EXPOSURE RECONSTRUCTION FOR A DIOXIN-EXPOSED COHORT: INTEGRATION OF SERUM SAMPLING DATA AND WORK HISTORIES

Aylward, LL[1]; Bodner, KM[2]; Collins, JJ[2]; Hays, SM[3]

[1] Summit Toxicology, LLP, Falls Church, VA USA; [2] Toxicology and Epidemiology Research and Consulting, The Dow Chemical Company, Midland, MI USA; [3] Summit Toxicology, LLP, Allenspark, CO USA

Abstract
The 2,192 workers at the Dow Chemical Company in Midland, Michigan engaged in the manufacture of pentachlorophenol and 2,4,5-trichlorophenol represent the largest single cohort ever studied for the health effects of dioxins. Work histories with job-specific exposure scores are available for the entire cohort, and recently serum dioxin measurements were conducted on 365 workers with chlorophenol exposures. This study presents a simple exposure reconstruction for these 2,192 workers that takes into account estimates of background exposures and the occupational exposure profile over time for each individual for selected congeners found to be associated with employment histories on these processes. Results of this exposure reconstruction effort can be used in epidemiologic studies of these workers to provide dose metric alternatives to exposure scores.

Methods
Blood data from retired workers. Blood samples were collected during 2004 and 2005 from 365 retired workers with at least one assignment in either a trichlorophenol or pentachlorophenol process. The samples were analyzed for dioxin, furan, and PCB congeners, and the results showed clear patterns related to the trichlorophenol and pentachlorophenol production assignments on a congener-specific basis.[1]

Work histories and exposure scores. Individual work histories including the start and stop date for each job assignment and a rating of the intensity of estimated exposure either to TCDD or higher chlorinated dioxins (TCDD or HOCDD score, respectively). These scores were estimated based on industrial hygiene data, process description, and occupational medical criteria (e.g., occurrence of chloracne in workers) and were time-specific.[2] The TCDD exposure intensity was rated with scores of 0, 1, 2, 3, or 4, while the higher chlorinated dioxin exposure intensity was rated with scores of 0, 1, or 2. The scores were not intended to be linearly related to actual exposure, and a zero score did not necessarily indicate no potential for exposure; rather the zero score indicated a minimal potential for exposure compared to other job assignments.

Background blood data and dose rate estimation. The University of Michigan Dioxin Exposure Study (UMDES) measured serum lipid-adjusted concentrations of dioxin in persons in Midland/Saginaw, Michigan (n=695) and from a reference area in Michigan (n=251) in 2005. The results of the blood sampling for persons aged 60 and over from the reference area (n=71) were used to characterize year 2005 "background" lipid-adjusted dioxin levels unrelated to employment at Dow.[3] Data from analysis of samples from the National Human Adipose Tissue Survey (NHATS) were used to characterize typical levels of dioxin congeners in persons of average age 30 in adults in the US in 1975.[4]

Based on these two sets of data, two calculations were performed in order to estimate likely background dose rates for each congener. First, the change in average concentration between 1975 and 2005 was modeled assuming a first-order elimination rate, *k*, and an average background dose rate over that 30 year time period:

$$C_{2005} = C_{1975}\, e^{-k(2005-1975)} + \frac{D_{post-1975}}{PBF * k}\left(1 - e^{-k(2005-1975)}\right) \qquad (1)$$

Where $D_{post\text{-}1975}$ is the average yearly dose rate in ng/kg-yr from 1975 to 2005 and *PBF* is percent body fat (assuming all compound distributes to lipid tissue in the body). A second calculation estimated the average yearly intake rate, $D_{pre\text{-}1975,}$ in ng/kg-yr starting at birth for individuals included in the Kang et al. (1990) data set that would result in the measured lipid-adjusted concentrations in 1975:

$$C_{2005} = \frac{D_{pre-1975}}{PBF * k}\left(1 - e^{-k(\Delta t)}\right) \qquad (2)$$

Where Δt is the period of time since birth. Because the period of time since birth was an input that varied among the individuals included in the Kang et al. (1990) study, a Monte Carlo simulation was implemented in Crystal Ball® to estimate background dose rates for these individuals. Table 1 documents the assumptions used in this modeling.

