ELIMINATION RATES FOR HIGHER CHLORINATED POLYCHLORINATED DIOXIN CONGENERS IN FORMER TRICHLOROPHENOL AND PENTACHLOROPHENOL WORKERS FROM MIDLAND, MI

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Introduction

Production of 2,4,5-trichlorophenol (TCP) and pentachlorophenol (PCP) may produce polychlorinated dibenzo-p-dioxin (PCDD) and dibenzofuran (PCDF) contaminants. Former workers on these processes at the Dow Chemical Company manufacturing facility in Midland, MI, were previously identified and blood samples collected in 2004-2005 from 375 individuals were analyzed for PCDDs and PCDFs [1, 2]. Concentrations of PCDD congeners were elevated over background levels in these workers at the initial sampling, with former TCP workers demonstrating primarily elevations in TCDD and former PCP workers demonstrating elevations over background of all higher chlorinated PCDD congeners (penta- through octa-chlorinated)[2]. This paper presents the results of a follow-up sampling and analysis effort on 56 workers selected from the original 375 workers. Apparent elimination rates based on changes in either serum lipid-adjusted concentration or changes in whole body congeners amounts were estimated for each of the PCDD congeners, and potential covariates that could influence elimination rates including age, body mass index (BMI), initial concentration, and smoking behavior[3], were evaluated.

Materials and methods

The study population included individuals selected from a cohort of former workers on the TCP and PCP manufacturing processes at the Dow Chemical Company facility in Midland, MI. [1, 2] Serum sampling, work histories, and questionnaire data were previously assembled in 2004-2005 for 375 former workers[1, 2, 4]. In this effort, a selected subset of participants from the 2004-2005 study was recalled. Briefly, a sampling strategy designed to oversample the individuals with the highest measured TCDD and OCDD concentrations in the 2004-2005 sampling effort was implemented, and 56 participants from the original 375 were recruited. On the day of examination in the fall of 2010, participants donated blood and completed the same questionnaire originally administered during the 2004-2005 sampling effort. Height, weight, and blood pressure were also measured. Blood samples were analyzed for PCDD/Fs and selected PCB congeners using the same laboratory and methods as used in the previous study[2].

Changes in measured concentrations of persistent compounds such as PCDDs and PCDFs reflect not only intrinsic elimination rates but also any ongoing intakes of the compounds[5, 6]. If current body concentrations are high relative to steady-state concentrations associated with current background intake rates, apparent elimination rates will approximate intrinsic elimination rates. If, on the other hand, background intakes are significant compared to current body concentrations, the estimates of apparent elimination rate will be lower than the intrinsic rates. No direct information regarding congener intake rates was available, so the elimination rates calculated here are net estimates of the rate of change of the congeners.

Apparent elimination rates were calculated in two ways, based on either changes in concentration or changes in estimated body amounts. For the former approach, concentrations of congener i in 2005 and 2010 and time between sampling dates, Δt, were used to estimate elimination rate k_i:

$$k_i = \ln(C_{i,2010} / C_{i,2005}) / \Delta t \quad (1)$$

For the latter approach, the congener concentrations in 2005 and 2010 were replaced by the estimated amounts, A, of congener i in the body:

$$A = 100 * PBF * BW * C_i \quad (2)$$

where PBF is percent body fat (as estimated using an age, sex, and BMI-specific formula[7]), BW is bodyweight in kg, and C_i is the serum lipid-adjusted concentration of congener i. The resulting amount A_i calculated for each time and congener was used in equation (1) above for calculating the apparent whole-body elimination rate. Elimination rates calculated using these two approaches were derived for each individual for each PCDD congener.

We investigated potential associations with covariates that could influence elimination rate by conducting univariate linear regressions between the calculated elimination rates and age, serum lipid-adjusted congener concentration in 2005, BMI, and smoking (current vs. former or non-smokers). We also stratified by whether the initial measured concentration in 2005 exceeded the 95th percentile of the NHANES general US sampling in 2003-2004 for individuals aged 60 and older and examined whether apparent elimination rates differed for these two groups for any congener.

