COMBINED INTAKE AND PHARMACOKINETIC MODEL TO PREDICT SERUM TCDD CONCENTRATIONS

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Introduction

The University of Michigan Dioxin Exposure Study (UMDES) was undertaken in response to concerns among the population of Midland and Saginaw Counties that the discharge of dioxin-like compounds from the Dow Chemical Company facilities in Midland has resulted in contamination of soils in the Tittabawassee River flood plain and areas of the City of Midland. There is concern that people's body burdens of polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) may be elevated because of the environmental contamination. A central goal of the UMDES was to determine the factors that explain variation in serum congener levels of PCDDs, PCDFs, and PCBs, and to quantify how much variation each factor explains. Overall study results are presented elsewhere.[1]

As a complement to the central goal of the study, a combined intake and physiologically based pharmacokinetic (PBPK) model was developed that allows for the prediction of serum 2378-TCDD values. The intake/PBPK model complements the goals of the study in two ways: it provides a comparison of expected contributions of various exposure factors based on values previously reported in the literature, and it provides insight into the contribution of historic intakes to current serum TCDD levels. This report describes the methods for calculating current and historic TCDD intake from meat and dairy, the physiological basis of the PBPK model, the results of the combined model using a hypothetical 80-year old male, and a preliminary comparison of model results with UMDES blood serum values for a subset of the study population.

Methods and Materials

Historic concentrations of dioxins and furans in food

The shape of the historic curve for TCDD in the terrestrial meat supply was modeled using a best fit curve obtained using meat PCDD/F TEQ data from Winters et al.[2] The general shape and peak year of this food supply PCDD/F curve is consistent with other dioxin intake models available in the literature[3] as well as with environmental PCDD/F measurement.[4] Specifically, the data suggest an increase in PCDD/F concentrations beginning in approximately 1940, peaking in approximately 1970, followed by a decrease to nearly pre-1940 concentrations (Figure 1).

A historic TCDD curve for each meat and dairy food class was then created by calibrating the general historic curve with recent measurements of TCDD in the food supply. [5,6,7,8] The fish historic curve was also calibrated using recent surveys of TCDD tissue concentrations.[9,10,11] It was, however, assumed that the ratio of peak to current value is less pronounced than for other pathways, because of the potential continued exposure to contaminated sediments (Figure 2).

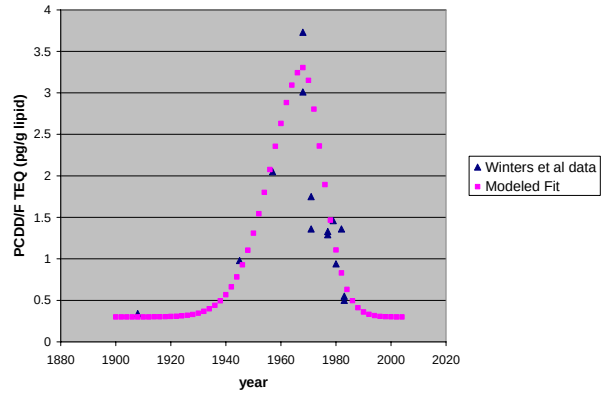

Figure 1: Change in PCDD/F TEQ values in meat with time.

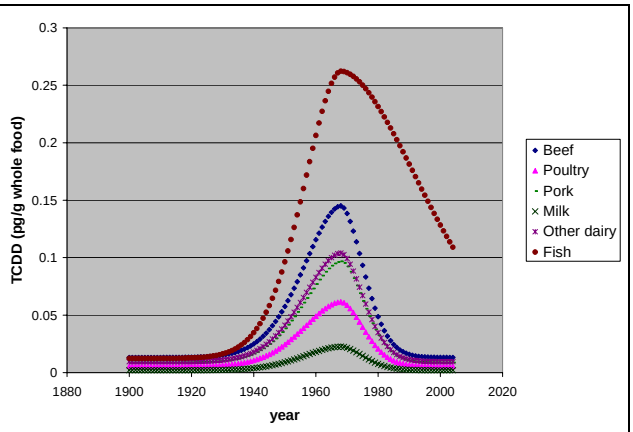

Figure 2: Modeled change in TCDD concentrations in fish, meat and dairy products with time.

Variation in dioxin intake rates for an individual: To determine the variation in intake of food with age and body-weight, a mean consumption rate curve as a function of age was fit to each meat and dairy group. The consumption rates were fit to data from USEPA Exposure Factors Handbook[12] as summarized in Wenning [13]. The annual TCDD intake rate for an individual attributable to each meat and dairy group was calculated by multiplying the annual consumption rate at the individual's age by the concentration in that food group for the appropriate year. The total annual intakes from all meat and dairy groups were summed for use as an input to the pharmacokinetic model.

Pharmacokinetic model: Building on the PBPK model from Van der Molen[14], body fat mass and body liver mass were adjusted to each individual as a function of BMI according to Gallagher et al.[15] Natural growth was simulated over the individual's life according to standard trends.[16] The PBPK model was then reprogrammed using Berkeley-Madonna[17] and used to simulate the change in serum TCDD levels in individuals born between 1900 and 1985.

