THE UNIVERSITY OF MICHIGAN DIOXIN EXPOSURE STUDY: FOLLOW-UP INVESTIGATION OF SUBJECTS WITH HIGH SERUM CONCENTRATIONS OF TEQ, 2,3,7,8-TCDD, 2,3,4,7,8-PeCDF, AND PCB-126

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Abstract

Introduction. This investigation compares serum outliers with non-outliers from the UMDES (n=904) to identify factors that may be associated with high serum concentrations for TEQ, 2,3,7,8-TCDD, 2,3,4,7,8-PeCDF, and PCB-126. Materials and Methods. An outlier was defined to be a subject with a serum result that was in the top 15 for either TEQ or any of the three congeners, which corresponded to approximately 2.5 studentized residuals above the respective means after adjustment for age, age^2, and body mass index. Results and Discussion. Overall, outlier status was not associated with consumption of wild game or sport fish from contaminated regions, and was not associated with contamination in house dust. Associations were observed between outlier status and soil contamination for 2,3,7,8-TCDD and 2,3,4,7,8-PeCDF, but these were likely confounded. There was no association between soil and serum PCB-126 among serum outliers, and, most significantly, there was no association between soil and serum TEQ. Other sources and/or pathways of exposure are likely to better explain high or outlier serum levels of TEQ and the three congeners among area residents.

Introduction

The University of Michigan Dioxin Exposure Study (UMDES) was motivated because of concerns about possible human exposure to dioxins discharged as a result of historical industrial activities of the Dow Chemical Company located in Midland, Michigan, USA. A number of investigations have documented widespread dioxin contamination of soils in Midland downwind of incineration activities at Dow (i.e., the plume area), and in the flood plain and river sediments of the Tittabawassee River downstream from the Dow plant [1,2]. The congener profiles of dioxin contamination in these two areas differ, with contamination in the plume area dominated by polychlorinated dibenzo-*p*-dioxins (PCDDs), and contamination in the flood plain of the Tittabawassee River dominated by two polychlorinated dibenzofurans (PCDFs), 2,3,7,8-TCDF and 2,3,4,7,8-PeCDF [1]. The focus of the UMDES has been to identify and quantify potential pathways of human exposure to dioxins in the contaminated areas.

The distributions of total toxic equivalency (TEQ) and each of the 29 congeners of PCDDs, PCDFs and dioxin-like polychlorinated biphenyls (PCBs) measured in serum are right-skewed, with a relatively small number of subjects with high or 'outlier' values [3,4]. Identification of potential pathways of exposure of subjects with the highest serum concentrations for TEQ and the congeners that contribute the most to serum TEQ is of particular interest since such subjects may be at greatest risk of adverse health effects. Knowledge and understanding of exposure pathways for outliers may also suggest interventions to prevent or reduce the most significant human exposures in the community. The present investigation describes serum outliers for TEQ, 2,3,7,8-TCDD, 2,3,4,7,8-PeCDF, and PCB-126, and compares the outliers with the non-outliers from the UMDES to identify factors that may be associated with having high serum concentrations for TEQ and the selected congeners.

Materials and Methods

The UMDES involved a two-stage clustered random sampling design to recruit subjects from five regions in the State of Michigan, USA. The regions were: the 100-year Federal Emergency Management Agency (FEMA) floodplain of the Tittabawassee River or whether the respondent reported flooding of the home by the Tittabawassee River (FP); the near-floodplain of the Tittabawassee River (NFP); the plume area in the City of Midland downwind from the historic incineration activities of the Dow plant (PL); elsewhere in Midland and Saginaw counties and parts of Bay county outside of the floodplain, near-floodplain and plume areas (MS); and Jackson and Calhoun counties (located more than 200 kilometers away from the Dow facilities in Midland) that served as a control area (JC). Eligible subjects were required to be at least 18 years old and to have lived in their homes for at least 5 years. Data collection for the main study was completed in 2004-2005, and involved an hour-long interview and obtaining blood, house dust, and soil samples for chemical analyses from eligible subjects. Overall, 946 subjects provided blood samples that were analyzed for the WHO 29 PCDDs, PCDFs and PCBs by Vista Analytical Laboratory (El Dorado Hills, California) using modified United States Environmental Protection Agency methods 8290 and 1668, Revision A [5,6]. Serum results are reported in parts per trillion (ppt) on a lipid adjusted basis; soil and dust results are reported in ppt on a dry weight basis. TEQ values are calculated using 2005 TEFs [7]. Full details of methods for the parent study are available elsewhere [1,8].

