Exposure Reconstruction for the TCDD-Exposed NIOSH Cohort Using a Concentration- and Age-Dependent Model of Elimination

Lesa Aylward[1], Robert Brunet[2], Thomas Starr[3], Elizabeth Delzell[4], Hong Cheng[4], Colleen Beall[4]

[1]Exponent, Inc., Alexandria, VA
[2]University de Montreal, Montreal, QC
[3]TBS Associates, Raleigh, NC
[4]University of Alabama Birmingham, Birmingham, AL

Introduction

Estimates of cumulative exposure to TCDD have been developed for several occupationally exposed cohorts by integrating job exposure matrices based on work histories with measured serum lipid TCDD levels [1-3]. These efforts relied on the assumption that elimination of TCDD occurred via a first-order process with a half-life of 7.1 to 8.7 years. Serum lipid levels measured years after last exposure for a subset of each cohort were combined with estimates of exposure intensity over time during employment to derive maximum likelihood estimates (MLEs) of the dose associated with one unit of the exposure index. These dose rates were then applied to the job exposure histories of each member of the full cohort to estimate cumulative exposures (termed either area under the curve [AUC] or cumulative serum lipid concentration [CSLC]). A meta-analysis combined such dose estimates and SMR measures from three cohorts to estimate the carcinogenic potency of TCDD in these populations[4].

Recent studies have demonstrated that the elimination of TCDD occurs via a concentration-dependent process: elimination occurs at a greater rate when body concentrations are relatively high, with effective elimination half-lives of less than 3 years at serum lipid levels above 1,000 ppt [5-7]. In addition, analysis of serial sampling data from subjects exposed to dioxin during the 1976 chemical reactor accident in Seveso, Italy, demonstrated an age-dependent slowing of elimination[7]. Here we present some results from application of a concentration- and age-dependent model of elimination (CADM) described by Aylward et al.[7] to the job

exposure matrix data for the cohort of TCDD-exposed chemical manufacturing workers studied by the U.S. National Institute for Occupational Safety and Health (the "NIOSH cohort"[1]). Herein we describe the process of exposure reconstruction, the impact of the CADM on dose estimates for the cohort, and the variability in the dose estimates obtained.

Methods

The database containing the job exposure matrix, work histories, measured serum lipid concentrations, chloracne history, and vital status information for each member of the cohort (n = 3538) was obtained from NIOSH. The job exposure matrix provided daily exposure index values that were specific to each plant, department, job, and time period. Work histories were available for each individual, allowing a set of time-specific exposure estimates (in terms of exposure index, designated $E_i(t)$) to be generated for the i^{th} individual in the cohort. For individuals with measured serum lipid TCDD concentrations above 10 ppt in 1987/1988 (n = 172; mean TCDD = 296.1 ppt; median = 100.8 ppt; range: 10.1 to 3,388.5 ppt), two possible relationships were investigated:

$$X_i = \beta_0 + G_i(E_i, k, \beta_1) + \varepsilon_i, \quad \text{or} \quad \ln(X_i) = \ln(\beta_0 + G_i(E_i, k, \beta_1)) + \varepsilon_i,$$

where X_i is the measured serum lipid concentrations in 1987 or 1988 of the i^{th} subject and G_i is the corresponding modeled serum lipid TCDD concentration at that time. G_i is a function of E_i, the time-specific exposure estimate; k, an elimination rate parameter (either constant, for a first-order kinetic model, or concentration- and age-dependent); β_0, an intercept term (either fixed at zero or allowed to vary for the regression), and β_1, the dose rate in ng corresponding to one unit of the exposure index. The residual errors ε_i were assumed to be independently, identically, and normally distributed random variables with zero mean and constant variance σ^2 for either untransformed or ln-transformed data. Details of the CADM are presented elsewhere[7,8]. For the collection of individuals with measured serum lipid TCDD concentrations above 10 ppt, MLEs for β_0 and β_1 were obtained by linear regression for four elimination model cases, summarized in Table 1.

