A PHARMACOKINETIC MODELING APPROACH TO INVESTIGATE THE PREDICTORS OF SERUM 12378-PECDD, 123678-HXCDD AND 23478-PECDF

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Introduction

The University of Michigan Dioxin Exposure Study was undertaken in response to concerns that the historical discharges by the Dow Chemical Company into the air and nearby river had resulted in elevated serum dioxin concentrations of polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) among the residents in Midland and Saginaw, Michigan. The serum levels of 17 PCDDs and PCDFs, and 12 polychlorinated biphenyls (PCBs) recognized by World Health Organization as dioxins and dioxin-like compounds, were measured in blood, household dust and house perimeter soils. The goal of the study is to identify the exposure pathways through which the dioxins may have reached the human population. It is also important to differentiate the past exposures from current and future exposures in the study because the historical exposures cannot be changed, while the present or future exposures can be mitigated. Since time-related factors are often correlated, we developed a pharmacokinetic (PK) modeling approach to reduce these correlations, accounting for time-related factors such as change of dioxin concentrations in food sources in different time periods, change in elimination half-lives with age, and change in amount of food consumed with age. Hao[1] has described the PK modeling approach in great detail and examined the predictors of serum 2378-TCDD. In this article, we extend the PK approach to the analyses of serum 12378-PeCDD, 123678-HxCDD and 23478-PeCDF.

Materials and methods

Before the regression is performed, we convert for each exposure variable the historical intake into a 2005 lifetime cumulated dioxin-based intake - called PK-transformed variables - accounting for historical variations in environmental concentrations as well as for changes in food intake and elimination rates with age. Then linear stepwise regressions are carried out for blood concentrations as a function of the PK-transformed variables and additional demographic variables. For each dioxin congener, we test the regression analyses in two approaches: without survey weights (unweighted model), and with survey weights (weighted model), while in both approaches, we include strata and clusters. Unweighted models provide reduced variance on the parameter estimates in the contaminated region because of oversampling, but limit the scope of inferences. The weighted models are representative of the population of the Midland/Saginaw and the referent counties of Jackson/Calhoun, but may result in wider (or narrower) confidence limits on parameter estimates. Hao[1] and Jolliet[2,3] have discussed the details of calculation of PK variables, and the stepwise regression strategy. To assess the impact of an individual variable on the serum for each participant, we estimate the predicted effect of the individual variable by multiplying its parameter estimate by the participant's value for that variable. This effect can be interpreted as the amount by which the serum is changed due to the individual variable. For each variable, rank ordering the effects for all the participants from lowest to highest shows the range and frequency of effects across the study population. The figures 1a-3d show the results for three key congeners.

Results and discussion

Table 1 presents the unweighted and weighted model results for the serum 12378-PeCDD, 123678-HxCDD and 23478-PeCDF. We first list the residential factors: living in Midland/Saginaw in 1940-1983 and living in the area with modeled air concentration from the Dow incinerator in 1940-1983 are the most important potential exposure pathways for the serum concentrations in the contaminated area; then smaller contributions are observed for factors associated with Dow contamination such as the intake through fish consumption from the Tittabawassee River, Saginaw River/Saginaw Bay (TR and SR/SB – only significant when considering the unweighted model) and consumption of meat from the floodplain of TR and SR/SB; additional exposure

variables contribute to the serum concentration but are not related to Dow, such as meat consumption from restaurants or store-bought and number of years lived on a property that was ever damaged by a fire in 1940-1983; lastly we present the demographic variables such as age and gender. Note that all the exposure variables are PK-transformed and lipid adjusted meaning that they are cumulated through people's lifetime. For the fish variable, since we have combined the local concentration data with the meals reported, the coefficient of 0.4 in the 23478-PeCDF unweighted model for the intake through fish consumption from TR and SR/SB corresponds to the fraction of the 2005 lipid adjusted cumulated intake absorbed after cooking and ingestion. There are a few variables designated as unstable meaning they lose the significance after removing up to three observations.

Table 1: Unweighted and weighted model results summary for serum 12378-PeCDD, 123678-HxCDD and 23478-PeCDF.

