

## Serum dioxin levels in former chlorophenol workers

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Using gas chromatography/mass spectrometry, we measured lipid-adjusted serum levels for all 2,3,7,8-substituted dioxins and furans, and four coplanar polychlorinated biphenyls in 62 workers with chlorophenol exposure and 36 workers without chlorophenol exposures working at the same plant during the same time. We oversampled among workers diagnosed with chloracne. Mean dioxin background levels from 36 nonchlorophenol workers were estimated as 6.0 parts-per-trillion (ppt) for 2,3,7,8 tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) and 67.5 ppt for 1,2,3,4,6,7,8 heptachlorodibenzo-*p*-dioxin (Hepta-CDD). We found different dioxin and furan profiles for trichlorophenol and pentachlorophenol (PCP) workers. Among trichlorophenol workers with chloracne, we found 2,3,7,8-TCDD (mean = 30.5 ppt) above background levels and among PCP workers with chloracne, we found high levels of Hepta-CDD (mean = 312.5 ppt) and other higher chlorinated dioxins and furans. Cumulative exposure estimates for dioxins for both 2,3,7,8-TCDD and the higher chlorinated dioxins created in the early 1980s for our epidemiology studies were highly correlated with serum dioxin levels when age and body mass index were taken into account. While workers previously diagnosed with chloracne had high serum dioxin levels, some workers without diagnosed chloracne also had high levels. Among tradesworkers with plant-wide responsibilities, we observed serum dioxins and PCB levels higher than background indicating workplace exposures. We estimate that the mean level of 2,3,7,8-TCDD present in the serum of workers on the date workplace exposure terminated was 267 ppt (ranging from 8 to 1184 ppt) assuming a 9-year half-life, 582 ppt (ranging from 10 to 2,641 ppt) assuming a 7-year half-life, and 1928 ppt (ranging from 22 to 17,847) when a toxicokinetic model is used. We conclude that our findings are consistent with other studies reporting high serum dioxin levels among chlorophenol workers after occupational exposures.

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### Introduction

Serum evaluations of persons with high dioxin exposures have been useful in estimating past exposures for health studies (Beck et al., 1989b; Sweeney et al., 1990; Neuberger et al., 1991; Ott et al., 1993; Flesch-Janys et al., 1995; Heederik et al., 1998; Coenraads et al., 1999). Many studies have shown that high serum dioxin levels can be measured many years after exposure and that workers with a history of chloracne, a skin condition associated with high dioxin exposure, typically have the highest dioxin body levels (Mocarelli et al., 1991; Coenraads et al., 1999).

The chlorophenol workers at the Midland, Michigan Dow Chemical plant have been studied for morbidity and mortality (Townsend et al., 1982; Bond et al., 1983, 1989b; Cook et al., 1986; Ott et al., 1987; Bodner et al., 2003). These workers had potential exposure to the chlorinated dioxins from production and use of 2,4,5-trichlorophenol (TCP) and pentachlorophenol (PCP). Production at the

Midland plant occurred from 1937 to 1980 for PCP and 1942 to 1979 for TCP. TCP and PCP production may generate polychlorinated dioxins and dibenzofurans as unintended by-products. The dioxins generated in TCP production often include 2,3,7,8 tetrachlorodibenzo-*p*-dioxin while dioxins generated in PCP production include mostly hexa-, hepta- and octa-chlorodibenzo-*p*-dioxins and some higher chlorinated furans. Furans and higher chlorinated dioxins are thought to share many of the same properties of TCDD based on laboratory evidence, although the health effects among humans from furans and the higher chlorinated dioxins have rarely been studied.

Previous studies have also examined the incidence of chloracne among these workers (Bond et al., 1987, 1989a, 1990). The highest incidence of chloracne occurred among TCP process workers and among PCP production and finishing workers. Of the 2192 workers with potential dioxin exposure, 2072 company medical records were available. Examination of these medical records indicated that 15% of these workers (313 of 2072) were diagnosed with definite or probable chloracne. Chloracne was uncommon among these workers before 1964 with 91% of the cases occurring between 1964 and 1979.

Most of the workers in this study were also included in both the International Agency for Research on Cancer

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(IARC) study, (Kogevinas et al., 1997) and the National Institute of Occupational Safety and Health (NIOSH) Dioxin Registry (Steenland et al., 1999). In addition to being the largest single group of workers in these studies, the Dow chlorophenol workers have the longest follow-up, a maximum of 55 years and a minimum of 24 years, of any study group in either of these combined studies.

