

AGE- AND SEX- SPECIFIC BACKGROUND HUMAN SERUM 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN LEVELS IN MICHIGAN, USA

Xixuan Chen¹, Elizabeth Hedgeman¹, Roderick J.A. Little¹, Michael R. Elliott¹, Brenda Gillespie¹, Shih-Yuan Lee¹, Billing Hong¹, Chiun-Wen Chang¹, Kristen Olson¹, Kristine Knutson¹, Lynn Zwica¹, Peter Adriaens¹, Avery Demond¹, James Lepkowski¹, Alfred Franzblau¹, Donald G. Patterson Jr.², David Garabrant¹

¹University of Michigan, Ann Arbor, MI; ²Centers for Disease Control and Prevention, Atlanta, GA

INTRODUCTION AND OBJECTIVES

- Background:** The University of Michigan Dioxin Exposure Study (UMDES) was conducted in response to concern that people's body burdens of dioxin-like compounds might be elevated in *Midland and Saginaw counties, Michigan*, because of environmental contamination from the Dow Chemical facilities in the City of Midland and sediments in the Tittabawassee River flood plain.
- Objective:** Our goal of the present study is to characterize and quantify the background levels of the serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure in residents of Michigan who live in areas with no unusual sources of exposure.
 - The mean, median, 75th percentile, and 90th percentile of the serum TCDD levels were estimated conditional on age and sex to control for confounding by these factors.

MATERIALS AND METHODS

- Data collection:** The population in *Jackson/Calhoun counties* was chosen as the reference population in the UMDES. The sample was collected in *summer 2005*. The participants were required to be 18 years or older, and to have lived in their current residence for at least five years. Participants who met Red Cross criteria for blood donation were invited to provide an 80 milliliter (ml) sample of blood. A total of **251 participants** gave blood samples. The serum TCDD concentrations were lipid adjusted, and measured in parts per trillion (ppt) or picograms/gram.
- NHANES 2001-2002:** One limitation of the Jackson/Calhoun data is that relatively few participants (n=20) were older than 75, especially males (n=3). However, 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). Our goal was to use information from the NHANES data to improve our estimates of the age- and sex-adjusted summary measures of serum TCDD concentrations in the Jackson and Calhoun population.
- Statistical analyses:**
 - The 615 non-Hispanic white observations from NHANES data were concatenated with the 215 observations from UMDES Jackson/Calhoun data, with an indicator for data source (1 for NHANES; 0 for UMDES).
 - A multiple imputation technique was performed to impute the TCDD levels for those below the limit of detection (LOD) in the combined data of NHANES and Jackson/Calhoun.
 - A base 10 logarithm transformation was applied to the serum TCDD concentrations.
 - To estimate the age- and sex- specific serum TCDD measures, survey weighted mean and quantile regressions were fitted on age, sex, data source indicator, and their two-way interaction terms.
 - Predictions of conditional measures of the serum TCDD levels were plotted in raw scale over age. Each value below the LOD was plotted using the average of its imputed values from the five imputed data sets.

RESULTS

Table 1: Comparisons of LOD and demographics between Jackson/Calhoun (n=251) and NHANES (n=615) populations

Factor	NHANES ^a (n=615)	Jackson/Calhoun (n=215)
Proportion of below LOD	85%	21%
Median LOD levels among non-detects	3.0 ppt	0.5 ppt
Median age (range)	48 (18,88) years	50 (20,85) years
Mean BMI (S.E.)	28 (0.4) kg/m ²	29 (0.5) kg/m ²
Mean pack-yrs smoking (S.E.)	12 (1.1)	12 (1.4)
Mean no. of children breast-fed (S.E.)	1.1 (0.2)	1.0 (0.2)

