ADVISORY COMMITTEE ON THE CDC STUDY OF THE
HEALTH OF VIETNAM VETERANS

Review of Comparison of Serum Levels of 2,3,7,8-TCDD with Indirect Estimates of Agent Orange Exposure In Vietnam Veterans

Fifth Letter Report

INSTITUTE OF MEDICINE

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Introduction

In May 1985, James Mason, then Acting Assistant Secretary of Health, contacted Frederick Robbins, then President of the Institute of Medicine (IOM), requesting the IOM to establish a committee to assist the Centers for Disease Control (CDC) in its conduct of epidemiologic studies on the health of Vietnam veterans. These studies are mandated by public laws 96-151 and 97-22. They represent a large and complex effort to determine the possible long-term health effects of exposure to herbicides, including Agent Orange, on the health of Vietnam veterans (the Agent Orange Study, AOS), the possible long-term health effects of military service in Vietnam (the Vietnam Experience Study, VES), and the risk of selected cancers (the Selected Cancer Study, SCS). In September, 1985, CDC contracted with IOM (1) to advise on the conduct of the three studies, (2) to advise on the interpretation of the data collected, and (3) to provide prepublication review of the CDC reports presenting analysis of these data.

To date, the IOM committee has submitted four letter reports to the CDC on the VES. The first report reviewed a semen analysis protocol and a validation plan for birth outcomes and was submitted to CDC in March 1986. The second letter report, submitted in September 1986, presented the committee's comments on the Mortality Report of the VES, an interim report on VES interview data, and a proposed birth record review study. The third letter report reviewed CDC drafts of introduction and methods chapters for their report on the telephone interview survey. The

fourth letter report commented on preliminary data from the VES medical and psychological examinations with selected findings from the VES telephone interview survey. This fifth letter report addresses the findings of a pilot study undertaken to validate the use of indirect estimates of opportunity for exposure of U.S. Army Vietnam combat veterans to Agent Orange. This CDC effort also seeks to determine if Vietnam veterans have higher levels of dioxin in their blood than a group of veterans of that era who did not serve in Vietnam. A recently developed assay for dioxin permits detection of very small quantities of it. This pilot study represents an important step in assessing if the AOS, which is currently on hold, can be pursued with the assistance of new methodologies to more precisely determine exposure to 2,3,7,8 - tetrachlorodibenzo-p-dioxin (TCDD or dioxin).

The original design of the AOS attempted to classify veterans' exposure to dioxin that occurred during military service. This was accomplished by determining proximity of troops to Agent Orange spray paths using military records to track troop movement and computer tapes to locate ground and air spraying patterns. However, it was found that military records do not permit a precise determination of opportunity for exposure to TCDD. The smallest personnel units that could be tracked were so large that dispersion of troops precluded determining precise locations for individuals. In addition, dispersion and degradation of dioxin made impossible the calculation of precise amounts available on the ground. In order to conduct a cohort study in which unexposed individuals could be compared to truly exposed individuals, a more precise index of exposure was needed.

Two recent discoveries made the achievement of more precise classification of individual exposures to dioxin more likely. First, a very sensitive, high-pressure liquid chromatographic (HPLC) method was devised to measure quantities of dioxin in blood as small as a few parts per trillion. Serum dioxin levels ascertained in this way were found to be highly correlated with those determined by the more accepted invasive method that involves surgical excision of adipose tissue for dioxin extraction and measurement. Second, preliminary studies indicated that the half-life of dioxin might be longer than was thought in the past. The possibility that dioxin from exposure that occurred 20 years ago could be detected in serum led to this pilot study.

All participants were selected from the pool of veterans who entered the U.S. Army between January 1, 1965 and December 31, 1971 and who served only one term of enlistment. Only those who had at least 16 weeks of active service time, who earned a military occupational specialty (MOS) other than "trainee" or "duty soldier", who were not known to have died during active duty, and who had a pay grade of E-5 or less at time of separation from active duty were eligible for inclusion. Army veterans included in the Vietnam cohort had to have served at least one tour of duty in Vietnam. The comparison group served in the United States or Germany. In addition, only those Vietnam veterans who had not been selected previously for the VES and who had served in a unit for which the Environmental Support Group (ESG) had locational data for the time period 10-1-66 through 3-31-69 could participate in this pilot study.

