gender, race, and other factors. This may lead to reported toxicant concentrations being too high or too low compared to the "true" toxicant concentrations. This communication proposes a numerical correction factor that should be applied to the observed creatinine concentrations before using them to report toxicant concentrations as per unit weight of urinary creatinine.

NHANES data for urinary 3-phenoxybenzoic acid, for 2013–2014 NHANES data for urinary cadmium and lead, and NHANES 2011–2012 data for urinary perchlorate, nitrate, and thiocyanate.

Subjects: Environmental Studies & Management; Mathematics & Statistics; Medicine, Dentistry, Nursing & Allied Health

Keywords: urine creatinine; 3-phenoxybenzoic acid; perchlorate; nitrate; thiocyanate; cadmium; lead

1. Introduction

1.1. Literature review and statement of the problem

Analyte concentrations in urine are often reported as creatinine-corrected concentrations. If observed analyte concentration was UAC_{Obs} and observed urine creatinine concentration was UCR_{Obs}, then creatinine corrected analyte concentration, UAC_{Corr1} is reported as UAC_{Obs}/UCR_{Obs}. Since, most of the times, UCR_{Obs} is measured in spot urine samples, rather than 24-h urine samples, hydration correction becomes necessary. Reporting of UAC_{Corr1}, rather than UAC_{Obs} is supposed to adjust for hydration correction. This mechanism of reporting UACs implicitly assumes that UCR_{Obs} are affected by urinary dilution only. Barr et al. (2005) used data from National Health and Nutrition Examination Survey (NHANES, www.cdc.gov/nchs/nhanes.htm) for the years 1988–1994 and showed that age, gender, race/ethnicity, and body mass index (BMI) also affect UCR_{Obs}. For example, Barr et al. (2005) showed non-Hispanic blacks (NHB) to have higher mean UCR_{Obs} than non-Hispanic whites (165.4 vs. 124.6 mg/dL) and females to have lower mean UCR_{Obs} than males (113.5 vs. 148.3 mg/dL). In addition, children aged 6–11 years and senior citizens aged ≥70 years old were shown to have the lowest levels of UCR_{Obs} (102.1 and 97.99 mg/dL, respectively) and those aged 12–19 and 20–29 years were shown to have the highest levels of UCR_{Obs} (161.5 and 161.8 mg/dL, respectively); UCR_{Obs} for the samples collected in morning was higher than for the samples collected in the evening; for a unit increase in BMI, UCR_{Obs} was found to increase by 1.3 g/dL, persons with diabetes had lower UCR_{Obs} than persons without diabetes; and kidney function was also shown to affect UCR_{Obs} (Barr et al., 2005). However, Stiegel, Pleil, Sobus, Angrish, and Morgan (2015) found poor correlation between kidney injury panel and UCR_{Obs}. In kidney stone patients with Type II diabetes, HbA1c was found to be correlated with UCR_{Obs} (Fram, Moazami, & Stern, 2015). Decreased UCR_{Obs} was found to be associated with sleep deprivation (Giskeodegard, Davies, Revell, Keun, & Skene, 2015).

Consequently, the values of UCR_{Obs} must be corrected for the effect of factors other than urinary dilution before computing creatinine-corrected analyte concentrations. If the corrected value of urinary creatinine is denoted as UCR_{Corr}, then "true" creatinine corrected analyte concentration denoted as UAC_{Corr2} should be computed as UAC_{Obs}/UCR_{Corr}. In order to account for the effect of all factors that affect UCR_{Obs}, Barr et al. (2005) recommended using unadjusted UAC_{Obs} in the regression models as dependent variable with UCR_{Obs} used as one of the independent variables. This author fully supports this recommendation. When UCR_{Obs} is used as one of the independent variables in statistical models, UAC_{Obs} continues to be reported in per unit volume of the urine, for example, ng/mL or µg/L. However, data on differences in UCR_{Obs} by age, gender, and race/ethnicity as provided by Barr et al. (2005) can still be used to compute UAC_{Corr2} as will be seen in this communication.

Recently, O'Brien, Upson, Cook, and Weinberg (2015) proposed a two-stage model to adjust for the effect of factors other than dilution on UCR_{Obs}. It would be of interest to compare the performance of single-stage adjustment model as proposed by Barr et al. (2005) and two-stage adjustment model as proposed by O'Brien et al. (2015). However, this may be a topic for future research and beyond the scope of this study as described in the next section.

1.2. Study objectives and proposed methodology

The sole objective of this study was to evaluate how traditional method of computing UAC, i.e. UAC_{Corr1} performs as compared with corrected method of computing UAC, i.e. UAC_{Corr2} for a selected number of urinary analytes. The correction factor needed to convert log 10 transformed values of UCR_{Obs} or log 10(UCR_{Obs}) to log 10 transformed values of UCR_{Corr} or log 10(UCR_{Corr}) will be determined by fitting a regression model for log 10(UCR_{Obs}) as the dependent variable and age, race/ethnicity, gender, and BMI as the independent variables. The regression slope β along with its standard error SE for 64 combinations of age, race/ethnicity, and gender to be presented as an Excel Table will provide a correction factor for each of these 64 demographic groups needed to convert log 10(UCR_{Obs}) to log 10(UCR_{Corr}). The data presented in this Table can be used in practical clinical situations where UCR_{Obs} and UAC_{Obs} are available but UAC_{Corr2} may be needed. A large data-set on UCR from NHANES for the period 2007–2010 will be used to fit the proposed model. The applicability of the correction factors developed by fitting the model for 2007–2010 will be tested for NHANES data for 2011–2012 and 2013–2014.

2. Materials and methods

All data available in the public domain from NHANES used for this study were collected by necessary approvals of the Institutional Review Boards of the National Center for Health Statistics and the Centers for Disease Control and Prevention.

2.1. Data source and data description

2.1.1. Urine creatinine database

Data from NHANES (www.cdc.gov/nchs/nhanes.htm) from demographic, urine creatinine (UCR), and body measure files for those aged ≥6 years for the period 2007–2014 were downloaded and match merged. The sampling plan for NHANES is a complex, stratified, multistage, probability cluster designed to be representative of the civilian, non-institutionalized U.S. population. Sampling weights are created in NHANES to account for the complex survey design, including oversampling, survey non-response, and post-stratification. A total of 31,964 participants with non-missing values of UCR were available for analysis. For the purpose of this study, overall database for 2007–2014 was split in to three databases, namely, data for 2007–2010, 2011–2012, and 2013–2014, respectively. Detailed sample sizes are given in Table 1. All data analyses completed for this study incorporated sampling weights as well as survey design characteristics, namely, stratification and clustering.

2.1.2. Databases for urine cadmium and lead; urine perchlorate, nitrate, and thiocyanate; and urine 3-phenoxybenzoic acid

In order to generate a database for 3-phenoxybenzoic acid (3-PBA), data from NHANES for 2009–2010 from demographic, body measures, and pyrethroids, herbicide, and organophosphate metabolite files were downloaded and match merged by the ID for each participant labeled as SEQN in NHANES data files. A total of 2,703 participants aged ≥6 years with non-missing values of 3-PBA were available for analysis. Details are given in Table 2. Percent observations at or above the limit of detection (LOD) for 3-PBA were 73.4%.

In order to generate a database for urinary cadmium (UCD) and lead (UPB), data from NHANES for 2013–2014 from demographic, body measures, and urinary metal files were downloaded and match merged by the ID for each participant labeled as SEQN in NHANES data files. A total of 2,681 participants aged ≥6 years for UCD and UPB were available for analysis. Details are given in Table 2. Percent observations at or above LOD for UCD were 89.3% and 97.2% for UPB.

In order to generate a database for urinary perchlorate (UPC8), nitrate (UNO3), and thiocyanate (UTHIO), data from NHANES for 2011–2012 from demographic, body measures, and UPC8, UNO3, and UTHIO files were downloaded and match merged by the ID for each participant labeled as SEQN in NHANES data files. A total of 2,506 participants aged ≥6 years were available for analysis. Details are given in Table 2. Percent observations at or above LOD for UPC8, UNO3, and UTHIO were 100, 99.7, and 99.9, respectively. All values below the LOD were imputed as LOD/Sqrt(2).

