Environment International 108 (2017) 212–220

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Serum polychlorinated biphenyls and leukocyte telomere length in a highly-exposed population: The Anniston Community Health Survey

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ARTICLE INFO

Keywords:
Polychlorinated biphenyls
Anniston Community Health Survey
Telomere length
Molecular epidemiology

ABSTRACT

Background: Serum polychlorinated biphenyls (PCBs) have previously been associated with longer leukocyte telomere length (LTL) in most, but not all, of the few previous studies. PCBs were produced in Anniston, Alabama from 1929 to 1971 and participants of the Anniston Community Health Survey (ACHS) were highly exposed.
Objectives: We evaluated serum levels of 35 PCBs and relative telomere length in 559 ACHS participants.
Methods: Relative LTL was measured in DNA extracted from blood clots. We assessed PCBs individually, grouped by chlorination, and summed PCBs. We used linear regression to assess the association between each PCB metric while adjusting for pertinent covariates.
Results: Serum PCBs were associated with longer LTL among white participants and the oldest age group of black participants. Among white participants, compared with those in the first quartile of sum PCBs those in the third quartile of sum PCBs had 8.09% longer relative LTL (95% CI: 1.99; 14.55) and those in the fourth had 7.58% longer relative LTL (95%CI: − 0.01; 15.76) (p-quadratic = 0.05). Among African American participants, serum PCBs were associated with longer relative LTL among those over age 64 only. Tests for interaction were not statistically significant.
Conclusions: We observed a non-linear positive association between serum PCBs and LTL among white participants. Serum PCBs were associated with longer LTL in the oldest age group of African Americans. This association may provide insight into the cancers previously associated with exposure to PCBs, melanoma and non-Hodgkin lymphoma, which have been associated with long LTL in previous studies.

1. Introduction

Polychlorinated biphenyls (PCBs) are a class of 209 organic synthetic chemicals with one to ten chlorine atoms attached to the biphenyl ring, that were previously used in a variety of commercial applications (Warner et al., 2012). Manufacture of PCBs was banned in the United States in 1977. Because of their persistence in the environment PCBs can be detected in air, seawater, lake and river sediments (Li et al., 2009; Warner et al., 2012). The toxicity a PCB congener exerts is dictated by the number and positioning of chlorines atoms on the two phenyl rings. Non-*ortho* PCBs are congeners lacking chlorines at the 2, 6, 2′, and 6′ position that bind to the aryl-hydrocarbon receptor (AhR) to exert dioxin-like effects. PCBs containing one chlorine in an *ortho* position (mono-*ortho*) bind to the AhR, but with less affinity than non-*ortho* PCBs (Lauby-Secretan et al., 2016). It is established that AhR binding induces the expression of a number of genes that contribute to carcinogenesis via deregulation of several cell-cycle and signal transduction pathways (Wall et al., 2015). Adverse health effects caused by PCBs independent of AhR binding are active areas of investigation. Alternate mechanisms of PCB-induced toxicity include oxidative stress, genotoxic effects, immune suppression, inflammatory response and endocrine disruption (Lauby-Secretan et al., 2016). The degree to which these mechanisms are exerted is likely congener and pathway specific.

Telomeres are caps on the ends of chromosomes consisting of tandem nucleotide repeats and an associated protein complex called “shelterin”. Telomeres maintain genomic stability by preventing the fusion of chromosomal ends, nucleolytic decay, and atypical recombination (O'Sullivan and Karlseder, 2010). Loss of telomeric DNA during cell division prevents the loss of critical chromatin. Critically short telomeres are recognized as damaged DNA and activate the DNA

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http://dx.doi.org/10.1016/j.envint.2017.08.018
Received 22 May 2017; Received in revised form 26 August 2017; Accepted 27 August 2017

damage response pathway leading to cellular senescence and apoptosis in normal cells (Sahin and DePinho, 2012). Aging, oxidative stress, and inflammation have been implicated in telomere shortening (Shin et al., 2010). Telomere shortening beyond critical lengths may lead to aberrant recombination, chromosomal fusion, and subsequent neoplasia (Wong et al., 2014). Alternatively, cells with longer telomeres may favor delayed senescence and thus have more potential to acquire genetic abnormalities and subsequent malignant transformation (Lan et al., 2009). Both short and long leukocyte telomere length (LTL) has been associated with increased risk of several types of cancer (Ma et al., 2011; Wentzensen et al., 2011). Short LTL has also been associated with increased risk of cardiovascular disease (Haycock et al., 2014) and type 2 diabetes (Willeit et al., 2014).

In vitro, immortalized human skin keratinocytes, hamster lung fibroblasts, immortalized lymphocytes, or human promyelocytic leukemia cells exposed to PCB 153, PCB 126, PCB 52, PCB 28, or 2-(4′-chlorophenyl)-1, 4-benzoquinone (PCB3pQ), have shortened telomeres (Jacobus et al., 2008; Senthilkumar et al., 2011; Senthilkumar et al., 2012; Xin et al., 2016; Ziegler et al., 2016). Conversely, PCB 138 and PCB 153 upregulate c-*myc* in vitro (Ghosh et al., 2007; Gribaldo et al., 1998). *C-myc* is a proto-oncogene that is involved in the reactivation of telomerase (Daniel et al., 2012). Exposure to PCBs is consistently associated with an increased risk of melanoma and to a lesser extent non-Hodgkin lymphoma (NHL) (reviewed by: (IARC et al., 2016)). Longer LTL has been associated with increased risk of melanoma (Caini et al., 2015) or NHL (Hosnijeh et al., 2014; Lan et al., 2009).

