

**HYPERTENSION AND SERUM 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) AND HYPERTENSION IN THE AIR FORCE VETERANS OF THE VIETNAM WAR**

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**Introduction**

We examined hypertension in relation to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure in veterans participating in the Air Force Health Study, an epidemiological investigation of veterans of Operation Ranch Hand, the unit responsible for the aerial spraying of herbicides, including Agent Orange, in Vietnam from 1962 to 1971. These data were gathered between 1982 and 1998 from Air Force veterans whose exposure in Vietnam occurred up to 35 years earlier.

**Methods and Materials**

The Air Force Health Study is an ongoing 20-year prospective epidemiologic study that seeks to determine if veterans of Operation Ranch Hand (the Air Force personnel who conducted aerial herbicide spray operations during the Vietnam conflict) have experienced adverse health that can be attributed to exposure to herbicides or their TCDD contaminant. Details of the study design and subject selection are described elsewhere<sup>1</sup>. A Comparison group of other Air Force veterans who served in Southeast Asia during the same period that the Ranch Hand unit was active but who were not involved with spraying herbicides was included. Comparison veterans were matched to Ranch Hands with respect to age, race and military occupation. All study subjects were male. Physical examinations were performed in 1982, 1985, 1987, 1992 and 1997. Participation was voluntary and informed consent was given at the examination sites.

We report analyses of hypertension and TCDD body burden among veterans who participated in the 1982, 1985, 1987, 1992 and 1997 studies. Beginning in 1987, blood from willing veterans was collected and TCDD was measured in serum at the Centers for Disease Control and Prevention and expressed as parts per trillion (ppt) serum lipid.

All veterans attending the 1987 physical examination were invited to give blood for the TCDD assay. Veterans with no quantifiable TCDD result in 1987, those who refused in 1987 and veterans new to the study in 1992 were invited to give blood for the assay at the 1992 examination; those with no quantifiable level in 1987 or 1992 were invited to give blood for the assay in 1997. Of the 2,121 veterans who attended the 1997 physical examination, at least one TCDD assay result was available for 2,101 (99.1 %). We assigned TCDD levels less than the limit of detection a value equal to one half of the limit of detection and levels greater than or equal to the limit of detection but less than the limit of quantitation a value equal to one half of the limit of quantitation.

At each examination each participant was asked if a doctor had ever told him that he had hypertension, and a physician made blood pressure measurements. All reported conditions that occurred after service in Southeast Asia and prior to April 1999 were verified by medical record review and were coded according to the International Classification of Diseases, 9<sup>th</sup> Edition, Clinical Modification (ICD-9-CM). We studied the occurrence of diagnosed hypertension (ICD 401). We did

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**Table 1.** Sample reduction, TCDD quintile ranges, and post-SEA hypertension in 2,417 Vietnam veterans.

Cohort	TCDD Quintile:[Range <sup>†</sup> ]	N	Hypertension		
			Pre-SEA <sup>‡</sup>	Net	Post-SEA
Comparison		1,571*	(21)	1,550	
No TCDD result		135	(0)	135	
Net		1,436	(21)	1,415	579 (40.9)
	1: [0.30 to 2.40]	288	(2)	286	70 (24.5)
	2: [2.42 to 3.42]	287	(5)	282	109 (38.7)
	3: [3.43 to 4.39]	287	(1)	286	118 (41.3)
	4: [4.40 to 5.75]	285	(7)	278	134 (48.2)
	5: [5.76 to 54.8]	289	(6)	283	148 (52.3)
Ranch Hand		1,111*	(14)	1,097	
No TCDD result		95	(0)	95	
Net		1,016	(14)	1,002	405 (40.4)
	1: [0.40 to 5.35]	203	(2)	201	52 (25.9)
	2: [5.38 to 9.10]	203	(3)	200	78 (39.0)
	3: [9.19 to 16.40]	204	(3)	201	88 (43.8)
	4: [16.47 to 35.50]	203	(4)	199	93 (46.7)
	5: [35.8 to 617.8]	203	(2)	201	94 (46.8)
Net		2,452	(35)	2,417	984 (40.7)

\*Compliant to at least one of five physical examinations (in 1982, 1985, 1987, 1992 or 1997).

<sup>†</sup>Parts per trillion., <sup>‡</sup>Prior to service in Southeast Asia.

not study blood pressure measurements because many study participants had taken or were taking medications to control their blood pressure. We excluded veterans with TCDD and those with diagnosed hypertension prior to their service in Southeast Asia. Missing TCDD levels were caused by refusal, noncompliance to the physical examination, death, or a failure of one or more quality control checks and insufficient sample to repeat the analysis. We grouped veterans within each cohort according to the quintiles of the TCDD distribution. Both the sample reduction and the net sample sizes by TCDD quintile and cohort are summarized in Table 1.

We computed body mass index (BMI) as weight (kg) divided by the square of height (m<sup>2</sup>). We defined a pack-year as smoking one pack of cigarettes per day for one year and a drink-year as drinking one shot of 80-proof whiskey (or, equivalently, 12 ounces of beer or 5 ounces of wine) per day for one year. We adjusted all analyses for age at the end of service in Southeast Asia, race (Black, nonblack), military occupation (officer, enlisted flyer, enlisted ground crew), BMI at the end of service in Southeast Asia, the change in BMI from the end of service in Southeast Asia to the TCDD measurement, lifetime cigarette smoking history up to the baseline physical examination in 1982 (pack-years), lifetime drinking history up to the baseline physical examination in 1982 (drink-years), serum