Comparison of model to UMDES study results: A systematic statistical analysis was conducted comparing the experimental and predicted variation of individuals with age and other factors, looking at the residual error (RE) - the standard error of the log of the estimate or the standard deviation of the log of residuals, as discussed by McKone.[18]

Results and Discussion

The concentration of a chemical in blood increases with its persistence in the body. For most of the PCDD/Fs and PCBs, long half-lives suggest that historical intakes must be taken into account in order to obtain reasonable predictions. To study how the present TCDD concentration in blood depends on present and past TCDD intake, the preliminary combined intake and PBPK model was applied to a hypothetical male individual born in 1925, weighing 80 kg, and who is 1.78 m tall. A diagram of the intakes from each meat and dairy group as a function of time is presented in Figure 3. Figure 4 shows the variation in blood concentration for the same individual; there is a delay of about 10 years between the maximum concentration in food and the maximum blood concentration.

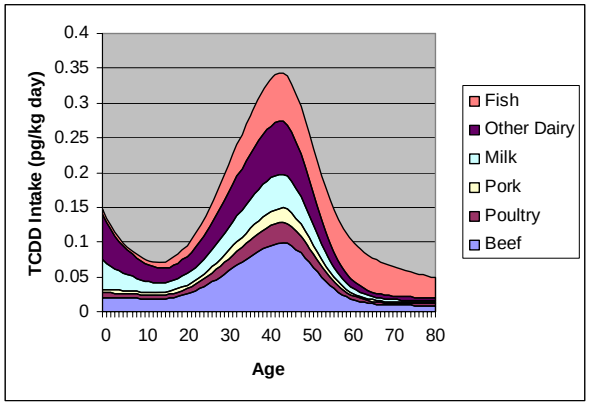

Figure 3: Change in TCDD intake rates per kg bodyweight and day for an 80 year-old individual weighing 80 kg and consuming average US values for fish, meat and dairy products.

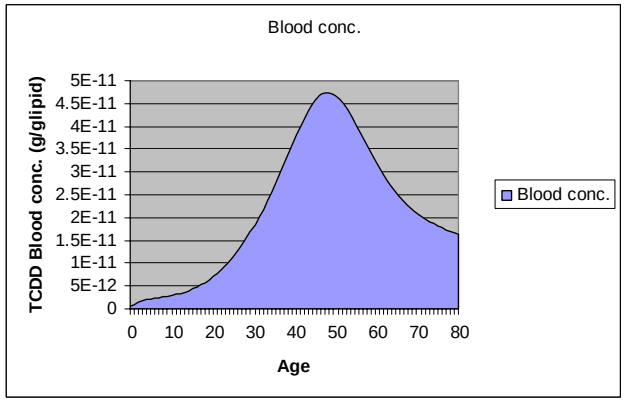

Figure 4: Change in TCDD serum concentration in an 80 year-old individual weighing 80 kg and consuming average US fish, meat and dairy products.
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Using the US consumption rates and modeled TCDD concentrations, figures for the US population similar to those presented in Figures 5 and 6 for a European situation will be generated. Figures 5 and 6 present how TCDD serum concentration varies in the population with age at different times. The shape of the serum concentration curve changes significantly with time due to both the reduction in food concentration and the increased accumulation with age. In 1975, it is convex with a clear saturation for people over the age of 50; it becomes almost linear by 2005. This analysis illustrates how present levels in blood are linked to dynamic changes over decades, underscoring the importance of understanding the time-dependence of the different systems in the environment and in the human population. This also demonstrates that in an exposure study such as UMDES, the interpretation of exposure and elimination (e.g., breastfeeding) events need to be considered in a dynamic perspective.

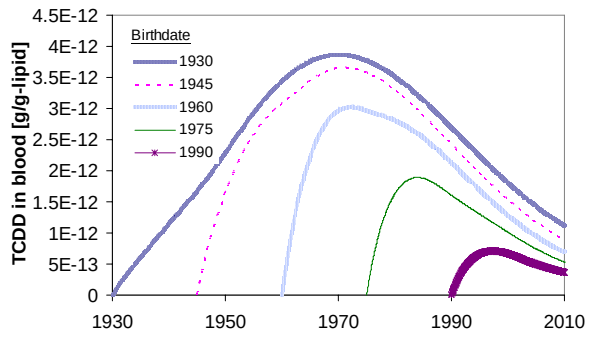

Figure 5: Change in TCDD serum concentration for individuals born between 1900 and 1985 for an average European situation

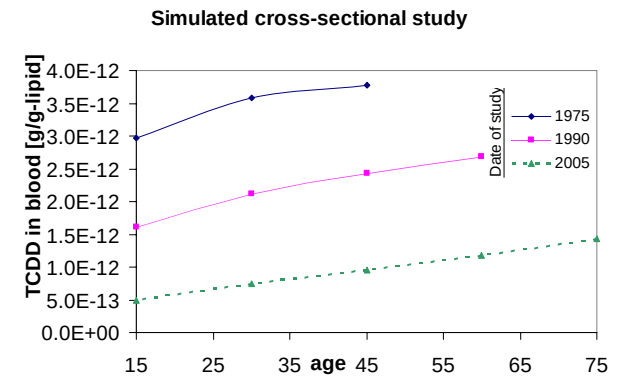

Figure 6: TCDD serum concentration in the population as a function of age, for different dates for an average European situation.

It is anticipated that similar trends will be apparent in the blood of US individuals and in the UMDES population. Results and discussion related to the prediction of UMDES serum TCDD values will only be available after complete study results have been presented to the affected communities in August of 2006.

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