PREDICTORS OF SERUM PCB CONCENTRATIONS IN PEOPLE FROM MICHIGAN, USA

Garabrant D[1], Hong B[1], Chen Q[2], Chang C-W[1], Jiang X[1], Franzblau A[1], Lepkowski J[3], Adriaens P[4], Demond A[4], Hedgeman E[1], Knutson K[1],Towey T[4], Gillespie BW[2]

[1]Risk Science Center and Department of Environmental Health Sciences, University of Michigan School of Public Health, 109 S Observatory, Ann Arbor, MI 48109; [2]Department of Biostatistics, University of Michigan School of Public Health, 109 S Observatory, Ann Arbor, MI 48109; [3]Survey Research Center, Institute for Social Research, University of Michigan, 426 Thompson Street, Ann Arbor, Michigan 48104; [4]Department of Civil and Environmental Engineering, University of Michigan College of Engineering, 1351 Beal, Ann Arbor, MI 48109.

Introduction: We studied factors that predict serum concentrations of the polychlorinated biphenyls (PCBs) for which World Health Organization Toxic Equivalency Factors (TEFs) exist (PCB 77, PCB 81, PCB 126, PCB 169, PCB 105, PCB 114, PCB 118, PCB 123, PCB 156, PCB 157, PCB 167, and PCB 189), using data from participants in the University of Michigan Dioxin Exposure Study (UMDES) in Midland and Saginaw Counties, Michigan, USA(6). Although the UMDES study focused on PCDD and PCDF exposures, PCBs were also measured in order to calculate TEQs, even though these compounds were not thought to have originated appreciably from the Dow Chemical Company operations in Midland, Michigan. Thus, this study provides a valuable opportunity to identify potential environmental exposure pathways for PCBs.

Methods: Eligible subjects were randomly selected from the populations of five counties in Michigan, USA. Three counties (Midland, Saginaw, and part of Bay Counties, MI) were chosen because of their proximity to the Dow Chemical Company and two counties (Jackson and Calhoun Counties, MI) were chosen as a reference population. 1324 adults age 18 years and over who had lived in their current residence for five or more years participated, of whom the 946 who were interviewed and gave blood samples are included in this analysis. Serum, household dust, and soil were analyzed for the PCB congeners recognized by the World Health Organization as having dioxin-like activity(8). Samples that fell below the limit of detection were estimated using $LOD/\sqrt{2}$. All serum results are lipid adjusted and survey weighted to reflect the entire referent population region. Multiple imputation procedures were used (five imputations) to impute missing values in explanatory variables. Participants were interviewed regarding potential exposure pathways (sport caught fish and game, diet, activities in the contaminated area, occupations, residential locations), demographics, smoking, and breast feeding. Samples of blood, soil, and household dust were analyzed for PCBs using HRGC/HRMS. Important factors were identified using forward stepwise selection. Data were analyzed using linear regression for complex survey data, in which the $\log_{10}$(serum PCB) was a linear function of predictors.

Linear regression models, using a forward stepwise selection procedure, were used to identify significant predictors of the log10 serum dioxin concentration. Five imputed data sets were used in each step, adjusted for all sample design features (including sampling weights, stratification and clustering). In the first phase, age, age^2, body mass index (BMI), sex, months of breast feeding, pack years of smoking, region, dioxin concentration in the top 1 inch soil around the house perimeter, and dioxin concentration in the garden soil were forced into the model. These factors were either important predictors from preliminary models or addressed the principal hypotheses under study. We then fitted a model on the forced-in variables, allowing the variable (selected from the 114 other potential variables) with the smallest combined p-value to enter at each step, and refitting the model. The combined p-value was calculated using Rubin's multiple imputation combining rule, averaging the regression coefficients, and accounting for between and within imputation variations (Rubin 1987). Variables once entered might be dropped if they were no longer significant as other variables were added. The stepwise selection procedure continued until the combined p values for all of the variables in the model (except for those forced in) were significant ($p<0.05$). Influential observations were examined. Explanatory variables were removed from the model if they were unstable (i.e., when statistical significance was dependent on three or fewer observations).

Results: Serum PCB concentrations were detectable in at least 98% of subjects for all congeners except PCB 81 (53% above LOD). The most important congener was PCB 126 because it typically contributes about 10% to the TEQ (using 2005 WHO TEFs)(8), whereas all the other PCBs combined contribute less than 10% to the TEQ.

