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Description Notes

Serum 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Levels in US Army Vietnam-Era Veterans

The Centers for Disease Control Veterans Health Studies

This study investigates whether military records can be used to identify US Army Vietnam veterans who were likely to be exposed to the herbicide Agent Orange. Serum levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a toxic contaminant in Agent Orange, were obtained for 646 ground combat troops who served in heavily sprayed areas of Vietnam and for 97 veterans who did not serve in Vietnam. The distributions of current TCDD levels in Vietnam and non-Vietnam veterans were nearly identical (mean in each group, ≈4 parts per trillion [ppt]). Only two men (both Vietnam veterans) had clearly elevated levels (>20 ppt). Levels of TCDD did not tend to increase with greater likelihood of exposure to Agent Orange, as estimated from either military records or self-reported exposure. This study is consistent with other studies and suggests that most US Army ground troops who served in Vietnam were not heavily exposed to TCDD, except perhaps men whose jobs involved handling herbicides.

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THE HERBICIDE Agent Orange, a 1:1 mixture of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid in diesel oil, was sprayed in South Vietnam from 1962 to 1970. The herbicide contained 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) at levels of less than 1 to more than 20 ppm[1,2] as a result of contamination of the 2,4,5-trichlorophenoxyacetic acid and possibly the 2,4-dichlorophenoxyacetic acid components. Heavy exposure to TCDD causes chloracne,[3] may be associated with certain cancers,[4] and may affect enzyme levels, porphyrin metabolism, and immune function.[3] Many Vietnam veterans are concerned that their health may have been affected by exposure to Agent Orange, especially by exposure to its TCDD contaminant.

In response to these concerns (Veterans Health Programs Extension and Improvement Act of 1979, Public Law 96-151 [HR 3892], 93 STAT 1092-1098; and Veterans' Health Care, Training, and Small Business Loan Act of 1981, Public Law 97-72 [HR 3499], 95 STAT 1047-1063), the Centers for Disease Control (CDC) is conducting two relevant studies: a "Vietnam experience" cohort study, comparing male US Army Vietnam veterans with other veterans,[5-7] and case-control studies of veterans' risks of six cancers suggested to be associated with exposure to TCDD. To evaluate the concerns about Agent Orange directly, the CDC proposed a cohort study in which the health of veterans exposed to Agent Orange would be compared with that of unexposed veterans, using records of military unit locations and herbicide spray locations to assess exposure. Evaluation of these records, however, suggested that they alone could not be used to estimate likelihood of exposure. For example, records may be unavailable for many of the herbicide applications most likely to have exposed troops.

Recent studies have shown that high TCDD levels can be detected 20 or more years after heavy exposure to Agent Orange[8-10] and that the half-life of TCDD in humans may be about seven years.[11] Results suggest that these TCDD levels may be used as an objective marker of exposure. The development of a serum assay[12] and its strong correlation with adipose tissue levels[10,13] made a large study of TCDD levels of veterans feasible. The study reported herein, the first large-scale study to evaluate TCDD levels in US Army veterans, was conducted to determine if military records can be used to identify veterans exposed to Agent Orange. The CDC compared current TCDD levels of Vietnam veterans with exposure estimates based on military records and with TCDD levels of veterans not serving in Vietnam.

SUBJECTS AND METHODS

Use of Military Records

The US military recorded the dates and locations of herbicide sprays in South Vietnam for Operation Ranch Hand missions[14] and for some other sprays.[15] Most herbicide was sprayed from fixed-wing aircraft in Operation Ranch Hand,[16] but herbicides also were sprayed from helicopters, trucks, and backpack equipment, especially around base camps. Some recorded sprays were of unknown type (herbicides or insecticides).

Military unit locations and personnel records were abstracted from military records by the US Army and Joint Services Environmental Support Group. The Environmental Support Group identified 65 US Army combat battalions (27 infantry, 25 artillery, seven armor or cavalry, and six engineering)

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that served 18 months or longer in the III Corps military region (encompassing Saigon) during 1967 and 1968. This region had the greatest volume of Agent Orange spraying of the four military regions in Vietnam, with heavy spraying in 1967 and 1968. After abstracting the daily company locations for a battalion for 1967 to 1968, the Environmental Support Group abstracted military service information for veterans who had served in that battalion during 1967 and 1968, including veterans' dates of service in various companies. The CDC used this information to compute exposure scores for individual veterans.

