

ASSOCIATION OF CAFFEINE CONSUMPTION AND SMOKING STATUS WITH THE SERUM CONCENTRATIONS OF POLYCHLORINATED BIPHENYLS, DIOXINS, AND FURANS IN THE GENERAL U.S. POPULATION: NHANES 2003–2004

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Smoking appears to enhance the body's clearance of dioxins and dioxin-like polychlorinated biphenyls (PCB) by inducing CYP1A2 activity based on studies with a limited number of participants. This hypothesis was evaluated by using data from National Health and Nutrition Examination Survey. Specifically, adult participants were identified and the sums of their serum lipid-adjusted concentrations of 12 polychlorinated dibenzo-*p*-dioxins/polychlorinated dibenzofurans (PCDD/PCDF) congeners, 33 PCB (total), 26 non-dioxin-like PCB, and 6 mono-*ortho* (dioxin-like) PCB were determined. In addition to evaluating the association of smoking, the association of caffeine consumption and the interaction between them was evaluated. Data analysis included regression models that were fitted with age, gender, race/ethnicity, and body mass index (BMI). R^2 varied from 34.8 to 66%. Smokers had significantly lower concentrations of total PCDD/PCDF than nonsmokers. New to this study, a significant interaction between caffeine consumption and smoking for total PCB was found. When caffeine was consumed less than once a day, smokers had higher concentrations of total PCB than nonsmokers. However, when caffeine was consumed at least once a day, smokers had lower concentrations than nonsmokers. A significant interaction between age and caffeine consumption frequency for each of the PCB groups was also observed. The differences in concentration between younger and older age groups were greater when caffeine was consumed at least once a day than when caffeine was consumed less frequently. Smoking and caffeine consumption need to be considered in the interpretation of human biomonitoring data because they appear to affect the serum concentrations of these chemicals.

While the research publications that describe investigations into the relation between caffeine consumption and persistent organic pollutants (POP) are sparse, some scientists have studied the influence of smoking on serum and human milk concentrations of polychlorinated dibenzo-*p*-dioxins (PCDD, dioxins), polychlorinated dibenzofurans (PCDF, furans), and polychlorinated biphenyls (PCB), and found that smokers had lower

concentrations than nonsmokers in females, but not in males. Fierens et al. (2005) found that while current male smokers had about 40% higher serum toxic equivalent (TEQ) for the sum of dioxin and furan than nonsmokers, the opposite was observed for females. Similar results were noted for four coplanar PCB. In a study of 372 participants living in northern Taiwan, Chen et al. (2005) observed that the total World Health Organization (WHO) TEQ

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for the sum of PCDD and PCDF increased with age, was higher for females than males, and was in the following order: passive smokers (17.7 pg TEQ/g lipid) > nonsmokers (15.7 pg TEQ/g lipid) > smokers (15.4 pg TEQ/g lipid). Uehara et al. (2007) in a study of 853 primiparas reported the concentrations of dioxin-like PCB in milk to be higher among never smokers (9.2 pg TEQ/g fat) than among current smokers (6.6 pg TEQ/g fat). The same was observed for total dioxins or the sum of PCDD, PCDF, and dioxin-like PCB. Uehara et al. (2007) also found that concentrations of total dioxins and dioxin-like PCB appeared lower in the milk of pregnant females aged 30–39 yr than in those who were 20–29 yr old, and postulated that the elimination of dioxins due to cigarette smoking may be enhanced in older mothers. Takekuma et al. (2006) showed similar results in human milk and, in addition, found a negative correlation between increased smoking and 2,3,4,6,7,8-hexachlorodibenzofuran concentrations. Hedley et al. (2006), in a study of dioxins in human milk, noted positive correlations between TEQ of dioxins and coplanar PCBs with age and the consumption of dairy products and seafood, but a negative correlation with ever smokers. Thus, these studies demonstrate that smoking is a potential confounder in the study of dioxins and dioxin-like compounds as indicators of exposure.

Ferriby et al. (2007) used data from the Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) for the survey period 2001–2002 to compute TEQ in serum of the sum of 17 PCDD/PCDF or TEQ_{PCDD/PCDF} and the sum of 9 PCB congeners (PCB-81, -105, -118, -126, -156, -157, -167, -169, and -189), or TEQ_{PCB}. Ferriby et al. (2007) also used the sum of 17 PCDD/PCDF and 9 PCBs or TEQ_{PCDD/PCDF/PCB}, and the sum of 17 PCDD/PCDF and three PCB congeners (PCB-81, -126, and -169), or TEQ_{PCDD/PCDF/81,126,169}. Data showed that both “age and gender appeared to confound the association between smoking status” and TEQ_{PCDD/PCDF/PCB}, and the TEQ_{PCDD/PCDF/PCB}

for nonsmokers 60+ yr old was 39% higher than smokers. Female smokers were found to have lower TEQ_{PCDD/PCDF/PCB} than nonsmokers, but these differences did not exist for males. Smokers were also found to have lower TEQ_{PCDD/PCDF/81,126,169} than nonsmokers for every age group, but these differences were not always statistically significant. However, as recognized by Ferriby et al. (2007), these interpretations were based on the inter-group comparison of confidence intervals for the means, which limited the ability to generalize the results.