We examined serum dioxin levels among a sample of these chlorophenol workers and comparison workers to determine if serum dioxin levels remain elevated many years after exposure. We will also assess exposure estimates used in previous epidemiology studies for 2,3,7,8-TCDD from the TCP exposures and the higher chlorinated dioxins and furans from the PCP exposure. The exposure estimates used in the previous epidemiology studies are referred to as TCDD from TCP exposure and H/OCDD from PCP exposures. The current study provides a rare opportunity to relate older exposure estimates, based on workplace monitoring, job history, and process changes developed previously for epidemiology studies, to dioxin levels in blood measured today.

## Methods

### *Study Group*

Of the 2192 Dow workers in the chlorophenol study, 1378 were alive on December 31, 2002. Of the 313 workers with a history of chloracne, 197 were alive including 23 who were still working in 2003. Since the original study group was overwhelmingly male (2187 of 2192), we included only males in the current study. We chose only men living within 50 miles of the Midland plant to allow us to use the company medical clinic for the serum collection. Three groups of chlorophenol workers were randomly sampled to reflect a (1) history of chloracne and employed mostly in the TCP area, (2) history of chloracne and employed mostly in PCP area, and (3) no history of chloracne and employed in either or both chlorophenol departments. We oversampled from the chloracne groups to assure we would include workers with the suspected highest exposure potential. Within each group, we randomly selected half who were currently employed and half who were not, in order to determine if employment status would impact study participation. Based on power calculations, we estimated that we would need serum from at least six exposed subjects in each of six categories (i.e., 36 total) to show a statistically significant elevation if, in fact, the subject TCDD levels were at least three times higher than background. We selected 72 workers to allow for nonparticipation.

A second group of workers was selected from men who had not been formally assigned to the chlorophenol departments, although some of these workers may have spent undocumented time in the chlorophenol departments

doing maintenance and clean-up. We matched them on birth date and hire date to the chlorophenol department workers to produce similar age and year of hire distributions between groups. There were 72 workers selected from nonchlorophenol departments.

We sent 144 letters to subjects. In all, 18 subjects were found to be not eligible for the study, for example, because their current address was outside of the required 50 mile radius of the clinic, or they were deceased. Of the remaining 126 subjects, 18 could not be contacted and three refused to participate. We scheduled 102 men for a clinic visit, and 99 showed up for the appointment. One participant could not complete the blood draw, resulting in 98 serum samples collected; 52 from the chlorophenol departments and 46 from the nonchlorophenol departments. The participation rate among chlorophenol department workers was 81% (52 of 64) and among nonchlorophenol workers was 74% (46 of 62).

We reviewed the individual job histories for the workers in the nonchlorophenol group. This review identified 10 of the 46 participants in the nonchlorophenol department group who worked in these trades' worker positions (i.e., boiler-maker, electrician, janitor, machinist, maintenance, millwright, painter or pipe-fitter with plant-wide responsibility who worked in the Midland plant between 1937 and 1980). We subsequently refer to the 10 workers in the nonchlorophenol departments with potential for chlorophenol exposures as "tradesworkers", and the 36 workers in the nonchlorophenol department group without plant-wide exposure potential as the comparison group.

### *Serum Collection and Analysis*

We collected, stored, and shipped the serum samples to Alta Analytical Laboratory. The analytical procedure followed the CDC protocol (without using the FMS-system) and method 8290 with some minor improvements and modifications to estimate the levels for 2,3,7,8-substituted dioxins and furans, and method EPA 1668 to estimate the levels for four coplanar polychlorinated biphenyls (PCBs), PCB77, PCB81, PCB126, and PCB169. All results are lipid adjusted (Byrd et al., 1998). Sera collection occurred at the Midland Dow Chemical medical clinic. Approximately 80 ml of blood was collected in vacutainer tubes (no anticoagulant or serum separator). Whole blood was allowed to clot for at least 20 min and then centrifuged for 15 min at 2500 r.p.m. The serum was transferred to rinsed glass vials with Teflon seals. The serum was stored at  $-20^{\circ}\text{C}$  until laboratory analysis. Serum from each study subject was sent to Alta Laboratory in El Dorado Hills, CA, USA. Alta Laboratory used high-resolution gas chromatography/mass spectrometry (GC/MS) to determine the levels for 2,3,7,8-substituted dioxins and furans and four coplanar PCBs, PCB77, PCB81, PCB126, and PCB169. Alta Laboratory is certified for dioxin and furan analysis in various environmental matrices and is frequently checked with quality control samples. To

determine the reproducibility of the GC/MS assay in this study, three nonstudy volunteers each donated 160 ml of blood. These samples were split and sent to Alta Laboratory. The GC/MS assays were tested for sensitivity by measuring the reproducibility of the duplicate analyses by calculating the coefficient of variation for the three test subjects with split samples. The coefficient of variation ranged from 1.4 to 13.4%. This range of variability was judged acceptable.