Procedures for obtaining names and personal data from military service records, and the process of tracing, contacting, interviewing, and examining participants were similar to those used in the Vietnam Experience Study (VES). The ESG had location data and service records on 14,479 Vietnam veterans. Each veteran's record was checked for eligibility criteria listed above; 994 were found to qualify for the study.

"Hit" scores were calculated for these 994 qualified Vietnam veterans. A hit represents each time a company was located within 2 kilometers of a reported Agent Orange spray path applied within the previous 6 days. The total number of hits assigned an individual was used to sort the veterans into groups whose likely TCDD exposure was "low," "medium," or "high." A total of 411 men with 5 or more hits (high group) were invited to participate in the pilot study, as were 201 men with 1 to 4 hits (medium group) and 385 with no hits (low group) were also invited. In addition, 200 veterans who did not serve in Vietnam were selected from 367 men who were interviewed for the VES but had not undergone medical or psychological examination. These 200 were frequency matched by race and age to the Vietnam veterans selected for this pilot study. None of the non-Vietnam veterans of the pilot study cohort had served in Korea, a consideration raised by reports that some Agent Orange had been used around the demilitarized zone.

The information used to locate veterans, provided by the Internal Revenue Service, the Social Security Administration, and other agencies

was turned over to Research Triangle Institute (RTI), the contractor responsible for telephone interviews for the pilot study as well as the VES. They traced and contacted study participants, and administered the same questionnaire that had been used in the VES. Of the 200 non-Vietnam veterans who completed the telephone interview under the VES, all were invited to have a medical and psychological examination at the Lovelace Foundation in Albuquerque, New Mexico. As part of the medical examination, each participant contributed 150 ml of serum for TCDD measurements. In addition to the standard medical history designed for the VES, more detailed information was sought on civilian exposure to herbicides and self-assessed herbicide exposure while in Vietnam. Of the 200 non-Vietnam veterans interviewed, blood samples were obtained from 103, or 52 percent. Of the 997 Vietnam veterans for which hit scores had been calculated, 979 were found to be eligible for the pilot study, and 871, or 89 percent of those who qualified, were interviewed. Of those who were interviewed, 665, or 76 percent, provided blood samples for the dioxin assay. There were no significant differences in participation rates among hit score groups.

The goal of the analyses was to examine the strength of the association between serum TCDD levels and other indirect indicators of Agent Orange exposure. The indirect indicators included: (1) hit scores as described above; (2) an "E3" score which reflects both time and distance from spray paths and takes into account a slower rate of dioxin degradation in soil that had been sprayed; (3) an area score that

reflected the amount of time an individual spent in large regions or zones known to have had frequent spray applications; (4) an unknown agents score for individuals whose paths crossed spray lines for which no data is available as to the substance sprayed; and (5) self-assessed exposure during and after military service.

The associations were evaluated by comparisons between groups and by regression models. Secondary analyses were done to evaluate data quality and sources of variation in TCDD levels. Three between-group comparisons were of a priori interest. These were "low" versus "high" Vietnam veterans, "low" versus "medium" versus "high" Vietnam veterans, and non-Vietnam veterans versus all Vietnam veterans. Another comparison of interest is non-Vietnam veterans versus "low" Vietnam veterans. The significance of differences between mean TCDD levels in these groups was evaluated by analysis of variance, using the Scheffe multiple comparison procedure. More detailed, multivariate analyses employed linear regression. Goodness of fit and validity of assumptions were assessed through examination of residuals from the regression models. Secondary analyses were used to verify that the results were not affected by the choice of statistical technique or by accounting for additional sources of variation.

Estimates of the association between indirect indices of exposure and serum TCDD levels expressed on a lipid basis were adjusted for a group of covariates judged to be potential confounders. These covariates were age,

race, body mass index, and self-reported, post-service exposures to herbicides at home or at work. Smoking history was added as a covariate after initial analyses had been completed. All of these covariates were included in each regression analysis. Effect modification for each exposure score was assessed using a stepwise regression modeling procedure to determine if interaction terms should be added to the model including the exposure score and all of the covariates. Serum lipids were not used as covariates because serum TCDD levels had been adjusted for total serum lipids and, if elevated serum TCDD should cause a change in serum lipids, adjusting for serum lipids could result in removing real differences in serum TCDD between two groups.