Table 1. Un-weighted sample sizes by age, gender, race/ethnicity, and survey year. Data from National Health and Nutrition Examination Survey 2007–2014

	Survey year							
	2007–2010		2011–2012		2013–2014		Total	
	N	%	*N*	%	*N*	%	*N*	%
Total	16,179	100.0	7,581	100.0	8,052	100.0	31,812	100.0
Males	8,085	50.0	3,828	50.5	3,950	49.1	15,863	49.9
Females	8,064	49.8	3,753	49.5	4,102	50.9	15,919	50.0
Non-Hispanic Whites	6,896	42.6	2,449	32.3	3,004	37.3	12,349	38.8
Non-Hispanic Blacks	3,316	20.5	2,066	27.3	1,790	22.2	7,172	22.5
Hispanics	5,115	31.6	1,765	23.3	2,067	25.7	8,947	28.1
Other race/ ethnicities	822	5.1	1,301	17.2	1,191	14.8	3,314	10.4
Age 6–11 years	2,368	14.6	1,235	16.3	1,236	15.4	4,839	15.2
Age 12–19 years	2,454	15.2	1,202	15.9	1,348	16.7	5,004	15.7
Age 20–29 years	1,774	11.0	906	12.0	903	11.2	3,583	11.3
Age 30–39 years	1,897	11.7	892	11.8	949	11.8	3,738	11.8
Age 40–49 years	1,970	12.2	858	11.3	990	12.3	3,818	12.0
Age 50–59 years	1,789	11.1	867	11.4	902	11.2	3,558	11.2
Age 60–69 years	1,866	11.5	850	11.2	897	11.1	3,613	11.4
Age ≥70 years	2,031	12.6	771	10.2	827	10.3	3,629	11.4

Table 2. Unweighted sample sizes for urinary 3-phenoxybenzoic acid for 2009–2010, urinary cadmium (UCD) and lead (UPB) for 2013–2014, and urinary perchlorate (UP8), nitrate (UNO3), and thiocyanate (USCN) for 2011–2012 by gender, race/ethnicity, and age. Data from National Health and Nutrition Examination Survey 2009–2010

	3-Phonoxybenzoic acid		UCD, UPB		UP8, UNO3, USCN	
	N	%	*N*	%	*N*	%
Total	2,703	100.0	2,681	100.0	2,506	100
Males	1,331	49.2	1,319	49.2	1,264	50.4
Females	1,372	50.8	1,362	50.8	1,242	49.6
Non-Hispanic Whites	1,188	44.0	952	35.5	820	32.7
Non-Hispanic Blacks	492	18.2	586	21.9	672	26.8
Hispanics	877	32.4	705	26.3	571	22.8
Others	146	5.4	398	14.8	443	17.7
Age: 6–11 years	383	14.2	405	15.1	401	16.0
Age: 12–19 years	398	14.7	454	16.9	393	15.7
Age: 20–64 years	1,449	53.6	1,428	53.3	1,338	53.4
Age: 65+ years	473	17.5	394	14.7	374	14.9

2.2. Laboratory methods

Urine creatinine was assayed by an enzymatic method using Roche/Hitachi Modular P Chemistry Analyzer in which creatinine is converted to creatine under the activity of creatininase. Details are provided at http://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/ALB_CR_H.htm#Description_of_Laboratory_Methodology. UPC8, UNO3, and UTHIO were measured by ion chromatography coupled with electrospray tandem mass spectrometry. Details are provided at http://wwwn.cdc.gov/Nchs/Nhanes/2009-2010/PERNT_F.htm#Description_of_Laboratory_Methodology. UCD and UPB were assayed by inductively coupled plasma-mass spectrometry in a multi-element analytical technique (http://wwwn.cdc.gov/Nchs/Nhanes/2009-2010/UHM_F.htm#Description_of_Laboratory_Methodology). 3-PBA was extracted using an automated solid phase extraction system (http://wwwn.cdc.gov/Nchs/Nhanes/2009-2010/UPHOPM_F.htm#Description_of_Laboratory_Methodology).

2.3. Outcome variables

Since the distribution of UCR_{Obs} was found to be positively skewed (skewness = 1.1, see Table 3), log 10 transformed values of UCR_{Obs} were used as the outcome/dependent variable for the regression model fitted to predict the values of UCR. log 10 transformed values of 3-PBA, UCD, UPB, UPC8, UNO3, and UTHIO were used to compute geometric means for these six analytes by both traditional as well as modified methods to compute creatinine-corrected urinary analyte concentrations.

2.4. Covariates/independent variables

Gender (males, females), race/ethnicity (non-Hispanic white or NHW, non-Hispanic black or NHB, all Hispanics or HISP, other unclassified race/ethnicities or OTH), and age (6–11 or A6, 12–19 or A12, 20–29 or A20, 30–39 or A30, 40–49 or A40, ≥50 or A50+ years) were used as the categorical covariates/independent variables and body mass index (BMI) was used as the continuous independent variable to fit regression model for UCR_{Obs}.

2.5. Statistical analysis

All data were analyzed using SAS University Edition (www.sas.com). Specifically, Proc SURVEYREG was used to compute unadjusted geometric means (UGM). Pairwise comparisons to evaluate

Table 3. Un-adjusted means and geometric means with 95% confidence intervals in mg/dL for urine creatinine by age, gender, and race/ethnicity for 2007–2010. Data from National Health and Nutrition Examination Survey 2007–2010

	Mean (95% CI)*	Geometric mean (95% CI)**
Males (*M*)	137.4 (133.7–141.2)	114 (110.6–117.6)
Females (*F*)	106.1 (103.3–108.8)	82.3 (79.9–84.8)
Non-Hispanic Whites (NHW)	115.3 (112.1–118.5)	91.5 (88.6–94.5)
Non-Hispanic Blacks (NHB)	160.3 (156.4–164.1)	132.6 (129–136.2)
Hispanics (HISP)	124.1 (120.6–127.6)	101.2 (98.2–104.2)
Other race/ethnicities (OTH)	109 (103.2–114.8)	86 (81.1–91.1)
Age 6–11 years (A6)	92 (89.3–94.7)	77.1 (74.4–79.9)
Age 12–19 years (A12)	147.2 (141.6–152.7)	122 (116.6–127.7)
Age 20–29 years (A20)	148.5 (142.5–154.4)	119.7 (113.7–126)
Age 30–39 years (A30)	129.5 (125.1–133.9)	104 (99.4–108.8)
Age 40–49 years (A40)	122.5 (118.1–127)	97.7 (93.8–101.8)
Age 50–59 years (A50)	110.7 (106.8–114.6)	86 (82.2–90.1)
Age 60–69 years (A60)	101.6 (97.2–106.1)	81.2 (77.4–85.3)
Age ≥ 70 years (A70)	97.6 (95–100.3)	79.8 (77.4–82.4)

*$M > F$ ($p < 0.01$), NHB > HISP > NHW > OTH ($p \leq 0.03$), all pairwise differences among age groups were statistically significantly different at $p \leq 0.02$ except those between A20 and A30 and between A60 and A70.

**$M > F$ ($p < 0.01$), NHB > HISP > NHW > OTH ($p \leq 0.04$), all pairwise differences among age groups were statistically significantly different at $p \leq 0.02$ except those between A6 and A60, A6 and A70, A20 and A30 and between A60 and A70.

statistical differences between UGMs were done using *t*-test. All pairwise UGMs were considered to be statistically significant if $\alpha < 0.05$.

