



Influence of age on serum dioxin concentrations as a function of congener half-life and historical peak food contamination

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Introduction & Objectives

Demographic factors have been found to be the most important contributors to population variation in serum TEQ, PCDDs, PCDFs, and dioxin-like PCBs. However, age is a surrogate for various exposures linked to other time-dependent factors, such as past changes in environmental exposure concentrations and changes in physiology and elimination half-life with time.

The aim of this paper is 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.

Methods

a) Theoretical approach and sensitivity study: Assess how age dependency is influenced by past peak environmental concentrations and human elimination half-lives of various dioxin-like compounds.

Apply the pharmacokinetic-based (PK) approach proposed by Jolliet et al.^{1,2} to various congeners in a systematic sensitivity analysis 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 1967 peak food contaminant concentrations to 2005 concentrations between factors 4.7, 9.3, 14.0 and 18.7
- iii. gender male/female
- iv. smoker vs. non smoker

b) UMDES regression based age coefficients: Carry out a regression analysis to study the variation in the age regression coefficients (coeff. b_{age}) of dioxins and furans congeners, as determined by a linear regression applied to the serum concentrations of the UMDES population³:

$$\log_{10} C_{blood} = +b_0 + b_{age} \cdot age + \dots + \sum_k b_k Q_k + error$$

Main factors of influence

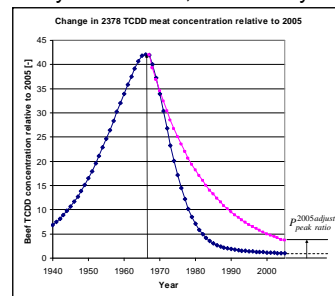
Two main parameters influence the age coefficient: the elimination half-lives ($\tau_{1/2}$ [year]) and the historic variation in peak height.

We combine these by calculating the **2005 adjusted peak ratio** (i.e. the 1967 peak food concentration decayed to 2005, divided by the 2005 concentration of congener j):

$$P_{peak\ ratio}^{2005\ adjusted} = \frac{C_{conc\ meat, j}(t_{peak} = 1967)}{C_{conc\ meat, j}(t = 2005)} \cdot e^{-\frac{(t-t_{peak})}{\tau_{1/2, j} \ln 2}}$$

$$P_{2378\ TCDD\ peak\ ratio}^{2005\ adjusted} = 42 \cdot e^{-\ln 2 / 10.8 \cdot (2005 - 1967)} = 3.6$$

$$P_{1234678_HpCDF\ peak\ ratio}^{2005\ adjusted} = 17 \cdot e^{-\ln 2 / 4.6 \cdot (2005 - 1967)} = 0.06$$



Age coefficient function of half-life or 2005 adjusted peak ratio

The age 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.

a) PK sensitivity study:

- The age slope increases with congener half-lives (Fig. 1: $R^2 = 0.71$) but relatively important fluctuations remain with varying peak ratios.
- The age regression coefficient is very well correlated with the Log 10 of the 2005 adjusted peak ratio (Fig. 2: $R^2 = 0.97$).

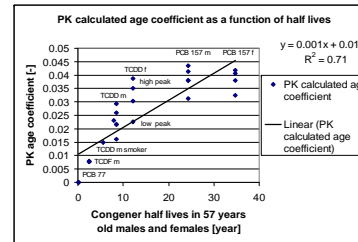


Figure 1. PK calculated age coefficient* as a function of half-life of the congener in human serum (*Increase in the log of serum dioxin concentration per unit age).

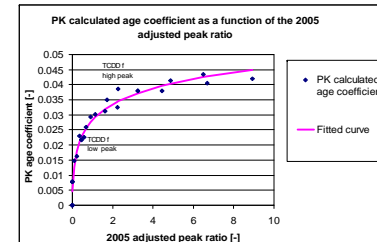


Figure 2. PK calculated age coefficients* as a function of the 2005 adjusted peak ratio: Fitted curve: $y_{approximation} = 0.028 + 0.018 \cdot \log_{10}(0.05 + P_{peak\ ratio}^{2005\ adjusted})$ ($R^2=0.97$)

b) UMDES regression based age coefficient:

- For the overall UMDES population, the congener half-life explains 40% of the variation in age coefficients of dioxins and furans (Fig. 3).
- 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 (Fig. 4).

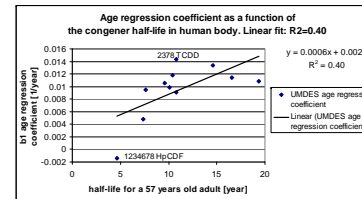


Figure 3. Variation in the UMDES age regression coefficient as a function of half-life of congener in human serum. Weighted average between male (44%) and females (56%)

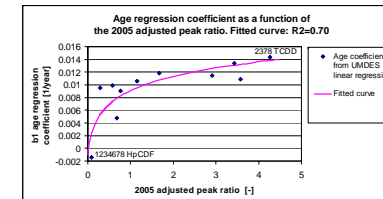


Figure 4. Variation in the UMDES age regression coefficient as a function of the 2005 adjusted peak ratio. Fitted curve: $y_{approximation} = 0.0090 + 0.0077 \cdot \log_{10}(0.05 + P_{peak\ ratio}^{2005\ adjusted})$, $R^2 = 0.70$

Conclusions

Variation in age coefficients among dioxin and furan congeners is well explained by accounting for both elimination half-lives and the historic variation in peak height. Both the theoretical and the UMDES regression based approach show that **the 2005 adjusted peak ratio is a good predictor of this variation in age coefficients.** Further investigations will be carried out on other congeners and substances for NHANES and the UMDES background population.

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