#### *Survey Questionnaire*

Information on residence, job history, and diet, including consumption of local fish and game, were obtained from a questionnaire patterned after the Agency for Toxic Substances and Disease Registries community questionnaire (Millette, 2002). Weight and height were measured at the time the questionnaire was administered to provide an estimate of body mass index (BMI), or height in meters divided by weight in kilograms squared.

#### *Analysis*

We used the methods described by Hornung and Reed (1990) to infer average levels of dioxins, furans, and PCBs for group samples with levels below the limits of detection. We summed the 2,3,7,8-substituted hexa-chlorodibenzo-*p*-dioxins (CDD), penta-chlorodibenzofurans (CDF), hexa-CDF, and hepta-CDF isomers and the coplanar PCBs. We found little difference in the results when examining the sum or the individual congeners, so we present only the sums of these congeners. We compared lipid-adjusted serum levels of workers who had potential dioxin or furan exposure with the blood levels of workers with no workplace dioxin or furan exposure experience using Dunnett's *t*-test for dioxin and furan congeners, the PCBs, and the TCDD toxic equivalents for the dioxin and furan congeners (TEQ) (Van den Berg et al., 1998). TEQ estimates provide a summing of the theoretical TCDD-like toxicity across all of the 2,3,7,8-congeners detected among study subjects and thus provide a basis for comparing the different dioxin and furan profiles received from either TCP or PCP.

We examined workplace-estimated dioxin exposure for TCDD and H/OCDD used in previous Dow epidemiology studies (Ott et al., 1987). These quantitative estimates were based upon extensive monitoring, product impurities, description of job duties, and process changes. The values were constructed to assess a relative exposure level among exposed workers. The values of TCDD and H/OCDD represent cumulative exposure estimates, or days in an exposure job times the relative exposure estimate for that job. The TCDD exposure intensity scores were based on a scale from 0 to 4; those for H/OCDD were based on a scale from 0 to 2. A 1 unit increase in score was considered equivalent to a 10-fold increase in potential exposure intensity and a score of 0 was regarded as baseline for the study.

We used multiple linear regression to test the relationship between these exposure estimates and the measured serum dioxins, furans, and PCBs taking into account age, current BMI, change in weight in the last 6 months, smoking status (current smoker or current nonsmoker), other jobs with potential dioxin exposure (other jobs included professional applicator of herbicides, lawn care industry, sod production, farming, forestry brush control, highway or railway clearance, foundry, hazardous waste worker, electrical worker handling transformers or an autoworker), and fish and game consumption from local area consumed in the last 6 months (yes or no). We chose food consumption in the last 6 months to be consistent with another study using a similar questionnaire (Millette, 2002). We evaluated residual plots to assess the fit of regression models, determine the influence of outliers, and assure regression assumptions were not violated. Eigenvalues were used to evaluate collinearity between independent variables. The log-transformed congener levels did not improve fit for most of the regression equations, so we present only the untransformed congener levels, sums of congener levels, and sums of the PCB levels in the regression analyses. We used SAS for all analyses (SAS Institute Inc., 1999).

We estimated serum dioxin levels for 2,3,7,8-TCDD at the time of last workplace exposure using two methods. The first method assumes a one-compartment first-order kinetic model with a half-life of 9 or 7 years (Flesch-Janys et al., 1996). The second method uses a recently developed toxicokinetic model elimination of 2,3,7,8-TCDD (Aylward et al., 2005). This model takes into account the concentration dependent elimination of 2,3,7,8-TCDD to the liver as well as the lipid partitioning from circulation into the large intestines. For high exposures using this model, elimination would be nonlinear with a more rapid initial elimination. We assumed that 6 ppt of 2,3,7,8-TCDD was background (i.e., the mean of our comparison group) and did the calculations on all chlorophenol workers with serum 2,3,7,8-TCDD levels above 6.0 ppt.