These earlier investigations suggested that the upregulated level of activity or induction of hepatic microsomal enzymes (cytochrome P-450; CYP) from exposure to mainstream tobacco smoke enhances the clearance of PCB and PCDD/PCDF from the body because of common metabolic pathways for these chemicals. Polycyclic aromatic hydrocarbons (PAH) in tobacco smoke enhance the level of activity of CYP1A2 because they are a ligand for the aryl hydrocarbon receptor (AhR) that enhances the transcription of this enzyme. PCB and PCDD/PCDF undergo enzymatic hydroxylation, which involves several cytochrome P-450 enzymes, to varying extents. Further, dioxins, furans, coplanar PCB, and, to a lesser extent, dioxin-like mono-*ortho* PCB bind to the AhR to upregulate the activity of CYP1A (DeVito et al. 1998). The *ortho*-substituted PCB, including the mono-*ortho* PCB, are metabolized by CYP2B enzymes (Ariyoshi et al. 1995). The upregulation of these enzymes leads to increased distribution of these chemicals to the liver from the central compartment as a result of receptor binding. Caffeine is effectively metabolized by CYP1A2 and induces this enzyme activity in a dose-dependent manner (Ayalogu et al. 1995). Thus, exposure to caffeine may enhance the elimination of POP chemicals, such as PCB and PCDD/PCDF. In addition, exposure to caffeine produces changes in serum lipid concentration that may affect the distribution of lipophilic chemicals, such as POP chemicals, in the body (Phillips et al. 1989). Caffeine use has been associated with increased serum triglyceride

concentrations in both genders and elevated serum high density lipoprotein cholesterol concentrations only in women (Du et al. 2005). A rise of approximately 2 mg/dl in total cholesterol was found to be associated with an increase of 1 cup of regular coffee per day (Wei et al. 1995). The change in cholesterol concentration was not reported to be related to the consumption of decaffeinated coffee, regular or decaffeinated tea, or cola with caffeine (Wei et al. 1995).

The main aim of this study was to investigate how smoking and caffeine consumption affected the serum lipid-adjusted concentrations of PCB and PCDD/PCDF by analyzing total PCB ($\Sigma\text{PCB}_{\text{TOT}}$), total non-dioxin-like PCB ($\Sigma\text{PCB}_{\text{ND}}$), total dioxin-like mono-*ortho* PCB ($\Sigma\text{PCB}_{\text{MO-DL}}$), and total dioxins/furans (ΣDF) in the general population by using data from NHANES. In addition, data were reported on how gender, race/ethnicity, age, and interactions between them, if any, affected the concentrations of these classes of chemicals. Patterson et al. (2009) also reported data from NHANES 2003–2004 using total PCB, but their purpose was for national surveillance. Thus, the report by Patterson et al. (2009) differs from this study in several areas, such as age of study participants and number of PCB congeners included in the total PCB index. In addition, the effects of smoking and caffeine consumption on these chemical indices were not studied. This study did not intend to evaluate the effects of smoking, caffeine, and other factors on the toxic equivalents of PCDD/PCDF/PCB.

MATERIALS AND METHODS

Publicly available NHANES data for the years 2003–2004 were downloaded. NHANES uses a complex, stratified, multistage probability sampling designed as representative of the civilian, noninstitutionalized U.S. population based on age, gender, and race/ethnicity. A detailed description of sample design specifications for NHANES 2003–2004 is discussed elsewhere (CDC 2005a). Sampling weights were created in NHANES to account for the

complex survey design, including oversampling, survey nonresponse, and poststratification. The study population included adults because of their greater prevalence of consumption of caffeinated beverages, smoking, and detection of PCDD/PCDF/PCB in serum than other age groups in the population. Further, the selection of adults allowed for a meaningful interpretation of the study findings since previous investigations on smoking and caffeine consumption were conducted with adult participants. Pregnant females were excluded because of their small sample size in the survey and unique physiology that can affect the concentrations of these chemicals (Wang et al. 2009). The assessment of caffeine consumption was determined from a food frequency questionnaire (described later), smoking status was by the serum cotinine concentration, and exposure to PCDD/PCDF/PCB was by the serum lipid-adjusted concentrations for these chemicals. Information on race/ethnicity and anthropomorphic measurements were obtained because they are known independent predictors for PCDD/PCDF/PCB in this population based on previous investigations with this survey (Jain and Wang 2010; Wang et al. 2009). Thus, the data set included participants aged 20 yr and over, race/ethnicity, body weight and height measurements, food frequency questionnaire (FFQ), pregnancy status, and serum lipid-adjusted concentrations of PCB, PCDD, PCDF, and cotinine. For this study, food frequency questionnaire weights, WTS_FFQ , as provided in NHANES were used.

Analytical methodologies used to measure serum PCB, PCDD, and PCDF (CDC 2008a; 2008b) and serum cotinine are discussed elsewhere (CDC 2005b). PCDD/PCDF and PCB were detected in serum by high-resolution gas chromatography/isotopic dilution high-resolution mass spectrometry. Serum total cholesterol and triglycerides were measured by an enzymatic method (CDC 2008c).

The FFQ was used to collect information on the frequency of food consumption during the past 12 mo. The NHANES FFQ

contains several types of questions. There are 151 frequency questions. The FFQ also enquires about the proportion of the time that certain types of foods ingested over the past 12 mo, such as sugar-free soft drinks, whole-grain foods, and light, low-fat or fat-free varieties of foods (CDC 2008d). The respondents were given a choice of several response categories from which to select. For example, when asked how many cups of coffee they consumed during the last 12 mo, some of the response categories from which they could select were: None, <1 cup a day, . . . , 5–6 cups per week, . . . , and 6 cups or more per day. These responses were converted to food frequencies per day by using the National Cancer Institute (NCI) DietCalc software (CDC 2008e). The daily food frequencies for tea, coffee, and caffeinated soft drinks were summed to arrive at caffeine consumption frequency. The caffeine consumption frequencies were dichotomized to create a categorical variable. If this summed daily frequency was less than 1, including 0, then the respondents were categorized as having consumed no caffeine or having consumed it less than once a day. If this summed daily frequency was 1 or greater than 1, then the respondents were categorized as having consumed caffeine at least once a day. However, the sum of these frequencies needs to be interpreted with caution because the frequencies for tea/coffee consumption were reported on a per-cup basis (e.g., 2–3 cups every week) and soft drinks frequencies were reported on a per-occurrence basis. Thus, the amount of caffeine consumed for these beverages can vary by this means of assessment. Participants with serum cotinine concentrations less than 10 µg/L were categorized as nonsmokers and those greater than or equal to 10 µg/L were categorized as smokers.

