SERUM DIOXIN LEVELS AND DEATH RATES AMONG TRICHLOROPHENOL AND PENTACHLOROPHOL WORKERS WITH CHLORACNE

James J. Collins[1], Kenneth Bodner[1], Lesa Aylward[2], Michael Wilken[1]

[1] The Dow Chemical Company, Midland, Michigan, USA; [2]Summit Toxicology, LLP, Falls Church, VA, USA

Introduction

Chloracne is an acute dermatologic condition first described over a century ago. The condition is predominantly facial, although the arms, chest, back, abdomen, genitalia and thighs may also be affected. Chloracne was initially thought to be caused by occupational exposure to chlorine, but later was recognized to be caused by exposure to a variety of cyclic organochlorine compounds including chloronaphthalenes, chlorobiphenyls, chloroazobenzenes, chloroazooxybenzenes, chlorodibenzodioxins and chlorodibenzofurans. Much of the research has focused on exposures to 2,3,7,8 tetrachlorodibenzo-*p*-dioxin (TCDD) which is though to be the most potent of the chloracnegens, although several studies also report on chloracne among workers exposed to pentachlorophenol (PCP).

The duration of symptoms for chloracne are thought to be related to the level of the dioxin or furan exposure.[1] It usually appears within a couple months after high exposure and disappears in most cases within a year but can persist for 30 years.[2] There have been estimates of the level of TCDD exposure required to result in chloracne. Severe cases of chloracne appeared at 12,000 ppt of TCDD in lipid-adjusted serum, but milder cases occurred at 650 to 1200 ppt.[1-3] While chloracne has been reported among PCP workers, we could find no estimates about what levels of the higher chlorinated dioxins in PCP would cause chloracne. It is also speculated that chloracne may occur at lower serum levels if the route of exposure is skin absorption.[4] Not all persons with high exposure to dioxins develop chloracne, but all persons with chloracne have high dioxin body levels.[2,5] While the most well known outbreaks of chloracne occurred after a single high exposure, chloracne also likely occurs after continual lower exposures allowing the dioxins to accumulate in the body before reaching a level that would cause chloracne.[6]

It has been proposed that a chloracne episode is a sentinel event with no health effects occurring in its absence.[7] However, others have proposed that chloracne occurs at exposure levels well above those necessary to cause health effects such as cancer.[8] We examine dioxin levels and cancer levels among chloracne cases diagnosed in workers with either trichlorophenol (TCP), PCP exposures, or both in Midland, Michigan to determine if cancer levels are related to dioxin exposures. We also compare workers with chloracne to chlorophenol workers at the same site who were not diagnosed with chloracne.

Table 1. Current levels of selected dioxin congeners for workers with only workplace pentachlorophenol or trichlorophenol exposure by chloracne diagnosis

2,3,7,8 Substituted Dioxins	All Chlorophenol		Only PCP Exposure		Only TCP Exposure	
	Chloracne (n=70) Mean (Range)	No Chloracne (n=295) Mean (Range)	Chloracne (n=31) Mean (Range)	No Chloracne (n=54) Mean (Range)	Chloracne (n=23) Mean (Range)	No Chloracne (n=214) Mean (Range)
TCDD	23 (1-176)	12 (0-145)	8 (1-29)	8 (0-38)	51 (2-176)	12 (0-105)
Sum of the 3 HxCDDs	197 (25-1,080)	83 (8-647)	292 (80-1,005)	127 (29-779)	113 (32-307)	97 (9-307)
HpDD	205 (10-1,1750)	84 (5-2,630)	285 (15-1,750)	140 (9-2,630)	57 (10-133)	70 (5-375)
OCDD	3,119 (67-45,100)	842 (45-31,100)	4,126 (151-15,500)	1,715 (70-31,100)	623 (67-1,550)	615 (45-3,490)
TEQ	82 (12-274)	49 (3-328)	75 (24-235)	47 (10-194)	90 (18-247)	48 (3-223)

Materials and Methods

Production of trichlorophenol (TCP) occurred from 1942 to 1979 and pentachlorophenol (PCP) from 1937 to 1980 at the Midland, Michigan site. Workers could have received exposure from TCP, PCP or both. Among the 2,192 chlorophenol workers, 1,615 had TCP exposure, 773 had PCP exposure, and 196 chlorophenol workers had exposure to both TCP and PCP. There were also 246 cases of chloracne that were diagnosed among these

chlorophenol workers (11%).[6,9] The diagnosis of the chloracne cases was based on a joint assessment between NIOSH and company researchers. Among the 246 cases of chloracne, 93 developed chloracne from exposure to TCP, 110 developed chloracne from PCP, and 43 workers developed chloracne from either TCP or PCP.