To our knowledge, five cross-sectional studies and one longitudinal study have addressed the association between serum PCBs and LTL. The first was a study of 84 healthy Korean participants that reported a positive association between serum levels of PCBs and LTL. However, the four study participants with the highest levels of serum PCBs had shorter telomeres (Shin et al., 2010). Three analyses of National Health and Nutrition Survey (NHANES) participants have also identified a positive association between serum PCBs and longer LTL (Mitro et al., 2015; Patel et al., 2016; Scinicariello and Buser, 2015). In the largest NHANES analysis, comprising 2175 participants, those in the highest quartile of sum PCBs (> 142.80 ng/g) had 11.63% longer telomeres (95% CI: 6.18; 17.35) than those in the lowest quartile (Scinicariello and Buser, 2015). Conversely, in a study of 207 participants occupationally exposed to PCBs and 104 non-occupationally exposed controls, LTL in lymphocytes, but not granulocytes, was shorter among those exposed to PCBs (Ziegler et al., 2016). In the only longitudinal study to date, serum levels of PCB 153 were associated with shorter LTL after ten years of follow-up (Guzzardi et al., 2016).

The Anniston Community Health Survey (ACHS) is a cross-sectional study of residents of Anniston, Alabama, where PCBs were manufactured from 1929 to 1971. ACHS participants have serum levels of PCBs 1.5 to 3.5 times greater than those of NHANES participants of the same age and race (Pavuk et al., 2014a). To test the hypothesis that PCBs are associated with LTL, we assessed the association between serum levels of 35 PCBs and relative LTL in this highly exposed group.

2. Methods

2.1. The Anniston Community Health Survey (ACHS)

ACHS participants were recruited and completed active study participation between 2005 and 2007. Two-stage address-based random sampling was used to select 3320 households from a commercial list of residential sites within Anniston city limits. Addresses in west Anniston, where the former PCB manufacturing facility was located, were intentionally oversampled. Of the addresses identified, 489 were vacant or non-residential and 890 could not be reached after multiple attempts. In total, 1110 households agreed to participate (39% response rate; 57% participation rate). We used the survey responses to identify participants who reported that a doctor diagnosed them with diabetes, hypertension, or cancer; years of education; smoking status; and other pertinent covariates. Of those who completed the survey, 765 agreed to a clinic visit where they donated fasting blood samples. After centrifuging, 2 ml of serum from each participant was frozen at the ACHS study office in Anniston. The specimens, including blood clot samples used for LTL measurement, were sent on dry ice to CDC's National Center for Environmental Health (NCEH) laboratory (Atlanta, GA), where they were stored at −70 °C until chemical analysis. All ACHS participants provided informed consent and study protocols were approved by the University of Alabama at Birmingham and University at Buffalo's Institutional Review Boards.

2.2. Exposure assessment

Serum levels of 35 PCBs were measured by the Center for Disease Control (CDC) National Center for Environmental Health laboratory using high-resolution gas chromatography/isotope dilution high-resolution mass spectrometry, as previously reported (Pavuk et al., 2014a; Sjodin et al., 2004). These congeners were selected because of their relevance to human exposure assessment as previously described. The coefficient of variation for duplicate samples ranged between 2.4 and 11.2 for each congener (Pavuk et al., 2014a). We did not analyze congeners with ≥40% of individuals below the limit of detection, which were: PCB 18, 44, 49, 52, 87, 101, 110, 128, 149, and 151.

2.3. Outcome assessment

Blood clot samples were shipped from the Center for Disease Control (CDC) National Center for Environmental Health laboratory to the University at Buffalo on dry ice in 2015, where they were then stored in at −80 °C until DNA extraction. DNA was extracted from stored blood clot samples using the PureGene protocol and clotspin baskets by Qiagen. Purified DNA was then stored at −80 °C prior to telomere assays. Immediately before analysis experimental DNA samples were re-quantified using the NanoDrop spectrophotometer and diluted to 4 ng/μl using PCR-grade water. Of ACHS participants who donated a blood sample, 585 had blood clot samples available to measure relative LTL. DNA was successfully extracted and relative LTL was measured in 560 of these samples. We excluded one participant who reported their race as Native American.