After excluding pregnant females by a urine pregnancy test and those who had missing values for smoking status based on serum cotinine, the database generated for this study contained a total of 1071 participants. Detailed sample sizes by demographic variables are provided in Table 1. However, additional

TABLE 1. Unweighted Sample Sizes by Gender, Race/Ethnicity, Age, Smoking, and Caffeine Consumption Status

Demographic group	Sample size	Percent of total
Total	1071	100
Gender		
Male	535	50.0
Female	536	50.0
Race/ethnicity		
Non-Hispanic White	615	57.4
Non-Hispanic Black	178	16.6
Mexican American	202	18.9
Other	76	7.1
Age		
20–29 yr	160	14.9
30–49 yr	330	30.8
50+ yr	581	54.2
Smoking status		
Nonsmokers	794	74.1
Smokers	277	25.9
Caffeine consumption status		
None or less than once a day	262	24.5
At least once a day	809	75.5

observations were excluded from each analysis because of missing values for outcome or dependent variables. Lipid-adjusted PCB, PCDD, and PCDF concentrations were used to generate four new variables. $\Sigma\text{PCB}_{\text{TOT}}$ included 33 congeners, namely, PCB-28, -44, -49, -52, -66, -74, -87, -99, -101, -105, -110, -118, -138/158, -146, -149, -151, -153, -156, -157, -167, -170, -172, -177, -178, -180, -183, -187, -194, -195, -196, -199, -206, and -209. Of the 33 congeners included in $\Sigma\text{PCB}_{\text{TOT}}$, 24 had less than 5% observations below the limit of detection, 7 had percent observations below the LOD between 5 and 20%, and PCB-167 and -195, respectively, had 24% and 24.6% observations below the LOD. $\Sigma\text{PCB}_{\text{MO-DL}}$ was the sum of the following dioxin-like congeners based on WHO toxic equivalency factor (TEF) (Van den Berg et al. 2006): PCB-105, -118, -156, -157, -167, and -189. $\Sigma\text{PCB}_{\text{ND}}$ was the sum of the following non-dioxin-like congeners: PCB-28, -66, -74, -52, -87, -99, -101, -110, -138/158, -146, -149, -151, -153, -170, -172, -177, -178, -180, -183, -187, -194, -195, -196, -199, and -206. ΣDF was computed using the sum of the following PCDD/PCDF congeners: 1,2,3,7,8-pentachlorodibenzo-p-dioxin; 1,2,3,4,7,8-

hexachlorodibenzo-*p*-dioxin (HxCDD); 1,2,3,6,7,8- HxCDD; 1,2,3,7,8,9- HxCDD; 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin; 1,2,3,4,6,7,8,9- octachlorodibenzo-*p*-dioxin; 2,3,4,7,8-pentachlorodibenzofuran; 1,2,3,4,7,8-hexachlorodibenzofuran (HxCDF); 1,2,3,6,7,8- HxCDF; 1,2,3,4,6,7,8-heptachlorodibenzofuran (HpCDF); 1,2,3,4,7,8,9-HxCDF; and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Of the 12 PCDD/PCDF congeners included in Σ DF, percentage observations below the LOD were between 0 and 20% for 5 of them, between 20 and 40% for 3 of them, between 40 and 60% for 1 of them, and the other 3, namely, 1,2,3,4,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, and 1,2,3,4,6,7,8,9-OCDF, had 60–69% observations below the LOD.

SUDAAN Proc DESCRIPT was used to compute unadjusted geometric means and their 95% confidence intervals by age, race/ethnicity, gender, caffeine consumption, and smoking status. SUDAAN Proc REGRESS was used to fit four multiple linear regression models: one each for Σ PCB, Σ PCB_{ND}, Σ PCB_{MO-DL}, and Σ DF. In each of these models, the logs of Σ PCB, Σ PCB_{ND}, Σ PCB_{MO-DL}, and Σ DF were used as dependent variables. Gender, age, race/ethnicity, smoking status, and caffeine consumption status (CCS) were used as the categorical independent variables, and, in addition, because body mass index (BMI) affects serum concentrations of PCB/PCDD/PCDF, BMI was also included as a continuous independent variable for the models. Serum total lipid concentration was the sum of the concentrations for triglycerides and total cholesterol: total lipids = $(2.27 \times \text{total cholesterol}) + \text{triglycerides} + 62.3 \text{ mg/dl}$ (Phillips et al. 1989). All values below the limit of detection (LOD) were imputed as $\text{LOD}/\sqrt{2}$. All two-way interactions between age, race/ethnicity, gender, smoking status, and CCS were also used as independent variables in the models. To avoid the models from being too complicated, three-, four-, and five-way interactions were not considered. Alpha was set at .05.

RESULTS

Unadjusted geometric means and related results are presented as supplemental information (Table 3).

