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# DRAFT

## 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) in Body Fat of Vietnam Veterans and Other Men

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Chicago, IL; and Veterans Administration Central Office, Washington, D.C.

Summary: TCDD in surgical biopsy specimens of fat from twenty  
veterans (A) reporting Agent Orange exposure in Vietnam, ten veterans (B)  
without Vietnam experience and (C) three Air Force officers recently  
exposed to Agent Orange and TCDD. In A 10/20, in B 2/10, and in C 2/3 men  
had detectable TCDD. The highest concentrations (in A) were 99 and 35  
ppt.; none others exceed 12 ppt. Gas chromatography - mass spectrometry  
currently cannot prove Agent Orange exposure.

The past three years have seen mounting concern over exposure to the  
defoliant 2,4,5-trichlorophenoxyacetic acid (2,3,5-T), an ingredient of  
Agent Orange used by the United States Armed Forces in Vietnam from 1965  
to 1971. Some lots of 2,4,5-T contained small amounts of a contaminant,  
2,3,7,8-tetrachlorodibenzo-p-dioxin, also called TCDD or "dioxin". TCDD  
is highly toxic to animals (1) and has been claimed to produce chronic and  
delayed adverse effects among American veterans who served in Vietnam.

TCDD accumulates preferentially in the body fat of experimental  
animals (2) and man (3). It has been postulated that the compound remains  
in adipose tissue for years and damages the individual who subsequently

loses fat and mobilizes the substance (4). TCDD has a half-life of 30 days in the fat of rats (5) and guinea pigs (7) and 105 to 125 days in the adipose tissue of cows (7). No one has investigated the possibility that TCDD remains more than eight years in the fat of veterans who served in Vietnam that long ago.

Analytic methods for identifying and measuring TCDD have been improved in recent years so that it is possible to assay fat for quantities as small as a few parts per trillion, i.e. a few picograms per gram or little more than 0.000000000001 gram of TCDD per gram of tissue (8). Because results were uncertain and the method complicated and difficult, a pilot trial seemed more appropriate than a full-scale study to determine whether the assay discriminates between veterans who were exposed to Agent Orange a decade or so earlier and men who were not. The study might also indicate whether specific symptoms were associated with detectible TCDD in an individual's body fat.

Subjects: Three groups of men served as subjects and all signed informed consents for biopsies. The smallest group of three Air Force officers had handled Agent Orange in field tests or in disposal operations and had worked with the herbicide and TCDD in a laboratory. All three reported repeated contact with the chemicals and all had been exposed within the prior two years.

The second and largest group of twenty volunteers was self-selected; each believed that he was exposed to Agent Orange in Vietnam prior to 1971 and all but one claimed health problems as a consequence. The exposure of these men was recorded as they reported; tours of duty in Vietnam and military classifications were obtained from service records.

The third or control group of ten veterans contained volunteers with no Vietnam service and no known exposure to Agent Orange or related chemicals. Their biopsies were obtained during otherwise necessary abdominal operations.

Methods: Surgeons removed 10 to 30 grams of subcutaneous fat from the abdominal wall under local anesthesia in the case of the 23 "exposed" men. A similar specimen was removed during operation from each of the ten "unexposed" controls. Precautions were taken before during and after the procedure to avoid contamination by products, e.g., hexachlorophene, that could contain TCDD. Specimens were collected in glass containers previously rinsed with acetone and dried before use. All tissues were refrigerated during shipment to the assay laboratory.

The methods of extraction, gas chromatography, and mass spectrometry are described by Gross (8) who performed the analyses. As he reports a second laboratory assayed 15 of the 23 specimens using a somewhat different technique; only Gross' results are considered here in order to maintain uniformity of the method used for all volunteers. The assays in both laboratories were performed without knowledge of which specimens came from "exposed" and which from "unexposed" men.

Each of the volunteers had a medical history, physical examination, and routine clinical chemistry. The clinical data were reviewed, seeking correlations between them and the assay results. The details of military service in Vietnam from the volunteer's report and his service record were examined to evaluate his exposure to Agent Orange using the dates, location, and nature of his service. From these a rough estimate of the likelihood of exposure was made without knowledge of the assay results.

