SERUM 2,3,7,8-TCDD CONCENTRATION IN A MICHIGAN, USA POPULATION WITH NO UNUSUAL SOURCES OF EXPOSURE

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Abstract

We investigated the background levels of serum 2,3,7,8-TCDD concentrations in Michigan, USA, using the population of Jackson and Calhoun counties as a reference population because it has no unusual sources of dioxin exposure. Serum TCDD levels conditional on age were studied, including the mean, median, 75th percentile, and 90th percentile, using survey-weighted mean regression and quantile regressions. Since there are relatively few people over the age of 75 in the sample of Jackson/Calhoun counties, the estimation of the mean, median, 75th percentile, and 90th percentile of the serum TCDD levels in Jackson/Calhoun were supplemented by data from the non-Hispanic whites in the NHANES 2001-2002 survey, which is drawn from a representative sample of the US population. Multiple imputation technique was employed to impute the serum TCDD levels for those below LOD. Our results show that serum TCDD levels increase in a log-linear relationship with age, and the serum TCDD increases more in females than in males as age increases.

Introduction

Dioxin is highly lipophilic and accumulates in foods derived from animal fats. Fat intake is the major source of dioxin among the general public[1]. Serum dioxin levels increase with age, likely as a result of the number of years of past exposure, higher levels of dioxins in the environment in the 1960's and 1970's than in recent years, and slowing metabolism with increasing age. Breast feeding is clearly associated with reduced body burdens of dioxin in women[2]. Our goal in this study is to estimate the serum 2,3,7,8-TCDD levels in a population that has no unusual sources of dioxin exposure, after adjusting for age and sex, so that these levels can be compared to the serum TCDD levels observed in Midland and Saginaw counties, where the Dow Chemical Company operations have led to contamination of soils.

Materials and Methods

The University of Michigan Dioxin Exposure Study (UMDES) was conducted to investigate whether people's body burdens of dioxins, furans, and PCBs are elevated because of the environmental contamination from the Dow Chemical facilities in Midland. The study participants were recruited from two populations in Michigan, USA, from area of Midland, Saginaw and part of Bay counties, and from Jackson and Calhoun counties. The purpose of including the population in the Jackson and Calhoun counties was to provide a referent group that is believed to have had background dioxin, furan and PCB exposures that are typical for residents of Michigan who live in areas that are not contaminated by dioxin-like compounds from Dow. In order to be eligible for participation in the UMDES study, subjects must be age 18 years or older and must have lived in their residence at least five years. In Jackson/Calhoun counties, the sampling used a two-stage area probability housing sample design, and a third stage of selection of an eligible person within each sample housing unit. Each eligible participant was asked to give an 80 mL sample of blood. Serum dioxin concentration was lipid adjusted, and measured in parts per trillion (ppt). Details of the survey design, questionnaire, and serum sampling methods and analyses can be found on our study website.[3] A total of 251 subjects from the Jackson and Calhoun counties who completed serum TCDD measures were included. One problem with our sample of Jackson and Calhoun counties is that relatively few people over the age of 75, especially males, were recruited into the study.

A substantial data set on serum TCDD levels in adults aged 20 to 85 exists in the 2001-2002 National Health and Nutrition Examination Survey (NHANES)[4]. We examined information from the NHANES subsample of 615 non-Hispanic whites (excluding pregnant women) who had complete TCDD measures. Table 1 shows that the NHANES non-Hispanic whites population and the Jackson/Calhoun population are similar on age, BMI, smoking, and breast feeding, though the NHANES have a higher proportion of males. Overall, the proportion of values below LOD was substantially higher in the NHANES data (85%) than in the Jackson and Calhoun data (21%), because the UMDES study relied on larger blood samples (80 ml) than did NHANES (8 ml). However, among people older than 75, the NHANES data have enough observations above the LOD.