Table 1: Values and distributions used in the Monte Carlo simulation of eq. 1and 2 to estimate the pre- and post-1975 average background dose rates by congener

Parameter	Values Used in Simulation			
	TCDD	Summed HxCDD	HpCDD	OCDD
C_{1975}, ppt lipid adjusted[a]	17.3	189.9	291.3	1395.2
C_{2005}, ppt lipid adjusted[b]	5.2	77.6	61.3	474.7
Mean half-life, yrs[c]	7.2 (normal dist., 30% CV)	13.1 (normal dist., 30% CV)	3.7 (normal dist., 30% CV)	6.7 (normal dist., 30% CV)
PBF, unitless	0.25 (point estimate)			
Δt, birth to 1975, yrs	21-39 (uniform distribution)			

[a] 1975 average concentrations for persons born between 1936 and 1954.[4] [b]2005 average concentrations for persons from reference area aged 60+.[3] [c]Estimates.[5]

Occupational Dose Rate Reconstruction. Models were constructed for each dioxin congener that was significantly elevated in trichlorophenol or pentachlorophenol workers compared to referents: one congener, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) which was observed to be significantly elevated in workers with a history of trichlorophenol process employment, and 3 other congener groups observed to be associated with a history of employment on the pentachlorophenol-related process: summed hexa-chlorinated dioxin congeners (sum of 1,2,3,4,7,8-, 1,2,3,6,7,8-, and 2,3,4,6,7,8-hexachlorodibenzo-p-dioxin [HxCDD]), 1,2,3,4,6,7,8-heptachlorinated dibenzo-p-dioxin (HpCDD), and octachlorodibenzo-p-dioxin (OCDD). The models were constructed with the following assumptions:

- A constant average dose was associated with a year of employment in any job with a given TCDD score (0 through 4) or given HOCDD score (0 through 2).
- Elimination occurred through a first-order process for each congener, independent of the concentration of that congener or any other congener. The central tendency for the half-life of elimination for each congener, $HL_{central}$ was set to previously estimated values.[5] The half-life was assumed to be constant throughout an individual's lifetime, but for each individual was considered to be related to body mass index (BMI) as measured in 2004-2005 as follows:

For 20<BMI<40:	$HL=HL_{central} * [1+0.03*(BMI-30)]$	(3a)
For BMI<20:	$HL=0.7 * HL_{central}$	(3b)
For BMI>40:	$HL=1.3 * HL_{central}$	(3c)

- Background exposure to each congener occurred at different rates during two time periods: from birth through 1/1/1975, and from 1/1/1975 until date of sampling.
- Bodyweight was assumed to be constant throughout the employee's life at the measured weight at the time of sampling in 2004-2005, and the percent body fat was assumed to be constant at 25%. All compounds were assumed to distribute solely in body fat.

For each individual, the serum concentration of any given congener at the time of measurement $C(t_m)$ can be represented as the sum of the residual concentrations due to occupational and background exposures. The occupational contribution was modeled as the time-dependent sum of contributions from each job assignment:

$$C_{occup}(t_m) = \sum_{i=1}^{n} \frac{D_i}{Vk}\left[(1-e^{-k(t_i-t_{i0})})*(e^{-k(t_m-t_i)})\right] \quad (4)$$

Where *i* indicates the job assignment, D_i is the dose rate in ng/yr associated with that job, *V* is the volume of distribution (for this modeling, the volume of distribution was assumed to be 0.25 of the measured body weight at the time of serum sampling, corresponding to an assumption of 25% body fat), *k* is the elimination rate (units of yr^{-1}, assumed constant), and t_{i0} and t_i are the start and end dates for the given job. Similarly, $C_{bkgrnd}(t_m)$ was modeled as follows using the background dose rates estimated as described above:

$$C_{bkgrnd}(t_m) = \frac{D_{pre-1975}}{Vk}\left[(1-e^{-k(1975-t_{birth})})*(e^{-k(t_m-1975)})\right] + \frac{D_{post-1975}}{Vk}\left(1-e^{-k(t_m-1975}\right) \quad (5)$$

Using the sum of these two expressions (equations 4 and 5), we conducted a regression in Microsoft Excel ® using the occupational and personal data for each individual to estimate optimum congener-specific estimates for the cohort average dose rate (D_i) associated with each of the 5 TCDD scores (0 through 4) or 3 HOCDD scores (0 through 2). We investigated a variety of residual functions for optimizing the regression and selected minimizing the sum of squares between modeled and measured concentrations in the 2004-2005 time period across the 365 individuals. This method emphasized data from individuals with higher measured serum lipid concentrations more heavily, which was deemed appropriate because these individuals are likely more informative about the occupational exposure rates of interest.

Results

Background and Occupational Dose Rates. Table 2 presents the results of the regression for background dose rates. The estimated average background exposure rates are reasonable in the context of previous estimates of temporal patterns in dioxin intakes in the US.[6] Application of the models to the work histories and exposure scores for the 365 sampled workers resulted in estimated occupational dose rates for each congener. Figure 1 shows the relationship between modeled and measured serum lipid concentrations of summed HxCDD congeners in 2005. Although the model was able to account for approximately half of the variance observed, the modeling results were consistently biased. The modeling consistently under-predicted the measured serum lipid concentrations of congeners in individuals with the highest measured values, and consistently overpredicted the concentrations in persons below the mean of typical referent values. The latter result is expected due to the use of average background intake rates and elimination rates, which would result in overprediction of blood concentrations in persons with lower-than-average intake or faster-than-average elimination.

