A Model to Evaluate Past Exposure to 2378-TCDD

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Introduction

Data from several studies suggest that concentrations of dioxins rose in the environment from the 1930s to about the 1960s/70s and have been declining over the last decade or two. The most direct evidence of this trend are lake core sediments[1,2,3,4,5]. Recent studies in both Europe[6] and the United States[7,8] have shown that dioxin body burdens tend to increase with age. It has been suggested that higher doses of dioxins in the past (with trends in dose histories perhaps mirroring the sediment core trends) may explain this trend. This paper describes a simple pharmacokinetic (PK) model which includes a dose component for 2378-TCDD (abbreviated TCDD) that varies over time. The overall model was fitted to age-related body burden data for TCDD from the United States, and the solutions for the time-varying dose component provide possible explanations of the age trend. The model and its application are significantly more complicated than can be explained in a short abstract; a longer manuscript is currently being prepared. This abstract provides an overview of the model and presents the initial results of its applications.

Methods

A. **PK Model.** A first order, one-compartment PK model was used to compute an individuals' TCDD concentration in body lipids through time. Specifically,

$$d\,a(t) / dt = f\,D(t) - k(t)a(t) \qquad (1)$$

$$c(t) = a(t) / [1000\,V(t)] \qquad (2)$$

where a(t) is the amount of TCDD in lipid (pg), c(t) is the TCDD concentration in lipid (pg/ml), D(t) is the exposure dose of TCDD (pg/yr), V(t) is the lipid volume (l), k(t) is the degradation rate (yrs^{-1}), and f is the fraction of dose absorbed into lipid compartment (unitless; assumed constant at 0.80 in this model). The dose function, D(t) of Equation (1), is calculated as 365 E(t) W(t), where E(t) is the daily exposure (pg/kg-day) and W(t) is body weight (kg).

Michalek et al.[9] showed that the degradation rate of TCDD in the body, k, was a function of percent body fat. Specifically, they modeled the relationship between k and proportion body fat as:

$$k(t) = k_0 + k_1\,[F(t) - 0.25] \qquad (3)$$

where k_0 and k_1 are fitted parameters and F(t) is the proportion body fat at time t. Here we set k_0 = 0.077 and k_1 = -.313; these are adjusted slightly from Michalek et al.[9] to take into account a better method for estimating body fat from body mass index.

B. **Predicting Human Concentration Data.** Consider an "average" male or female born in a certain year in this century and suppose that F(t), W(t), and V(t) are known for this person. Then with

the PK parameters k_0, k_1, and f fixed as above, knowledge of the exposure function E(t) allows a numerical solution of the model (1,2) giving TCDD concentrations versus time. By combining males and females from different birth years, the mean concentrations at different calendar years in different age and sex groups can be calculated and compared with actual means from human data. In the next section, C, we show how different possible exposure functions E(t) are generated and how the predicted compared to the actual data is used to make inferences about past exposure. Here we first describe how the average physiologic functions F, W, and V were derived and then summarize the human TCDD concentration data.

The functions F (proportion body fat) and W (weight) were based on data from NHANES II[10], which provided average body weight and average Body Mass Index (BMI) by age and sex. A model predicting proportion body fat from BMI, age, sex[11] was then used to set F(t) for males and females and V(t) was defined as, W(t) F(t).

Table 1 summarizes the human lipid concentration data utilized in this effort. All of these studies focused on persons with no known direct exposure to dioxins and as such, measure the effect of background exposure levels. Andrews[8] measured TCDD in adipose tissue of surgical patients in Missouri. The Air Force Ranch Hand[12] study measured TCDD in blood lipids of control subjects,

Table 1. Mean Human Lipid TCDD Concentrations Reported in Various U.S. Studies.

