DEATH RATES AMONG WORKERS EXPOSED TO 2,3,7,8-TCDD IN THE MANUFACTURE OF TRICHLOROPHENOL

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

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

Abstract
We examine death rates among 1,615 workers exposed to 2,3,7,8-TCDD in trichlorophenol manufacture and formulation. Vital status was followed from 1940 to 2003. Exposure to 2,3,7,8-TCDD was modeled based on a serum evaluation of 365 of these workers. All causes of death combined, all cancers combined, and lung cancers were at or below expected levels. While observed deaths from non-Hodgkin's lymphoma, soft tissue sarcoma, diabetes, and ischemic heart disease were greater than expected, they did not increase linearly with increasing exposure to 2,3,7,8-TCDD. Overall, we found no coherent evidence of increased cancer risk from exposure to 2,3,7,8-TCDD. Our study highlights the wide range of cancer rates and lack of consistency across studies

Introduction
Three studies have been used for human cancer risk assessment for dioxins. These studies were chosen because the populations were large, there was a long observation period, the exposures had been assessed by serum dioxin evaluations, and incidences of chloracne indicated the potential for high exposure.[1-3] These studies all report an increased risk of all cancers combined and two of the three studies report an increase in lung cancer and ischemic heart disease. The US EPA has used these 3 studies in draft risk assessment document to classify TCDD as a human carcinogen and to quantify lifetime average body burden of TCDD that would increase the lifetime risk of death from cancer at all sites.

The international Agency for Research on Cancer classified 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) as a known human carcinogen based on animal studies and mechanistic information. However, the epidemiology data was thought to be limited. Increased risk of all cancers combined, lung cancer, non-Hodgkin's lymphoma (NHL), and soft tissue sarcoma were seen in some studies but not all.[4] Some non-cancer effects such as type 2 diabetes and ischemic heart disease have also been occasionally associated with dioxin exposures.[3, 5]

Recently, we completed an extensive dioxin serum evaluation of trichlorophenol workers in Midland, Michigan who had been studied previously for cancer.[6, 7] Eleven percent of these workers were found to have chloracne.[8] We update this study with additional vital status follow-up and provide new exposure estimates based on this serum dioxin evaluation. This study is similar to the three used by the US EPA in their draft assessment. Our study is large, has a significant number of serum dioxin evaluations to assist in exposure estimation, has high exposure given the prevalence of chloracne, and has a long observation period. This study should provide an important addition for risk assessment for dioxins and help determine the consistency of findings across studies.

Materials and Methods
We identified 1,615 workers with TCP exposure. 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 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.[9]

We used serum dioxin levels collected from 365 chlorophenol workers to produce a model to estimate historical exposure levels of TCDD for the trichlorophenol workers. The occupationally-related blood lipid area under the curve for TCDD for each TCP worker over time is used as our estimate of cumulative dose. At the end of follow-up, the area under the curve for the 1,615 workers ranged from 2 to 112,253 ppt-years

with mean of 3,933 and a median of 598. We constructed three exposed groups by dividing the person-years approximately equally in each group while achieving whole number cut points.

Results and Discussion

There were 662 deaths (SMR=0.9, 95%CI 0.9-1.0) and 177 cancers (SMR=1.0, 95%CI 0.8-1.1) among the 1,615 TCP workers shown in Table 1. Overall, there were fewer lung cancers than expected (SMR=0.7, 95%CI 0.5-0.9) but more deaths from NHL (SMR=1.3, 95%CI 0.6-2.5), STS (SMR=4.1, 95%CI 1.1-10.5) diabetes (SMR=1.1, 95%CI 0.6-1.8), and ischemic heart disease (SMR=1.1, 95%CI 0.9-1.2) than expected.

Table 1. Observed (Obs) and expected (Exp) deaths, standardized mortality ratios (SMR), 95% confidence intervals (95%CI), for selected causes of death with exposure to 2,3,7,8-TCDD compared to the US population.

