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Use of Biologic Samples as a Surrogate for Exposure to Agent Orange

A. Concept Proposed by the Centers for Disease Control - 6/17/86

This concept is in compliance with the recommendation of the Science Subpanel that "a method additional to" military records must be used in assessing ground troop exposure to herbicides. Appendix VII (by Dr. Marilyn Fingerhut) of that report is appended here as a review of the scientific basis for this concept, providing evidence for a long half-life of 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) stored at low levels in human adipose tissue. Another study found that 14 years after the last known application of Agent Orange the levels of TCDD in adipose tissue in people living in the south of Vietnam were on average higher than those living in the north (1). Also see the attached figure showing data from fat biopsies taken years after dioxin exposure ceased in documented industrial and environmental exposures in the USA .

CDC is currently conducting a "Phase I" study to evaluate the feasibility of measuring TCDD in plasma. If feasible, this method would allow serial follow-up of anyone potentially exposed to dioxin, since repeated fat biopsies are usually unfeasible. "Phase I" is being done by measuring paired specimens of adipose tissue and plasma taken from 30 "low exposure" people who bank their own blood prior to elective surgery in Atlanta, and similar paired specimens taken from known "high exposure" people in Missouri. The results of "Phase I" will guide us whether to use plasma (as expected from preliminary data) or fat as the basis for "Phase II".

The purpose of "Phase II" is to validate the best method (if any) of estimating Agent Orange exposure indices from military records of Vietnam veterans by correlating such indices for each veteran with the level of TCDD measured in his plasma or fat. It is anticipated that 400 participants will be needed in this study: 150 in a "low exposure" group and 250 in a combined "high exposure" group. Selection of participants would be done in collaboration with the ESG and would be based insofar as possible on those men about which a fairly large amount of data has already been collected. Each participant would have differing levels of probable exposure estimated by each of the methods described below.

1. Acute (close proximity to a recent recorded application).

A daily score based on 2 or less days from the time of application, with a declining weighted value for distances up to 2 kilometers to allow for wind drift and imprecision of troop location.

2. Chronic (close proximity to the site of a recorded application).

A daily score based on time spent within 2 kilometers, with a declining weighted value for distances up to that limit to allow for wind drift and imprecision of troop location.

3. Chronic and acute (residence within a high-spray combat zone).

A daily score unweighted as to distance, since all ground combat troops spent most of their nights and some of their days in "fire-bases", which usually had herbicides applied periodically to clear the perimeter.

4. Self-assessment of exposure by structured interview.

Statistical analyses will determine how well each of the indirect estimates of the opportunity for exposure correlates with the tissue TCDD levels. The results will aid in determining the scientific feasibility of conducting a full-scale Agent Orange study for health outcomes as well as determining the most appropriate method, if any, for estimating possible exposure. If the results of such a study do not show adequate correlation between measured TCDD levels and any exposure estimation method, or if the "high exposure" groups have levels in the range of U.S. background levels, then it would have demonstrated that an Agent Orange exposure study to examine possible health effects in Vietnam veterans is not feasible. If this concept is approved, the CDC/AOP staff is prepared, with appropriate consultation, to develop a detailed study protocol, including sampling and analytic methods, along with detailed arrangements needed with ESG.

Phase I is scheduled for completion by the end of August, 1986, provided that the laboratory can complete all specimen processing by then.

Phase II cannot be given an exact completion date without thorough development of a protocol with ESG and without knowing the results of Phase I, which would tell us if we can go with plasma or not. If so, we could produce at least preliminary data by the end of 1986.

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1. Schecter E, Ryan J, et al. Agent Orange in Vietnam: Follow-up Studies of Dioxin Levels in Adipose Tissue and Milk Samples from Hanoi and Ho Chi Minh City Hospitals, 1984. Annual Meeting, Am. P.H. Assoc. Washington, D.C., November 17-21, 1985.