To be eligible for this outlier investigation, a subject must have been a participant in the parent study, completed an initial interview, provided a blood sample for chemical analyses, and been an 'outlier' for serum TEQ, 2,3,7,8-TCDD, 2,3,4,7,8-PeCDF or PCB-126. For the purposes of this investigation, an outlier was defined to be a subject with a serum result that was in the top 15 for either TEQ, 2,3,7,8-TCDD, 2,3,4,7,8-PeCDF or PCB-126, which corresponded to approximately 2.5 studentized residuals above the respective means after adjustment for age, age^2, and body mass index (BMI). Some subjects qualified to be an outlier in more than one group so the total number of outliers in the four groups is only 42, not 60.

Outliers were compared to non-outliers in the parent study (n = 904). Because of the small number of outliers, all comparative analyses are univariate. Statistical analyses included descriptive statistics, and comparisons of outliers to non-outliers using various modeling approaches, depending on the nature of the variables being compared. Modeling approaches included survey linear regression based on log scale, survey logistic regression, survey Poisson regression, survey ordered logistic regression, survey multinomial (polytomous) logistic regression, and survey linear regression. Models were constructed using survey weights to accurately reflect the distributions in the underlying populations. Statistical analyses were performed using SAS version 9.1 and STATA version 10 [9,10].

Results and Discussion

The median and mean for serum TEQ were 71.4 and 72.5 ppt, respectively, for outliers versus 19.2 and 22.6 ppt for the remaining UMDES. The median and mean for serum 2,3,7,8-TCDD were 13.5 and 15.2 ppt, respectively, for outliers versus 1.6 and 2.4 ppt for the remaining UMDES. The median and mean for serum 2,3,4,7,8-PeCDF were 16.9 and 18.2 ppt, respectively, for outliers versus 5.5 and 6.4 ppt for the remaining UMDES. The median and mean for serum PCB-126 were 270 and 262 ppt, respectively, for outliers versus 16.6 and 27.1 ppt for the remaining UMDES. Each of the outlier groups differed significantly ($p<0.01$) from the remaining UMDES population.

Overlap varied among outlier groups. Ten of 15 TEQ outliers were also PCB-126 outliers. Only three of 2,3,7,8-TCDD outliers were also TEQ outliers, and only four 2,3,4,7,8-PeCDF outliers were also TEQ outliers. The differing patterns of association of the outlier groups suggest that the sources and/or pathways of exposure contributing to outlier status differed among congeners.

The percentage of females appeared to vary among the outlier groups compared to the rest of the UMDES study population, with significantly more women among 2,3,7,8-TCDD outliers. TEQ, 2,3,7,8-TCDD and PCB-126 outliers were significantly older compared to the rest of the subjects in the UMDES, while 2,3,4,7,8-PeCDF outliers did not differ in age from the rest of the UMDES population. Change in BMI had a small association only among

TEQ outlier cases. Smoking had no association with outlier status. Breastfeeding was inversely associated with outlier status among females for PeCDF and PCB-126, but the numbers were small. (See Table 1)

None of the outlier groups reported recent (i.e., in the last five years) consumption of sport fish or wild game from contaminated regions significantly more frequently than the rest of the UMDES study population. Contaminated regions included the Tittabawassee River, the Saginaw River, or Saginaw Bay, or the flood plains of these bodies of water. While the number of subjects in the outlier groups is small (n=15), which would limit the power of such comparisons, it is notable that approximately 90% of all outliers reported no recent fish or game consumption from contaminated regions (similar to the rest of the UMDES), which strongly suggests that game and/or fish consumption from contaminated regions played little or no role in achieving outlier status. (See Table 2)