For the mortality analysis, person-years at risk were accumulated from January 1, 1940, from the date at which chloracne diagnosed, or the first exposure to TCP or PCP whichever is later. Vital status follow-up has been completed through 2003. Death certificates were obtained from the states in which the employees died. Standardized mortality ratios (SMRs) for cause-specific mortality of the TCP workers compared to the US population are calculated using OCMAP.[10] We focus on the cancers that IARC has identified as a concern. These cancers include all cancers combined, lung cancer, non-Hodgkin's lymphoma (NHL), and soft tissue sarcoma (STS).[11] Some non-cancer effects such as type 2 diabetes and ischemic heart disease have also been occasionally associated with dioxin exposures and we report on deaths associated with these causes as well.[12,13]

The collection of serum for evaluation of dioxin levels has been described previously.[14] We determined dioxin levels for 365 of the 2,192 (17%) chlorophenol workers and 70 of the 246 (28%) chlorophenol workers with chloracne. In the present study we will examine the 2,3,7,8-substituted chlorinated dioxins which include, TCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD.

Results and Discussion

Table 1 presents the current dioxin levels for the 70 chlorophenol workers with chloracne and the 295 chlorophenol workers without chloracne who took part in the serum dioxin study. Among all chlorophenol workers, the levels for 2,3,7,8 substituted chlorinated dioxins and the dioxin TEQ are higher for the workers with chloracne compared to workers without chloracne in every case. We also examine these dioxins and the TEQ for workers with only PCP and TCP exposures. As expected, workers with PCP exposure have higher levels of HxCDD, HpCDD and OCDD than workers with only TCP exposures who have higher levels of TCDD. Also, workers with chloracne have higher levels of the dioxin contaminates found in PCP and TCP than the chlorophenol workers without chloracne. However, for each congener examine there is considerable overlap in the ranges.

Figure 1. Chloracne Diagnosis in Pentachlorophenol and Trichlorophenol Workers Exposed to Dioxins

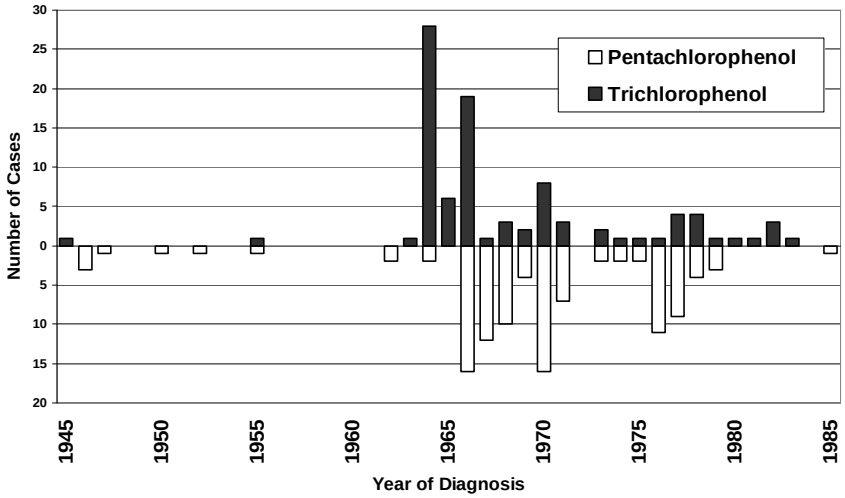

Figure 1 presents the year of diagnoses for the 93 cases of chloracne from TCP exposure and the 110 cases of chloracne from PCP exposure. We do not show the chloracne cases in the figure where both TCP and PCP exposure may have occurred. Before 1964, there were only a handful of cases of chloracne from either PCP or TCP exposure. Between 1964 and 1966, however, there were 53 cases of chloracne diagnosed from exposure to TCP. This outbreak of chloracne has been described previously.[15] In addition, between 1966 and 1971, there were 65 diagnosed cases of chloracne from PCP exposure. There was also a smaller outbreak of chloracne among both TCP and PCP workers that occurred between 1976 to 1979.

