

**EFFECTS OF TCDD ON THYROID METABOLISM IN US AIR FORCE
HERBICIDE SPRAYERS**

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Introduction

The Air Force Health Study (AFHS) is a 20-year prospective study of health, mortality and reproductive outcomes in veterans of Operation Ranch Hand, the Air Force unit responsible for the aerial spraying of herbicides, including Agent Orange, in Vietnam from 1962 to 1971.¹⁻³ Other Air Force veterans who were not involved with spraying herbicides were included as Comparisons. Approximately 19 million gallons of herbicides, including Agent Orange, was sprayed by Operation Ranch Hand from fixed wing C-123 aircraft in the south of Vietnam for purposes of defoliation and crop destruction. Agent Orange was contaminated in the production process with 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) [mean=3 parts per million (ppm), range: 0.5 to 50 ppm]. Results of animal studies⁴⁻⁷, studies in infants⁸⁻¹⁰ and some occupational studies in chemical workers¹¹⁻¹³ suggest that TCDD may be involved in alterations of thyroid function manifested primarily as decrease in thyroxine (T4) and increase in thyroid stimulating hormone (TSH) levels. The present study examines potential physiological changes and health effects related to thyroid function in association with TCDD blood in US Air Force veterans.

Methods

Data were available for 1,009 Ranch Hand and 1,429 Comparison veterans compliant to any of five examinations in 1982, 1985, 1987, 1992, and 1997. The 1987 examination included measurement of serum TCDD levels by high-resolution gas chromatography and high-resolution mass spectrometry.¹⁴ Each veteran was assigned to one of four exposure categories based on his exposure group (Ranch Hand, Comparison), TCDD concentration, and half-life extrapolated Vietnam-era TCDD concentration, named Comparison, Ranch Hand Background (<10 parts per trillion (ppt)), Ranch Hand Low Elevated (10 to 94 ppt), and Ranch Hand High Elevated (>94 ppt). Demographic characteristics of included US Air Force veterans are presented in Table 1.

We analyzed thyroxine (total T4), thyroid stimulating hormone (TSH), triiodothyronin percent uptake (T3% uptake), the free thyroxine index (FTI), and thyroid diseases against serum TCDD levels. Self reported thyroid diseases were verified by medical record review. The International Classification of Diseases (ICD 9-CM) codes 240 to 246 were used to identify thyroid diseases. We used analyses of covariance to contrast the mean of logarithmically transformed TSH, total T4, T3% uptake, and FTI, in the Ranch Hand High, Low and Background categories with the Comparison category. We used a repeated measures linear model for longitudinal analyses of thyroid biochemical parameters over all five physical examinations and logistic regression to evaluate the association between the presence of abnormal thyroid hormone levels or the presence of thyroid disease and TCDD category. All analyses were adjusted for age, race, and military occupation.

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Table 1. Demographic characteristics of US Air Force veterans by TCDD category

	Comparison	Ranch Hand		
		Background	Low	High
Mean TCDD [(SD) ppt]	4.6 (2.9)	5.8 (2.3)	15.6 (4.1)	69.4 (67.9)
Median	4.1	5.7	14.7	45.7
Range	0.4-54.8	0.6-10.0	10.0-25.6	18.0-617.8
Extrapolated Mean ^a TCDD [(SD) ppt] ^a			55.0 (18.0)	302.5 (327.3)
Median			51.7	194.7
Range			27.2-93.8	94-3290.2
Age (years)	48.8 (7.7)	49.9 (7.4)	50.2 (7.7)	46.3 (7.2)
BMI [(SD) kg/m ²]	27.8 (4.1)	26.4 (3.4)	27.9 (3.9)	28.9 (3.9)
Black [Number (%)]	77 (6.1)	21 (5.1)	24 (8.7)	13 (4.7)
Military occupation				
Officer	481 (38)	253 (61)	107 (39)	9 (3)
Enlisted flyer	203 (16)	51 (12)	57 (21)	59 (21)
Enlisted ground crew	580 (46)	110 (27)	111 (40)	209 (75)
Drink Years (Median)	15.8	13.7	16.5	15.3
Pack Years (Median)	7.9	8.0	7.9	8.0

^a Half-life extrapolated at the end of the last tour of duty in Vietnam.

