EFFECT OF AGE AND HISTORICAL INTAKE ON BLOOD DIOXIN CONCENTRATIONS: PHARMAKOKINETIC MODELING TO SUPPORT STATISTICAL ANALYSES

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Abstract

We develop a method to convert historical intake of dioxin-like compounds of a given individual into a 2005 adjusted intake value. Three successive correction factors need to be applied. 1) Present food intakes are corrected to account for the change of intake with age, as a child eats less than an adult. 2) The second factor accounts for historical changes in dioxin concentration in the food chain, with a peak around 1968. 3) The half-life of each congener in the body is used to decay past intake over time. This approach is used as a pre-treatment of food intake variables - expressed in a 2005 actualized number of meals over lifetime - before performing the statistical regression analysis. It also provides insights on an adequate statistical model for predicting blood as a function of food intake and age.

Introduction

A central goal of the University of Michigan Dioxin Exposure Study (UMDES) is to determine the factors explaining variation in serum congener levels of polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs). To understand the effect of intake on current serum concentration levels, it is necessary to account for historical intake of persistent congeners and to decay past concentrations over time as a function of their half-lives. High autocorrelation between the answers to questionnaires for intake in last 5 years and for intake in previous periods makes it difficult to differentiate between the effect of subsequent periods. Moreover, it is difficult to account for the effect of age in a cross-sectional study for persistent organic pollutants with long half-lives in humans as it is confounded with the influence of historical change in concentrations. There is, therefore, a need to develop an innovative and robust approach - inspired by Pharmacokinetic modeling - to account for intakes prior to the cross sectional study, decay in the body between the intake and the sampling time, and variations of the concentration of dioxins in the environment, as a pre-treatment of certain inputs of the statistical analysis.

Materials and Methods

The main idea of this pre-treatment is to convert past food intake into a 2005 adjusted food intake, analogous to the financial conversion from a past value into a present value (actualized value), accounting for inflation. The 2005 actualized intake of a given congener j through a given food item k (e.g. k=beef) taken in during a previous calendar year t can be calculated as a function of three unitless corrections factors (*CF*) that modify the eaten quantity in 2005 as reported in the UMDES food questionnaire ($Q^{i,2005}_{food,k}$ e.g. the number of meals of beef per year reported in 2005 by an individual i).

$$\begin{aligned} Q^{i,2005}_{actualized\,k,j}(t) &= Q^{i,2005}_{food,k} \cdot CF^{i}_{food,k}(age(t)) \cdot CF_{conc,k,j}(t) \cdot CF^{i}_{decay,j}(age,t) \\ &= Q^{i,2005}_{food,k} \cdot CF^{i}_{overall,k,j}(age,t) \end{aligned} \quad (1)$$

with

1) CF_{food} :correction factor for the changes in amount of food consumed at different ages.
2) CF_{conc} : correction factor for the relative change in congener concentration in the food with calendar year.
3) CF_{decay} :correction factor for the metabolic decay in the body between year of intake t and year of blood measurement[1,2].

The present study explains each of these correction factors in detail and carries out a short sensitivity study on how the actualized intake is affected depending on the considered calendar year and age of the considered person in 2005.

Determination of correction factors

a) Food correction, accounting for age-dependent generic variations in quantities of food consumed

The standardized quantity of food item k, eaten by a generic individual i, as a function of his or her age has been determined on the basis of the EPA Exposure Factors Handbook to reflect the food intake per kg bodyweight for representative consumers, using the following formula (coefficients in table 1, figure 2a).

$$Q^{ST}_{food,k}(age) = \alpha_k - \beta_k \cdot age + \gamma_k \cdot (1 - e^{(-(age/\delta_k)^{\varepsilon_k})}) \quad \text{[g/day]} \qquad (2)$$

Table 1. Coefficients of equation 2, describing the standard intake of food with age, for the 50% percentile food intake (higher percentile for fish to be representative for fish consumers)

	k=Beef	k=Poultry	k=Pork	k=Fish
α_k [g/day]	17.61	7.814	2.42	6
β_k[g/day/year]	0.3279	0.0574	0.0265	0.005
γ_k [g/day]	41.75	18.89	4.412	15
δ_k [g/day]$_1$	14.5	10.29	12.81	15
ε_k [-]	1.812	1.809	2.485	4

The standard corrective factor for food is then calculated for each year as a ratio of the considered food food consumption in calendar year t, divided by his consumption of the same food item in 2005 (figure 2b). The correction is relatively small as the factor ranges between 0.4 and 1.6.