We examine SMRs for selected cancers and other diseases among the 247 chloracne cases and all PCP and TCP workers including the chloracne cases in Table 2. Total deaths are at or below expected levels for chloracne cases and all PCP and TCP workers. All cancers combined are slightly less than expected (SMR=0.9, 95%CI 0.6-1.4) among workers with chloracne, but at expected levels for both PCP workers (SMR=1.0, 95%CI 0.8-1.2) and TCP workers (SMR=1.0, 95%CI 0.8-1.1). Statistically significant deficits of lung cancer are observed for the chloracne cases (SMR=0.4, 95%CI 0.1-1.0) and also for TCP workers (SMR=0.7, 95%CI 0.5-0.9). PCP workers have lung cancer rates at expected levels (SMR=1.0, 95%CI 0.6-1.4). SMRs for NHL and STS are greater than expected for chloracne cases and both PCP and TCP workers. The 2 deaths for STS represent a statistically significant excess among chloracne cases, although one of these deaths has been misclassified on the death certificate.[16] The observed number of deaths from diabetes is slightly below expected levels and ischemic heart disease is slight above expected levels among chloracne cases. For PCP and TCP workers both diabetes and ischemic heart disease are slightly greater than expected.

Table 2. Observed deaths, standardized mortality ratios (SMRs), and 95% confidence intervals (CI) by cause among 246 male workers with chloracne compared to the US population.

Cause of Death (ICDA-10 Rubric)	**Workers with Chloracne SMR (95%CI)**	**PCP Ever SMR (95%CI)**	**TCP Ever SMR (95%CI)**
All causes (A00-Y89)	0.7(0.7-1.0)	0.9(0.9-1.1)	0.9(0.9-1.0)
Total malignant neoplasms (C00-C97)	0.9(0.6-1.4)	1.0(0.8-1.2)	1.0(0.8-1.1)
Lung (C33-C34)	0.4(0.1-1.0)	1.0(0.6-1.4)	0.7(0.5-0.9)
Non-Hodgkin's lymphoma (C82,C83.0-C83.8, C84,C85.1-C85.9)	1.9(0.2-6.8)	2.4(1.0-4.7)	1.3(0.6-2.5)
Soft tissue sarcoma (C49)	13.6(1.6-49.2)*	2.2(0.0-12.1)	4.1(1.1-10.5)*
Diabetes (E10-E14)	0.9(0.1-3.2)	1.1(0.5-2.2)	1.1(0.6-1.8)
Ischemic heart disease (I20-I25)	1.1(0.8-1.5)	1.2(0.9-1.3)	1.1(0.9-1.2)
Persons	246	773	1,615
Person-years of observation	7,364	27,035	58,742
Unable to locate death certificate	0	0	1

* Includes one misclassified renal clear-cell carcinoma

We find workers diagnosed with chloracne from TCP, PCP or both have dioxin exposure levels much higher than workers who are not diagnosed with chloracne. However, there is considerable overlap in the ranges of exposures between the workers with and without chloracne indicating that not all workers with high dioxin levels develop chloracne. We also observed that the chlorophenol workers who were only exposed to TCP workers had elevated levels of TCDD while the workers only exposed to PCP had elevated levels of the higher chlorinated dioxins including the 3 HxCDDs, the HpCDD and the OCDD. These findings are consistent with several other studies of TCP and PCP workers.

There have been at least two other studies which have examined death rates among workers with chloracne, one in Nitro, West Virginia and the other in Ludwigshafen, Germany .[17,18] The study in Nitro found an increase risk of lung cancer, bladder cancer,, and STS among workers with chloracne who also had exposure to 4-aminobiphenyl, a potent bladder carcinogen. However, while the numbers were small, the chloracne cases without exposures to 4-aminobiphenyl had no increased cancer rates. The study in Ludwigshafen reported an excess of all cancers combined, but there were no soft tissue sarcomas.

We observed death rates and cancer rates among the workers diagnosed with chloracne comparable to the US population and consistent with chlorophenol workers without chloracne. We did observe a statistically significant increase in STS among chloracne cases based on 2 deaths. However, the small numbers, and the fact that one of the cases was misclassified, argue for caution in assessing etiology. If, as has been argued, a chloracne episode is a sentinel event with no health effects occurring in its absence, we find little evidence for increased risk of cancer, ischemic heart disease, or diabetes. However, these findings will have to be evaluated in the context of other studies of persons with chloracne and other studies of chlorophenol workers.

Acknowledgements

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