CANCER RATES AND SERUM DIOXIN LEVELS AMONG CHLOROPHENOL WORKERS WITH CHLORACNE

James J. Collins[1], Kenneth Bodner[1], Gregory Bond[1], Lesa L. Aylward[2], Robert A. Budinsky[1], Michael L. Carson[1]

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

Abstract
We examined death rates among 246 chemical manufacturing workers in Midland, Michigan who developed chloracne after exposure to trichlorophenol and/or pentachlorophenol. Workers diagnosed with chloracne had higher serum dioxin levels than those without chloracne. Among the chloracne diagnosed workers, the standardized mortality ratio for all cancers combined was 0.9 (95% Confidence Intervals (CI) 0.6-1.4), lung cancer was 0.4 (95%CI 0.1-1.0), non-Hodgkin's lymphoma was 1.9 (95%CI 0.2-6.8) and soft tissue sarcoma was 13.6 (95%CI 1.6-49.2). We observed no trend with increasing exposures to dioxins. Since the number of observed deaths is small, these findings will have to be evaluated in the context of other studies of persons with chloracne and other studies of chlorophenol workers. However, we see no evidence of increased death rates among these workers with chloracne.

Introduction
Chloracne, an acute dermatological condition, was first described over a century ago and was initially thought to be caused by occupational exposure to nascent chlorine. Later, it was recognized that chloracne could be caused by exposure to a variety of cyclic organochlorine compounds including dioxins and furans. Much of the research has focused on exposures to 2,3,7,8 tetrachlorodibenzo-*p*-dioxin (TCDD) with respect to chloracne since it has been recognized as a "hallmark" of this exposure. Persons with exposures to PCBs and pentachlorophenol also have developed chloracne, and dioxin or furan contaminants in these products were thought to be the cause.

Table 1. Current and modeled area under the curve (AUC) levels of selected dioxin congeners for chlorophenol workers with and without chloracne.

Dioxin Congener	Current Levels (ppt) Mean (Range)		Modeled Area Under the Curve (ppt-years) Mean (Range)	
	Chloracne (n=70)	No Chloracne (n=295)	Chloracne (n=246)	No Chloracne (n=1,946)
2,3,7,8-TCDD	23 (1-176)	12 (0-145)	12,258 (6-112,253)	1,918 (0-69,236)
1,2,3,6,7,8-HxCDD	197 (25-1,080)	83 (8-647)	16,671* (14-182,944)	3,063* (0-137,293)
1,2,3,4,6,7,8-HpDD	205 (10-1,750)	84 (5-2,630)	307,752 (0-4,390,948)	50,034 (0-4,987,458)
OCDD	3,119 (67-45,100)	842 (45-31,100)	899,018 (144-10,756,856)	146,612 (2-11,418,828)
TEQ	82 (12-274)	49 (3-328)	17,093 (8-113,366)	2,739 (0-70,213)

* These totals include the sum of 1,2,3,4,7,8-, 1,2,3,6,7,8-, and 2,3,4,6,7,8-HxCDD.

Chloracne is an acute condition with the duration of symptoms 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] 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.[6]

Some researchers have 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 cancer levels among 246 chloracne cases diagnosed in chlorophenol workers in Midland, Michigan to determine if cancer levels are related to dioxin exposures. We examine all major cancer sites, with a focus on the cancers that IARC concludes were seen in some studies. These cancers include all cancers combined, lung cancer, non-Hodgkin's lymphoma (NHL), and soft tissue sarcoma.[9] 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.[10,11]

Materials and Methods

Among the 2,192 chlorophenol workers in Midland, Michigan, 246 cases of chloracne have been identified.[6,12] The diagnosis of the chloracne cases was based on a joint assessment with NIOSH and the company. 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.[13]

