LOGISTIC REGRESSION MODELS FOR HIGH SERUM 2,3,7,8-TCDD CONCENTRATIONS IN RESIDENTS OF MIDLAND, MICHIGAN, USA

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Abstract

The objective of this presentation is to identify environmental factors in Midland/Saginaw Counties, Michigan, USA, associated with increased risk of having unusually high serum 2,3,7,8-TCDD concentrations. We defined having a high serum TCDD level as having a level higher than the 90th percentile of the Jackson/Calhoun residents of the same age and sex. We used logistic regression to identify factors associated with increased risk of high serum TCDD levels. The study indicated that living in Midland/Saginaw/Bay Counties was associated with increased risk of high serum TCDD levels, but it was not related to living on contaminated soil or having contaminated house dust. It is widely held that diet is the predominant source of the human body burden of dioxins and this study supports a conclusion that fish consumption is a risk factor for high serum TCDD levels.

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 factors that predict residents' body burden, 946 people participated in an interview and gave blood samples for analysis of the WHO 29 dioxin-like compounds. Soil and household dust samples were 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 identify factors associated with odds of being above the referent population 90th percentile of serum TCDD concentrations, using survey-weighted logistic regression models.

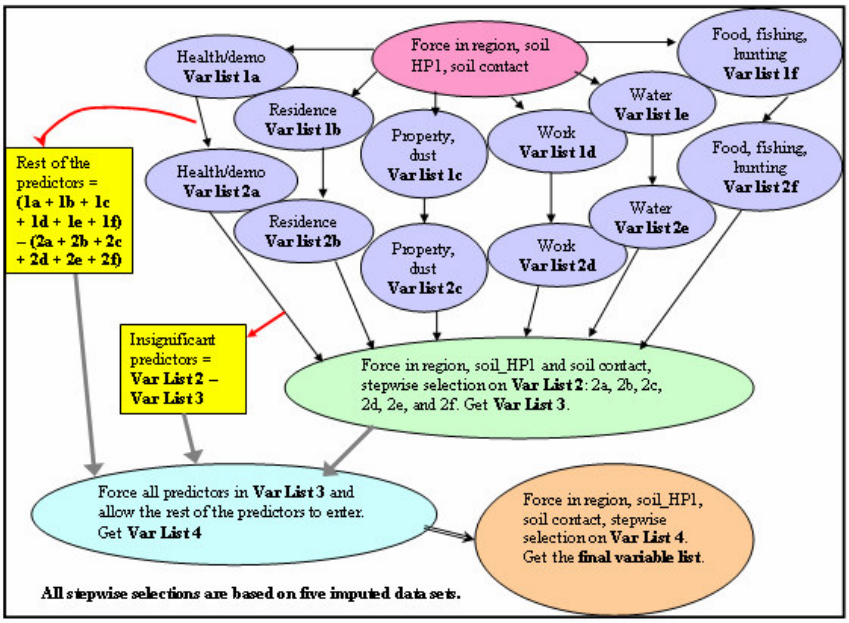
Materials and Methods

The entire protocol for the University of Michigan Dioxin Exposure Study can be found on our study website.[1] 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 complete an interview, donate an 80 milliliter whole blood sample, have their household dust collected, and have their soil sampled. 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, household dust, and soil were analyzed for the 29 congeners recognized by the World Health Organization as having dioxin-like activity, including 2,3,7,8-TCDD [2]. A total of 946 serum samples were collected from the population in the five studied regions[1]; 243 samples were from residents of the Midland/Saginaw (M/S) floodplain region, 205 from the M/S near floodplain region, 204 from M/S out of floodplain region, 43 from M/S Plume, and 251 from the Jackson/Calhoun (J/C) region (which was the referent population). All serum results were lipid adjusted, and results below the limit of detection (LOD) were substituted with LOD/$\sqrt{2}$ for analysis.

The outcome of interest in this presentation is a binary variable on serum 2, 3, 7, 8-TCDD concentration (high versus normal). For a Midland female, if her serum TCDD level is higher than the 90th percentile of the Jackson/Calhoun females at her age, then her serum TCDD will be defined as high. A similar definition was also

applied for Midland males. [3] A total of 695 participants from Midland and Saginaw counties were included in the present analysis.

Figure1. Logistic regression modeling strategy



A multi-stage stepwise logistic regression modeling strategy (Figure 1) was first employed to screen the important factors that are associated with odds of being high. Specifically, three variables of interest were forced into all stages of variable selections, including region, soil contact 0-1" TCDD, and garden soil 0-6" TCDD. In the first stage, the potential predictors were selected section by section (health, residence history, property use, work history, recreational activities, and food consumption) to obtain a set of potential covariates (Var list 3 in Figure 1). Then the selected variables were forced into the second stage stepwise selection process and the variables removed in the first stage were allowed to enter (resulting in Var List 4). In the final stage, a stepwise selection was done among the variables in Var List 4. A p-value of 0.1 was used the criterion for variables to be included or removed from the first stage of variable selection, and a p-value of 0.05 was used in the last two stages. All stepwise selections were based on 5 imputed data sets. Functional forms for the final variable list (Figure 1) were studied. Finally, a survey weighted logistic regression model was fitted. The sensitivity and specificity between the true observed binary outcome and predicted outcome were examined to see if the logistic regression has a good fit. All statistical analysis were performed using statistical software SAS 9.1.[4]

Results

Some important findings from the logistic regression model are shown in Table 1.