The IOM advisory committee convened a full committee meeting to review the pilot study data and the resulting CDC report. CDC requested that the committee conduct its assessment expeditiously so as to permit the use of the committee's deliberations in presenting the pilot study findings to OTA and others involved in the design and conduct of the AOS. Thus, the committee wrote this report prior to adjourning.

This fifth letter report is submitted to inform CDC of the committee's findings and recommendations regarding the interpretation and presentation of data from the TCDD pilot study.

Objectives and Design

The committee understands the objective of the pilot study is to determine whether various indirect methods for estimating exposure to dioxin--based on historical data and self-reports--can be used as a basis for classifying exposure status of veterans, who could subsequently be included in a large, retrospective cohort study. (These indirect measures are described in the Introduction section of this letter report.) The committee finds the CDC report has strayed from this objective; the committee believes that objectives have been confused with methodological issues. These concerns are discussed in more detail below.

The objective of the pilot study is to test the validity of indirect measures of exposure. A cohort study is intended to relate the development of disease in a population to prior differences in exposure to some factor within that population. Such a study is feasible only if an available measure of exposure has been demonstrated to distinguish different degrees of exposure within the population to be investigated. Accordingly, the feasibility of a cohort study of Agent Orange exposure among Vietnam veterans depends on the demonstration that one or more measures of exposure will reliably distinguish among veterans with different exposures.

In order to assess the appropriateness of using the indirect measures described previously as indices of true exposure, a more precise and

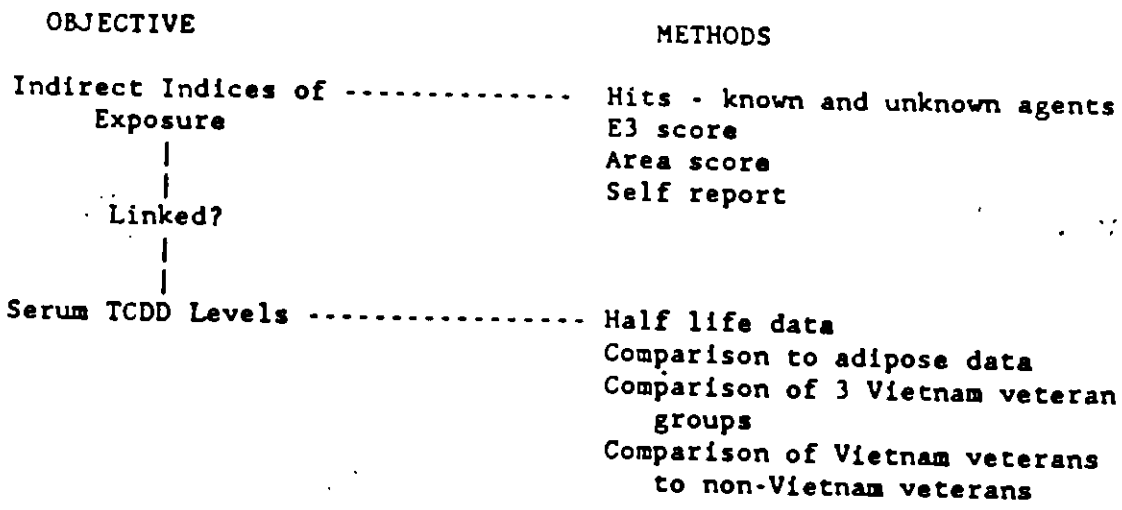
objective methodology was needed. The very sensitive HPLC assay for serum dioxin levels was proposed to meet this need. The method used to evaluate the indirect measures sought correlations between the indirect indicators of exposure and serum TCDD levels. However, evaluating the capacity of the TCDD assay to accurately reflect prior exposure required a series of separate exercises. First, CDC conducted a study on the half-life of dioxin, using sera from Ranch Hand veterans from 1982 and 1987. Ranch Hand veterans served in the Air Force and were responsible for the aerial distribution of herbicides and insecticides, including Agent Orange. Second, TCDD serum levels were compared to those found in the "gold standard" dioxin assay of adipose tissue. Third, CDC compared the levels of TCDD in the blood of the three Vietnam veteran groups, categorized according to the various indirect measurements. Last, CDC compared serum TCDD levels of veterans who served in Vietnam to those who did not.

