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【论著】

Serum Dioxin and Furan Levels among Trichlorophenol and Pentachlorophenol Workers with Chloracne

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Abstract：[Objective] To determine if serum dioxin levels are higher among trichlorophenol (TCP) or pentachlorophenol (PCP) workers with and without chloracne and to examine characteristics of workers with chloracne. [Methods] We collected blood from 26 PCP workers, 12 TCP workers, and 36 workers with no PCP or TCP exposure and measured dioxin levels. Chloracne was determined by examining plant medical records. [Results] We observed higher serum levels of the toxic equivalency (according to the World Health Organization) based on 2378-TCDD for 12378-PeCDD, 123678-H_6CDD, 123789-H_6CDD, and 123678-H_6CDF among the PCP workers with chloracne compared to the PCP workers with no chloracne. There were no significant differences in serum levels for the TCP workers by chloracne status, although the 2378-TCDD levels were higher among the participants who previously had chloracne (43.6 ppt vs. 16.4 ppt). The putative risk factors for chloracne of younger age at first exposure and more years since first exposure were observed in the TCP workers but not the PCP workers. Chloracne in the PCP workers was associated with longer duration of exposure prior to the diagnosis. [Conclusion] Chloracne is a good indicator for high dioxin exposures, and TCP and PCP workers have distinctively different serum profiles of dioxin congeners.

Key Words：chloracne; pentachlorophenol; trichlorophenol; dioxin; serum

High exposure to chlorinated dibenzo-p-dioxins has been associated with the acute skin condition, chloracne[1]. Several studies have determined that while trichlorophenol (TCP) workers with chloracne have high serum levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin(2378-TCDD), some trichlorophenol workers without chloracne also have high 2378-TCDD levels[2,3]. Similar findings have been observed among pentachlorophenol(PCP)workers with chloracne but with higher chlorinated dioxins predominating[4]. A report on subjects from Seveso, Italy, the contaminated site from a 1976 trichlorophenol industrial accident, compared serum 2378-TCDD levels between chloracne subjects and control subjects[5]. The chloracne subjects who currently had higher 2378-TCDD levels were younger at the time of the accident and were more likely to have light color hair than subjects without chloracne.

The incidence of chloracne among the more than 2000 chlorophenol workers in Midland, Michigan has been described[6,7]. Unlike other study groups, dioxins exposure in this cohort was not the result of an accident or explosion. Investigators concluded that

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younger age at first exposure, duration of exposure and intensity of exposure to trichlorophenol or pentachlorophenol were significant risk factors for chloracne[6]. We reported the serum dioxin levels in a small sub-group of these chlorophenol workers who were exposed to TCP and PCP[4]. The availability of serum data permitted additional analyses to investigate serum dioxin profiles and other factors as predictors of chloracne.

1 Methods

1.1 Blood Collection

The design of this study has been previously described[4]. Briefly, we collected serum from a random sample of current and past employees of The Dow Chemical Company who worked in the production of PCP(1937-1980) or TCP (1942-1979). We oversampled workers with a previous diagnosis of chloracne. The comparison participants were employed during the same time period and had no documentation of working in any chlorophenol department. We collected 80 milliliters blood at the company medical facility. Whole blood was centrifuged after being allowed to clot and the serum was transferred to rinsed glass vials with Teflon seals and stored at –20 ℃ until analysis.

The samples were shipped frozen to Alta Analytical Laboratory, El Dorado Hills, California. Analytical procedure determined the levels for 2,3,7,8-substituted dioxins(2378-TCDD, 12378-P_5CDD, 123478-H_6CDD, 123678-H_6CDD,123789-H_6CDD, 1234678-H_7CDD, OCDD), furans (2378-TCDF, 12378-P_5CDF, 23478- P_5CDF, 123478-H_6CDF, 123678-H_6CDF, 234678-H_6CDF, 123789-H_6CDF, 1234678-H_7CDF, 1234789-H_7CDF, OCDF), and 4 coplanar PCBs(PCB77, PCB81, PCB126, and PCB169). We also calculated the total toxic equivalency based on 2378-TCDD according to the World Health Organization (WHO) for the dioxins and furans[8]. The laboratory used high resolution gas chromatography/mass spectrometry to determine the levels for 2,3,7,8-substituted chlorinated dioxins and furans following the procedures described in EPA Method 8290 and Method 1668 for PCB measurement[9]. Lipid determination followed the procedure used by CDC[10]. We used the methods described by Hornung and Reed to infer average levels of dioxins when the levels were below the limit of detection[11]. All results were lipid-adjusted.