- There was no significant effect on the serum TCDD concentration from living in any of the Midland/Saginaw population regions (FP, near FP, Not FP) compared to living in the Midland plume population.
- Neither the TCDD concentrations in soil taken from the top 1" around the house perimeter nor in garden soil (taken at 0-6" depth) was significantly associated with high serum TCDD.
- Neither the TCDD concentrations in household dust nor in any other soil samples were significantly associated with high serum TCDD.
- Income was negatively associated with high levels of serum TCDD.
- Pack years of cigarette smoking was negatively associated with high levels of serum TCDD.
- The number of years living in the Midland and Saginaw counties was positively associated with high serum TCDD. Specifically, for each year of living in these areas, the odds of having a high level of serum TCDD was increased by 10%.
- Eating fish, whether store-bought fish or caught in the Tittabawassee River/Saginaw River/Saginaw Bay, was positively associated with high levels of serum TCDD. For each year of eating store-bought fish, the odds of being high was multiplied by 1.078 times, while for each year of consumption of fish from the Tittabawassee River/Saginaw River/Saginaw Bay, the odds of being high was multiplied by 1.1 times.

Table 1. Factors that predict serum TCDD concentrations in logistic regression model.

Variable Label	Logistic Regression	
	Odds Ratio	P-value
Variables forced into model		
Region-M/S FP	0.520	0.118
Region- M/S Near FP	1.846	0.231
Region- M/S Not FP	0.673	0.300
House perimeter 0-1” soil	0.983	0.651
Garden Soil 0-6”	1.037	0.306
Health/Demographic variables		
Income	0.860	0.027
No. of pack-years (pack-yrs)	0.966	0.005
Residence history		
No. of years living in Midland, Saginaw, and Bay Counties	1.103	<0.001
Property Use		
No. of years using a wood burning stove or fireplace between 1960 and 1979 (years)	1.129	<0.001
Fish/fishing		
No. of years eating any fish from 1960 to 1979 (years)	1.078	0.026
No. of years eating sport caught fish from Tittabawassee River or Saginaw River/Bay after 1980 (years)	1.100	0.015

Discussion

The objective of this analysis was to identify factors that predict having an unusually high serum TCDD concentration among the Midland/Saginaw population, using logistic regression methods. The outcome variable was dichotomous: either having or not having a high serum TCDD level, where a high level was defined as being above the 90th percentile of the Jackson/Calhoun population, specific to age and gender.

It is important to identify factors that lead to high serum TCDD levels because they may be different than the factors that lead to changes in the mean (as would be modeled in a linear regression). People with high serum TCDD levels are of special concern, especially if factors associated with high serum levels can be altered to prevent future exposure. We were most interested in determining whether contaminated soil and household dust were associated with the odds of having high serum TCDD levels, and they were not. None of the soil TCDD measurements, regardless of from where on the property they were taken, was associated with increased odds of having a high serum TCDD level.

The results regarding living in the different regions of Midland/Saginaw should be interpreted carefully, since the reference group was the participants who lived in the Midland plume, downwind of the Dow facility, an area that was subjected to aerosol deposition of dioxins in the past. There was no significantly increased or decreased risk of having a high serum TCDD among the populations in the other three areas of Midland and Saginaw counties. The choice of the plume population as the reference group was arbitrary - the goal of this part of the analysis was to see if living in any particular area was associated with increased or decreased risk of high serum TCDD levels. What this means is that, after controlling for other factors in the model, there is no clearly increased risk of having a high serum TCDD level from living in any specific area within Midland or Saginaw counties.

In contrast, the number of years lived in Midland, Saginaw, and Bay counties combined was associated with increased risk of high serum TCDD. Our models suggest that this association was not explained by age or by having lived on contaminated soil, but was due to other factors related to living in this region. Because the half life of TCDD in soil is long, current soil concentrations likely reflect past concentrations. The number of years

the respondent used a wood burning stove or fireplace was also significantly associated with increased odds of having a high serum TCDD level.

This analysis also reveals that fish consumption (from any source, including store bought, restaurants, or sport caught from any location) between 1960 and 1979 was associated with increased risk of having a high serum TCDD level. Consuming fish caught from the Tittabawassee River/Saginaw River/Saginaw Bay after 1980 was also associated with increased risk of having a high serum TCDD level. The odds ratios for fish consumption reflect the risk per year of consumption, so consuming fish from the contaminated river for 30 years would produce a high risk of being in the upper tail of the serum TCDD distribution. Most importantly, this study provides insight into the environmental factors associated with having unusually high serum dioxin levels. It is widely held that diet is the predominant source of the human body burden of dioxins and this study supports a conclusion that fish consumption is a risk factor for high serum TCDD levels. Living on contaminated soil having contaminated house dust appear to have little association with increased serum TCDD levels.

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References

1. Garabrant DH, Franzblau A, Gillespie B, Lin X, Lepkowski J, Adriaens P, Demond A. The University of Michigan Dioxin Exposure Study. Study Protocol. www.umdioxin.org.
2. Van den Berg M. Project for the re-evaluation of human and mammalian toxic equivalency factors (TEFs) of dioxins and dioxin-like compounds. ToxSci Advance Access 2006.
3. Chen Q, Hedgeman E, Little RJA, Elliott MR, Gillespie BW, Lee S-Y, Hong B, Chang C-W, Olson K, Knutson K, Zwica L, Adriaens P, Demond A, Lepkowski J, Franzblau A, Patterson D, Garabrant D. Organohalogen Comp 2007 (forthcoming).
4. SAS Institute. *SAS/STAT User's Guide Version 9*. Cary, NC: SAS Institute Inc., 2004.