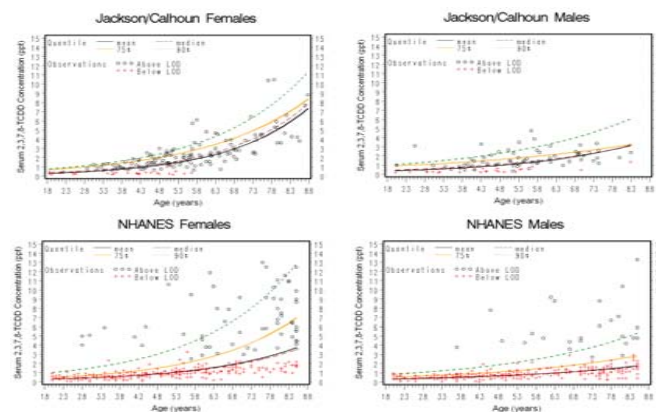
^a non-Hispanic whites (excluding pregnant women) in 2001-2002 NHANES

Table 2: Results of linear and quantile regressions of log10 serum TCDD concentrations

Factor	mean ^a	median ^b	75 th percentile ^b	90 th percentile ^b
Intercept	0.110 (0.031)***	0.153 (0.029)***	0.334 (0.038)***	0.412 (0.027)***
age-50	0.020 (0.002)***	0.020 (0.002)***	0.016 (0.002)***	0.017 (0.003)***
sex (male=1)	-0.094 (0.041)***	-0.098 (0.049)**	-0.111 (0.068)	-0.033 (0.069)
data source (NHANES=1)	-0.139 (0.049)**	-0.202 (0.052)***	-0.123 (0.073)	0.098 (0.097)
(age-50)*sex	-0.005 (0.002)*	-0.006 (0.003)*	-0.007 (0.003)**	-0.005 (0.005)
(age-50)*data source	-0.003 (0.002)	-0.003 (0.004)	0.002 (0.004)	0.0002 (0.005)
sex*data source	-0.040 (0.084)	-0.005 (0.074)	-0.038 (0.086)	-0.184 (0.138)

^a Predicted conditional mean is obtained by fitting a linear regression.
^b Predicted conditional median, 75th percentile, and 90th percentile are obtained by fitting quantile regressions. Results are reported as estimate (standard error) p-value; ***p-value<0.01; **p-value<0.05; *p-value<0.1. Log10(predicted median of serum TCDD) = predicted median of log10(serum TCDD) = 0.153 + 0.02(age-50) - 0.098(sex) - 0.202(source) - 0.006(age-50)(sex) - 0.003(age-50)(source) - 0.005(sex)(source)

Figure 1: Comparisons of predicted mean, median, 75th percentile, and 90th percentile of serum TCDD levels by sex between Jackson/Calhoun and NHANES populations



DISCUSSION

- Serum TCDD concentrations increase with age, and the rates of increase over age are greater among females than males. Thus, the age- and sex-specific serum TCDD measures in the reference population are more appropriate for comparisons to other populations.
- The mean and quantile regression models allow mean and percentiles to be calculated for any specific age and sex. These methods and results have wide application in studies of concentrations of toxins in human serum and in environmental samples.
- The Jackson/Calhoun population is similar to the general US population for serum TCDD exposure. This implies that the Jackson/Calhoun population is a valid reference population for serum TCDD levels for other populations in Michigan and perhaps in the U.S.
- Values below the limit of detection are common in studies of dioxin-like compounds.
 - Simple ways of handling values below LOD (for example: LOD/√2) do not account for imputation uncertainty and depend on the sample volume and the LOD levels of the measurement methods.
 - Alternatively, multiple imputations based on statistical models for the observed measures can be employed to impute the values below LOD.
- In the multiple imputations, we assumed that the serum TCDD levels follow a truncated lognormal distribution.
 - The Jackson/Calhoun population was found to have elevated age- and sex- specific mean and median serum TCDD levels compared to the NHANES non-Hispanic white population, which were fitted mostly based on the imputed values for the NHANES data.
 - If the truncated lognormal assumption is reasonable, then this significance should be true.
 - If the truncated lognormal assumption is not well supported (although it is better than those simple approaches, such as LOD/√2), then the significance in the mean and median regressions fitted mostly based on the imputed values are questionable.

Financial support for this study comes from the Dow Chemical Company through an unrestricted grant to the University of Michigan.