Results: The assay results are reported in Table I. Details and comparisons with those from the second laboratory are given by Gross (8). Where the assay is indicated as negative despite an apparently detectible amount of TCDD, the chemist was unable to confirm the identity as TCDD.

One of the three Air Force officers with known exposure had no identified TCDD in his fat. The unidentified substance in his case and the TCDD measured in the other two officers was never more than 3 parts per trillion (3 picograms per gram) above the limit of detection.

Of the twenty veterans from Vietnam, seven had no detectible TCDD with the limit of detection at 2 to 6 parts per trillion (ppt). Another two (numbers 6 and 8) had detectible material that could not be validated as TCDD and the results for two (numbers 11 and 14) were considered equivocal because the measured value was only questionably above the detection limit. Four of the nine remaining Vietnam veterans had TCDD in amounts from 5 ppt to 7 ppt. Five men had TCDD in concentrations above those of the controls. One (number 26) had 63 to 99 ppt; another (number 10) had \_\_\_\_ to 35 ppt.

Of the ten "unexposed" veterans, two had TCDD identified in their fat; neither had more than 8 ppt. Two other veterans (numbers 17 and 32) had values low enough to be considered equivocal and in five instances the detected material was not validated as TCDD. The remaining veteran had no detectible TCDD. No specimen was submitted for the assigned number 22.

Veterans were divided into three groups on the basis of exposure in Vietnam to Agent Orange. One contained the three volunteers (numbers 10, 19 and 26) who were judged to be most heavily exposed. They included handling the defoliant among their duties in Vietnam. Five other veterans judged to have had little likelihood of exposure to Agent Orange

either because their location was removed from the areas sprayed (numbers 1, 15 and 34), because the dates of their Vietnam duty (numbers 13 and 28) or its short duration (number 1) reduced the chances of exposure, or because the description of exposure was questionable (number 34). The remaining twelve Vietnam veterans appear to have had an intermediate likelihood of exposure, i.e. between that of the other groups.

Among the most heavily exposed men, two (numbers 10 and 26) had the highest TCDD content in their body fat but the other man (number 19) had no identifiable TCDD. Two of the lightly exposed men (numbers 1 and 13) had no detectible TCDD but the other three did have.

Six of the twelve men judged to have had intermediate exposure were ground combat troops; three had TCDD in their fat, three did not. Of the six other veterans, two had detectible TCDD and three did not; one with a doubtful level was a helicopter gunner who described some contact with Agent Orange.

Table II summarizes the clinical information regarding all twenty Vietnam veterans. Seven of them (numbers 9, 13, 15, 26, 27, 29 and 30) reported some health problems beginning during a tour of duty in Vietnam. No two, however, reported the same symptoms. The remaining thirteen veterans reported no illness in Vietnam although only one reported good health at all times. Among the nineteen veterans with current medical complaints, symptoms and diagnoses varied widely without any common pattern. Five had mental problems ranging from nervousness to schizophrenia (numbers 9, 13, 15, 30 and 34) and three had experienced difficulties of reproduction, namely, spontaneous abortion by the wives of

two (numbers 11 and 15) and congenital heart disease in the son of a third (number 16).

Four of the seven veterans who reported difficulties while in Vietnam had no TCDD detected; the other three had 7 to 99 ppt. The five veterans with mental problems included three without detectible TCDD and three whose assays results were 5 to 7 ppt. One of three veterans reporting reproductive problems had no detected TCDD, one had a doubtful level, and one had 7 ppt. Detectible TCDD in the body fat could not be correlated with clinical chemical findings.

Discussion: Gross (8) concluded that his assay is capable of detecting and measuring a few parts per trillion of TCDD in human fat. The present technique is, however, difficult and delicate and may not be free of error. The determinations require surgical biopsy, a minor operation, performed under conditions that avoid contamination with TCDD.

TCDD has been found in substances other than 2,4,5-T (1). It and closely related chemicals could have been acquired by "exposed" and "unexposed" veterans from the civilian environment long after they left military service. There is no known source of TCDD, however, in the surroundings of a steel mill crane operator and student nor of an artist, the two men with the greatest concentrations of the compound. It is impossible to determine when, in what amounts, and from what source the subjects could have acquired TCDD.

