DEATH RATES AMONG TRICHLOROPHENOL WORKERS EXPOSED TO DIOXINS

James J. Collins[1], Kenneth Bodner[1], Lesa L. Aylward[2], Michael Wilken[1], Cathy Bodnar[1], Robert A. Budinsky[1], Michael L. Carson[1]
[1]The Dow Chemical Company, Midland, MI, USA; [2]Summit Toxicology, LLP, Falls Church, VA, USA

Introduction
The international Agency for Research on Cancer classified 2,3,7,8-TCDD as a known human carcinogen based on animal studies and mechanistic information. However, the epidemiology data was thought to be limited because of inconsistent findings across studies. 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.[1] Some non-cancer effects such as type 2 diabetes and ischemic heart disease have also been occasionally associated with dioxin exposures.[2,3]

Recently, we completed an extensive dioxin serum evaluation of trichlorophenol workers in Midland, Michigan who had been studied several years ago.[4,5] These workers had high rates of chloracne presumably due to 2,3,7,8-TCDD exposure.[6] We use the serum dioxin evaluations from a sample of these workers to develop exposure estimates for all trichlorophenol or 2,4,5-T workers and evaluate cancer and disease risk. Our study is large, has a significant number of serum dioxin evaluations to assist in exposure estimation, and has a long observation period. This study should provide important new information for assessing disease risk and 2,3,7,8-TCDD exposure.

Materials and Methods
We identified 1,615 workers with potential 2,3,7,8-TCDD exposure at the Midland, Michigan plant in the US. We accumulated person-years at risk from January 1, 1940 or from the date at which a trichlorophenol or a 2,4,5-T 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 workers compared to the US population are calculated using OCMAP.[7]

A serum dioxin evaluation of a large sample of these trichlorophenol or 2,4,5-T workers indicated that 2,3,7,8-TCDD levels were greater than unexposed workers and background levels in the community.[4] We used these serum dioxin levels to produce a model to estimate historical exposure levels of 2,3,7,8-TCDD for all the 1,615 workers.[8] The occupationally-related blood lipid area under the curve for 2,3,7,8-TCDD for each 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 trichlorophenol or 2,4,5-T workers shown in Table 1. Overall, there were fewer buccal cavity and pharynx cancers (SMR=0.0, 95% CI 0.0-0.9), digestive organs and peritoneum cancers (SMR=1.0, 95% 0.7-1.3), lung cancers (SMR=0.7, 95%CI 0.5-0.9), kidney cancer (SMR=0.4, 95%CI 0.1-1.5), non-malignant respiratory disease (SMR=0.8, 95%CI 0.6-1.0), cirrhosis of the liver (SMR= 0.4, 95%CI 0.1-0.8) and all external causes of death(SMR=1.0, 95%CI 0.7-1.2) than expected. There were more deaths from prostate cancer, bladder cancer, Hodgkin's disease, 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.

We examine disease risk for diseases of *a priori* interest by exposure level in Table 2. With the possible exception of ischemic heart disease, there is no increasing trend with cumulative exposure to 2,3,7,8-TCDD for of these diseases. For all cancers combined, there are fewer deaths than expected in the highest exposed category, $\geq$ 1000 ppt-years. For lung cancer, the highest exposure category has a statistically significant

deficit of lung cancer (SMR=0.4, 95%CI 0.2-0.7). Although based on small numbers, the SMRs for soft tissue sarcoma 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.[9] The other 3 deaths from STS included two malignant fibrous histiocytomas and one angiosarcoma.

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
Buccal cavity and pharynx (C00-C14)	0	4.3	0.0	0.0-0.9
Digestive organs and peritoneum (C15-C25)	43	45.0	1.0	0.7-1.3
Lung (C33-C34)	46	65.0	0.7	0.5-0.9
Prostate (C61)	21	14.7	1.4	0.9-2.2
Kidney (C64-C65)	2	4.8	0.4	0.1-1.5
Bladder (C66-C68)	6	4.8	1.2	0.5-2.7
Malignant melanoma (C43)	2	3.1	0.6	0.1-2.3
Central nervous system (C70-C72)	3	5.1	0.6	0.1-1.7
Hodgkin's disease (C81)	2	1.1	1.8	0.2-6.4
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
All other cancers	39	28.7	1.4	1.0-1.9
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
Non-malignant respiratory disease (J00-J99)	44	57.6	0.8	0.6-1.0
Cirrhosis of liver (K70, K74)	6	16.3	0.4	0.1-0.8
All external cause of death (V01-Y89)	57	59.7	1.0	0.7-1.2
Persons	1,615			
Person years	58,742			
Unable to locate certificate	1			

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

Several characteristics contribute to the importance of this study. This is the largest single-plant group of trichlorophenol or 2,4,5-T 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.[10,11]

Each of the four studies of industrial workers with exposure estimates based on serum dioxin evaluations found increased total cancer rates with increasing exposure to 2,3,7,8-TCDD.[12-16] However, we find no association of total cancers with 2,3,7,8-TCDD. Indeed, overall our study group had cancer rates slightly less than expected.

It is possible, that the exposure levels in our study might be too low relative to the previous studies to demonstrate an exposure response. However, this explanation seems unlikely since such a large portion of the workers in our study developed chloracne. Further, these four previous studies while finding an increased risk for all cancers combined, found no particular cancer site consistently increased in each of the studies. For instance exposure responses were reported for digestive cancers in the study of Ott et al. lung cancer in the study of Steenland et al., but no specific cancer sites in Flesch-Janys et al.[3,13,14] We find no specific cancer site produces an exposure response in our study.