**Table 2.** Relative risk of hypertension by quintile of TCDD relative to the first quintile of the Comparison group.

TCDD Quintile	Model 1* RR (95 % CI)	Model 2* RR (95 % CI)	Model 3* RR (95 % CI)
<b>Comparison</b>			
1	Reference for both groups		
2	1.42 <sup>§</sup> (1.07 to 1.88)	1.45 <sup>§</sup> (1.09 to 1.93)	1.51 <sup>  </sup> (1.13 to 2.01)
3	1.52 <sup>  </sup> (1.15 to 2.01)	1.44 <sup>§</sup> (1.09 to 1.90)	1.39 <sup>§</sup> (1.05 to 1.84)
4	1.82 <sup>¶</sup> (1.39 to 2.38)	1.63 <sup>¶</sup> (1.24 to 2.14)	1.62 <sup>¶</sup> (1.23 to 2.14)
5	1.88 <sup>¶</sup> (1.44 to 2.46)	1.65 <sup>¶</sup> (1.25 to 2.16)	1.58 <sup>  </sup> (1.20 to 2.08)
<b>Ranch Hand</b>			
1	0.77 (0.55 to 1.09)	0.93 (0.65 to 1.31)	1.02 (0.72 to 1.45)
2	1.36 (1.00 to 1.85)	1.41 <sup>§</sup> (1.03 to 1.92)	1.48 <sup>§</sup> (1.09 to 2.03)
3	1.48 <sup>§</sup> (1.10 to 1.99)	1.44 <sup>§</sup> (1.07 to 1.95)	1.43 <sup>§</sup> (1.06 to 1.93)
4	1.81 <sup>¶</sup> (1.36 to 2.43)	1.67 <sup>¶</sup> (1.24 to 2.24)	1.60 <sup>  </sup> (1.19 to 2.15)
5	1.98 <sup>¶</sup> (1.48 to 2.66)	1.75 <sup>¶</sup> (1.30 to 2.37)	1.60 <sup>  </sup> (1.18 to 2.16)

\*Unadjusted for covariates. †Adjusted for military occupation, race, age at the end of service in Southeast Asia, and BMI at the end of service in Southeast Asia. ‡Adjusted for military occupation, race, age at the end of service in Southeast Asia, and BMI at the end of service in Southeast Asia, drink-years, pack-years, change in body mass index from the end of service in Southeast Asia to the TCDD measurement, lipids (total cholesterol, HDL cholesterol and triglycerides in the serum used for the TCDD measurement), family history of hypertension, and family history of stroke. § Significantly different from 1.0 (p<0.05). || Significantly different from 1.0 (p<0.01). ¶ Significantly different from 1.0 (p<0.001).

lipids (total cholesterol, HDL cholesterol, and triglycerides) measured in the serum used for the TCDD measurement, family history of hypertension (yes, no), and family history of stroke in first degree relatives (father, mother, or sibling) (yes, no). We estimated the relative risk of hypertension in the 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup> TCDD quintile in the Comparison group and all five TCDD quintiles in the Ranch Hand group relative to the 1<sup>st</sup> TCDD quintile in the Comparison group. All analyses were stratified by year of birth in 5-year intervals (II1920, 1921-1925, 1926-1930, 1931-1935, 1936-1940, 1941-1945, 1946-1950). We conducted two-sided testing with a significance level of 5% throughout and used SAS® software (SAS Institute, Carey, NC).

**Results and Discussion**

The median TCDD in the Ranch Hand group (11.6 ppt) was significantly greater than the median (3.9 ppt) in the Comparison group (p<0.001). The two groups were similar with regard to all measured demographic attributes, partly due to the matching on age, race and military occupation. The mean total cholesterol, HDL cholesterol, triglycerides, and the percentage with a family history of hypertension or

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stroke were also similar in both groups. We found no difference in the risk of hypertension between the Ranch Hand and comparison cohorts (RR=1.02, 95 % CI 0.90 to 1.16, p=0.76).

Body mass index was a correlate of both hypertension and TCDD. Veterans who were heavier early in life were at increased risk of hypertension; 60.9 % of Comparisons (42 of 69) and 63.0 % of Ranch Hands (29 of 46) with BMI<sup>30</sup> kg/m<sup>2</sup> at the end of their tour of duty in Southeast Asia were subsequently diagnosed as hypertensive, a significant increase in both cohorts (p<0.001 and p=0.006, respectively, after adjustment for age).

Table 2 summarizes the relative risk of hypertension by quintile of serum TCDD in the Comparison and Ranch Hand cohorts, with the lowest quintile of the Comparison group as the referent, for each of three statistical models: 1) unadjusted, 2) adjusted for military occupation, race, age at the end of service in Southeast Asia, and BMI at the end of service in Southeast Asia, and 3) adjusted for military occupation, race, age at the end of service in Southeast Asia, and BMI at the end of service in Southeast Asia, drink-years, pack-years, change in body mass index from the end of service in Southeast Asia to the TCDD measurement, lipids (total cholesterol, HDL cholesterol and triglycerides in the serum used for the TCDD measurement), family history of hypertension, and family history of stroke. The relative risks were significantly increased in the 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup> quintiles of the Comparison group both cohorts using each of the three models and in the Ranch Hand group using models 2 and 3.

We found no difference in the risk of hypertension between a cohort with exposure to TCDD-contaminated herbicides in Vietnam and a matched comparison cohort (RR=1.02, 95 % CI 0.90 to 1.16, p=0.76). However, within each of the two cohorts, serum TCDD was significantly and adversely related to the risk of hypertension. This relation was not explained by differences in lifestyle (such as alcohol consumption) or family history of hypertension, BMI at the end of service in Southeast Asia, changes in BMI, serum triglyceride levels, although all of these contributed significantly to the model. A possible explanation for this pattern is that tissue TCDD level, is indicative of metabolic factors that are causal in the development of hypertension.

## Reference

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