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Relative Doses of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Using Alternative Dosimetrics: Comparison of the the NIOSH and Ranch Hand Populations

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Abstract

We present an analysis and extrapolation of the serum sampling data for the NIOSH and Ranch Hand populations using area-under-the-curve (AUC) of serum lipid TCDD concentration and peak and average serum lipid TCDD concentration. Compared to the NIOSH cohort, Ranch Hand members have experienced much lower biological exposures to TCDD, with many of the Ranch Hand members demonstrating TCDD exposures indistinguishable from background. Cancer epidemiology from the two populations is discussed in light of the relative exposure information.

Introduction

We previously presented a comparative analysis of the cancer dose-response for TCDD-induced carcinogenesis in rats and in workers in the NIOSH cohort of occupationally exposed persons using dosimetrics based upon the area-under-the-curve (AUC) of serum dioxin.¹⁾ The NIOSH cohort exhibited elevations in mortality from all cancers combined and for respiratory cancers. In order to add to our understanding of the carcinogenic dose-response for TCDD in humans, we are extending this analysis to data for two additional exposed populations: the United States Air Force "Ranch Hand" population and a subset of the Seveso population. We describe our preliminary analysis of the Ranch Hand data in this paper.

Methods

Members of the United States Air Force who served in Vietnam in units spraying herbicides (Ranch Hands) were exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin and carry elevated body burdens of TCDD compared to the general population.²⁾ The health status and mortality rates of the Ranch Hands compared to a control population of Air Force personnel who served in southeast Asia in the same time period are being tracked in an ongoing study using periodic medical examinations and mortality ascertainment.

We analyzed the biological dose of TCDD in this population using three biologically-based dosimetrics: peak serum lipid TCDD concentration (C_{peak}), lifetime area-under-the-curve

(AUC), and lifetime average serum lipid TCDD concentration. The AUC and C_{peak} were calculated using measured serum TCDD concentrations for the Ranch Hand population and the AUC and C_{avg} were calculated for the NIOSH cohort of occupationally exposed persons.

Briefly, the measured serum TCDD level at time of last exposure was used to calculate half-life for elimination and extrapolated back to time of first exposure for each individual during the study. It was assumed that serum level at time of first exposure was the same as in a three-part concentration. The AUC was estimated to estimate AUC, C_{peak} , and C_{avg} . A 1987 sample was below 1 ppt through his entire life. The AUC for 100 individuals, while overestimated, was within 10% of the true value.

The most recent serum TCDD concentration was measured on December 31, 1993.³⁾ The AUC was calculated for the whole group and for subgroups (flyer and nonflyer). Because this is a small number of cancer deaths, we noted that more than 20

Results and Discussion

Figures 1A, B are presented respectively, for the four groups. Table 1 presents the SMR for the whole and for the subgroups. The SMR was elevated only for the death from cancer.

Compared to the NIOSH cohort, the Ranch Hand population has experienced TCDD exposure and the low mortality rate from cancer dose-response compared to the NIOSH cohort.

Acknowledgements

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(AUC), and lifetime average serum lipid TCDD concentration (C_{avg}). These dosimetrics were calculated using measured serum lipid TCDD levels from the 1987 physical examination of the Ranch Hand population and demographic and tour-of-duty data on each individual. AUC, C_{peak} , and C_{avg} were calculated using the same methods we used previously to analyze the NIOSH cohort of occupationally exposed workers in the United States.⁴⁾

Briefly, the measured serum level from 1987 was back-extrapolated to an estimated peak level at time of last exposure (end of last tour of duty in the Ranch Hand unit) using a 7.5 year half-life for elimination and simple first-order kinetics. We assumed a constant rate of exposure for each individual during the tour(s) of duty sufficient to result in the estimated peak. Finally, we assumed that serum levels before exposure were constant at 5 ppt. These assumptions resulted in a three-part concentration time curve (time before, during, and after exposure) which we used to estimate AUC, C_{peak} , and C_{avg} for each individual. If the measured serum level from the 1987 sample was below 10 ppt, the individual was assumed to have had a constant serum level of 5 ppt through his entire life. This assumption may have underestimated exposure for some individuals, while overestimating exposure for others.

The most recent mortality analysis for the Ranch Hand cohort includes follow-up through December 31, 1993.³⁾ The mortality data in this study are reported for the Ranch Hands as a group and for subgroups defined by rank (officer, enlisted) and military occupation (flyer, nonflyer). Because this is a relatively young population (average age 58 in 1993), the expected number of cancer deaths are low. Although the average age of this population is low, it should be noted that more than 20 years have passed since last exposure for nearly the entire cohort.

Results and Discussion

Figures 1A, B and C present the distribution of the calculated AUC, C_{avg} , and C_{peak} respectively, for the four Ranch Hand subgroups compared to the NIOSH exposure duration groups. Table 1 presents the SMRs for all cancer mortality for the Ranch Hand population as a whole and for the subgroups described above from the most recent analysis.³⁾ The all-cancer SMR was elevated only in the nonflying officer group, but this elevation was based on a single death from cancer.

Compared to the NIOSH cohort, the Ranch Hand population experienced much lower TCDD exposure, regardless of dose measure used; many of the Ranch Hand cohort appear to have experienced TCDD exposures that are indistinguishable from background. This low exposure and the low number of deaths experienced to date, due to cancer make a quantitative cancer dose-response comparison between these two groups of little value.

Acknowledgements

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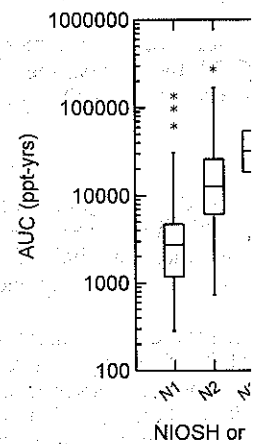
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Table 1: All cancer SMRs and 95% confidence intervals for Ranch Hands (mortality through Dec. 31, 1993)³⁾

Exposure Group	All Cancer SMR (Obs/Expected)	95% C.I.
Flying officer	87 (10/11.48)	44-155
Flying enlisted	102 (8/7.85)	47-194
Nonflying officer	173 (1/0.58)	9-850
Nonflying enlisted	83 (11/13.32)	44-155
All Ranch Hands	90 (30/33.22)	58-125

Figure 1: Box plot comparing Hand populations, by exposure rank and flight status for 1997. The box plots correspond to exposure rank and flight status for 1997: flying officers, nonflying officers, flying enlisted, and nonflying enlisted. Estimated lifetime area under the curve (AUC) for peak serum lipid TCDD concentrations (ppt-yr) is shown for each group.



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Figure 1: Box plot comparisons of serum lipid TCDD dosimetrics for the NIOSH and Ranch Hand populations, by exposure duration for the NIOSH cohort (groups N1, N2, N3, and N4 correspond to exposure durations of <1, 1 to <5, 5 to <15, and ≥ 15 years, respectively) and by rank and flight status for Ranch Hands (groups RH12, RH3, RH4, and RH5 correspond to flying officers, nonflying officers, flying enlisted, and nonflying enlisted, respectively). Figure A: Estimated lifetime area under the curve (AUC) of serum lipid TCDD concentration (ppt-yrs). Figure B: Estimated lifetime average serum lipid TCDD concentration (ppt). Figure C: Estimated peak serum lipid TCDD concentration (ppt).

