INFLUENCE OF AGE ON SERUM DIOXIN CONCENTRATIONS AS A FUNCTION OF CONGENER HALF-LIFE AND HISTORICAL PEAK FOOD CONTAMINATION

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Introduction

A central goal of the University of Michigan Dioxin Exposure Study (UMDES) is to determine the factors that explain variation in serum congener levels of polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like polychlorinated biphenyls (PCBs).

Demographic factors have been found to be the most important contributors to population variation in serum TEQ, PCDDs, PCDFs, and dioxin-like PCBs[1]. Among the demographic factors, age was a major determinant of population variation in serum concentration. However, the age influences the different dioxin-like congeners differently. In addition, age is a surrogate for various effects linked to other time-dependent factors, such as past changes in environmental exposure concentrations and changes in physiology with time. The aim of this paper is therefore to identify the determinants of the influence of age in the serum population regression analysis, and to eventually predict this factor as a function of both the congener properties and historical factors.

Materials and Methods

a) Theoretical approach and sensitivity study: The pharmacokinetic-based (PK) approach proposed by Jolliet et al.[2,3] accounts for intake of contaminants prior to the cross-sectional study, decay in the body burden between the intake and the sampling time, and historic changes in the concentration of dioxins in the environment. This approach is applied to various congeners by carrying out a systematic sensitivity analysis. The sensitivity analysis is used to assess how age dependency is influenced by key factors, such as past peak environmental concentrations of dioxin-like compounds, and congener half-lives in the body (based on review work by Milbrath et al,[4]). The sensitivity analyses have been carried out according to a factorial plan, varying: i) congener half-lives between 0.08 years (PCB77), 2.5 years (TCDF), 8.5 years (TCDD) and 24.3 years (PCB 157); ii) the ratio of 1968 peak food contaminant concentrations to 2005 concentrations between a factor 4.7, 9.3, 14.0 and 18.7; iii) gender via its influence on percent body fat and consequences to serum half-lives in humans; and iv) smoker vs non smoker. This enables us to determine the structural relationship of the expected variations in age dependency as a surrogate for various mechanisms.

b) Regression analysis on the age-related coefficients: Regression coefficients for age and other significant demographic variables on dioxins, furans, and four of the PCBs were determined using a linear regression model applied to the overall UMDES population[5]. The age regression coefficient can be interpreted as “change of log of the serum concentration per increase of one age unit", controlling for all other variables in the model. We will carry out a regression analysis to analyze the variations in the age and age^2 regression coefficients across congeners as a function of the parameters identified in the above-described sensitivity study. At this stage, we will focus on dioxins and furans, as results on all dioxin-like PCBs are not yet available.

Results

a) Sensitivity study: A first sensitivity analysis shows how the log of predicted dioxin concentration varies with age for different half-lives in the body and for various magnitudes of the peak in food contamination. As expected, the log of the serum concentration increases mostly linearly with age. The slope of this linear relation also represents the change in the log of the serum concentration per increase of one age unit and corresponds to the age regression coefficient of the regression analysis[3]. This analysis enabled us to identify the following main tendencies and influence factors:

- As previously shown[3], the age slope increases with increasing congener half-lives. Figure 1 demonstrates the increase in the age regression coefficient with the congener half-life in the body,

resulting in an R^2 of 0.66. Relatively important fluctuations remain however; with the highest peak ratios leading to the highest age coefficients.
- For short half-lives, there is little increase in concentration with age. The height of the peak in 1968 has no influence, since present serum concentrations only depend on present and recent emissions.
- At intermediate half-lives (4 to 10 years), increasing peak heights lead to significant increases in age slopes.
- At long half-lives in the body (>10 years), the initial increase with age is strong. Above 60 years old, a saturation phenomenon is observed, as reflected by the significant negative age square coefficients of the regression analysis. This is linked to the lower environmental concentrations observed before and after the maximum peak in 1968, which also influences the 2005 measured concentration when the half-life is long.
- The interaction term between age and gender can be explained by the 11.5% average greater body fat for females compared to males for the same Body Mass Index[6]. The higher fat reservoir among females corresponds on average to a 47% increase in half-life.

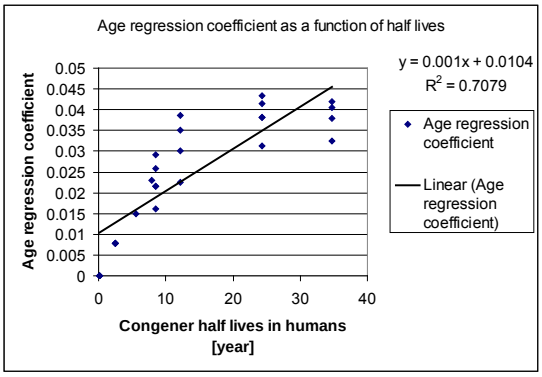

Figure 1. Age regression coefficient* as a function of half-life of the congener in human serum (*Increase in the log of serum dioxin concentration per unit age).

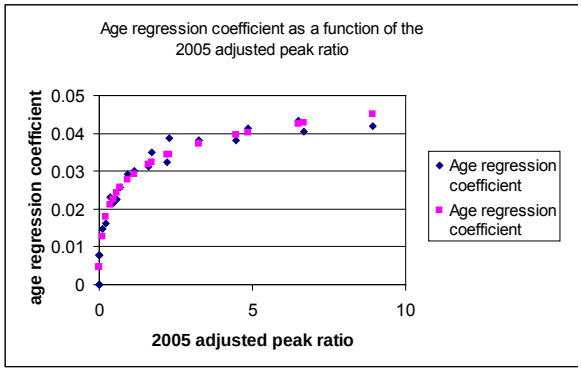

Figure 2. Age regression coefficients* as a function of the 2005 adjusted peak ratio. Approximation $y_{approximation} = 0.028 + 0.018 \cdot Log_{10}(0.05 + P_{peak\ ratio}^{2005adjusted})$ (R^2=0.97)

We propose to combine the influence of half-life in the body ($\tau_{1/2,j}$, years) and historic variation in peak food contamination by calculating the 2005 adjusted peak ratio (i.e. the 1968 peak food concentration decayed to 2005, divided by the 2005 concentration of congener j):

$$P_{peak\ ratio}^{2005adjusted} = \frac{C_{conc\ meat,j}(t_{peak} = 1968)}{C_{conc\ meat,j}(t = 2005)} \cdot e^{-\ln 2 / \tau_{1/2,j}(t_{peak} - t))}$$

The age coefficient is then displayed as a function of the base 10 logarithm of the 2005 adjusted peak ratio (figure 2). The age regression coefficient is very well correlated with the base 10 logarithm of the 2005 adjusted peak ratio, i.e. $Log_{10}(0.05 + P_{peak\ ratio}^{2005adjusted})$, increasing the explained variability to R^2=0.97.

b) Regression analysis on the age-related coefficients:
Based on these findings, variation in the age and age^2 regression coefficients across congeners are studied as a function of both congener half-life in the body and the height of the environmental concentration peak in 1968 relative to 2005.

For the overall UMDES population, the variation in congener half-life explains 40% of the variation in the age regression coefficients of the considered serum dioxin and furan congeners; all coefficients are calculated as a weighted average between male (44%) and females (56%). Up to 70% of the variability is explained when the magnitude of the peak is accounted for and the age regression coefficient is correlated with the base 10 logarithm of the 2005 adjusted peak ratio.

Further investigations are required on the remaining congeners. This approach will be applied in the future for the UMDES background population and the NHANES measurements to test whether similar trends are obtained.

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