

SERUM TCDD AND HEPATIC ABNORMALITIES IN VETERANS OF OPERATION RANCH HAND

Joel E. Michalek¹, Norma S. Ketchum¹, and Matthew P. Longnecker²

Air Force Research Laboratory, Brooks Air Force Base, Texas 78235-5250, USA¹, Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709, USA²

Introduction

To address concerns among Vietnam War veterans about the consequences of exposure to Agent Orange and other TCDD-contaminated herbicides, Congress in late 1978 directed the Air Force to begin planning the Air Force Health Study to evaluate the health, survival and reproductive experience of Air Force (Operation Ranch Hand) veterans

In this report from the Air Force Health Study, we examined the level of exposure to TCDD in relation to the prevalence of liver disease and hepatomegaly through March 1993, and in relation to the results of the liver function tests measured at the 1992 physical examination [alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyltransferase (GGT), lactic dehydrogenase (LDH), alkaline phosphatase, and total bilirubin]¹.

Materials and Methods

The Air Force Health Study is a 20-year prospective epidemiologic study begun in 1982 to determine whether veterans of Operation Ranch Hand, the men who conducted herbicide spray operations during the Vietnam war, have experienced adverse health as a consequence of exposure to herbicides or their TCDD contaminant. Ranch Hand veterans were exposed to herbicides during flight operations and maintenance of the aircraft and herbicide spray equipment. The study compares the health, reproductive experience and survival of Ranch Hand veterans, the index subjects, with a comparison group of other Air Force veterans involved with C-130 aircraft missions in Southeast Asia during the same period (1962 to 1971) that the Ranch Hand unit was active. Comparison veterans had similar training as that of Ranch Hands and were not involved with spraying herbicides in Southeast Asia. Comparisons were matched to Ranch Hands on date of birth, race (Black, non-black) and military occupation (officer pilot, officer navigator, nonflying officer, enlisted flyer, enlisted ground crew). In 1982, 1985, 1987 and 1992, participants were examined and medical records were retrieved and coded. Participation was voluntary and consent forms were signed at the examination site.

Among Ranch Hands having a TCDD level greater than 10 parts per trillion (ppt) serum lipid, the value we regard as an upper limit for background levels, we estimated the initial TCDD dose at the end of their service in Vietnam using a first order model with a constant half-life of 8.7 years. We assigned each veteran to one of four exposure categories, named "Comparison", "Background", "Low", and "High", according to his exposure group (Comparison, Ranch Hand), TCDD level and estimated initial TCDD level. The Comparison category was comprised of Comparison veterans

with TCDD levels less than or equal to 10 ppt. The Background category was comprised of Ranch Hand veterans with TCDD levels less than or equal to 10 ppt. We assigned Ranch Hands with TCDD levels greater than 10 ppt and estimated initial TCDD levels less than or equal to 94.1 ppt to the Low category and those with TCDD levels greater than 10 ppt and estimated initial TCDD levels greater than 94.1 ppt to the High category, where 94.1 ppt was the median estimated initial TCDD level among all Ranch Hands having TCDD levels greater than 10 ppt.

In 1992, ALT, AST, GGT, LDH, alkaline phosphatase, and total bilirubin were measured in serum with the Paramax Analytical System (Baxter Diagnostics Inc., Irvine, CA). The between-assay coefficient of variation at three different concentrations of ALT ranged from 3.4% to 11.5%, for AST ranged from 1.7% to 6.2%, for GGT ranged from 2.0% to 5.6%, for LDH ranged from 1.9% to 2.7%, for alkaline phosphatase ranged from 3.9% to 4.4%, and for total bilirubin ranged from 3.6% to 9.7%.

At each examination: 1) each participant was asked if a doctor had ever told him that he had an enlarged liver, cirrhosis or other liver condition, 2) a physician determined the presence or absence of hepatomegaly by palpation, and 3) the presence or absence of liver function test abnormalities was determined by laboratory examination. All conditions so identified that occurred after service in Southeast Asia and prior to April 1993 were verified by medical record review and were coded according to the *International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM)*. We grouped liver conditions into hepatomegaly (ICD 789.1), nonalcoholic chronic liver disease and cirrhosis (ICD 571.4-571.6, 571.8, 571.9) and other liver disorders [other disorders of the liver (ICD 573.0-573.9), nonspecific elevation of levels of transaminase or lactic acid dehydrogenase (ICD 790.4), other nonspecific abnormal serum enzyme levels (ICD 790.5), and nonspecific abnormal results of function studies of the liver (ICD 794.8)]. We also separately report results for three specific components of other liver disorders: unspecified disorders of the liver (ICD 573.9), nonspecific elevation of transaminase or LDH (ICD 790.4) and other nonspecific abnormal results of function studies of the liver (ICD 794.8). Abnormal levels of AST, ALT or LDH were coded as ICD 790.4 and abnormal levels of GGT were coded as ICD 794.8. AST, ALT, GGT, LDH, alkaline phosphatase and total bilirubin were measured at every physical examination. Because the liver function test results for 1992 were not consistently different from those of previous examinations, we chose to present only the 1992 results in this report.

Measures of smoking and drinking were derived from interview responses. We asked each veteran to identify periods during his life in which he drank alcoholic beverages and periods in which he did not drink. We asked him to specify how much he drank each day during each of the periods that he drank. Based on this information, we computed the number of drink-years of alcohol consumption, where we defined one drink-year as the equivalent of drinking 1.5 ounces of 80-proof whiskey (or, equivalently, 5 ounces of wine or 12 ounces of beer) per day for 1 year. Current alcohol use was based on reported alcohol consumption for the month prior to completing the questionnaire (dichotomized to >1 drinks/day, 0-1 drinks/day). Current cigarette smoking was based on self-report at the time the questionnaire was administered and was categorized as "yes" or "no". Smoking history was computed based on reported lifetime history of cigarette smoking and was measured in pack-years, where one pack-year was defined as smoking 365 packs of cigarettes per year. Exposure to industrial chemicals and degreasing chemicals represent lifetime exposure

based on self-report and were categorized as "yes" or "no". We defined percent body fat (PBF) as $PBF = 1.26 \times BMI - 13.305$, where BMI is the body mass index [weight (kg) divided by the square of height (m)].