1.2 Data Analysis

We calculated mean serum dioxin, furan and PCB levels for each group of workers. Previous studies[12] furnished dates of first exposure, intensities of dioxin exposure, and chloracne diagnosis dates. Each group of PCP and TCP exposed workers was compared to those with a diagnosis of chloracne and to the comparison group using a Student's t-test in SAS[13]. We also calculated the means for 2378-TCDD and 123678-H_6CDD by different risk factors as presented in previous papers. We selected 123678-H_6CDD for the PCP workers because a recent profile of congeners among this group demonstrated that 123678-H_6CDD contributed the greatest percentage to the toxic equivalency according WHO(TEQ-WHO) [4].

1.3 Estimating Exposure

We developed exposure estimates for all survey workers back to their date of first workplace exposure. We describe these estimates elsewhere[14]. Briefly, we used a qualitative exposure characterization from an earlier study to group all TCP and PCP exposed jobs into similar exposed groups. This qualitative exposure assessment was based on detailed work history, industrial hygiene monitoring, and the presence of chloracne cases among groups of workers. We used a simple one-compartment, first-order pharmacokinetic model and assumed elimination rates as previously estimated from a worker population[15]. We integrated the pharmacokinetic model with the work history information detailing dates of assignment to jobs and estimated the average dose for each congener associated with jobs in each exposure category in the presence of background exposures based on the residual serum concentration of each congener in the sampled individuals. Since dioxins remain in the body for long periods, we use the area under the curve for each dioxin considering both intake and elimination to represent the cumulative workplace dioxin exposure above background.

2 Results

2.1 Serum Dioxin Levels

Among the 35 men with a history of chloracne, 17 worked solely in the PCP manufacturing area and 9 had job assignments exclusively in the TCP area. The seven remaining workers worked in both manufacturing areas. Among the 17 chlorophenol workers with no history of chloracne, 9 worked in PCP and 3 worked in TCP. These individuals were hired between 46 and 60 years since the time of serum collection. The mean serum levels of 21 dioxin congeners were compared between participants who worked in PCP manufacturing with a history of chloracne and with no chloracne(Table 1). The TEQ and most individual dioxin levels were significantly higher among the chloracne men than the comparison group. Two of the furans were also significantly higher. When comparing the exposed men with and without chloracne, the significantly different means were limited to the TEQ, 2378-TCDD, 12378-P_5CDD, 123678-H_6CDD, 123789-H_6CDD, and 123678-H6CDF. We plotted the serum levels for 123678-H_6CDD for the participants with or without a history of chloracne (Figure 1). The serum levels for this congener are higher for most of the workers for chloracne compared to workers without.