Relative LTL was measured using monochrome multiplex quantitative polymerase chain reaction as described by Cawthon (2009). All assays were conducted using 96-well plates and the BioRad CFX-96 Touch real time PCR. Briefly, 6.6 μl of DNA were added to each well. The other reagents in the 25 μl PCR were 12.5 μl Sybr green master mix, 5 μl betaine, and 0.225 μl of the four primers. The four primers 5′-3′ were telg: ACA CTA AGG TTT GGG TTT GGG TTT GGG TTT GGG TTA GTG T, telc: TGT TAG GTA TCC CTA TCC CTA TCC CTA TCC CTA TCC CTA ACA, hbgu: CGG CGG CGG GCG GCG CGG GCT GGG CGG CTT CAT CCA CGT TCA CCT TG, and hbgd: GCC CGG CCC GCC GCG CCC GTC CCG CCG GAG GAG AAG TCT GCC GTT. The thermocycling profile was as follows: 1 cycle of 15 min at 95 °C; 2 cycles of 2 s at 98 °C and 30 s at 49 °C; 36 cycles of 2 s at 98 °C, 30 s at 59 °C, 15 s at 74 °C with signal acquisition, 30 s at 84 °C, and 15 s at 85 °C with signal acquisition. The signal acquisition at 74 °C provides the cycle thresholds for telomeres and the signal acquisition at 85 °C provides the cycle thresholds for the single copy gene human beta-globin (hbg). Five concentrations of pooled human genomic DNA (Promega) generated via three-fold serial dilution: 150, 50, 16.7, 5.5, and 1.85 ng were included in each plate in duplicate to generate standard curves.

BioRad CFX manager software was used to determine the telomere (T) and single copy gene (S) values for each experimental sample using the standard curve. These values were then used to generate a T/S ratio for each sample which was averaged. Samples with a relative LTL < 1.00 have an average LTL shorter than that of the reference DNA and samples with a relative LTL > 1.00 have an average LTL longer

than the reference DNA (Cawthon, 2009).

Experimental samples were analyzed in triplicate and the average was reported. The average measures intra-class correlation coefficient for experimental samples was 0.79. Seven percent of samples were analyzed in blind duplicate; the coefficient of variation for these samples was 7.4%.

2.4. Statistical analyses

We used multiple imputation to address missing information on pertinent covariates and values for PCBs for samples that were below the limit of detection. The percent of participants with values above the limit of detection is presented in Table 1. The PROC MI procedure in SAS was used to generate five data sets with plausible values imputed for those missing. We used the Markov chain Monte Carlo method which generates a chain of values long enough that the elements stabilize to the distribution of the variable of interest (Yuan, 2010). Each of the five imputed datasets was analyzed individually using standard statistical procedures. These results were then combined using PROC MIANALYZE to reflect the uncertainty due to the missing values. The first imputed dataset was used to generate percentile cut-points and when presenting counts of participants in tables.

We used multivariable linear regression to calculate beta coefficients for the association between natural log-transformed LTL and natural log-transformed PCBs as a continuous variable and quartiles of PCBs. Resulting β coefficients from the continuous PCB analyses were transformed to estimate the predicted percent change in relative LTL per doubling of exposure to serum PCBs using the formula: percent difference in T/S ratio = $[e^{\beta*(\ln 2)} - 1]^*100$. For analyses where participants were grouped by quartiles of PCBs, we used the first quartile as the reference category and used the formula: percent difference in T/S ratio = $[e^{\beta - 1}] * 100$. We also estimated p-values for linear and quadratic trend using a grouped linear and grouped quadratic term.

All analyses were stratified by race. Analysis of covariance (ANCOVA) was used to assess the difference in mean serum levels of sum PCBs by select characteristics, adjusting for age and total lipids. PCBs have varying molecular structures, which can dictate their biochemical impact on humans (Aminov et al., 2013) and there are several ways to classify serum concentrations of PCBs. We grouped congeners based on the number and positions of the chlorines (Table 1).

Table 1
Classification scheme for polychlorinated biphenyls.

Grouping/PCB	% > LOD
Mono-ortho	
28	84.1
66	80.3
74	99.6
105	95.2
118	99.8
156	98.2
157	89.8
167	88.2
189	75.7
Di-ortho	
99	99.1
138–158	99.8
146	97.7
153	100
170	99.8
172	89.3
180	99.6
194	96.3
Tri and tetra-ortho	
177	93.2
178	92.5
183	94.5
187	99.1
195	88.9
196	98.8
199	98.4
206	98.9
209	95.2

The underline signifies less than or equal to.

Potential confounders were identified via their association with PCBs and/or LTL in the scientific literature. We considered age, total serum lipids, plate, physical activity (moderate and vigorous physical activity yes/no), alcohol consumption, smoking status (never, former, current), BMI, years of education, sex, self-reported diagnosis of any cancer, and diabetes. All models were minimally adjusted for age in years, age in years squared, total lipids, and 96-well plate. Serum lipids are also strongly associated with serum PCBs, and how to handle serum lipids in studies of the health effects of PCBs is a thoroughly researched topic (O'Brien et al., 2016; Schisterman et al., 2005). In addition to adjusting for total lipids, we also performed analyses using lipid-adjusted values of PCBs and analyses with lipid-adjusted values of PCBs and total lipids included as a covariate. We adjusted for 96-well plate in order to control for potential between-plate variability. Sex and BMI were forced into adjusted models. Differences in adiposity can introduce variability in the pharmacokinetics of lipid soluble compounds, including PCBs (Wolff et al., 2007). All other covariates were included if they changed the point estimate between sum PCBs and relative LTL by at least 10%.