Modeled occupational dose rates for HpCDD, and OCDD showed an inverse pattern, with higher dose rates associated with lower exposure scores, and a similar pattern was observed for the middle dose scores for TCDD. This finding was robust to various assumptions about half-life and background dose rate. Omission of several individuals with the highest measured serum concentrations in 2004-2005 resulted in a reversal of this pattern for some congeners, but the appropriateness of omission of these individuals from the regression is questionable.

Discussion

The approach described here will allow for an estimate of occupationally-related area under the curve exposure (TEQ or individual congener) for individuals in the Dow worker cohort for use in epidemiological studies of this cohort. For persistent compounds such as PCDD/Fs, such estimates, which account for the time-dependent accumulation and elimination behavior of the compounds, may provide a more biologically relevant metric of exposure than cumulative exposure scores. However, there are important limitations to the approach described here, including the use of point estimates for several parameters that vary among individuals or over time (bodyweight, etc.) and an assumption of constant average dose rates in the occupational environment and average background intake rates. Also, this analysis did not implement a concentration-dependent elimination model for TCDD due to the lack of such concentration-dependent models for the other congeners of interest in this analysis and due to computational limitations.[7] As a result, dose and AUC estimates presented here are likely to substantially underestimate actual doses in the cohort.

Finally, the estimates of elimination rates derived in a previous study for each congener were used in this effort to estimate average background intake rates and occupational dose rates.[5] We attempted to use the dataset to independently estimate these parameters, but the background intake and elimination rate parameters were highly correlated, and could not be resolved independently. Thus, the occupational dose rates estimated here are dependent upon the elimination rate and background dose rates assumed in this analysis and cannot be taken as externally valid estimates. As a consequence, although the dose estimates and resulting AUC estimates derived in this analysis can be used for internal analyses of this cohort, they should not be regarded as absolute estimates that can be extrapolated to environmental or other exposure circumstances.

Table 2: Parameter estimates from regression

Parameter		Parameter Estimates by Congener			
		TCDD	**HxCDD**	**HpCDD**	**OCDD**
$HL_{central}$, yrs*		7.2	13.1	3.7	6.7
Background	$D_{pre\text{-}1975}$, ng/kg-yr	0.44	4.1	14	39
	$D_{post\text{-}1975}$, ng/kg-yr	0.11	0.65	2.9	11.3
Occupational	$D_{score=0}$, ng/yr	278	376	0.1[a]	6,470
	$D_{score=1}$, ng/yr	598	5,410	574,000	782,000
	$D_{score=2}$, ng/yr	7,410	5,990	170,000	394,000
	$D_{score=3}$, ng/yr	2,990	NA[c]	NA[c]	NA[c]
	$D_{score=4}$, ng/yr	63,800	NA[c]	NA[c]	NA[c]
R^2		0.50	0.66	0.49	0.49
p[d]		<0.0001	<0.0001	<0.0001	<0.0001

* From ref. 5. [a] Constrained in solver, result is minimum allowed value. [b] TCDD dose rates were estimated based on TCDD scores; dose rates for the other three congeners were estimated based on HOCDD scores. [c] HOCDD scores had values of 0, 1, and 2 only. [d] F-ratio test for goodness of fit.

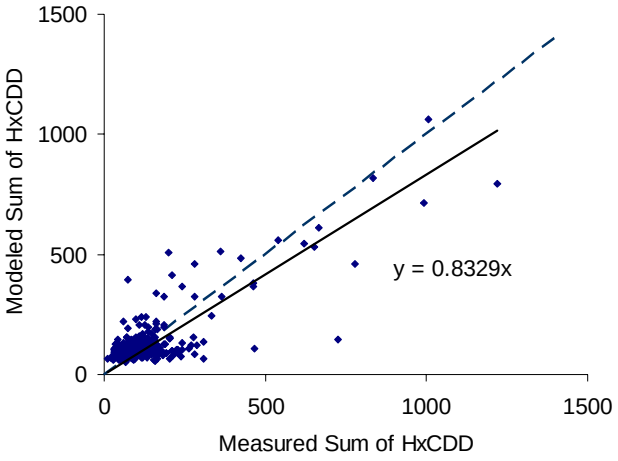

Figure 1: Modeled vs. measured sum of HxCDD congeners in 2005 based on the model described above. Dotted line indicates ideal 1:1 correspondence; solid line shows the linear regression with zero intercept demonstrating the model's underprediction of actual measured values.

References

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