Effect of age, race/ethnicity, gender, and BMI Females showed statistically significant lower adjusted geometric means (AGM) for Σ PCB_{ND}, but higher AGM for Σ PCB_{MO-DL} and Σ DF than males (Table 2). Non-Hispanic black individuals (NHB) displayed statistically significant higher AGM than both non-Hispanic whites (NHW) and Mexican Americans (MA) for both Σ PCB_{ND} and Σ PCB_{MO-DL} (Table 2). For example, the AGM for Σ PCB_{ND} in NHB was twofold higher than MA (174.7 ng/g lipid vs. 85.6 ng/g lipid). For Σ PCB_{MO-DL}, this difference was about the same (1.9-fold higher). For Σ PCB_{TOT}, the concentrations were in the order 20–29 yr < 30–49 yr < 50+ yr for each race/ethnicity, and they were statistically significantly different from each other (Figure 1). In addition, statistically significant differences among race/ethnic groups were found for 30–49 yr and 50+ yr old only and, in each case, Σ PCB_{TOT} was in the order NHB > NHW > MA. The AGM for Σ DF rose with an increase in age, from 215.8 pg/g lipid for Y21–29 to 486.6 pg/g lipid for Y50+ (Table 2). However, the differences were statistically significant only for Y21–29 and Y30–49 when compared to Y50+. There was a statistically significant decrease in Σ PCB_{TOT} (slope = -0.001) and Σ PCB_{ND} (slope = -0.008) with an elevation in body mass index. No statistically significant associations were found between body mass index and either Σ PCB_{MO-DL} or Σ DF (data not shown).

Effect of smoking and caffeine consumption A statistically significant interaction between age and CCS was found for Σ PCB_{TOT}, Σ PCB_{ND}, and Σ PCB_{MO-DL}, and between smoking and CCS for Σ PCB_{TOT} (Figure 2). In each case where age and CCS had statistically significant interactions (Figure 2, A–C), those who were 50+ yr old had higher concentrations of Σ PCB_{TOT}, Σ PCB_{ND}, and Σ PCB_{MO-DL}.

TABLE 2. Adjusted Geometric Means (AGM) With 95% Confidence Intervals for Lipid-Adjusted Concentrations of Total Non-Dioxin-Like PCB, Total Mono-*ortho* Dioxin-Like PCB, Total PCB, and Total Dioxins and Furans*

Demographic Group	$\Sigma\text{PCB}_{\text{ND}}^{**}$	$\Sigma\text{PCB}_{\text{MO-DL}}^{**}$	$\Sigma\text{PCB}_{\text{TOT}}^{**}$	ΣDF^{***}
Males	138.0 (130.6–145.7)	13.6 (12.4–14.9)	174.3 (165.8–183.3)	296.0 (270.6–323.7)
Females	125.4 (116.1–135.3) ^{&}	15.3 (14.1–16.5) ^{&}	163.6 (151.7–176.4)	371.3 (340.4–404.9) ^{&}
Non-Hispanic Whites	129.3 (122.3–136.7)	14.2 (13.0–15.6)		321.4 (289.6–356.7)
Non-Hispanic Blacks	174.7 (153.5–198.8) ^{&&}	17.9 (15.1–21.2) ^{&&}		357.8 (307.4–416.5)
Mexican Americans	85.6 (79.2–92.6) ^{&&&}	9.3 (8.3–10.4) ^{&&&}		349.5 (314.3–388.5)
All others	164.7 (132.0–205.5)	19.1 (15.0–24.3)		383.0 (303.9–482.8)
Age 21–29 yr				215.8 (184.1–252.9)
Age 30–49 yr				270.9 (238.8–307.2)
Age 50+ yr				486.6 (434.7–544.7) ^{###,###}
None or less than once a day caffeine consumption				286.6 (251.4–326.7)
At least once a day caffeine consumption				345.1 (316.2–376.7) [%]
Nonsmoker	130.7 (123.4–138.4)	14.7 (13.5–16.0)		347.1 (316.2–381.0)
Smoker	133.8 (123.6–144.8)	13.6 (11.9–15.4)		289.3 (263.4–317.8) ^{%%}

*AGMs are not presented if the effect was involved in an interaction effect.

**In ng/g lipid.

***In pg/g lipid.

[&]Statistically significant differences between males and females ($p = .02$ for total PCBND, $p < .0001$ for total PCBMO-DL, $p = .01$ for total DF).

^{&&}Statistically significant differences between Non-Hispanic Whites and Non-Hispanic Blacks ($p < .0001$ for total PCBND, $p = .01$ for total PCBMO-DL).

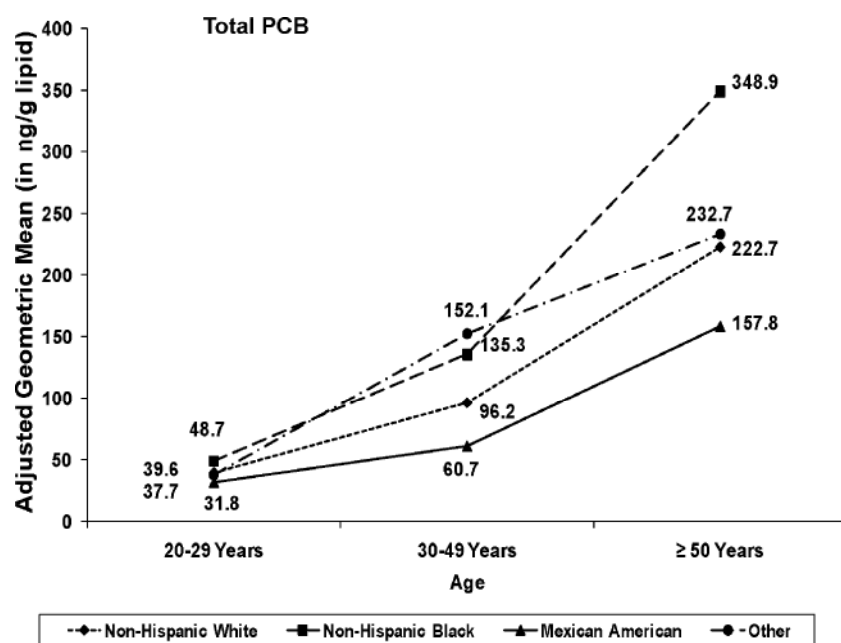
^{&&&}Statistically significant differences between Mexican Americans and Non-Hispanic Blacks ($p < .0001$).