When this study began, the Environmental Support Group had abstracted company locations for 50 of the 65 identified battalions. For each day of the study and for each company in these 50 battalions, five exposure scores were computed from the dates and map coordinates of herbicide sprays and from military unit locations. Scores were then assigned to each Vietnam veteran by using the dates he served in various companies.

Exposure Scores

Estimated half-lives of TCDD in the environment depend on environmental conditions. The half-life may be a few hours on foliage,[17] several days on or near the soil surface,[17-19] and several years if adsorbed to soil.[20-23] The five different scoring methods based on military records reflect these varying environmental half-lives and different assumptions about completeness of data on troop and spray locations.

The intermediate score reflects possible exposure during the first few days after spraying. This score is the weighted number of days on which at least one location for a company was within 2 km of a recorded Agent Orange spray within six days after the spray; the weight was the number of different sprays this close to a company location. The distance 2 km was chosen because the dispersion of herbicide from Operation Ranch Hand sprays could cover a path hundreds of meters wide and because unit locations could be imprecise, in part due to movement around recorded locations. In selecting subjects, we sampled all men with a high intermediate score in an attempt to include those most likely to have been exposed.

Four other scores also use military records to estimate exposure. The slow score is the weighted number of days a company was within 2 km of an Agent Orange spray after any earlier spray, with weights computed for a five-year half-life (similar to the decay of TCDD adsorbed to soil). Because some recorded sprays of "unknown" material undoubtedly were of Agent Orange, unknown agent intermediate and slow scores also were computed for these sprays. The remaining score based on military records, the area score, is the number of days a company was in one of five large, heavily sprayed regions, which included 70% of the recorded Agent Orange sprays in III Corps during 1967 and 1968. This score depends less on precise military unit location information than do the other scores.

Two other scores were the number of days of self-reported direct exposure and of indirect exposure to herbicides during military service, derived from a structured interview. Direct exposure includes spraying herbicides or being present during spraying, handling herbicides, and getting herbicides on one's skin or clothing. Indirect exposure includes walking through or clearing vegetation in a previously sprayed area.

Few pairs of these scores are well correlated. Spearman correlations among the records-based scores were less than .40, except for three pairs of scores (slow and area, the two intermediate scores, and the two unknown-agent scores), for which the correlations were between .50 and .60. The correlation between the two self-reported scores was .38. All correlations between the records-based and self-reported scores were less than .10. These low correlations indicate that the different scores could reflect different sources of exposure.

The records-based scores were computed from relatively complete data on military unit location. For half of the veterans studied, locations were available for their military units for at least 96% of their days in Vietnam, and three fourths had a location available for at least 89% of those days.

Selection of Participants

All veterans in this study served a single term of enlistment (minimum, 16 weeks; usually two to three years) in the US Army. Each had a military occupational specialty other than "duty soldier" or "trainee" and was discharged at pay grade E-5 or lower (this excluded officers). Deceased veterans were excluded; deaths were identified from the records of various US government agencies and from tracing individual veterans.[24]

In addition to these basic eligibility criteria, Vietnam veterans must have served in Vietnam during 1967 and 1968 in a company for which the Environmental Support Group had abstracted locations. Men who served only in headquarters and headquarters companies were excluded because locations for these companies were considered unreliable for estimating exposure. Vietnam veterans served an average of about 320 days in Vietnam.

When this study began, personnel records had been abstracted for 14 473 Vietnam veterans, 816 of whom had died. Key data were missing or inconsistent for 253 men, and exposure scores could not be computed for an additional 3677 because no locations were available for their Army units. We selected 994 Vietnam veterans by stratifying the 9727 eligible men according to the intermediate Agent Orange score. We included all those with a score of 5 or more. For comparison, we sampled men with scores of 1 through 4 and selected all veterans least likely to have been exposed (score of 0, unknown-agent intermediate score of 0 or 1, and at most 44 days for which the unit location was unknown). During the study, 15 veterans were found to be incligible (seven were dead, five were mentally handicapped or in prison, and three did not meet basic eligibility criteria), leaving 979 eligible Vietnam veterans. The Environmental Support Group verified that each veteran was present in his company on each day he had an opportunity for exposure according to the intermediate score.