Contribution to Adjusted R^2 (%)	PCB_77	PCB_81	PCB_126	PCB_169
Overall (Stable factors only)	**10.92**	**28.18**	**43.90**	**79.01**
Demographic factors	6.69	18.66	31.16	60.62
Residence factors	0.00	-0.22	0.18	0.00
Soil/Household Dust	0.33	0.89	0.00	0.00
Property use factors	1.36	0.68	1.03	0.50
Work history factors	0.00	0.00	0.18	0.12
Water activities factors	0.75	6.62	0.00	0.00
Fish consumption and fishing	0.25	1.96	2.46	0.98
Meat/Dairy consumption and hunting	0.02	0.37	-0.05	0.81

The overall model explained 79% of the variance in the serum PCB169, 44% for PCB126, 28% for PCB 81, and 11% for PCB 77. Demographic factors were the most important predictors of all PCB congeners, explaining 61%, 31%, 19%, and 7% of the variance in the serum PCB 169, PCB 126, PCB 81, and PCB 77, respectively. Residence factors, which represented the region in which each participant presently lived and which showed whether there was a difference in the mean serum TEQ in comparison to the Jackson/ Calhoun population, after adjustment for all other factors, explained little of the variation in serum PCB concentrations. Soil and household dust levels explained less than one percent of the overall variation in each PCB congener.

Figure 1. Relationship between serum PCB 77 and age.

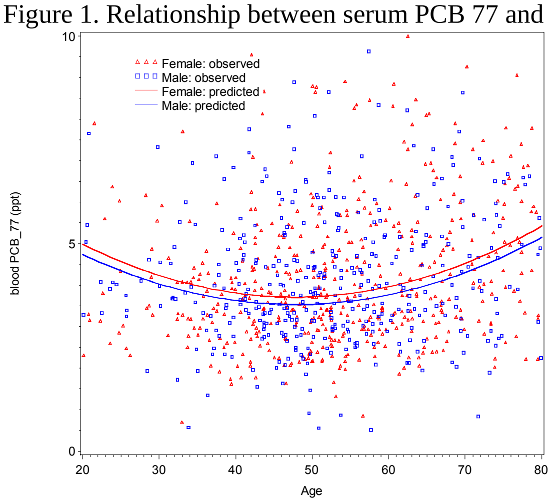


Figure 2. Relationship between serum PCB 81 and age and BMI gain.

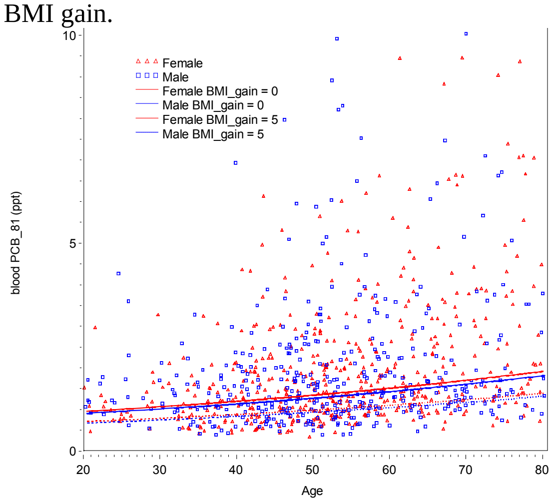


Figure 3. Relationship between serum 126 and age, sex, and BMI loss.

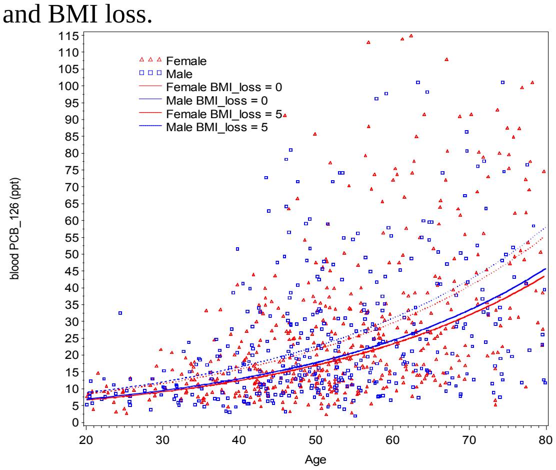
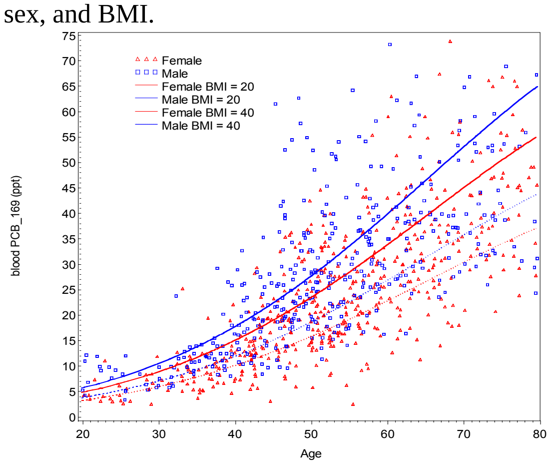


