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Urinary Concentrations of the Antibacterial Agent Triclocarban in United States Residents: 2013–2014 National Health and Nutrition Examination Survey

Xiaoyun Ye[*], **Lee-Yang Wong**, **Prabha Dwivedi**, **Xiaoliu Zhou**, **Tao Jia**, and **Antonia M. Calafat**

Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia 30341, United States

Abstract

Triclocarban is widely used as an antibacterial agent in personal care products, and the potential for human exposure exists. We present here the first nationally representative assessment of exposure to triclocarban among Americans ≥6 years of age who participated in the 2013–2014 National Health and Nutrition Examination Survey. We detected triclocarban at concentrations above 0.1 μg/L in 36.9% of 2686 urine samples examined. Triclocarban was detected more frequently in adolescents and adults than in children, and in non-Hispanic black compared to other ethnic groups. In univariate analysis, log-creatinine, sex, age, race, and body surface area (BSA) were significantly associated with the likelihood of having triclocarban concentrations above the 95th percentile. In multiple regression models, persons with BSA at or above the median (≥1.86 m^2) were 2.43 times more likely than others, and non-Hispanic black and non-Hispanic white were 3.71 times and 2.23 times more likely than "all Hispanic," respectively, to have urinary concentrations above the 95th percentile. We found no correlations between urinary concentrations of triclocarban and triclosan, another commonly used antibacterial agent. Observed differences among demographic groups examined may reflect differences in physiological factors (i.e., BSA) as well as use of personal care products containing triclocarban.

Graphical Abstract

[*]Corresponding Author: Phone: 770-488-7502; xay5@cdc.gov (X.Y.).

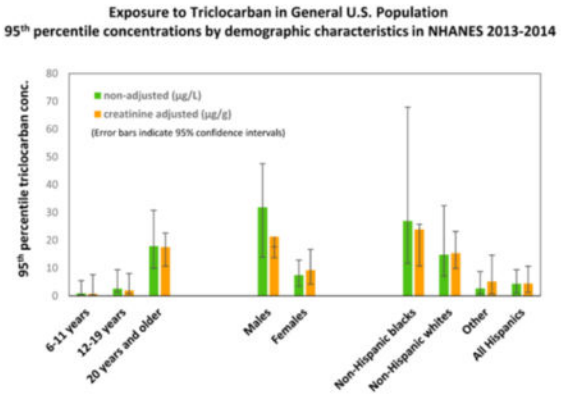
ORCID

Xiaoyun Ye: 0000-0001-5837-2542

Notes

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the US Department of Health and Human Services.

The authors declare no competing financial interest.



INTRODUCTION

3,4,4′-Trichlorocarbanilide (triclocarban) is used as an antibacterial agent in a variety of consumer and personal care products including bar soap, detergent, deodorant, shaving cream, and shampoo.[1–3] Several studies listed triclocarban as active ingredient in about 85% of antibacterial bar soaps examined in the U.S. market, with levels ranging between 0.5% (or 0.005 g/g) and 1.5% (or 0.015 g/g).[4,5] Triclocarban is also used in cleansing preparations in hospitals and other medical settings where the potential risk for the transmission of infections is high.[3]

Human exposure to triclocarban occurs mainly through dermal contact; inhalation of triclocarban-containing dust and ingestion of triclocarban contaminated water and food may also occur.[6,7] The potential adverse health effects of triclocarban in humans are still largely unknown, but previous studies suggested that triclocarban could act as an endocrine disruptor, both in cell-based assays and in rats[8–14] and induced breast cell premalignancy as a cocarcinogen.[15] The reference dose in humans, calculated using the no adverse effect level from a 2 year chronic toxicity rat study, is 0.025 mg kg bw^{-1} d.[16] Epidemiologic data are limited to one study—to evaluate prenatal exposure to triclocarban, triclosan, and parabens and potential adverse birth outcomes in an immigrant population of mothers and their neonates—which reported suggestive associations (albeit no longer present in sensitivity analyses) for triclocarban.[17] Furthermore, recent studies suggested that triclocarban could potentially contribute to bacterial resistance to antibiotics.[18]

