Effect of age and historical intake on blood dioxin concentrations: Pharmacokinetic modeling to support statistical analyses

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Introduction and Objectives

High correlation between past & 2005 food intake variables generate high uncertainty on parameters estimates

→ How to address the UMDES autocorrelation problem?

What are the main factors responsible for the elevated levels of dioxin blood concentrations in older people?

Objectives:

1. Explore and explain the confounding effect of age, taking into account that older people potentially :
   - consumed food for a longer period of time
   - at much higher concentrations (dioxin peak ~1970)
   - and have slower elimination rates
2. Provide insights on an adequate statistical model for predicting blood conc. as a function of food intake and age

Method: modeling to support statistical analysis

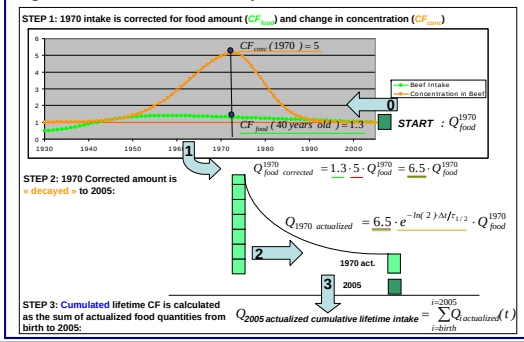
Actualize food quantities of the 2005 UMDES food questionnaire for the effect of age and time by considering :

1. Changes in amount of food consumed at different ages
2. Changes in historical concentrations in food
3. Variations in apparent elimination rates

$$Q^{2005}_{actualized}(t) = Q^{1970}_{food} \cdot CF_{food}(age(t)) \cdot CF_{conc}(t) \cdot CF_{elim}(age,t)$$

→ Produce 2005 equivalents of meals ingested that can be used in a statistical model

Fig. 1: Actualization of past food intakes for 2005



Results: Correction factors for food, conc. and elim.

Fig. 2: CF_{food} - change of food intake with age

Standard changes of food intake with age obtained from the US EPA exposure factor handbook compared to 2005

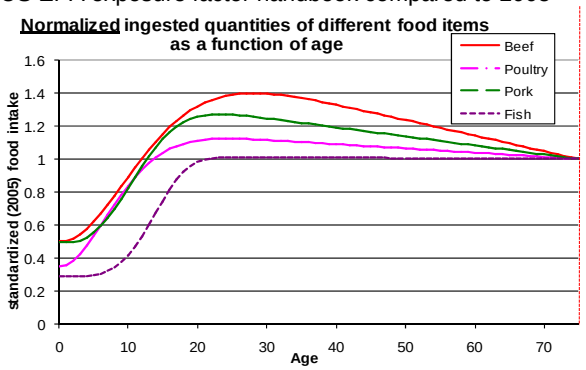


Fig. 3: CFconc - changes in historical concentration in food

1978 normalized Trend of TCDD in different fish species (1978-2005) and in sediments (1900-1978)

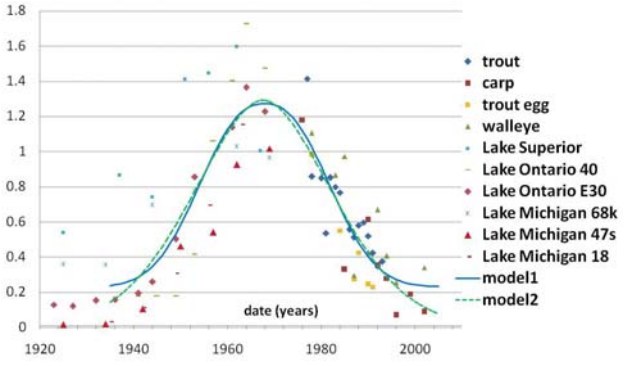


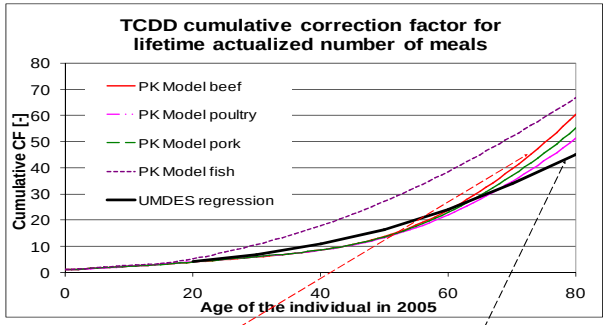
Fig. 4: CF_{elim} - Correction for past elimination in humans

Linear models of half-lives as a function of age, smoking status and percent body fat (pbf), see poster Half-Lives (Milbrath et al.)

$$t_{1/2}(age_i, smoke_i, pbf_i)_i = \beta_{0(age)} + \beta_{age} * age_i * smoke_i * \frac{pbf_i}{pbf_{ref(age_i)}}$$

Results: 2005 actualized cumulated intake and model

Fig. 5: $CF_{cumulative}$:Correction for lifetime adjusted number of meals



Comparison of $CF_{cumulative}$ (--) with the UMDES regression(--) for age, age² and BMI: excellent agreement

$$C_{blood} \propto CF^{2005}_{cumulative}(t) \cdot Q^{2005}_{food} \cong 10^{(b1 \cdot age + b2 \cdot age\hat{}2 + b3 \cdot BMI)} (b_0 + \sum_k b_k Q_{food,k})$$

Fig. 6a UMDES number of meat meals

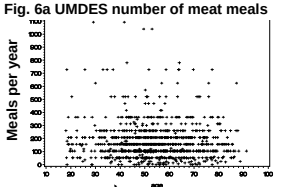
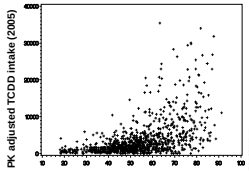
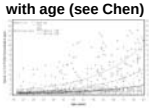


Fig. 6b Lifetime adjusted number of meat meals (TCDD)



Lifetime adjusted number of meals Better reflects the pattern of serum concentration with age (see Chen)



$$Q^{2005}_{food} \cdot CF^{2005,TCDD}_{cumulative}(t) \cong Q^{2005}_{food,cumulative\ lifetime\ adjusted}$$

Conclusions

- Introducing historical changes in concentration and metabolic elimination lead to a better understanding of the role of age
- Predicted vs observed serum TCDD with age: Good agreement!
- The model suggests a multiplicative model for age and BMI (that affect decay) x an additive term for exposure variables (food,…)
- Cumulative correction factor useful to adjust the number of meals

Acknowledgement

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