Study (Reference)	Year	Age Group/Sex	Mean TCDD (pg/ml)	Sample Size	Standard Error of Mean
NHATS 82 [7]	1982	0-14 M/F	4.2	178	0.69
		15-44 M/F	6.8	312	0.87
		45-80 M/F	5.5	273	0.84
NHATS 87 [7]	1987	0-14 M/F	2.0	146	0.82
		15-44 M/F	4.4	318	0.52
		45-80 M/F	9.4	401	0.41
EPA/VA [13]	1972	20-36 M	19.8	27	1.2
	1975	23-39 M	17.3	29	1.2
	1978	26-42 M	11.6	57	1.2
	1981	29-45 M	12.6	82	1.2
Andrews et al. [8]	1986	18-29 M/F	4.0	14	0.95
		30-39 M/F	5.9	30	0.65
		40-49 M/F	5.5	25	0.71
		50-59 M/F	8.0	22	0.76
		60-79 M/F	9.5	37	0.59
Air Force Ranch Hand [12]	1987	35-39 M	3.8	168	0.23
		40-44 M	4.0	280	0.18
		45-49 M	4.6	165	0.23
		50-54 M	4.7	232	0.20
		55-59 M	4.8	142	0.25
		60-64 M	5.0	33	0.52
		65-69 M	6.2	35	0.51

subjects not thought to have had direct contact with Agent Orange, unlike the exposed, or "Ranch Hand" study subjects. The National Human Adipose Tissue Surveys[7] (NHATS) are nationwide surveys of lipids from surgical patients and cadavers. The 1982 and 1987 NHATS utilized composite samples to measure TCDD levels; age group mean concentrations were estimated using a linear additive model[7]. The EPA/VA study[13] analyzed stored non-composite samples from NHATS surveys dating from 1970 to 1982. Altogether, these studies supplied 22 age group means to which we tried to fit our model.

C. **Generating and Evaluating Exposure Curves.** Although there is no direct empirical measure of long term TCDD exposure trends for the general population, levels in lake core sediments provide an indirect indicator. For this analysis, we treat the pattern in lake core sediments as indicative of general TCDD levels circulating in the environment; this assumption is partially supported by levels found in archived herbage samples[2]. Lake core sediments show a steady rise from the 1920's or so until the 60's or early 70's, after which they start to decline[1,4,5]. Additionally, we have assumed that changes in human exposure levels generally follow changes in circulating levels in the environment. These assumptions allow us to use the lake core profile to develop the following parameterized exposure function, which allows for a single peak in the exposure versus time curve:

$$E(t) = b + \exp [\, h - s_b (u-t)^r \,] \qquad t < u \qquad (4a)$$

$$E(t) = b + \exp [\, h - s_f (t-u)^r \,] \qquad t >= u \qquad (4b)$$

Here u is the time of peak exposure, b is the exposure level at baseline (pg/kg-day), e^h is the ratio of peak exposure above baseline to baseline exposure (unitless), s_b and s_f are rates of decline in exposure going backward (s_b) and forward (s_f) in time from the peak year, and r is the steepness parameter. Here r was assumed to be fixed and was varied in tests between 0.5, 1.0, and 2.0.

A Bayesian strategy was used to fit the above function to the human concentration data summarized in Table 1. In the Bayesian framework, prior knowledge or belief about the parameters, here u, b, h, s_f, and s_b, enables the construction of a prior distribution. Prior knowledge here refers to the above-mentioned sediment core and herbage data, as well as an estimate of the current TCDD exposure dose. This latter estimate, of 0.17 pg/kg-day, was calculated by multiplying concentrations of TCDD in exposure media (mainly food) by average contact rates, to arrive at an estimate of 12 pg TCDD/day[14], and then dividing by a 70 kg adult. Prior knowledge translated to the following constraints placed on the exposure function E(t): 1) the year of peak exposure between 1940 and 1980, 2) the ratio of peak to 1900 exposure dose is between 2 and 200, 3) a maximum of 20% was allowed for rates of decline one year before and after peak exposure, 4) the 1900 and 1990 exposure doses have a range of 0 to 0.5 pg/kg-day, and 5) the ratio between peak and 1990 exposure dose was between 1 and 100. With these constraints in place, the prior distribution on the parameters was the uniform distribution.

Consideration of how different exposure functions E(t) fit the human concentration data summarized in Table 1 leads to an updating of the prior distribution to give an a-posteriori (parameter) distribution; parameters leading to better fits of the data are favored relative to parameters giving worse fits. Specifically, this was done by assuming that the human concentration data (i.e., the group means) were normally distributed with standard deviations given by the reported standard errors of the means. Based on the a-posteriori distribution, central estimates and 95% intervals for various functions of the past exposure curve can be calculated; these are the main focus of the results section below.