Table 1: Comparisons of LOD and demographics between JC and NHANES

Factor	NHANES (n=615)	Jackson/Calhoun (n=251)
No. and proportion of below LOD	525 (85.37%)	52 (20.72%)
LOD levels among non-detections (median + range)	2.97 (1.13, 5.80)	0.54 (0.26, 3.19)
No. and proportion of males	302 (48.04%)	92 (38.14%)
Age (median + S.E. +range)	48.15 (0.88) (18,88)	49.86 (1.26) (20,85)
BMI (mean + S.E.)	27.87 (0.35)	28.69 (0.53)
Pack-yrs (mean + S.E.)	11.51 (1.06)	12.47 (1.42)
Female only: No. of children breast fed (mean + S.E.)	1.11 (0.15)	1.04 (0.15)

Our goal was to use information from the NHANES data, particularly among people over age 75, to improve our estimates of the age adjusted mean, median, 75th percentile, and 90th percentile serum TCDD concentration in the Jackson and Calhoun population. The NHANES data set was concatenated with the UMDES Jackson and Calhoun data. The data source was retained (NHANES=1 and UMDES=0), survey sampling weights were standardized within each data source by dividing by their respective mean sampling weights, and important demographic information was retained, including age, BMI, BMI gain and loss in the past year, sex, smoking status, breast feeding (for females), education, and annual household income.

A base 10 logarithm transformation was applied to the serum TCDD concentrations. The multiple imputation technique described by Lubin et al. (2004) was employed to impute serum TCDD concentrations below the limit of detection (LOD) conditional on all the measured demographic information and on the data source.[5] Five imputed data sets were generated. Three quantile regression models (median, 75th percentile, and 90th percentile) as well as the mean regression model were fitted on the 5 imputed data sets separately, with age, data source, gender, and their two-way interaction terms as predictors. All models were adjusted for survey-sampling weights. The survey weighted mean regression model was performed using the SURVEYREG procedure in SAS.[6] The quantile regression coefficients were obtained from weighted quantile regression, and the standard errors of the regression coefficients were computed using Bootstrapping.[7] The estimates for each parameter from five imputed data sets were averaged to get the combined parameter estimate, and the combined standard error was calculated by accounting for between and within imputation variances.[8] The residuals from the four models (mean, median, 75th percentile, and 90th percentile) were checked. Predictions of conditional mean, median, 75th percentile, and 90th percentile of serum TCDD levels among the Jackson and Calhoun population were plotted in raw scale over age, stratified by gender. All analyses were performed using SAS 9.1.[6]

Results

Table 2 shows results of the four regression models with parameter estimates and p values (combined from five imputed data sets). In order to interpret the intercepts from these models, we consider women aged at 50 from Jackson/Calhoun. Their median, 75th percentile, and 90th percentile serum TCDD levels are $10^{0.153}$ = 1.42 ppt, $10^{0.334}$ = 2.16 ppt, and $10^{0.412}$ = 2.58 ppt, respectively. Age is a strong positive predictor, and the median and 75th percentile increase faster among females than among males as they get older. Specifically, the median and 75th percentile serum TCDD concentrations among female Jackson/Calhoun residents would be increased by 58% ($10^{0.02*10\ years}$-1) and 45%, respectively, for each 10 years increase in age. While for male Jackson/Calhoun residents, the median and 75th percentile serum TCDD would be increased by 38% ($10^{(0.02-0.006)*10\ years}$) and 23%, respectively, for each 10 years increase in age. The results from the linear regression and the median regression are close.

Table 2: Results of mean and quantile regressions of base 10 logarithm of serum TCDD concentrations

Factor	Linear regression (mean)	Quantile Regression (median)	Quantile Regression (75th percentile)	Quantile Regression (90th percentile)
Intercept	0.110 (0.031)***	0.153 (0.029)***	0.334 (0.038)***	0.412 (0.027)***
Age-50 (years)	0.020 (0.002)***	0.020 (0.002)***	0.016 (0.002)***	0.017 (0.003)***
Gender (Male=1)	-0.094 (0.041)**	-0.098 (0.049)**	-0.111 (0.068)	-0.033 (0.069)
source (NHANES=1)	-0.139 (0.049)***	-0.202 (0.052)***	-0.123 (0.073)	0.098 (0.097)
(Age-50)*Gender	-0.005 (0.002)**	-0.006 (0.003)*	-0.007 (0.003)**	-0.005 (0.005)
(Age-50) * Source	-0.003 (0.002)	-0.003 (0.004)	0.002 (0.004)	0.0002 (0.005)
Gender*source	-0.040 (0.084)	-0.005 (0.074)	-0.038 (0.086)	-0.184 (0.138)

Results are reported as estimate + (standard error) + P-value; ***P-value<0.01; **P-value<0.05; *P-value<0.1.

