ehp ENVIRONMENTAL HEALTH PERSPECTIVES
ehponline.org

Concentrations of the Sunscreen Agent, Benzophenone-3, in Residents of the United States: National Health and Nutrition Examination Survey 2003–2004

Antonia M. Calafat, Lee-Yang Wong, Xiaoyun Ye, John A. Reidy, and Larry L. Needham

doi:10.1289/ehp.11269 (available at http://dx.doi.org/)
Online 21 March 2008

NIEHS
National Institute of Environmental Health Sciences

National Institutes of Health
U.S. Department of Health and Human Services

Concentrations of the Sunscreen Agent, Benzophenone-3, in Residents of the United States: National Health and Nutrition Examination Survey 2003–2004

Authors:

Antonia M. Calafat, Lee-Yang Wong, Xiaoyun Ye, John A. Reidy, Larry L. Needham

Authors' affiliation:

Division of Laboratory Sciences

National Center for Environmental Health

Centers for Disease Control and Prevention

Atlanta, Georgia, USA

Name and address of corresponding author:

Antonia M. Calafat

Division of Laboratory Sciences

National Center for Environmental Health

Centers for Disease Control and Prevention

4770 Buford Hwy., NE, Mailstop F53

Atlanta, GA 30341, USA

Telephone: (770) 488-7891. Fax: (770) 488-4371. E-mail: Acalafat@cdc.gov

Running title

Exposure Assessment of the US Population to Benzophenone-3

Keywords

Benzophenone-3, biomonitoring, exposure, human, NHANES 2003–2004, sunscreen, urine

Acknowledgments

We thank John Ekong for technical assistance. Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. The authors declare they have no competing financial interests.

List of Abbreviations

Benzophenone-3	BP-3
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
LOD	Limit of detection
LSGM	Least squares geometric mean
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio

Outline of Section Headers

Abstract

Introduction

Materials and Methods

Results

Discussion

References

Tables

Figure Legend

Figure

Abstract

Background: The capability of benzophenone-3 (BP-3) to absorb and dissipate ultraviolet (UV) radiation facilitates its use as a sunscreen agent. BP-3 has other uses in many consumer products (e.g., as fragrance and flavor enhancer, photoinitiator, UV curing agent, polymerization inhibitor).

Objectives: To assess exposure to BP-3 in a representative sample of the U.S. general population aged 6 years and older.

Methods: We analyzed 2,517 urine samples collected as part of the 2003–2004 National Health and Nutrition Examination Survey using automated solid-phase extraction coupled to high-performance liquid chromatography–tandem mass spectrometry.

Results: We detected BP-3 in 96.8% of the samples. The geometric mean and 95th percentile concentrations were 22.9 μg/L (22.2 μg/g creatinine) and 1,040 μg/L (1,070 μg/g creatinine), respectively. Least square geometric mean (LSGM) concentrations were significantly higher ($P \leq 0.04$) for females than for males, regardless of age. LSGM concentrations were significantly higher for non-Hispanic whites than for non-Hispanic blacks ($P \leq 0.01$), regardless of age. Females were more likely than males (adjusted odds ratio [OR], 3.5; 95% confidence interval [CI], 1.9–6.5), and non-Hispanic whites were more likely than non-Hispanic blacks (adjusted OR, 6.8; 95% CI, 2.9–16.2) to have concentrations above the 95th percentile.

Conclusions: Exposure to BP-3 was prevalent in the general U.S. population during 2003–2004. Differences by sex and race/ethnicity probably reflect differences in use of personal care products containing BP-3.

Introduction

Benzophenone-3 (2-hydroxy-4-methoxybenzophenone, oxybenzophenone [BP-3]), a commonly used sunscreen agent that absorbs and dissipates ultraviolet radiation, is used in a variety of cosmetic products (Gonzalez et al. 2006; National Library of Medicine, National Institutes of Health 2007; Rastogi 2002). BP-3 also has been used as ultraviolet stabilizer in plastic surface coatings for food packaging to prevent polymer or food photodegradation (Suzuki et al. 2005) and is approved by the Food and Drug Administration as an indirect food additive.

Human exposure to BP-3 has not been associated with adverse health effects and acute toxicity from BP-3 is low. However, results from animal studies—primarily dietary studies that affected body weight gain—showed alterations in liver, kidney, and reproductive organs in rats and mice administered BP-3 dermally and orally (National Toxicology Program 1992). Although the maximum dose that could be administered dermally was similar to the lowest orally administered dose which produced little systemic toxicity, these results suggested oral and dermal exposure routes might affect the animals similarly (National Toxicology Program 1992). BP-3 also shows estrogen-like activity in vitro and in vivo (Schlumpf et al. 2004b; Schlumpf et al. 2001; Schlumpf et al. 2004a; Schlumpf et al. 2003; Suzuki et al. 2005), although in one study BP-3's estrogenic activity was only observed in the presence of a rat liver preparation suggesting metabolic activation of BP-3 (Morohoshi et al. 2005). BP-3 can also display antiandrogenic activity in vitro (Ma et al. 2003; Schreurs et al. 2005). Thus, BP-3 might exhibit endocrine disrupting action via both mechanisms in animals. Therefore, in vivo effects due to these combined activities should be further investigated.