To address potential bias due to differential sample availability we considered inverse probability weighting (IPW) scoring methods described by Littman et al. (2010). Using all of data from all 1110 Anniston residents that completed the baseline survey, we developed unconditional logistic regression models, stratified by race, where the dependent variable was inclusion in these analyses. We considered covariates that may be associated with LTL and/or serum PCBs. These covariates were: age in years, education, sex, BMI, smoking status, moderate physical activity, vigorous physical activity, having health insurance, having a personal health care provider, able to afford to see a doctor, income, cancer diagnosis, diabetes, high cholesterol, heart attack, heart disease, heart failure, hypertension, and marital status. Covariates were included if they had a p-value ≤ 0.20. An inverse propensity score was calculated for each participant and survey procedures were used in our primary analyses to weight participants by their propensity to be included in these analyses. We note that the ACHS participants included in the analyses presented herein were similar to the entire sample of 1110 Anniston residents that completed the survey with regards, to age, education level, smoking status, and BMI.

Potential effect modification by age, BMI, and sex was assessed via a stratified analysis and the statistical significance of the effect measure modification was tested using a product term for the covariate and serum PCBs in the adjusted linear regression models. These covariates were selected because effect measure modification has been observed in previous scenarios. African-Americans tend to have longer telomeres than whites (reviewed by: (Rewak et al., 2014)). Additionally, there have been racial differences in other biomarker analyses and PCBs in ACHS, particularly with regards to serum lipids (Aminov et al., 2014). In previous studies, reported associations between exposure to PCBs and several outcomes have varied by sex (Elobeid et al., 2010; Lee et al., 2012).

Statistical analyses were conducted using SPSS version 21.00 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) and SAS Enterprise Guide version 4.3 (SAS Institute, Cary, NC).

3. Results

Select characteristics and their association with LTL are presented in Table 2. LTL was inversely associated with age; a one-year increase in

Table 2
Percent differences in relative telomere length by select characteristics and race.

	White n = 332				African American n = 227				p interaction[b]
	N	% Difference[a]	95% CI		N	% Difference[a]	95% CI		
Age (years)									0.56
Per 1-year increase		− 0.08	− 0.17	0.02		− 0.10	− 0.20	0.01	
< 48	99	Referent			83	Referent			
48–64	106	0.47	− 3.50	4.60	78	1.08	− 2.76	5.11	
> 64	127	− 3.92	− 7.56	− 0.14	66	− 3.64	− 7.45	0.32	
p for trend		0.03				0.08			
Sex									0.004
Male	100	Referent			68	Referent			
Female	232	− 2.22	− 5.53	1.20	159	5.26	1.65	9.01	
Body mass index (kg/m^2)									0.29
< 25	90	Referent			51	Referent			
25–29.9	114	− 1.67	− 5.87	2.72	56	1.76	− 2.41	6.11	
≥ 30	128	− 0.82	− 4.79	3.30	120	− 1.29	− 5.90	3.54	
p for trend		0.66				0.28			
Years of education									0.65
< 12	109	Referent			66	Referent			
12	131	3.06	− 0.75	7.01	98	1.66	− 2.39	5.87	
> 12	92	3.39	− 0.80	7.75	63	4.68	0.12	9.45	
p for trend		0.10				0.04			
Smoking									0.54
Never	125	Referent			109	Referent			
Former	99	− 0.08	− 3.93	3.93	39	− 4.42	− 8.80	− 0.16	
Current	108	− 3.86	− 7.51	− 0.06	79	− 1.64	− 5.26	2.11	
Cancer									0.56
No	268	Referent			205	Referent			
Yes	64	− 1.05	− 5.10	3.18	22	1.08	− 4.54	7.03	
Diabetes									0.10
No	272	Referent			159	Referent			
Yes	60	− 1.25	− 5.36	3.03	67	3.77	0.01	7.68	

	All participants			
Race	N	% Difference[a]	95% CI	
White	332	Referent		
African American	227	1.71	− 0.67	4.15

[a] Percent difference estimates were calculated using multiple linear regression and are adjusted for age in years, age squared, and plate. Age estimates are only adjusted for plate.
[b] p for interaction was generated via the inclusion of an interaction term that included race and the variable of interest in linear regression models.

age was associated with a 0.08% decrease in relative LTL among whites (95% CI: − 0.17; 0.02) a 0.10% decrease in LTL among African Americans (95% CI: − 0.20; 0.01). Additionally, the oldest quartile of age had the shortest telomeres among both whites and African Americans.

Results of linear regression models assessing the association between serum PCBs grouped by chlorination are presented in Table 3. Among white participants all PCB groupings were generally associated with longer LTL. Di-*ortho* PCBs were linearly associated with longer LTL, compared with the first quartile, those in the fourth quartile had 9.72% longer telomeres (95% CI: 2.09; 17.93, p trend = 0.01). Conversely the association between tri- and tetra-*ortho* PCBs and LTL was quadratic, those in the third highest quartile had 8.77% longer telomeres (95% CI: 2.30; 15.66) and those in the highest quartile had 5.45% longer telomeres (95% CI: -2.22; 13.73, p quad = 0.01) than those in the first. Although tests for statistical interaction were not significant, the observed association between serum PCBs and longer LTL was limited to white participants. To account for the non-linear association between LTL and PCBs we modeled interaction terms using splines and they were similarly statistically non-significant (results not shown). Inverse probability weighting did not substantially alter our results (not shown).