The CDC pilot study report states on page 2 that "The secondary objective was to see if Vietnam veterans have TCDD levels higher than a similar group of veterans of that era who did not go to Vietnam." The committee does not feel that this should be viewed as an objective. Rather, it should be seen as one of the methods used to approach the main objective of assessing the utility of the indirect indicators of exposure. This issue is not raised for pedantic or semantic reasons, but rather to alert CDC that such an approach will raise false expectations concerning the results of this study. Moreover, the train of logic, as it currently exists in the CDC report, has led to recommendations and conclusions that the committee finds untenable. This point is discussed in more detail later in this report.

The following diagram depicts the components of the pilot study as the committee understands them and as discussed above.

Figure 1

Structure of the CDC Evaluation of Measures of Exposure to Agent Orange



The logic underlying the current pilot study appears to be as follows: (1) The selection of any particular measure as the basis for characterization of exposure to Agent Orange depends on its validity in relation to known exposure. (2) Unfortunately, there is no basis for certainty of exposure status from members of the intended study population as a whole. In this report, the use of troop locations in the III Corps area, and selection of non-Vietnam veterans with no known military exposure to Agent Orange were adopted as the basis for distinguishing possible exposure levels, from "none" to "high." (3) Surrogate measures of exposure can be provided by adipose tissue or serum assays for TCDD. Having demonstrated excellent correspondence of serum and tissue assays, CDC has relied on serum assays for this purpose.

The TCDD levels found in sera of pilot study participants do not appear to differ from those reported in the general population and are thus not distinguishable from current "background" levels. Similarly, TCDD levels observed in the Vietnam veterans group are consistent across exposure category and do not differ from those who did not serve in Vietnam. None of the indirect indices appears to be related to the serum TCDD levels.

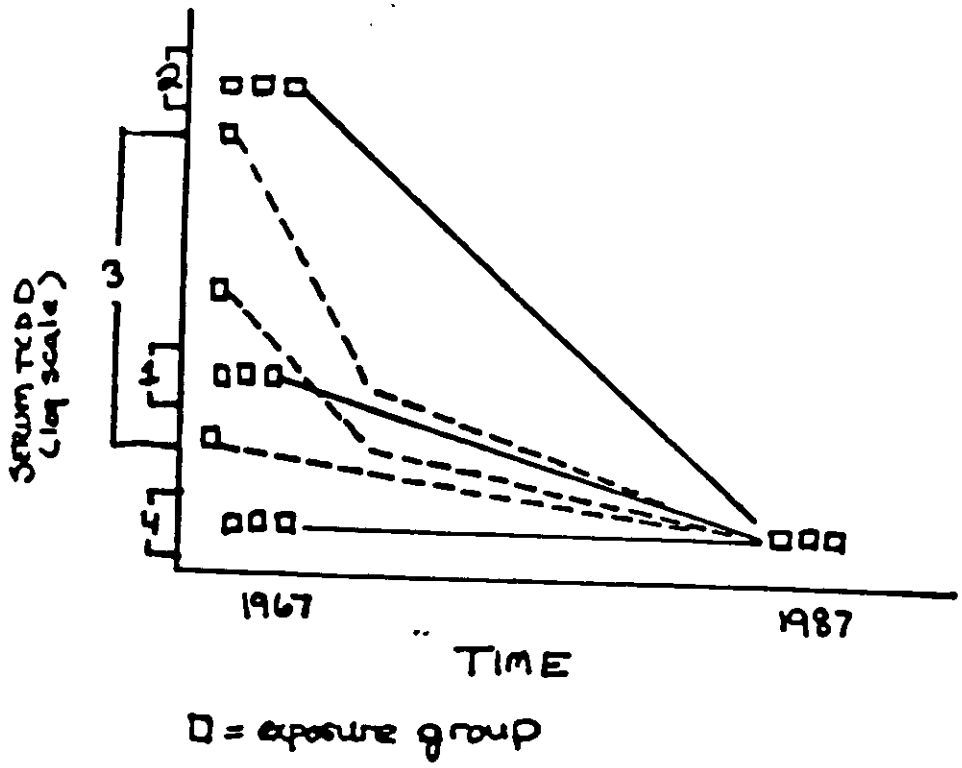
However, the committee notes that the serum assays available for the intended study population are limited by the fact that they are based on current blood samples, obtained in 1987, some 20 years after the exposures of interest. Moreover, the committee expresses concern that the current levels observed may not necessarily have any relation to actual exposures that occurred 20 years ago. There are several possible conditions that could have occurred between 1967 and 1987 that might result in the TCDD levels observed today; a description of several possible conditions is presented below and summarized in Figure 2. These descriptions are intended to be examples of possible scenarios that could lead to similar TCDD serum levels currently found among pilot study subjects; they are not intended to be an exhaustive enumerstion of all possibilities.