## **Results**

The means and the ranges of the group characteristic and exposure potential are shown in Table 1 for unexposed workers, exposed workers, and the subgroups of exposed workers. The ages of the participants ranged from 47 to 92 years but the average ages were not significantly different among the unexposed (63.4 years) or exposed workers (62.7 years). The tradesworkers as an exposed group were the oldest (70.4 years) and the workers with a history of chloracne from PCP exposure the youngest (56.7 years). The body mass indices ranged from 20 to 50.9 kg/m<sup>2</sup> and exposed workers had higher BMIs than the comparison group (31.3 kg/m<sup>2</sup> for the exposed workers *versus* 28.8 kg/m<sup>2</sup> for

**Table 1.** Arithmetic means and ranges for selected characteristics of sampled groups.

	Chlorophenol exposed workers			All exposed workers mean (range)	Comparison group mean (range)
	Chloracne (TCP)* mean (range)	Chloracne (PCP)* mean (range)	Chlorophenol department, no chloracne mean (range)		
Age (years)	66.8 (48-83)	56.7 (47-92)	60.5 (47-84)	62.7 (47-92)	63.4 (47-86)
Body mass index (kg/m <sup>2</sup> )	28.8 (20.0-50.9)	32.8* (21.6-48.3)	31.9 (25.4-44.2)	31.4* (20.0-50.9)	28.8 (21.8-40.0)
Weight change in pounds last 6 months	-1.4 (-14.0 to 0.0)	-5.2 (-35.0 to 0.0)	-1.2 (0.0-10.0)	-1.8 (-35.0 to 15.0)	-1.0 (-20.0 to 0.0)
Local fish consumption last 6 months	29%	33%	47%	34%	22%
Local game consumption last 6 months	35%	28%	18%	26%	22%
Current smoker	6%	6%	12%	8%	6%
Other job with potential exposure	59%	61%	35%	48%	39%
2,3,7,8-TCDD exposure estimate <sup>a</sup>	95,572.5* (522.4-514792.6)	288.2* (10.7-1069.3)	1,971.7* (5.9-24640.7)	26,829.6* (0.0-514792.6)	0.0
Other dioxins exposure estimates <sup>a</sup>	1,953.8* (7.3-12007.2)	2531.2* (174.1-10636.6)	592.5* (1.3-2948.7)	1,433.0* (0.0-12007.2)	0.0
Number	17	18	17	62	36
			Tradesmen with plant-wide duties mean (range)		
			70.4 (56-84)		
			32.2 (24.4-49.8)		
			+2.8 (0.0-15.0)		

<sup>a</sup>Exposure estimates derived from industrial hygiene monitoring taken from Ott et al. (1987) study.

\*Significantly different than comparison group.

the comparison workers). Exposed workers lost more weight in the past 6 months on average than the comparison workers and were somewhat more likely to eat local game and fish and somewhat more likely to be smokers. As mentioned, a cumulative dose index was calculated in previous studies for each worker by summing daily weighted exposure intensity estimates across all jobs. The workers in the chloracne-TCP group had the highest mean TCDD exposure intensity score estimates, 95,572.5, and the workers in the chloracne-PCP group had the highest mean H/OCDD intensity score estimates, 2531.2.

Table 2 presents the unadjusted means for each of the congeners for the five groups of workers. The unexposed workers had a mean 2,3,7,8-TCDD level of 6.0 ppt and a mean TEQ level of 32.7 ppt. These values are within the range of background levels recently described for persons in the US of these ages (Patterson et al., 2004). The chloracne-TCP group had the highest mean 2,3,7,8-TCDD levels (30.5 ppt) and a range of 1.9 to 176.0 ppt. This group of workers also had the highest mean OctaCDD (3865.2 ppt), highest sum of the Hepta-CDFs (21.0 ppt) and the highest TEQ (86.8 ppt). The chloracne-PCP participants had the highest mean sum of Hexa-CDDs (249.8 ppt), and the highest 1,2,3,4,6,7,8-Hepta-CDD (312.5 ppt). 2,3,7,8-TCDD levels for this group (9.9 ppt) were slightly higher than the comparison group (6.0 ppt). Chlorophenol workers without a history of chloracne had relatively low 2,3,7,8-TCDD levels (7.9 ppt), and a TEQ of 40.3 ppt that was only slightly higher than that of the comparison group. Tradesworkers had relatively high 2,3,7,8-TCDD levels (20.7 ppt), 1,2,3,7,8-Penta-CDD levels (31.7 ppt), 1,2,3,4,6,7,8-Hepta-CDD levels (264.4 ppt), sum of the four PCB levels (120.9 ppt), and TEQ level (85.0 ppt). The comparison group had the lowest levels for all congeners with the exception of 2,3,7,8-TCDF, and OCDF, but some of these measures were below the detection limits. Since many of our measurements for 2,3,7,8-TCDF and OCDF were below detection limits, we did not include these congeners in further analysis.