The focus of pharmaceuticals and ingredients in personal care products, including organic sunscreen agents, as environmental pollutants is increasing because these compounds may enter the aquatic environment not primarily as a result of manufacturing practices but from their steady and widespread use in human and veterinary daily activities. Furthermore, little is known about the potential hazards associated with recurring human or ecological exposures to these synthetic substances, many of which are bioactive (Daughton 2002; Daughton and Ternes 1999). BP-3, one of these substances, has been detected in surface waters (Balmer et al. 2005; Cuderman and Heath 2007), drinking water (Loraine and Pettigrove 2006; Stackelberg et al. 2004), and wastewater (Balmer et al. 2005; CDC 2003; Loraine and Pettigrove 2006) in North America and in Europe.

The widespread inclusion of sunscreen agents in personal care and consumer products (Gonzalez et al. 2006; National Library of Medicine, National Institutes of Health 2007; Rastogi 2002) increases the potential for human exposure to BP-3. Data support the absorption of BP-3 through human skin (Gonzalez et al. 2006; Hayden et al. 2005; Janjua et al. 2004; Jiang et al. 1999; Sarveiya et al. 2004). Application of some of these products to large areas of the body and frequent reapplication increase the daily systemic absorption of BP-3. In some cases, as much as 10% of the applied dose can be absorbed (Jiang et al. 1999).

Like many xenobiotics, BP-3 undergoes Phase I and Phase II biotransformations. In rats, after oral and dermal administrations of 100 mg of BP-3 per kg of body weight (Kadry et al. 1995; Okereke et al. 1993; Okereke et al. 1994; Okereke et al. 1995), the parent compound and three oxidative metabolites (2,4-dihydroxylbenzophenone; 2,2'-

dihydroxy-4-methoxybenzophenone; and 2,3,4-trihydroxybenzophenone) were detected in plasma, tissues, and urine. Urine was the major route of excretion; BP-3 and its metabolites were excreted mainly as glucuronide conjugates (Kadry et al. 1995; Okereke et al. 1993). Similarly, BP-3 and 2,4-dihydroxylbenzophenone were detected in human urine collected after a volunteer applied a commercially available sunscreen (Felix et al. 1998). These data suggest the conjugated species of BP-3 and its metabolites in urine can be used as biomarkers of exposure. Oxidative metabolites of BP-3 can themselves be used as sunscreen agents. Although BP-3 can be biotransformed to several metabolites, exposure to BP-3 can be assessed by measuring the total (free plus conjugated) concentrations of BP-3 in urine.

The detection of BP-3 in the aquatic environment and the wide use of products containing BP-3 have raised interest about assessing human exposure to this compound for risk-assessment purposes. We report here the first nationally representative data on the urinary concentrations of BP-3 in the U.S. general population 6 years of age and older, stratified by age group, sex, and race/ethnicity.

Materials and Methods

The National Health and Nutrition Examination Survey (NHANES), conducted continuously since 1999 by the Centers for Disease Control and Prevention (CDC), assesses the health and nutritional status of the civilian noninstitutionalized U.S. population 2 months of age and older (CDC 2003). The survey includes household interviews; medical histories; standardized physical examinations; and collection of biologic specimens, some of which can be used to assess exposure to environmental

chemicals. NHANES 2003–2004 included examinations of 9,282 people (CDC 2006a). We measured BP-3 by analyzing a random one-third subset of urine samples (n=2,517) collected from NHANES participants 6 years of age and older. Because this subset was randomly selected from the entire set, it maintained the representativeness of the survey. Participants provided informed written consent; parents provided informed written consent for their children.

Urine specimens were shipped on dry ice to CDC's National Center for Environmental Health and stored frozen at or below –20 ºC until analyzed. We measured total (free plus conjugated species) concentrations of BP-3 in urine by online solid-phase extraction coupled to high-performance liquid chromatography–tandem mass spectrometry described in detail elsewhere (Ye et al. 2005a). Briefly, conjugated BP-3 in 100 μL of urine was hydrolyzed using β-glucuronidase/sulfatase (*Helix pomatia*; Sigma Chemical Co., St. Louis, MO). After hydrolysis, samples were acidified with 0.1 M formic acid; BP-3 was preconcentrated by online solid-phase extraction, separated by reversed-phase high-performance liquid chromatography, and detected by atmospheric pressure chemical ionization–tandem mass spectrometry. Because a stable isotope-labeled BP-3 was not available, we used $^{13}C_{12}$-bisphenol A as internal standard (Ye et al. 2005a). The limit of detection (LOD), calculated as $3S_0$, where S_0 is the standard deviation as the concentration approaches zero (Taylor 1987), was 0.34 μg/L, and the precision ranged from 17.6% (at 18.5 μg/L) to 16.2% (at 46 μg/L). Low-concentration (~20 μg/L) and high-concentration (~45 μg/L) quality control materials, prepared from pooled human urine, were analyzed with standard, reagent blank, and NHANES samples (Ye et al. 2005a).