^{##}Statistically significant differences between age groups 21–29 and 50+ yr ($p < .001$).

^{###}Statistically significant differences between age groups 30–49 and 50+ yr ($p < .001$).

[%]Statistically significant differences between those who consumed caffeine at least once a day as compared to those who either did not consume caffeine or consumed it less than once a day ($p = .012$).

^{%%}Statistically significant differences between smokers and nonsmokers ($p = .002$).

**FIGURE 1.** Adjusted geometric means for lipid-adjusted serum concentrations of $\Sigma\text{PCB}_{\text{TOT}}$ by age and race/ethnicity.

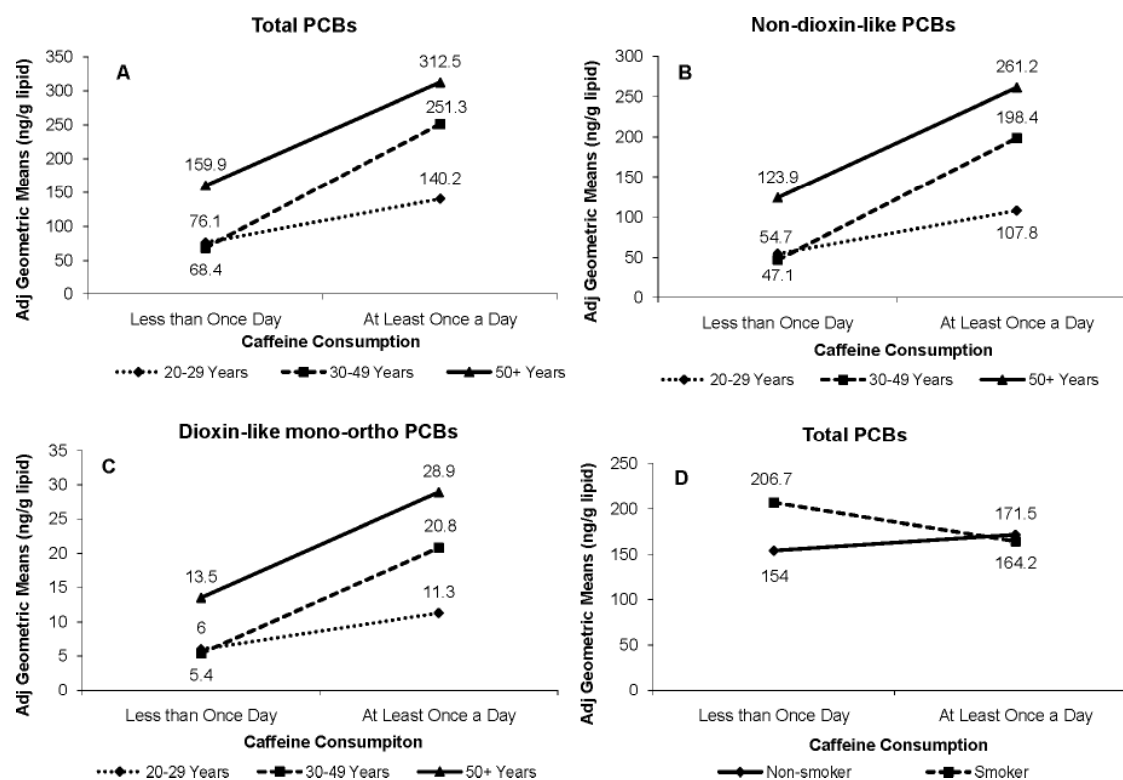


FIGURE 2. Adjusted geometric means for lipid-adjusted serum concentrations of (A) total PCB ($\Sigma\text{PCB}_{\text{TOT}}$) by age and caffeine consumption status, (B) non-dioxin-like PCB ($\Sigma\text{PCB}_{\text{ND}}$) by age and caffeine consumption status, (C) dioxin-like mono-ortho PCB ($\Sigma\text{PCB}_{\text{MO-DL}}$) by age and caffeine consumption status, and (D) total PCB ($\Sigma\text{PCB}_{\text{TOT}}$) by smoking and caffeine consumption status. Statistically significant interactions between age and caffeine consumption status for $\Sigma\text{PCB}_{\text{TOT}}$ ($p = .01$), $\Sigma\text{PCB}_{\text{ND}}$ ($p = .02$), and $\Sigma\text{PCB}_{\text{MO-DL}}$ ($p = .02$); and for smoking and caffeine consumption status for $\Sigma\text{PCB}_{\text{TOT}}$ ($p = .012$).

than those who were 20–29 yr old, irrespective of CCS. The same was observed for those who were 30–49 yr old except for when caffeine was either not consumed or was consumed less than once a day. In the latter situation, those who were 20–29 yr old had similar concentrations of $\Sigma\text{PCB}_{\text{TOT}}$, $\Sigma\text{PCB}_{\text{ND}}$, and $\Sigma\text{PCB}_{\text{MO-DL}}$ to those who were 30–49 yr old. When concentrations of $\Sigma\text{PCB}_{\text{TOT}}$, $\Sigma\text{PCB}_{\text{ND}}$, and $\Sigma\text{PCB}_{\text{MO-DL}}$ were compared for the two caffeine consumption statuses, only for the group 50+ yr old, those who consumed caffeine at least once a day displayed markedly higher levels than those who either not consumed it or consumed it less than once a day.