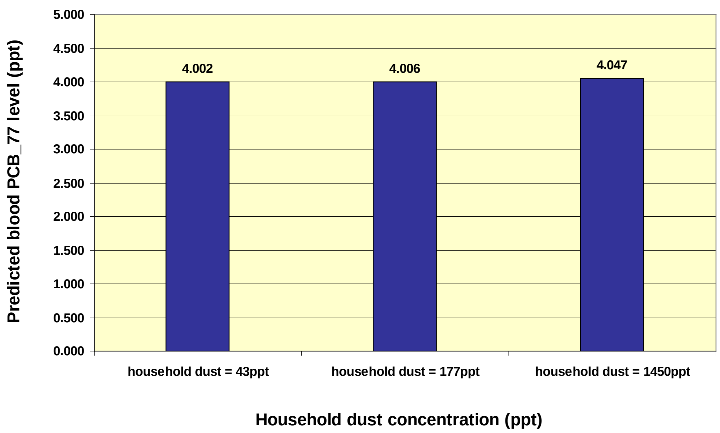
Figure 4. Relationship between serum PCB 169 and age, sex, and BMI.



The linear regression analyses showed age^2 was positively associated with serum PCB 77 (Figure 1), while age was associated with serum PCB 81 (Figure 2) and PCB 126 (Figure 3), and age and age^2 were associated with PCB 169 (Figure 4). The explanation for the convex shape for PCB 77 is unclear and it should be emphasized that the entire regression model explains only a small percentage of the variation in serum PCB 77, so the age relationship has little explanatory value. The serum PCB concentration rose modestly with age for PCB 81 and more dramatically for PCB 126 and PCB 169. Sex was not a significant predictor of PCB 77, 81, or 129, whereas it was for PCB 169, with females having lower levels than males at all ages. Body mass index (BMI) showed no relationship with PCB 77. However, there was a negative relationship between BMI and serum PCB 169. In contrast, a gain in BMI was inversely associated with PCB 81 and a loss of BMI was positively associated with PCB 129. These results in the aggregate suggest that there is a complex relationship between body lipid mass and serum PCBs, and that a reduction in the lipid mass is associated with higher serum PCB concentrations. Smoking was inversely associated with serum PCB 81 and PCB 126, but not PCB 77 or PCB 169.

The soil PCB concentration was not associated with any serum PCB congener, regardless of whether we examined soil around the house perimeter, in gardens, or near the Tittabawassee River. Living in the flood plain of the Tittabawassee River was associated with increased serum PCB 81 concentrations, whereas living in the near flood plain was associated with increased serum PCB 126. Household dust PCB 77 concentration (ng PCB/g dust, or ppt) was associated with increased serum PCB 77 levels, but the magnitude of the association was small (Figure 5), such that an increase of household dust PCB 77 from 43 ppt to 1,450 ppt (1,407 ppt difference) was associated with an increase in predicted serum levels from 4.002 ppt to 4.047 ppt (0.043 ppt difference). Household dust PCB 81 loading (pg PCB81/meter^2) was associated with serum PCB 81 concentration. The subjects had lived in their homes for an average of 18-20 years, so these relationships represent long-term exposures.

Figure 5. Relationship between household dust PCB 77 concentration and serum PCB 77 concentration.



Although there were a number of other findings related to potential environmental exposure pathways which showed statistically significant positive or negative associations, there was no consistent pattern across PCB congeners. Living on a farm in the 1940s-1950s and eating caught fish from any source (sport caught, store bought, restaurant) were positively associated with serum levels of PCB 126. None of the other environmental exposure factors we investigated related to the Midland/Saginaw area was a significant predictors of serum PCB 81 or PCB 126 levels. Serum PCB 77 levels were associated with eating any fish other than walleye or perch caught from the Saginaw River/Bay during the past 5 years, and with hunting more than once per month in these areas after 1980. For PCB 169, although no fish consumption variables were significant positive predictors, hunting in the Saginaw River/Bay area in 1960-79 and fishing in this area after 1980 were significant positive predictors. These findings were counterbalanced by significant inverse associations for hunting in the same area after 1980. There were no significant associations between any PCB congener and consumption of meat or game from the contaminated areas. Consumption of deer liver in the past 5 years (not specific to the contaminated area) was associated with increased PCB 169, but not other congeners.