The multiple regression analyses for each of the congeners appear in Table 3. Age, BMI, other non-Dow job with potential exposure, working as a tradesworker, and the TCDD exposure estimate collectively were good descriptors of intersubject variation for 2,3,7,8-TCDD. Variation in these factors described 78% of the total variance among subjects. Good descriptors of intersubject variation for 1,2,3,7,8-Penta-CDD include BMI, working as a tradesworker, the 2,3,7,8-TCDD exposure estimate, and the H/OCDD exposure estimate. Variation in these factors explained 57% of the total variance. Local game consumption, BMI, working as a tradesworker, and the H/OCDD exposure estimate were good descriptors for the sum of the Hexa-CDDs. Variation in these factors produced 72% of the total variance among subjects. With the exception of local game

**Table 2.** Arithmetic mean and range of lipid-adjusted serum dioxin level by exposure group in parts per trillion (ppt).

Congeners in ppt	Chlorophenol exposed workers				All exposed workers mean (range)	Comparison group mean (range)
	Chloracene (TCP) mean (range)	Chloracene (PCP) mean (range)	Chlorophenol department, no chloracene mean (range)	Tradesmen with plant-wide duties mean (range)		
2,3,7,8 TCDD	30.5* (1.9-176.0)	9.9 (1.5-28.7)	7.9 (2.7-34.4)	20.7 (3.0-59.2)	16.7* (1.5-176.0)	6.0 (1.1-23.1)
1,2,3,7,8-PentaCDD	23.7* (3.5-72.2)	22.0* (6.6-76.4)	13.0 (6.5-23.8)	31.7* (6.1-74.8)	21.6* (3.5-76.4)	10.9 (3.7-35.1)
Sum of 2,3,7,8-substituted Hexa-CDDs	229.3* (30.9-1219.0)	249.9* (79.9-990.2)	117.0 (57.1-167.5)	192.8 (22.5-354.0)	198.6* (22.5-1219.0)	87.0 (32.3-206.3)
1,2,3,4,6,7,8 Hepta-CDD	196.8 (27.9-1410.0)	312.5* (40.6-1750.0)	106.0 (38.4-347.0)	264.4 (20.3-1220.0)	216.4* (20.3-1750.0)	67.5 (23.9-169.0)
Octa-CDD	3865.2 (194.0-45100.0)	3460.7 (555.0-13200.0)	1205.2 (232.0-4420.0)	2502.6 (104.0-10800.0)	2798.7* (104.0-45100.0)	483.2 (133.0-2100.0)
2,3,7,8-TCDF	0.1 (0.0-1.3)	0.3 (0.0-1.9)	0.3 (0.0-2.1)	0.4 (0.0-2.0)	0.3 (0.0-2.1)	0.4 (0-2.9)
Sum of 2,3,7,8-substituted PentaCDFs	10.5 (3.9-17.2)	10.9 (4.5-16.8)	9.5 (4.7-17.3)	15.7* (5.1-24.7)	11.2 (3.9-24.7)	9.5 (2.9-28.2)
Sum of 2,3,7,8-substituted Hexa-CDFs	20.0 (6.2-57.3)	24.3* (5.2-59.4)	17.7 (8.4-30.6)	27.5* (4.0-48.1)	21.8* (4.0-59.4)	16.4 (3.6-28.8)
Sum of 2,3,7,8-substituted Hepta-CDFs	21.0* (5.1-90.2)	17.0 (7.1-41.0)	12.9 (4.9-29.4)	14.5 (4.4-29.6)	16.6* (4.4-90.2)	11.3 (3.9-24.5)
OctaCDF	0.1 (0.0-1.4)	0.1 (0.0-1.0)	1.1 (0.0-10.5)	0.4 (0.0-3.2)	0.4 (0.0-10.5)	3.4 (0.0-77.7)
Sum of four PCBs	77.4 (16.8-231.2)	81.4 (21.6-307.0)	73.2 (33.3-143.6)	120.9* (48.4-203.3)	84.4 (16.8-307.0)	74.6 (24.2-226.1)
TEQ-WHO for PCDD/F	86.8* (11.4-273.0)	68.4* (23.2-233.3)	40.3 (20.8-61.3)	85.0* (16.0-193.0)	68.4* (11.4-273.0)	32.7 (10.7-96.7)
Number	17	18	17	10	62	36

\*Significantly different than comparison group.