TCDD was found in some persons who report exposure to Agent Orange and in others who were never in Vietnam. On the other hand, some veterans from Vietnam had no detectible TCDD and the same is true of veterans who were never in Vietnam. The low level of TCDD in two Air Force officers and its absence in another is of special interest since their exposure to

TCDD is certain and more recent than that of the veterans.

Among the twenty Vietnam veterans there was no uniformity of symptoms, either immediately after exposure, at the time of biopsy, or during the intervening period. No one symptom or group of symptoms was common to veterans with detectible TCDD in their fat. The presence of TCDD did not mean ill health nor did its absence indicate good health. No detailed statistical analysis was attempted of this small pilot series.

The TCDD content in the fat was very small, not exceeding 100 ppt. Since TCDD accumulates in fat more than in other tissues, the average body concentration would be much lower. Even if all tissues contained 100 ppt., however, the concentration would be 0.1 microgram per kilogram of body weight, too far below the demonstrated toxic dose to threaten health.

Conclusions: The present assay for TCDD in fat tissue does not offer a satisfactory routine test for exposure to Agent Orange, providing neither clear evidence of contact with that specific defoliant nor of absence of such contact. The assay technique is difficult and not readily available, fat samples must be obtained by surgical biopsy, and the source of any TCDD detected is uncertain. The current assay method does provide a research tool under proper conditions and for specific purposes, e.g., for determining the rate of disappearance of TCDD after known exposure.

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Table I. TCDD in Human Fat Samples (after Gross (6))

Veterans with Military Service in Vietnam

<u>Subject</u>	<u>TCDD Presence</u>	<u>TCDD Concentration (parts per trillion)</u>
1	Neg.	nd (5) <sup>b</sup>
6	Neg. <sup>a</sup>	5 (3)
8	Neg. <sup>a</sup>	5 (3)
9	Neg.	nd (3)
10	Pos.	12 (2)
		16 (4)
		35 (9)
		23 (4)
11	Dfl. <sup>c</sup>	3 (2)
12	Pos.	9 (3)
13	Neg.	nd (2)
14	Dfl.	4 (3)
15	Pos.	7 (4)
16	Neg.	nd (4)
19	Neg.	nd (3)
24	Pos.	5 (3)
25	Pos.	12 (4)
26	Pos.	63 (6)
		99 (10)
27	Neg.	nd (6)

<u>Subject</u>	<u>TCDD Presence</u>	<u>TCDD Concentration (parts per trillion)</u>
28	Pos.	7 (5)
29	Pos.	13 (5)
30	Neg.	nd (3)
34	Pos.	5 (3)

Air Force Officers

2	Pos.	5 (2)
3	Neg. <sup>a</sup>	4 (1)
4	Pos.	6 (2)

Veterans with Military Service Outside Vietnam

5	Neg. <sup>a</sup>	4 (4)
7	Neg. <sup>d</sup>	3 (2)
17	Dfl.	4 (3)
18	Neg.	nd (4)
20	Pos.	5 (4)
21	Neg. <sup>d</sup>	6 (3)
23	Pos.	8 (2)
31	Neg. <sup>d</sup>	7 (4)
32	Dfl.	4 (4)
33	Neg. <sup>d</sup>	14 (7)

- a. Cannot be considered positive (Pos.) because of poor validation (substance detected probably not TCDD) and contaminant removed on repeat analysis.
- b. "nd" means "not detectible". Value in parentheses is limit of detection of TCDD.
- c. "Doubtful" (Dfl.) indicates that result would be considered positive at 2.5:1 signal: noise ratio negative at 3:1 ratio.
- d. Cannot be considered positive because of poor validation (substance detected probably not TCDD).