Results

Goodness of fit results showed that the exposure model with r=0.5 fit the human data much worse than the models with r=1 or r=2, each which fit the data about as well. These models (r=1,2) also fit much better than any model assuming constant past exposure. Below we focus on predicted characteristics of exposure based on the r=1 and r=2 models.

Figures 1a,b display some exposure curves with optimal fit to the data. For both r=1 and r=2, there is marked divergence in these curves even though the fits of each are quite similar. As would be expected, this divergence increases as one goes further back in time. For r=1 (Figure 1(a)), these curves differ greatly until about the late 1960's, after which point they are all quite similar. A similar trend is seen for r=2 (Figure 1(b)), although the curves here are also similar for times early in the century, as well as from the late 1960's on. Comparing the r=1 and r=2 models, the profiles are roughly similar from the late 60's onward, except that the r=1 curves show a more gradual decline than the r=2 curves.

Table 2 gives expected values and 95% credible sets for various functions of exposure. Here E(40-49), for example, refers to the average exposure dose over the period 1940 to 1949 while E(peak10) refers to the average exposure over the ten year consecutive period with the highest exposure. In terms of central estimates, the peak year, E(peak10), E(60-69), and E(70-79) are about 35% higher with r=2 compared with r=1 while the E(80-89) values are within 0.03 pg/kg-day of each other. The r=1 model predicts considerably higher doses before 1960 than does the r=2 model. As suggested by the figures, the width of the 95% credible sets for functions averaging dose over a decade generally increases as time gets further in the past. Before the 1950's, the credible sets are so wide that little can be said except that the levels were lower than peak levels. For both r=1 and r=2, the 95% credible set is less than a two-fold range for E(60-69) and E(peak10), less than 0.07 for E(80-89) and less than 9 years for peak year; further, these credible sets are largely overlapping for the two different r values. The 95% credible sets for both r=1 and r=2 are within the interval 1.2 to 2.4 pg/kg-day for E(60-69) and E(peak10), within the interval 1962 to 1971 for peak year and less than 0.11 pg/kg-day for E(80-89).

Table 2. Expected Values and 95% Credible Sets for Functions of Exposure (E in pg/kg-day).

	r=1		r=2	
Exposure Function	Expected Value	Credible Set (95%)	Expected Value	Credible Set (95%)
E(10-39)	0.26	0.02-0.70	0.06	0.03-0.19
E(40-49)	0.53	0.09-0.96	0.11	0.03-0.63
E(50-59)	0.90	0.50-1.16	0.28	0.04-1.11
E(60-69)	1.42	1.17-1.77	1.91	1.26-2.39
E(70-79)	0.39	0.32-0.47	0.29	0.09-0.56
E(80-89)	0.072	0.057-0.104	0.045	0.016-0.084
E(Peak10)	1.45	1.18-1.81	1.97	1.31-2.40
Peak Year	1966	1963-1969	1967	1962-1971

Figures 2a,b show surfaces of predicted TCDD concentrations in males by birth and specimen year derived using two of the optimal exposure curves (the curves labeled "A" in Figures 1(a) and 1(b), respectively.). Both figures clearly show that, for all birth cohorts, individual concentrations have been declining since 1970. For a given year in the late 80's however, it is also evident that concentrations tend to increase with age. For 1987, the figures show 2.5-4 fold increases from age 20 to 40 and about 1.4 fold increases from age 40 to 65. In earlier years, a different age trend may hold, however. For 1974, the surface in Figure 2(b) shows slight decreases in concentrations as age increases from 20 to 65. Besides past exposure history, the age trend in TCDD concentrations also depends on the fact that degradation rates vary with age, due to age related changes in percent body fat. If past exposure were constant, then our model predicts that average concentrations in males would increase 12% from age 20 to age 40 and 12% from age 40 to age 65; for females the increases would be 36% from age 20 to age 40 and 21% from age 40 to age 65.

Sensitivity analyses revealed that moderate changes in the prior distribution (e.g., in the plausibility limits) had rather small impact on the central estimates of exposure characteristics. Moderate changes in the pharmacokinetic parameters k_0 and k_1 (i.e., using the lower or upper 95% confidence limits) produced fairly large changes in the central estimates for pre-1960's exposure; however, peak year, E(60-69), E(peak10) and E(80-89) were only moderately effected.

