A PHARMACOKINETIC MODELING APPROACH TO INVESTIGATE THE PREDICTORS OF SERUM TEQ BASED ON FOUR CONGENERS: 2378-TCDD, 12378-PECDD, 123678-HXCDD AND 23478-PECDF

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Introduction

The University of Michigan Dioxin Exposure Study (UMDES) 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 for 946 participants in four contaminated counties and one referent area. 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 continue to contribute to the serum concentrations and 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[1,2] has described the PK modeling approach in great detail and examined the predictors for serum 2378-TCDD, 12378-PeCDD, 123678-HxCDD and 23478-PeCDF, four key PCDD/PCDF congeners. Rather than studying the effects of individual dioxin congener separately, in this article, we mainly focus on analyzing the Toxic Equivalent (TEQ) based on the above four key congeners. TEQ is a weighed sum of a few dioxin congeners. It is a better measurement than directly summing the dioxins since it accounts for the variation of toxicity among different dioxin congeners. Therefore, TEQ is calculated by multiplying each dioxin compound by its respective Toxic Equivalency Factor (TEF) value that reflects the toxicity, and summing these products. We will focus on the prediction of TEQ based on the four key congeners (TEQ_4) instead of the TEQ based on all 17 PCDD/PCDF congeners (TEQ_{17}) since TEQ_4 constitutes as large as 83% of TEQ_{17} in UMDES data.

Materials and methods

In this section, we briefly illustrate the model fitting procedure described in Hao[1,2] and how we extend the model results from four key congeners to TEQ_4. The main idea is to convert the historical dioxin intake into a 2005 lifetime cumulated dioxin-based intake of each congener and of the TEQ_4, which are called PK-transformed variables, and then perform the linear stepwise regressions of serum dioxin concentration on 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, thereby allowing inferences for these populations, but have larger variances than the unweighted models.

For each dioxin congener, we assessed the effect of an individual variable on the serum by multiplying its parameter estimate by the participant's value, and this product describes the amount by which the individual's serum is predicted to change due to this variable. For each exposure variable, we estimated its impact on TEQ_4 by multiplying their congener-specific effects by TEFs, and summing the products. This article describes the procedure based on the unweighted models, while weighted model results as presented by Hao[1,2] can be combined in the same manner. The procedure is illustrated with the following example. The PK-variable "Number of years having lived in Midland/Saginaw during 1940-1983" is significant in models of serum 2378-TCDD, 12378-PeCDD and 23478-PeCDF. First for each of the three congeners, we multiply its respective "Midland/Saginaw" variable with the parameter estimate. This product is called effect of the "Midland/Saginaw" variable, and it can be interpreted as the amount by which the individual's serum is predicted to change as a consequence of this factor. Then we multiply each of the three effects by its TEF, in our case, 1 for 2378-TCDD, 1 for -12378-PeCDD and 0.3 for 23478-PeCDF, as well as 0.1 for 123678-HxCDD. Results focus on the impact of six regional exposure variables on the TEQ_4.

Results and discussion

Figure 1 presents the observed serum of TEQ_4 (yellow) versus TEQ_{17} (yellow and blue), showing that these four congeners account for about 83% of the TEQ_{17}.

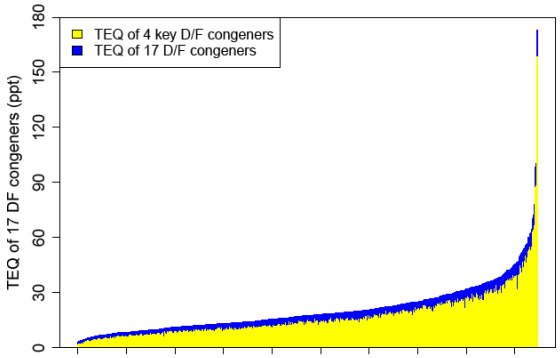

Figure 1. Serum of TEQ_4 vs TEQ_{17}

Hao[1,2] have provided the complete unweighted and weighted model results for the serum 2378-TCDD, 12378-PeCDD, 123678-HxCDD and 23478-PeCDF. For each model, we have categorized the significant variables into three groups: exposure variables related to local contamination, exposure variables from other sources, and demographic variables. Since the predicted serum increase due to Dow contamination is our primary interest, we will only discuss below the graphical outputs based on the six exposure variables related to local contamination.

Figures 2a-2f present the impact of six regional predictors that reflect the potential pathways related to Midland/Saginaw contamination on serum TEQ_4 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 from the current exposures. The largest contributor comes from having lived in Midland/Saginaw during 1940-1983, which has an estimated effect on 592 participants ranging from 0 ppt to 20 ppt. The modeled air concentration from the Dow incinerator during 1940-1983 also plays an important role with the effect ranging from 0 ppt to 20 ppt and with 604 participants affected. Both contributors 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 exposure and increase in serum concentration. Consumption of fish from contaminated area is associated with an estimated effect ranging from 0 to 7.5 ppt serum increase with 414 people affected, and consumption of meat from contaminated area is associated with an estimated effect ranging from 0 to 15.5 ppt serum increase with 25 people affected. Both the effects from fish and meat are dominated by the historical effects prior to 2000 (blue and yellow areas under the

curve). Fishing in contaminated rivers is associated with an estimated effect ranging from 0 to 6.8 ppt serum increase with 398 people affected, and having water activities in contaminated rivers is associated with an estimated effect ranging from 0 to 1.2 ppt serum increase with 506 people affected. Both variables show 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 for fishing and water activity variables, meaning that there is likely an upper estimate for the recent exposures for both variables.