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)	**Obs**	**Exp**	**SMRs**	**95% CI**
All causes () INSERT CODES BELOW? OR OMIT?	95	113.6	0.7	0.7-1.0
Total malignant neoplasms ()	27	28.8	0.9	0.6-1.4
Buccal cavity & pharynx	1	0.6	1.6	0.0-8.6
Digestive organs & peritoneum	6	7.0	0.9	0.3-1.9
Lung	4	10.0	0.4	0.1-1.0
Prostate	1	2.7	0.4	0.0-2.1
Bladder & other urinary	2	0.8	2.5	0.3-9.1
Kidney	0	0.7	0.0	0.0-5.1
Malignant melanoma of skin	0	0.5	0.0	0.0-8.2
Central nervous system	2	0.7	2.8	0.3-10.2
Hodgkin's disease	0	0.1	0.1	0.0-28.8
Non-Hodgkin's lymphoma	2	1.1	1.9	0.2-6.8
Leukemia & aleukemia	1	1.1	0.9	0.0-5.2
Cancer of all other lymphopoietic tissue	0	0.5	0.0	0.0-7.4
Soft tissue sarcoma	2*	0.1	13.6	1.6-49.2
Diabetes	2	2.3	0.9	0.1-3.2
Ischemic heart disease	35	31.7	1.1	0.8-1.5
Persons	246			
Person-years of observations	7,364			
Unable to locate death certificate	0			

* Includes one misclassified renal clear-cell carcinoma

We developed exposure estimates for all 246 workers with chloracne from a dioxin serum evaluation of 375 workers using a first-order toxicokinetic model. Since these workers may have developed chloracne from either exposures on either the trichlorophenol (TCP) or pentachlorophenol (PCP) processes, we must consider the different congener profiles for TCP and/or PCP exposures.[14] Therefore, we modeled TCDD, hexa-chlorinated dioxins (sum of 1,2,3,4,7,8-, 1,2,3,6,7,8-, and 2,3,4,6,7,8-hexachlorodibenzo-p-dioxin [HxCDD]), 1,2,3,4,6,7,8-heptachlorinated dibenzo-p-dioxin (HpCDD), octachlorodibenzo-p-dioxin (OCDD) and toxic equivalency for these dioxins only based on TCDD toxicity equivalents (TEQ). We then estimated the area under

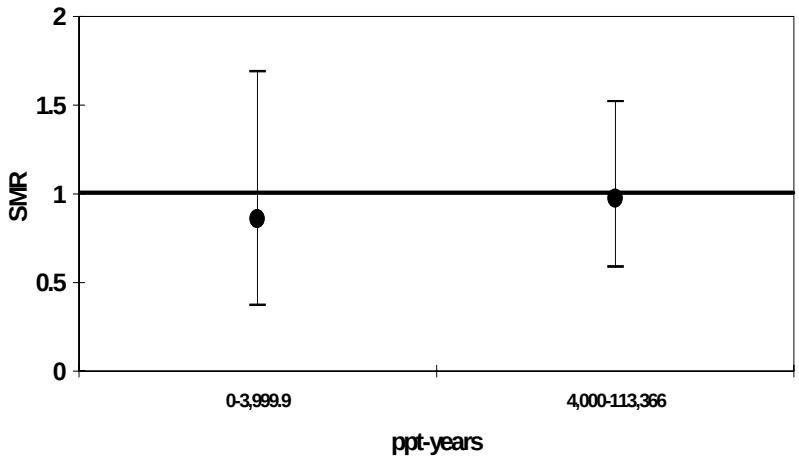
the curve for each congener and the TEQ taking into account dioxin exposures during workplace chlorophenol exposures. The area under the curve for these congeners and the TEQ represent an estimate of the total cumulative workplace dioxin exposure above background at any point in a career, although the exposure estimates derived for these workers may not be translatable to environmental or other exposure estimates discussed elsewhere.[15]

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. These data were used to develop cumulative exposure estimates for the 246 workers with chloracne and the 1,946 without chloracne. For every congener and the TEQ the current mean levels are higher for the workers with chloracne compared to workers without chloracne. For instance, workers diagnosed with chloracne had a current mean OCDD of 3,119 ppt compared to 842 ppt for workers with no diagnosed chloracne. However, for each congener examine there is considerable overlap in the ranges. As expected when these current dioxin levels are modeled to estimate the AUC in ppt-years, the workers diagnosed with chloracne have higher mean levels than workers without chloracne but there is still considerable overlap in the ranges. Using these model values, we constructed 2 exposed groups for the 246 workers diagnosed with chloracne by dividing the person-years approximately equally in each group while achieving whole number cut points.

