DEATH RATES AMONG PENTACHLOROPHENOL WORKERS EXPOSED TO HIGHER CHLORINATED DIOXINS

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Introduction

Historically, pentachlorophenol (PCP) was one of the most highly used pesticides employed as a fungicide, herbicide, insecticide, and bactericide in industrial, agricultural, and domestic settings.[1] Since the early 1980's, PCP has been classified as a restricted use pesticide in the US by the EPA because the product contains dioxins as contaminants.[1]

There have been several epidemiology studies on persons exposed to PCP but the exposures were often not well defined, the study sizes were generally small and the follow-up periods were often short. The International Agency for Research on Cancer (IARC) classifies pentachlorophenol as possibly carcinogenic to humans based on sufficient animal data but inadequate data in humans. However, IARC does classify the dioxin, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), as a known human carcinogen based on animal studies and mechanistic information.[2] However, TCCD is not a contaminant in PCP.[2] The dioxin contaminants found in PCP include 123478-HxCDD, 123678-HxCDD, 123789-HxCDD, 1234678-HpCDD, and OCDD.

PCP was manufactured in the Dow Chemical Company's Midland, Michigan plant from the late 1930's until 1980. The PCP workers at this plant based on serum dioxin evaluation were found to have higher serum levels of 123478-HxCDD, 123678-HxCDD, 123789-HxCDD, 1234678-HpCDD, and OCDD, but not TCDD.[3] A portion of these workers developed chloracne, a hallmark of high dioxin exposure.[4] When the mortality levels of these workers were examined several years ago, most causes of death were at or below expected levels with the exception of cancers of kidney, stomach ulcers, and cirrhosis of the liver.[5]

We update this earlier study with additional follow-up and develop exposure estimates based on serum dioxin evaluation of a sample of these workers. We believe this is the largest single plant study ever of PCP manufacturing workers, has a maximum of 64 years of follow-up, and is the first study to use biomonitoring of PCP workers to estimate past exposures to dioxins.

Materials and Methods

We identified 773 workers with PCP exposure from a total of 2,192 chlorophenol workers at the Midland, Michigan plant. While the previous study found only 770 chlorophenol workers, we added three workers based upon work history information indicating potential PCP exposure. 196 of these 773 workers also had exposure to TCP. TCP workers as a group have higher levels of TCDD and the ones who also worked with PCP had high levels of 123478-HxCDD, 123678-HxCDD, 123789-HxCDD, 1234678-HpCDD, and OCDD.[3] We accumulated person-years at risk from January 1, 1940, or from the date at which a PCP department assignment first appeared in the work history, whichever is later. Vital status follow-up was completed through 2003. Death certificates were obtained from the states in which the employees died.

The development of dioxin exposure estimates for the PCP workers has been described elsewhere.[6] Briefly, we used a qualitative exposure characterization from an earlier study to group all PCP exposed jobs into one of 3 similar exposed groups.[7] We selected a sample of workers based on time spent in these similar exposed groups and drew blood from 128 former PCP workers and measured the levels of dioxins, furans, and PCBs.[3] Since high dioxin exposures remain in the body for many years, we modeled past dioxin levels for HxCDD, HpCDD, and OCDD for all PCP workers and the TCDD levels among those PCP workers who also had TCP exposure based on their time spent in one or more of the similar exposed groups. The model produced time-dependent accumulation and elimination of these dioxins. We then summed the

predicted HxCDD, HpCDD, OCDD and TCDD levels weighted by toxicity equivalent to TCDD (TEQ) as recommended by the WHO to produce a summary score.[8]

Table 1. Standardized mortality ratios (SMR), 95% confidence intervals (95%CI), and observed deaths (Obs) for selected causes of death with exposure to pentachlorophenol for the previous study and the current update.