We analyzed the data using Statistical Analysis System (version 9.1.3; SAS Institute, Cary, NC) and SUDAAN (version 9.0.1; Research Triangle Institute, Research Triangle Park, NC). SUDAAN calculates variance estimates after incorporating the sample population weights, nonresponse rates, and sample design effects. We calculated the percentage of detection and the geometric mean and distribution percentiles for both the volume-based (in μg/L urine) and creatinine-corrected (in μg/g creatinine) concentrations. For concentrations below the LOD, as recommended for the analysis of NHANES data (CDC 2006b), we used a value equal to the LOD divided by the square root of 2 (Hornung and Reed 1990).

A composite racial/ethnic variable based on self-reported data defined three major racial/ethnic groups: non-Hispanic black, non-Hispanic white, and Mexican American. We included participants not defined by these racial/ethnic groups only in the total population estimate. Age, reported in years at the last birthday, was stratified in groups (6–11, 12–19, 20–59, and 60 years and older) for calculation of the geometric mean and the various percentiles.

We used analysis of covariance to examine the influence of several variables, selected on the basis of statistical, demographic and biologic considerations, on the concentrations of BP-3. For the multiple regression models, we used the variables described below and all possible 2-way interactions to calculate the adjusted least square geometric mean (LSGM) concentrations. LSGM concentrations provide geometric mean estimates (in μg/L) after adjustment for all covariates in the model. Because the distributions of BP-3 and creatinine concentrations were skewed, these variables were log transformed. We analyzed two separate models: one for adults (≥20 years old) and one

for children and teenagers (≤19 years old). We considered age (continuous), age-squared, sex, race/ethnicity, and log-transformed creatinine concentration for both models. When the model included both age and age-squared, we centered age by subtracting 50 from each participant's age, thus avoiding multi-colinearity and obtaining the least weighted correlation between these two variables (Bradley and Srivastava 1979). Additionally, to further evaluate the relation between the log-transformed BP-3 concentration and age, we used age group (20–29, 30–39, 40–49, and 50 years and older) as a categorical variable in the model and generated a bar chart of LSGM concentrations by age group.

To reach the final reduced model, we used backward elimination with a threshold of $P<0.05$ for retaining the variable in the model, using Satterwaite-adjusted F statistics. We evaluated for potential confounding by adding each of the excluded variables back into the final model one by one and examining changes in the β coefficients of the statistically significant main effects or interactions. If addition of one of these excluded variables caused a change in a β coefficient by ≥10%, we re-added the variable to the model.

We also conducted weighted univariate and multiple logistic regressions to examine the association of BP-3 concentrations above the 95th percentile with sex, age group, and race/ethnicity for all ages.

Results

We detected BP-3 in 96.8% of the 2,517 samples at concentrations ranging from 0.4–21,700 µg/L; the geometric mean and 95th percentile concentrations were 22.9 µg/L (22.2 µg/g creatinine) and 1,040 µg/L (1,070 µg/g creatinine), respectively (Table 1).

The final model for adults included sex, race/ethnicity, age, age-squared (P=0.038), creatinine concentration (log scale), and the interaction terms creatinine*sex (P<0.001) and age*race/ethnicity (P=0.04) (Table 2). Females had significantly higher BP-3 concentrations (P≤0.04) than males, regardless of creatinine level (Tables S1 and S2). Although BP-3 concentrations increased linearly as log creatinine increased for both sexes (P<0.001), the increase was more pronounced for males than for females (β for male is 1.12 and β for female is 0.65, Table 2). Also, as age increased, BP-3 LSGM concentrations showed a significant quadratic trend for Mexican Americans (P=0.016) and a significant linear positive trend for non-Hispanic blacks (P=0.022) but no significant linear or quadratic trend for non-Hispanic whites (Figure 1). LSGM concentrations of BP-3 for non-Hispanic whites were significantly higher than for non-Hispanic blacks, regardless of age (P≤0.01), and significantly higher than for Mexican Americans only for 20- to 29-year-olds (P=0.01). LSGM concentrations of BP-3 were significantly higher for Mexican Americans than for non-Hispanic blacks only for 30- to 39-year-olds (P=0.01) (Tables S1 and S2).

The final model for children and adolescents included sex (P<0.001), race/ethnicity, age, creatinine concentration (log scale) (P<0.001), and a race/ethnicity*age (P=0.01) interaction term (Table 2). LSGM concentrations of BP-3 increased as log creatinine increased (β=0.77, p<0.001). LSGM BP-3 concentrations (in μg/L) for girls (30.2 [95% confidence interval (CI), 21.4–42.6]) were significantly higher (P<0.001) than for boys (16.1 [95% CI, 13.2–19.8]). BP-3 concentrations also decreased linearly as age increased (P=0.0005) for non-Hispanic whites but not for Mexican Americans and non-Hispanic blacks (Figure 1, Table S3). LSGM concentrations of BP-3

for non-Hispanic whites were significantly higher than LSGM concentrations for non-Hispanic blacks, regardless of age, and for Mexican Americans only at younger ages ($P<0.001$ [at 8.5 years] and $P<0.01$ [at 12 years]) (Table S4). LSGM BP-3 concentrations were significantly higher for Mexican Americans than for non-Hispanic blacks only for older children ($P=0.01$, at both ages 12 and 15.6 years, $P=0.03$ at 17.4 years) (Table S4).