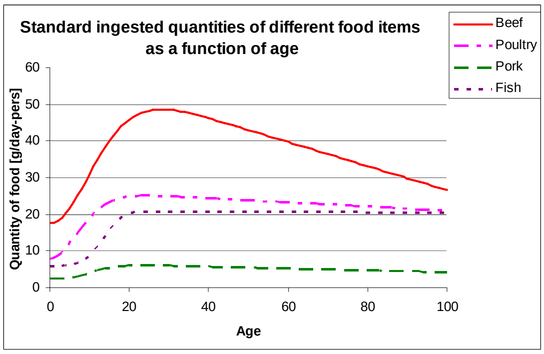

Figure 2a. Variation in quantities of food eaten as a function of age

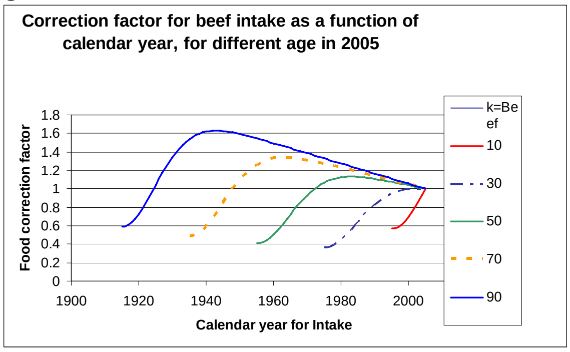

Figure 2b. Corrective factor for beef (CF^i_{beef}, unitless) as a function of the calendar year of intake, for individuals of 10 to 90 years old in 2005.

b) Correction for changes in food concentration with calendar year

Wenger et al.[3] fitted measured variation in dioxin concentration in fish from the Great-Lakes adapting the functional form suggested by Pinsky and Lorber[4]. A similar relationship was fitted for meat and milk as described by Towey et al. [5], based on Winters et al.[6] TEQ data, combined with more recent data from Ferrario et al.[7,8] and latest USDA survey[9]:

$$C_{conc,k,j}(t) = a_k + (b_k - a_k)e^{(-c_{bk}(t_{peak}-t)^{d_k})} \quad \text{while } t < \text{tpeak} \qquad (3a)$$

$$C_{conc,k,j}(t) = a_k + (b_k - a_k)e^{(-c_{ak}(t-t_{peak})^{d_k})} \quad \text{while } t \geq \text{tpeak} \qquad (3b)$$

The resulting correction factor is equal to the ratio of the concentration of congener j in calendar year t of ingestion divided by the concentration of the same food item in 2005 (figure 3).

Concentration correction	Terrestrial	Fish
t_{peak}	1968	1968
a_k	0.3	0
b_k	2.2	1.29
c_{bk}	0.006	0.00401
c_{ak}	0.015	0.00401
d_k	1.9	1.81

Table 2. Parameters of the TCDD historical function (equ. 3a and 3b).

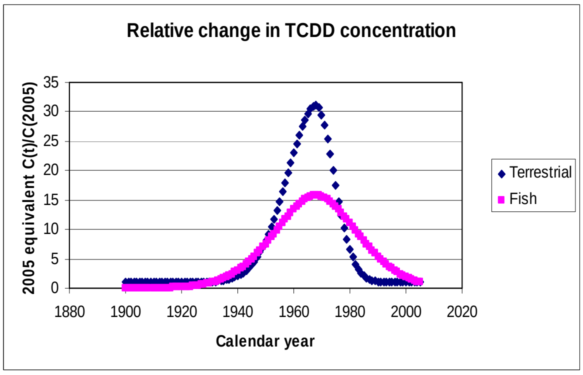

Figure 3. Correction factors describing the relative change in TCDD concentration in the food with calendar year.

c) Correction for decay in the body

Based on a comprehensive review of the literature[1,2], the main factors influencing the half-life of dioxins and dioxin-like compounds are a high TEQ body burden, smoking, age, gender, and body fat. The third correction factor describes the elimination of the congener j in the body between a calendar year t and the year of blood measurements:

$$CF^{i}_{met,j}(t) = e^{-\bar{k}^{i}_{B,j}(2005-t)} \tag{4}$$

where $\bar{k}^{i}_{B,j}$ [1/year] is the average apparent body elimination rate of the standardized individual i for congener j, from age(t) until age in 2005. The determinants of the elimination rates are discussed in a detailed literature review and analysis by Milbrath et al.[2] (equation (1) and (2) and table 1), assuming a linearly increasing half life with age (0.4 years for an infant and 7.2 years at 50 years old for TCDD) and a correction with body fat, smoking status and number of month breastfeeding:

Figure 4 shows that for young adults, TCDD decay is rapid and only the last years contribute. However, for a 70 to 90 year old person, decay is much slower, leading to high contribution of past exposures since 1960.

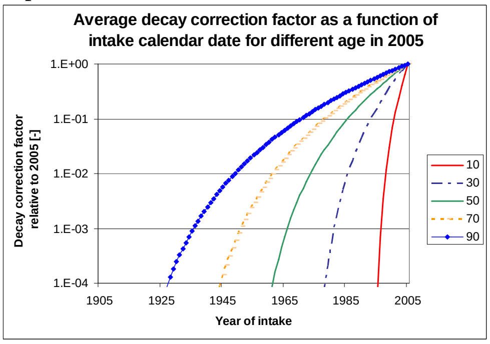

Figure 4. Correction factor to adjust for decay of past intakes in the body, for individuals of 10 to 90 years old in 2005.

