PREDICTORS OF 7 DIOXIN CONGENERS IN BACKGROUND U.S. POPULATIONS: DATA FROM TWO MICHIGAN COUNTIES AND THE U.S. NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES)

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Introduction: Serum dioxin concentrations in populations exposed to industrial or other sources of pollution are often compared to serum concentrations in populations exposed only to background levels. However, data from appropriate comparison populations are not always available. Modeling background dioxin concentration as a function of demographic and other variables can allow prediction of background levels for an individual with specific characteristics. Such models could also elucidate the routes of dioxin exposure and elimination.

This investigation modeled serum concentrations for 7 dioxin congeners (2,3,7,8 TCDD, 1,2,3,7,8 PeCDD, 1,2,3,4,7,8 , 1,2,3,6,7,8 HxCDD, 1,2,3,7,8,9 HxCDD, 1,2,3,4,6,7,8 HpCDD, and 1,2,3,4,6,7,8,9 OcCDD) in populations exposed only to background levels of exposure. Two data sources were used: (1) the University of Michigan Dioxin Exposure Study (UMDES), and (2) the National Health and Nutrition Examination Survey (NHANES). The UMDES collected serum samples from subjects 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 demographic and health data from a sample of non-institutionalized residents of the U.S., and measured serum dioxin levels in a subset of these subjects. This study presents prediction models for serum levels of seven dioxin congeners 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 area, 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. Serum samples were collected in 2005-2006 from subjects who consented and were medically eligible to give blood as defined by the American Red Cross. House dust, soil, and vegetation samples (not reported here) were collected from the homes and property of consenting subjects who owned their homes and/or properties. 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.[2,3] Lipid-adjusted concentrations were reported; values below the limit of detection (LOD) were identified, and the LOD was given in each case.

NHANES data are available as a downloadable database of national health and vitality information for a sample of the United States population[4]. The NHANES data for this study 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. Lipid-adjusted concentrations are given; results below the LOD were identified, and reported as LOD/√2.

Statistical Methods: The UMDES and NHANES data were analyzed separately. For each, the $\log_{10}$ serum dioxin level was the outcome variable in a likelihood-based regression for left-censored (below LOD) data, assuming a lognormal distribution. For Figure 1, predicted values were based on models that included only age, age^2, sex, race, and interactions as significant. For Table 2, potential predictors included demographic (age, sex, race, BMI, and BMI loss or gain in the past year), and lifestyle (pack-years of smoking, a measure of breastfeeding, and numbers of complete and incomplete pregnancies). Selected two-way interactions were tested. Backward selection was used to remove non-significant variables. The regression models used survey weights to adjust for the probabilities of sample selection and non-response, and allow inference to the entire two-county population (UMDES) or the U.S. population (NHANES). Multiple imputation was used to handle missing data in UMDES. We used the generalized R^2 to estimate explained variation. We used the same covariates in the UMDES and NHANES models, with three exceptions: First, although the NHANES sample was designed with substantial racial diversity, the UMDES sample was over 90% Caucasian. Therefore, race effects were tested in the NHANES models, but not in the UMDES models. Second, the UMDES collected the months of breastfeeding for each child (which was summarized as number of months breastfed after 1980), and NHANES collected the number of children breastfed. Third, the UMDES collected data on lifetime consumption of specific foods, but NHANES collected data on past-24-hour food consumption for a wider variety of specific foods. (Food results reported separately.) SAS® version 9.1 (SAS Institute Inc., Cary, NC, USA, 2007) was used for data management, and the Stata version 9.2 intreg procedure (StataCorp., College Station, Texas, USA, 2007) was used for left-censored regression.

Results and Discussion: The UMDES interviewed 1324 subjects, of whom 946 provided serum samples, 251 from Jackson or Calhoun Counties. NHANES had ~1158 subjects with serum dioxin measures, with slight variation in sample size by congener. 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 (survey weighted).