For participants with urinary concentrations above the 95th percentile of BP-3, sex ($P<0.001$) and race/ethnicity ($P=0.03$), but not age, were significantly associated univariately. In the final multiple logistics regression, sex ($P<0.001$) and race/ethnicity ($P=0.03$) were significant (Table S5). Females were 3.5 times more likely than males to be above the 95th percentile (adjusted odds ratio [OR], 3.5; 95% CI, 1.9–6.5). Non-Hispanic whites were 6.8 times more likely to have BP-3 concentrations above the 95th percentile (adjusted OR, 6.8; 95% CI, 2.9–16.2) than were non-Hispanic blacks, and Mexican Americans were four times more likely to be above the 95th percentile (adjusted OR, 4.04; 95% CI, 1.1–15.5) than were non-Hispanic blacks. We found no significant difference between non-Hispanic whites and Mexican Americans.

Discussion

The detection of BP-3 in almost all samples suggests that exposure to BP-3 was widespread in the U.S. general population during 2003–2004. This high level of detection most likely resulted from routine use of consumer products that contain BP-3, such as sunscreen, skin care lotion, lipstick, and hair spray (National Library of Medicine, National Institutes of Health 2007). The wide range of urinary concentrations—10% of participants had BP-3 concentrations below 2.3 μg/g creatinine and 5% had

concentrations above 1,070 µg/g creatinine (Table 1)—may be related to lifestyle differences that result in exposure differences (vide infra) and to individual variations in bioavailabilty, distribution kinetics, or metabolism of BP-3.

The frequent detection of BP-3 and the magnitude and range of urinary concentrations in NHANES 2003–2004 are comparable with data from two smaller studies in the United States. In 30 anonymous adult volunteers with no documented BP-3 exposure, we detected BP-3 in 90% of samples, and total urinary concentration (free plus conjugates) of BP-3 ranged from the LOD (0.5 µg/L) to 3,000 µg/L (Ye et al. 2005b). In a pilot study of 90 prepubertal girls from New York City, Cincinnati, and Northern California, we detected BP-3 in 86% of samples (Wolff et al., 2007). The creatinine-adjusted geometric mean concentration of BP-3 (30.8 µg/g) for these girls was similar to that for NHANES 2003–2004 children aged 6–11 years (25.8 µg/g creatinine).

The relation between age and LSGM BP-3 concentrations differed by race/ethnicity (Figure 1). These differences most likely result from increased use of sunscreen or other personal-care products containing BP-3 by people with light skin pigmentation. For instance, sunscreen use among non-Hispanic whites is reportedly higher than for non-Hispanic blacks and other race/ethnic groups of outdoor workers and the general population (Briley et al. 2007; Pichon et al. 2005). Likewise, differences by age might reflect differences in use of personal-care products that contain BP-3. Non-Hispanic white parents may apply sunscreen regularly to protect their young children from sunburn, whereas teenagers might not apply sunscreen as often (Jones and Saraiya 2006; Livingston et al. 2007). Non-Hispanic white adults in their 20s and 40s might be more preoccupied about their skin appearance than non-Hispanic whites in their 30s (who

may devote more time to work and family responsibilities than to themselves) or people in their 50s (who may see little benefit in applying sunscreen at older ages).

We found differences by sex in the adjusted LSGM concentrations of BP-3. Compared with males, females tend to use more sunscreen (Eide and Weinstock 2006; Hall et al. 1997; Jones and Saraiya 2006) and other personal-care products that may contain BP-3. Therefore, higher concentrations of BP-3 for females than for males most likely result from their higher exposure to BP-3.

Females and non-Hispanic whites not only had significantly higher LSGM concentrations than males and non-Hispanic blacks, respectively, but they also were more likely to exhibit concentrations of BP-3 above the 95th percentile. In particular, females were 3.5 times more likely than males and non-Hispanic whites were 6.8 times more likely than non-Hispanic blacks to have BP-3 concentrations above the 95th percentile. Mexican Americans were about 4 times more likely than non-Hispanic blacks to present BP-3 concentrations above the 95th percentile. Although young children had LSGM concentrations of BP-3 comparable to those of adults in their 20s and 40s, age was not significantly associated with having concentrations above the 95th percentile. Our data suggest that females and non-Hispanic whites represent two segments of the general population with higher exposures to BP-3 than other demographic groups.

Protection against sunburn and squamous cell carcinoma by application of sunscreens is important, even though the use of sunscreen may not protect against melanoma, the deadliest form of skin cancer (Lin and Fisher 2007). Sun protection is critical for outdoor workers who are at higher risk for squamous cell carcinoma than other population groups (Pichon et al. 2005) and in situations where sun exposure, even

during peak times, is unavoidable. In other situations, although behavioral measures, such as wearing a hat, sunglasses, and sun protective clothes and avoiding the sun during peak exposure times, can reduce the risk for skin damage, sunscreens may be the primary means of sun protection, especially in societies that value outdoor activities (Lautenschlager et al. 2007). Toxicologic and epidemiologic data on BP-3, one of these sunscreens, are lacking. Nevertheless, the NHANES 2003–2004 data demonstrating Americans' exposure to BP-3 can be used to establish a nationally representative baseline assessment of exposure to this sunscreen agent and may promote the use of biomonitoring to complement the questionnaire or survey information in studies designed to evaluate sun-safety practices. These NHANES 2003-2004 data could also be of benefit in a risk assessment for BP-3 if indicated by toxicologic or epidemiologic studies.