Current area of residence of TEQ and PCB-126 outliers did not differ significantly from the rest of the UMDES study population. In contrast, 2,3,4,7,8-PeCDF outliers were significantly more likely to currently reside in the floodplain or near-floodplain of the Tittabawassee River compared to the non-outliers in the UMDES. 2,3,7,8-TCDD outliers were significantly more likely to have ever resided in the plume area, but current residence in the plume area did not differ significantly from the rest of the UMDES. The contrasting results of current versus past residence in the plume region for 2,3,7,8-TCDD outliers suggest that there was an exposure pathway associated with outlier status in the plume region that is no longer active. (See Table 2)

Employment at Dow or any other chemical company was not associated with serum outlier status. (See Table 2)

Soil and dust results of outliers are summarized in Table 3. Note that the number of outlier cases varied; soil and dust samples were not obtained from all subjects. Household dust contamination had no association with outlier status, except for a borderline association for 2,3,7,8-TCDD. Note that the statistically significant associations shown for 2,3,7,8-TCDD and 2,3,4,7,8-PeCDF in dust among PCB-126 serum outliers are in the 'wrong' direction. (See Table 3)

House perimeter top one inch soil contamination and maximum soil contamination from the property of subjects were not associated with TEQ or PCB-126 serum outlier status. In contrast, house perimeter top one inch soil contamination and maximum soil contamination from the property of subjects were significantly associated with 2,3,7,8-TCDD and 2,3,4,7,8-PeCDF serum outlier status. While these latter results suggest the possibility that direct soil contact contributed to outlier status for 2,3,7,8-TCDD and 2,3,4,7,8-PeCDF outliers, there are a number of reasons to suspect that these associations may be due to confounding. First, there is no biological or mechanistic reason that direct soil exposure would be associated with outlier status for 2,3,7,8-TCDD and 2,3,4,7,8-PeCDF but not for TEQ or PCB-126, particularly since soil levels of PCB-126 among UMDES study participants were generally greater than soil levels of 2,3,7,8-TCDD and 2,3,4,7,8-PeCDF. Second, the absence of associations between serum outlier status and contamination in house dust conflicts with the soil results for 2,3,7,8-TCDD and 2,3,4,7,8-PeCDF. If direct soil contact were important, then one would expect house dust to have a similar or even stronger association. Third, multivariate models of serum levels of TEQ and individual congeners have failed to find any significant associations with soil or house dust parameters [3]. Fourth, in the case of 2,3,7,8-TCDD there is a circumstance that would be consistent with the current finding of historical residence in the plume being associated with outlier status, but not current residence in the plume area, and that also may explain the potential confounding of soil and serum outlier status for 2,3,7,8-TCDD. Airborne emissions from Dow incineration activities were much greater in the past, but diminished in recent decades, and such emissions were rich in PCDDs. Persons who resided in the plume area in the past would have had opportunity for inhalation exposure to airborne emissions; airborne emissions would also result in contamination of soil (and house dust) in the plume area. Hence, the association of serum and soil levels of 2,3,7,8-TCDD could be due to confounding by past airborne deposition in the plume region. Finally, particular behaviors that contribute to exposure may vary by region, e.g., in the case of 2,3,4,7,8-PeCDF,

data suggest that food, particularly consumption of animals and/or vegetables raised in contaminated areas of the flood plain, can be an important indirect pathway of exposure to contamination in soil [11].

Overall, the results suggest that outlier status for major congeners, and particularly for TEQ, was not associated with consumption of wild game or sport fish from contaminated regions, and was not related to direct contact with contamination in house dust. 2,3,4,7,8-PeCDF outliers were significantly more likely to currently reside in the floodplain or near-floodplain of the Tittabawassee River compared to the non-outliers in the UMDES. 2,3,7,8-TCDD outliers were significantly more likely to have ever resided in the plume area, but current residence in the plume area did not differ significantly from the rest of the UMDES. The observed associations between outlier status and soil contamination for 2,3,7,8-TCDD and 2,3,4,7,8-PeCDF were likely confounded. There was no association between soil PCB-126 and serum PCB-126 among serum outliers, and, most significantly, there was no association between soil TEQ and serum TEQ among outliers. Other sources and/or pathways of exposure are likely to better explain high or outlier serum levels among area residents.

