

Epidemiology Comments on the EPA Draft Risk Assessment

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Characterizing the potential health risks from dioxin exposures has challenged toxicologists and epidemiologists for decades. Some of the very early work on the potential health effects from dioxins was done by The Dow Chemical Company (Dow), where, for instance, the first long term animal bioassay and first cohort mortality study on trichlorophenol workers exposed to 2,3,7,8-TCDD were conducted^{1,2} Since these early studies, Dow has continued to play an active role in furthering the science of assessing health risks from dioxins.

Over the past 30 years, Dow epidemiologists have updated the original cohort mortality study four times and have improved exposure assessment through the use of serum dioxin measurements on a sample of exposed workers.³⁻¹⁰ Dow scientists have also examined other health effects in these workers, including male-mediated reproductive outcomes,¹¹ blood chemistries, morbidity, self-reported symptoms,¹² and chloracne.¹³⁻¹⁵ Other than chloracne and possibly soft tissue sarcoma, no health effect have been found to be related to 2,3,7,8-TCDD.

Recently, a university group working with Dow scientists completed a study of former trichlorophenol workers at a Dow site in New Zealand. This investigation also employed a serum dioxin analysis to estimate past exposures to 2,3,7,8-TCDD, and concluded that there was no increased risk of any cause of death related to dioxin exposures.¹⁶⁻¹⁹

Using the same serum analysis methods, Dow scientists also studied effects of higher chlorinated dioxins, such as 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD, which are found in pentachlorophenol manufacture. These investigations likewise failed to find a correlation between worker mortality rates for any cause of death and workplace dioxin exposures. On the other hand, they did detect an increased risk of non-Hodgkin lymphoma in exposed workers that was not related to dioxin levels.^{20,21 8,22}

Dioxin exposure estimates in these studies benefitted from the availability of complete work history records and detailed industrial hygiene monitoring, which were validated by serum dioxin measurements and further corroborated at the US Dow location by the presence of chloracne among 12% of the workers. Chloracne findings are consistent with serum-derived exposure estimates of some US site workers that may have been 1,000 times above background.⁷

The use of serum analyses in these studies was valuable in reducing exposure misclassification and providing confidence in the modeling of the exposure-response. The US study is known to have the longest follow-up of any dioxin study ever done, 36 years on average and in some cases, up to 62 years.⁷ The use of serum measurements, the

quality of work history records, the extended length of follow-up, the variety of measured outcomes, and the demonstrated high levels of exposure combine to make these some of the most definitive studies ever conducted on dioxin-related health effects in chlorophenol workers. Other than the known chloracne relationship, Dow workers show little evidence of ill effects from dioxin exposures.

In their Dioxin Reassessment, the EPA concludes that TCDD is carcinogenic in humans. They claim the conclusion is based in part on "(m)ultiple occupational epidemiology studies showing strong evidence of an association between TCDD exposure and increased mortality from all cancer..." and "(e)pidemiology studies showing an association between TCDD exposure and certain cancers in individuals accidentally exposed to TCDD in Seveso..." , Dow's experience with its intensely-studied populations of exposed workers do not support the conclusions reach by the EPA.