Previous dose estimates for the NIOSH cohort used in recent meta-analyses were based on the assumption of a linear relationship between the untransformed X_i and G_i, in conjunction with a first-order elimination model with an 8.7 year half-life and β_0 fixed at zero[1,4]. In this study, using the identified MLEs for β_0 and β_1 for each model case and regression assumption, we estimated profiles of serum lipid concentration vs. time based on the exposure index profiles for each member of

the full cohort and calculated estimated total AUC through the end of follow-up. These are compared to the estimates of Steenland et al.[1] for the NIOSH cohort (median values reported by Crump et al.[4]). Steenland et al. and Crump et al. used AUC estimates lagged by 15 years in their dose-response evaluations; however, other cohort dose estimates have not included lag times[2,3] as reported in Crump et al.[4], so we present both lagged and unlagged AUC estimates using the 8.7-yr half-life model, and unlagged estimates for the other models. To make comparisons easier, cohort septiles were defined as in Steenland et al.[1,9], by first ordering the cohort by total AUC and then dividing the cohort into septiles containing equal numbers of total deaths; this results in different individuals and different numbers of individuals in each septile depending on the kinetic model and regression assumption (details not shown).

Results

The choice of regression model (untransformed or ln-transformed) strongly influences the MLE estimates of β_0 and β_1. Figures 1a and 1b illustrate the residual sum of squares as a function of β_1 for the first-order model (8.7 year half-life) for the untransformed and ln-transformed regression models (β_0 fixed at zero for this example). For the untransformed linear regression, β_1 is almost entirely determined by the persons with measured TCDD levels >100 ppt in 1987/1988. In contrast, for the ln-transformed regression, β_1 depends on the whole range of measured TCDD values. Regression based on ln-transformed values thus allows for a more balanced weighting of all the serum data, which range over three orders of magnitude.

The MLEs and confidence intervals for β_0 (ppt) and β_1 (ng TCDD/unit of the exposure index) for the different models with regression on ln-transformed values are summarized in Table 2. The MLEs of β_0 and β_1 vary widely, reflecting the impact on their estimated values of different assumptions regarding elimination kinetics. The CADM-Mean and CADM-LCI provide improved model performance over the first-order half-life models. Figure 2 presents the ratio of measured to modeled concentrations vs. modeled concentrations at the time of measurement for the 8.7 year half-life model (untransformed regression, β_0 fixed at zero, 6.1 ppt background, all as used previously[1]) and the CADM-Mean model, ln-transformed regression with MLE values for β_1 and β_0. The CADM-Mean model results in lower residual variance. However, as shown in Figure 3, both models display bias, with modeled values generally lower than measured values for those individuals with higher measured values in 1987/1988.

Application to the full cohort of the various elimination models, with their parameter sets and corresponding MLE β_0 and $\beta_1$values, allows estimation of the total AUC through end of follow-up for each member of the cohort. Table 3 presents the median AUC estimates by septile for several combinations of assumptions regarding kinetic and regression models and lagging of exposure.

Discussion

Large variations in dose estimates (several-fold) were obtained for the more-highly exposed members of this cohort, whether assuming first-order (constant half-life) or CADM kinetics. Considerable residual variation is attributable to specification of kinetic model parameters (half-life or hepatic elimination rate) and to choice of regression procedure (linear on the untransformed or ln-transformed values and whether a non-zero intercept, β_0, was included). Such uncertainty and variability has not to date been illuminated or discussed in exposure reconstruction efforts for dioxin-exposed occupational cohorts. Risk assessments based on such reconstructions likewise have not addressed this issue, but rather have relied on point estimates of exposure (single estimates of the mean or median of modeled AUC) for various subcohorts. While uncertainty in measures of association (e.g., confidence intervals on standardized mortality ratios) have been incorporated into previous risk assessments, uncertainty and variability in dose estimates has not yet been taken adequately into account in the supporting dose-response assessments [1,4,10].

Our exposure reconstruction effort resulted in relatively poor agreement between measured and modeled serum TCDD levels regardless of the model assumptions used, with modeled values often discrepant by an order of magnitude from corresponding measured values. This variability probably reflects the limitations of the job exposure matrix and the kinetic models (none of the models can account for inter-individual variation in elimination efficiency), as well as a lack of data on body weight changes and other characteristics of individuals that can influence substantially the kinetics of TCDD elimination. Regardless of the method used, there were important differences in the modeled vs. measured values, although the residual variance was reduced by use of the CADM model in conjunction with linear regression on the ln-transformed values.