Congener	12378-PeCDD		123678-HxCDD		23478-PeCDF	
Factor	unweighted	weighted	unweighted	weighted	unweighted	weighted
Exposure variables linked to local contamination						
No. of years lived in Midland/Saginaw in 1940-1983	17.9^{***}	22.4^{***}			38.2^{***}	30.7^{***}
No. of years of air concentration in 1940-1983	1835.5^{*}		6835.6^{*}			
Fish intake from TR and SR/SB					0.4^{**}	
No. of meals of meat from TR and SR/SB	0.01^{a***}	0.02^{***}	0.05^{***}	0.06^{***}	0.03^{***}	0.03^{***}
No. of meals of root vegetables, fruit or other vegetables grown in flood plain of TR and SR/SB				-0.02^{a*}		
No. of days fishing in TR and SR/SB	0.04^{*}		0.3^{**}	0.2^{***}		0.05^{a*}
No. of days of water activities in TR and SR/SB					0.04^{**}	
Other exposure variables						
No. of meals of meat that were store-bought or bought in a restaurant.				0.01^{*}		
No. of meals of root vegetables, fruit or other vegetables grown somewhere else or store-bought	-0.001^{*}		-0.003^{*}		-0.001^{*}	
No. of years lived on a farm/property where crops, livestock or poultry were raised in 1940-1983	17.8^{**}		88.0^{***}	48.4^{a*}	49.5^{*}	
No. of years lived on a property that ever damaged by a fire while living in 1940-1983		128.9^{a**}		962.4^{a***}		
No. of years worked in waste disposal, metal scrap yards or water treatment facility		7.2^{***}		50.5^{a***}		9.5^{***}
No. of years lived on a property where trash or yard waste were burnt in 1940-1983						29.2^{a**}
No. of days did hunting in the surrounding areas of Kalamazoo river or other Michigan lakes or rivers						0.04^{*}
Lifetime consumption from other food excluding the food items collected in the interview				0.003^{*}		
Demographic variables						
Age at interview-50	0.08^{***}	0.09^{***}	1.0^{***}	0.7^{***}	0.1^{***}	0.1^{***}
Sex (1 for female; 0 for male)	0.8^{***}	1.0^{***}		6.4^{**}		
Sex ×(age at interview-50)	0.1^{***}	0.09^{***}		0.3^{*}		
Change of BMI	-0.2^{**}		-1.2^{***}		-0.2^{***}	-0.2^{***}
Lifetime smoking status (1 for ever; 0 for never)			-2.7^{*}			
Total no. of months all children were breast-fed	-0.04^{***}	-0.03^{***}	-0.3^{***}	-0.2^{***}	-0.06^{***}	-0.04^{**}
No. of times a woman had been pregnant but without giving birth to				2.8^{*}		
No. of children a woman had given birth to			1.4^{**}		0.3^{*}	0.3^{a*}
Income			-0.4^{*}			
Whether the participant is Hispanic or Latino					-1.1^{*}	-1.3^{a*}
Intercept	5.2^{***}	5.0^{***}	43.6^{***}	29.5^{***}	6.2^{***}	5.7^{***}

[a] Unstable factors which lose significance after the removal of up to 3 observations.

Significance codes *:0.01 ≤ *p*-value< 0.05; **: 0.001 ≤ *p*-value < 0.01; ***: *p*-value < 0.001

Figures 1a-3d present the impact of regional predictors that reflect the potential pathways related to Midland/Saginaw contamination based on the unweighted model results. Each figure shows the ranked histogram for all 946 study participants from lowest to highest. Contributions of exposures prior to 1983 are plotted in blue, between 1984-2000 in yellow, and in red for the recent five years, which can help differentiate the historical impact earlier in participant's life and the current exposures.

Results for 12378-PeCDD serum concentrations are shown in figures 1a-1d. The largest contributor to 12378-PeCDD comes from having lived in Midland/Saginaw counties during 1940-1983. Its estimated effect ranges from 0 ppt to 7.5 ppt with 592 people influenced. The modeled air concentration from the Dow incinerator during 1940-1983 also plays an important role with the effect ranging from 0 ppt to 7 ppt and with 604 participants affected. Both of the variables are related to having lived in Midland/Saginaw and are major predictors to the serum, however, they are considered past exposures which no longer contribute to present increases in serum concentrations. Fishing in TR and SR/SB has an estimated effect on 398 people, ranging from 0 ppt to 3.8 ppt and showing a low proportion of the past exposure. Since historical dioxin concentrations in sediments and local environment in TR and SR/SB are not available, we have assumed a constant concentration across years, meaning that there is likely an upper estimate of current versus past exposure. This also applies to the fishing variable for 123678-HxCDD and water activity variable for 23478-PeCDF. Figure 1d shows the effect of meat consumption from TR and SR/SB ranging from 0 ppt to 4.2 ppt with only 25 people affected, and we can see that the historic exposure prior to 2000 (blue and yellow areas under the curve) dominates.

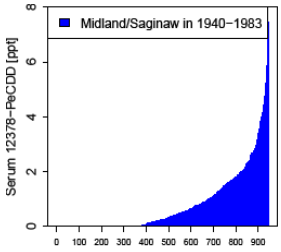

Figure 1a. Effect of living in Midland/Saginaw in 1940-1983 on the serum 12378-PeCDD.

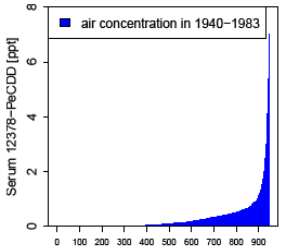

Figure 1b. Effect of modeled air concentration from the Dow incinerator in 1940-1983 on the serum 12378-PeCDD.

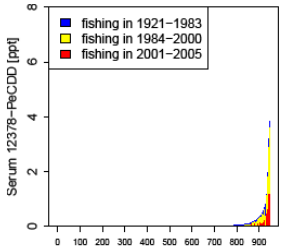

Figure 1c. Effect of lifetime fishing in TR and SR/SB, separated in 3 periods on the serum 12378-PeCDD.