References

1. Kociba RJ, Keyes DG, Beyer JE, Carreon RM, Wade CE, Dittenber DA, Kalnins RP, et al. Results of a Two-Year Chronic Toxicity and Oncogenicity Study of 2,3,7,8-TCDD in Rats. *Toxicol Appl Pharmacol* 1978;46:279-303.
2. Cook RR, Townsend JC, Ott MG, Silverstein LG. Mortality Experience of Employees Exposed to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD). *J Occup Med* 1980;22(8):530-532.
3. Cook RR, Bond GG, Olson RA, Ott MG. Update of the Mortality Experience of Workers Exposed to Chlorinated Dioxins. *Chemosphere* 1987;16(8/9):2111-2116.
4. Ott MG, Olsen RA, Cook RR, Bond GG. Cohort Mortality Study of Chemical Workers with Potential Exposure to the Higher Chlorinated Dioxins. *J Occup Med* 1987;29(5):422-429.
5. Bond GG, McLaren EA, Lipps TE, Cook RR. Update of Mortality Among Chemical Workers with Potential Exposure to the Higher Chlorinated Dioxins. *J Occup Med* 1989;31(2):121-123.
6. Bodner KM, Collins JJ, Bloemen LJ, Carson M. Cancer risk for chemical workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Occup Environ Med* 2003;60:672-675.
7. Collins JJ, Bodner K, Aylward LL, Wilken M, Bodnar CM. Mortality rates among trichlorophenol workers with exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Am J Epidemiol* 2009;170:501-506.
8. Collins JJ, Bodner K, Wilken M, Haidar S, Burns CJ, Budinsky RA, Martin GD, Carson ML, Rowland JC. Serum concentrations of chlorinated dibenzo-p-dioxins and dibenzofurans among former Michigan trichlorophenol and pentachlorophenol workers. *J Exp Sci Environ Epidemiol* 2007;17:541-548.
9. Collins JJ, Bodner K, Burns CJ, Budinsky RA, Lamparski LL, Wilken M, Martin GD, Carson ML. Body mass index and serum chlorinated dibenzo-p-dioxin and dibenzofuran levels. *Chemosphere* 2007;66:1079-1085.
10. Burns CJ, Collins JJ, Budinsky RA, Bodner K, Wilken M, Rowlands JC, Martin CD, Carson ML. Factors related to dioxin and furan body levels among Michigan workers. *Environ Res* 2008;106:250-256.
11. Townsend JC, Bodner KM, Van Peenen PFD, Olson RD, Cook RR. Survey of Reproductive Events of Wives of Employees Exposed to Chlorinated Dioxins. *Am J Epidemiol* 1982;115(5):695-713.
12. Bond GG, Ott MG, Brenner FE, Cook RR. Medical and Morbidity Surveillance Findings Among Employees Potentially Exposed to TCDD. *Br J Ind Med* 1983;40(3):318-324.
13. Bond GG, Cook RR, Brenner FE, McLaren EA. Evaluation of Mortality Patterns Among Chemical Workers with Chloracne. *Chemosphere* 1987;16(8/9):2117-2121.
14. Bond GG, McLaren EA, Brenner FE, Cook RR. Incidence of Chloracne Among Chemical Workers Potentially Exposed to Chlorinated Dioxins. *J Occup Med* 1989;31(9):771-774.
15. Bond GG, McLaren EA, Lipps TE, Cook RR. Effect of Reclassification of Chloracne Cases. *Journal of Occupational Medicine* 1990;32(5):423.

16. McBride DI, Burns CJ, Herbison GP, Humphry NF, Bodner K, Collins JJ. Mortality in employees at a New Zealand agrochemical manufacturing site. *Occup Med* 2009;doi:10.1093/occmed/kqp030.
17. McBride DI, Collins JJ, Humphry NF, Bodner KM, Aylward LL, Burns CJ, Wilken M. Mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin at a trichlorophenol plant in New Zealand. *J Occup Environ Health* 2009;51(9):1049-1056.
18. Aylward LL, Bodner KM, Collins JJ, Wilken M, McBride D, Burns CJ, Hays SM, Humphry N. TCDD exposure estimation for workers at a New Zealand 2,4,5-T manufacturing facility based on serum data. *Journal of Exposure Science and Environmental Epidemiology* 2010;doi:10.1038/jes.2009.31(20):417-426.
19. Burns CJ, Collins JJ, Humphry N, Bodner KM, Aylward LL, D M. Correlates of serum dioxin to self-reported exposure factors. *Environmental Research* 2010;110:131-136.
20. Ramlow JM, Spadacene NW, Hoag SR, Stafford BA, Cartmill JB, Lerner PJ. Mortality in a cohort of pentachlorophenol manufacturing workers, 1940-1989. *J Occup Med* 1996;30:180-194.
21. Collins JJ, Bodner K, Aylward LL, Wilken M, Swaen G, Budinsky RA, Rowlands C, Bodnar CM. Mortality rates among workers exposed to dioxins in the manufacture of pentachlorophenol. *J Occup Environ Med* 2009;51:1212-1219.
22. Collins JJ, Budinsky RA, Burns CJ, Lamparski LL, Carson ML, Martin GD, Wilken M. Serum dioxin levels in former chlorophenol workers. *J Exp Science Environ Epi* 2006;16:76-84.