consumption, the same factors were good descriptors for the sum of the Hepta-CDDs. Variation in these factors produced 45% of the total variance. The only good descriptor of the OctaCDD was the H/OCDD exposure estimate. Variation in these factors produced 48% of the variance. Age, recent weight change, and being a tradesworkers, were important descriptors of the sum of the Penta-CDFs with variation in these factors producing 29% of the variance. The sum of the Hexa-CDFs was related to BMI, recent weight change, being a tradesworker, and the H/OCDD exposure estimate. Variation in these factors described 41% of the total variance. The Hepta-CDFs were only related to the H/OCDD exposure estimate and this equation has an  $R^2$  of 0.25 ( $P=0.0077$ ). BMI was the only good descriptor of the Octa-CDF. Good descriptors of intersubject variation for the sum of the four PCBs were age, local fish consumption, and working as a tradesworker. Variation in these factors described 33% of the variance among subjects. The TEQ was related to age, BMI, recent weight change, working as a tradesworker, the TCDD exposure estimate, and the H/OCDD exposure estimate. Neither smoking nor histories of chloracene were significant predictors of any congener or congener sums when considered with all other factors.

In all, 30 of the 52 chlorophenol workers had 2,3,7,8-TCDD levels, which were higher than background found in this study of 6.0 ppt. We estimate that the mean level of 2,3,7,8-TCDD present in the serum of these 30 workers on the date workplace exposure terminated was 267 ppt (ranging from 8 to 1184 ppt) assuming a 9-year half-life, 582 ppt (ranging from 10 to 2641 ppt) assuming a 7-year half-life, and 1928 ppt (ranging from 22 to 17,847) when the toxicokinetic model proposed by Aylward et al. (2005) is used.

## Discussion

This study has some workers with the longest interval between last occupational exposure to dioxins and furans and an analysis of current serum levels as shown in Table 4 (Wolfe et al., 1988; Andrews et al., 1989; Needham et al., 1999). Dioxin and furan levels remain above background levels many decades after exposure cessation. The results of our study are consistent with other studies of persons with high environmental or occupational exposure especially considering our long relative interval between last exposure and blood draw. The back-extrapolated levels of serum dioxins to last date of workplace exposure indicate that workers in this study have levels that were in the range of other chlorophenol workers (Beck et al., 1989b; Sweeney et al., 1990; Ott et al., 1993).

Chlorophenol workers in the current study have higher serum dioxin and furan levels than the comparison group. We are also able to distinguish the TCP exposures from the PCP

**Table 3.** Linear multiple regression unstandardized parameter estimates for selected predictors of dioxins, furans, and sum of four PCBs.

