PREDICTORS OF SERUM 2378-TCDD CONCENTRATION IN A BACKGROUND POPULATION IN MICHIGAN, USA

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Abstract: Background U.S. levels of 2,3,7,8-TCDD were estimated for a 2-county area of Michigan (the University of Michigan Dioxin Exposure Study), and for the entire U.S. using a population-based sample (National Health and Nutrition Examination Survey). Mean levels by age and gender are presented. The additional effects of weight loss, smoking, breastfeeding, and other variables were also investigated using regression models. In general, the vast majority of background values are less than 10 ppt. Larger values tend to occur with older age and female gender. Weight loss tends to increase serum concentrations, and both smoking and breastfeeding tend to reduce serum concentrations.

Introduction: Serum dioxin concentrations in heavily exposed populations are often compared to populations exposed only to background levels. Modeling dioxin as a function of demographic and lifestyle variables in a background population can allow prediction of background values in different populations, and can aid in understanding the mechanism of dioxin elimination.

This investigation was carried out using two data sources: (1) the University of Michigan Dioxin Exposure Study (UMDES), and (2) the National Health and Nutrition Examination Survey (NHANES). The UMDES collected samples of serum, house dust, soil, and vegetation from subjects (and their homes and property) living in Michigan, USA in areas potentially exposed to dioxin-like compounds as well as areas presumably exposed only to background levels of these compounds. The NHANES collected data from non-institutionalized residents of the U.S., and measured serum dioxin levels in 1228 of these subjects. This study presents prediction models for serum 2,3,7,8-TCDD levels in both the UMDES background region and the NHANES study.

Materials and Methods: The UMDES was carried out in Michigan, USA, in Midland, Saginaw and parts of Bay County (all potentially exposed areas) and in Jackson and Calhoun Counties (control areas, and the focus of this analysis). A two-stage probability household sampling design was used.[1] Eligible subjects were at least 18 years of age, lived in their current residence for at least 5 years, and provided written informed consent. A detailed exposure questionnaire asked several hundred questions including demographics, smoking history, pregnancy history, occupational exposure, food consumption, and other questions possibly related to human body burden. In addition, serum samples were collected from subjects who consented and were medically eligible to give blood as defined by the American Red Cross. Chemical analyses were performed by Vista Analytical Laboratory, Inc. (El Dorado Hills, California, USA) for the World Health Organization designated 29 PCDD, PCDF, and dioxin-like PCB congeners using US Environmental Protection Agency (EPA) methods 8290 and 1668.[3,4] Values below the limit of detection (LOD) were identified, and the LOD was given in each case.

The National Health and Nutrition Examination Survey (NHANES) is a publicly available database of national health and vitality information for a sample of the United States population. The NHANES data were taken from the 2001-2002 sample release. All individuals answered a general questionnaire covering health, diet and social-demographics; medically eligible persons were asked to donate a blood specimen, and a sub-sample of 1228 persons aged 20 years and older was selected for additional analysis of serum dioxins and furans.

Chemical analyses and lipid measurements were performed by the Centers for Disease Control and Prevention laboratories. Results below the LOD were identified, and reported as LOD/√2.

Statistical Methods: For the UMDES data, the $\log_{10}$ serum dioxin level was the outcome variable in a linear regression model with demographic, lifestyle, food, and other variables as potential predictors. Values below the LOD were replaced with the LOD/√2. Covariates included age, sex, BMI, BMI loss in the past year, pack-years of smoking, months of breastfeeding the first child, and number of incomplete pregnancies. Selected interactions were tested. Residual plots were examined to confirm that model assumptions of normality and homoscedasticity were met. Backward selection was used to remove non-significant variables. The regression models used survey weights to adjust for the probability of sample selection and allow inference to the entire two-county population (SAS proc surveyreg).

The NHANES regression analyses required a different strategy because the majority of values (87%) were below the LOD. We used likelihood-based regression methods for left-censored data, assuming a lognormal distribution (SAS proc lifereg). We used the generalized R^2 to estimate explained variation, although it may yield an underestimate with censored data. Unfortunately, this method did not permit the inclusion of survey weights, which would have allowed inference to the entire U.S. population. We used the same covariates as in the UMDES model, with one exception. The NHANES data did not collect the months of breastfeeding the first child, but instead collected the number of children breastfed. SAS® version 9.1 was used for all analyses.