2.5.1. Analysis of urine creatinine data

First a regression model with log 10(UCR_{Obs}) as dependent variable and age, gender, race/ethnicity, and BMI as dependent variables for NHANES 2007–2010 data was fitted. The regression slopes (β) and their standard errors (SE) for each of the 64 categories formed by 2 genders, 4 race/ethnicities, and 8 age categories were computed. Values of log 10(UCR_{Corr}) were computed for each participant in each of the 64 categories by subtracting a randomly drawn normal variate $N(\beta_i, SE^2_i)$ for the *i*th category from log 10(UCR_{Obs}). Table 4 provides β and SE for each of these 64 categories. Next,

Table 4. Slopes and standard errors of slopes by combinations of age, gender, and race/ethnicity (CATS_G_R_A) for the model fitted for log 10 transformed values of urine creatinine with CATS_G_R_A and body mass index used as independent variables in the model*. Data from National Health and Nutrition Examination Survey 2007–2010

Row	Gender	Race/ethnicity	Age in years	Slope	Standard error
1	Male	Non-Hispanic White	6–12	0.148096	0.0605576
2			12–19	0.315778	0.0553185
3			20–29	0.294669	0.0568377
4			30–39	0.200626	0.0574311
5			40–49	0.208201	0.057859
6			50–59	0.178453	0.0530254
7			60–69	0.143568	0.0525619
8			≥70	0.135787	0.0550916
9		Non-Hispanic Black	6–12	0.221922	0.0566471
10			12–19	0.399809	0.0591483
11			20–29	0.430921	0.0557101
12			30–39	0.386519	0.0589081
13			40–49	0.30341	0.0597381
14			50–59	0.303954	0.0605754
15			60–69	0.265808	0.0581445
16			≥70	0.268518	0.065233005
17		Hispanic	6–12	0.129248	0.057357
18			12–19	0.277913	0.0554802
19			20–29	0.269241	0.0518996
20			30–39	0.244965	0.0570431
21			40–49	0.24595	0.052828
22			50–59	0.214864	0.0541762
23			60–69	0.157343	0.0520925
24			≥70	0.176694	0.0590139
25		Other race/ethnicity	6–12	0.118987	0.0831046
26			12–19	0.253322	0.0617044
27			20–29	0.213729	0.0607875
28			30–39	0.234844	0.0552653
29			40–49	0.187221	0.064117693
30			50–59	0.233232	0.0609498
31			60–69	0.142311	0.072895093
32			≥70	0.212541	0.062668111

(*Continued*)

Table 4. (*Continued*)

Row	Gender	Race/ethnicity	Age in years	Slope	Standard error
33	Female	Non-Hispanic White	6–12	0.088864	0.0517534
34			12–19	0.219043	0.0587706
35			20–29	0.160863	0.0572401
36			30–39	0.078432	0.063614285
37			40–49	0.045087	0.0573441
38			50–59	−0.04519	0.0534013
39			60–69	−0.03239	0.0566947
40			≥70	−0.00956	0.0547967
41		Non-Hispanic Black	6–12	0.125388	0.0621399
42			12–19	0.330725	0.0614309
43			20–29	0.352766	0.053506
44			30–39	0.254497	0.05949
45			40–49	0.217059	0.0561932
46			50–59	0.172472	0.065020643
47			60–69	0.111914	0.060535
48			≥70	0.096324	0.0586921
49		Hispanic	6–12	0.054322	0.0586872
50			12–19	0.24098	0.0520909
51			20–29	0.168985	0.059269
52			30–39	0.142251	0.0538136
53			40–49	0.053249	0.0593633
54			50–59	0.048277	0.0624553
55			60–69	−0.00275	0.0607953
56			≥70	−0.04502	0.065866793
57		Other race/ethnicities	6–12	0.03117	0.062504891
58			12–19	0.218774	0.078029721
59			20–29	0.152808	0.092518613
60			30–39	0.053096	0.083483762
61			40–49	0.058179	0.0594316
62			50–59	−0.10556	0.068935688
63			60–69	−0.21646	0.080355112
64			≥70	0	0

*N used in the model was 15,997, R^2 was 15.4%, and slope for body mass index was 0.0073716.

a regression model for NHANES 2007–2010 data with log 10(UCR_{Corr}) as the dependent variable and age, gender, race/ethnicity, and body mass index as the independent variable was fitted. If the procedure of modifying log 10(UCR_{Corr}) from log 10(UCR_{Obs}) was a success, in the model with log 10(UCR_{Corr}) as the dependent variable, the model effect of age, gender, and race/ethnicity should no longer be statistically significant. These results are provided in Table 5. The adequacy of method to modify log 10(UCR_{Corr}) from log 10(UCR_{Obs}) was further tested by applying the modification procedure to NHANES data for 2011–2012 and 2013–2014. These results are provided in Table 6.

Table 5. Model effect statistics when regression models were fitted for log 10 transformed values of urine creatinine in mg/dL uncorrected and corrected for the effect of age, gender, race/ethnicity, and body mass index for the levels of urine creatinine. Data from National Health and Nutrition Examination Survey 2007–2010

		Uncorrected model		Corrected model	
		F	*p*	*F*	*p*
Cats 64, body mass index	Model	448.4	<0.01	33.6	<0.01
	Intercept	22899.5	<0.01	18174.6	<0.01
	Cats	186.6	<0.01	1.5	0.13
	Body mass index	375.1	<0.01	387.2	<0.01
	N	15997		15997	
	R^2	15.4%		3.0%	
Age, gender, race/ethnicity, body mass index	Model	290.1	<0.01	74.2	<0.01
	Intercept	22071.2	<0.01	18243.7	<0.01
	Gender	606.9	<0.01	0.0	0.99
	Race/ethnicity	129.7	<0.01	0.0	0.99
	Age	119.1	<0.01	0.1	1.00
	Body mass index	383.3	<0.01	383.0	<0.01
	N	15997		15997	
	R^2	14.4%		3.0%	

Table 6. Model effect statistics when regression models were fitted for log 10 transformed values of urine creatinine in mg/dL corrected for the effect of age, gender, race/ethnicity, and body mass index for the levels of urine creatinine. Data from National Health and Nutrition Examination Survey 2011–2014

		Survey year			
		2011–2012		2013–2014	
		F	*p*	*F*	*p*
Age, gender, race/ethnicity, body mass index	Model	78.03050541	<0.01	114.7671801	<0.01
	Intercept	5,048.981344	<0.01	3,579.002001	<0.01
	Gender	0.187158739	0.67	0.216593718	0.65
	Race/ethnicity	2.652692216	0.08	2.444985999	0.10
	Age	3.612729443	0.01**	4.05724393	0.01*
	Body Mass Index	125.6361483	<0.01	81.7091196	<0.01
	N	7,499		7,986	
	R^2	5.3%		5.1%	

*Statistically significant differences between those aged 20–29 years old and 30–39 years old ($p = 0.01$), 60–69 years old ($p = 0.04$) and ≥70 years old ($p = 0.02$); between those aged 30–39 and 60–69 years old ($p = 0.01$); and between those aged 60–69 and ≥70 years old ($p = 0.03$) were observed.

**Statistically significantly differences between those aged 12–19 and 60–69 years old ($p = 0.02$) and ≥70 years old and between those aged 30–39 and 60–69 years old ($p = 0.03$) were observed.