US Army veterans who did not serve in Vietnam were included as a reference group. These men, all of whom entered the Army between 1965 and 1971, were sampled from men interviewed near the end of the Vietnam Experience Study but who had not been selected to attend the medical examination phase of the study and who served in the continental United States or Germany. The 200 men invited to participate were a random sample from the 367 who met these eligibility criteria, frequency-matched by race (white or nonwhite) and age (younger than 40 years old on Jan 1, 1986) to the Vietnam veterans originally selected.

Data Collection

Data were obtained by methods similar to those used in the Vietnam Experience Study.[5-7] The Research Triangle Institute (Research Triangle Park, NC) and its subcontractor, Equifax Inc (Atlanta), located the veterans, and the Research Triangle Institute conducted a telephone interview. All 871 Vietnam veterans interviewed were invited to take part in a medical examination at Lovelace Medical Foundation (Albuquerque), as were the 200 non-Vietnam veterans who had been interviewed during the Vietnam Experience Study.

As part of the medical examination, serum samples were collected for TCDD measurements, and men were questioned about exposure to herbicides during military service, civilian work, and at home.

Laboratory Methods

Serum samples were collected under a standard protocol. Each participant fasted overnight and then ate a low-fat, low-cholesterol breakfast. About two hours later, 450 mL of blood was collected in a 500-mL bag that did not contain anticoagulant. A sample of the collection bags was tested for TCDD and its analytic interferences; none showed contamination. Serum samples were separated, then stored at −70°C. Analysis of TCDD and serum lipid was done at the Division of Environmental Health Laboratory Sciences, Center for Environmental Health and Injury Control, CDC. We used only laboratory runs that met quality-control criteria.

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin was analyzed by high-resolution gas chromatography/high-resolution mass spectrometry.[12,24] Values are on a lipid weight basis, in units of parts per trillion (ppt), calculated by dividing TCDD on a whole weight basis by total serum lipid content. In general, 100 g of serum was analyzed, with a TCDD detection limit of 3 parts per quadrillion on a whole weight basis, or roughly 1 ppt on a lipid weight basis. Less than 1% of the samples were below this limit; these "nondetects" were given a value of 0 for analysis. Replicate analyses of quality-control pools indicate a coefficient of variation of about 20%.

Statistical Methods

Results of this and other studies suggest that TCDD levels can be described by a log-normal distribution.[25] Some TCDD values were 0 (the nondetects), so the logarithm of the TCDD value plus one was used in analysis of variance and linear regression models. These models were used to verify that adjustment for potential confounders does not affect the associations observed in univariate analyses between exposure scores and TCDD levels. To reduce skewness, all continuous scores except the area score were used as the logarithm of one plus the score in these models. Detectable levels in each cohort were adequately described by a log-normal distribution ($P>.06$), based on the Kolmogorov statistic.[26]

Current age, race (white or nonwhite), body mass index (kilograms per meter squared), and self-reported civilian occupational and home exposures to herbicides were judged a priori to be potential confounders. Smoking history, alcohol consumption, and region of residence were included as additional covariates based on preliminary data analyses. Continuous covariates were used as categorical variables, generally based on quartiles.[27]

RESULTS

Participation

Of the 979 eligible Vietnam veterans, 900 (92%) were located and 871 completed the interview. Of the 29 located but not interviewed, 27 refused to participate and two could not be contacted. Blood samples were obtained from 665 Vietnam and 103 non-Vietnam veterans. Results of TCDD analyses that met laboratory quality-control criteria were obtained for 646 Vietnam veterans and 97 non-Vietnam veterans, or 66% and 48%, respectively, of those eligible for the study. Participation was similar among the three exposure groups used to select Vietnam veterans.