Death category (ICD-10 code)	**All PCP Workers**		**PCP Workers excluding 196 workers with TCP Exposure**	
	# of deaths	**SMR (95% CI)**	**# of deaths**	**SMR (95% CI)**
All causes (A00-Y89)	370	0.9 (0.9-1.0)	275	0.9 (0.8-1.0)
All cancers (C00-C97)	94	1.0 (0.8-1.2)	71	1.0 (0.8-1.3)
Esophagus (C15)	2	0.8 (0.1-2.9)	2	1.1 (0.1-3.8)
Stomach (C16)	4	1.2 (0.3-3.1)	3	1.1 (0.2-3.2)
Large intestine (C18)	10	1.2 (0.6-2.3)	7	1.1 (0.4-2.3)
Rectum (C20-21)	1	0.5 (0.0-2.9)	1	0.6 (0.0-3.6)
Biliary passages and liver (C22, C24)	0	0.0 (0.0-1.7)	0	0.0 (0.0-2.3)
Pancreas (C25)	5	1.1 (0.3-2.5)	3	0.8 (0.1-2.4)
Other digestive (C17, C19, C23, C26, C48)	0	0.0 (0.0-4.7)	0	0.0 (0.0-5.7)
Larynx (C32)	2	1.7 (0.2-6.2)	2	2.2 (0.3-8.1)
Bronchus, trachea, lung (C33-34)	30	1.0 (0.6-1.4)	25	1.1 (0.7-1.6)
All other respiratory (C30-31, C37-C39)	0	0.0 (0.0-11.7)	0	0.0 (0.0-14.9)
Prostate (C61)	8	1.0 (0.4-1.9)	7	1.0 (0.4-2.1)
Testes and other male genital (C60, C62-63)	0	0.0 (0.0-12.5)	0	0.0 (0.0-15.9)
Kidney (C64-65)	4	1.7 (0.5-4.4)	4	2.3 (0.6-5.8)
Bladder and other urinary (C66-68)	2	0.7 (0.1-2.7)	1	0.5 (0.0-2.6)
Malignant melanoma (C43)	1	0.7 (0.0-4.0)	0	0.0 (0.0-3.6)
Central nervous system (C70-72)	1	0.4 (0.0-2.3)	0	0.0 (0.0-2.1)
Hodgkin's disease (C81)	0	0.0 (0.0-6.4)	0	0.0 (0.0-8.2)
Non-Hodgkin's lymphoma (C82, C83.0-83.8, C85.1-85.9)[1]	8	2.4 (1.0-4.7)	7	2.8 (1.1-5.7)
Leukemia and aleukemia (C91-95)	2	0.6 (0.1-2.0)	1	0.4 (0.0-2.0)
Other lymphopoietic (C88, C90, C96)	2	1.3 (0.2-4.6)	2	1.7 (0.2-6.0)
Soft tissue sarcoma (C49)	1	2.2 (0.0-12.1)	0	0.0 (0.0-10.7)
Diabetes mellitus (E10-14)	8	1.1 (0.5-2.2)	7	1.2 (0.5-2.6)
Cerebrovascular disease (I60-69)	25	1.1 (0.7-1.6)	17	0.9 (0.5.1.6)
Ischemic heart disease (I20-25)	131	1.1 (0.9-1.3)	99	1.0 (0.8-1.3)
Non-malignant respiratory disease (J00-99)	24	0.8 (0.5-1.1)	19	0.7 (0.4-1.2)
Ulcer of stomach & duodenum (K25-27)	5	3.0 (1.0-7.1)	4	3.0 (0.8-7.6)
Cirrhosis of liver (K70, K74)	8	1.0 (0.4-2.0)	8	1.3 (0.6-2.6)
Accidents (V01-X59)	20	1.1 (0.7-1.6)	14	1.0 (0.5-1.6)
Missing Certificates	0		0	
Persons	773		577	
Person-years	27,035		20,472	

We use the area under the curve for the TEQ to represent the cumulative workplace dioxin exposure above background at any point in the worker's career. The exposure-response analyses use 3 categories for the TEQ, and were constructed by dividing the person-years approximately equally in each group while

achieving whole number cut points. Standardized mortality ratios (SMRs) for cause-specific mortality of the PCP workers compared to the US population were calculated using OCMAP.[9] The causes of death for exposure response analyses were selected based on findings from previous evaluations studies.

Results and Discussion

There were 370 deaths (SMR=0.9, 95%CI 0.9-1.0) and 94 cancer deaths (SMR=1.0, 95%CI 0.8-1.2) among the 773 PCP workers with 27,035 person years of observation as shown in Table 1. The number of deaths and cancers is almost double the number observed in the previous study. With the single exception of NHL (SMR=2.4, 95%CI 1.0-4.7), all causes of death examined have confidence limits which include an SMR of 1.0. The SMRs of concern in previous study were reduced in the current study. The SMR for kidney cancer in the current study was 1.7 compared to 2.3 in the previous study, the SMR of 3.0 for ulcers in current study compared to 3.6 in the previous study, and the SMR for cirrhosis was 1.0 in the current study to 1.1 in the previous study. We did observe one soft tissue sarcoma death in the current study when none was present in the previous study. If we exclude the 196 PCP workers who also had TCP exposure the SMRs change very little. Subsequently, we will report the results for all 773 PCP workers and use the TEQ to represent the dioxins exposure.