Table 7. Creatinine corrected and modified creatinine-corrected geometric means (GM) with 95% confidence intervals for 3-phenoxybenzoic acid by age, gender, and race/ethnicity. Data from National Health and Nutrition Examination Survey 2009–2010

	Creatinine corrected GM in ng/mg creatinine	Modified creatinine corrected GM in ng/mg creatinine
6–11 (A6)	0.744 (0.537–1.031)	0.986 (0.72–1.351)
12–19 (A12)	0.347 (0.302–0.399)	0.668 (0.585–0.762)
20–64 (A20+)	0.429 (0.401–0.46)	0.613 (0.572–0.658)
65+ (A65+)	0.42 (0.377–0.467)	0.477 (0.423–0.538)
Males (*M*)	0.377 (0.348–0.409)	0.636 (0.588–0.688)
Females (*F*)	0.507 (0.453–0.566)	0.612 (0.549–0.683)
Non-Hispanic White (NHW)	0.451 (0.416–0.488)	0.608 (0.565–0.655)
Non-Hispanic Black (NHB)	0.354 (0.282–0.444)	0.678 (0.542–0.847)
Hispanics (HISP)	0.414 (0.379–0.452)	0.62 (0.566–0.681)
Other race/ethnicities (OTH)	0.55 (0.415–0.73)	0.705 (0.523–0.951)
Statistically Significant Differences	A6 > A12 ($p < 0.01$), A6 > A20+ ($p < 0.01$), A6 > A65+ ($p < 0.01$), A12 < A20+ ($p < 0.01$), A12 < A65+ ($p = 0.04$), M < F ($p < 0.01$), NHW > NHB ($p = 0.03$), NHB < OTH ($p = 0.01$), HISP < OTH ($p = 0.047$)	A6 > A12 ($p = 0.01$), A6 > A20+ ($p < 0.01$), A6 > A65+ ($p < 0.01$), A12 > A20+ ($p < 0.01$), A12 > A65+ ($p < 0.01$)

2.5.2. Analyses of data for 3-PBA, UCD, UPB, UPC8, UNO3, and UTHIO

Data for 3-PBA, UCD, UPB, UPC8, UNO3, and UTHIO were analyzed in two different ways. First, UGM_{Corr1} by gender, age, and race/ethnicity, based on the values of $UAC_{Corr1} = UAC_{Obs}/UCR_{Obs}$ were computed, then UGM_{Corr2} by gender, age, and race/ethnicity, based on the values of $UAC_{Corr2} = UAC_{Obs}/UCR_{Corr}$ were computed. These results are provided in Table 7 for 3-PBA, in Table 9 for UPC8, UNO3, and UTHIO, and in Table 8 for UCD and UPB.

3. Results

3.1. Urine creatinine statistics

When the distribution of an analyte is positively skewed, the mean of the distribution is supposed to be substantially higher than its geometric mean (GM) and that is exactly what was observed for the distribution of UCR_{Obs} (Table 3). Irrespective of age, gender, and race/ethnicity, means were generally higher than GM by about 20–30%. For example, for females, while mean was 106.1 mg/dL, the GM was 82.3 mg/dL (Table 3) for a difference of about 29%.

In order to fit the model for log 10(UCR_{Obs}), 64 age, gender, race/ethnicity were used as the categorical independent variable and category representing OTH females aged ≥70 years was used as the reference category. The regression slopes (β) with respect to the reference category with their standard errors (SE) for the other 63 categories are given in Table 4. In order to analyze data for any urinary analyte, a randomly drawn value of β from $N(\beta,SE^2)$ for a specific gender-age-race/ethnicity category as listed in Table 4 should be subtracted from the observed log 10 transformed value of UCR or log 10(UCR_{obs}) to compute the corrected log 10 transformed value of UCR or log 10(UCR_{Corr}). For example, if log 10(UCR_{obs}) for a NHB male, aged 41 year was 2.3 mg/dL, then as listed in Table 4, Row 13, a randomly drawn variate from $N(0.30341,0.597381^2)$ should be subtracted from 2.3. If this randomly drawn variate from $N(0.30341,0.597381^2)$ was 0.385, then log 10(UCR_{Corr}) will be 2.3–0.385 or 1.915 and UCR_{Corr} will be $10^{1.915}$ or 82.2 mg/dL.

Table 8. Creatinine corrected and modified creatinine-corrected geometric means (GM) with 95% confidence intervals for urinary cadmium and lead by age, gender, and race/ethnicity. Data from National Health and Nutrition Examination Survey 2013–2014

Demographic group	Creatinine corrected GM in ng/mg creatinine	Modified creatinine corrected GM in ng/mg creatinine
Urine cadmium		
Age: 6–11 years (A6)	0.054 (0.05–0.059)	0.071 (0.066–0.077)
Age: 12–19 years (A12)	0.058 (0.053–0.064)	0.11 (0.1–0.121)
Age: 20–64 years (A20+)	0.16 (0.153–0.169)	0.229 (0.215–0.243)
Age: 65+ years (A65+)	0.318 (0.281–0.358)	0.366 (0.328–0.409)
Males (*M*)	0.118 (0.108–0.128)	0.198 (0.183–0.214)
Females (*F*)	0.174 (0.162–0.186)	0.21 (0.195–0.226)
Non-Hispanic White (NHW)	0.15 (0.137–0.163)	0.201 (0.185–0.218)
Non-Hispanic Black (NHB)	0.136 (0.114–0.162)	0.256 (0.22–0.299)
Hispanics (HISP)	0.113 (0.1–0.127)	0.167 (0.151–0.186)
Other race/ethnicities (OTH)	0.183 (0.155–0.216)	0.24 (0.208–0.277)
Statistically significant differences	A6 < A20+ ($p < 0.01$), A6 < A65+ ($p < 0.01$), A12 < A20+ ($p < 0.01$), A12 < A65+ ($p < 0.01$), A20+ < A65+ ($p < 0.01$), M < F ($p < 0.01$), NHW > HISP ($p < 0.01$), NHW < OTH ($p = 0.04$), HISP < OTH ($p < 0.01$)	A6 < A12 < A20+ < A65+ ($p < 0.01$), NHW < NHB ($p < 0.01$), NHW > HISP ($p < 0.01$), NHW < OTH ($p = 0.04$), NHB <HISP ($p < 0.01$), HISP < OTH ($p < 0.01$)
Urine lead		
Age: 6–11 years (A6)	0.331 (0.297–0.37)	0.436 (0.391–0.487)
Age: 12–19 years (A12)	0.182 (0.16–0.208)	0.345 (0.304–0.392)
Age: 20–64 years (A20+)	0.317 (0.3–0.336)	0.453 (0.424–0.484)
Age: 65+ Years (A65+)	0.513 (0.465–0.565)	0.591 (0.535–0.652)
Males (M)	0.315 (0.293–0.339)	0.531 (0.493–0.571)
Females (F)	0.325 (0.303–0.348)	0.392 (0.366–0.42)
Non-Hispanic White (NHW)	0.329 (0.306–0.353)	0.442 (0.411–0.476)
Non-Hispanic Black (NHB)	0.282 (0.251–0.317)	0.532 (0.48–0.589)
Hispanics (HISP)	0.301 (0.276–0.328)	0.446 (0.406–0.489)
Other race/ethnicities (OTH)	0.351 (0.311–0.396)	0.461 (0.408–0.52)
Statistically significant differences	A6 < A12 ($p < 0.01$), A6 < A65+ ($p < 0.01$), A12 < A20+ ($p < 0.01$), A12 < A65+ ($p < 0.01$), A20+ < A65+ ($p < 0.01$), NHW > NHB ($p = 0.02$), NHW > HISP ($p = 0.02$), NHB < OTH ($p < 0.01$), HSP < OTH ($p < 0.01$)	A6 > A12 ($p < 0.01$), A6 > A65+ ($p < 0.01$), A12 < A20+ ($p < 0.01$), A12 < A65+ ($p < 0.01$), A20+ < A65+ ($p < 0.01$), M > F ($p < 0.01$), NHW < NHB ($p < 0.01$), NHB > HISP ($p < 0.01$)

Based on UCR_{Obs}, males were found to have statistically significantly higher means (137.4 vs. 106.1 mg/dL, $p < 0.01$, Table 3) as well as GMs (114.0 vs. 82.3 mg/dL, $p < 0.01$, Table 3) than females. The order of means as well as GMs by race/ethnicity was NHB (160.3, 132.6 mg/dL) > NHW (115.3, 91.5 mg/dL) > HISP (124.1, 101.2 mg/dL) > OTH (109.0, 86.0 mg/dL) and all pairwise differences were statistically significant ($p \leq 0.04$, Table 3). Those aged 12–19 and 20–29 years had the highest means and GMs and those aged 6–11 and ≥70 years had the lowest means and GMs (Table 3).