Possible scenarios include the following: (1) All three Vietnam veteran groups (high, medium, and low) could have been similarly exposed during the war, but their levels were not sufficiently high in the late 1960s to prevent them from decaying to background level today. (2) All three exposed Vietnam veterans groups could have had significantly higher

blood levels than background in 1967, but with the passage of time all TCDD concentrations had decayed to the same level, as was seen in the 1987 serosurvey. (3) The three groups could have differed in actual exposure in Vietnam, and if their blood had been sampled then, differences could have been seen in TCDD levels. However, decay rates for dioxin may not be uniform; that is, they may vary based on initial concentration. Therefore, it is possible that while the three groups may have differed 20 years ago, differential decay has resulted in all falling within background range today. (4) None of the veterans ever had serum dioxin concentrations above background.

Figure 2

Relationship between Current and Prior TCDD Serum Levels



Note: Numbers on vertical axis correspond to scenarios listed in text.

It is not possible to distinguish among the alternative explanations without further knowledge about the decay rate of TCDD in humans. If the three veteran groups had similar exposures in Vietnam, the classification of the veterans by the indirect measures of exposures would be invalid. If they differed in initial concentration but all fell currently within background range, then indirect measures of exposure might be a more valid indicator for exposure level than current TCDD serum levels. If, however, the decay rate was not constant, it would be unclear whether the indirect indicators of exposure could serve as robust markers of exposure.

It is evident that assumptions regarding the rate of decay of TCDD weigh heavily on an interpretation of current TCDD levels as an appropriate basis for judging the validity of indirect measures of exposure that occurred in 1967. The committee strongly recommends that CDC lay out alternative explanations for the lack of correspondence between the indirect measures and current TCDD level and that they make explicit those assumptions that underlie the rejection of the indirect measures as a basis for classifying exposure status in the AOS cohort.

Methodology

The committee finds the pilot study design to be well conceived and implemented. Subject ascertainment was carefully conducted using the same rigorous eligibility criteria reported in the VES, and the rationale for selecting subjects was clearly stated. The committee found that CDC made very good use of historical material. The indirect exposure scores were well constructed and evaluated, and the rationale for each category of historical exposure included in this study was well presented.

The committee finds the statistical methodologies used in the pilot study to be appropriate, reasonable, and well executed, and CDC's descriptions of methodological issues to be very clear and well presented. The committee finds that data reduction issues were carefully planned and implemented in this study. CDC used appropriate scoring procedures for both the indirect and direct measures of exposure. The committee perceives the calculation and estimates for sample size and power to be appropriate.

However, the committee feels that the descriptions of half-life models and estimates lack the depth and detail necessary for a complete and convincing final document. It would be extremely helpful if the pilot study report stated <u>in detail</u> all of the assumptions underlying half-life estimates. It would also be useful to include a discussion of the effect of a positive background level on estimates. In addition, a thorough, well-documented discussion is needed to address the difficulties inherent

in making extrapolations in TCDD levels backward through time. Such a discussion might include the possibility of a model that incorporates varying rates of degradation and the resulting effects of such modeling. In general, a clearer picture of what half-life is and of how this impinges on this study will help the reader make sense of this difficult and important issue.