The AGM values for ΣDF for those who consumed caffeine at least once a day were higher than for those who either did not consume caffeine at all or consumed it less than once a day (345.1 pg/g lipid vs. 286.6 pg/g

lipid, Table 2). Smokers had lower ΣDF concentrations than nonsmokers (289.3 pg/g lipid vs. 347.1 pg/g lipid, Table 2). The only statistically significant interaction between smoking and CCS was for $\Sigma\text{PCB}_{\text{TOT}}$ (Figure 2D). When caffeine either was not consumed or was consumed less than once a day, smokers showed higher concentrations of $\Sigma\text{PCB}_{\text{TOT}}$ than nonsmokers (206.7 pg/g lipid vs. 154 pg/g lipid). However, when caffeine was consumed at least once a day, nonsmokers displayed higher concentrations of $\Sigma\text{PCB}_{\text{TOT}}$ than smokers (171.5 pg/g lipid vs. 164.2 pg/g lipid).

DISCUSSION

In blood (serum) (Chen et al. 2005; Ferriby et al. 2007; Flesch-Janys et al. 1996) and human milk (Hedley et al. 2006; Takekuma

TABLE 3. Unadjusted Geometric Means with 95% Confidence Intervals for Lipid-Adjusted Concentrations of Total Non-Dioxin-Like PCB (PCBND), Total Mono-Ortho Dioxin-like PCB (PCBMO-DL), Total PCB (PCBTOT) and Total Dioxins and Furans (DF).

Demographic variable	$\Sigma\text{PCB}_{\text{ND}}^*$	$\Sigma\text{PCB}_{\text{MO-DL}}^*$	$\Sigma\text{PCB}_{\text{TOT}}^*$	ΣDF^{**}
All	132.0 (123.9–140.7)	14.5 (13.1–16.0)	169.5 (159.3–180.3)	333.4 (306.2–362.9)
Males	140.4 (128.1–153.9)	13.9 (12.4–15.72)	177.7 (163.0–193.8)	298.2 (268.4–331.4)
Females	124.4 (116.5–132.9) ^{&}	15.0 (13.6–16.6)	161.9 (151.6–172.9)	372.3 (338.7–409.4) ^{&}
Non-Hispanic Whites	136.2 (125.5–147.7)	15.1 (13.3–17.1)	174.3 (161.4–188.2)	337.6 (303.9–374.9)
Non-Hispanic Blacks	156.8 (136.3–180.3)	16.2 (13.8–19.0)	200.0 (177.0–226.1)	327.5 (277.6–386.5)
Mexican Americans	66.6 (58.6–75.7) ^{&&, &&&}	7.3 (6.4–8.2) ^{&&, &&&}	90.8 (81–101.7) ^{&&, &&&}	303.7 (262.5–351.3)
All Others	150.7 (104.7–217.0)	16.3 (11.4–23.3)	193.2 (138.2–270.2)	329.4 (277.9–390.5)
Age 21–29 Years	51.3 (46.1–57.1)	5.6 (5.0–6.4)	73.0 (65.1–81.8)	210.8 (180.3–246.4)
Age 30–49 Years	109.8 (103.0–117.1) [#]	11.4 (10.2–12.8) [#]	141.0 (132.3–150.3) [#]	270.7 (243.0–301.5) [#]
Age 50+ Years	248.4 (228.1–270.5) ^{##, ###}	27.7 (24.4–31.6) ^{##, ###}	299.3 (276.0–324.6) ^{##, ###}	496.7 (438.6–562.5) ^{##, ###}
None or less than once a day caffeine consumption	113.6 (95.6–134.9)	12.6 (10.4–15.3)	147.2 (124.4–174.3)	275.7 (236.5–321.3)
At least once a day caffeine consumption	137.5 (126.9–149.0)	15.0 (13.4–17.2) [%]	176.0 (162.5–190.5)	351.1 (320.4–384.8) [%]
Non-Smoker	135.4 (126.6–144.7)	15.5 (13.9–17.2)	173.7 (162.5–185.7)	361.0 (322.5–404.1)
Smoker	123.0 (106.1–142.5)	12.0 (10.3–14.0) ^{%%}	157.8 (136.0–183.1)	263.5 (246.7–281.6)

*in ng/g lipid **in pg/g lipid &Statistically significant differences between males and females ($p = 0.001$) &&Statistically significant differences between Mexican Americans and Non-Hispanic Whites ($p < 0.01$) &&&Statistically significant differences between Mexican Americans and Non-Hispanic Blacks ($p < 0.01$) #Statistically significant differences between age groups 21–29 and 30–49 Years ($p < 0.04$) ##Statistically significant differences between age groups 21–29 and 50+ Years ($p < 0.04$) ###Statistically significant differences between age groups 30–49 and 50+ Years ($p < 0.04$) %Statistically significant differences between those who consumed caffeine at least once a day as compared to those who either did not consume caffeine or consumed it less than once a day ($p < 0.01$) %%Statistically significant differences between smokers and non-smokers ($p < 0.01$)