Table 9. Creatinine corrected and modified creatinine-corrected geometric means (GM) with 95% confidence intervals for urinary perchlorate, nitrate, and thiocyanate by age, gender, and race/ethnicity. Data from National Health and Nutrition Examination Survey 2011–2012

Demographic group	Creatinine corrected GM in ng/mg creatinine	Modified creatinine corrected GM in ng/mg creatinine
Urine perchlorate		
Age: 6–11 years (A6)	5.559 (5.046–6.124)	7.274 (6.467–8.181)
Age: 12–19 years (A12)	2.699 (2.503–2.911)	5.205 (4.86–5.574)
Age: 20–64 years (A20+)	3.218 (2.998–3.455)	4.56 (4.325–4.808)
Age: 65+ years (A65+)	3.729 (3.178–4.374)	4.353 (3.745–5.06)
Males (M)	3.117 (2.839–3.423)	5.221 (4.809–5.669)
Females (F)	3.647 (3.417–3.892)	4.413 (4.17–4.671)
Non-Hispanic White (NHW)	3.578 (3.353–3.819)	4.793 (4.507–5.097)
Non-Hispanic Black (NHB)	2.277 (2.104–2.464)	4.297 (4.007–4.608)
Hispanics (HISP)	3.51 (2.938–4.192)	5.227 (4.372–6.248)
Other race/ethnicities (OTH)	3.593 (3.197–4.037)	4.79 (4.326–5.303)
Statistically significant differences	A6 > A12 ($p < 0.01$), A6 > A20 ($p < 0.01$), A6 > A65 ($p < 0.01$), A12 < A20+ ($p < 0.01$), A12 < A65+ ($p < 0.01$), A20 < A65 ($p = 0.048$), M < F ($p < 0.01$), NHW > NHB ($p < 0.01$), NHB < HISP ($p < 0.01$), NHB < OTH ($p < 0.01$)	A6 > A12 ($p < 0.01$), A6 > A20 ($p < 0.01$), A6 > A65 ($p < 0.01$), A12 < A65 ($p < 0.01$), A20 < A65 ($p < 0.01$), M < F ($p < 0.01$), NHW > NHB ($p = 0.04$), NHB < HISP ($p = 0.03$)
Demographic group	Creatinine corrected GM in µg/mg creatinine	Modified creatinine corrected GM in µg/mg creatinine
Urinary nitrate		
Age: 6–11 years (A6)	68.039 (63.314–73.116)	89.028 (82.049–96.6)
Age: 12–19 Years (A12)	42.162 (39.563–44.932)	81.295 (76.678–86.19)
Age: 20–64 years (A20+)	48.479 (45.098–52.113)	68.696 (64.839–72.782)
Age: 65+ years (A65+)	39.44 (35.884–43.349)	46.049 (42.143–50.316)
Males (M)	44.126 (41.788–46.595)	73.911 (71.132–76.799)
Females (F)	51.442 (47.715–55.46)	62.255 (58.095–66.714)
Non-Hispanic White (NHW)	50.059 (47.084–53.222)	67.056 (62.47–71.979)
Non-Hispanic Black (NHB)	34.876 (33.115–36.729)	65.804 (63.345–68.359)
Hispanics (HISP)	45.769 (42.359–49.454)	68.158 (63.565–73.084)
Other race/ethnicities (OTH)	57.706 (52.176–63.821)	76.936 (70.328–84.165)
Statistically significant differences	A6 > A12 ($p < 0.01$), A6 > A20+ ($p < 0.01$), A6 > A65+ ($p < 0.01$), A12 < A20+ ($p < 0.01$), A20+ > A65+ ($p = 0.02$), M < F ($p < 0.01$), NHW > NHB ($p < 0.01$), NHW < OTH ($p = 0.02$), NHB < HISP ($p < 0.01$), NHB < OTH ($p < 0.01$), HISP < OTH ($p < 0.01$	A6 > A20+ ($p < 0.01$), A6 > A65+ ($p < 0.01$), A12 > A20+ ($p < 0.01$), A12 > A65+ ($p = 0.04$), A20+ > A65+ ($p = 0.01$), M < F ($p < 0.01$), NHW < OTH ($p < 0.01$), NHB < OTH ($p < 0.01$)
Urinary thiocyanate		
Age: 6–11 years (A6)	1.277 (1.161–1.404)	1.671 (1.506–1.854)
Age: 12–19 years (A12)	0.958 (0.831–1.104)	1.847 (1.594–2.14)
Age: 20–64 years (A20+)	1.383 (1.295–1.478)	1.96 (1.847–2.08)
Age: 65+ years (A65+)	0.926 (0.81–1.058)	1.081 (0.943–1.238)

(*Continued*)

Table 9. (*Continued*)		
Males (M)	1.196 (1.112–1.287)	2.004 (1.851–2.17)
Females (F)	1.287 (1.171–1.413)	1.557 (1.423–1.703)
Non-Hispanic White (NHW)	1.414 (1.311–1.525)	1.894 (1.745–2.056)
Non-Hispanic Black (NHB)	1 (0.897–1.115)	1.887 (1.694–2.104)
Hispanics (HISP)	0.964 (0.822–1.13)	1.435 (1.226–1.68)
Other race/ethnicities (OTH)	0.993 (0.866–1.138)	1.324 (1.159–1.512)
Statistically significant differences	A6 > A12 ($p < 0.01$), A6 > A65 ($p < 0.01$), A12 < A20+ ($p < 0.01$), A20+ > A65+ ($p < 0.01$), NHW > NHB ($p < 0.01$), NHW > HISP ($p < 0.01$), NHW > OTH ($p < 0.01$)	A6 > A20+ ($p < 0.01$), A6 > A65+ ($p < 0.01$), A20+ > A65+ ($p < 0.01$), A20+ > A65+ ($p < 0.01$), M > F ($p < 0.01$), NHW > HISP ($p < 0.01$), NHW > OTH ($p < 0.01$), NHB > HISP ($p < 0.01$, NHB > OTH ($p < 0.01$)

3.2. Adequacy of fitted models for UCR_{Obs}

Neither gender-age-race/ethnicity categories nor gender, age, and race/ethnicity remained statistically significant after the models were fitted for the modified values of log 10(UCR_{Obs}) or log 10(UCR_{Corr}) for the 2007–2010 data as would be expected. However, R^2 decreased about 15% to about 3% (Table 5) as would be expected. This is explained further in the Discussion section. However, when the models for log 10(UCR_{Corr}) were fitted for 2011–2012 and 2013–2014 data, while the model effects of gender and race/ethnicity still remained statistically insignificant, effect of age became statistically significant (Table 6).

3.3. Statistics for 3-PBA

UGMs for 3-PBA based on UCR_{obs} and UCR_{Corr} are presented in Table 7. UGMs based on UCR_{Corr} were higher than those based on UCR_{obs} irrespective of age, gender, and race/ethnicity. Males had lower UGMs than females ($p < 0.01$) based on UCR_{obs} but these differences were not observed for UGMs based on UCR_{Corr} (Table 7). Similarly, based on UCR_{obs}, UGMs for NHW > NHB ($p = 0.03$) but these differences disappeared for UGMs based UCR_{Corr} (Table 7).

3.4. Statistics for UCD

UGMs for UCD based on UCR_{obs} and UCR_{Corr} are presented in Table 8. UGMs based on UCR_{Corr} were higher than those based on UCR_{obs} irrespective of age, gender, and race/ethnicity. However, the magnitude by which UGMs for UCD_{Corr2} was higher than UGMs for UCD_{Corr1} varied by gender, race/ethnicity, and age. For example, for females, UGM for UCD_{Corr2} was 0.210 ng/mg creatinine and UGM for UCD_{Corr1} was 0.174 ng/mg creatinine or a difference of about 21%. For those aged 12–19 years, UGM for UCD_{Corr2} was 0.11 ng/mg creatinine and UGM for UCD_{Corr1} was 0.058 ng/mg creatinine or a difference of about 90%. Males had lower UGM for UCD_{Corr1} than females ($p < 0.01$, Table 8) but UGMs between males and females for UCD_{Corr2} were not statistically significantly different (Table 8). NHW had lower UGMs for UCD_{Corr2} than NHB ($p < 0.01$) but these differences were not observed between the UGMs based on UCD_{Corr1}.

