SERUM TCDD AND COGNITIVE FUNCTIONING IN VETERANS OF OPERATION RANCH HAND

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Introduction

To address the concerns of veterans, Congress, and the public about the consequences of exposure to Agent Orange and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the Air Force has been conducting a 20-year prospective study of veterans of Operation Ranch Hand, the unit responsible for handling and aerially spraying herbicides in Vietnam from 1962 through 1971. These men were exposed to herbicides while loading spray tanks, maintaining the aircraft and spray equipment, and in flight. Participants of the Air Force Health Study were administered physical and psychological examinations in 1982, 1985, 1987, 1992 and 1997.

In addition to concerns about physical health problems, veterans and their family members have expressed concern about the impact of Agent Orange exposure on cognitive functioning, such as attention and concentration skills, monitoring and regulation of memory information, and processing complex information. In this analysis, we examine the association between cognitive functioning and Agent Orange exposure by examining neuropsychological test results of Vietnam veterans participating in the Air Force Health Study[1].

Materials and Methods

The goal of the study is to determine whether veterans of Operation Ranch Hand have experienced adverse health effects due to exposure to herbicides or their TCDD contaminant. Health indices and the cumulative mortality experience of Ranch Hand veterans are contrasted with those of a comparison group of Air Force veterans who served in Southeast Asia during the same period as Ranch Hand veterans but were not involved with spraying herbicides. Comparison veterans are matched to Ranch Hand veterans on age, race, and military occupation. All Ranch Hand and comparison veterans are male.

During the 1987 examination, blood from willing participants was collected and assayed for TCDD. Veterans with no quantifiable TCDD result in 1987, those who refused TCDD testing in 1987, and subjects new to the study in 1992 were also asked to give blood for the assay at the 1992 examination. Participation was voluntary and written informed consent was obtained at the examination site after a complete description of the study and a full explanation of all procedures. For the purpose of this analysis, we excluded veterans with no TCDD measurement, those with a non-quantifiable TCDD result, and comparison veterans with a TCDD result greater than 10 parts

per trillion (ppt) in lipid, the value we regard as a threshold for background TCDD exposure. This resulted in inclusion of 937 Ranch Hand and 1,052 comparison veterans in these analyses.
We estimated the initial TCDD dose at the end of the last tour of duty in Vietnam in Ranch Hand veterans having current TCDD levels greater than 10 ppt, using a first-order model with a constant half-life of 8.7 years. We assigned each veteran to one of four exposure categories: comparison, background, low, and high. The comparison category comprised comparison veterans who had a 1987 or 1992 TCDD measurement less than or equal to 10 ppt. The background category comprised Ranch Hand veterans with a 1987 or 1992 TCDD measurement of less than or equal to 10 ppt. Ranch Hand veterans with a 1987 or 1992 TCDD measurement greater than 10 ppt were assigned to low or high TCDD categories if their initial TCDD levels were less than or equal to 94 ppt or greater than 94 ppt, respectively. The cut point separating the low and high categories (94 ppt) was the median initial TCDD level among all Ranch Hand veterans having 1987 or 1992 TCDD levels greater than 10 ppt. On the basis of these categorizations, we included 1,052 comparison veterans, 388 Ranch Hand veterans with background TCDD levels, 274 Ranch Hand veterans with low TCDD levels, and 275 Ranch Hand veterans with high TCDD levels.

Cognitive Assessment:
To assess cognitive functioning, we administered the Halstead-Reitan (HR) Neuropsychological Test Battery, a widely used assessment of a variety of cognitive and behavioral functions; the Wechsler Adult Intelligence Scale-Revised (WAIS-R), a standard measure of intelligence; the Wechsler Memory Scale (WMS), a standard measure of memory functions; and the reading subtest of the Wide Range Achievement Test (WRAT). For the HR, the test battery included the Category Test (total number of errors), the Tactual Performance Test (time to completion in minutes using dominant hand, non-dominant hand, and both hands; total time for the three trials; number of shapes reproduced from memory (tactual memory); and the total number of blocks drawn in proper relationship to other blocks on memory trial (localization)), the Seashore Rhythm Test (number of correct responses), the Speech-Sounds Perception Test (number of errors), the Finger-Tapping Test (average number of taps over five consecutive 10-second trials on dominant and non-dominant hands), measurements of grip strength (in kilograms), and Trail-Making Tests A and B (time to completion in seconds). We also calculated the Halstead Impairment Index on the basis of scores from the first seven HR measures. In addition to examining the Impairment Index as a continuous variable, we examined Impairment Index score categories. Impairment Index scores between 0 and 0.2 were categorized as normal, scores between 0.3 and 0.4 as mild, scores between 0.5 and 0.7 as moderate, and scores between 0.8 and 1.0 as severe. For the WAIS-R, we examined age adjusted scores on the information, digit span, vocabulary, arithmetic, comprehension, similarities, picture completion, picture arrangement, block design, object assembly, and digit symbol subscales. We also examined the verbal intelligence quotient (IQ), performance IQ, and full-scale IQ scores. For the WMS, we analyzed scores from the logical memory (immediate and delayed recall), visual reproduction (immediate and delayed recall), and associated learning subtests. For the WRAT, we examined the raw reading score. All cognitive function tests were administered in 1982.

