ASSOCIATION OF SOIL DIOXIN CONCENTRATION WITH SERUM DIOXIN CONCENTRATIONS IN MIDLAND, MICHIGAN, USA

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Abstract The objective of this presentation is to discuss the relationship between soil dioxin concentrations and blood serum dioxin concentrations in Midland, Michigan USA. The subjects in our study had lived, on average, for 20-25 years in their current properties in an area where there has been substantial soil contamination by dioxins. In regression models in which we considered soil dioxins as a continuous variable we found a statistically significant association between the serum TEQ and the maximum soil concentration found on the property. However, the magnitude of the association was small (an increase of 0.0000585 pg/g in mean $\log_{10}$ serum TEQ per 10 ppt increase in soil TEQ) and the variation in serum TEQ explained by this factor was 0.012%. We also found statistically significant associations between soil and serum 2,3,4,7,8 PentaCDF, 2,3,7,8 TCDD and PCB126; the magnitude of these associations was small and the variation explained by the soil parameter was quite small. In conclusion, it appears that prolonged living on soil contaminated with dioxins is a minor contributor to the body burden of dioxins. Our study was quite large (946 subjects) and was capable of finding very small associations to be statistically significant.

Introduction The University of Michigan Dioxin Exposure Study (UMDES) was undertaken in response to concerns among the population of Midland and Saginaw Counties (Michigan, USA) that the discharge of dioxin-like compounds from the Dow Chemical Company facilities in Midland, Michigan (USA) has resulted in contamination of soils in the Tittabawassee River flood plain and areas of the City of Midland, leading to an increase in residents' body burdens of PCDDs, PCDFs and PCBs. To understand the relationship between soil contamination and residents' body burden, 946 people participated in an interview and gave blood samples for analysis of the WHO 29 dioxin-like compounds. Soil samples were taken from 766 of their residential properties and analyzed for the same set of congeners. The participants were a multistage, stratified sample of the general population of five counties in Michigan, USA. The objective of this presentation is to discuss the relationship between soil dioxin concentrations and blood serum dioxin concentrations.

Materials and Methods The entire protocol for the University of Michigan Dioxin Exposure Study can be found on our study website. Briefly, adults age 18 and over who had lived in their current residence for five or more years were eligible to participate. Eligible subjects were randomly selected from the populations of five counties in Michigan, USA and invited to donate an 80 milliliter whole blood sample for analysis. Three counties (Midland, Saginaw, and Bay Counties, MI) were chosen because of their proximity to the Dow Chemical Company and two counties (Jackson and Calhoun Counties, MI) were chosen as a reference population. Serum was analyzed for the 29 congeners recognized by the World Health Organization[4] as having dioxin-like activity, including TCDD. Samples that fell below the limit of detection were estimated using LOD/$\sqrt{2}$. All results shown are lipid adjusted and survey weighted to reflect the entire referent population region. Soil samples were collected from the properties of the participants

In order to be eligible for soil sampling in UMDES, the respondent had to have lived in their residence at least five years and had to be an owner of the property. A more detailed description of the populations and respondent selection methodology is reported in Lepkowski, et al. (2006)[2]. The locations of soil sampling stations at each residence are shown in Adriaens, et al. (2006)[3]. Each residence yielded the following composite soil samples for analysis: house perimeter 0-1 inch depth composite; house perimeter 1-6 inch depth composite; garden soil 0-6 inch depth composite (referred to as soil contact 0-6 inch), and if the property was in the Tittabawassee River flood plain, the flood plain 0-1 inch depth composite and the flood plain 1-6 inch depth

composite. For each property, we also calculated the maximal dioxin concentration found in any sample found on the property.

The relationship between serum dioxins and soil dioxins was modeled using linear regression, in which the outcome variable was the $\log_{10}$ serum dioxin concentration and the predictors were soil dioxin measurements, variables derived from the questionnaire, and household dust dioxin concentrations. For each dioxin congener, a set of demographic variables (age, age^2, sex, pack-years of smoking, BMI, months a woman breastfed for the first time, and region) and soil variables (house perimeter 0-1 inch depth composite dioxin concentration and the soil contact 0-6 inch depth composite dioxin concentration) were forced into the model, then backwards stepwise selection was used to identify other variables that were significant predictors of the serum dioxin concentration. Additional analyses were run, in which the demographic variables and other predictors (not including soil) were entered and each soil variable was forced in a separate model. The purpose of these models was to estimate the effect of each soil variable on the serum dioxin concentration, regardless of the soil variable's statistical significance.