3.5. Statistics for UPB

UGMs for UPB based on UCR_{obs} and UCR_{Corr} are presented in Table 8. UGMs based on UCR_{Corr} were higher than those based on UCR_{obs} irrespective of age, gender, and race/ethnicity. Statistically significant differences for UGMs between males and females were not observed for UPB_{Corr1} but males had higher UGM than females for UPB_{Corr1} ($p < 0.01$, Table 8). The order in which UGMs for UPB_{Corr1} by race/ethnicity was observed was OTH > NHW > HISP > NHB but the order in which UGMs for UPB_{Corr2} was NHB > OTH > HISP > NHW (Table 8). While NHW had higher UGM for UPB_{Corr1} than NHB ($p = 0.02$), the reverse was observed for UPB_{Corr2} ($p < 0.01$, Table 8).

3.6. Statistics for UPC8

UGMs for $UPC8_{Corr2}$ were consistently higher than UGMs for $UPC8_{Corr1}$. However, the magnitude of differences between UGMs for $UPC8_{Corr1}$ and $UPC8_{Corr2}$ varied with age, gender, and race/ethnicity. For example, UGMs for A12 were 2.699 and 5.205 ng/mg creatinine for $UPC8_{Corr1}$ and $UPC8_{Corr2}$, respectively, for a difference of about 93%. For OTH, UGMs for A12 were 3.593 and 4.790 ng/mg creatinine for $UPC8_{Corr1}$ and $UPC8_{Corr2}$, respectively (Table 9), for a difference of about 22%. While UGMs for A12 were statistically lower than for A20+ ($p < 0.01$) for $UPC8_{Corr1}$, these differences were not observed for $UPC8_{Corr2.}$ The order of UGMs by race/ethnicity for $UPC8_{Corr1}$ was OTH > NHW > HISP > NHB but for $UPC8_{Corr2}$, the order was HISP > NHW > OTH > NHB (Table 9).

3.7. Statistics for UNO3

UGMs for $UNO3_{Corr2}$ were consistently higher than UGMs for $UNO3_{Corr1}$. However, the magnitude of differences between UGMs for $UNO3_{Corr1}$ and $UNO3_{Corr2}$ varied with age, gender, and race/ethnicity. For example, UGMs for A12 for $UNO3_{Corr1}$ and $UNO3_{Corr1}$ were 42.162 and 81.295 µg/mg creatinine, respectively (Table 9), for a difference of 93%. On the other hand, UGMs for A65+ $UNO3_{Corr1}$ and $UNO3_{Corr1}$ were 39.44 and 46.049 µg/mg creatinine, respectively (Table 9), for a difference of 17%. While UGMs for $UNO3_{Corr1}$ between A12 and A20+ were statistically significantly different (2.699 vs. 3.218 µg/mg creatinine, $p < 0.01$, Table 9), these differences were not statistically significantly different for $UNO3_{Corr2}$.

3.8. Statistics for UTHIO

UGMs for $UTHIO_{Corr2}$ were consistently higher than UGMs for $UTHIO_{Corr1}$. However, the magnitude of differences between UGMs for $UTHIO_{Corr1}$ and $UTHIO_{Corr2}$ varied with age, gender, and race/ethnicity. For example, UGMs for A6 for $UTHIO_{Corr1}$ and $UTHIO_{Corr1}$ were 1.277 and 1.671 µg/mg creatinine, respectively (Table 9), for a difference of 31%. On the other hand, UGMs for NHB for $UTHIO_{Corr1}$ and $UTHIO_{Corr1}$ were 1.0 and 1.887 µg/mg creatinine, respectively (Table 9), for a difference of about 89%. While for $UTHIO_{Corr1}$, NHW had statistically significantly higher $UTHIO_{Corr1}$ ($p < 0.01$, Table 9) than NHB, these differences were not found to be statistically significant for $UTHIO_{Corr2}$. On the other hand, NHB had statistically significantly higher $UTHIO_{Corr2}$ ($p < 0.01$, Table 9) than HISP, these differences were not found to be statistically significant for $UTHIO_{Corr1}$.

4. Discussion

Traditional methods to compute creatinine-corrected analyte concentrations in urine ignore variability in the observed levels of urine creatinine due to factors other than hydration. In this paper, a modified method to compute creatinine-corrected analyte concentrations that also adjusts for variability in the observed urine creatinine measurements due to age, gender, race/ethnicity, and BMI was presented. Regression slopes (β) of correction factors with their standard errors (SE) that need to be applied to the observed values of urine creatinine before using them in the denominator to compute creatinine-corrected analyte concentrations were presented for 64 combinations of 2 genders, 8 age groups, and 4 racial/ethnic groups in Table 4. A random number from a normal distribution, $N(\beta,SE^2)$ should be used to adjust (subtract) log 10 transformed observed values of urine creatinine for an individual located in one of the 64 age-race/ethnicity-gender categories before creatinine-corrected analyte concentrations are computed for that particular individual. Analysis tool pack freely available in Excel can be easily used to generate this random number by providing mean β and SE as the standard deviation.

4.1. Urine creatinine levels

Order of observed urine creatinine means and geometric means (Table 3) by age, gender, and race/ethnicity in this study was the same as reported by Barr et al. (2005). However, for every age, gender, and race/ethnic category, means reported by Barr et al. (2005) were higher than those observed in this study. For example, while mean reported by Barr et al. (2005) for NHW was 124.6 mg/dL, the mean observed for this study was 115.3 mg/dL, a difference of 9.3 mg/dL. For those aged 12–19 years, the mean reported by Barr et al. (2005) was 161.5 mg/dL, the mean observed for this study was 147.2 mg/dL, a difference of 14.3 mg/dL. On the other hand, for those aged 40–49 years, the

mean reported by Barr et al. (2005) was 124.6 mg/dL, the mean observed for this study was 122.5 mg/dL or the differences were minimal. The data reported by Barr et al. (2005) were for the years 1998–1994 and the data reported for this study were for the years 2007–2010. It is possible that the levels of UCR over time may have decreased. More work will be needed to confirm this observation and explain the factors that may be responsible for decreasing time trends in the observed levels of UCR.

4.2. Adequacy of the model fitted for UCR_{Corr}

The sole purpose of fitting a model for UCR_{Corr} was to remove the variability in UCR_{Obs} that can be attributed to gender, age, and race/ethnicity. If the fit for the model for UCR_{Corr} was a success, estimated model effects for gender, age, and race/ethnicity should not be statistically significant. And, in fact, this is what was observed (Table 5). In the model fitted for UCR_{Obs}, estimated correction factors to be applicable to UCR_{Obs} were based on 64 combinations of age, gender, and race/ethnicity with the combination representing OTH females aged ≥70 being used as the reference category. It is certainly possible to use different numbers (lower or higher) of the combinations of age, gender, and race/ethnicity with a different combination of age, race/ethnicity, and gender, for example, NHB males aged 20–29 years as the reference category. It should not make a major difference but it is unknown in what way, this could have affected the estimated correction factors and the final model fit. Since the sole purpose of fitting a model for UCR_{Corr} was to remove the variability attributable to gender, age, and race/ethnicity, R^2 for the model for UCR_{Corr} should be expected to be smaller than the R^2 for the model for UCR_{Obs} and that is exactly what was observed (Table 5).

There is always a concern that a model fitted for one data-set may not perform well when used for a different data-set. In order to address that concern, correction factors estimated by fitting model for UCR_{Obs} for NHANES 2007–2010 data were used to fit models for UCR_{Corr} for both NHANES 2011–2012 and 2013–2014 data-sets. While model effects remained statistically insignificant for both gender and race/ethnicity for models for both 2011–2012 and 2013–2014 data-sets, model effect for age was observed to be statistically significant for the models for both 2011–2012 and 2013–2014 data (Table 6). However, out of a total of 28 possible pairwise combinations of eight age groups, only four pairwise comparisons for 2013–2014 data-set and three pairwise comparisons for 2011–2012 data-set were found to be statistically significant.