The association between relative LTL and individual congeners that were statistically significant are presented in Table 4. PCBs 105, 118, 167, 99, 153, 183, 187,196, and 199 were associated with significantly longer relative LTL among whites. PCB 118 was associated with longer relative LTL among African American participants; we did not observe any other significant associations among African American participants.

The primary strategy we used for lipid adjustment was to model wet weight values of PCBs with total lipids included as a covariate. We assessed two alternative strategies to adjust for serum lipids; these were lipid adjusted values of PCBs or lipid adjusted values while including total lipids as a covariate. Neither alternate lipid adjustment method substantially altered our results (not shown).

Analyses stratified by age and race are presented in Table 5. We did not observe any evidence of effect modification by age among white participants. When we restricted analyses to African Americans over age 64, we observed a non-significant positive association between each grouping of PCBs and relative LTL. For instance, a doubling of exposure to sum PCBs was associated with 2.43% longer relative LTL (95% CI: − 0.17; 5.09). Results were similar when we excluded prevalent cases of cancer. We did not observe evidence of effect measure modification by BMI or sex (results not shown).

4. Discussion

In a large cross-sectional study of residents near a former PCB manufacturing plant, we observed a positive association between serum

Table 3
Percent differences[a] in leukocyte telomere length by serum polychlorinated biphenyls (PCBs), Anniston Community Health Survey Participants.

	White				African American				p for interaction
	N	% Difference	95% CI		N	% Difference	95% CI		
Mono-ortho PCBs									
Per doubling of exposure		1.46	− 0.38	3.33		− 0.21	− 1.47	1.07	0.43
< 179.0 ppt	103	Referent			37	Referent			
179.0–390.2 ppt	98	5.22	− 0.22	10.95	41	0.36	− 6.10	7.25	
390.2–866.5 ppt	88	2.25	− 3.38	8.20	52	3.70	− 3.40	11.31	
> 866.5 ppt	43	9.58	2.23	17.46	97	0.09	− 6.69	7.36	
p for trend		0.06				0.93			
p quadratic		0.78				0.24			
Di-ortho PCBs									
Per doubling of exposure		1.80	0.05	3.57		− 0.56	− 1.82	0.72	0.15
< 904.4 ppt	103	Referent			37	Referent			
904.4–1915.0 ppt	107	7.67	2.24	13.38	32	0.63	− 6.38	8.15	
1915.0–4456.2 ppt	82	9.03	3.03	15.39	58	− 1.06	− 7.84	6.21	
> 4456.2 ppt	40	9.72	2.09	17.93	100	− 3.79	− 10.41	3.31	
p for trend		0.01				0.10			
p quadratic		0.06				0.42			
Tri and tetra-ortho PCBs									
Per doubling of exposure		0.89	− 0.85	2.65		− 0.24	− 1.47	1.01	0.37
< 284.9 ppt	101	Referent			39	Referent			
284.9–713.4 ppt	102	6.62	0.88	12.69	37	1.54	− 5.51	9.12	
713.4–1848.6 ppt	81	8.77	2.30	15.66	59	− 1.67	− 8.63	5.82	
> 1848.6 ppt	48	5.45	− 2.22	13.73	92	− 0.35	− 7.45	7.30	
p for trend		0.14				0.71			
p quadratic		0.01				0.82			
ΣPCBs									
Per doubling of exposure		1.46	− 0.26	3.21		− 0.45	− 1.72	0.83	0.24
< 1403.61 ppt	107	Referent			37	Referent			
1403.61–3141.40 ppt	98	7.11	1.60	12.92	36	− 1.24	− 7.95	5.97	
3141.40–7345.35 ppt	84	8.09	1.99	14.55	57	0.49	− 6.49	8.01	
> 7345.35 ppt	43	7.58	− 0.01	15.76	97	− 2.70	− 9.37	4.46	
p for trend		0.06				0.37			
p quadratic		0.05				0.46			

[a] Adjusted for age in years, age in years squared, total lipids, plate, smoking status, diabetes, education, alcohol use in the past 30 days, sex, and body mass index.

PCBs and LTL among white participants, but not African Americans. Among African Americans we only observed a positive association between serum PCBs and LTL among the oldest participants only. However, tests for statistical interaction were not significant.