Most demographic and other characteristics of Vietnam veterans, summarized in Table 1, were similar to those of veterans who did not serve in Vietnam. Herbicide exposure was an important exception: Vietnam veterans were much more likely than non-Vietnam veterans to report exposure to herbicides during military service, but less likely to report civilian exposure. These characteristics, as well as length of service in Vietnam and reported combat intensity, were similar in the Vietnam veterans in the three exposure groups defined by the intermediate score.

Demographic and military characteristics as well as exposure scores were similar for Vietnam veterans for whom TCDD values were and were not obtained. In contrast, interviewed Vietnam veterans for whom TCDD results were not obtained were less likely to report exposure to herbicides during military service or physical health problems after discharge from service than were Vietnam veterans for whom TCDD results were obtained (Table 2).

Table 1.—Selected Characteristics of 743 US Army Vietnam-Era Veterans With Serum 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Level Measurements

Characteristic	Vietnam Veterans (N=646)	Non-Vietnam Veterans (N=97)
Demographic characteristics		
Mean age, y	40	39
Race, % nonwhite	26	22
Region of residence, %		
West	20	19
Northeast	16	16
Other	64	65
Current health characteristics		
Smoking, % current cigarette smokers	49	49
Alcohol use, mean No. of drinks per mo	62	54
Mean body mass index, kg/m²	27	27
Mean total serum lipid level, mg/dL	631	606
Self-reported herbicide exposure, %*		
Military		
Direct	25	6
Indirect	71	6
Civilian occupational, any	20	33
Home use, any	33	44

*Exposure as reported at an interview during a medical examination during 1986 and 1987.

Table 2.—Selected Self-reported Characteristics of 871 Interviewed US Army Vietnam Veterans*

Characteristic	Vietnam Veterans	
	TCDD Level (N=646)	No TCDD Level (N=225)
Herbicide exposure in Vietnam, %†		
Direct	33	24
Indirect	72	58
None	28	41
Overall health poor or fair, %	29	18
No. of hospitalizations since discharge, %		
1 or 2	39	34
≥3	18	8
No. of health problems due to exposure to Agent Orange, %		
1	14	8
≥2	14	6

*All responses were obtained during a telephone interview during 1986 and 1987. TCDD indicates 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

†These questions were less detailed than the corresponding questions in the medical examination interview.

TCDD Levels and Exposure Scores

The distributions of current TCDD levels in the 646 Vietnam and 97 non-Vietnam veterans are similar, with a mean and median in each group of about 4 ppt (Figure and Table 3). These findings were confirmed by analysis of variance models, in which service in Vietnam was not associated with TCDD level, after adjusting for age, race, region of residence, body mass index, smoking history, alcohol consumption, and reported civilian herbicide exposure ($P=.23$).

The TCDD levels of veterans did not tend to increase with increases in any of their five exposure scores based on military records or with increases in either of their self-reported exposure scores. In each group defined by one of these scores, the median TCDD level was between 3.2 and 4.3 ppt (Table 4), and each of the 75th and 90th percentiles was not more than 0.5 ppt greater than the corresponding percentile in non-Vietnam veterans. Cross-tabulation by pairs of scores also did not identify veterans who were likely to have elevated levels. Regression models using individual scores, pairs of scores, or all seven scores also showed no trend toward higher TCDD levels in veterans with higher exposure scores or more self-re-