Costs:

1. Phase II TCDD Validation Study - - - - - \$ 1,500,000

(This cost estimate is based on a sample (or less)
of 400 veterans and includes laboratory
and interview/exam contractor costs, which
will vary with the type of specimen needed.)

2. Additional contractual costs associated with
conduct of Phase II

Option I: Termination of contracts - - - - - \$ 1,915,000
plus unknown final
settlement costs. *

Option II: Suspension (dormancy) of contracts - - \$ 2,105,000
plus unknown final
costs for LMF dormant
period. *

* Note: If the Agent Orange study is not conducted, the unit cost of the Vietnam Experience study interviews and examinations will increase, since the contractors have amortized their fixed costs over a minimum of 30,000 interviews and 10,000 medical examinations. In addition there would be other negotiated costs associated with a termination.

Utilization of Biological Samples to Assess Exposure to Agent Orange

Recent advancements in the analytic sensitivity of laboratory instruments have made it possible to analyze very low concentrations of 2,3,7,8-TCDD in samples of human fat (1). The results of several independent efforts (2-4) indicate that there is a background average level of 2,3,7,8-TCDD in human fat of approximately 7 parts per trillion (ppt) (range 0-20 ppt).

One study analyzed fat samples from volunteer Vietnam veterans (4). The results indicated that two veterans classified by the Veterans Administration as "heavily exposed" to Agent Orange had fat levels of 2,3,7,8-TCDD of 35 and 99 ppt. The remaining 10 veterans who were classified as "lightly exposed" and "possibly exposed" had levels between 3 and 13 ppt. Four veterans who had no service in Vietnam had levels between 4 and 8 ppt.

The results of this study indicate that it may be possible to distinguish high exposure to Agent Orange by analysis of fat samples. The results also indicate that veterans classified as "lightly exposed" to Agent Orange have only background levels of 2,3,7,8-TCDD in their fat, the same levels as are found in the U.S. population in general.

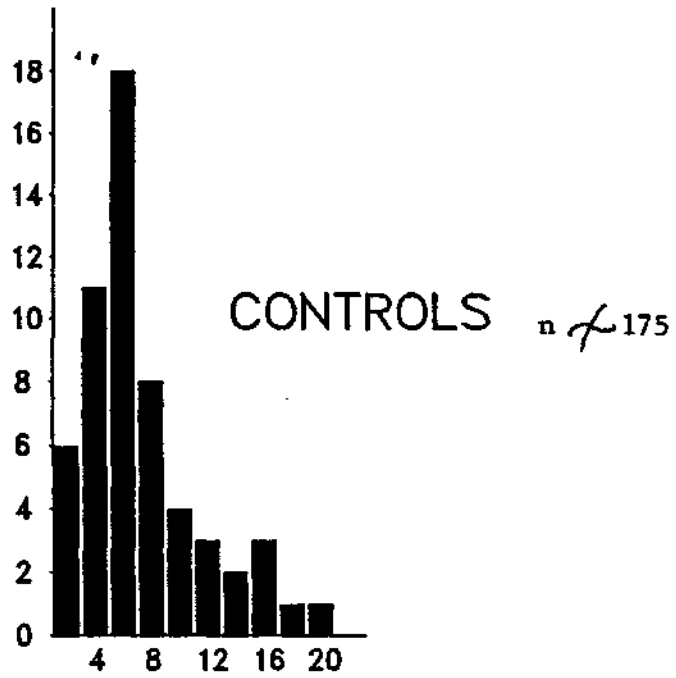
Analysis of fat is a difficult method for several reasons. A surgical or suction procedure is necessary to obtain 20 grams of fat (about the size of an egg) and the cost is about \$1,000 per sample. Efforts are underway currently to analyze a large volume of serum (200 ml) to detect low levels of 2,3,7,8-TCDD. Data are also being sought which would describe the distribution of 2,3,7,8-TCDD between adipose tissue and serum in the human body. Success with the serum method would provide a method to recognize levels of exposure which were high enough to raise levels of 2,3,7,8-TCDD above background levels in the population.