The committee also notes that blood was not available for a significant portion of both cohorts; blood samples were obtained from only 52% of the non-Vietnam veteran group and from 68% of the Vietnam veteran group. The committee urges CDC to present all available data on donor response and characteristics in the body of their report. The committee strongly recommends that a detailed comparison of donors to non-donors be presented, along with other appropriate analyses to deal with the issue of the validity of the data, which will surely arise given the non-donation rates.

The committee found the laboratory procedures to be articulately presented and well executed. The committee was impressad by the CDC's management system for collecting, storing, coding, and processing specimens for the HPLC assay of serum TCDD. Data appeared to be handled in an exemplary manner, keeping all the CDC staff involved in this study blinded as to the source of the sample. The committee had access to the findings of the Blue Ribbon panel that reviewed the HPLC assay in August 1987, and concurs with their findings that the analytical methods and quality control measures are appropriate and well executed.

Analyses

The committee found the analyses of the pilot study data to be extensive and well presented. The rationale for the selection of a priori confounders was sound and well described. Although the analyses were judged to be fairly complete, the committee would like to suggest the following additional analyses:

- It would be very helpful to see a table that presents the intercorrelations among the various measures of exposure.

- Analyses that examined the associations between the various indirect indices of exposure and TCDD serum levels were reported at the meeting but not included in the report; these data should certainly be included in the final draft.

- It would be useful to include a table in which each of the 5 indirect measures is dichotomized (high = + versus low = -) and the categories listed with sample size and corresponding mean TCDD levels. An example is presented below.

Figure 3

Indirect Measures		Serum Dioxin Levels		
Score 1	Score n	Sample Size	Mean TCDD Level (ppt)	(+/- S.E.)
+	+	n1	x1	( )
+	-	n2	x2	( )
-	-	nz	xz	( )

o It is possible that there exist descriptors of experiences that occurred during service (other than the indirect measures of exposure examined here) that correlate with current TCDD levels in this sample. This possibility might be explored by comparing the characteristics of military experience among Vietnam veterans with serum TCDD levels in the upper 10th or 25th percentile with those below this level. The feasibility of this additional analysis depends, of course, on the extent and availability of additional descriptive data for the pilot sample.

o Additional analyses should be conducted to examine the possibility of a relationship existing between indirect measures of exposure (with the exception of self-reported exposure) and health outcomes measured at medical and psychological examinations conducted at Lovelace. This analysis may provide additional information that can be brought to bear upon the question of the validity of the indirect measures. In addition, this analysis may provide a way of identifying some of the health outcomes suitable for later case-control studies. However, the committee recognizes that these analyses would have to be carried out after the completion of this pilot study report.

Conclusions and Recommendations

The committee expresses substantial reservations about the conclusions and recommendations presented in the CDC pilot study report. The committee believes that the conclusions as they are now stated are not fully supported by the evidence provided in this report.

Moreover, the committee urges that the recommendations as currently stated in the CDC pilot study report be deleted; they appear to reach well beyond the data presented and to incorporate information that goes beyond the scope of the current investigation. Instead, the committee feels that a separate document is needed to address the issues raised by the CDC's recommendations. If such a document is created, the committee would recommend including a complete history of all of the various Agent Orange studies. This historical review should include a detailed accounting of all of the various attempts to design and conduct such a study, and it should include a full and detailed explication of all the arguments relating to the questionable utility of a cohort design, given what is now known about exposure measurements.

The committee offers the following points regarding the conclusions and recommendations as stated in the CDC pilot study report:

- In the first conclusion, the last sentence, beginning "Therefore, it is not possible to use ..." should be dropped. It should be noted that there exists the possibility that current TCDD levels may not be suitable as a measure of past exposure, nor do current TCDD levels appear to support the validity of any indirect measures.