4.3. Urinary creatinine corrected analyte concentrations – two alternate approaches

In order to compare the mean or geometric mean values of UAC_{Corr1} and UAC_{corr2}, it is necessary to understand the factors and the direction of effect they may have on both the numerators and denominators used in computing UAC_{Corr1} and UAC_{corr2}. As has been shown in this study as well as by Barr et al. (2005), NHB had higher levels of UCR than NHW. As such, in order to neutralize the effect of race/ethnicity on UCR_{Obs}, UCR_{Obs} will need to be adjusted downwards for NHB and upwards for NHW or $UCR_{Corr} < UCR_{Obs}$ for NHW and $UCR_{Corr} > UCR_{Obs}$ for NHB. If race/ethnicity did not affect UAC_{Obs}, then $UAC_{Corr1} > UAC_{Corr2}$ for NHB and $UAC_{Corr1} < UAC_{Corr2}$ for NHW. If race/ethnicity does affect both UCR_{Obs} and UAC_{Obs}, then the difference in mean or geometric mean values of UAC_{Corr1} and UAC_{Corr2} may be small or large, positive or negative. Consequently, small differences, if so observed between UAC_{Corr1} and UAC_{Corr2}, should not be of concern nor it should be concluded that adjustment in the values of UCR_{Obs} is of no significance. Emphasis should be placed on appropriate analytical methodology and the research has proven that the values of UCR_{Obs}, in addition to urinary dilution, are also affected by age, gender, race/ethnicity, BMI, and possibly other factors. It should also be remembered that there are multiple factors, possibly in opposite directions, which affect UCR_{Obs}. For example, for NHB children 6–11 years old, UCR_{Obs} need to be adjusted downward because of NHB race/ethnicity but upwards because of age. In order to compare the adequacy of analyte estimates based on UCR_{Corr}, it will be unwise to make comparisons between the analyte levels based on UCR_{Obs} and UCR_{Corr} as alluded to above. Pairwise analyte differences based on the use of UCR_{Obs} and UCR_{Corr} can switch from being (i) statistically significant to statistically insignificant as was seen for male–female differences for 3-PBA (Table 7) and for A12-A20+ differences for UPC8, (ii) statistically insignificant to statistically significant as was seen for NHW–NHB differences for UCD (Table 8), and (iii) statistically

significant in one direction to statistically significant in the opposite direction as was seen for NHW–NHB differences for UPB and A12-A20+ differences for UNO3. No correspondence should be inferred for the urinary analyte concentrations based on the use of UCR_{Obs} and UCR_{Corr}.

UCR_{Obs} as well as UCR_{Corr} based concentrations of 3-PBA for this study were found to be substantially higher than both UCR_{Obs} based concentrations of 3-PBA reported by Barr et al. (2010) for NHANES data for 1999–2000 and 2001–2002, respectively, irrespective of age, gender, and race/ethnicity. For example, geometric mean for UCR_{Obs} based 3-PBA concentration for males for this study was found to be 0.377 ng/mg creatinine but 0.210 ng/mg creatinine for 1999–2000 and 0.269 ng/gm creatinine for 2001–2002 by Barr et al. (2010). Also, 3-PBA concentrations were usually reported to be higher for 2001–2002 than for 1999–2000 indicating increasing levels of 3-PBA with time (Barr et al., 2010). In a recent study, Jain (2015) confirmed increasing trends in levels of 3-PBA when 2009–2010 levels were compared with 2001–2002 levels. There was no difference in this study and the study by Barr et al. (2010) in the order in which 3-PBA levels by age and gender were observed but while the order of UCR_{Obs} based 3-PBA concentrations reported by Barr et al. (2010) was NHB > NHW > Mexican Americans, the order observed for this study was NHW > HISP > NHB. However, the order based on UCR_{Corr} was NHB > HISP > NHW (Table 7).

Chen, Kim, Chung, and Dietrich (2013), based on NHANES 2007–2008 data reported UCD_{corr1} GM levels to be 0.07 and 0.25 µg/g creatinine for adolescents aged 12–19 years and adults aged ≥20 years, respectively. For this study, UCD_{Corr1} levels were 0.058 and 0.16 µg/g creatinine for adolescents aged 12–19 years and adults aged 20–64 years, respectively, and UCD_{Corr2} levels were 0.11 and 0.229 µg/g creatinine for adolescents aged 12–19 years and adults aged 20–64 years, respectively (Table 8). Wu, Schaumberg, and Park (2014) reported UCD levels to be 0.29 µg/L among those aged ≥40 years. Using data from NHANES 1999–2000, Navas-Acien et al. (2005) reported UCD levels among those aged ≥40 years to be 0.36 µg/L. This indicates decreased UCD levels over time. Based on data from NHANES 2003–2010, for females aged 17–39 years old, adjusted geometric means for UCD were reported to be 1.771, 1.088, 1.534 µg/L for NHW, NHB, and Mexican American females, respectively (Jain, 2013a). Based on the data from NHANES 1999–2004, UCD_{Corr1} were reported to be 0.22 µg/g creatinine (Richter, Bishop, Wang, & Swahn, 2009) which except for those who were 65+ years old and females are substantially higher than what was found in this study. This may be indicative of decreasing urine cadmium levels over time. Also, Richter et al. (2009) reported UCD_{Corr1} to be 0.09, 0.09, 0.14, 0.27, 0.40, 0.46 µg/g creatinine for those who were aged 6–11, 12–19, 19–35, 35–50, 50–65, and 65+ years, respectively, each of which is higher than what was found for this study for the data for 2013–2014. Similar differences were noted for males (0.18 vs. 0.118 µg/g creatinine in this study), females (0.26 vs. 0.174 µg/g creatinine in this study), NHW (0.23 vs. 0.15 µg/g creatinine in this study), and NHB (0.20 vs. 0.136 µg/g creatinine in this study).

Based on data from NHANES 2003–2010, for females aged 17–39 years old, adjusted geometric means for UPB were reported to be 0.429, 0.412, 0.569 µg/L for NHW, NHB, and Mexican Americans females, respectively (Jain, 2013a). Using data from NHANES 1999–2000, Navas-Acien et al. (2005) reported UPB levels among those aged ≥40 years to be 0.79 µg/L. Based on data from NHANES 1999–2004, UPB_{Corr1} were reported to be 0.66 µg/g creatinine (Richter et al., 2009) which are substantially higher than what was found in this study for 2013–2014. This may be indicative of decreasing urine lead levels over time. Also, Richter et al. (2009) reported UPB_{Corr1} to be 0.97, 0.43, 0.48, 0.65, 0.80, 0.91 µg/g creatinine for those who were aged 6–11, 12–19, 19–35, 35–50, 50–65, and 65+ years, respectively, each of which is higher than what was found for this study. Similar differences were noted for males (0.65 vs. 0.315 µg/g creatinine in this study), females (0.67 vs. 0.325 µg/g creatinine in this study), NHW (0.64 vs. 0.329 µg/g creatinine in this study), and NHB (0.66 vs. 0.282 µg/g creatinine in this study).

Jain (2013b) used 2003–2008 data from NHANES and reported unadjusted UGM levels for UPC8 among females aged 15–44 years to be 2.99 ng/mL. Steinmaus, Miller, Cushing, Blount, and Smith (2013) reported higher levels of UPC8 in 2007–2008 vs. 2001–2002 (5.98 vs. 5.34 ng/mL).

Schreinemachers, Sobus, Williams, and Ghio (2015) used NHANES data 2005–2008 for those aged 12–59 years and reported UPC8 levels to be 4.28 ng/mL among males and 3.53 ng/mL among females. For NHANES 2001–2002, Schreinemachers (2011) reported UPC8 levels to be 5.99 ng/mL among males and 5.03 among females. Ko et al. (2014) reported UPC8 levels among adults aged ≥20 years to be 3.38 ng/mL for NHANES 2005–2006.

Jain (2013b) used 2005–2008 data from NHANES and reported unadjusted UGM levels for UNO3 among females aged 15–44 years to be 40.1 ng/L. For NHANES 2001–2002, Schreinemachers (2011) reported UNO3 levels to be 71.23 mg/L among males and 58.43 mg/L among females. Ko et al. (2014) reported UNO3 levels among adults aged ≥20 years to be 40.36 ng/L for NHANES 2005–2006.