et al. 2004; Uehara et al. 2007), smokers were found to have lower concentrations of Σ DF and dioxin-like PCBs than nonsmokers. It was postulated that increased levels of smoking resulted in lower concentrations of these chemicals by enhancing their elimination from the body (Takekuma et al. 2004; Chen et al. 2005). As previously suggested (Chen et al. 2005), this may be because smoking induces the activity of cytochrome P-450 enzymes (CYP1A2), which enhances the metabolism and elimination of these chemicals. Constituents such as PAH in tobacco smoke can induce CYP1A2 by binding to the AhR. In fact, Fitzgerald et al. (2005), Petersen et al. (2006), and Flesch-Janys (1996) suggested that smoking induces CYP1A2. Similar results to past studies were found in our study of serum concentration of lipid-adjusted Σ DF and dioxin-like mono-*ortho* Σ PCB, when adjustment was not made for other factors that influence the concentrations of these chemicals. For example, smokers had about 37% lower concentrations of Σ DF than nonsmokers (Table 3). These results remained unchanged (Table 2) for only Σ DF when adjustment was made for other factors that influence chemical concentrations. The same was observed for Σ PCB_{TOT} (Figure 2D) when caffeine was consumed at least once a day. However, Σ PCB_{TOT} was observed to be higher in smokers than in nonsmokers among participants who consumed caffeine at less than once a day. Other investigators reported a similar association between smoking and total PCB concentration (Deutch and Hansen 1999; Lackmann et al. 2000; McGraw and Waller 2009), although the observation varies by congener (Cerna et al. 2008) and setting (Apostoli et al. 2005; Donato et al. 2006; Pereg et al. 2002). A lower serum chemical concentration among smokers does not necessarily equate to higher rates of clearance; for example, the distribution of some of these chemicals to the liver can increase because of protein binding from CYP1A2 induction (Hakk et al. 2009; DeVito et al. 1998). Further, the distribution of lipophilic chemicals, such as PCB and PCDD/PCDF, to tissue compartments with a high lipid content, such as adipose tissue, may

affect the rate of clearance of these of chemicals from the body (Milbrath et al. 2009). In this study, BMI was inversely associated with concentrations of Σ PCB_{TOT} and Σ PCB_{ND} and included as a covariate in the multiple linear regression models.

Petersen et al. (2006) indicated that dioxin-like mono-*ortho* PCB congeners 105 and 118 are metabolized by CYP1A2 based on a caffeine metabolism study of Faroese residents. However, any association between di-*ortho* PCB congeners, such as PCB 153, or Σ PCB and the ratio of caffeine metabolites was not found. In this study, smokers displayed higher concentrations of Σ PCB_{TOT} than nonsmokers when caffeine either was not consumed or was consumed less than once a day, but nonsmokers had higher concentrations of Σ PCB_{TOT} than smokers when caffeine consumption was at least once a day (Figure 2D). However, for dioxin-like mono-*ortho* and non-dioxin-like Σ PCBs (Table 2), a statistically significant difference was not found in concentrations between smokers and nonsmokers. These observations based on smoking status are consistent with those reported by other investigators, such as higher concentrations of total PCB and di-*ortho* substituted PCB, but no marked differences in mono-*ortho* PCB, in smokers compared to nonsmokers (Cerna et al. 2008; Deutch and Hansen 1999; Lackmann, et al. 2000; McGraw and Waller 2009; Pereg et al. 2002). A potential explanation for this difference in observations for the various classes of PCB is that the constituents in mainstream tobacco smoke induce and inhibit enzymatic activities to varying degrees that preferentially affect non-dioxin-like Σ PCB and dioxin-like PCB. For example, the non-dioxin-like PCB, such as PCB 153, and mono-*ortho* PCB are metabolized by CYP2B, which is not induced by dioxin-like PCB or PAH via the AhR (Ariyoshi et al. 1995). Further, ligands to the AhR inhibit the activities of CYP2 and CYP3A, which alter the clearance and concentrations of PCB in the body (Petersen et al. 2007; Shaban et al. 2005).

In addition, while Uehara et al. (2007) found a decrease in the concentration of Σ DF

in smokers with an increase in age, this was not seen in our study. In fact, smoking was not found to be a factor that affected change in concentrations with age for either Σ PCB or for Σ DF. Those who were 50+ yr old were almost always found to have statistically significantly higher concentrations than those who were 20–29 or 30–49 yr old (Table 2 and Figure 2, A–C), irrespective of caffeine consumption status, race/ethnicity, or gender. However, concentrations for those who were 20–29 yr old were almost never statistically significantly different from concentrations for those who were 30–49 yr old. It is noteworthy that between-age-group differences were substantially narrower when caffeine either was not consumed or was consumed less than once a day than when caffeine was consumed at least once a day (Figure 2, A–C). For example, for Σ PCB_{TOT} (Figure 2A), the difference in concentration among the 3 age groups was 172.3 ng/g lipid when caffeine was consumed at least once a day and the difference when caffeine either was not consumed or was consumed less than once a day was 91.5 ng/g lipid. Similarly, the difference in the concentrations between race/ethnicity was narrower for those 20–29 yr old than for those 50+ yr old (16.9 ng/g lipid vs. 191.1 ng/g lipid, respectively, Figure 1). While females in this study showed higher concentrations of Σ DF than males, no statistically significant interaction was noted between gender and smoking status. Fierens et al. (2005) observed lower concentrations of PCDD/PCDF in smokers than in nonsmokers for females, but there were higher concentrations of PCDD/PCDF in smokers than in nonsmokers for males. While these observations, based on gender and age, suggest the influence of metabolic enzyme activity on the concentrations of PCB and PCDD/PCDF, they are likely to be influenced by physiologic, genetic, and environmental factors as well. For example, an age-dependent decrease in hepatic blood flow decreases first-pass metabolism of toxicants, and the induction of metabolic enzyme activity by sex hormones leads to differences in concentrations of xenobiotics between men and

women. Further investigations on this topic are needed to clarify the contributions of these various factors on the concentrations of POP in the body.

Ongoing exposure to chemicals that accumulate in the body, such as POP, result in higher concentrations in older people. Significant evidence of this was found in this study for PCB as well as for Σ DF, even after the adjustments were made for other factors that affect these concentrations (Table 2 and Figure 2, A–C). In addition, a higher percentage body fat was suggested to be positively linked to Σ DF concentrations (Chen et al. 2005). For the data analyzed in this study, 30.1% males and 35.4% females were obese ($\text{BMI} \geq 30 \text{ kg/m}^2$). Thus, females have a relatively higher percentage body fat or BMI as compared to males, and higher concentrations of dioxins (Chen et al. 2005). Similar findings were noted not only for Σ DF but also for dioxin-like mono-*ortho* Σ PCB (Table 2). However, the opposite was found for non-dioxin-like PCB and Σ PCB_{TOT}, although the latter was not statistically significant (Table 2). The reason for this observation between these classes of chemicals based on BMI is not known, but a difference in the pattern of distribution of these chemical classes in the body might serve as an explanation (DeVito et al. 1998).