Cause of Death (ICDA-10 Rubric)	Obs	Exp	SMR	95% CI
All causes of death (A00-Y89)	662	719.3	0.9	0.9-1.0
All malignant neoplasms (C00-C97)	177	184.5	1.0	0.8-1.1
Lung (C33-C34)	46	65.0	0.7	0.5-0.9
Non-Hodgkin's lymphoma (C82,C83.0-C83.8,C84,C85.1-C85.9)	9	6.9	1.3	0.6-2.5
Soft tissue sarcoma (C49)	4*	1.0	4.1	1.1-10.5
Diabetes (E10-E14)	16	14.4	1.1	0.6-1.8
Ischemic Heart Disease (I20-I25)	218	200.9	1.1	0.9-1.2
Persons	1615			
Person years	58742			
Unable to locate certificate	1			

** Includes one misclassified renal clear-cell carcinoma, 2 malignant fibrous histiocytomas and an angiosarcoma (see text).*

We examine disease risk by exposure levels in Figures 1 through 3. The SMRs and 95% confidence intervals (95%CI) by exposure category for all cancers combined are shown in Figure 1. There is no increasing trend with cumulative increasing exposure to 2,3,7,8-TCDD.

Figure 1. Standardized mortality ratios (SMR) and 95% confidence intervals by part per trillion (ppt) years of 2,3,7,8-TCDD exposure for all cancers combined.

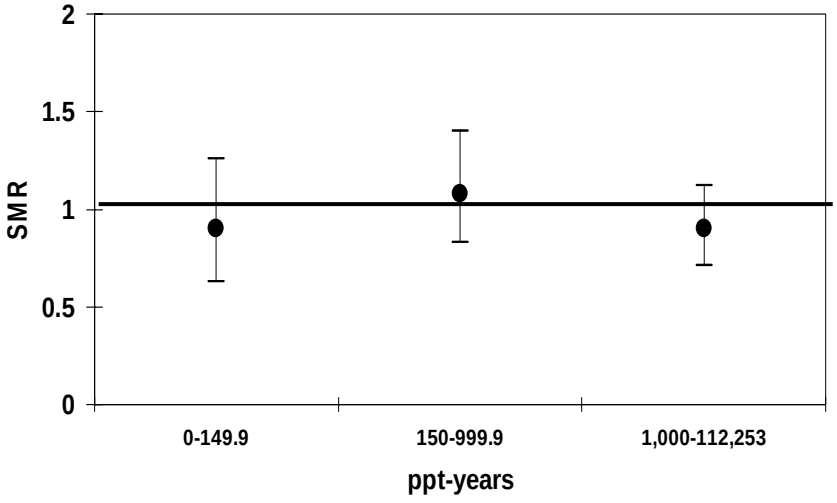
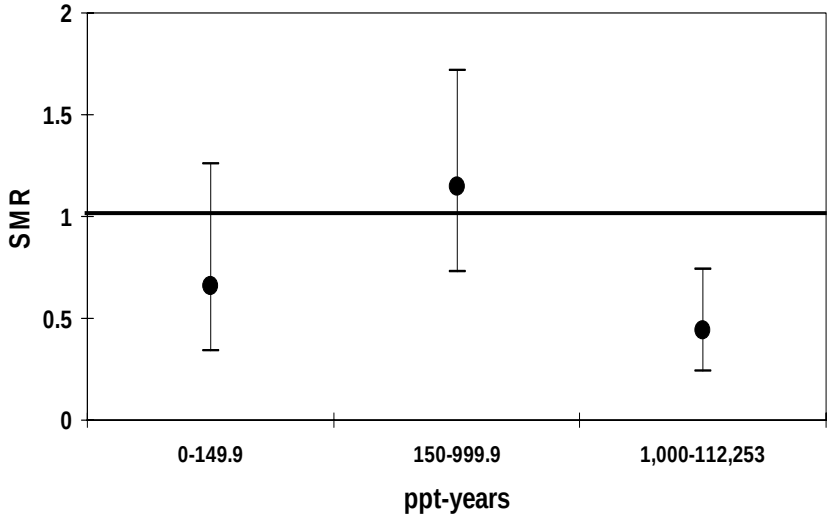


Figure 2 presents the same exposure categories for lung cancer. We find no trend with exposure level and the highest exposure category has a statistically significant deficit of lung cancer (SMR=0.4, 95%CI 0.2-0.7). Figure 3 presents the cumulative exposure categories for ischemic heart disease. The first two