We examine selected diseases by cumulative exposure levels of the TEQ in Table 2. With the possible exception of kidney cancer, we observed no increasing SMR with increasing cumulative exposure level. Although not shown, we find similar patterns when the analyses were done with each of the dioxin congeners found in PCP. For kidney cancer, non-Hodgkin's lymphoma, and cirrhosis the highest SMR occurred in the highest exposure category, while for lung cancer and diabetes the lowest SMR occurs in the highest category.

Table 2. Standardized mortality ratios (SMRs), number of observed deaths (obs), and 95% confidence intervals (95% CI) by cumulative area under the curve for TEQ for selected causes of death.

Death category	**0-324.9 ppt-years SMR (95% CI)[obs]**	**325-1499.9 ppt-years SMR (95% CI) [obs]**	**≥1500 ppt-years SMR (95% CI) [obs]**
All causes of death	0.9(0.7-1.2)[70]	0.8(0.7-1.0)[109]	1.0(0.9-1.2)[191]
All cancers	1.2(0.7-1.9)[22]	0.8(0.51.1)[24]	1.1(0.8-1.5)[48]
Lung	1.1(0.5-2.4)[7]	1.0(0.5-1.8)[11]	0.8(0.4-1.4)[12]
Kidney	0.0(0.0-7.9)[0]	1.2(0.0-7.0)[1]	2.8(0.5-8.3)[3]
Soft tissue sarcoma	0.0(0.0-35.5)[0]	0.0(0.0-22.9)[0]	5.1(0.1-28.3)[1]
Non-Hodgkin's lymphoma	2.9(0.4-10.6)[2]	0.9(0.0-4.8)[1]	3.4(1.1-7.9)[5]
Ischemic heart disease	1.2(0.8-1.7)[24]	1.0(0.7-1.4)[39]	1.1(0.9-1.5)[68]
Diabetes	1.4(0.2-5.2)[2]	1.6(0.4-4.1)[4]	0.6(0.1-2.2)[2]
Ulcer	3.3(0.1-18.4)[1]	6.0(1.2-17.5)[3]	1.2(0.0-6.7)[1]
Cirrhosis of the liver	0.5(0.0-2.9)[1]	0.4(0.0-2.1)[1]	1.8(0.6-3.8)[6]
Persons	746	589	342
Person-Years	8,876	9,009	9,150

This is the largest single-plant group of PCP workers ever studied for cancer risk for the higher chlorinated dioxins. No other group of PCP workers has been observed for so long, 1940 to 2003. The exposure estimates in this study are based on detailed work history information combined with the largest serum dioxin study ever done on PCP workers. This study is the first to estimate the levels of all the higher chlorinated dioxins associated with PCP. The exposure assessment based on serum dioxin evaluation is validated in part by extensive industrial hygiene monitoring and presence of chloracne cases among workers thought to be highly exposed.

Overall, the death and cancer rates for these workers are unremarkable. The single exception may be the numbers of non-Hodgkin's lymphoma which are greater than expected but do not show a trend with exposure level. Other studies of pentachlorophenol workers have not consistently found increased risk of non-Hodgkin's lymphoma.[10] Non-Hodgkin's lymphoma has been identified as possibly being associated with 2,3,7,8-TCDD exposure.[2,10]

In a previous study of these workers, kidney cancer, stomach ulcers, and cirrhosis of the liver, were a concern. In this update, all the SMRs for these three diseases were lower than the previous study and, with the possible exception of kidney cancer, none were related to exposure level. While this study cannot rule out an association with kidney cancer and exposures to higher chlorinated dioxins, the numbers were small and there have been inconsistent finding across other studies of pentachlorophenol workers.[1]

We have documented high exposures to the chlorinated dioxins associated with PCP exposures. The potential health effects of these higher chlorinated dioxins have only rarely been studied where exposure levels have been verified by biomonitoring. Other than possibly non-Hodgkin's lymphoma, we find little evidence for increased cancer or other disease risk from exposure to these higher chlorinated dioxins.

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