Table 1 Arithmetic mean lipid-adjusted serum dioxin levels by exposure group

Congeners	PCP Workers(ppt)		TCP Workers(ppt)		Comparison group(ppt)
	Chloracne *n*=17	No chloracne *n*=9	Chloracne *n*=9	No chloracne *n*=3	No chloracne *n*=36
TEQ-WHO for PCDD/F	65.9*	34.8$^+$	81.1*	54.0	32.7
2378-TCDD	9.7	4.2$^+$	43.6*	16.4	6.0
12378-P_5CDD	21.4*	11.6$^+$	19.1*	16.3	10.9
123478-H_6CDD	17.2*	10.2	9.1	10.4	7.5
123678-H_6CDD	190.2*	92.6$^+$	96.5	110.5	71.8
123789-H_6CDD	29.9*	12.0$^+$	9.4	10.3	8.0
1234678-H_7CDD	294.6*	121.3	53.0	88.4	67.5
OCDD	3 373.7*	1 653.3$^+$	543.8	789.0	483.2
2378-TCDF	0.5	0.5	0.3	0.4	0.6
12378- P_5CDF	0.5	0.4	0.4	0.5	0.6
23478- P_5CDF	10.6	8.5	9.5	10.5	9.2
123478- H_6CDF	11.2	8.2	6.9	8.2	7.7
123678- H_6CDF	10.5*	6.7$^+$	6.5	8.0	7.3
234678- H_6CDF	2.3	1.6	0.7	2.3	1.6
123789- H_6CDF	0.4	0.4	0.4	0.6	0.4
1234678-H_7CDF	17.0*	13.9	18.0	12.2	11.3
1234789- H_7CDF	0.5	0.5	0.5	0.4	0.5
OCDF	1.5	2.7	1.5	1.6	4.5
Sum of four PCBs	80.8	60.2	70.6	91.6	74.9

[Note]*: Different than comparison at $P < 0.05$; $^+$: Different than chloracne group at $P < 0.05$.

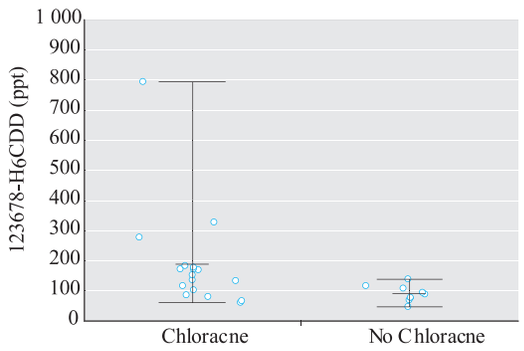

Figure 1　Serum levels of 123678-H_6CDD among PCP exposed workers

Only the TEQ, 2378-TCDD and 12378-P_5CDD were significantly higher in the chloracne group working with TCP compared to the reference group. There were no differences with the remaining dioxins and furans. The workers with chloracne had higher levels of these three dioxins measures than TCP workers without chloracne. However, these levels were not significantly different. For example, Levels of 2378-TCDD among the chloracne group (43.6 ppt) were higher than among workers with no history of chloracne (16.4 ppt), but did not attain statistical significance.

2.2　Characteristics of workers with chloracne

Table 2 shows the mean serum levels and the standard deviations for 2378-TCDD and 123678-H_6CDD for both chloracne and non-chloracne groups. The mean serum levels of 2378-TCDD were higher among individuals in TCP chloracne group who were first exposed at a young age, and exposed longer ago. Workers with no chloracne did not demonstrate these findings. Serum levels were highest among the workers with more than 60 months exposure prior to their chloracne diagnosis. Most of the TCP chloracne workers had worked in a high intensity TCDD exposure job prior to chloracne diagnosis, and they had the highest mean 2378-TCDD serum levels.

Conversely, the PCP chloracne group was not characterized by higher 123678-H_6CDD levels among those exposed at a younger age, nor among those with more years since first exposure. Serum 123678-H_6CDD levels seemed to follow a dose-response with increasing levels and increasing duration of exposure before the chloracne diagnosis. All 16 men with a diagnosis date had worked in a job with potential for high H/OCDD exposure and low TCDD intensity.

Table 2　Mean serum level and standard deviation (SD) in parts per trillion lipid-adjusted for suspected risk factors among subjects with and without chloracne

Risk factors	2378-TCDD(ppt-lipid adjusted) in TCP workers						123678-H_6CDD(ppt-lipid adjusted) in PCP workers					
	Chloracne			No Chloracne			Chloracne			No Chloracne		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Age at first exposure, years												
<25	4	58.3	81.6	1	11.3		14	138.5	58.4	8	94.6	28.5
≥25	5	31.9	26.3	2	19.0	21.8	3	431.7	324.2	1	76.8	
Years since first exposure												
<40	3	32.8	38.8	2	22.9		14	189.1	183.3	7	97.4	29.4
≥ 40	6	49.1	64.4	1	3.6		3	195.6	122.4	2	75.9	5.9
Duration of exposure, months*												
<6	2	15.4	6.4				9	133.1	70.0			
6-11	3	37.6	37.2				2	153.5	26.2			
12-59	2	11.2	9.7				5	280.2	289.6			
≥60	2	113.4	88.5				1	328.0				
Highest intensity of 2378-TCDD exposure*												
0	0						1	172.0				
1	1	10.9					15	196.2	181.4			
2	2	19.0	1.3				0					
3	0						0					
4	6	57.3	64.6				0					
Highest intensity of H/OCDD exposure*												
0	1	10.9					0					
1	0						0					
2	8	47.7	57.4				16	194.7	175.4			