Results and Discussion: The UMDES interviewed over 1300 subjects, of whom 946 provided serum samples, 251 from Jackson/Calhoun. Of the Jackson/Calhoun samples, 21% fell below the LOD. The median LOD was 0.5 ppt. In the NHANES study, 1228 subjects had serum 2,3,7,8-TCDD levels measured, although 87% were below the LOD. The median LOD was 2.8 ppt, and the mean (s.d.) LOD was 2.9 (1.0). Figure 1 shows similar overall effects of age and gender, although the UMDES estimates are slightly larger. The estimates from UMDES are more precise because the data are based on larger sample volumes, which led to smaller LOD values.

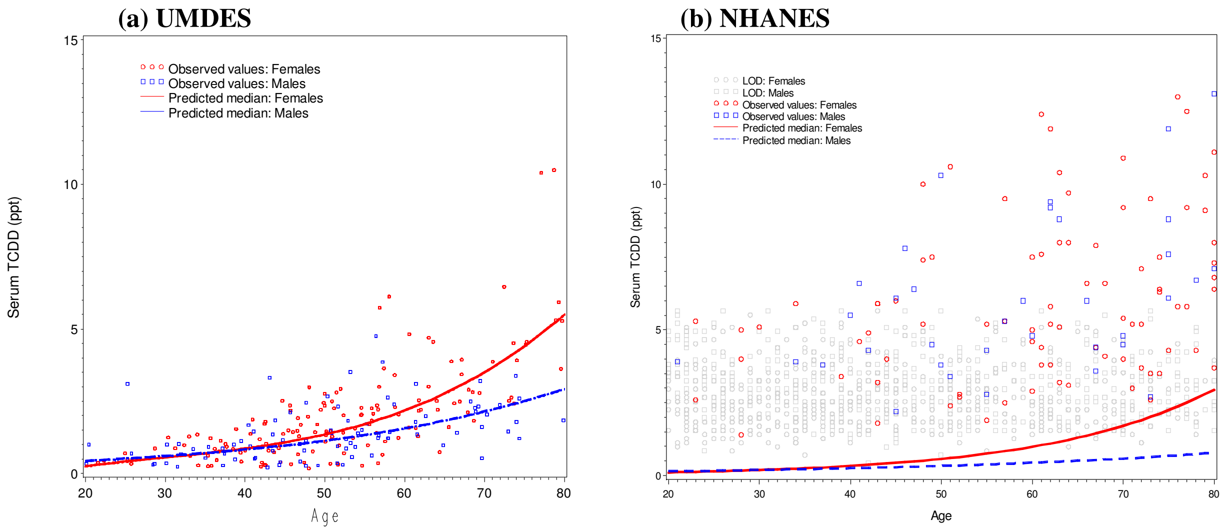

Figure 1. Plots of serum 2,3,7,8-TCDD data and model predicted means by age and gender for both (a) UMDES and (b) NHANES. In (b), for values below the LOD, the LOD itself is plotted (grey circles). One value of 42.7 ppt for a 65-year-old male (BMI=39.9, BMI loss in past year=1.1) was omitted from the NHANES plot to show more detail for the other values.

Characteristics of subjects from the two groups are given in Table 1 below. The two groups are reasonably similar with respect to demographic characteristics.

Table 1. Characteristics of subjects from two background population groups.

	UMDES (n=251): Two Michigan Counties	**NHANES (n=1228):** U.S. Population
	Mean (s.d.) or %	***Mean (s.d.) or %***
Age (years)	52.3 (15.2)	49.1 (18.7)
Sex: Female	63%	54%
Body Mass Index (BMI)	28.8 (6.3)	28.2 (6.1)
BMI loss in past year	1.0 (1.7)	0.7 (1.8)
Smoking (packyears)	13.0 (18.6)	23.4 (28.3)
Breastfeeding (% of women)	53%	43%
# Incomplete Pregnancies	0.5 (1.5)	0.8 (1.2)

Table 2 below shows the final models for the two groups. Both models show effects of age, sex, BMI, BMI loss, and breastfeeding, but the UMDES model had more power to detect interactions and other effects. The R^2 for the UMDES model (54%) increases somewhat after adding diet and occupational variables (63%).

Table 2. Regression results predicting serum 2,3,7,8-TCDD levels from two background populations.