Early research on the metabolism of triclocarban in rats indicated that the major biliary and fecal metabolites were free and conjugated triclocarban and 2′-hydroxy-triclocarban.[19,20] In a previous study, we also identified free and conjugated triclocarban, 3′-hydroxy-triclocarban, and 2′-hydroxy-triclocarban as the major urine and serum metabolites in Sprague–Dawley rats.[21] Data on the metabolism of triclocarban in humans also exist.[22–24] In a group of six healthy volunteers, after taking a shower with commercial 0.6% triclocarban containing soap, *N*-glucuronide triclocarban was the major urinary metabolite.[24] Therefore, concentrations of urinary species of triclocarban have been used as valid biomarkers of exposure.[21,25–32]

Because of the well-known use of triclocarban in personal care and consumer products and the environmental persistence of this chemical, triclocarban has been detected in the environment[6,7,33–36] and the potential for human exposure to this chemical exists. Of interest, however, exposure to triclocarban in the United States may change in the future. In September 2016, the U.S. Food and Drug Administration (FDA) issued a final rule establishing that triclocarban and 18 other active ingredients used in over-the-counter antiseptic wash products (e.g., hand washes, body washes) can no longer be marketed.[37] To increase the understanding of the extent of exposure to triclocarban and to set reference ranges which may be used to evaluate whether FDA's rule impacts exposure to triclocarban in the future, we measured the urinary concentrations of triclocarban in participants of the 2013–2014 National Health and Nutrition Examination Survey (NHANES). We also examined the associations between sociodemographic and physiological factors and triclocarban concentrations.

MATERIALS AND METHODS

NHANES, conducted annually since 1999 by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC), is an ongoing survey designed to measure the health and nutritional status of the civilian noninstitutionalized U.S. population.[38] The survey includes household interviews, standardized physical examinations, and collection of medical histories and biologic specimens, some of which are used to assess exposure to environmental chemicals.[38] The NCHS Research Ethics Review Board reviewed and approved the NHANES study protocol. All participants gave informed written consent; parents or guardians provided consent for participants <18 years of age.[38]

For this study, we analyzed 2686 spot urine specimens collected from a random one-third subset of persons ≥6 years of age. Because the subset was random, the representative design of the survey was maintained. The samples were shipped on dry ice to the CDC's National Center for Environmental Health and stored at or below −20 °C until analyzed. We measured the concentrations of total (free plus conjugated) triclocarban in 100 μL of urine by an online solid-phase extraction coupled to high-performance liquid chromatography–isotope dilution–tandem mass spectrometry (online SPE–HPLC–MS/MS) approach modified from a previous published method.[39] The online SPE–HPLC–MS/MS system consisted of several Agilent 1200 modules (Agilent Technologies, Wilmington, DE, U.S.A.) and an ABSciex 5500QTRAP mass spectrometer (Applied Biosystems, Foster City, CA, U.S.A.) equipped with an atmospheric pressure chemical ionization interface. The SPE column was LiChro-CART RP-18 ADS (25 × 4 mm^2, Merck KGaA, Germany) and the HPLC column was Chromolith High Resolution RP-18e (100 × 4.6 mm^2, Merck KGaA, Germany). Triclocarban was purchased from Sigma–Aldrich Laboratories, Inc. (St. Louis, MO) and $^{13}C_6$-triclocarban was obtained from Cambridge Isotope Laboratories, Inc. (Andover, MA). The limit of detection (LOD) was 0.1 μg/L, using 100 μL of urine. The accuracy, calculated from the recovery of three spiking levels (1.0, 5.0, and 10.0 μg/L), ranged from 101% to 105%. We prepared low-concentration (~1.3 μg/L) and high-concentration (~7.8 μg/L) quality control materials (QCL and QCH, respectively) with pooled human urine and analyzed them with standards, reagent blanks, and NHANES samples. The triclocarban concentrations in QC materials were comparable to the 75th and 90th percentile

concentrations of triclocarban obtained from a pilot study (data not shown). The precision of the measurements, expressed as the relative standard deviation of inter and intraday measurements of NHANES 2013–2014 samples in a period of approximately 9 months, was 10.8% for QCL and 6.8% for QCH. For each analytical run, we evaluated the QC concentrations using standard statistical probability rules[40] and examined the concentrations of reagent blanks (of note, we did not detect triclocarban in any of the reagent blanks analyzed). We analyzed each NHANES sample once except when the original measurement of either the sample or the QCs analyzed along with it did not meet prespecified requirements (e.g., out-of-control QCs, concentration above the highest calibrator). Details of the analytical procedures used are available on the NHANES Web site.[41]

We used Statistical Analysis System (SAS) (version 9.3; SAS Institute Inc., Cary, NC) and SUDAAN (version 10; Research Triangle Institute, Research Triangle Park, NC). SUDAAN incorporates sample weights and design variables to account for the complex design of NHANES. We used the environmental subsample population B weights to produce estimates that are representative of the U.S. population.

