DEATH RATES AMONG WORKERS EXPOSED TO HIGHER CHLORINATED DIOXINS IN THE MANUFACTURE OF PENTACHLOROPHENOL

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Abstract
We examine death rates among 773 workers exposed to higher chlorinated dioxins in pentachlorophenol manufacture. Vital status was followed from 1940 to 2003. Exposure to 123478-HxCDD, 123678-HxCDD, 123789-HxCDD, 1234678-HpCDD, and OCDD was modeled based on a serum evaluation of 365 of these workers. The number of deaths from all causes combined, all cancers combined, and lung cancer, diabetes, and ischemic heart disease were near expected levels and there was no increasing trend with increasing exposure to the higher chlorinated dioxins. Standardized mortality ratios (SMR) of kidney cancer and stomach ulcers, a concern from a previous study, were lower in the current study. We did observe one soft tissue sarcoma death (SMR=2.2, 95% confidence interval (CI) 0.1-12.1), and 8 deaths from non-Hodgkin's lymphoma (SMR=2.4, 95% CI 1.0-4.8). Other than chloracne and possibly non-Hodgkin's lymphoma, we find little evidence for increased disease risk from exposure to these higher chlorinated dioxins.

Introduction
Pentachlorophenol (PCP) was manufactured in the Dow Chemical Company's Midland, Michigan plant from the late 1930's until 1980. These workers have been studied previously for mortality levels and chloracne incidence.[1, 2] PCP was used as a fungicide, herbicide, insecticide, and bactericide in industrial, agricultural, and domestic settings. In a previous study, some PCP workers were found to have higher serum levels of 123478-HxCDD, 123678-HxCDD, 123789-HxCDD, 1234678-HpCDD, and OCDD than unexposed workers or community members.[3]

There are several studies which examined the potential carcinogenic effect of PCP. While some studies report an association with cancer, others do not. We are updating a study which examined mortality levels of 770 PCP workers followed from 1940 to 1989 and adding exposure estimates based on serum dioxin evualtions.[2] In that study, most causes of death were at or below expected levels with the exception of cancers of kidney, and stomach ulcers.

We update this earlier study and examine causes of death of concern in the previous study and focus on the cancers that IARC concludes may be associated with exposure to dioxins. These cancers include all cancers combined, lung cancer, non-Hodgkin's lymphoma (NHL), and soft tissue sarcoma.[4] Non-cancer effects such as type 2 diabetes and ischemic heart disease have been occasionally reported to be associated with dioxin exposures, therefore we report on these outcomes also.[5, 6] In addition, we create a new exposure assessment based upon an extensive serum dioxin evaluation.

Materials and Methods
We identified 773 workers with PCP exposure from a total of 2,192 chlorophenol workers at the Midland, Michigan site. While the previous study found only 770 chlorophenol workers, we added three workers based upon work history information. We accumulated person-years at risk from January 1, 1940, or from the date at which a TCP 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. Standardized mortality ratios (SMRs) for cause-specific mortality of the PCP workers compared to the US population were calculated using OCMAP.[7]

We also examine exposure response for cancers and other causes of deaths. The estimated exposure levels based on dioxin serum evaluation for the 2,3,7,8-substituted hexa- (HxCDD), hepta- (HpCDD), and octa-dioxins (OCDD) and toxic equivalency for dioxins based on TCDD toxicity (TEQ) are derived from extensive serum dioxin evaluations and a model described in an accompanying paper. We estimated the

area under the curve for each congener and the TEQ taking into account dioxin exposures during workplace chlorophenol exposures. The area under the curve for these congeners and the TEQ 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 hexa, hepta, and octa-dioxins and the TEQ, and were constructed by dividing the person-years approximately equally in each group while achieving whole number cut points.

Table1. Lipid adjusted (pg/g lipid) serum concentrations of selected 2,3,7,8-substituted dioxins measured in pentachlorophenol (PCP) workers penta- and trichlorophenol (PCP/TCP)workers and non-exposed worker referents.