	UMDES: Two Michigan Counties		***NHANES: U.S. Population***	
	Coefficient	p-value	Coefficient*	p-value
Age	0.0117	0.0000	0.013	<.0001
Sex (female)	-0.2424	0.0701	0.270	0.4755
BMI	0.0068	0.0381	0.020	0.0148
BMI loss (past yr)	-0.0238	0.3440	0.033	0.0176
Breastfed	0.0153	0.0361	-0.053	0.0123
Incomplete Pregnancy	-0.1824	0.0000	---	---
Pack-years	-0.0031	0.0108	--	--
Age*sex	0.0065	0.0075	0.011	0.0016
BMI*sex	--	--	-0.021	0.0377
Age*BMI loss	0.0011	0.0209	--	--
Age*Breastfed	-0.0006	0.0020	--	--
Age*Incomplete Pregnancy	0.0032	0.0000	--	--
R^2 (*100%)	Adjusted R^2 = 54%		Generalized R^2 = 22%	
R^2 after addition of diet and occupational variables (*100%)	Adjusted R^2 = 63%		---	

*Coefficients divided by 2.303 (=ln(10)) to make comparable to coefficients from UMDES model.

Figure 2 illustrates two interactions found in the UMDES model above: (a) the interaction between gender and BMI loss, with females having a more exaggerated elevation of serum dioxin with BMI loss than men; (b) the increasing effect of breastfeeding by age.

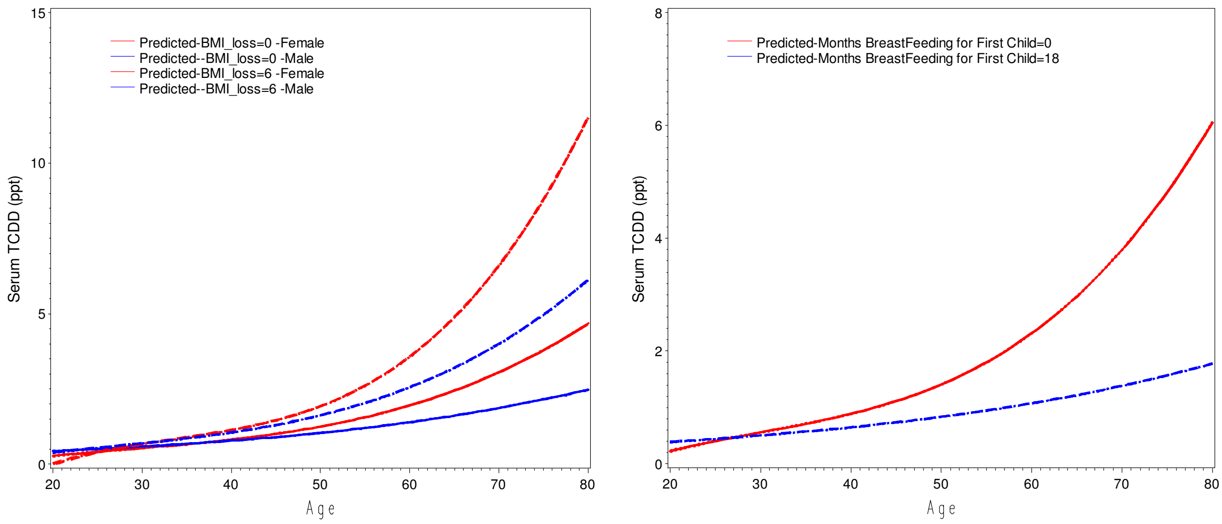

Figure 2. Illustrations of (a) BMI loss by gender interaction, and (b) breastfeeding by age interaction effects.

In conclusion, the strongest predictors of higher background 2,3,7,8-TCDD serum levels were older age and female gender. Adjusting for these factors, the Jackson/Calhoun population appeared to have slightly higher serum levels (by a few ppt) than the U.S. population; however, precise estimation was impossible with the majority of NHANES values below the LOD. In addition, serum levels significantly increased with recent weight loss, and decreased with breastfeeding and smoking. These effects are consistent with previously reported effects. The effects of occupation and food consumption were small but non-trivial.

A strength of both studies was the population-based sampling, allowing valid inference back to the source population. The low LOD in UMDES allowed more detailed modeling. Limitations include the problem of high LOD values in NHANES.

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