- The committee recommends changing the phrase "serum TCDD levels" to "present serum TCDD levels" in the second conclusion.

o The committee recommends deleting the third conclusion. The conclusion that a full-scale cohort study is not feasible goes well beyond the scope of this study, which was conducted to assess the validity of indirect indices of exposure. If such an expansive statement is offered, it certainly warrants argumentation and documentation. The committee did not find support for this conclusion in the pilot study report.

o In the fourth conclusion, the committee recommends replacing "heavy occupational exposure" with "heavy military occupational exposure" to reinforce the notion that this is a study of veterans and not a study of occupational exposure in general. The committee also recommends deleting the last sentence of this recommendation, which begins, "Serum TCDD levels may also ...." The committee finds that making conjectures about future studies related to other populations is not appropriate for this report.

o The committee recommends deleting the fifth and final conclusion. The first two sentences simply repeat the methods and the findings discussed in detail in other sections of the report. The final statement, suggesting that the findings of this study should be reassuring to veterans, constitutes conjecture that is not appropriate to this presentation of conclusions. Moreover, it is not clear that the findings presented in this pilot study warrant complete abatement of concern. Little can be said with certainty about the TCDD levels in men 20 years ago. Moreover, background levels detected some years later do not provide assurance that no health effects will ultimately

surface. Given the insufficiency of data relating the level of exposure to health outcome in humans, delayed effects of low or high doses could become apparent years after exposure occurred.

o The committee recommends striking the first recommendation, because it goes well beyond what was found in this study. Extensive, additional documentation would be needed to support this recommendation as it stands, and such documentation may not be appropriate for this report, given its stated objectives.

o Similarly, the committee recommends deleting the second and third recommendations. Advocating the wide dissemination of these results to "relieve their concern" is not appropriate. There remain other possibilities that exposure could have occurred and that it simply cannot be detected 20 years later. While there remains the need to explore the possibility of conducting case-control studies, it is not appropriate to discuss who should be responsible for those studies in this report. Attempting to direct the efforts of other agencies of the federal government (i.e., the Veterans Administration) is not within the purview of CDC. This pilot study report is essentially a methods paper; recommendations such as these confuse the stated purpose of the study.

Overall Presentation of Material

The committee found the CDC pilot study report to be well written, clear, and well organized. The committee was impressed with the quality of the report, especially given the significant time constraints under which CDC was operating. However, the committee would like to make the following suggestions regarding the scope of this document.

- A review of the pharmacologic and toxicologic literature on dioxin must be included, with special attention paid to data regarding dose-dependent kinetics, where available. Such a review should include a discussion of the kinetics of dioxin as well as other compounds found in Agent Orange that could be potentially toxic. The committee urges CDC to provide as detailed discussion of pertinent data derived from other studies as is possible.

- A more complete discussion of the differences in rates of metabolism of TCDD, as alluded to on page 10, is needed. This discussion should include a quantitative statement regarding the range in rates identified to date, and should discuss the meaning of the differences in rates as well as possible variations in the pharmacokinetics of dioxin, an area that remains to be clearly defined. Diversity in metabolic rates will impinge upon the value of the data intended to determine if health effects are related to prior exposure.

o A complete enumeration of all analyses conducted for this pilot study, including those that did not yield significant differences or associations, should be provided, perhaps in an appendix.

o Within the literature review of the health effects of dioxin, it would be very helpful also to include a discussion of the health effects associated with the non-dioxin constituents of the herbicide Agent Orange that have been considered potentially toxic.

o The time that elapsed between reputed exposure and measurement of serum dioxin levels plays a critical role in the interpretation of the data presented in the CDC report. The committee urges CDC to include in its final document a full discussion of the range of possible consequences that the passage of time may have on their data and how this might affect their conclusions.

The committee strongly suggests that a balanced presentation of the advantages and disadvantages of indirect indices of exposure and serum TCDD levels would be useful in this report. For example, an advantage of serum TCDD includes its presumed capacity to serve as an objective biochemical marker of exposure. However, its disadvantages include its high cost and the incomplete understanding surrounding half-life and metabolism of TCDD. The advantages ascribed to indirect measures are low cost and the fact that no venipuncture is required. However, indirect measures are subject to bias of recall (self-report). Furthermore, a heightened potential for misclassifying exposure greatly decreases precision. The committee notes the importance of the assumptions

underlying half-life in the interpretation of the results presented in the CDC report, and the committee urges CDC to make explicit those assumptions and their relationship to the interpretation of their findings.