The recent advances in laboratory analytic techniques could be used to ascertain whether veterans in the various exposure categories of the CDC Agent Orange study have levels of 2,3,7,8-TCDD above the background levels in the population. For example, a sample of veterans currently meeting criteria for the CDC Agent Orange study category of "high likelihood of exposure" and a sample of veterans from the non-exposed category could be asked to provide fat (or possibly serum) specimens for analysis. An evaluation of the results should provide insight into the adequacy of the military records to select truly exposed and truly unexposed individuals. Additionally, the results should indicate whether the levels of 2,3,7,8-TCDD are significantly different from the levels in the general U.S. population.

Analysis of fat (or serum) from other populations could also provide valuable insights. Several studies are currently underway in which analysis of fat is being conducted on Vietnam veterans, chemical workers, and persons with residential and recreational exposures to 2,3,7,8-TCDD. Analysis of fat (or serum) could also be conducted on selected individuals in the CDC Vietnam Experience study who have known high or low levels of exposure. Samples of fat already collected from Ranch Hand participants during elective surgery could be analyzed and compared to the levels of exposure experienced by the individuals.

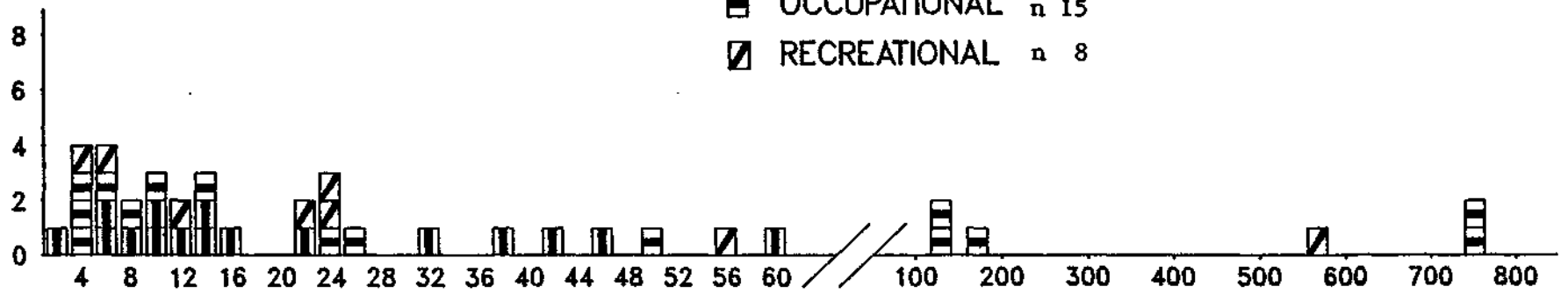
1. Patterson DG, et al. High resolution gas chromatography/high-resolution mass spectrophotometric analysis of human adipose tissue for 2,3,7,8-TCDD. Anal. Chem 1986; 58:705-716.
2. Graham M, Hileman FD, Kirk D, et al.: Background human exposure to 2,3,7,8-TCDD. Fourth International Symposium on Chlorinated Dioxins and Related Compounds, 1984; Ottawa, Canada; October 16-18.
3. Graham M, Hileman FD, Wendlong J, Wilson JD. Chlorocarbons in adipose tissue samples. Fifth International Symposium on Chlorinated Dioxins and Related Components, 1985. Bayreuth FRG, September 16-19.2508R
4. Gross ML, Lay JO, Lyon PA, et al.: 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in adipose tissue of Vietnam veterans. Environ Res 1984; 33:261-268.

NUMBER OF PERSONS



EXPOSED

- ▨ RESIDENTIAL n 16
- ▤ OCCUPATIONAL n 15
- ▧ RECREATIONAL n 8



DIOXIN ADIPOSE LEVEL (parts per trillion)