The modeling approach and lagging assumptions previously adopted by Steenland et al.[1] for the NIOSH cohort result in the most conservative (i.e., lowest) estimates of serum lipid concentrations of any of the modeling choices evaluated here, often by several-fold. Thus, cancer dose-response assessments based on the original exposure reconstructions for the NIOSH and other occupationally exposed cohorts

likely overstate the potency of TCDD as a human carcinogen by a significant amount.

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References
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Table 1: Model cases evaluated and rationale

Elimination Model Case	Rationale
First-order, 8.7 yr half-life	Used previously for estimation of AUC for NIOSH cohort with β_0 set to zero.[1]
First-order, 7.1 yr half-life	Model and approximate half-life used to estimate doses for the BASF [3] and Hamburg cohorts[2]
CADM-Mean hepatic elimination parameter	Model developed by Carrier et al. (1995) and modified and parameterized based on serial elimination data sets from Seveso male patients, mean parameter set[7]
CADM-LCI hepatic elimination parameter	Same as above with lower 95th percent confidence bound on mean hepatic elimination rate parameter

Table 2: MLEs of β_0 (ppt in lipid) and β_1 (ng TCDD/unit of exposure index) and 90% confidence intervals for four model cases based on subcohort of NIOSH workers with measured serum lipid TCDD concentrations in 1987/1988. Parameters estimated through regression on ln-transformed data.

	Regression with non-zero β_0			Regression with β_0 =zero	
Model Case	β_0 (90% C.I.[a])	β_1 (90% C.I.[a])	p^b	β_1 (90% C.I.[a])	p^b
8.7 yr HL	21 (13, 30)	3.8 (2.9, 4.8)	--	7.3 (6.1, 8.7)	--
7.1 yr. HL	21 (13, 31)	6.0 (4.6, 7.8)	0.50	11.7 (9.8, 14.0)	0.5
CADM-LCI	12 (5, 22)	31 (20, 47)	<0.05	48 (36, 65)	<0.0003
CADM-Mean	8.3 (1, 19)	134 (80, 210)	<0.08	180 (130, 250)	<0.0002

[a] Asymptotic likelihood ratio test-based confidence intervals. [b] F-ratio test, each model compared to 8.7 yr HL model, 170 and 170 df (for non-zero β_0), or 171 and 171 df (for β_0 =zero).

Table 3: Median AUCs (ppt-yrs) by septile for model cases from Table 1 with regression on untransformed or ln-transformed data, and regression intercept β_0 forced to zero or not.

Model Case	8.7 yr HL[a]	8.7 yr HL[b,c]	7.1 yr HL[b,c]	7.1 yr HL[b,e]	7.1 yr HL[b,e]	CADM-LCI[b,e]	CADM-LCI[d,e]	CADM-Mean[b,e]
Septile								

Model Case Septile	8.7 yr HL[a]	8.7 yr HL[b,c]	7.1 yr HL[b,c]	7.1 yr HL[b,e]	7.1 yr HL[b,e]	CADM-LCI[b,e]	CADM-LCI[d,e]	CADM-Mean[b,e]
1	260	300	300	300	680	250	500	450
2	400	460	460	580	980	1,300	1,200	2,600
3	850	840	960	1,700	1,700	3,900	3,400	7,000
4	1,900	2,200	2,800	5,900	3,700	8,900	7,300	18,000
5	4,400	5,900	7,600	16,000	9,200	18,000	14,000	41,000
6	12,000	20,000	26,000	57,000	30,000	45,000	32,000	120,000
7	60,000	86,000	120,000	250,000	130,000	200,000	130,000	550,000

[a] Values as reported in Crump et al. (2003), with exposure lagged 15 years; [b] β_0 fixed at zero with associated β_1, Table 2; [c] Regression on untransformed values; [d] β_0 and β_1 set to MLE estimates from Table 2; [e] Regression on ln-transformed values.