Discussion: This study has strengths that make it valuable. Since it is a population-based study, the results apply to the general population of Midland and Saginaw Counties. Few other studies have concurrent measurements of serum, soil, and household dust PCBs, as we have, nor do they include as many subjects. Our serum analyses were based on large samples (80 ml of blood yielding at least 25 ml of serum for analyses), which allowed us to have measurable PCB levels for almost all subjects (except for PCB 81, for which 53% had measurable levels). Few other studies have achieved these levels and, as a result, have been limited by large numbers of non-detectable serum levels. This large body of data allowed us to examine the contributions of many potential exposure pathways to serum PCB levels. These results indicate that demographic factors, especially age and changes in BMI, are important predictors of serum PCDF levels. Other studies also show the importance of age on serum PCB levels (1, 5). Our results are of particular value because they illustrate the different relationships of specific PCB congeners with age, sex, and BMI and they provide a foundation for identifying which demographic factors are likely to be important predictors of serum levels in future studies.

Meat and meat products, dairy products, and fish and other seafood are believed to contribute more than 90% of the total exposure to PCBs in the human population (3, 4, 7). Although studies report the contaminant levels in foodstuffs, few have modeled the reported consumption of foods in relation to serum levels, as we have done. A study of the Czech general population living in the vicinity of a chemical factory producing chlorinated herbicides and pesticides showed that ambient exposures to PCDDs were not important contributors to serum PCDDs, but that consumption of home produced eggs was associated with increased serum PCDDs, PCDFs, and PCBs (2).

Our results confirm the dietary contribution of some foods such as fish and deer liver to specific PCB congeners. These results show evidence that eating fish from the Saginaw River/Bay contributes to serum PCB 77 concentrations and that hunting and fishing in this area is associated with serum PCB 169. Our results also indicate that demographic factors such as age and BMI change are more important predictors of serum PCB concentrations. As contamination of the food supply with PCBs decreases over time, the relationship of food intake to serum levels is likely to evolve. In this respect, our study has particular value, since it is based on contemporaneous data from a stable population in an industrialized state in which hunting, fishing, and consumption of sport caught fish and game are common. Future studies should focus on consumption of fish, meat, game, dairy products and eggs from the contaminated areas to further investigate the contributions of these sources to serum concentrations. Recent data on fish and game contamination will allow more precise estimates of the intake of PCBs from these sources and will allow more precise modeling to be completed.

Acknowledgements
Support for this study comes from the Dow Chemical company through an unrestricted grant to the University of Michigan. The University of Michigan has complete independence to design, carry out and report the results of the study. The authors are grateful to Drs. Linda Birnbaum, Ronald Hites, Paolo Boffetta, and Marie Haring Sweeney for their guidance as members of the University of Michigan Dioxin Exposure Study (UMDES) Scientific Advisory Board. Opinions contained in this report are those of the authors and do not necessarily reflect those of the Dow Chemical Company or members of the UMDES Scientific Advisory Board.

References

1. Bates MN et al. Persistent organochlorines in the serum of the non-occupationally exposed New Zealand population. Chemosphere 2004;54:1431-43.
2. Cerna M et al. Levels of PCDDs, PCDFs, and PCBs in the blood of the non-occupationally exposed residents living in the vicinity of a chemical plant in the Czech Republic. Chemosphere 2007;67:S238-S246.
3. Domingo JL, Bocio A. Levels of PCDD/PCDFs and PCBs in edible marine species and human intake: a literature review. Environ.Int. 2007;33:397-405.
4. Faroon OM et al. Polychlorinated biphenyls: human health aspects. Concise International Chemical Assessment Document 55, i-60. 2007. Geneva, Switzerland, World Health Organization.
5. Ferriby LL et al. Evaluation of PCDD/F and dioxin-like PCB serum concentration data from the 2001-2002 National Health and Nutrition Examination Survey of the United States population. J Expo.Sci Environ Epidemiol. 2007;17:358-71.
6. Garabrant D et al. Factors that predict serum dioxin concentrations in Michigan, USA. 27th International Symposium on Halogenated Persistent Organic Pollutants. Organohalogen Compounds 69, 206-209. 2007.
7. Hsu MS et al. A total diet study to estimate PCDD/Fs and dioxin-like PCBs intake from food in Taiwan. Chemosphere 2007;67:S65-S70.
8. Van den Berg M et al. The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicol Sci 2006;93:223-41.