	2,3,7,8 TCDD estimate (SE)	1,2,3,7,8-Penta-CDD estimate (SE)	Sum of Hexa-CDDs estimate (SE)	1,2,3,4,6,7,8 Hepta-CDD estimate (SE)	Octa-CDD Estimate (SE)	Sum of Penta-CDFs estimate (SE)	Sum of Hexa-CDFs estimate (SE)	Sum of Hepta-CDFs estimate (SE)	OCDF estimate (SE)	Sum of 4 PCBs estimate (SE)	TEQ-WHO estimate (SE)
Intercept	-31.19* (10.30)	-24.27* (10.34)	-161.0 (94.36)	-312.33 (209.38)	-2039.22 (3737.38)	-4.68 (4.52)	-7.04 (8.94)	10.11 (10.39)	19.72* (7.98)	-21.48 (42.52)	-77.93* (28.97)
Age	0.22* (0.11)	0.21 (0.11)	1.35 (1.00)	0.28 (2.22)	-2.09 (39.60)	0.14* (0.05)	0.09 (0.09)	-0.05 (0.11)	-0.15 (0.08)	1.42* (0.45)	0.64* (0.31)
BMI	0.73* (0.21)	0.70* (0.21)	4.98* (1.90)	11.37* (4.21)	65.00 (75.15)	0.17 (0.09)	0.56* (0.18)	0.14 (0.21)	-0.32* (0.16)	0.08 (0.85)	2.19* (0.58)
Recent weight loss/gain	0.26 (0.18)	0.32 (0.19)	2.74 (1.69)	3.05 (3.75)	107.14 (66.88)	0.20* (0.08)	0.36* (0.16)	-0.10 (0.19)	-0.07 (0.14)	0.49 (0.76)	1.03* (0.52)
Local fish consumption	-1.11 (2.50)	-1.16 (2.51)	3.34 (22.91)	15.47 (50.83)	808.37 (907.31)	0.93 (1.10)	0.53 (2.17)	-2.26 (2.52)	1.50 (1.94)	44.04* (10.32)	-1.21 (7.03)
Local game consumption	-1.19 (2.82)	3.16 (2.83)	53.71* (25.79)	33.80 (57.22)	1610.54 (1021.38)	0.15 (1.23)	2.34 (2.44)	-0.14 (2.84)	2.46 (2.18)	-10.65 (11.62)	8.18 (7.92)
Smoker	0.80 (4.17)	-1.28 (4.18)	-12.64 (38.15)	-17.65 (84.65)	587.04 (1151.03)	-1.18 (1.83)	-0.47 (3.61)	7.44 (4.20)	-2.31 (3.23)	-25.89 (17.19)	-2.32 (11.71)
Other job with potential exposure	5.35* (2.37)	1.49 (2.38)	-2.95 (21.72)	28.28 (48.21)	-138.70 (860.48)	-0.25 (1.04)	1.52 (2.06)	2.58 (2.39)	2.36 (1.84)	-10.66 (9.79)	6.89 (6.67)
Tradesworker	12.68* (3.83)	18.81* (3.85)	96.46* (35.13)	182.88* (77.96)	2396.00 (1391.66)	5.59* (1.68)	10.62* (3.33)	2.44 (3.87)	-0.17 (2.97)	40.01* (15.83)	47.06* (10.79)
2,3,7,8-TCDD exposure estimate <sup>a</sup>	2.81* (0.20)	0.63* (0.20)	1.71 (1.81)	2.69 (40.31)	238.00 (720)	-0.007 (0.008)	0.12 (0.17)	-2.25 (2.00)	0.25 (1.54)	-9.67 (8.19)	3.57* (0.55)
Hx/Hp/OCDD exposure estimate <sup>a</sup>	2.85 (5.68)	338.00* (57.03)	597.70* (52.0)	6633* (1155)	14533.5* (2061.7)	1.10 (2.49)	194* (49.3)	130* (57.35)	0.58 (4.40)	-143 (235)	107.20* (16.00)
Chloracene	-1.09 (2.94)	-0.45 (2.95)	-3.68 (27.00)	6.02 (59.92)	-672.33 (1069.61)	0.84 (1.29)	0.06 (2.55)	5.34 (2.97)	-2.98 (2.28)	12.82 (12.17)	-1.44 (8.29)
R <sup>2</sup>	0.78	0.57	0.72	0.45	0.48	0.29	0.41	0.25	0.13	0.33	0.66
P-value of regression model	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0013	<0.0001	0.0077	0.3344	0.0002	<0.0001

\*P-value < 0.05.

<sup>a</sup>Cumulative exposure estimates used in Bodner et al.(2003) study multiplied by 10,000, see text.

**Table 4.** Levels of 2,3,7,8-TCDD and estimated time from exposure to blood draw in studies of highly exposed persons.

Population	Number of serums analyzed	Estimated time between last potential exposure and blood draw	Range of 2,3,7,8-TCDD serum levels in ppt <sup>a</sup>	Reference
Seveso, Italy	424	1	2–56,000	Needham et al. (1999)
Hamburg, Germany (Boehringer-Ingelheim)	48	5–37	15–300	Flesch-Janys et al. (1996)
Missouri Horse Arena	16	14	5–577 <sup>b</sup>	Andrews et al. (1989)
NIOSH Dioxin Registry	136	15–37	2–3,389	Sweeney et al. (1990)
Ranch Hand	147	16–25	<5–313	Wolfe et al. (1988)
Austria	9	17	98–659	Neuberger et al. (1991)
Netherlands	47	18–43	1.9–194	Heederik et al. (1998)
Ludwigshafen, Germany (B.A.S.F)	138	20–36	<1–553	Ott et al. (1993)
Midland, U.S.A	52	24–63	2–176	Present study

<sup>a</sup>Serum lipid adjusted.<sup>b</sup>Serum whole weight with no lipid adjustment.

exposures when we took into account potential confounding factors in the regression analyses. As would be expected, TCP exposure was related to high serum 2,3,7,8-TCDD, and 1,2,3,7,8-Penta-CDD levels. Similarly, PCP exposure was related to high serum 1,2,3,7,8-Penta-CDD, Hexa-CDDs, Hepta-CDDs, Octa-CDD, Hexa-CDFs, and Hepta-CDFs levels. These findings are consistent with other studies of TCP and PCP workers (Ott et al., 1993; Schecter et al., 1996; Heederik et al., 1998; Coenraads et al., 1999; Ryan and Schecter, 2000).