Our results are consistent with four of the six previous analyses of serum PCBs and LTL. A positive association between LTL and serum concentrations of several PCBs was reported in a study of 84 healthy Korean individuals (Shin et al., 2010). Serum PCBs have been associated with longer LTL in three separate analyses of NHANES participants (Mitro et al., 2015; Patel et al., 2016; Scinicariello and Buser, 2015). In the largest analysis of NHANES participants, when compared with those in the first quartile of sum PCBS, those in the highest quartile had 11.63% longer LTL (95% CI: 6.18; 17.35) (Scinicariello and Buser, 2015). We note that ACHS participants have serum levels of PCBs 1.5–3.5 times higher than NHANES participants of the same race and age category (Pavuk et al., 2014a). Conversely, serum PCBs were associated with shorter LTL in lymphocytes in a study of 207 German individuals occupationally exposed to PCBs via employment for a transformer recycling company. When compared with 104 healthy non-exposed controls, those occupationally exposed had a LTL of lymphocytes 0.77 kb shorter than expected (95% CI: − 0.93; − 0.61) (Ziegler et al., 2016). In the only longitudinal study to date, serum levels of PCB 153 at baseline were associated with shorter LTL ten years later (r = − 0.071, p-value 0.02) (Guzzardi et al., 2016).

In our study, serum PCBs were associated with longer LTL among all white participants but only the oldest category of African Americans. Tests for statistical interaction were not significant, thus it should be noted that these findings could be attributed to chance. Additionally, the age-stratified analyses should be considered exploratory. Mitro and colleagues reported that serum levels of two non-*ortho* PCBs, PCB 126 and PCB 169, were associated with longer LTL among both white and non-Hispanic black NHANES 2001–2002 participants, but not Mexican Americans (Mitro et al., 2015). Racial differences in LTL are important to consider in epidemiologic studies. African Americans tend to have longer telomeres (Hunt et al., 2008; Lynch et al., 2016; Rewak et al., 2014) and a faster rate of telomere attrition than whites (Diez Roux et al., 2009), although this is not observed in all studies (Diez Roux et al., 2009; Okuda et al., 2002), including ours. Additionally, a statistical interaction by race has been reported in studies of cardiovascular disease and LTL (Carty et al., 2015). The biologic mechanism for an association between serum PCBs and longer LTL among white but not African American participants is unclear and warrants further investigation.

Our results are inconsistent with the findings of prior in vitro studies that observed telomere shortening because of exposure to PCB 153, PCB 126, PCB 52, PCB 28, or 2-(4′-chlorophenyl)-1, 4-benzoquinone (PCB3pQ) (Jacobus et al., 2008; Senthilkumar et al., 2011; Senthilkumar et al., 2012; Xin et al., 2016; Ziegler et al., 2016). Alternative mechanisms by which PCBs may induce telomere lengthening have been proposed (Scinicariello and Buser, 2015). Namely, through activation of the proto-oncogene c-*myc* (Ghosh et al., 2007; Gribaldo et al., 1998), which in turn induces telomerase expression (Gabay et al., 2014).

Cells with longer telomeres have a greater proliferative potential and may be more likely to acquire somatic mutations (Hanahan and Weinberg, 2011). Long LTL has been associated with increased risk of non-Hodgkin's lymphoma (NHL) (Lan et al., 2009) and melanoma (Anic et al., 2013; Burke et al., 2013; Han et al., 2009; Nan et al., 2011). Exposure to PCBs has also been associated with increased risk of NHL and melanoma, which offers a compelling biologic rationale for the

Table 4
Percent difference[a] in relative telomere length by serum polychlorinated biphenyls (PCBs), ACHS participants.