We calculated the geometric mean and distribution percentiles for the volume-based (in micrograms per liter) and creatinine-corrected (in micrograms per gram creatinine) concentrations by age, sex, and race/ethnicity. For concentrations below the LOD, as recommended for the analysis of NHANES data,[42] we used a value equal to the LOD divided by the square root of 2.[43] We defined four major racial/ethnic groups based on self-reported data: non-Hispanic black, non-Hispanic white, “all Hispanic,” and “other.” We stratified age, reported in years at the last birthday, in three groups: 6–11, 12–19, and ≥20 years.

We also conducted weighted univariate and multivariate logistic regressions to examine associations of triclocarban concentrations above the 95th percentile (a value selected to represent much higher than average concentrations) with sociodemographic and physiological variables known to be associated with exposures to other environmental chemicals used in personal care products:[44] sex, age group, race/ethnicity, household income, and creatinine. Self-reported annual household income was available in $5,000 increments (ranging from < $5,000 to > $75,000). To obtain comparable number of participants in each income group, we categorized income as < $20,000, $20,000–$45,000, $45,000–$75,000, and > $75,000. Creatinine concentrations, used to adjust for the dilution of the urine, showed a skewed distribution and were log-transformed for data analysis. Because human expose to triclocarban occurs mainly through dermal contact, we also included body surface area (BSA) and body mass index (BMI) in the models. However, because of the strong correlation (Pearson correlation coeficient =0.7) between BMI and BSA, we only included BSA. We calculated BSA using Du Bois formula[45] and stratified BSA to below and above the NHANES median (<1.86 m^2 vs ≥1.86 m^2).

To reach the final multivariate logistic regressions model, we used backward elimination including all the two-way interaction terms, with a threshold of $p < 0.05$ for retaining the variable in the model, using Satterwaite-adjusted F statistics. We evaluated potential effect modifier by adding each of the excluded variables back into the final model one by one and

examining changes in the β coeficients of the statistically significant main effects. If addition of one of these excluded variables caused a change in a β coeficient by ≥10%, then the variable was readded to the model.

Triclosan, another widely used antibacterial agent in the market, shares similar applications as triclocarban in many personal care products.[46] For comparison purposes, we used the publicly available 2013–2014 NHANES biomonitoring data on triclosan[47] to determine the detection frequency of triclosan, and evaluate the nonparametric Kendall's Tau-b correlation of urinary concentrations of triclocarban and triclosan among the same 2013–2014 NHANES participants, taking into account of the left censor of triclocarban and triclosan concentrations.

RESULTS

Triclocarban was detected in 36.9% of the 2686 urine samples at concentrations ranging from >LOD (0.1 μg/L) to 588 μg/L. The 95th percentile concentration was 13.4 μg/L (14.6 μg/g creatinine) (Table 1). Triclocarban was detected more frequently in adolescents and adults (>37%) than in children (22.0%), and more frequently in non-Hispanic black (64.1%) than in the other ethnic groups (28.7%–33.6%). Non-Hispanic black is the only demographic group with geometric mean above the LOD, at 0.397 μg/L (0.293 μg/g creatinine) (Table 1). We also detected triclocarban more frequently among low household income persons (<$20 000) than among other household income groups (44.9% vs 32.6%–36.7%).

We observed an upward trend of the 95th percentile of triclocarban concentrations (unadjusted or creatinine-adjusted) with age (Table 1). For example, the 95th percentile creatinine-adjusted triclocarban concentration increased from 0.778 μg/g creatinine to 17.6 μg/g creatinine from children to adults 20 years of age and older. Among the different race/ethnic groups, the highest 95th percentile triclocarban concentration were for non-Hispanic black (27.0 μg/L [23.9 μg/g creatinine]) (Table 1). Males appeared to have higher 95th percentile triclocarban concentration than females (31.9 μg/L [21.3 μg/g creatinine] vs 7.50 μg/L [9.33 μg/g creatinine]; Table 1).