We compared mean scores on the cognitive function scales by TCDD exposure category, adjusting for a number of demographic, military, and medical variables using main effects linear regression models with no stepwise reduction. We assessed the significance of differences between each of the three Ranch Hand TCDD exposure categories and the comparison category with 95%

confidence intervals for the difference of least-square means. We used logistic regression models to analyze the categorized Impairment Index. All analyses were conducted using SAS™ software (SAS/STAT™, 1997).

The adjustment variables included military occupation (officer, enlisted flyer, enlisted ground crew), age (in years at the time of the 1982 physical examination), race (black, non-black), drinking history (drink-years), marital status (married, not married), combat exposure, psychiatric diagnoses, and psychotropic medication use. Military occupation served as a surrogate for education because most officers were college educated, and most enlisted personnel were high school educated. We defined a drink-year as drinking one two-ounce shot of 80 proof whiskey, 12 ounces of beer, or 5 ounces of wine per day for 1 year.

We assessed combat exposure with a combat index designed for this study. The combat index was computed as a weighted sum of indicators of positive responses to fifteen questions, with positive (yes) responses indicated by 1 and negative (no) responses indicated by 0. The questions (and weights) were: Did you receive combat pay? (1), Crash land or bail out or were you shot down? (1), Receive sniper or sapper fire in or around the base? (1), Move killed or wounded personnel? (2), Serve as a forward air controller? (1), Fly the same aircraft when a fellow crewmember was wounded or killed? (2), Fly in the same formation or the same sortie when a fellow crewmember was wounded or killed? (1), Fly an aircraft that received battle damage? (1), Receive incoming artillery or rocket fire at your home base or camp? (1), Encounter mines or booby traps? (1), Engage VC or NVA in a firefight? (2), Did you kill VC or NVA in strafing or bombing runs? (2), Were you wounded? (2), Captured by the enemy? (2), Was a close friend killed in action? (2). Each veteran was assigned to one of four strata depending on whether his sum fell into the ranges 0-2, 3-5, 6-8, or 9 or greater, the approximate quartiles of the distribution.

We collected information on psychiatric diagnoses and psychotropic medication use during the 1982 physical examination. If the veteran reported that he had experienced mental or emotional illnesses, his written consent was obtained to access medical records in order to verify the diagnosis. We classified psychiatric diagnoses according to International Classification of Disease (ICD) codes following the ICD-9-Clinical Modification convention. Dichotomous (yes/no) variables for each of the following categories of psychiatric diagnoses were entered into the model for conditions verified by medical records: organic psychotic conditions (ICD codes 290-294), other psychoses (ICD codes 295-299), neurotic personality and other non-psychotic disorders (ICD codes 306-316, 300-302), and substance abuse (ICD codes 303-305). We classified medications according to American Hospital Formulary Service codes. By reviewing medical records, we verified the use of psychotropic medications, defined as psychotherapeutic agents (formulary code 28:16); antimanic agents (formulary code 28:28); or anxiolytics, sedatives and hypnotics (formulary code 28:24).

Results and Discussion

We found few significant differences in measures of cognitive functioning among veterans in the four TCDD categories. Although not significant, there was a decreasing trend in the mean HR tactual memory task among Ranch Hand veterans towards those with high TCDD levels (background: Mean = 6.21, low: Mean = 6.05, high: Mean = 5.98). The mean differences with the

comparison veterans were relatively small and of uncertain clinical significance. We found statistically significant differences on the HR finger-tapping and grip-strength tasks. Ranch Hand veterans in the low category scored lower than comparison veterans on the finger-tapping test (dominant hand: mean difference = -1.03, 95% CI = -1.87 to -0.19; non-dominant hand: mean difference = -0.83, 95% CI =-1.63 to -0.04), and Ranch Hand veterans in the background category scored lower than comparison veterans on non-dominant hand grip strength (mean difference = -1.04, 95% CI = -1.96 to -0.11). No significant or meaningful decrements were found in any Ranch Hand TCDD category with regard to the WAIS-R or WRAT results.

However, there was some indication that memory function may be affected among the veterans in the high TCDD category (Table 1). Ranch Hand veterans in the high category scored significantly lower than comparison veterans on both the immediate and delayed recall trials of the WMS logical memory task (immediate recall: mean difference = -0.5, 95% CI = -0.91 to -0.09; delayed recall: mean difference = -0.42, 95% CI = -0.80 to -0.03).

Table 1 Adjusted Wechsler Memory Scale means* by TCDD exposure category

Measurement	Comparison (N=1,195)	Ranch Hand Background (N=398)	Low (N=262)	High (N=264)
Logical Memory	7.45	7.28	7.23	6.95†
Logical Memory Delayed Recall	4.95	4.97	4.63	4.53§
Associate Learning	16.11	16.08	15.95	16.08
Visual Reproduction	9.62	9.74	9.73	9.59
Visual Reproduction Delayed Recall	8.33	8.51	8.37	8.26

*Adjusted for age, military occupation, race, drink years, marital status, substance abuse, combat exposure, organic psychotic conditions, other psychoses, psychotropic medication, neurotic personality and other psychotic disorders.
†$p<0.05$, p-value for contrast with the Comparison category.
§$p<0.05$, p-value for contrast with the Comparison category.

Our study found statistically significant differences between veterans with the highest TCDD levels and comparison veterans on several measures of memory functioning. Although these differences were statistically significant, they were relatively small, and additional research is needed to determine the robustness of these findings and to assess their clinical significance.

Reference

1. Barrett D., Morris R, Akhtar F, and Michalek J. (2001) (In submission).