References

Balmer ME, Buser HR, Muller MD, Poiger T. 2005. Occurrence of some organic UV filters in wastewater, in surface waters, and in fish from Swiss lakes. Environ Sci Technol 39:953-962.

Bradley RA, Srivastava SS. 1979. Correlation in Polynomial Regression. Am Statist 33:11-14.

Briley JJ, Lynfield YL, Chavda K. 2007. Sunscreen use and usefulness in African-Americans. J Drugs Dermatol 6:19-22.

CDC. 2003. National Health and Nutrition Examination Survey. National Center for Health Statistics. Available: http://www.cdc.gov/nchs/about/major/nhanes/intro_mec.htm [accessed 11 May 2007].

-----. 2006a. Analytic and Reporting Guidelines. The National Health and Nutrition Examination Survey (NHANES). Available: http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/nhanes_analytic_guidelines_dec_2005.pdf [accessed 12 March 2007].

-----. 2006b. General Documentation on Laboratory Data. General Information about the NHANES 2003-2004 Laboratory Methodology and Public Data Files. Available: http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/lab_c_generaldoc.pdf [accessed 30 July 2007].

Cuderman P, Heath E. 2007. Determination of UV filters and antimicrobial agents in environmental water samples. Anal Bioanal Chem 387:1343-1350.

Daughton CG. 2002. Environmental stewardship and drugs as pollutants. Lancet 360:1035-1036.

Daughton CG, Ternes TA. 1999. Pharmaceuticals and personal care products in the environment: Agents of subtle change? Environ Health Perspect 107:907-938.

Eide MJ, Weinstock MA. 2006. Public health challenges in sun protection. Dermatol Clin 24:119-124.

Felix T, Hall BJ, Brodbelt JS. 10-5-1998. Determination of benzophenone-3 and metabolites in water and human urine by solid-phase microextraction and quadrupole ion trap GC-MS. Anal Chim Acta 371:195-203.

Gonzalez H, Farbrot A, Larko O, Wennberg AM. 2006. Percutaneous absorption of the sunscreen benzophenone-3 after repeated whole-body applications, with and without ultraviolet irradiation. Br J Dermatol 154:337-340.

Hall HI, May DS, Lew RA, Koh HK, Nadel M. 1997. Sun protection behaviors of the US white population. Prev Med 26:401-407.

Hayden CGJ, Cross SE, Anderson C, Saunders NA, Roberts MS. 2005. Sunscreen penetration of human skin and related keratinocyte toxicity after topical application. Skin Pharmacol Physiol 18:170-174.

Hornung RW, Reed LD. 1990. Estimation of average concentration in the presence of nondetectable values. Appl Occup Environ Hyg 5:46-51.

Janjua NR, Mogensen B, Andersson AM, Petersen JH, Henriksen M, Skakkebaek NE, et al. 2004. Systemic Absorption of the Sunscreens Benzophenone-3, Octyl-Methoxycinnamate, and 3-(4-Methyl-Benzylidene) Camphor After Whole-Body Topical Application and Reproductive Hormone Levels in Humans. J Investig Dermatol 123:57-61.

Jiang R, Roberts MS, Collins DM, Benson HAE. 1999. Absorption of sunscreens across human skin: an evaluation of commercial products for children and adults. Br J Clin Pharmacol 48:635-637.

Jones SE, Saraiya M. 2006. Sunscreen use among US high school students, 1999-2003. J Sch Health 76:150-153.

Kadry AM, Okereke CS, Abdelrahman MS, Friedman MA, Davis RA. 1995. Pharmacokinetics of Benzophenone-3 After Oral-Exposure in Male-Rats. J Appl Toxicol 15:97-102.

Lautenschlager S, Wulf HC, Pittelkow MR. 2007. Photoprotection. Lancet 370:528-537.

Lin JY, Fisher DE. 2007. Melanocyte biology and skin pigmentation. Nature 445:843-850.

Livingston PM, White V, Hayman J, Dobbinson S. 2007. Australian adolescents' sun protection behavior: Who are we kidding? Prev Med 44:508-512.

Loraine GA, Pettigrove ME. 2006. Seasonal variations in concentrations of pharmaceuticals and personal care products in drinking water and reclaimed wastewater in Southern California. Environ Sci Technol 40:687-695.

Ma RS, Cotton B, Lichtensteiger W, Schlumpf M. 2003. UV filters with antagonistic action at androgen receptors in the MDA-kb2 cell transcriptional-activation assay. Toxicol Sci 74:43-50.

Morohoshi K, Yamamoto H, Kamata R, Shiraishi F, Koda T, Morita M. 2005. Estrogenic activity of 37 components of commercial sunscreen lotions evaluated by in vitro assays. Toxicology in Vitro 19:457-469.

National Library of Medicine, National Institutes of Health. Household products database. Available: http://hpd.nlm.nih.gov/index.htm [accessed 4 June 2007].