TABLE II. SUMMARY OF CLINICAL INFORMATION

<u>SUBJ:</u>	<u>Non-Service Exposures</u>	<u>Immediate Symptoms</u>	<u>Intermediate Health</u>	<u>Current Symptoms</u>	<u>Findings and/or Diagnoses</u>
1	Chlorine; chemotherapy; radiation	None given <sup>(a)</sup>	Temporoparietal tumor; "kidney condition"	None	Malignant astrocytoma-1976
6	Radiation - tonsils 1950	None given	Acoustic tumor	Headaches; facial pain	Acoustic neuroma - 1979; thyroid nodule - 1976
8	Alcohol, cocaine, marijuana use	None given	No reported difficulty	Ulcer after cut	Chronic ulceration of finger
9	None <sup>(b)</sup>	Numbness & tingling	Rhinitis; "back condition"	Numbness, tingling; fatigability; fever; "psychiatric & sexual problems"	Hostility; abdominal tenderness pharyngeal edema
10	None	None given	Back pain; otitis media; wart	"Stomach condition"	Plantar wart
11	None	None given	Wife aborted at 3-4 months	Intermittent chest pain & dyspnea; urinary frequency - infertility	None
12	None	None given	Butterfly facial rash after alcohol or anxiety as before Vietnam	None	Butterfly rash on face & forehead

(a) "None" indicates that record states a negative reply

(b) "None given" indicates that record indicates neither positive or negative reply

TABLE II. SUMMARY OF CLINICAL INFORMATION

<u>SUBJ:</u>	<u>Non-Service Exposures</u>	<u>Immediate Symptoms</u>	<u>Intermediate Health</u>	<u>Current Symptoms</u>	<u>Findings and/or Diagnoses</u>
13	Heroin for 3 yrs 4 yrs ago	Plantar warts	Mastectomy for gynecomastia - 1978	Swollen lids & red conjunctiva; nervousness; tingling of fingers & toes; periodic weakness	Jumpy; small non-tender axillary nodes
14	Farm and photographic chemicals; lawn fertilizers	None given <sup>(b)</sup>	Kidney stone - 1975; pleurisy & pneumonia; PPD pos. - 1969; blood in stools	Chest pain; forehead cyst; lipoma; mole; hernia	Sarcoidosis; inguinal hernia; lipoma; cyst
15	Cleaning agents; heavy alcohol use	Rash on legs; occasional diarrhea; "jungle rot" of toe-nails & groin	Nervousness; wife aborted; "nervous breakdown" - 1972	Recurrent extremity swelling; "nerves"; rash	Schizophrenia; onychomycosis; pigmented areas on legs
16	None (a)	None given	Sen-congenital heart disease - 1971	Dry cough; foot problems since service	Lt. great toe contracture; tenia pectis
19	None	None given	No statement	Painful leg edema veins	Varicose veins
24	Heroin until 3 yrs ago	None given	Painful knee & leg swelling after exercise	Groin pain; low back pain	Hemorrhoids; palpable liver; hernia
25	Insecticides	None given	Recurrent dry patches on back & shoulders; peptic ulcer	Pain, swelling left knee, post-traumatic	Arthritis; chronic cholecystitis; fatty liver; hypertension; tenia versicolor

(a) "None" indicates that record states a negative reply

(b) "None given" indicates that record indicates neither positive or negative reply

TABLE II. SUMMARY OF CLINICAL INFORMATION

<u>SUBJ:</u>	<u>Non-Service Exposures</u>	<u>Immediate Symptoms</u>	<u>Intermediate Health</u>	<u>Current Symptoms</u>	<u>Findings and/or Diagnoses</u>
26	None <sup>(a)</sup>	None given <sup>(b)</sup>	Crampy abdominal pain; allergy to fish & IVP dye	Severe rectal itch; occasional generalized skin itch	Pruritis ani; possible urticaria
27	None	Tingling, swelling of hands & feet; insomnia from pain	Tingling of fingers & toes hematemesis; back pain	Reynaud-like reaction; weakness of extremities	Stiff fingers & toes bilateral limp
29	None	None given	Amoebic dysentery; pluerisy in Vietnam; "weak" before discharge; hypertension at discharge; crampy abdominal pain - "Polycystic kidney"	Early morning weakness, normal by evening	Duodenitis; marginal hypertension
30	Primary light oils, benzene toluene, etc.	Cough, asthma made worse	Nervousness	Intermittent pruritic rash on flexor surface of arms	Expiratory rhonchi
34	None	None given	Multiple, generalized lipomata	Chronic anxiety; dyspnea; blurred vision; palpitations; chest pain, stomach pain; facial flushing; infraorbital "water blisters"; hypertension	Abdominal nodules (possible lipomata)

(a) "None" indicates that record states a negative reply

(b) "None given" indicates that record indicates neither positive or negative reply