	White			African American		
	%Difference	95% CI		%Difference	95% CI	
PCB 99						
Per doubling of exposure	1.65	0.36	2.94	− 0.05	− 1.17	1.08
< 29.15 ppt	Referent			Referent		
29.15–71.60 ppt	2.31	− 2.13	6.97	− 2.42	− 8.74	4.32
71.60–189.60 ppt	4.67	− 0.40	9.99	2.22	− 4.68	9.63
> 189.60 ppt	8.84	1.77	16.41	− 0.49	− 7.20	6.71
p for trend	0.01			0.90		
p for quadratic	0.69			0.64		
PCB 105						
Per doubling of exposure	1.77	0.40	3.15	0.18	− 0.57	0.93
< 7.75 ppt	Referent			Referent		
7.75–19.10 ppt	2.01	− 2.43	6.66	1.30	− 4.14	7.05
19.10–58.20 ppt	3.46	− 1.84	9.03	7.15	1.55	13.05
> 58.20 ppt	10.45	3.50	17.87	1.01	− 4.12	6.41
p for trend	0.01			0.52		
p for quadratic	0.25			0.03		
PCB 118						
Per doubling of exposure	1.87	0.55	3.21	0.02	− 1.07	1.12
< 49.60 ppt	Referent			Referent		
49.60–121.60 ppt	3.05	− 1.60	7.93	− 0.62	− 6.71	5.87
121.60–361.80 ppt	4.70	− 0.69	10.38	6.05	− 0.65	13.21
> 361.80 ppt	9.88	2.76	17.49	− 0.24	− 6.89	6.88
p for trend	0.01			0.88		
p for quadratic	0.68			0.05		
PCB 153						
Per doubling of exposure	1.75	0.26	3.26	− 0.74	− 1.94	0.47
< 278.75 ppt	Referent			Referent		
278.75–564.95 ppt	5.40	0.53	10.51	0.67	− 6.06	7.89
564.95–1398.50 ppt	7.08	1.64	12.82	2.39	− 4.42	9.70
> 1398.50 ppt	7.62	0.57	15.15	− 1.64	− 8.26	5.46
p for trend	0.02			0.40		
p for quadratic	0.19			0.15		
PCB 167						
Per doubling of exposure	1.33	− 0.20	2.89	− 0.02	− 1.20	1.17
< 10.88 ppt	Referent			Referent		
10.88–22.55 ppt	2.08	− 3.00	7.43	1.87	− 5.52	9.83
22.55–57.20 ppt	3.82	− 1.65	9.58	1.73	− 5.27	9.24
> 57.20 ppt	8.58	1.54	16.10	− 0.50	− 7.45	6.98
p for trend	0.02			0.63		
p for quadratic	0.57			0.33		
PCB 183						
Per doubling of exposure	1.60	0.05	3.17	− 0.13	− 1.34	1.09
< 18.65 ppt	Referent			Referent		
18.65–39.25 ppt	2.59	− 2.12	7.53	− 0.53	− 7.08	6.49
39.25–93.40 ppt	5.79	0.42	11.45	3.08	− 3.74	10.37
> 93.40 ppt	6.24	− 0.80	13.79	0.43	− 6.36	7.72
p for trend	0.03			0.83		
p for quadratic	0.63			0.40		
PCB 187						
Per doubling of exposure	1.22	− 0.19	2.64	− 0.26	− 1.42	0.92
< 68.65 ppt	Referent			Referent		
68.65–159.50 ppt	5.56	0.42	10.95	2.52	− 4.62	10.20
159.50–394.75 ppt	7.67	1.96	13.70	4.38	− 3.07	12.40
> 394.75 ppt	6.01	− 0.98	13.49	0.73	− 6.65	8.70
p for trend	0.04			0.73		
p for quadratic	0.07			0.09		
PCB 196						
Per doubling of exposure	1.21	− 0.43	2.87	− 0.24	− 1.57	1.10
< 47.00 ppt	Referent			Referent		
47.00–110.85 ppt	6.30	0.53	12.40	0.45	− 6.38	7.78
110.85–249.35 ppt	8.59	2.02	15.59	− 1.35	− 8.59	6.46
> 249.35 ppt	9.23	1.32	17.76	− 0.96	− 8.11	6.73
p for trend	0.02			0.67		
p for quadratic	0.16			0.93		
PCB 199						
Per doubling of exposure	0.51	− 0.96	1.99	− 0.60	− 1.82	0.65
< 51.75 ppt	Referent			Referent		
51.75–132.10 ppt	4.98	− 0.78	11.07	− 3.28	− 9.85	3.77

(continued on next page)

Table 4 *(continued)*

	White			African American		
	%Difference	95% CI		%Difference	95% CI	
132.10–318.30 ppt	7.65	0.92	14.83	− 4.34	− 11.13	2.96
> 318.30 ppt	2.45	− 4.78	10.23	− 3.63	− 10.50	3.76
p for trend	0.55			0.49		
p for quadratic	0.01			0.33		

[a] Adjusted for age in years, age in years squared, total lipids, plate, smoking status, diabetes, education, sex, alcohol use in the past 30 days, and body mass index.

Table 5
Percent differences in relative telomere length per doubling of exposure to polychlorinated biphenyls (PCBs), by age and race, ACHS participants.

Race	% Difference[a]	95% CI		% Difference[a]	95% CI		% Difference[a]	95% CI		p for interaction*
	Age in years									
White	< 48 years			48–64 years			> 64 years			
	n = 99			n = 106			n = 127			
Mono-ortho	1.14	− 2.33	4.75	0.11	− 3.66	4.04	2.54	− 0.13	5.27	0.84
Di-ortho	2.03	− 1.92	6.14	1.40	− 1.96	4.88	1.44	− 1.24	4.19	0.75
Tri and Tetra-ortho	1.64	− 2.78	6.26	1.10	− 1.95	4.25	0.22	− 2.20	2.69	0.94
ΣPCBs	1.38	− 2.10	4.98	1.29	− 2.06	4.75	1.57	− 1.22	4.45	0.65
African American	< 48 years			48–64 years			> 64 years			
	n = 83			n = 78			n = 66			
Mono-ortho	− 0.06	− 2.53	2.48	− 1.27	− 3.42	0.92	2.33	− 0.30	5.03	
Di-ortho	− 0.89	− 3.33	1.62	− 1.49	− 3.72	0.79	2.21	− 0.36	4.84	
Tri and tetra-ortho	− 0.56	− 3.17	2.12	− 1.10	− 3.17	1.01	2.56	0.11	5.07	
ΣPCBs	− 0.74	− 3.23	1.82	− 1.42	− 3.64	0.85	2.43	− 0.17	5.09	

[a] Adjusted for age in years, age in years squared, total lipids, plate, diabetes, education, alcohol use in the past 30 days, sex, and body mass index. Percent difference reflects predicted difference in doubling of exposure.