Table 2. Standardized mortality ratios (SMRs), number of observed deaths (obs), and 95% confidence intervals (95% CI) by cumulative area under the curve for 2,3,7,8-TCDD for selected causes of death.

Death category	**0-149.9 ppt-years SMR (95% CI)[obs]**	**150-999.9 ppt-years SMR (95% CI) [obs]**	**≥1000 ppt-years SMR (95% CI) [obs]**
All causes of death	0.9(0.8-1.1)[144]	0.9(0.8-1.0)[201]	0.9(0.8-1.0)[317]
All cancers	0.9(0.6-1.3)[35]	1.1(0.8-1.4)[62]	0.9(0.7-1.1)[80]
Lung cancer	0.7(0.3-1.3)[9]	1.1(0.7-1.7)[23]	0.4(0.2-0.7)[14]
Soft tissue sarcoma	4.2(0.1-23.6)[1]	3.2(0.1-17.9)[1]	4.7(0.6-17.0)[2]*
Non-Hodgkin's lymphoma	2.0(0.4-5.7)[3]	1.4(0.3-4.0)[3]	0.9(0.2-2.7)[3]
Ischemic heart disease	1.0(0.7-1.4)[40]	1.0(0.8-1.3)[63]	1.1(0.9-1.4)[115]
Diabetes	1.3(0.4-3.3)[4]	1.1(0.4-2.6)[5]	1.0(0.4-2.1)[7]
Persons	1,604	1,183	642
Person-Years	20,072	19,737	18,934

** Includes one misclassified renal clear-cell carcinoma.*

A causal relationship with all cancers combined in the absence of a specific cancer site consistently elevated across studies would be unique. Some have argued that dioxin may be late stage carcinogen producing cancers at many organ sites. This hypothesis does not explain the lack of consistency of specific cancer site findings across studies, howver. Others have proposed that confounding exposures could be producing the all cancer risk seen in many of the dioxin studies.[17] We think a dioxin etiology seems unlikely given the wide range of specific cancer risks seen across studies and other occupational exposures could be producing the all cancer increase.

Since the last update of this study a few years ago, two additional deaths categorized as soft tissue sarcoma have occurred.[5] The two new deaths were an angiosarcoma and malignant fibrous histiocytoma. The four presumed soft tissue sarcoma deaths all occurred and were diagnosed in the same small community of Midland, Michigan. Given the attention that the earlier soft tissue sarcoma deaths received, diagnostic bias might be a concern. 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.[9]

Our study produced very different results for all cancer risk and lung risk among workers exposed to relatively high levels of 2,3,7,8-TCDD than the three previous studies which have been used in cancer risk assessment. We find no consistent evidence that these trichlorophenol or 2,4,5-T workers have an increased risk of cancer collectively or in any type of cancer or disease that can be attributed to 2,3,7,8-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 2,3,7,8-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. IARC. Polychlorinated Dibenzo-para-dioxins and Polychlorinated Dibenzofurans. IARC Monogr Eval Carcinog Risks Hum 1997;69.
2. IOM. Veterans and Agent Orange: Update 2004. Washington, D.C.: National Academies Press, 2005.
3. Steenland K, Piacitelli L, Deddens J, Fingerhut M, Chang LI. J Natl Cancer Inst 1999;91(9):779-786.
4. Collins JJ, Bodner K, Wilken M, Haidar S, Burns CJ, Budinsky RA, Martin GD, Carson ML, Rowland JC. *J Exp Sci Environ Epidemiol* 2007;17:541-548.
5. Bodner KM, Collins JJ, Bloemen LJ, Carson M. *Occup Environ Med* 2003;60:672-675.
6. Bond GG, McLaren EA, Brenner FE, Cook RR. *J Occup Med* 1989;31(9):771-774.

7. Marsh GM, Youk AO, Stone RA, Sefcik S, Alcorn C. *J Occup Environ Med* 1998;40:351-362.
8. Aylward LL, Bodner KM, Collins JJ, Hays SM. *Organohalogen Compounds* 2007;69:2063-2066.
9. Suruda AJ, Ward EM, Fingerhut MA. *Epidemiology* 1993;4(1):14-19.
10. Ott MG, Olsen RA, Cook RR, Bond GG. *J Occup Med* 1987;29(5):422-429.
11. Bond GG, McLaren EA, Lipps TE, Cook RR. *Journal of Occupational Medicine* 1990;32:423.
12. Steenland K, Deddens J. *Ind Health* 2003;41:175-180.
13. Ott MG, Zober A. *Occup Environ Med* 1996;53:606-612.
14. Flesch-Janys D, Steindorf K, Gurn P, Becher H. *Environmental Health Perspective* 1998;106 (suppl.2):665-672.
15. Cheng H, Aylward L, Beall C, Starr TB, Brunet RC, Carrier G, Delzell E. *Risk Anal* 2006;26:1059-1071.
16. Hooiveld M, Heederick D, Kogevinas M, Boffetta P, Needham LL, Patterson DG, Bueno-de-Mesquita HB. *Am J Epidemiol* 1998;147(9):891-901.
17. Smith A, Lopipero P. *Am J Epidemiol* 2001;153(11):1045-1047.