	UMDES (n=251): Two Michigan Counties	**NHANES (n=1158):** U.S. Population
	Mean (s.e.) or %	***Mean (s.e.) or %***
Age (years)	49.9 (1.3)	46.3 (.76)
Sex: Female	61.9%	51.6%
Body Mass Index (BMI)	28.7 (.52)	28.0 (.27)
BMI loss in past year	1.1 (.13)	0.7 (.06)
Smoking (packyears)	12.6 (1.4)	10.1 (.81)
Breastfeeding (% of women)	16.8%	23.4%
# Incomplete Pregnancies	0.5 (.13)	0.3 (.04)
Race: Caucasian (non-Hispanic)	93.6%	73.2%
Black (non-Hispanic)	4.8%	10.2%
Hispanic (UM) / Mexican American (NH)	1.2%	6.9%

The percent below the LOD and the median LOD are given in Table 2 for each congener and study. The percents below LOD ranged from 0% to 21% in UMDES, and 1.4% to 87% in NHANES. The median LODs ranged from 0.5 to 3.2 ppt in UMDES, and from 1.9 to 143 ppt in NHANES. Table 2 below shows the final models for each congener and group. Both models show effects of age, sex, race (NHANES only), BMI, BMI loss and/or gain, smoking and breastfeeding. Due to lower LODs (largely due to the collection of larger serum volumes), the UMDES model had more statistical power to detect interactions and other effects.

Table 2. Congener concentration percentiles, half-lives, and regression results predicting dioxin levels from two background populations: UMDES (UM; two Michigan counties), and the National Health and Nutrition Examination Survey (NHANES, NH).

	2,3,7,8 TCDD		1,2,3,7,8 PeCDD		1,2,3,4,7,8 HxCDD		1,2,3,6,7,8 HxCDD		1,2,3,7,8,9 HxCDD		1,2,3,4,6,7,8 HpCDD		1,2,3,4,6,7,8,9 OcCDD	
Median (75th, 90th)	1.8 (2.6, 4.5)	2.1 (2.8, 4.0)	5.1 (7.1, 10.0)	2.6 (6.5, 13.7)	5.5 (7.5, 10.3)	3.7 (6.3, 12.7)	41.0 (54.5,7 5.7)	40.2 (66.8, 110)	6.7 (9.0, 13.1)	4.4 (8.1, 14.6)	33.5 (54.2, 75.2)	43.1 (76.0, 128.0)	247 (404, 569)	365.0 (630, 1040)
% below LOD (median LOD)	20.7% (.5)	87.3% (1.9)	1.6% (1.6)	66.4% (2.0)	11.6% (2.6)	65.9% (3.0)	.8% (2.6)	7.1% (3.5)	10.0% (3.2)	58.6% (3.2)	0.4% (2.1)	1.4% (4.3)	0%	18.3% (143.1)
Half-life in human body	7.2 yrs		11.2 yrs		9.76 yrs		13.1 yrs		5.1 yrs		4.92 yrs		6.73 yrs	
	UM Beta (p-val)	**NH Beta (p-val)**	**UM Beta (p-val)**	**NH Beta (p-val)**	**UM Beta (p-val)**	**NH Beta (p-val)**	**UM Beta (p-val)**	**NH Beta (p-val)**	**UM Beta (p-val)**	**NH Beta (p-val)**	**UM Beta (p-val)**	**NH Beta (p-val)**	**UM Beta (p-val)**	**NH Beta (p-val)**
Age [a]	.0121 (<.001)	.0116 (.005)	.0119 (<.001)	.0188 (<.001)	.0134 (<.001)	.0215 (<.001)	.0126 (<.001)	.0174 (<.001)	.0101 (<.001)	.0098 (<.001)	.0066 (<.001)	.0091 (<.001)	.0089 (<.001)	.0117 (<.001)
Age^2 [a]	-.00011 (.130)	.00018 (.047)	-.00006 (.026)	.000009 (.932)	-.00014 (.030)	-.0001 (.068)	-.00013 (.001)	-.0001 (.020)			.00002 (.715)	-.00002 (.700)	-.00011 (.006)	-.00006 (.168)
Sex (female)	.0618 (.058)	.2261 (.006)	.0229 (.385)	.0926 (.119)	.0313 (.383)	.0258 (.516)	.0157 (.543)	.0444 (.153)	.0656 (.047)	.1448 (.002)	.0020 (.949)	.0352 (.277)	.1738 (<.001)	.2338 (<.001)
BMI [a]	.0069 (.033)				.0049 (.024)			-.0029 (.024)	.0094 (<.001)		.0129 (<.001)	.0151 (<.001)	.0101 (<.001)	.0122 (<.001)
BMI loss (past yr)	.0260 (<.001)									.0246 (.005)				.0206 (<.001)
BMI gain (past yr)											-.0760 (<.001)		-.0178 (.047)	
Breastfeeding [b]			-.0035 (.007)				-.0045 (.004)	-.0265 (.004)						
Incomplete Pregnancy [d]							.0320 (.042)							-.0277 (.004)
Ever Smoked (UMDES model only)											-.1344 (.002)		-.0845 (.008)	
Pack Years	-.0028 (.013)				-.0041 (<.001)	-.0031 (.004)			-.0024 (.009)		-.0046 (<.001)	-.0133 (<.001)		
Race[e] (Mexican American) (NHANES only)								-.1576 (<.001)						
Race[e] (Non-Hispanic Black) (NHANES only)		.2163 (.039)		.1424 (.082)		.1572 (.008)		.1082 (.015)		.1481 (.007)				.1354 (<.001)
Age[a]*Race [e](Non-Hispanic Black (NHANES only))				.0078 (<.001)										