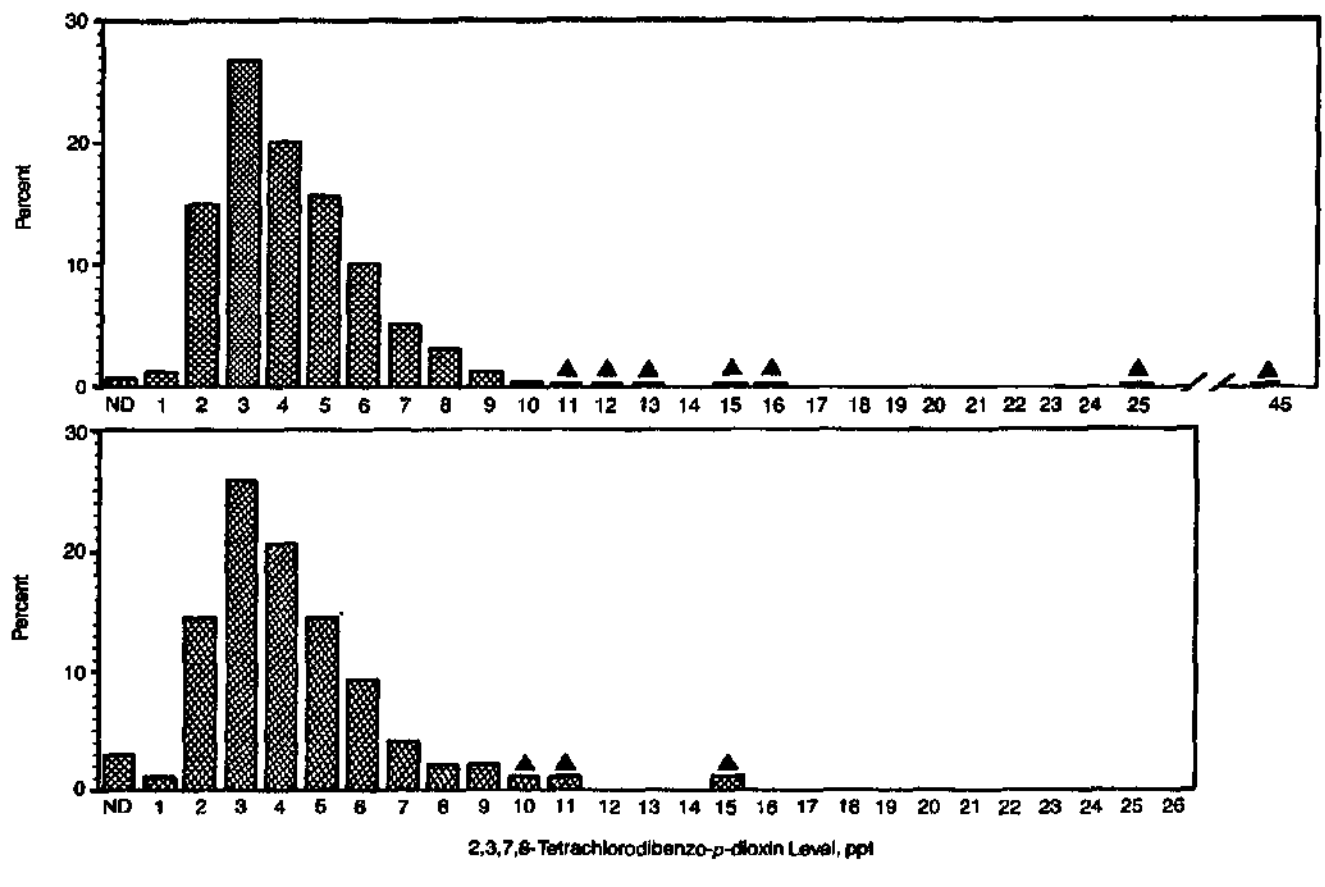
Table 3.—Distribution of Current Serum 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Levels in 743 Vietnam-Era Veterans, 1987

Place of Service	Mean ± SD	Percentile				
		25th	50th	75th	90th	95th
Non-Vietnam (n = 97)	4.1 ± 2.3	2.8	3.8	4.9	7.2	9.2
Vietnam (n = 646)	4.2 ± 2.6	2.8	3.8	5.1	6.8	7.8

Table 4.—Median Current Serum 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Levels in 646 US Army Vietnam Veterans*

Score Category	Exposure Scores						
	Based on Military Records					Based on Self-reported Exposure at Interview	
	Agent Orange Score		Unknown-Agent Score		Area Score‡		
	Intermediate†	Slow‡	Intermediate§	Slow‡		Direct§	Indirect‡
Minimal	. . .	3.8	3.8	3.7	4.0	3.8	3.9
Low	3.9	3.9	3.9	3.7	3.6	3.2	3.6
Medium	3.4	3.8	3.8	3.9	3.9	3.8	3.6
High	3.6	3.5	3.4	3.6	3.7	4.3	4.3
P	.21	.83	.89	.81	.57	.06	.06