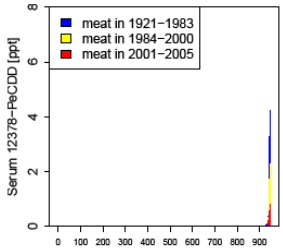

Figure 1d. Effect of lifetime meat consumption from TR and SR/SB, separated in 3 periods on the serum 12378-PeCDD.

Results for 123678-HxCDD serum concentrations are presented in figures 2a-2c. Air concentration in 1940-1983 contributes up to 31 ppt. Fishing in TR and SR/SB ranges from 0 ppt to 30 ppt, and meat consumption from TR and SR/SB ranges from 0 ppt to 20 ppt. Considering the maximum serum concentration for 12378-HxCDD is 189 ppt, these regional exposure variables only explain relatively small fractions of the serum concentration.

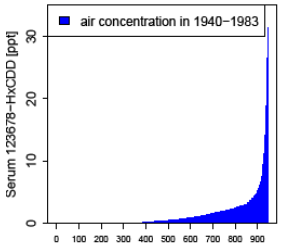

Figure 2a. Effect of modeled air concentration from the Dow incinerator in 1940-1983 on the serum 123678-HxCDD.

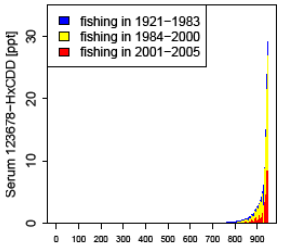

Figure 2b. Effect of lifetime fishing in TR and SR/SB, separated in 3 periods on the serum 123678-HxCDD.

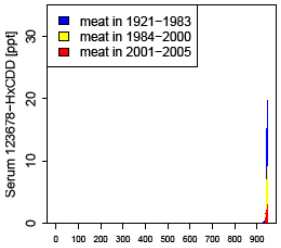

Figure 2c. Effect of lifetime meat consumption from TR and SR/SB, separated in 3 periods on the serum 123678-HxCDD.

Results for 23478-PeCDF are presented in figures 3a-3d. Having lived in Midland/Saginaw in 1940-1983 is associated with 8.4 ppt serum increase. Air concentration does not enter the model which could be anticipated

since we are not aware that furans were discharged through the incinerator. 23478-PeCDF is of great interest with regard to fish consumption from TR and SR/SB because it is present in high concentrations in river sediments downstream of Dow. In figure 3b, consumption of fish from contaminated area is associated with a maximum of 7 ppt serum increase, however, on average, the contribution among the population is small, and most is related to remote, not recent exposures. Meat consumption from TR and SR/SB is associated with a maximum of 5.2 ppt increase in the serum of which most is due to exposure prior to 2000. Water activity variable in the TR and SR/SB is associated with 4.0 ppt increase in serum with 506 people affected.

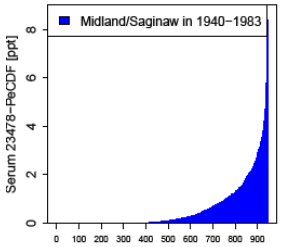

Figure 3a. Effect of living in Midland/Saginaw in 1940-1983 on the serum 23478-PeCDF.

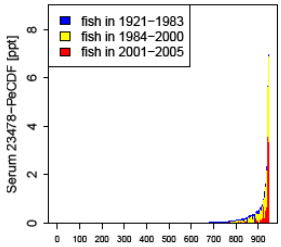

Figure 3b. Effect of lifetime fish intake in TR and SR/SB, separated in 3 periods on the serum 23478-PeCDF.

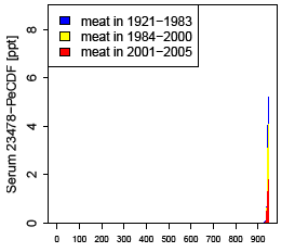

Figure 3c. Effect of lifetime meat consumption from TR and SR/SB, separated in 3 periods on the serum 23478-PeCDF.

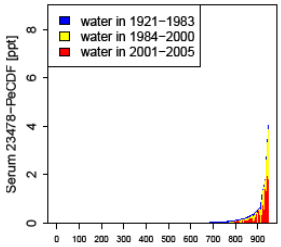

Figure 3d. Effect of lifetime water activities from TR and SR/SB, separated in 3 periods on the serum 23478-PeCDF.

Overall the PK-results are consistent across the different congeners, showing a) a dominant influence of past exposure from having lived in the area and having been exposed to air concentration (for the dioxins) in 1940 and 1983 and b) a much smaller effect of recent exposure due to meat, fish as well as fishing and water activities. This also confirms previous results from the linear model regressions[5]. The effects of air concentration and fish consumption from the contaminated areas were not evident in the weighted models, which raises questions about the interpretation of these results: When the weights are included there is no significant effect of fish consumption from the contaminated areas and air concentration becomes marginally significant in 12378-PeCDD and 123678-HxCDD. The difference between the weighted and unweighted models may be related to an interaction between these predictors and the region in which participants lived. This explanation needs to be clarified, since these two variables were created to obviate the role of the region variables. Further analyses are underway.

Acknowledgements

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