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Table 1: Comparison of Demographic Factors of Serum Outliers to the Non-Outliers in the UMDES Study Population

	TEQ n=15	2,3,7,8-TCDD n=15	2,3,4,7,8-PeCDF n=15	PCB-126 n=15	Other UMDES[a] n=904
Gender [% female]	74.9	96.6***	19.4	29.4	57.1
Age, years [median/mean (range)] [t6]	58.1/57.5*** (43.9-86.6)	53.1/55.5** (32.4-77.9)	48.5/48.6 (24.5-82.3)	57.4/58.7** (43.9-78.7)	50.4/51 (18-91.2)
BMI change, kg/m^2 [median/mean (range)] [t6]	-1.3/-1.1** (-3.2-0)	0/-0.6 (-3-2.3)	-1.1/-1.3 (-24.3-4.6)	0/-0.2 (-3.7-1.6)	0/-0.2 (-9.4-9.1)
Smoking, pack years [median/mean (range)] [t3]	0/10.3 (0-40)	0/7.7 (0-30)	10.5/11.7 (0-52.5)	3/9.3 (0-40)	0.4/12.5 (0-145)
No. of children[b] [median/mean (range)] [t3]	2/1.7 (1-4) (n=6)	1/1.3* (0-6) (n=12)	3/2.9*** (1-5) (n=6)	1/1.3** (1-5) (n=4)	2/2.2 (0-12) (n=511)
No. months breast feeding[b] [median/mean (range)] [t3]	6/8.3 (0-36) (n=6)	0/5.2 (0-39) (n=12)	1/1.2*** (0-12) (n=6)	4/3.4*** (0-4) (n=4)	0/6.3 (0-120) (n=511)

[a]excludes the outliers; [b]female participants only; [t3]survey Poisson regression; [t6]survey linear regression; *** *p-value* < 0.01; ** *p-value* < 0.05; * *p-value* < 0.10

Table 2: Comparison of Recent Fish & Game Meals, Region of Residence, and Occupation of Serum Outliers to the Non-Outliers in the UMDES Study Population

	TEQ n=15	2,3,7,8 TCDD n=15	2,3,4,7,8 PeCDF n=15	PCB 126 n=15	Other UMDES[a] n=904
[c]Game meals from contaminated areas [%] [t4]					
-never	90.8	90.3	98	91.7	92.6
-less than one meal/month	0.5	0	0	0.5	5.6
-more than one meal/month	8.7	9.7	2	7.8	1.8
[c]Fish meals from contaminated areas [%] [t4]					
-never	89.9	96.5	87.6	90.5	88.7
-less than one meal/month	9.3	3.5	7	8.5	9.3
-more than one meal/month	0.8	0	5.4	1	1.9
Current residence [%] [t5, f]					
-Floodplain	1.2	0.5*	14.2**	1	1.1
-Near Floodplain	2.8	1.5	12.2*	1.6	1.1
-Other Midland/Saginaw	31.7	83.9	59.9	44.1	43.8
-Midland Plume	8.4	14	0[e]	0[e]	3.4
-Jackson/Calhoun	55.9	0[e]	13.6	53.3	50.7
Ever resided in Plume [%] [t2]	8.4	38.3***	0[e]	0[e]	5.5
Ever worked at Dow [%] [t2]	1.3*	0[e]	6.5	1.2*	5.8
Ever worked at Other Chemical Co. [%] [t2]	0.8	0[e]	2	0.7	4

[a]excludes the outliers; [c]in past five years; [t2]survey logistic regression; [t4]survey ordered logistic regression; [t5]survey Multinomial (polytomous) logistic regression (outliers vs otherUMDES); *** *p-value* < 0.01; ** *p-value* < 0.05; * *p-value* < 0.10; [e]cannot test cell because of zero entry; [f]Other Midland/Saginaw used as base outcome

Table 3: Comparison of Soil and House Dust Contamination of Serum Outliers to the Non-Outliers in the UMDES Study Population