The univariate regression model included sex, age group (children, adolescent, adults), race/ethnicity, household income category, BSA (at or above vs below the median), and log-transformed creatinine concentration as a continuous variable. Sex (p = 0.0085), age (p = 0.0100), race/ethnicity (p = 0.0172), BSA (p = 0.005), and log-transformed creatinine concentration (p = 0.001) were significantly associated with the likelihood of triclocarban urinary concentration to be above the 95th percentile, but not household income (p = 0.8162). Males were 2.27 times more likely than females to have triclocarban concentrations above the 95th percentile [unadjusted odds ratio (OR) (95% Confidence Interval (CI)) = 2.27 (1.27–4.04)] (Figure 1A). Adults (≥20 years of age) were 4.74 times more likely than children (unadjusted OR = 4.74; 95% CI, 1.77–13.27) to have triclocarban concentrations above the 95th percentile, but the differences between adolescents and children were not statistically significant (Figure 1A). Compared to all Hispanic, the likelihood of having triclocarban concentrations above the 95th percentile was higher for non-Hispanic black [unadjusted OR (95% CI) = 4.07 (2.13–7.77) and non-Hispanic white [unadjusted OR (95%

CI) = 2.39 (1.43–3.93)] (Figure 1A), but not significantly different for the "other" ethnic group. Persons with BSA at or above the median were 2.98 times more likely than persons with BSA below the median to have triclocarban concentrations above the 95th percentile [unadjusted OR (95% CI) = 2.98 (1.75–5.08)] (Figure 1A).

We initially included sex, race/ethnicity, age group, BSA, and log-transformed creatinine concentration and their two-way interaction terms in the multivariate logistics regression model; only BSA ($p = 0.0049$), race/ethnicity ($p = 0.016$), and log-transformed creatinine concentration ($p = 0.0059$) were retained in the final model. Persons with BSA at or above the median were 2.43 times more likely than persons with BSA below the median to have triclocarban concentrations above the 95th percentile [adjusted OR (95% CI) = 2.43 (1.37–4.33)] (Figure 1B). Non-Hispanic black and non-Hispanic white were 3.71 times and 2.23 times more likely than all Hispanic to have triclocarban concentrations above the 95th percentile [adjusted ORs (95% CI) = 3.71 (2.05–6.71) and 2.23 (1.33–3.74), respectively], but the odds of having triclocarban concentrations above the 95th percentile was not significantly different between "all Hispanic" and the "other" ethnic group (Figure 1B). For every unit increase of log-transformed creatinine, the expected change was 3.21 [adjusted OR (95% CI) = 3.21 (1.48–6.97)] (Figure 1B).

The Kendall's Tau-b correlation between urinary log transformed concentrations of triclocarban and triclosan was very minimal (correlation coeficient <0.001) among the U.S. population ≥6 years of age during 2013–2014.

DISCUSSION

We detected triclocarban, an antibacterial agent used in a variety of personal care products, in about one-third (36.9%) of Americans from NHANES 2013–2014. Of interest, the detection frequency and concentration ranges are comparable to results from previous studies in which triclocarban was detected in 28% ($N = 50$) and 35% ($N = 158$) of American adults with median urinary concentrations <0.1 μg/L.[21,28] However, triclocarban was detected (LOD = 0.021 μg/L) in 86.7% of 181 urine samples collected in 2007–2009 from pregnant women in New York City, with a median concentration of 0.21 μg/L.[29] Outside the United States, triclocarban was rarely detected among Canadian women, potentially due to the use of a method with relatively low sensitivity (LOD = 1.1 μg/L) to quantify triclocarban.[25] Similarly, triclocarban was only detected in 4% of 100 samples collected from Greek children and adults between 2 and 87 years.[26] In contrast, triclocarban was detected in 18% to 54% of urine from Danish pregnant women and in 25% of first morning voids from paired Danish mother and children samples, with median concentrations for all studies below 0.1 μg/L (LODs = 0.01 μg/L).[30–32] More recently, triclocarban was reported to be detected in 99% of 209 urine samples collected from healthy Chinese adults of two cities, with median concentration of 0.28 μg/L (LOD = 0.01 μg/L).[27] Differences in urinary concentrations of triclocarban may exist geographically perhaps because of differences in production volumes, country-specific regulations, or patterns of use, but may also be related to differences in study populations (e.g., race/ethnicity), study design (e.g., timing of urine collection), and analytical detection methods.