National Toxicology Program. 1992. NTP Technical Report on Toxicity Studies of 2-Hydroxy-4-methoxybenzophenone (CAS Number: 131-57-7) Administered Topically and in Dosed Feed to F344/N Rats and B6C3F1 Mice. National Toxicology Program, U.S. Department of Health and Human Services.

Okereke CS, Abdelrahman MS, Friedman MA. 1994. Disposition of benzophenone-3 after dermal administration in male rats. Toxicol Letters 73:113-122.

Okereke CS, Barat SA, Abdelrahman MS. 1995. Safety Evaluation of Benzophenone-3 After Dermal Administration in Rats. Toxicol Letters 80:61-67.

Okereke CS, Kadry AM, Abdelrahman MS, Davis RA, Friedman MA. 1993. Metabolism of Benzophenone-3 in Rats. Drug Metab Dispos 21:788-791.

Pichon LC, Mayer JA, Slymen DJ, Elder JP, Lewis EC, Galindo GR. 2005. Ethnoracial differences among outdoor workers in key sun-safety behaviors. Am J Prev Med 28:374-378.

Rastogi SC. 2002. UV filters in sunscreen products - a survey. Contact Derm 46:348-351.

Sarveiya V, Risk S, Benson HAE. 2004. Liquid chromatographic assay for common sunscreen agents: application to in vivo assessment of skin penetration and systemic absorption in human volunteers. J Chromatogr B-Anal Technol Biomed Life Sci 803:225-231.

Schlumpf M, Cotton B, Conscience M, Haller V, Steinmann B, Lichtensteiger W. 2001. In vitro and in vivo estrogenicity of UV screens. Environ Health Perspect 109:239-244.

Schlumpf M, Durrer S, Maerkel K, Ma R, Conscience M, Fleischmann I, et al. 2003. Endocrine activity and developmental toxicity of UV filters. Toxicol Sci 72:649.

Schlumpf M, Jarry H, Wuttke W, Ma R. 2004a. Estrogenic activity and estrogen receptor beta binding of the UV filter 3-benzylidene camphor comparison with 4-methylbenzylidene camphor. Toxicology 199:109-120.

Schlumpf M, Schmid P, Durrer S, Conscience M, Maerkel K, Henseler M, et al. 2004b. Endocrine activity and developmental toxicity of cosmetic UV filters - an update. Toxicology 205:113-122.

Schreurs RHMM, Sonneveld E, Jansen JHJ, Seinen W, van der Burg B. 2005. Interaction of polycyclic musks and UV filters with the estrogen receptor (ER), androgen receptor (AR), and progesterone receptor (PR) in reporter gene bioassays. Toxicol Sci 83:264-272.

Stackelberg PE, Furlong ET, Meyer MT, Zaugg SD, Henderson AK, Reissman DB. 2004. Persistence of pharmaceutical compounds and other organic wastewater contaminants in a conventional drinking-water treatment plant. Sci Total Environ 329:99-113.

Suzuki T, Kitamura S, Khota R, Sugihara K, Fujimoto N, Ohta S. 2-15-2005. Estrogenic and antiandrogenic activities of 17 benzophenone derivatives used as UV stabilizers and sunscreens. Toxicol Appl Pharmacol 203:9-17.

Taylor JK. 1987. Quality Assurance of Chemical Measurements. Chelsea, MI:Lewis Publishers.

Ye XY, Kuklenyik Z, Needham LL, Calafat AM. 2005b. Quantification of urinary conjugates of bisphenol A, 2,5-dichlorophenol, and 2-hydroxy-4-methoxybenzophenone in humans by online solid phase extraction-high performance liquid chromatography-tandem mass spectrometry. Anal Bioanal Chem 383:638-644.

-----. 2005a. Automated on-line column-switching HPLC-MS/MS method with peak focusing for the determination of nine environmental phenols in urine. Anal Chem 77:5407-5413.

Table 1. Geometric mean and selected percentiles of benzophenone-3 concentrations in urine for the US population 6 years of age and older: data from NHANES 2003–2004[a]