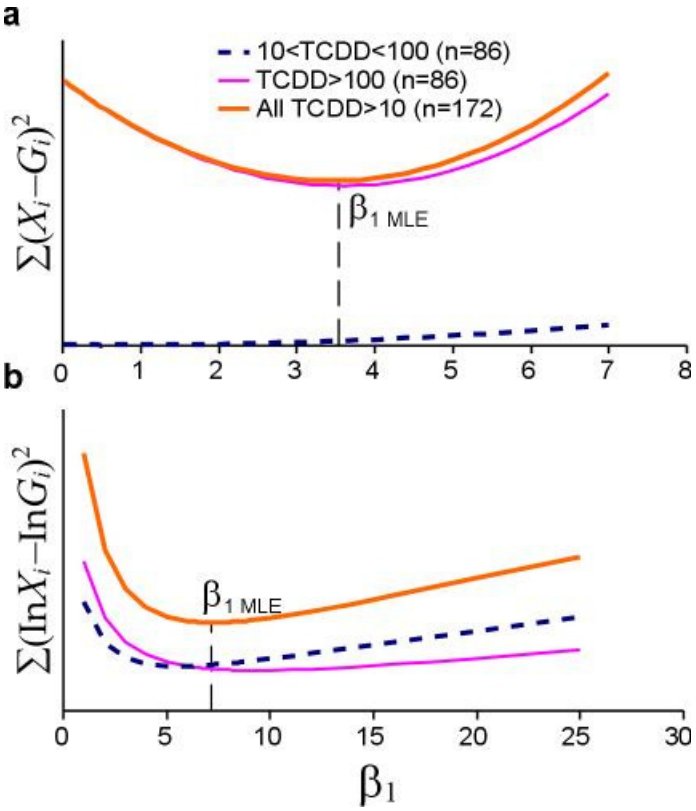

Figure 1: Residual sum of squares, 8.7 yr half-life first order model comparing regression on a) untransformed values or b) ln-transformed values. In 1a, data from persons with measured TCDD concentrations below 100 ppt in 1987/1988 contribute little to the determination of $\beta_{1\ MLE}$, while those in the upper half of measured TCDD concentrations dominate. In 1b, data throughout the range of measured values contribute about equally. Modeling by Steenland et al. (2001) utilized regression on the

untransformed data.

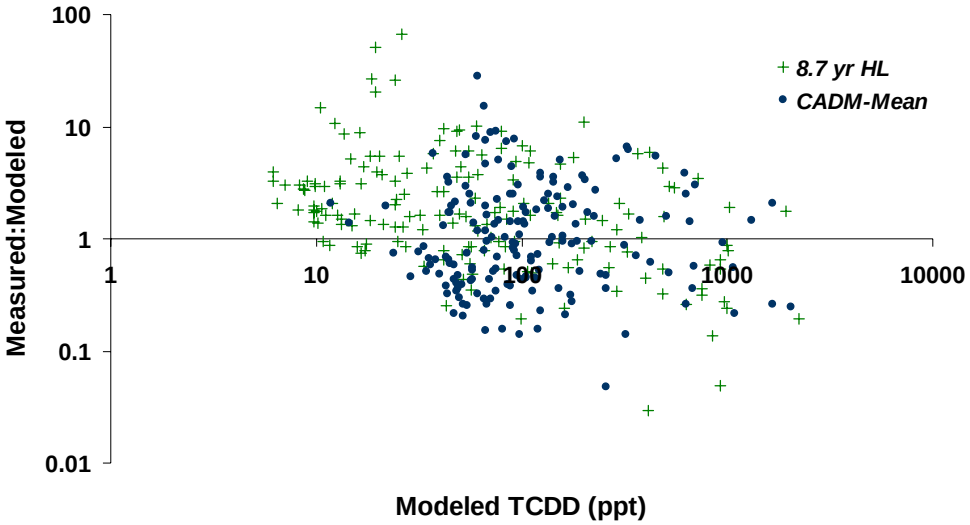

Figure 2: The ratio of measured to modeled serum lipid TCDD concentrations in 1987/1988 for 172 members of the NIOSH cohort with measured values above 10 ppt in 1987/1988 and available exposure index assessments for two model cases: a) first-order elimination assumption with 8.7 yr half-life, regression on untransformed values, with β_0 set to zero (method used by Steenland et al. 2001); and b) CADM-Mean parameter set and regression on ln-transformed values with regression intercept as in Table 2. Use of the CADM with the described regression method significantly reduces the residual variance.