In conducting this analysis, we have attempted to base modeling assumptions and inputs on empirical data where possible. Since the data on human body burdens, environmental levels and dietary exposure are limited both in quantity and representativeness, it is unclear how well the model predicts actual past trends. However, we do believe the approach provides a reasonable beginning for exploring the possibilities for past exposure scenarios. With refinements in approach and improvements in data, this effort can lead to the development of reasonable estimates of past dioxin exposure to the general population.

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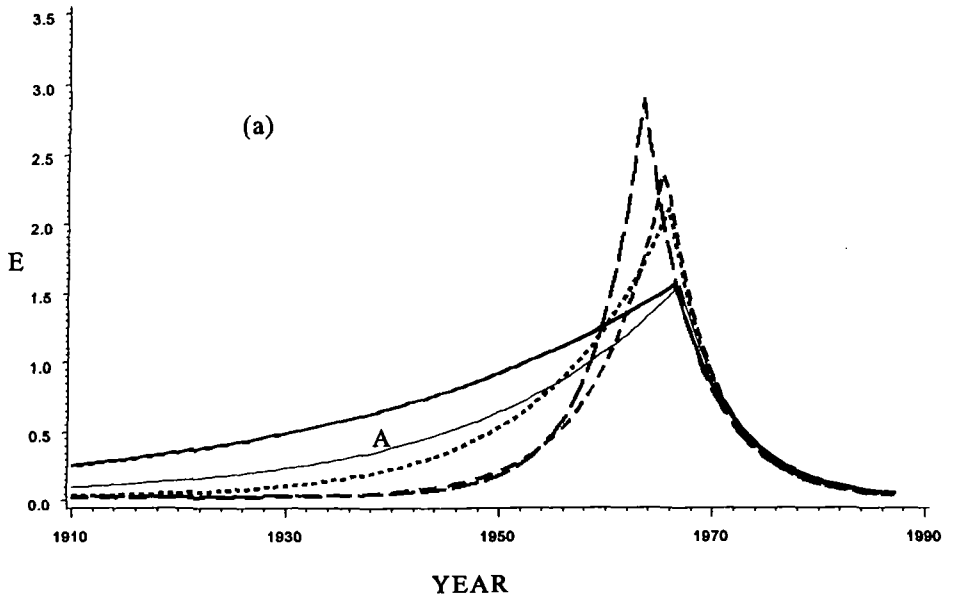

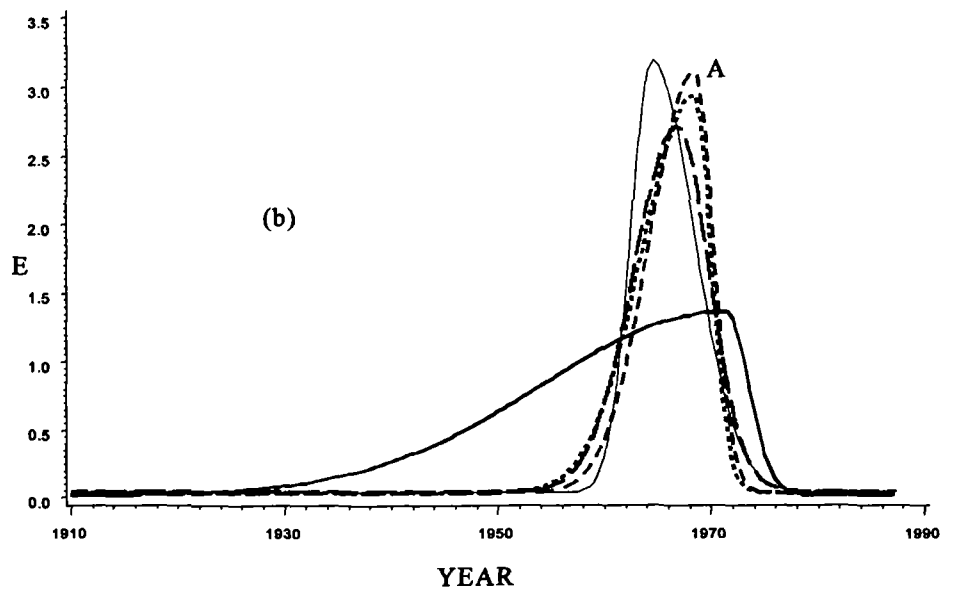

Figure 1. Best-fit reconstructed exposure doses (E, in units of pg/kg-day) plotted against calendar year for the exposure model with r = 1 [in figure (a)] and r = 2 (b). The curves marked "A" in (a) and (b) are the ones for which 3-d calendar year/birth year lipid TCDD concentrations are shown in Figure 2.