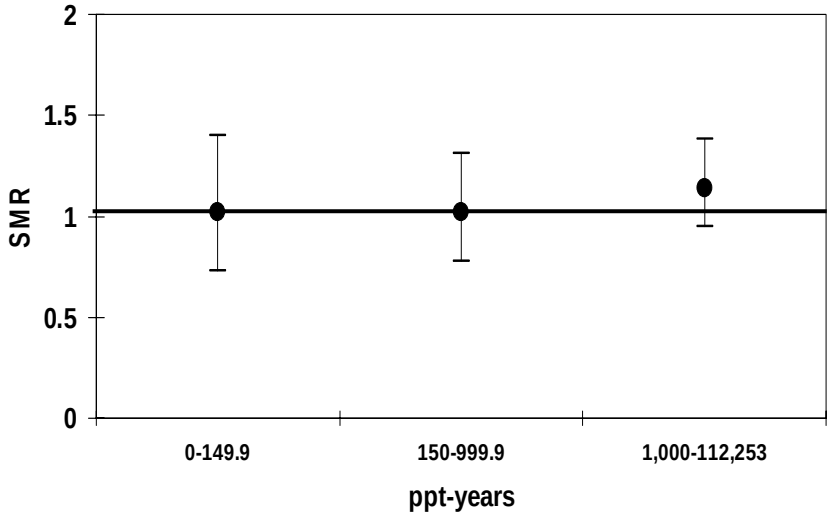
exposure categories have observed ischemic heart disease deaths at expected levels while the highest exposure category has slightly more observed deaths than expected deaths (SMR=1.1, 95%CI 0.9-1.4).

Figure 2. Standardized mortality ratios (SMR) and 95% confidence intervals by part per trillion (ppt) years of 2,3,7,8-TCDD exposure for lung cancer.



There were no increasing trends with exposure category for any of the causes that IARC concludes could be related to TCDD exposures (not shown). Although based on small numbers, the STS SMRs by exposure levels are 4.2 (95% CI 0.6-17.0), 3.2 (95% CI 0.1-17.9), and 4.7 (95% CI 0.6-17.0), One of the deaths in the highest exposure category was misclassified as an STS.[10] The other 3 deaths from STS included two malignant fibrous histiocytomas and one angiosarcoma.

Figure 3. Standardized mortality ratios (SMR) and 95% confidence intervals by part per trillion (ppt) years of 2,3,7,8-TCDD exposure for ischemic heart disease.



Several characteristics contribute to the importance of this study. This is the largest single-plant group of trichlorophenol workers ever studied for the health effects of 2,3,7,8-TCDD, and we believe that no other group has been followed 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. 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.[6, 8, 11]

Overall, the death and cancer rates for these workers are unremarkable and are in stark contrast to the three similar studies discussed. The single exception may be the rates for STS, but the small number of STSs in our study, the potential for misdiagnosis, the diversity of the types of STS, the lack of an exposure-response, and the lack of similar findings in other studies argue for caution in assessing etiology for this cancer category.[10]

Our study produced very different results for all cancer risk and lung risk among workers exposed to relatively high levels of TCDD than the three previous studies which have been used in cancer risk assessment. We find no consistent evidence that these TCP workers have an increased risk of cancer collectively or in any type of cancer or disease that can be attributed to TCDD exposure. The lack of consistent findings across these four human studies on cancer risk from highly exposed workers evinced from serum dioxin evaluations indicates that TCDD at levels experienced in manufacturing operations may not be carcinogenic to humans.

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.

Reference List

1. Flesch-Janys D, Steindorf K, Gurn P, Becher H. *Environmental Health Perspective.* 1998;106 (suppl.2):665-672.
2. Ott MG, Zober A. *Occup Environ Med.* 1996;53:606-612.
3. Steenland K, Piacitelli L, Deddens J, Fingerhut M, Chang LI. *J Natl Cancer Inst.* 1999;91(9):779-786.
4. IARC. *IARC Monogr Eval Carcinog Risks Hum.* 1997;69.
5. IOM. *Veterans and Agent Orange: Update 2004*. Washington, D.C.: National Academies Press; 2005.
6. Collins JJ, Bodner K, Wilken M, et al. *J Exp Sci and Environ Epi.* (in press).
7. Bodner KM, Collins JJ, Bloemen LJ, Carson M. *Occup Environ Med.* 2003;60:672-675.
8. Bond GG, McLaren EA, Lipps TE, Cook RR. In: Med JO, ed. Vol 32; 1990:423.
9. Marsh GM, Youk AO, Stone RA, Sefcik S, Alcorn C. *J Occup Environ Med.* 1998;40:351-356.
10. Suruda AJ, Ward EM, Fingerhut MA. *Epidemiology.* 1993;4(1):14-19.
11. Ott MG, Olsen RA, Cook RR, Bond GG. *J Occup Med.* 1987;29(5):422-429.