Variable[b]	Geometric mean	Selected percentile						Sample size
		10th	25th	50th	75th	90th	95th	
Total	22.9 (18.1–28.9)	2.20 (1.50–2.60)	5.80 (4.70–7.10)	18.0 (15.3–23.1)	94.0 (67.5–123)	364 (225–570)	1040 (698–1390)	2517
	22.2 (17.6–28.0)	2.28 (1.73–2.89)	5.24 (4.27–6.21)	16.2 (12.7–21.6)	82.0 (58.7–108)	409 (283–577)	1070 (686–1600)	2514
Age group								
6–11 years	21.2 (16.4–27.3)	3.60 (2.40–4.50)	6.70 (5.20–9.50)	17.2 (14.9–25.9)	63.6 (38.7–102)	154 (106–246)	227 (154–618)	314
	25.8 (19.5–34.1)	4.30 (2.86–5.19)	8.25 (5.98–10.5)	22.4 (14.4–33.7)	83.6 (41.0–131)	171 (132–365)	427 (171–710)	314
12–19 years	22.9 (18.0–29.3)	3.30 (2.30–4.10)	7.80 (5.60–9.60)	20.0 (16.1–25.1)	66.5 (45.2–93.8)	170 (137–240)	407 (183–717)	715
	17.2 (13.7–21.5)	3.17 (2.24–4.03)	5.86 (4.81–6.93)	12.9 (10.3–16.5)	42.9 (29.5–57.7)	136 (91.7–239)	350 (173–646)	713
>20 years	23.1 (18.0–29.6)	1.80 (1.20–2.40)	5.50 (4.50–6.70)	18.1 (14.7–23.3)	108 (72.1–140)	450 (315–733)	1200 (769–1750)	1488
	22.8 (17.8–29.1)	1.98 (1.48–2.59)	4.89 (3.71–6.12)	16.2 (12.7–21.9)	93.2 (66.0–130)	486 (361–700)	1330 (880–1880)	1487
Sex								
Female	30.7 (23.7–39.8)	2.50 (1.80–3.40)	7.30 (5.40–9.10)	26.0 (20.2–34.1)	137 (105–172)	596 (403–769)	1340 (776–1790)	1288
	35.5 (27.1–46.4)	3.16 (2.28–4.13)	7.42 (5.83–9.39)	28.2 (20.2–37.0)	144 (101–224)	686 (491–1130)	1850 (1220–2580)	1286
Male	16.8 (13.2–21.3)	1.80 (1.30–2.20)	5.00 (4.30–5.90)	13.6 (11.4–16.8)	54.4 (33.2–86.5)	178 (134–324)	567 (238–1350)	1229

	13.6	(10.8–17.1)	1.82	(1.55–2.16)	3.81	(3.33–4.87)	10.2	(8.36–12.9)	40.0	(24.9–62.5)	169	(93.3–316)	378	(229–685)	1228
Race/Ethnicity																
Non-Hispanic white	27.7	(20.3–37.8)	2.30	(1.50–3.00)	6.80	(5.10–8.60)	23.5	(16.8–32.0)	120	(83.6–162)	501	(316–769)	1250	(733–2070)	1092
	28.3	(20.6–38.8)	2.55	(1.80–3.62)	6.07	(4.88–8.33)	21.9	(14.6–32.7)	116	(73.5–175)	510	(380–760)	1330	(852–2410)	1091
Mexican American	16.5	(10.9–25.1)	2.30	(1.70–3.70)	5.00	(3.70–6.60)	11.9	(8.30–18.3)	45.5	(25.9–78.2)	176	(68.7–346)	412	(178–2180)	613
	15.1	(9.44–24.0)	2.39	(1.68–3.26)	4.10	(2.95–6.71)	11.0	(6.95–16.0)	40.7	(18.3–85.8)	158	(87.4–362)	595	(118–1860)	612
Non-Hispanic black	12.8	(9.38–17.4)	2.10	(1.30–2.70)	4.60	(3.20–6.20)	10.2	(7.40–14.3)	34.2	(22.8–50.6)	127	(90.8–176)	209	(143–499)	652
	8.78	(6.49–11.9)	1.50	(1.05–2.35)	3.18	(2.42–4.14)	6.80	(5.27–9.00)	19.6	(13.5–33.4)	78.1	(46.8–139)	185	(79.8–536)	651

[a] Concentrations are given in in μg/L. Shaded type denotes measure in μg/g creatinine. The 95% confidence intervals are shown in parentheses. [b] Participants not defined by the three racial/ethnic groups shown were included only in the total population estimate.

Table 2. Coefficients for the significant variables from the multiple regression models of the benzophenone-3 urinary concentration (log-transformed) by age group