The models described above assume that there is a linear relationship between soil dioxin concentration and the $\log_{10}$ serum dioxin concentration. In order not to base our analyses on this assumption, we also converted the soil dioxin concentrations to categorical variables, so that we could estimate their relationship to the serum dioxin concentration without assuming any linear relationship. In addition, we calculated the R^2 for each regression model, which is the percent variation in the outcome that is explained by the model, and when we compared models we calculated the increase in R^2 after adding a soil variable to the model. The TEQs were calculated using the 2005 WHO TEFs[4].

Results and Discussion The first set of regression models (Table 1) show the relationship between $\log_{10}$ serum dioxins and soil dioxins as continuous variables, in which the house perimeter 0-1 inch composite dioxin concentration and the soil contact 0-6 inch composite dioxin concentration were forced into the model. The maximal dioxin concentration found in any sample found on the property was allowed to enter the model. Values highlighted in blue are statistically significant.

Table 1. Parameter estimates for soil dioxins as predictors of serum dioxins

	TEQ		2,3,4,7,8 PeCDF		2,3,7,8 TCDD		PCB_126	
R square	72.56		66.71		67.17		53.34	
Parameter	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
Soil house perimeter 0-1"	-1.74E-04	0.1898	-1.04E-04	0.2030	-0.0010	0.6526	0.0006	4.64E-22
Soil contact 0-6"	5.30E-04	0.1632	6.79E-05	0.5342	0.0071	0.0013	5.17E-04	0.0014
Maximum soil concentration	9.88E-06	0.0094	-	-	-	-	-	-

*Each model is adjusted for several other variables derived from the questionnaire

The house perimeter soil 0-1" dioxin concentration was not significantly related to the blood dioxin concentration for the TEQ, for PeCDF, or for TCDD, but was significantly related for PCB126 (p = 4.64E-22). The parameter estimate indicates that each increase of 5 pg/g (ppt) in the house perimeter soil 0-1" PCB126 was associated with an increase in the mean $\log_{10}$ serum PCB126 level of 0.0006*5 = 0.003 pg/g. The soil contact 0-6" dioxin concentration was not significantly related to the blood dioxin concentration for the TEQ or for PeCDF, but was significantly related for TCDD (p = 0.0013) and for PCB126 (p = 0.0014). The parameter estimate indicates that each increase of 5 pg/g (ppt) in the soil contact 0-6" TCDD was associated with an increase in the mean $\log_{10}$ serum TCDD level of 0.0071*5 = 0.036 pg/g. Each increase of 5 pg/g (ppt) in the soil contact 0-6" PCB126 was associated with an increase in the mean $\log_{10}$ serum PCB126 level of 0.000517*5 = 0.0026 pg/g. Each of these models is adjusted for all other factors in the model.

The maximum soil TEQ concentration was significantly associated with serum TEQ concentration (p = 0.0094). The parameter estimate indicates that each increase of 10 pg/g (ppt) in the maximum soil TEQ was associated with an increase in the mean $\log_{10}$ serum TEQ level of 0.00000988*10 = 0.0000988 pg/g. Each of these models is adjusted for all other factors in the model. The R^2 indicates that the regression model explains approximately

73% of the variation in serum TEQ in the population, 67% of the variation in serum PeCDF, 67% of the variation in serum TCDD, and 54% of the variation in serum PCB126. These models indicate that a large proportion of the total variation in blood dioxin concentration is explained by the variables in the model. However, very little of the variation is explained by the soil dioxin variables.

Table 2 shows a series of models in which one soil variable was forced into each model. Table 2 gives the parameter estimate, p-value, and change in R^2 from the addition of the soil variable to the model. For the TEQ, none of the soil variables was a significant predictor of the serum TEQ, except for the maximum soil concentration. The parameter estimate indicates that each increase of 10 pg/g (ppt) in the maximum soil TEQ was associated with an increase in the mean $\log_{10}$ serum TEQ level of 0.00000585*10 = 0.0000585 pg/g. The addition of the maximum soil concentration increased the model R^2 by 0.004 percent, indicating that the soil TEQ explained only a very small proportion of the variation in serum TEQ in the population. This model gave a different parameter estimate for the maximum soil concentration than shown in Table 1 because the model in Table 1 included the house perimeter 0-1" soil concentration and the soil contact 0-6" concentration, which were forced into the model. Thus, Table 1 indicated the effect of the maximum soil concentration after controlling for the other soil variables in the model, whereas Table 2 indicates the effect of the maximum soil concentration when no other soil variables are in the model. Both models indicate that the effect of soil TEQ on serum TEQ is small, both in terms of the parameter estimate and in terms of the explained variation.