Congeners	PCP Workers (n=85) Mean	PCP/TCP Workers (n=43) Mean	Non-Exposed Worker Referents (n=37) Mean
123478-HxCDD	16.1*	15.2*	7.5
123678-HxCDD	150.6*	161.2*	74.7
123789-HxCDD	20.2*	16.0	8.6
1234678-HpCDD	192.6*	148.7	68.7
OCDD	2,594*	2,331*	509

** Significance <0.05 one-tailed test based on Student's t comparing PCP and PCP/TCP exposed to worker referent.*

Table 1 presents the current dioxin levels for the 85 pentachlorophenol workers who took part in the serum evaluation with 37 workers with no workplace chlorophenol exposure. These data were used to develop exposure estimates for the 773 workers with PCP exposure. Workers with PCP exposures had higher serum lipid concentrations of 123478-HxCDD, 123678-HxCDD, 123789-HxCDD, 1234678-HpCDD, and OCDD than other workers at the site not exposed to PCP.

Table 2. 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.

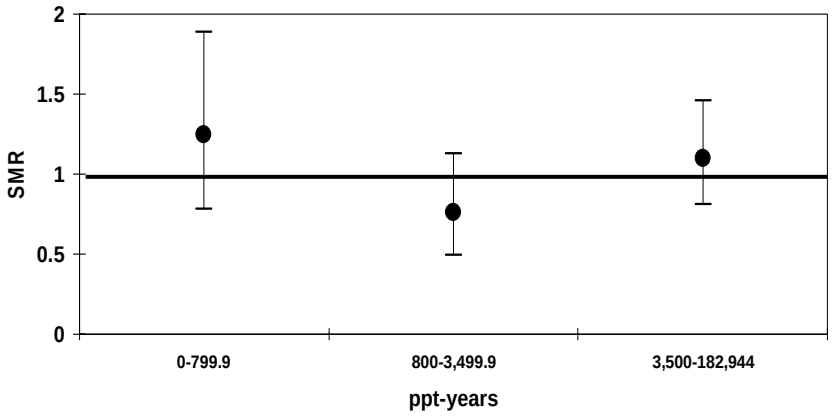
Cause of Death (ICDA-10 Rubric)	Ramlow et al. 1996	Current Study
	SMR (95%CI)[Obs]	SMR (95%CI)[Obs]
All causes of death	0.9 (0.8-1.1) [229]	0.9 (0.9-1.0) [370]
All malignant neoplasms (C00.-97.)	1.0 (0.7-1.3) [50]	1.0 (0.8-1.2) [94]
Lung (C33.-C34.)	0.9 (0.5-1.5) [16]	1.0 (0.6-1.4) [30]
Kidney	2.3 (0.5-6.7) [3]	1.7 (0.5-4.4) [4]
Non-Hodgkin's lymphoma (C82, C83.0-C83.8, C84, C85.1-C85.9)	2.0* (0.7-4.7) [5]	2.4 (1.0-4.7) [8]
Soft tissue sarcoma	0.0 (0.1-18.4) [0]	2.2 (0.0-12.1) [1]
Diabetes	1.2 (0.3-3.0) [4]	1.1 (0.5-2.2) [8]
Ischemic heart disease	1.0 (0.8-1.3) [86]	1.1 (0.9-1.3) [131]
Ulcer of the stomach and duodenum	3.6 (1.2-8.3) [5]	3.0 (1.0-7.1) [5]
Years of follow-up	1940-1989	1940-2003
Persons	770	773
Person years	Not Reported	27,035
Unable to locate certificate	0	0

* Includes non-Hodgkin's lymphoma, multiple myeloma, and other lymphatic cancers.

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 over 27,035 person years of observation as shown in Table 2. 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. Kidney cancer risk in the current study was 1.7 (95% CI 0.5-5.4) less than 2.3 (95% CI 0.5-6.7) in the previous study, and the SMR of 3.0 (95% CI 1.0-7.1) for ulcers of the stomach and duodenum in current study was also less than 3.6 (95% CI 1.2-8.) in the previous study, with no additional deaths from this cause reported. We did observe one soft tissue sarcoma death in the current study when none was present in the previous study.