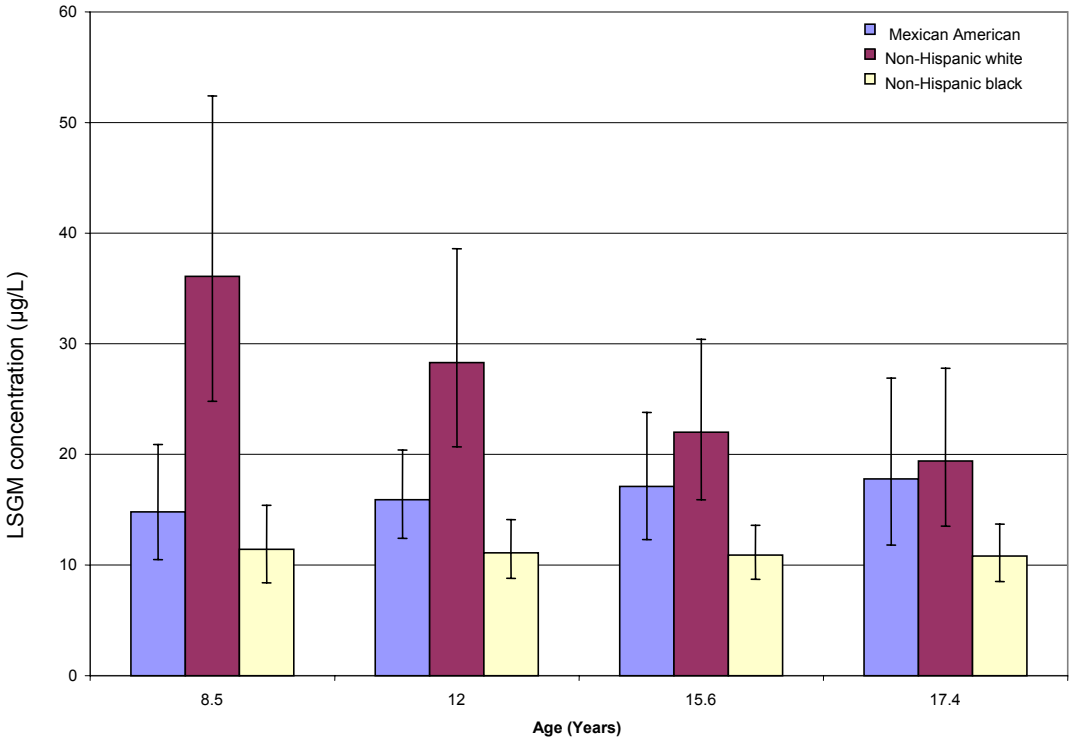
Variables	Children and adolescents (6-19 years old) β coefficient (P-value)	Adult (≥20 years old) β coefficient (P-value)
Intercept	-0.33985 (0.14913)	-0.08999 (0.73675)
Sex		
Male	-0.27143 (0.00079)	-1.39213 (0.00079)
Female	Reference	
Race/ethnicity		
Mexican American	0.01857 (0.91283)	0.24104 (0.15686)
Non-Hispanic white	0.73888 (0.00035)	0.48352 (0.00001)
Non-Hispanic black	Reference	
Age	-0.00243 (0.73485)	0.00155 (0.50696)[a]
Creatinine concentration (log transformed)	0.76653 (<0.001)	0.64519 (0.00008)
Age squared (centered)		-0.00018 (0.03848)
Race/ethnicity*Age		
Mexican American	0.01139 (0.4116)	-0.00365 (0.2125)[a]
Non-Hispanic white	-0.02787 (0.0249)	-0.00784 (0.02026)[a]
Non-Hispanic black	Reference	

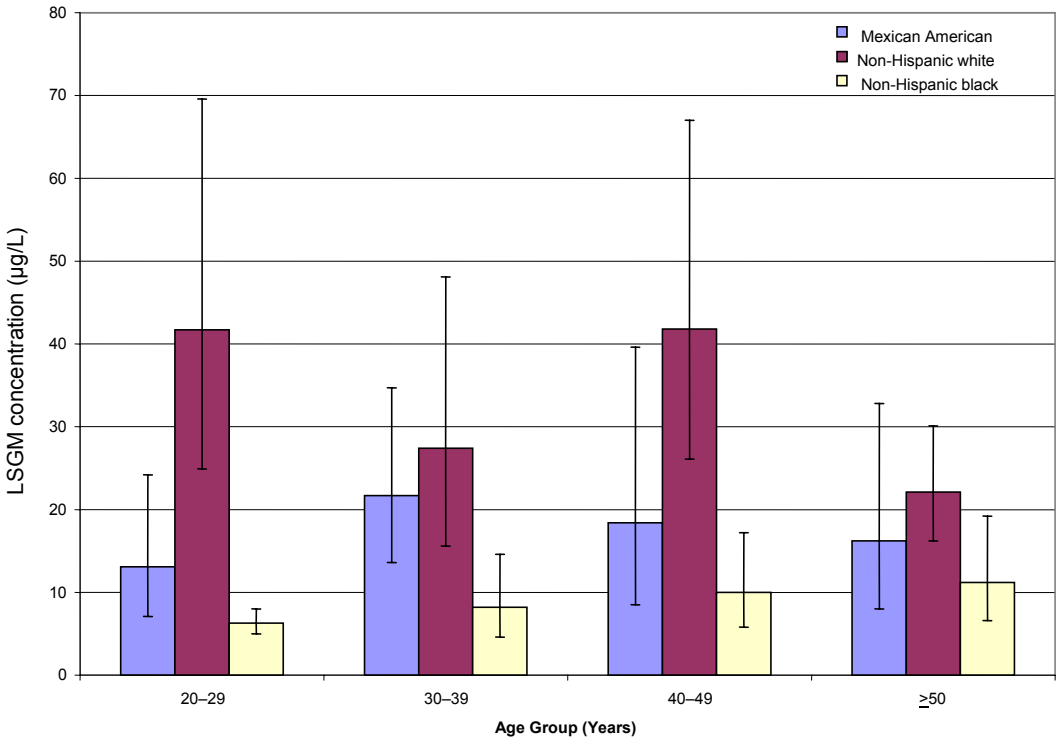
Gender*log creatinine	
Male	0.47423 (0.00811)
Female	Reference

[a]Age centered at 50 years.

Figure legend

Figure 1. Least squares geometric mean concentrations of benzophenone-3 (BP-3) (in μg/L) by age and race/ethnicity: A) children and adolescents and B) adults. The error bars indicate 95% confidence intervals.


Mexican American
Non-Hispanic white
Non-Hispanic black
LSGM concentration (µg/L)
60
50
40
30
20
10
0
8.5
12
15.6
17.4
Age (Years)


Mexican American
Non-Hispanic white
Non-Hispanic black
LSGM concentration (µg/L)
80
70
60
50
40
30
20
10
0
20–29
30–39
40–49
≥50
Age Group (Years)