* p for interaction represents tests for significance of three-way interaction term including age in years, race, and PCBs.

observed association between serum PCBs and long LTL (Joyce and Hou, 2015). In a cohort study of 24,865 capacitor-manufacturing workers exposed to PCBs mortality from melanoma was elevated among those employed for three months or more [standardized mortality ratio = 1.41, 95% CI: 1.01; 1.91] (Ruder et al., 2014). Case-control studies, including nested case-control studies that measured PCBs prior to diagnosis of NHL, have generally reported that exposure to PCBs are associated with an increased risk of NHL (reviewed by: (Kramer et al., 2012)). An analysis of three nested case-control studies from three prospective cohort studies reported that serum PCBs were consistently associated with elevated risk of NHL. For instance, when compared with the first quartile of PCB 153 those in the fourth were at a 3.6-fold higher odds of being a NHL case (95% CI: 1.3; 9.9) (Engel et al., 2007).

Our study has several limitations that should be considered when interpreting our results. Non-*ortho* dioxin-like PCBs were not assessed in ACHS, which may be important with regards to PCBs and LTL (Mitro et al., 2015). The cross-sectional design of ACHS implies that temporality between exposure to PCBs and LTL is unclear. Exposure to PCBs may be associated with chronic diseases that could lead to telomere shortening. Furthermore, the rate of telomere shortening may be more etiologically relevant than absolute LTL (Hou et al., 2015), thus additional longitudinal studies are needed.

We used several approaches to identify and reduce potential confounding. LTL generally shortens with age (Muezzinler et al., 2013) and older age is a strong predictor of serum PCBs generally and among ACHS participants (Pavuk et al., 2014a). Since we observed a positive association between serum PCBS and LTL among whites and thoroughly adjusted for age, it seems unlikely that confounding by age is an alternate explanation for our results. Other potentially important confounders that were not addressed in this analysis because the information was not available are pack-years of smoking, secondhand smoke exposure, and diet. We only had a relatively crude measure of tobacco smoke exposure, which was a categorical variable that included never, former, and current smoking. However, adjustment for smoking status strengthened the measures of association we reported among white participants. Thus, if we had a more precise measure of smoking history we would expect to see an even stronger positive association between serum PCBs and white participants. Closer adherence to the Mediterranean Diet, which emphasizes fish consumption, has been associated with longer telomeres (Crous-Bou et al., 2014; García-Calzón et al., 2015; Zhou et al., 2016), while local fish consumption is a predictor of serum PCBs in ACHS (Pavuk et al., 2014b). We did not have information on non-local dietary components and the prevalence of local fish consumption in ACHS was high. Adjustment for other lifestyle factors often associated with diet, such as diabetes, physical activity, and BMI did not substantially alter our results, which provides limited reassurance that unmeasured confounding is not an alternative explanation for our results. Perceived stress, which has been associated with shorter LTL (Mathur et al., 2016), should also be considered as potential confounder in our study because ACHS participants were aware of the environmental contamination and resulting litigation. It seems unlikely that confounding by perceived stress would lead to our observed results, since we found that serum PCBs were associated with longer LTL and all our study participants were residents of Anniston.

Selection bias is another potential limitation, as with most recent epidemiologic studies we had a relatively low response rate of potential participants. Individuals who enroll in epidemiologic studies tend to be more health conscious than those who do not and in our study ACHS participants may be more aware of PCB contamination and litigation than those who opted not to participate. Additionally, this analysis relied on stored blood samples, which were not available for all participants, either because they did not have any remaining blood samples or chose not to donate a blood sample. If inclusion in this analysis was associated with both LTL and serum concentrations of PCBs, then there may be a distortion in our findings. We used IPW to partially address the potential selection bias and found that the measures of association were either unchanged or strengthened (results not shown). This

provides some reassurance that selection bias is not a likely alternative explanation for our results. However, the IPW method was based on ACHS participants that at least completed the survey, which does not include Anniston residents who declined to participate.

Our study has several important strengths. Serum PCBs were well-characterized; the reported coefficients of variation were between 2.4 and 11.2% for each congener (Pavuk et al., 2014a). All samples in our study were extracted using the same method; previous studies have indicated that telomere length can vary by DNA extraction method (Hofmann et al., 2014). We also had good quality control for measures for the LTL assay. The intra-class correlation coefficient for LTL was 0.79 and the coefficient of variation for these samples analyzed in blind duplicate was 7.4%. Furthermore, Anniston represents a unique setting to conduct these analyses because the residents of Anniston were exposed to extremely high levels of PCBs and there is wide variability in exposure.

In conclusion, in a highly exposed population we observed a positive association between serum PCBs and LTL among all white participants and the oldest group of African American participants. Our findings build on the expanding body of research indicating that PCBs are associated with longer LTL. However, future prospective studies that address potential confounding factors, particularly diet and weight change, measure LTL across different tissues, and assess incidence of disease are needed to further elucidate our findings.

Acknowledgements

This work was supported by funding by the National Cancer Institute (NCI) grant R25CA113951 and the intramural research program of NCI/NIH.

Conflict of interest

J.R. Olson has served as an expert witness for the plaintiffs in legal actions relating to exposure of residents of Anniston, Alabama, to PCBs.

The other authors declare they have no actual or potential competing financial interests.

Disclaimer

This article was prepared while Catherine Callahan was employed at the University at Buffalo. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government.

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