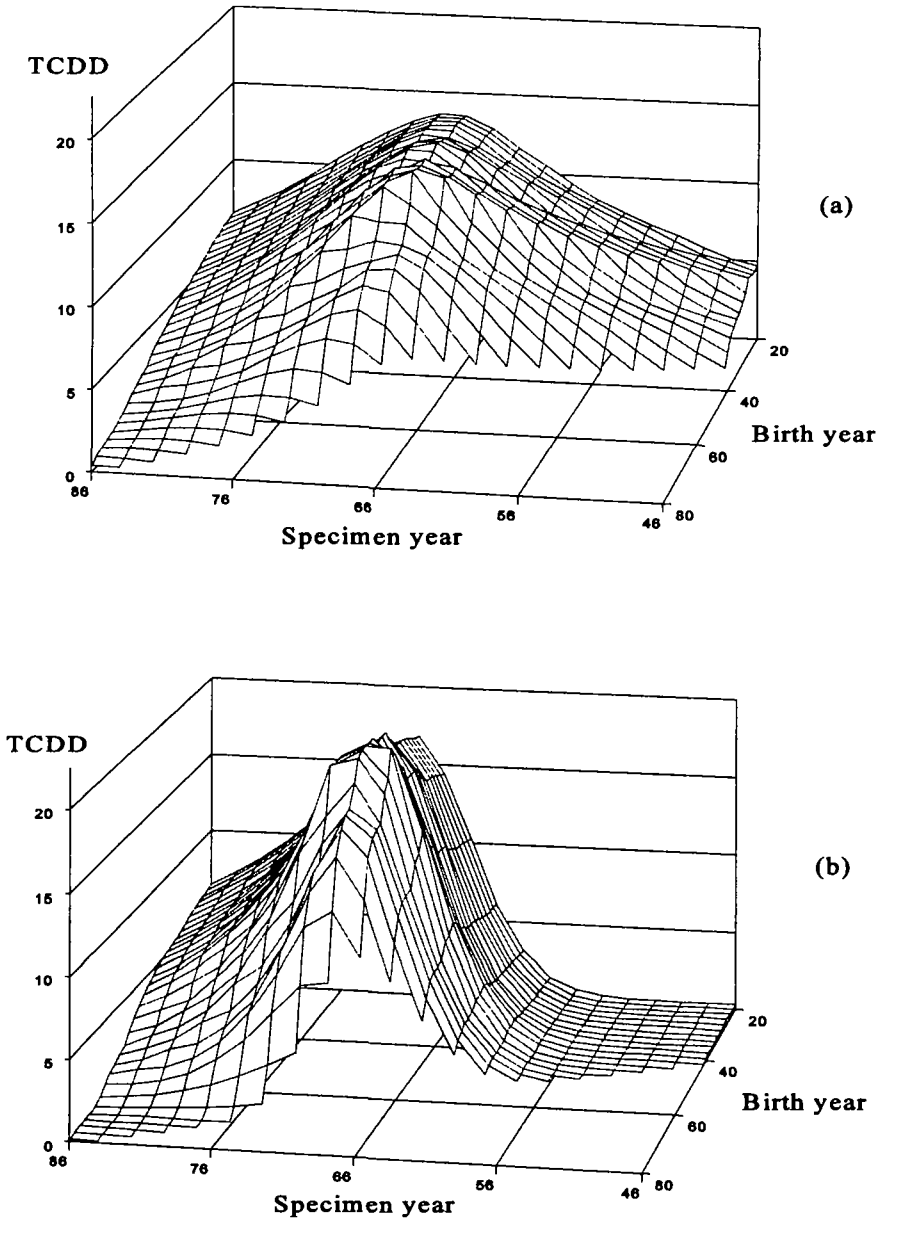

Figure 2. Predicted TCDD lipid concentration (TCDD, in units of pg/ml) as a function of when sampling occurs (specimen year) and when an individual is born (birth year). The surfaces in 2(a) and 2(b) were derived using the exposure curves labeled "A" in Figure 1(a) and 1(b), respectively