Results and Discussion

Table 2 presents the SMR for selected causes of death and cancers. Deaths in the categories all causes and all cancers are at or below expected levels. Specific cancer sites that have been associated with TCDD exposures by IARC include lung cancer, non-Hodgkin's lymphoma (NHL), and soft tissue sarcoma (STS). Observed deaths from lung cancer (4 observed, 10.0 expected) are below expected levels while observed death for NHL (2 observed, 1.1 expected), and STS (2 observed, 0.1 expected) are above expected levels. The 2 deaths for STS represent a statistically significant excess although one case has been recognized to have a mis-attributed cause of death recorded on the death certificate.[16] SMRs for cancers of other sites are unremarkable. The observed number of deaths from diabetes is slightly below expected levels and ischemic heart disease is slight above expected levels.

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



We examine disease risk by exposure levels in Figure 1 for all cancers combined using modeled estimates of the TEQ AUC. The SMRs and 95% confidence intervals (95%CI) for the two TEQ exposure categories for all cancers combined are shown. Both SMRs are less than 1.0 and are consistent with no increased risk for either low or highly exposed workers with chloracne. The same analysis for ischemic heart disease (not shown) shows similar levels and patterns.

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. Death rates and cancer rates among the workers diagnosed with chloracne are comparable to the US population and we see no increasing rates with increasing exposure. We did observe a statistically significant increase in STS 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 chlorophenol workers.

Acknowledgements
This study was funded by The Dow Chemical Company. The study conduct was pursuant to review and oversight by a Human Subjects Review Board in Midland, Michigan.

References

1. Jansing P, Korff R. J Dermatological Science 1994;8:91-95.
2. Mocarelli P, Needham LL, Marocchi A, Patterson DG, Brambilla P, Gerthoux PM, Meazza L, Carreri V. J Toxicol Environ Health 1991;32:357-366.
3. Coenraads PJ, Olie K, Tang NJ. Br J Dermatol 1999;141:694-697.
4. Neuberger M, Rappe C, Bergek S, Cai H, Hansson M, Jager R, Kundi M, Lim CK, Wingfors H, Smith AG. Environ Res Section A 1999;81:206-214.
5. Neuberger M, Landvoigt W, Derntl F. Int Arch Occup Environ Health 1991;63:325-327.
6. Bond GG, McLaren EA, Brenner FE, Cook RR. J Occup Med 1989;31(9):771-774.
7. Yamamoto O, Tokura Y. Journal of Dermatological Science 2003;32:85-94.
8. Schecter A, Birnbaum L, Ryan JJ, Constable JD. Environmental Research 2006;101:419-428.
9. IARC. Polychlorinated Dibenzo-para-dioxins and Polychlorinated Dibenzofurans. IARC Monogr Eval Carcinog Risks Hum 1997;69.
10. IOM. Veterans and Agent Orange: Update 2004. Washington, D.C.: National Academies Press, 2005.
11. Steenland K, Piacitelli L, Deddens J, Fingerhut M, Chang LI. J Natl Cancer Inst 1999;91(9):779-786.
12. Bond GG, McLaren EA, Lipps TE, Cook RR. Effect of Reclassification of Chloracne Cases. In: Med JO, ed. Vol. 32, 1990;423.
13. Marsh GM, Youk AO, Stone RA, Sefcik S, Alcorn C. J Occup Environ Med 1998;40:351-356.
14. Collins JJ, Bodner K, Burns CJ, Wilken M, Budinsky RA, Lamparski LL, Martin GD, Rowland JC, Haidar S, Carson M. Organohalogen Compounds 2006;68:740-742.
15. Aylward LL, Bodner KM, Collins JJ, Hays SM. Organohalogen Compounds 2007.
16. Suruda AJ, Ward EM, Fingerhut MA. Epidemiology 1993;4(1):14-19.