Results and discussion

The characteristics of the participant population at the time of sampling in 2004-2005 and in 2010 are presented in Table 1. The average BMI in the population was nearly unchanged, and in general, the individuals in the group had relatively stable bodyweights between the two sampling episodes. Smokers comprise a relatively low proportion of the group.

Summary statistics of the measured concentrations of PCDD congeners are presented in Table 2. For comparison, the 95th percentile concentrations for each PCDD congener from the NHANES 2003-2004 sampling cycle for individuals ages 60 and over are also presented. Substantial declines are apparent for all of the PCDD congeners between the first and second sampling effort in the study participants.

The estimated first order apparent elimination rates based on changes in serum lipid-adjusted concentrations (eq. 1) are presented in Figure 1. Because of the relatively stable bodyweights, the estimated elimination rates based on changes in the estimated amount of each congener in the body are very similar to those based on changes in concentration (results not shown). The corresponding first-order elimination half-lives are presented in Table 3, with comparison to previously published estimates[3, 8]. The estimated half-lives derived in this study are similar to those estimated in earlier efforts, although the half-life estimates for PeCDD and 1,2,3,6,7,8-HxCDD are somewhat shorter in this study than in previous studies, and the half-life for HpCDD estimated here is somewhat longer.

No statistically significant associations were observed between apparent elimination rates and covariates including age, BMI, and current smoking. This is in direct contrast to the results reported by Flesch-Janys et al. (1996)[3], who reported negative associations between elimination rate and age and BMI and positive associations with smoking across several congeners. The difference in results may be due in part to the fact that the range of age and body fat levels (or BMI) in the current study is narrower than in the earlier study, and the current study population has a relatively low proportion of current smokers. As a result, there may be insufficient variation in these parameters to allow resolution of statistically significant relationships among this cohort.

Previous evaluations of the elimination kinetics of TCDD have demonstrated a concentration dependence of elimination rate, with higher elimination rates at higher serum lipid concentrations [9]. No dependence of elimination rate on concentration in 2004-2005 was observed in this study for TCDD or any other congener. This may be due to the relatively low concentrations of TCDD and other congeners in this study compared to the previous analysis, in which such behavior became apparent only at TCDD concentrations approaching or exceeding approximately 1,000 ppt in serum lipid[9].

An apparent concentration-dependence of estimated elimination rates can also occur when the ongoing background exposure rates are non-negligible relative to current body concentrations[10]. Under that condition, apparent elimination rates decrease and approach zero as body concentrations approach steady-state with current exposure rates. The lack of any detectable trend of slowing of elimination at the lower concentration range in this study for these congeners suggests that current background exposure levels (and theoretical steady-state serum lipid concentrations corresponding to those intake levels) are quite low compared to the body concentrations in the study participants. When the group was stratified into those above and below the age-specific NHANES 95th percentile, no statistically significant difference in elimination rates between the two

groups was observed for any congener. Further modeling efforts will address characterization or bounding of likely background intake rates based on this dataset.

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Table 1: Description of population of former trichlorophenol and pentachlorophenol workers (n=56) at sampling in 2005 and 2010.

Parameter	2004-2005	2010
Age, yrs [mean (SD)]	63.3 (7.1)	68.5 (7.0)
BMI [mean (SD)]	32.0 (4.3)	32.1 (4.6)
Estimated % body fat [mean (SD)]	36.7 (5.1)	38.1 (5.5)
Current smoking [n, (%)]	8 (14.3%)	7 (12.5%)

Table 2: The concentrations of PCDD congeners identified in 2005 as elevated in this population compared to referents are provided in pg/g lipid, mean (range), at two sampling time periods. The age-specific 95th percentile from the NHANES 2003-2004 dataset is provided for comparison.