*The range of values of each score was two to three orders of magnitude. *P* indicates significance of the test for the variability of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin levels among the groups indicated.
†Intermediate score was used to select veterans. Low group includes 298 veterans; medium group, 167 veterans; and high group, 191 veterans.
‡Groups based on approximate quartiles of scores; 141 to 168 veterans in each group. For the indirect score, minimal exposure is no reported exposure.
§Minimal exposure is a score of 0 (375 veterans for the unknown-agent intermediate score and 482 for direct exposure). The other groups are based on approximate tertiles of those with some potential exposure, with 41 to 133 veterans in each of these groups.



Distribution of current serum 2,3,7,8-tetrachlorodibenzo-*p*-dioxin levels in US Army Vietnam (top) (N = 646) and non-Vietnam (bottom) (N = 97) veterans. ND indicates nondetectable; ppt, parts per trillion; and closed triangle, one man.

ported exposures to herbicides in Vietnam. Levels were not elevated in veterans who served in any one company or battalion.

Table 4 does suggest some variability in TCDD levels among the groups defined by each of the self-reported exposure scores. However, the 75th and 90th percentiles of the TCDD levels were not elevated in either the 41 veterans reporting the most frequent direct exposure or the 153 men reporting the most frequent indirect exposure to herbicides in Vietnam.

Nine Vietnam veterans had TCDD levels of 10 ppt or higher, two of whom had levels above 20 ppt (25 and 45 ppt). The veteran whose level was 45 ppt reported no exposure (military or civilian) to herbicides; the veteran whose level was 25 ppt reported 180 days of indirect military exposure to herbicides (about the 85th percentile, half the days he served in Vietnam) and one day of home use, but no other exposure. These two men each reported their health status as "excellent" and did not attribute any health problems to Agent Orange exposure. Self-reported herbicide exposure was unremarkable in the other seven men whose levels were above 10 ppt. Four reported direct exposure to herbicides during military service (up to 15 days), four reported indirect exposure (up to 130 days), and one reported occupational exposure (200 days).

To study the possibility that results might have been distorted ("confounded") by differences between study groups, we examined the associations between TCDD levels and the characteristics listed in Table 1. No characteristic was a good predictor of TCDD level, and most were similarly distributed between groups (Table 1) so that confounding was unlikely. Lack of confounding was confirmed by regression models that included appropriate indicator terms for each covariate. These models showed no trend toward higher TCDD levels in veterans with higher exposure scores or more self-reported herbicide exposure after adjustment for covariates.

COMMENT

This is the first report on TCDD levels in a large group of US Army Vietnam veterans. The CDC conducted this study to determine if exposure scores based on military records of troop locations and spray locations can identify a large number of men exposed to Agent Orange, as would be needed for a large cohort study. The five different methods that use these records incorporate a wide variety of assumptions about sources of possible TCDD exposure and about the completeness and accuracy of the military records. None of the indirect measures of exposure, and neither type of self-reported exposure to herbicides, identified Vietnam veterans who were likely to have currently elevated serum TCDD levels. In particular, only two Vietnam veterans (0.3% of the sample) had serum TCDD levels greater than 20 ppt, and neither had an unusually high exposure score. It is unlikely, therefore, that military records can be used to identify a large number of US Army veterans who might have been heavily exposed to TCDD in Vietnam. In addition, the distributions of current TCDD levels were nearly identical in Vietnam and non-Vietnam veterans.

The similarity between current TCDD levels in Vietnam and non-Vietnam veterans in this study is not entirely due to elimination of TCDD since service in Vietnam. Other studies, some of which used adipose tissue samples, have found that a substantial proportion of people with documented heavy exposure to TCDD continue to have levels above 20 ppt 15 or more years after exposure. Levels of TCDD higher than 100 ppt have been found 15 or more years after the last known exposure to TCDD in Vietnam veterans[8-10,28] and civilians.[25,29] Recent results suggest a TCDD half-life in humans of about seven years, independent of initial TCDD level.[12] Moreover, serum TCDD levels correlate strongly with adipose levels.[30,19] As a result, we should have found more than two veterans with high current TCDD levels if many men in our study had been heavily exposed in Vietnam.