Results

Cross-sectional analyses found statistically significantly increased TSH means at the 1985 and 1987 examinations in the High category and a significant increasing trend across the four TCDD categories in 1982, 1985, 1987 and 1992 (Table 2). Inclusion of veterans taking thyroid medication at the time of the hormone level measurements did not influence the direction or magnitude of the estimates. No significant differences between any Ranch Hand TCDD category and the Comparison category with regard to mean levels of total T4 (Table 2), T 3 % uptake, or FTI (data not shown) were observed at any examination.

A repeated-measures analysis found significantly elevated TSH means in the High and Low TCDD categories from the mean in the Comparison category ($p=0.008$, and $p=0.04$, data not shown). Longitudinal analyses of total T 4 and T 3 % uptake found no significant mean differences between any Ranch Hand TCDD category and the Comparison category.

In the High TCDD category the odds of abnormally high TSH levels were consistently elevated at all five examinations, but none reached statistical significance (data not shown). We also analyzed abnormally low T4 levels, association between thyroidal or microsomal antibodies, but did not observe any significantly increased or decreased risk in any Ranch Hand TCDD category (data not shown). We found no significant relation between the occurrence of thyroid disease and TCDD category (Table 3).

Discussion

Cross sectional analyses provided modest evidence of a dose-response elevation in mean TSH in relation to TCDD category at all five examinations. The longitudinal analysis of TSH versus TCDD category provided stronger support for a dose-response elevation in the mean TSH. The odds of thyroid

Table 2. Mean^a levels of TSH by year of physical examination and TCDD category

	1982	1985	1987	1992	1997	
TSH ^b						
Comparison		3.46	1.12	0.83	1.36	1.58
Ranch Hand Background		3.51	1.15	0.84	1.39	1.63
Low		3.55	1.17	0.87	1.40	1.66
High		3.63	1.22	0.90	1.44	1.65
p for trend		0.03	0.01	0.003	0.05	0.06
Thyroxin (T4)						
Comparison		7.94	7.26	7.47	7.65	6.84
Ranch Hand Background		8.04	7.27	7.56	7.61	6.87
Low		7.98	7.41	7.54	7.68	7.00
High		7.88	7.22	7.56	7.53	6.98
p for trend		0.44	0.94	0.73	0.38	0.40

^a Geometric least-square means, adjusted for age, race, and military occupation.

^b Thyroid hormone levels in IU/ml

Table 3. Thyroid stimulating hormone means by TCDD category

	Comparison	Ranch Hand		
		Background	Low	High
Mean ^{ab} (1987 Mean ^c)	-0.17 (0.99)	-0.13 (1.02)	-0.09 (1.07)	-0.06 (1.14)
Mean Difference	0	0.05	0.09	0.11
P-value ^d		0.19	0.04	0.008

^a Least-square means, adjusted for birth year and race. ^b Hormone measure is log transformed and standardized (mean = 0, standard deviation = 1). ^c Unadjusted mean in 1987. ^d P-values for contrasts of Ranch Hand and Comparison TCDD category means.

Table 3. Thyroid diseases by TCDD exposure category

Disease	Comparison	Ranch Hand			
		Background	Low	High	
Non-toxic nodular goiter	Number (%)	23 (1.6)	6 (1.4)	4 (1.4)	2 (0.7)
	OR ^a	1.0	0.7	0.8	0.6
	95 % CI		0.3-1.8	0.3-2.4	0.1-2.8
Hypothyroidism	Number (%)	11 (0.8)	6 (1.4)	3 (1.1)	2 (0.7)
	OR ^a	1.0	1.7	1.4	0.9
	95 % CI		0.6-4.8	0.4-5.2	0.2-4.5
Any thyroid disease	Number (%)	50 (3.5)	13 (3.0)	8 (2.9)	12 (4.2)
	OR ^a	1.0	0.9	0.8	1.3
	95 % CI		0.4-1.6	0.4-1.7	0.6-2.5
Any thyroid disease	Number (%)	111 (7.8)	37 (8.4)	20 (7.1)	20 (6.9)
	OR ^a	1.0	1.1	1.0	0.8
	95 % CI		0.7-1.6	0.7-1.6	0.5-1.4

^a Adjusted for age, race, and military occupation.

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disease was not significantly increased in the Ranch Hand High category. Our findings are in agreement with observations from animal experiments and two studies of human infants suggesting that exposure to TCDD can affect the thyroid pituitary axis leading to increased TSH levels.⁸⁻⁹ Together with results describing higher risk of diabetes mellitus in

Ranch Hand and Comparison veterans²⁻³ it provides a further evidence of endocrine disruptive effects of TCDD in adults. Further follow-up will be necessary to understand the relation, if any, between thyroid disease and TCDD levels.

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