Figure 1. Standardized mortality ratios (SMR) and 95% confidence intervals by part per trillion (ppt) years of exposure to HxCDD for all cancers combined.



We examine all cancers combined by cumulative exposure levels of summed HxCDD congeners in Figure 1. We find no increasing risk of cancer mortality with exposure. Although not shown we find similar patterns with the other congeners. We also examine lung cancer risk by exposure levels in Table 3 and use four dioxin estimates to evaluate this risk. We find no increasing risk of lung cancer with increasing cumulative exposure to any of the dioxin congeners or the TEQ. In all cases, the SMR in the highest exposure category is lower than the lowest exposure category for all metrics. Although not presented, we also find no increasing trend with exposure for all causes of death, diabetes, or ischemic heart disease.

We did not examine trends for the remaining causes because of the small number of observed deaths in these categories. However, in the previous study, the SMR for kidney cancer in the highest dioxin exposure category was 4.4 (95% CI 0.5-15.9) while in the current study the SMR is 2.8 (0.6-8.3) based on the TEQ metric. We also note that in the highest TEQ exposure category in the current study, the SMR for NHL is 3.4 (95% CI 1.1-7.9) based on 5 deaths.

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 industrial 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 rates for non-Hodgkin's lymphoma, which are greater than expected and appear to be related to exposure levels. Nevertheless, the number of non-Hodgkin's lymphoma cases is small and it is difficult to come to a conclusion based on a single study. Other studies of pentachlorophenol workers have not consistently found increased risk of non-Hodgkin's lymphoma.[5] Non-Hodgkin's lymphoma has been identified as possibly being associated with 2,3,7,8-TCDD exposure, but, as for pentachlorophenol, the findings across studies are inconsistent.[4, 5]

Table 3. Standardized mortality ratios (SMR) and 95 % confidence limits (95% CI) for lung cancer by exposure categories for dioxin congeners related to pentachlorophenol exposure.

Congener	Categories in ppt-years	Low SMR(95%CI)	Medium SMR(95%CI)	High SMR(95%CI)
HxCDD*	0-799.9=Low, 800-3499.9=Medium, 3500+=High	1.3 (0.5-2.7)	0.8 (0.4-1.6)	0.9 (0.5-1.5)
HpCDD	0-10,999.9=Low, 11,000-54,999,9=Medium, 55,000+=High	1.2 (0.5-2.3)	0.9 (0.4-1.7)	0.9 (0.5-1.6)
OCDD	0-39,999.9=Low, 40,000-189,999.9=Medium, 190,000+=High	1.3 (0.5-2.5)	0.8 (0.4-1.5)	0.9 (0.5-1.6)
TEQ	0-324.9=Low, 325-1,499.9=Medium, 1,500+=High	1.2 (0.5-2.4)	1.0 (0.5-1.8)	0.8 (0.4-1.5)

* Sum of the three 2,3,7,8-substituted HxCDD congeners.

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 chloracne and possibly non-Hodgkin's lymphoma, we find little evidence for increased death risk from exposure to these higher chlorinated dioxins.

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References

1. Bond GG, McLaren EA, Brenner FE, Cook RR. *J Occup Med.* 1989;31(9):771-774.
2. Ramlow JM, Sapdacene NW, Hoag SR, Stafford BA, Cartmill JB, Lerner PJ. *J Occup Med.* 1996;30:180-194.
3. Collins JJ, Bodner K, Wilken M, et al. *J Exp Sci and Environ Epi.* (in press).
4. IARC. Polychlorinated Dibenzo-para-dioxins and Polychlorinated Dibenzofurans. *IARC Monogr Eval Carcinog Risks Hum.* 1997;69.
5. IOM. *Veterans and Agent Orange: Update 2004*. Washington, D.C.: National Academies Press; 2005.
6. Steenland K, Piacitelli L, Deddens J, Fingerhut M, Chang LI. *J Natl Cancer Inst.* 1999;91(9):779-786.
7. Marsh GM, Youk AO, Stone RA, Sefcik SS, Alcorn CA. *J Occup Environ Med.* 1998;40:351-362.