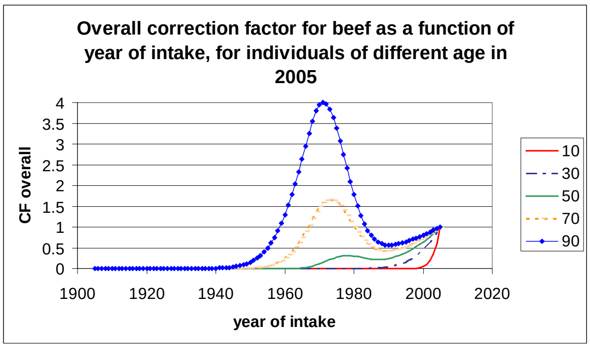

Figure 5. Correction factors to adjust a past beef meal to a 2005 actualized number of meals, for individuals of 10 to 90 years old in 2005.

Results: Overall and cumulative correction factor for an intake in calendar year t

Multiplying the three correction factors (provided in figures 2b, 3 and 4), we obtain an overall correction factor used to calculate a 2005 actualized number of meals (figure 5). The points along each curve are then summed up from birth up to 2005 to calculate a 2005 actualized cumulative number of meal over lifetime as a function of the age of each individual in 2005:

$$Q^{i,2005}_{lifetime\ adjusted\ k,j}(age) = \sum_{t=birthdate}^{2005} Q^{i,2005}_{adjusted\ k,j}(t) = Q^{i,2005}_{food,k} \cdot \sum_{t=birthdate}^{2005} CF^{i}_{overall,k,j}(t) \tag{5}$$

Figures 6a and 6b compare this lifetime cumulate adjustment factor for TCDD and TCDF., showing that:

- The TCDD lifetime actualized number of meals is 10 times the number of meals eaten in 2005 for an individual who is 40 years old in 2005. It increases to more than 50 times for an 80 year old person.
- As TCDF has a much shorter half-life in humans than TCDD (2 years for a 50 year old versus 7.2 years for TCDD), its lifetime actualized number of meals is 10 times smaller. As a consequence, intake prior to the 1980s has little influence.

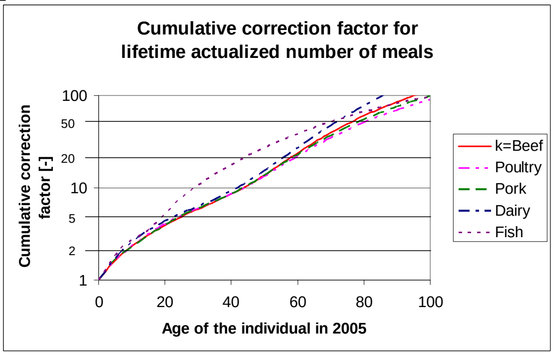

Figure 6a. Cumulative lifetime adjustment factor as a function of the age of the individual in 2005. TCDD (log scale)

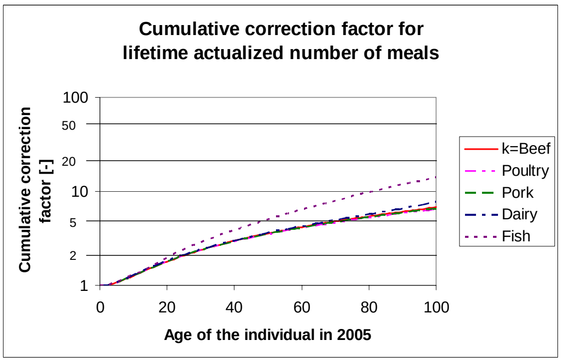

Figure 6b. Cumulative lifetime adjustment factor as a function of the age of the individual in 2005. TCDF (log scale)

Discussion of consequences for the statistical analysis

Figures 6a and 6b show that the overall relationship between the logarithm of the integrated factor and age is approximately linear between 20 and 80 years of age. This suggests that an adequate statistical model for predicting blood as a function of food intake should be composed of an exponential term for age (and possibly for factors affecting decay rate) that multiplies a multi-linear sum of diet intakes.

Gillespie et al.[10] applied the present method to illustrate how the cumulative correction factors can be used as a pre-treatment of food intake variables - expressed in a 2005 actualized cumulative number of meals over lifetime - before performing the statistical regression analysis. The lifetime cumulative number of meals clearly increases with age. It is likely to be a better predictor of blood concentration than the 2005 number of meals as blood concentration is observed to increase with age.

Acknowledgements

Financial support for this study comes from the Dow Chemical Company through an unrestricted grant to the University of Michigan. The authors acknowledge Ms. Sharyn Vantine for her continued assistance and Drs. Linda Birnbaum, Ron Hites, Paolo Boffetta and Marie Haring Sweeney for their guidance as members of our Scientific Advisory Board.

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