Compared with triclosan, another commonly used antibacterial agent that has been monitored by NHANES since 2003,[44] the detection frequency of triclocarban is about two times lower (36.9% vs 78%) in NHANES 2013–2014, even though the method used is more sensitive for the detection of triclocarban than of triclosan (LOD = 1.7 μg/L). Triclosan was not only detected more frequently, but also at much higher concentrations (median = 9.30 μg/L [6.90 μg/g creatinine]) than triclocarban in the U.S. population ≥6 years of age during 2013–2014. These data suggest that human exposure to triclocarban may not be as prevalent as that of triclosan, perhaps because of differences in the extent of the application or use of these two chemicals in antibacterial consumer products. Differences in pharmacokinetics (e.g., absorption, distribution, metabolism, elimination) may also contribute to the observed differences in urinary concentrations of triclocarban and triclosan.[23,48,49] For instance, among 10 healthy adult Swedish volunteers exposed to a single oral dose of 4 mg triclosan by swallowing an oral mouthwash solution, 54% (median among 10 volunteers) of the dose was excreted in urine within the first 4 days after exposure.[48] However, two independent ^{14}C-triclocarban exposure studies in humans reported that approximately 25% of a triclocarban oral dose was excreted in urine within 10 (oral administration) to 20 (intravenous administration) days.[23,49]

Furthermore, we observed no strong correlation between urinary concentrations of triclocarban and triclosan in NHANES 2013–2014, similar to the findings from a previous study on pregnant women from Brooklyn, New York.[29] Although triclocarban and triclosan are both used in personal care products, because of differences in water solubility (<0.1 mg/L [triclocarban] vs 10 mg/L [triclosan]),[2] triclocarban is more frequently used in solid products (e.g., bar soap) while triclosan is preferably used in liquid or paste products.[1,3] Positive associations between urinary triclosan concentrations and household income were reported among NHANES 2003–2004 participants,[44] but we did not observe such an association with triclocarban in the current study. By contrast, we detected triclocarban more frequently among low household income persons than among other household income groups, however, the reasons for such differences are, at present, unknown.

Despite the low detection frequency of triclocarban in the U.S. population ≥6 years of age during 2013–2014, a small percentage of Americans (as illustrated by the 95th percentile concentration) may have experienced higher exposure to this compound perhaps from life style choices. Of interest, even though females had higher geometric mean urinary triclocarban concentration than males in a previous study,[27] we observed that males were two times more likely than females and adults were about four times more likely than children to exhibit concentrations of triclocarban above the 95th percentile. The higher likelihood of having triclocarban concentrations above the 95th percentile in adults compared with children and in males compared with females might be related to BSA. BSA is higher in males than in females[50] and in adults compared to children. Considering that people are exposed to triclocarban mainly through dermal contact, the fact that persons with BSA at or above the median were 2.43 times more likely than others to have triclocarban concentrations above the 95th percentile may be related to these persons' higher potential for dermal absorption through use of triclocarban-containing products. Non-Hispanic black had the highest geometric mean and widest concentration ranges of triclocarban as well as the highest likelihood of having concentrations of triclocarban above the 95th percentile

compared to other race/ethnic groups. We speculate that the higher likelihood of non-Hispanic black to be more exposed to triclocarban than other ethnic groups might reflect life style habits, such as increased use of triclocarban-containing personal care products.

In summary, we present the first nationally representative assessment of exposure to triclocarban among Americans 6 years of age and older during 2013–2014. Although the detection frequency and urinary concentrations of triclocarban in the U.S. general population were relatively low, concentrations among certain subgroups, especially males, adults, and non-Hispanic black, were higher than among others. BSA and race were significantly associated with the likelihood of having triclocarban concentrations above the 95th percentile. Higher exposure potential for males and adults was likely related to these persons' higher BSA compared to females and children, while higher concentrations of triclocarban in non-Hispanic black compared to other race/ethnicities might reflect non-Hispanic black's life style choices. Research to identify the sources and potential routes of human exposure to triclocarban may shed light into the observed differences in urinary 95th percentile concentrations of triclocarban based on BSA, sex, age, and race/ethnicity.