Several reasons provide a basis for why MA have the lowest concentrations of PCB and Σ DF. While dietary differences may exist between MA and other races/ethnicities, the differences in chemical concentrations among these groups may also be due to the country of birth. Those who were born in Mexico are likely to accumulate lower concentrations of PCB and Σ DF because of differences in industrialization between Mexico and United States. For the data used in this study, 54.5% of the MA were born in Mexico. The length of residence in the United States might also affect the concentrations of POP. MA resided in the United States for a mean of 15.6 yr (minimum = 0.5 year, maximum = 55 yr), which is an average of 40.5% (31.1–49.9%) of their lifetimes. Thus, MA were living in United States a relatively small percentage of their lives; this may

be reflected in their serum concentrations of Σ DF and PCB. With time and longer exposure to an environment with higher levels of POP, these differences among races/ethnicities decrease.

This is one of a few studies that have comprehensively analyzed data on selected POP that are available through NHANES, and provides simultaneous and interactive analysis of the association of smoking and caffeine consumption on concentrations of POP. While unadjusted concentrations (Table 3) of PCB and Σ DF rose with an increase in caffeine consumption, these results were retained for Σ DF (Table 2) even after adjustments for other factors were made. The same was true for PCB (Figure 2, A–C), although there were exceptions. For smokers, Σ PCB_{TOT} appeared to decrease (Figure 2D) with an increase in caffeine consumption frequency. The reason that smokers had decreased concentrations of Σ PCB_{TOT} with increased caffeine consumption, but nonsmokers did not, is unknown. The complex interactions between the constituents in beverages, such as coffee, and caffeine might be involved in these effects and warrant further investigation. If the impact of smoking on CYP1A was an independent effect, then smokers need to have lower chemical concentrations than nonsmokers, irrespective of the level of caffeine consumption. Because this was not found in this study, other factors likely contributed to the higher concentrations of Σ PCB_{TOT} in smokers than nonsmokers among infrequent caffeine consumers. It is not known whether increasing caffeine consumption is counteracting the effects of mainstream tobacco smoke on the level of enzymatic activity in the body. It is possible that caffeine or another chemical derived from the source of the caffeine (Williams et al. 2000) alters the effects of tobacco smoke, but Fitzgerald et al. (2005) could not confirm this.

This study indicates the need for future research activities based on its findings and limitations. In order to limit the concern with small sample sizes, those who did not consume caffeine at all were integrated with those

who consumed caffeine less than once a day and without differentiating the source of caffeine, such as coffee, tea, and soft drink. It is not known how the results might have been different if there were an exclusive category for each of these variables. In addition, the use of self-reported 12-mo food frequencies converted to daily consumption frequency is questionable due to memory lapse and reliability in reporting the frequency of use over a 12-mo period. A food frequency questionnaire or a food diary asking respondents to recall food frequencies over a shorter period of time may provide more reliable results. However, a 12-mo food frequency questionnaire was used previously for a similar study (Zhang et al. 2009). In addition, frequency of caffeine consumption does not provide any information about the dose or actual amount of caffeine consumed per day or per occurrence because different caffeine-containing products may contain different amounts of caffeine. In fact, even coffee purchased from different outlets may contain different amounts of caffeine (McCusker et al. 2003). In addition, the FFQ used does not provide information about the duration of consumption (e.g., weeks, months, years) or the use of other products that may contain caffeine, for example, over-the-counter and prescription drugs, and nutritional supplements. Finally, there was no information about the lifestyles of those who used caffeine less than once a day and those who used it more often to assist in determining the duration of caffeine consumption. For example, it was not known whether frequency of caffeine consumption, particularly those who consumed caffeine less than once a day, was because of a sustained condition, such as a tachydysrhythmia, or whether these individuals just temporarily consumed caffeine less often for personal reasons. A study using caffeine biomarkers (Klebanoff et al. 1998) or an investigation with a control group for caffeine consumption and smoking might have provided more interpretable results.

While percent of observations below the LOD was not much of a concern for fitting 3 models for PCB because the highest

percentage below the LOD was 24.6%, 3 of the 12 PCDD/PCDF had percentage observations below the LOD between 60% and 69%. For this reason, the null results presented here for PCDD/PCDF needs to be viewed with caution.

In conclusion, this study suggests that smoking and caffeine consumption need to be considered in the interpretation of human biomonitoring data on PCB and PCDD/PCDF because they appear to affect the serum concentrations of these chemicals. Smoking and the consumption of caffeine at less than once a day were independently associated with lower concentrations of PCDD/PCDF than not smoking and the consumption of caffeine on a more frequent basis. The relation between smokers and nonsmokers for PCB depended on the caffeine consumption status. Among people who consumed caffeine at less than once a day, smokers had higher concentrations of total PCB than nonsmokers. However, when caffeine was consumed at least once a day, nonsmokers had higher concentrations of total PCB than smokers. These observations need to be confirmed in other populations and in a prospective study. In addition, an investigation of the similarity of molecular properties between these POP might be important. In this investigation, while models for coplanar PCB were fitted, these results were not presented because the R^2 obtained was only 5%. A model for coplanar PCBs will require additional variables to explain the variability associated with these chemicals, and this can be accomplished in the future. In addition, as suggested by Chen et al. (2005), it may be important to take a closer look at the relation between CYP1A2 activity and the level of smoking.

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