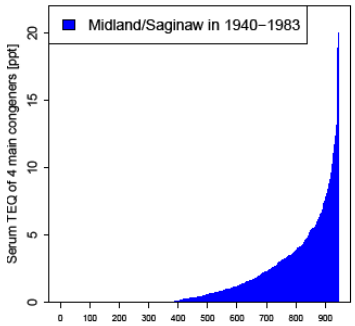

Figure 2a. Effect of having lived in Midland/Saginaw in 1940-1983 on the serum TEQ of 4 main congeners.

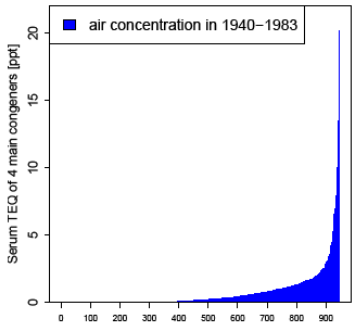

Figure 2b. Effect of high modeled air concentration from the Dow incinerator in 1940-1983 on the serum TEQ of 4 main congeners.

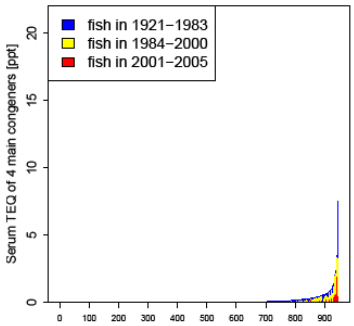

Figure 2c. Effect of fish consumption in TR and SR/SB, separated in 3 periods, on the serum TEQ of 4 main congeners.

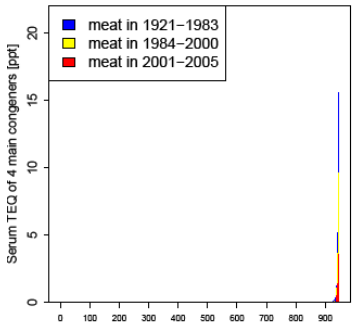

Figure 2d. Effect of meat consumption in TR and SR/SB, separated in 3 periods, on the serum TEQ of 4 main congeners.

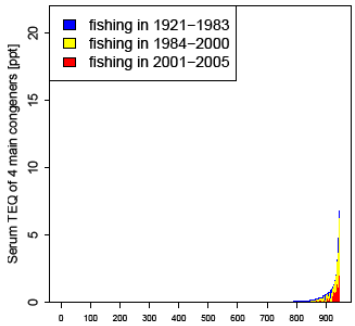

Figure 2e. Effect of days of fishing from TR and SR/SB, separated in 3 periods, on the serum TEQ of 4 main congeners.

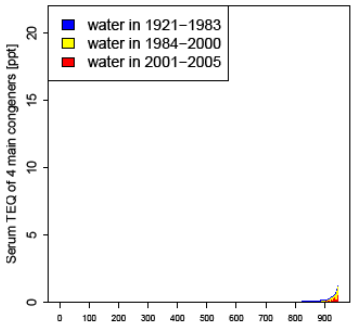

Figure 2f. Effect of days of having water activities from TR and SR/SB, separated in 3 periods, on the serum TEQ of 4 main congeners.

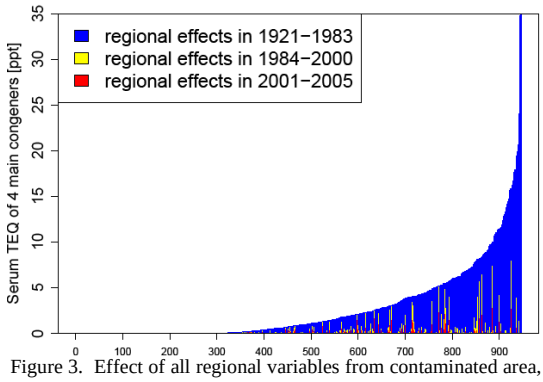

Figure 3. Effect of all regional variables from contaminated area, separated in 3 periods, on the serum TEQ of 4 main congeners.

Figure 3 shows that combining all the regional variables leads to an overall increase in serum TEQ_4 less than 35 ppt, with 99% of the participants below 19.4 ppt. Restricting the analysis to recent exposures (red), the TEQ_4 serum increase amounts to maximum of 3.7 ppt, with 99% of the participants below 1.5 ppt. Exposures from years 1984-2005 (red and yellow) contribute a maximum of 9.7 ppt, with 99% of the participants below 4.1 ppt.

The effects of air concentration and fish consumption from the contaminated areas were different in the unweighted and 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 for 12378-PeCDD and 123678-HxCDD, while remaining significant for 2378-TCDD. This difference may be related to an interaction between certain predictors and the region in which participants lived. This explanation needs to be clarified and further analyses are underway.

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