Table 2. Parameter estimates for models in which each soil variable is forced to enter separately

	TEQ			2,3,4,7,8 PeCDF			2,3,7,8 TCDD			PCB_126		
Parameter	Estimate	p-value	ΔR²(%)	Estimate	p-value	ΔR²(%)	Estimate	p-value	ΔR²(%)	Estimate	p-value	ΔR²(%)
Soil house perimeter 0-1"	-7.76E-05	0.5215	0.022%	-9.83E-05	0.2264	0.046%	0.0026	0.2957	0.004%	6.53E-04	6.08E-21	0.980%
Soil house perimeter 1-6"	5.26E-06	0.0811	0.004%	-4.50E-06	0.0319	0.012%	0.0045	0.1971	0.086%	9.97E-04	0.1184	0.322%
Flood plain 0-1"	1.57E-05	0.4449	0.000%	3.48E-05	0.1166	0.008%	-7.04E-04	0.5622	0.000%	3.36E-03	0.0573	0.014%
Flood plain 1-6"	2.96E-05	0.0768	0.004%	4.47E-05	0.0020	0.020%	1.44E-04	0.9059	0.000%	1.61E-03	0.1047	0.012%
Soil contact 0-6"	4.42E-04	0.2399	0.118%	9.62E-06	0.9285	0.000%	0.0065	6.68E-07	0.414%	5.69E-04	7.40E-04	0.360%
Maximum soil concentration	5.85E-06	0.0294	0.004%	-3.97E-06	0.0510	0.010%	0.0030	0.1306	0.038%	6.09E-04	1.43E-14	1.278%

*Each model is adjusted for several other variables derived from the questionnaire

For PeCDF, the house perimeter 1-6" soil was significantly negatively associated with the serum PeCDF, and the flood plain 1-6" soil was significantly positively associated. There is no clear explanation for the negative association. For the flood plain 1-6" soil, the parameter estimate indicates that each increase of 10 pg/g (ppt) in the soil PeCDF was associated with an increase in the mean $\log_{10}$ serum PeCDF level of 0.0000447*10 = 0.000447 pg/g. The addition of the flood plain 1-6" soil concentration increased the model R^2 by 0.02 percent. The results indicate that the effect of soil PeCDF on serum PeCDF is small, both in terms of the parameter estimate and in terms of the explained variation. For TCDD, the soil contact 0-6" soil was significantly positively associated with the serum TCDD and the parameter estimate indicates that each increase of 5 pg/g (ppt) was associated with an increase in the mean $\log_{10}$ serum TCDD level of 0.0065*5 = 0.0325 pg/g. The addition of the soil contact 0-6" TCDD concentration increased the model R^2 by 0.414 percent. The results indicate that the effect of soil TCDD on serum TCDD is relatively small, both in terms of the parameter estimate and in terms of the explained variation.

For PCB126, the house parameter 0-1" soil was significantly positively associated with the serum PCB126 and the parameter estimate indicates that each increase of 10 pg/g (ppt) was associated with an increase in the mean $\log_{10}$ serum PCB126 level of 0.000653*10 = 0.00653 pg/g. The soil contact 0-6"soil was significantly positively associated with the serum PCB126 and the parameter estimate indicates that each increase of 10 pg/g (ppt) was associated with an increase in the mean $\log_{10}$ serum PCB126 level of 0.000569*10 = 0.00569 pg/g. The maximum soil concentration was significantly positively associated with the serum PCB126 and the parameter estimate indicates that each increase of 10 pg/g (ppt) was associated with an increase in the mean $\log_{10}$ serum PCB126 level of 0.000609*10 = 0.00609 pg/g. Regardless of which soil sample was included, the addition of the soil PCB126 concentration increased the model R^2 by less than 1.5 percent. The results indicate that the effect of soil PCB126 on serum PCB126 is relatively small, both in terms of the parameter estimate and in terms of the explained variation.