	TEQ	2,3,7,8 TCDD	2,3,4,7,8 PeCDF	PCB-126	Other UMDES[a]
House perimeter soil (0-1 inch) TEQ	6.3/26.5 (1.4-257) (n=14)	12.3/44.1* (3.9-257) (n=13)	60.1/62.3*** (2.5-112) (n=8)	1.8/13.1 (1.4-1680) (n=13)	4.4/14.1 (0.4-2300) (n=904)
House perimeter soil (0-1 inch) 2,3,7,8-TCDD	0.2/10.4 (0.1-117) (n=14)	3.6/18.6** (0.3-117) (n=13)	1.4/1.6*** (0.6-3.2) (n=8)	0.3/0.8 (0.1-7.1) (n=13)	0.4/2.7 (0-97.4) (n=904)
House perimeter soil (0-1 inch) 2,3,4,7,8-PeCDF	1.1/6.4 (0.2-60.3) (n=14)	2/10.5 (1-114) (n=13)	68/72.5 *** (1.2-147) (n=8)	0.8/13 (0.2-2330) (n=13)	1.3/9 (0.1-3340) (n=904)
House perimeter soil (0-1 inch) PCB-126	3.1/16.7 (1-103) (n=14)	3.8/16.1 (1.2-103) (n=13)	4/7.8 (1.7-22.2) (n=8)	3.1/5 (1-42.8) (n=13)	4.1/12.8 (0.1-1330) (n=904)
Highest soil measurement TEQ	6.4/36.8 (1.8-816) (n=14)	12.3/68.8* (3.9-3250) (n=13)	76.1/539*** (10.5-4460) (n=8)	1.8/20.1 (1.4-7260) (n=13)	5.2/38.5 (0.4-11200) (n=904)
Highest soil measurement 2,3,7,8-TCDD	0.3/12.5 (0.1-140) (n=14)	4.7/22** (0.5-140) (n=13)	2.3/17.2** (1.4-132) (n=8)	0.3/1 (0.1-65) (n=13)	0.5/3.1 (0-187) (n=904)
Highest soil measurement 2,3,4,7,8-PeCDF	2.6/12.9 (0.2-1040) (n=14)	2/26.6 (1.1-4240) (n=13)	101/730.5*** (9.4-6670) (n=8)	0.8/22.1 (0.2-9480) (n=13)	1.7/46.7 (0.1-18600) (n=904)
Highest soil measurement PCB-126	3.1/57.1 (1.3-565) (n=14)	3.8/76.1 (1.4-565) (n=13)	10.2/19.2* (2.4-82.4) (n=8)	3.1/5.3 (1.3-195) (n=13)	4.6/16.6 (0.1-1330) (n=904)
House dust TEQ	36.8/26.5 (3.9-85.3) (n=14)	30.2/26.4 (5-85.3) (n=13)	10.7/18.3 (5.9-85.3) (n=9)	12.6/15.6 (3.3-187) (n=13)	16.1/34.4 (1.4-1750) (n=904)
House dust 2,3,7,8-TCDD	0.3/1 (0.1-8.4) (n=14)	0.9/2.2* (0.2-8.4) (n=13)	0.6/0.5 (0.1-2.5) (n=9)	0.2/0.3*** (0.1-2.5) (n=13)	0.4/0.8 (0-12.3) (n=904)
House dust 2,3,4,7,8-PeCDF	0.9/1.8** (0.6-9.9) (n=14)	1.6/2.9 (0.7-22.8) (n=13)	1.5/4.3 (1.1-44.2) (n=9)	0.6/1.4*** (0.2-210) (n=13)	1.9/3.7 (0.2-512) (n=904)
House dust PCB-126	13.3/18.3 (4.3-59.8) (n=14)	14.8/22.4 (4.6-67.8) (n=13)	21.3/22.4 (3.5-110) (n=9)	22.4/24.7 (4.3-71.8) (n=13)	12.9/53.7 (1.5-2580) (n=904)

Cell entries: median/mean (range) (n=number of subjects); all values shown are ppt on a dry weight basis; [a]excludes the outliers; all models performed using survey linear regression based on log scale, *** *p-value* < 0.01; ** *p-value* < 0.05; * *p-value* < 0.10