[Note] Diagnosis date was missing for 2 participants；0's in the *n* column indicates there are no subjects in this category；*: Exposure and intensity that occurred before the chloracne diagnosis.

3　Discussion

This study provides a unique perspective on workers with chloracne. Unlike at Seveso, many of the individuals were exposed to dioxins other than 2378-TCDD. Since the exposures were occupationally related, it is unclear if the chloracne was triggered by a single high exposure or cumulative exposure over time. Few studies have documented chloracne in workers exposed to PCP. The current study shows that the particular congeners associated with current dioxin levels are dependent upon whether the primary exposure was to TCP or PCP. We found that the H_6CDD's were consistently higher among the men with chloracne and PCP exposure while 2378-TCDD levels were higher among workers with TCP exposures.

As an occupational cohort, this study was limited to individuals exposed as adults. The serum levels among the TCP chloracne

group suggests that exposure at age less than 25 is a risk factor for chloracne, which is consistent with the risk demonstrated in Seveso for younger children. However, this relationship was not borne out among the PCP chloracne group. It may be that the higher chlorinated dioxins act differently in the etiology of chloracne than 2378-TCDD. The small sample size, however, precluded further testing of this hypothesis. We are currently collecting serum on additional workers that may facilitate testing these observations.

A potential weakness of any study of persons exhibiting chloracne is that the date of diagnosis may occur days or months after the onset of symptoms. In our study, only 50% (n=26) of the workers with medically diagnosed chloracne were able to identify themselves as having or not having a medical history of chloracne. Eleven subjects with medically diagnosed chloracne had reported the onset of symptoms within one year of the diagnosis date whereas three respondents reported symptoms beginning as many as six years before the diagnosis date.

We compared the current serum dioxins levels of employees who had PCP or TCP exposure as much as 60 years ago. Current 2378-TCDD levels remain high among men with a history of chloracne and TCP exposures compared to participants with no chloracne from these exposures. The congener 123678-H_6CDD is higher among the men with PCP work history and past diagnosis of chloracne and appears to serve well as a marker of dioxin exposure from PCP.

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患有氯痤疮的三氯苯酚和五氯苯酚接触工人血清二恶英和呋喃的水平

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摘要：[目的]调查患有或不患有氯痤疮的三氯苯酚（trichlorophenol，TCP）或五氯苯酚（pentachlorophenol，PCP）接触工人血清的二恶英水平，并观察患氯痤疮工人的特征。[方法]收集26名PCP工人、12名TCP工人和36名没有PCP和TCP暴露史工人的血样，并测定二恶英含量。氯痤疮的确定根据工厂医疗记录。[结果]PCP工人中，患氯痤疮与未患氯痤疮的工人相比具有更高毒性当量（根据世界卫生组织）的2378-TCDD，12378-PeCDD，123678-H_6CDD，123789-H_6CDD 和123678-H_6CDF水平。而在TCP工人中，虽然曾患有氯痤疮的工人血清中2378-TCDD水平较高，但与未患有氯痤疮者的血清水平上并无明显差异。氯痤疮的公认危险因素有首次暴露年龄较小和距第一次暴露的时间较长等，但仅在接触TPC工人中得到证实。PCP工人患氯痤疮和诊断前较长的接触时间相关。[结论]氯痤疮是二恶英高暴露的良好指标。TCP和PCP接触工人的血清二恶英同系物具有明显不同的特点。

关键词：氯痤疮；五氯苯酚；三氯苯酚；二恶英；血清

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