Jain (2013b) used 2005–2008 data from NHANES and reported UGM levels for UTHIO among females aged 15–44 years to be 1.2 ng/L which are similar to the creatinine-corrected levels reported here for 2009–2010. Steinmaus et al. (2013) reported UTHIO levels to be 2.41 ng/mL for NHANES 2001–2002 and 2.53 ng/mL for NHANES 2007–2008. For NHANES 2001–2002, Schreinemachers (2011) reported UTHIO levels to be 2.84 mg/L among males and 2.02 mg/L among females. Ko et al. (2014) reported UTHIO levels among adults aged ≥20 years to be 1.129 ng/L for NHANES 2005–2006.

4.4. Summary and conclusion

Since, urine creatinine levels are not only affected by hydration but also by factors like age, gender, race/ethnicity, BMI, and possibly by diabetes and impaired kidney function and possibly by yet unknown factors, it is necessary that any analysis of urinary concentrations of the chemicals of interest allow adjustments for all factors, to the degree possible, that affect urinary concentration levels of creatinine. This study was focused on the development of methodology where traditional per mg or per g creatinine analyte concentrations need to be reported. As compared to the traditional method of computing creatinine-corrected analyte concentrations in which observed analyte concentration is divided by the observed creatinine concentration, a method that uses modified creatinine concentration in the denominator in place of the observed creatinine concentration was suggested. In this study, a correction factor that can be used to modify observed creatinine concentrations before using them as the denominator to compute per mg or per g creatinine concentrations was estimated for 64 combinations of age, gender, and race/ethnicity. Table 4 developed in this study provides the correction factor β with its standard error SE of this correction factor for these 64 combinations of age, gender, and race/ethnicity. Once a participant is identified as being in one of these 64 categories, a random number drawn from a $N(\beta,SE^2)$ distribution can be used to adjust observed creatinine concentrations before being used as the denominator in computing per g or per mg creatinine analyte concentrations.

Funding
The author received no direct funding for this research.

Author details
Ram B. Jain[1]
E-mail: Jain.ram.b@gmail.com
[1] 2959 Estate View Court, Dacula, GA, USA.

Citation information
Cite this article as: An improved approach to report creatinine-corrected analyte concentrations in urine, Ram B. Jain, *Cogent Environmental Science* (2016), 2: 1259880.

References

Barr, D. B., Wilder, L. C., Caudill, S. P., Gonzalez, A. J., Needham, L. L., & Pirkle, J. L. (2005). Urinary creatinine concentrations in the U.S. population: Implications for urinary biologic monitoring measurements. *Environmental Health Perspectives, 113*, 192–200.

Barr, D. B., Olsson, A. O., Wong, L.-Y., Udunka, S., Baker, S. E., Whitehead, Jr., R. D., … Needham, L. L. (2010). Urinary concentrations of metabolites of pyrethroid insecticides in the general U.S. population: National Health and Nutrition Examination Survey 1999–2002. *Environmental Health Perspectives, 118*, 742–748. doi:10.1289/ehp.0901275

Chen, A., Kim, S. S., Chung, E., & Dietrich, K. N. (2013). Thyroid hormones in relation to lead, mercury, and lead exposure in the National Health and Nutrition Examination Survey, 2007–2008. *Environmental Health Perspectives, 121*, 181–186. doi:10.1289/ehp.1205239

Fram, E. B., Moazami, S., & Stern, J. M. (2015). The effect of disease severity on 24-h urine parameters in kidney stone patients with Type II diabetes. *Urology, pii*, S0090–4295(15)00992-9. doi:10.1016/j.urology.2015.10.013

Giskeodegard, G. F., Davies, S. K., Revell, V. L., Keun, H., & Skene, D. J. (2015). Diurnal rhythms in the human urine metabolome during sleep and total sleep deprivation. *Science Reports, 5*, 14843. doi:10.1038/srep14843

Jain, R. B. (2013a). Effect of pregnancy on the levels of urinary metals for females aged 17–39 years old: Data from National Health and Nutrition Examination Survey 2003–2010. *Journal of Toxicology and Environmental Health: Part A., 76*, 86–97. doi:10.1080/15287394.2013.738171

Jain, R. B. (2013b). Impact of pregnancy and other factors on the levels of urinary perchlorate, thiocyantae, and nitrate among females aged 15–44 years: Data from National Health and Nutrition Examination Survey: 2003–2008. *Chemosphere, 91*, 82–887.

Jain, R. B. (2015). Variability in the levels of 3-phenoxybenzoic acid by age, gender, and race/ethnicity for the period 2001–2002 versus 2009–2010 and its association with thyroid function among general US population. *Environmental Science and Pollution Research.* doi:10.1007/s11356-015-5954-9

Ko, W.-C., Liu, C.-L., Lee, J.-J., Liu, T.-P., Yang, P.-S., Hsu, Y.-C., & Cheng, S.-P. (2014). Negative association between serum parathyroid hormone levels and urinary perchlorate, nitrate, and thiocyanate concentrations in U.S. adults: The National Health and Nutrition Examination Survey 2005–2006. *PLoS ONE, 9*, e115245. doi:10.1371/journal.pone.0115245

Navas-Acien, A., Silbergeld, E. K., Sharrett, A. R., Calderon-Aranda, E., Selvin, E., & Guallar, E. (2005). Metals in urine and peripheral arterial disease. *Environmental Health Perspectives, 113*, 164–169. doi:10.1289/ehp.7329

O'Brien, K. M., Upson, K., Cook, N. R., & Weinberg, C. R. (2015). Environmental chemicals in urine and blood: Improving methods for creatinine and lipid adjustment. *Environmental Health Perspectives.* doi:10.1289/ehp.1509693

Richter, P. A., Bishop, E. E., Wang, J., & Swahn, M. H. (2009). Tobacco smoke exposure and levels of urinary metals in the U.S. youth and adult populations: The National Health and Nutrition Examination Survey (NHANES) 1999–2004. *International Journal of Environmental Health and Public Health, 6*, 1930–1936. doi:10.3390/ijerph6071930

Schreinemachers, D. M. (2011). Association between perchlorate and indirect indicators of thyroid dysfunction in NHANES 2001–2002, a cross-sectional, hypothesis-generating study. *Biomarker Insights., 6*, 135–146. http://dx.doi.org/10.4137/BMI

Schreinemachers, D. M., Sobus, J., Williams, M., & Ghio, A. (2015). Perchlorate exposure is associated with oxidative stress and indicators of serum iron homeostasis among NHANES 2005–2008 subjects. *Biomarker Insights., 10*, 9–19. doi:10.4137/BMI.S20089

Steinmaus, C., Miller, M. D., Cushing, L., Blount, B. C., & Smith, A. H. (2013). Combined effect of perchlorate, thiocyanate, and iodine on thyroid function in the National Health and Nutrition Examination Survey 2007–8. *Environmental Research, 123*. doi:10.1016/j.envres.2013.01.005.

Stiegel, M. A., Pleil, J. D., Sobus, J. R., Angrish, M. M., & Morgan, M. K. (2015). Kidney injury biomarkers and urinary creatinine variability in nominally healthy adults. *Biomarkers, 20*, 436–452. http://dx.doi.org/10.3109/1354750X.2015.1094136

Wu, E. W., Schaumberg, D. A., & Park, S. K. (2014). Environmental cadmium and lead exposures and age-related macular degeneration in US adults: The National Health and Nutrition Examination Survey 2005–2008. *Environmental Research, 133*, 17–184.

Cogent Environmental Science **(ISSN: 2331-1843) is published by Cogent OA, part of Taylor & Francis Group.**

Publishing with Cogent OA ensures:

- Immediate, universal access to your article on publication
- High visibility and discoverability via the Cogent OA website as well as Taylor & Francis Online
- Download and citation statistics for your article
- Rapid online publication
- Input from, and dialog with, expert editors and editorial boards
- Retention of full copyright of your article
- Guaranteed legacy preservation of your article
- Discounts and waivers for authors in developing regions

Submit your manuscript to a Cogent OA journal at www.CogentOA.com