Congener	2004-2005	2010	NHANES 95th %ile[a]
TCDD	21.1 (2.0-160)	12.9 (1.2-104)	7.9
PeCDD	19.7 (4.0-66.3)	14.2 (4.1-47.7)	17.7
1,2,3,4,7,8-HxCDD	16.0 (3.5-59.2)	10.5 (1.6-34.0)	15.10
1,2,3,6,7,8-HxCDD	137 (24.7-510)	94.3 (21.3-349)	104
1,2,3,7,8,9-HxCDD	19.4 (3.8-68.2)	11.3 (1.5-51.4)	16.2
HpCDD	160 (17.6-624)	87.1 (11.7-414)	132
OCDD	1920 (150-9680)	1120 (129-5940)	1180

[a]NHANES 2003-2004 sampling, 95th percentile for persons aged 60 and older [11]

Table 3: Estimated half-lives (years) of elimination for selected dioxin congeners from this study (n=56) and two previous studies.

Congener	This study Median (q25-q75)[a]	Flesch-Janys et al. (1996)[3] Median	Rohde et al. (1999)[8] Mean
TCDD	6.4 (4.9-8.1)	7.2	8.7
PeCDD	10.2 (6.9-15.8)	15.7	13.9
1,2,3,4,7,8-HxCDD	8.1 (5.9-12.8)	8.4	13.9
1,2,3,6,7,8-HxCDD	9.5 (6.0-14.4)	13.1	11.6
1,2,3,7,8,9-HxCDD	6.2 (5.1-9.5)	4.9	7.7
HpCDD	6.8 (5.0-9.7)	3.7	4.3
OCDD	7.5 (5.3-10.0)	6.7	8.7

[a] 25th to 75th percentile

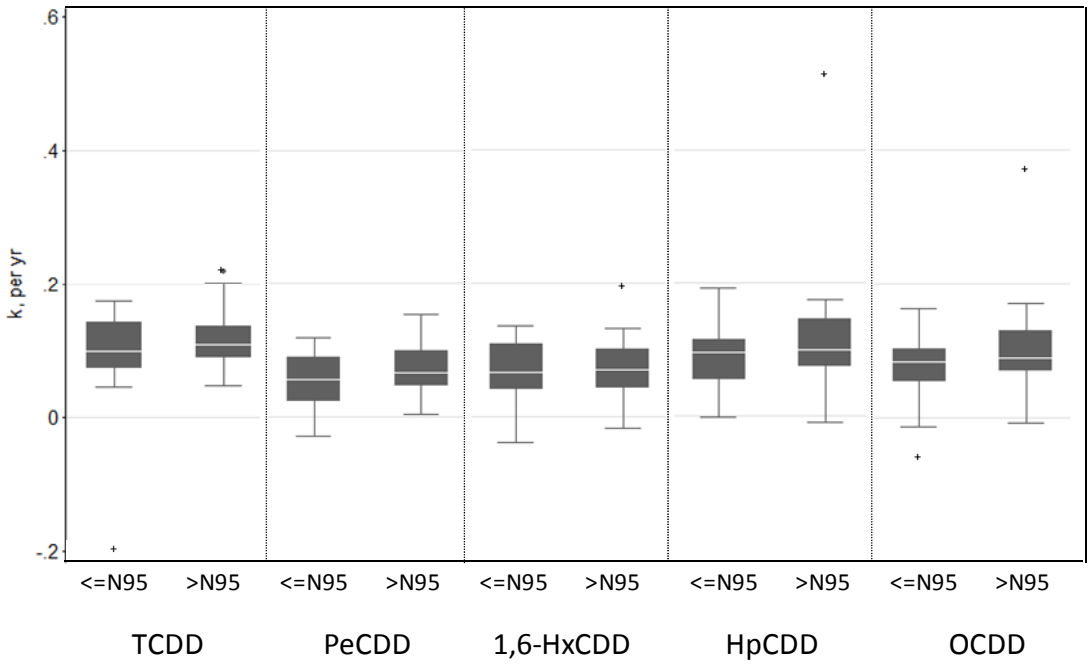

Figure 1: Distribution of apparent elimination rates for selected PCDD congeners. Rates are reported for each congener for participants with serum lipid concentrations in 2004-2005 that are less than or equal to or greater than the NHANES 95th percentile for persons aged 60 and over (<=N95 and >N95, respectively).