Our failure to detect a difference in TCDD levels between the cohorts is unlikely to result from a sample size that was too small. This study could have detected differences even if only a moderate proportion of Vietnam veterans had elevated TCDD levels while they were in Vietnam. For example, assuming first-order kinetics, a half-life of seven years, and a background level of 4 ppt, a TCDD level of 33 ppt drops to about 8 ppt after 20 years, and a level of 18 ppt drops to 6 ppt. Thus, the current mean TCDD level in Vietnam veterans should be 1 to 2 ppt higher than that of non-Vietnam veterans if at least 25% of Vietnam veterans had levels above about 30 ppt while in Vietnam. This study had 99% power to detect such a difference in the mean level, using a two-sided test at the .05 level. No such difference was observed.

There is no indication of selection bias or confounding in this study. Among Vietnam veterans for whom records were abstracted, demographic and military service characteristics of veterans selected for study were similar to those of veterans who were not selected. Interviewed Vietnam and non-Vietnam veterans were similar with respect to most measured characteristics (Table 1). Civilian herbicide exposure was reported somewhat more often by non-Vietnam veterans, but adjustment for this exposure did not affect our results. Similarly, results were not affected by adjustment for other potential confounders, including age, race, body mass index, region of residence, smoking, and alcohol consumption.

Although participation rates in this study were modest (66% of the Vietnam and 48% of the non-Vietnam veterans), indirect evidence suggests this was unlikely to cause bias. Demographic, military, and health characteristics, such as smoking and alcohol consumption, were similar in the interviewed veterans who did and who did not provide blood. Only nine interviewed veterans gave a medical condition as a reason for not attending the medical examination; in the literature, TCDD has not been documented to cause any of these conditions. Interviewed Vietnam veterans for whom TCDD levels were measured, however, reported poorer health and more exposure to herbicides than those for whom values were not obtained (Table 2). Thus, the TCDD levels in this study are not likely to be spuriously low due to poorer participation by veterans who may have had health problems related to TCDD or who thought they were exposed to herbicide. If anything, the opposite may be true.

Results from this study cannot necessarily be generalized to other Vietnam veterans since our sample was not random. All Vietnam veteran participants served in the heavily sprayed III Corps area during 1967 and 1968, and, as a result of the selection method, 611 of the 646 for whom TCDD values were obtained (more than 94%) served in one of five battalions (three infantry, one cavalry, and one artillery). In addition, the study did not include veterans from a relatively small group with a high potential for exposure, the chemical corps.[5,10]

Despite these limitations, our results are consistent with those of the three other studies of current TCDD levels in Vietnam veterans. In those studies, investigators found elevated current levels (>20 ppt) only in veterans who had handled herbicides in Vietnam. Kahn et al[9,10] reported elevated levels in some Operation Ranch Hand and chemical corps veterans, but not in other ground troops. Schecter et al[28] also found elevated levels in some Operation Ranch

Hand veterans, but none in ground troops. Gross et al[8] found elevated TCDD levels in three veterans classified as "heavily exposed" to Agent Orange but did not report their source of exposure or branch of service. In this context, our results are not surprising, as only about 5% of the Vietnam veterans in our study reported spraying herbicides or handling spray equipment during military service.

Except for two veterans who had levels greater than 20 ppt, current serum TCDD levels in this study are essentially the same in the Vietnam veterans and the comparable group of veterans who did not serve in Vietnam. It seems, therefore, that most US Army ground combat troops who did not handle or spray herbicides were not heavily exposed to TCDD in Vietnam.

The CDC has prepared a comprehensive report of the findings from this study for other federal agencies. Copies can be obtained from the Centers for Disease Control, 1600 Clifton Rd NE, C-25, Mailstop F-16, Atlanta, GA 30333.

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