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ABBREVIATIONS USED

BMI
Body Mass Index

BSA
Body Surface Area

CDC
Centers for Disease Control and Prevention

CI
Confidence Interval

FDA
Food and Drug Administration

LOD
Limit of Detection

NCHS
National Center for Health Statistics

NHANES
National Health and Nutrition Examination Survey

Online SPE-HPLC-MS/MS

Online solid phase extraction-high performance liquid chromatography- tandem mass spectrometry

OR
Odds Ratio

SAS
Statistical Analysis System

QC
Quality Control

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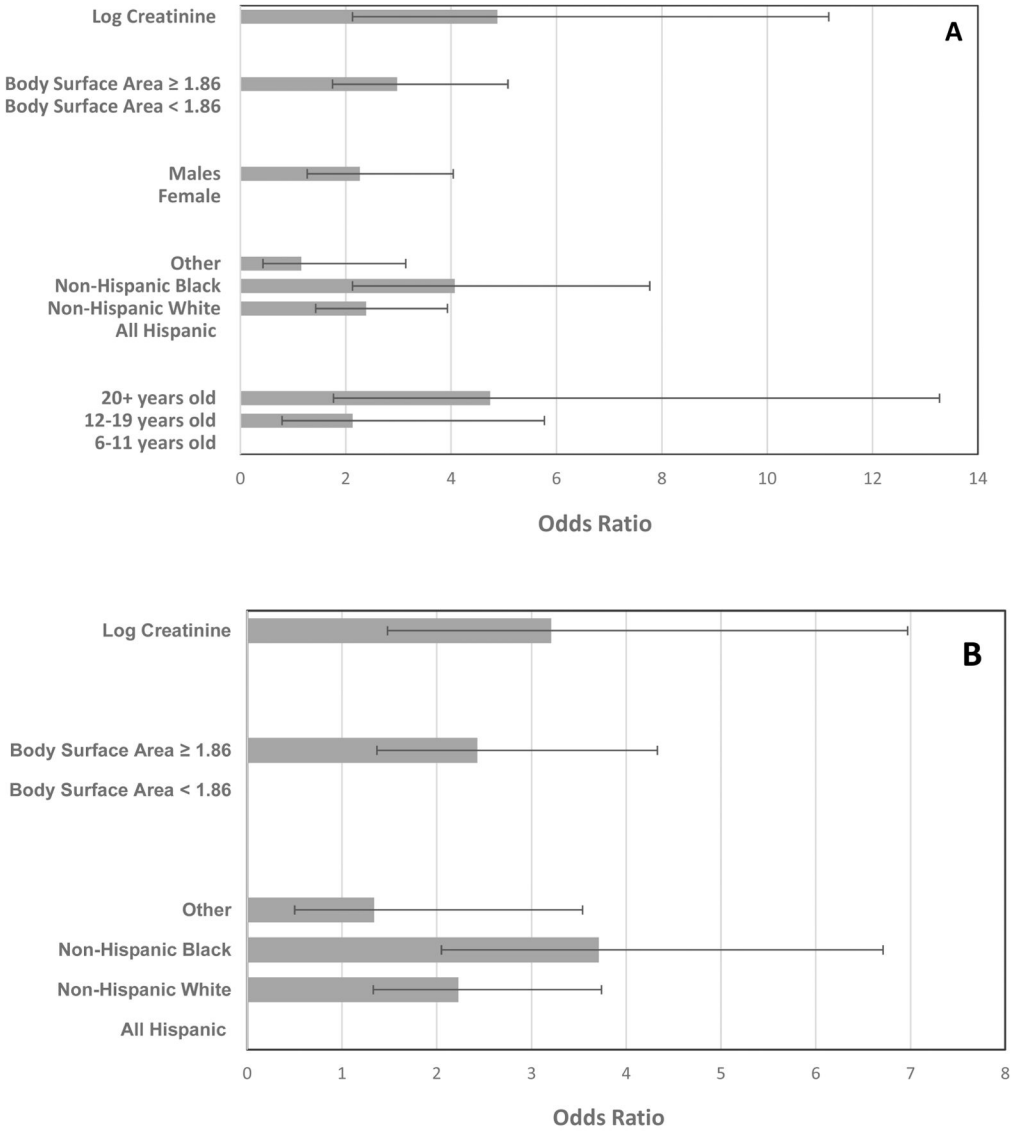

Figure 1.