As mentioned earlier, the chlorophenol workers from the Midland plant have been included in the NIOSH Dioxin Registry (Steenland et al., 1999; Piacitelli et al., 2000). Recent analyses of this Registry have omitted workers with PCP and TCP exposure to “avoid possible confounding of 2,3,7,8-TCDD effects with PCP” (Steenland et al., 1999). Our evaluation of serum dioxin levels in this study indicated that PCP and TCP workers have similar TEQs based on congener potencies to 2,3,7,8-TCDD. If the TEQ basis for evaluating dioxin carcinogenicity is valid, our PCP workers have exposure levels similar to our TCP workers.

Chloracne has been shown to result after high dioxin exposure (Beck et al., 1989a; Mocarelli et al., 1991; Ott et al., 1993). We found that a history of chloracne was not useful for estimating serum dioxin levels when exposure estimates for the dioxins and furans are taken into account. However, exposed workers with a history of chloracne did have higher serum levels of dioxin and furans on average than did workers without a history of chloracne. Workers with a history of chloracne from mostly TCP exposures have high serum 2,3,7,8-TCDD and 1,2,3,7,8-Penta-CDD levels and workers with a history of chloracne mostly from PCP exposure had high serum levels from the higher chlorinated dioxins and furans relative to chlorophenol workers who did not develop chloracne (Beck et al., 1989b). Thus, a history of chloracne is a useful predictor of high dioxin or furan exposures. However, we observed several chlorophenol

workers who did not develop chloracne who had higher serum dioxin and/or furan levels than workers who developed chloracne. Relying only on chloracne as a marker of high exposure in a study may exclude workers with significantly higher exposures (Mocarelli et al., 1991). Actual measurement of dioxins and furans in serum still remain the most sensitive marker of high exposure.

We did observe some participants with high serum dioxin and furan levels who worked in nonchlorophenol departments. These men were largely tradesworkers who had the potential to work in the chlorophenol departments occasionally. These workers had relatively high dioxin serum levels indicating they may have received considerable past exposures and their congener profiles indicated that may have received both TCP and PCP exposures. This finding has been observed in other studies where exposures to dioxins often include some workers not formally assigned to the departments (Neuberger et al., 1991; Coenraads et al., 1999; Ryan and Schecter, 2000). These tradesworkers had relatively high serum levels of 2,3,7,8-TCDD and TEQ levels ranging as high as 59 and 193 ppt, respectively. We also observed that other jobs outside the plant contributed to higher serum dioxin levels. Significant dioxin exposures may occur among workers who have not been formally assigned to chlorophenol operations. Therefore, comparison groups for studies of dioxin health effects should be carefully chosen to assure minimal occupational dioxin exposure had occurred. Serum evaluations of comparison groups should be considered when there is a concern about the possibility of other occupational exposures.

We found two associations of diet with dioxins or PCBs. Local game consumption was associated with the sum of Hexa-CDDs, and local fish consumption was associated with PCBs. These two associations could be chance findings since we examined many congeners. The association with local game consumption and the Hexa-CDDs may well be a chance finding since this congener group has not been found

at elevated levels in local game or fish. However, the association with local fish consumption and PCBs could be real since other studies have observed an association between fish consumption and serum PCBs levels, (Schwartz et al., 1983) and because local fish do have measurable PCB levels which warranted a State advisory to limit consumption.

We also found that age and BMI were important predictors of serum dioxin levels. In the case of 2,3,7,8-TCDD, there was an increase of 2.2 ppt for every 10 years of age and an increase of 7.3 ppt for an increase of 10 kg/m<sup>2</sup> in BMI. Ranges of serum dioxin levels have been presented by age groups with older persons exhibiting much larger ranges of levels than younger persons (Wittsiepe et al., 2000; Harden et al., 2004; Patterson et al., 2004). Given the strength of the BMI effect on serum dioxin levels in our study, BMI should also be considered with age when comparing workers in occupational settings or persons in community exposure assessments.

In conclusion, we found higher than background serum dioxin and furan levels among former TCP and PCP workers. TCP workers had different serum profiles of dioxins and furans than did the PCP workers. We also found high dioxin, furan, and PCB levels among some workers outside the chlorophenol departments indicating that the selection of comparison groups and individuals for exposure assessment or health studies must be performed carefully. The exposure estimates for TCDD and the higher chlorinated dioxins developed in previous studies did predict current serum dioxin levels, thus providing some validation for exposure estimates used in prior studies.

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