We included in the analysis of liver conditions veterans (N=2,602) who volunteered for at least one physical examination (Ranch Hand: 1,109, Comparison: 1,493). We excluded 240 veterans (Ranch Hand: 100, Comparison: 140) who had missing TCDD measurements, 39 (Ranch Hand: 5, Comparison: 34) who had detectable TCDD results less than the LOQ, and 28 who received no result (Ranch Hand: 12, Comparison: 16), 25 Comparison veterans with TCDD levels greater than 10 ppt, and 17 (Ranch Hand: 5, Comparison: 12) with a history of liver disease prior to their service in Southeast Asia. After these exclusions, the numbers of veterans included in the analysis of hepatic disease were Comparison: 1,266, Background: 420, Low: 284, High: 283. We excluded veterans with detectable TCDD levels less than the LOQ because we could not quantify their levels and, therefore, could not assign them to an exposure category.

Statistical analyses of AST, ALT, GGT, LDH, alkaline phosphatase and total bilirubin were restricted to the 2,233 veterans who volunteered for the 1992 physical examination (Ranch Hand: 953, Comparison: 1,280). We excluded 35 veterans (Ranch Hand: 12, Comparison: 23) who had missing TCDD measurements, 27 who had detectable TCDD levels less than the LOQ (Ranch Hand: 3, Comparison: 24), 17 (Ranch Hand: 7, Comparison: 10) who received no result, 24 Comparison veterans with TCDD levels greater than 10 ppt, 4 veterans (Ranch Hand: 3, Comparison: 1) with fever (temperature $\geq 100^\circ$ F) at the time the blood was drawn and 7 (Ranch Hand: 4, Comparison: 3) who tested positive for hepatitis B surface antigen. The resultant numbers of veterans included in the analyses by TCDD category were Comparison: 1,195, Background: 398, Low: 262, High: 264. We adjusted analyses of history of liver disease for birth year (continuous variable), PBF (continuous variable), race (Black, nonBlack), military occupation (officers, enlisted flight engineers, enlisted ground crew), lifetime industrial chemical exposure (yes or no), lifetime degreasing chemical exposure (yes or no), lifetime drinking history (drink-years) and lifetime smoking history (pack-years). When analyzing ALT, AST, GGT, LDH, alkaline phosphatase, and total bilirubin, we additionally adjusted for current alcohol use (dichotomized to >1 drinks/day, 0-1 drinks/day) and current smoking.

Results and Discussion

The adjusted odds of hepatomegaly among veterans in the High category was nonsignificantly increased relative to veterans in the Comparison category (adjusted OR=1.4, 95% CI 0.7 to 3.1). The percentages of veterans in the Low (27.2%) and High (36.0%) categories who had a history of other liver disorders were greater than the percentage of veterans in the Comparison category (25.7%) and the adjusted odds of other liver disorders was significantly increased in the High category relative to the Comparison category (adjusted OR=1.6, 95% CI 1.2 to 2.1). There was an excess of nonspecific elevation of levels of transaminase or LDH in the High category; 6.6% of the veterans in the High category and 2.5% of veterans in the Comparison category were diagnosed with this condition (adjusted OR=2.7, 95% CI 1.4 to 5.1). The adjusted odds of other nonspecific abnormal results of function studies of the liver was significantly increased in the High category (adjusted OR=1.4, 95% CI 1.0 to 2.0). No excess was apparent for any of the other component conditions.

The mean GGT (Table 1) in the High category (mean=43.6 U/L) was significantly increased relative to the comparison group. Among Ranch Hands, the mean GGT increased with TCDD category at every examination (shown only for 1992). The mean alkaline phosphatase in the Low category (73.2 U/L) was significantly increased.

Table 1 Mean hepatic laboratory measurements at the 1992 physical examination by TCDD exposure category

Measurement	Comparison (N=1,195)	Ranch Hand		
		Background (N=398)	Low (N=262)	High (N=264)
AST	24.4	24.0	24.0	23.8
ALT	27.5	26.5	26.9	27.1
GGT	40.0	38.5	41.7	43.6 [§]
LDH	146.8	147.2	147.6	145.7
Alkaline Phosphatase	70.2	72.0	73.2 [¶]	71.4
Total Bilirubin	0.62	0.62	0.62	0.59

§p≤0.05, p-value for contrast with the Comparison category on natural logarithm scale.

¶p=0.02, p-value for contrast with the Comparison category on natural logarithm scale.

Overall, Ranch Hand veterans with the highest TCDD exposure were more likely than Comparisons to have a history of abnormal serum enzyme levels and liver function test results. The liver disorders associated with TCDD exposure primarily reflected earlier increases in ALT and continued increased levels of GGT. Evidence of clinically significant liver disease associated with TCDD exposure was limited to the increase in hepatomegaly, which was as an equivocal finding. The increased levels of ALT and GGT in the most highly exposed may have been due to confounding or reverse causality, thus these data provide no strong evidence of TCDD or herbicide-induced liver disease among veterans of Operation Ranch Hand.

Reference

1. Michalek, J., Ketchum N., and Longnecker M. (2001) Ann Epidemiol (In press).