Odds ratios for having urinary triclocarban concentration above the 95th percentile in different demographic population groups from the (A) univariate and (B) multiple logistic regression analyses. Error bars indicate the 95% confidence intervals.

Table 1

Geometric Mean and Selected Percentiles of Triclocarban Concentrations [μg/L (95% CI)] by Demographic Characteristics in Urine for the U.S. Population ≥6 Years of Age[a,b]

		Select Percentile (95% CI)					
	Geometric Mean (95% CI)	50th	75th	90th	95th	Detection Frequency (%)	Sample Size
Total	d	<LOD[c]	0.200 (.200–.200)	2.20 (1.20–4.10)	13.4 (8.00–24.5)	36.9	2686
	d	<LOD	0.275 (.248–.306)	1.96 (1.00–4.17)	14.6 (8.93–21.3)		2684
Age groups (years)							
6–11	d	<LOD	<LOD	0.300 (.200–.500)	0.900 (.400–5.50)	22.0	409
	d	<LOD	<LOD	0.413 (.323–.725)	0.778 (.389–7.77)		409
12–19	d	<LOD	0.200 (.100–.200)	0.900 (.400–1.90)	2.60 (1.40–9.40)	37.3	462
	d	<LOD	0.200 (.146–.248)	0.559 (.380–.888)	1.97 (.769–8.70)		462
20+	d	<LOD	0.200 (.200–.300)	3.40 (1.80–7.00)	17.9 (10.0–30.8)	38.5	1815
	d	<LOD	0.292 (.261–.333)	3.20 (1.67–7.07)	17.6 (10.7–22.9)		1813
Gender							
Males	d	<LOD	0.200 (.200–.400)	3.50 (1.60–9.90)	31.9 (13.9–47.6)	38.6	1285
	d	<LOD	0.250 (.185–.306)	3.00 (1.07–9.86)	21.3 (13.7–28.3)		1284
Females	d	<LOD	0.200 (.100–.200)	1.70 (.600–3.50)	7.50 (3.50–12.9)	35.3	1401
	d	<LOD	0.292 (.250–.357)	1.65 (.700–4.17)	9.33 (4.17–14.9)		1400
Race/ethnicity							
All Hispanic	d	<LOD	0.100 (<LOD-.200)	0.600 (.300–2.10)	4.40 (1.10–9.40)	28.7	690
	d	<LOD	0.192 (<LOD-.233)	0.617 (.351–1.35)	4.48 (1.24–10.6)		690
Non-Hispanic black	0.397 (.295–.536)	0.200 (.100–.300)	1.10 (.700–2.00)	11.3 (6.00–17.9)	27.0 (11.7–67.9)	64.1	609

	Geometric Mean (95% CI)	Select Percentile (95% CI)				Detection Frequency (%)	Sample Size
		50th	75th	90th	95th		
	0.293 (.220–.391)	0.172 (.127–.235)	0.741 (.513–1.11)	7.90 (2.41–19.3)	23.9 (10.8–28.9)		609
Non-Hispanic white	d	<LOD	0.200 (.100–.200)	2.00 (.800–4.50)	14.8 (7.10–32.5)	34.4	988
	d	<LOD	0.278 (.233–.333)	2.06 (.800–7.12)	15.4 (9.87–22.6)		987
Other	d	<LOD	0.100 (.100–.200)	0.600 (.300–1.20)	2.70 (.800–8.80)	33.6	399
	d	<LOD	0.212 (.172–.250)	0.600 (.368–1.67)	5.19 (.750–12.2)		398

[a] Data from NHANES 2013–2014.

[b] CI, confidence interval. NHANES, National Health and Nutrition Examination Survey. Gray lines denote measure in μg/g creatinine.

[c] <LOD means less than the limit of detection (LOD). LOD = 0.1 μg/L.

[d] Not calculated. Proportion of results below limit of detection was too high to provide a valid result.

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