For example: 1. Predicted mean of $\log_{10}$(serum TCDD) = 0.110 + 0.02(age-50) - 0.094(gender) - 0.139(source) - 0.005(age-50)(gender) - 0.003(age-50)(source) - 0.04(gender)(source)

2. Log_{10}(predicted median of serum TCDD) = predicted median of $\log_{10}$(serum TCDD) = 0.153 + 0.02(age-50) - 0.098(gender) - 0.202(source) - 0.006(age-50)(gender) - 0.003(age-50)(source) - 0.005(gender)(source)

The predicted mean, median, 75th percentile, and 90th percentile conditional on age are plotted in Figure 1 and Figure 2. The background serum TCDD levels are higher among older people than among younger people in Jackson/Calhoun population. In addition, the serum TCDD increases more quickly in females than in males. These plots also show the value of estimating background levels for different ages.

Figure 1: Prediction of the mean, median, 75th percentile, and 90th percentile of TCDD levels among males

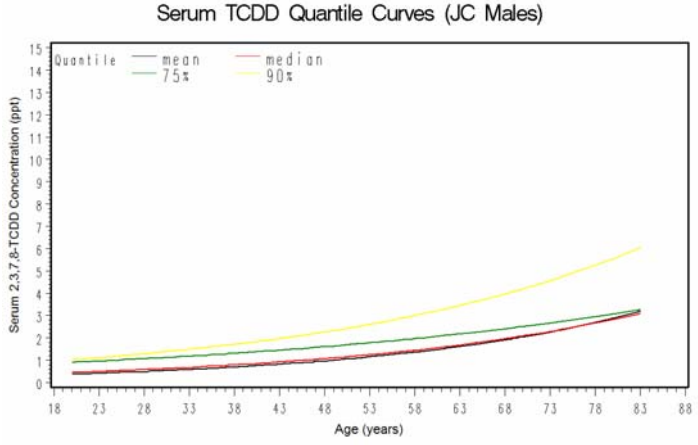
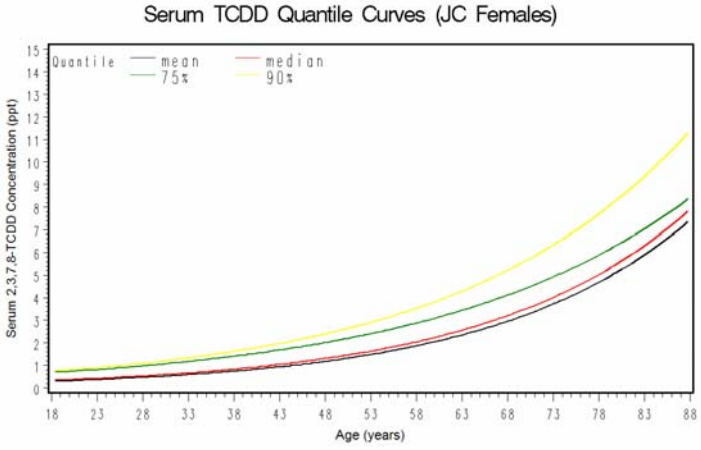


Figure 2: Prediction of the mean, median, 75th percentile, and 90th percentile of TCDD levels among females



Discussion

This study shows that the mean, median, 75th percentile, and 90th percentile of serum TCDD concentrations increase with age, and the rates of increase in the mean, median, and 75th percentile are greater among females than males. Using the NHANES data enhanced our understanding of the distribution of serum TCDD values among older people in the Jackson/Calhoun population.

The methods described above have value to the UMDES study because we can estimate age-adjusted quantiles of serum TCDD for comparison to the population of Midland/Saginaw. For each resident in Midland/Saginaw we can compare the serum TCDD level to the background level of people of the same age and sex in Jackson/Calhoun to see whether the serum TCDD level is elevated. Moreover, with multiple quantile curves, different researchers can define different quantile curves as their reference levels according to their research interests. This age adjusted quantile estimates using quantile regression provide better estimates of quantiles than the traditional method of calculating the population quantiles without adjusting for age, or of adjusting for a limited number of age groups. One limitation of this study is that we only have data on adults and that the findings may not apply to children.

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