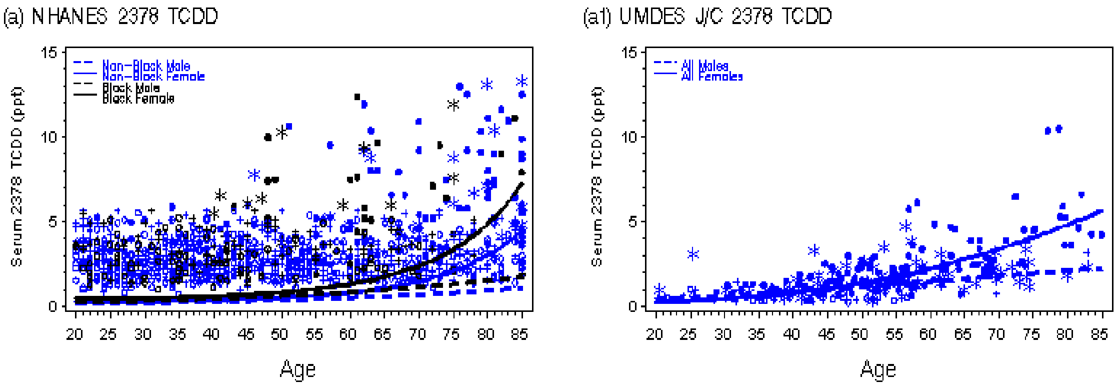
[a] Age and BMI are centered around the mean values (UMDES Mean Age=52, Mean BMI=29; NHANES Mean Age=38, Mean BMI=27).
[b] Breastfeeding definition varies by population (UMDES Total months breastfeeding after 1980; NHANES Number of children breastfed at least 1 month).
[c] Complete pregnancies truncated at 6. [d] Incomplete pregnancies truncated at 3. [e] The reference group for race is Caucasian.
***Additional significant interactions: **TCDD, UM**: Sex*Age[a] (β=.0099, p=.002). **HpCDD, UM**: Sex*BMI gain (β=.0721, p<.001), **HpCDD, NH:** Sex*BMI[a] (β=-.0152, p=.008), **Age*Pack Years[a]** (β=.0006, p=.001), **Age^2*Pack Years[a]** (β=-.00001, p<.005), **OcCDD, NH:** (β=-.0154, p<.001).

The strongest predictors of higher dioxin serum levels for all 7 congeners were older age and female gender. Blacks had significantly higher levels of serum dioxins for 6 of the 7 congeners (all but HpCDD), and Hispanics had significantly lower levels for HxCDD. Serum levels were significantly higher with greater BMI and recent weight loss, particularly in congeners with shorter half-lives. Lower serum levels were significantly associated with recent weight gain, breastfeeding and smoking. Recent weight gain was significant for the two congeners with the shortest half-lives. Breastfeeding was significant for the two congeners with the longest half-lives. Smoking was significant for the 5 congeners with shorter half-lives.

Figure 1 (below) shows raw data with predicted mean values by age, gender and race (NHANES only) for TCDD. (Other congeners not given due to space limitations.) In general, estimates are similar in UMDES and NHANES; race effects in NHANES are mainly seen at older ages.

A strength of both studies is the population-based sampling, allowing valid inference back to the source populations. The low LOD in UMDES allowed more detailed modeling. Limitations include the high LOD values in NHANES 2001-2002 data. Future steps include modeling of food variables, and analysis of the newly released 2003-2004 NHANES data (released May 2007).

Figure 1. Plots of serum congener concentrations and model predicted means by age, gender and race (NHANES only) for both (a) UMDES and (b) NHANES for TCDD. For values below the LOD, the LOD itself is plotted (grey circles). The highest TCDD value of 42.7 ppt for a 65-year-old male (BMI=39.9, BMI loss in past year=1.1 kg/m^2) was omitted from the NHANES plot to show more detail for the other values.



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