Models based on categories of soil dioxin concentration were examined for each of the six soil variables by each of the three dioxin congeners (TEQ, PeCDF, and TCDD) (18 models, not shown). There was a statistically significant positive association between the flood plain 0-1" soil TEQ middle category (50 percentile to 90 parts per trillion) and the blood TEQ ($p = 0.02$). However, there was no evidence of higher blood TEQ in the highest soil TEQ category. For the other seventeen models, there was no clear relationship between the soil dioxin level and the blood dioxin level. For all eighteen models, the change in R^2 due to the inclusion of the soil dioxin parameter was less than 0.5%, indicating that in no instance did the soil dioxin explain any appreciable part of the variation in blood dioxin levels.

Discussion We performed a comprehensive study of the relationship between soil dioxins and serum dioxins among people who lived in a region that has substantial soil contamination to ascertain whether living on contaminated soil was an important exposure pathway. Both continuous and categorical models were examined, and all models were adjusted for other predictors of serum dioxin concentration. In the models in which we considered soil dioxins as a continuous variable, we found a statistically significant association between the serum TCDD and the soil contact 0-6" TCDD concentration. The magnitude of the association was an increase of 0.0325 pg/g in the mean $\log_{10}$ serum TCDD per 5 ppt increase in soil TCDD and the variation in serum TCDD explained by this factor was 0.56%. We also found a statistically significant association between the serum TEQ and the maximum soil concentration found on the property. However, the magnitude of the association was small (an increase of 0.0000585 pg/g in mean $\log_{10}$ serum TEQ per 10 ppt increase in soil TEQ) and the variation in serum TEQ explained by this factor was 0.012%. Because our study was quite large (including 946 subjects), the analyses were capable of finding very small associations to be statistically significant. Similarly, we found statistically significant associations between the floodplain 1-6" soil PeCDF and serum PeCDF; between the house parameter 0-1" soil PCB126 and serum PCB126; between the soil contact PCB126 and serum PCB126; and between the maximum soil PCB126 concentration and serum PCB126. However, the magnitude of these associations was small and the R^2 explained by the soil parameter was quite small. In conclusion, it appears that living on soil contaminated with dioxins contributes very little to the body burden of dioxins. The subjects in our study had lived, on average for 20-25 years, in their current properties. This indicates that, even in the instance of prolonged residence on contaminated soil, there is little or no relationship between soil dioxins and serum dioxin concentrations. Our study was restricted to subjects aged 18 and older. The relationship between soil and blood dioxin levels in children may differ from what we have observed in adults.

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References

1. University of Michigan Dioxin Exposure Study. http://www.umdioxin.org
2. Lepkowski J, Olson K, Ward B, Ladronka C, Sinibaldi J, Franzblau A, Adriaens P, Gillespie BW, Chang SC, Chen Q, Demond A, Gwinn D, Hedgeman E, Knutson K, Lee SY, Sima C, Swan S, Towey T, Zwica L, Garabrant D. Survey methodology in an environmental exposure study: methods to assure sound inference. Organohalogen Comp. Vol 82, 2006.
3. Adriaens P, Demond A, Towey T, Chang SC, Chen Q, Franzblau A, Garabrant D, Gillespie B, Gwinn D, Hedgeman E, Hong B, Knutson K, LaDronka K, Lee CY, Lepkowski J, Olson K, Sima C, Sinibaldi J, Ward B, Zwica L. Measurements of soil concentrations of pcdd/pcdf/pcb from a community in Michigan, USA. Organohalogen Comp. Vol 82, 2006.
4. Van den Berg M, Birnbaum L, Denison M, De Vito M, Farland W, Feeley M, Fiedler H, Hakansson H, Hanberg A, Haws L, Rose M, Safe S, Schrenk D, Tohyama C, Tritscher A, Tuomisto J, Tysklind M, Walker N, Peterson RE. Toxicological Sciences 2006; 93: 223.
5. Van den Berg M, Birnbaum L, Bosveld ATC, Brunstrom B, Cook P, Feeley M, Giesy JP, Hanberg A, Hasegawa R, Kennedy SW, Kubiak T, Larsen JC, Van Leeuwen FXR, Liem AKD, Nolt C, Peterson RE, Poellinger L, Safe S, Schrenk D, Tillitt D, Tysklind M, Younes M, Waern F, Zacharewski T. *Environmental Health Perspectives* 1998; 106:775.