Columbia University
School of Public Health

THE FACULTY OF MEDICINE
DIVISION OF HEALTH ADMINISTRATION

600 WEST 168th STREET
New York, N.Y. 10032

JUN 19 1990

correspondence address:
117 St. Johns Place
Brooklyn, N.Y. 11217
(718)-230-8822

June 18, 1990

Admiral Elmo R. Zumwalt, Jr.
1500 Wilson Boulevard
Arlington, Virginia 22209

Dear Admiral Zumwalt,

As per our telephone conversation, enclosed are some materials which I hope may be useful to you in the preparation of your testimony before Congressman Weiss' subcommittee on June 26. Basically, I have included a background piece on the Selected Cancers Study, which I hope is not too professorial in its tone. We've tried to explain some basics of epidemiology and how the Selected Cancers Study fails to meet its original purpose and some of its major flaws. We've tried to show how the Institute of Medicine report actually makes the same criticisms that we make, but uses so much jargon that only the specialist can understand the report.

I have also included a copy of CDC Director Roper's testimony before the House Veterans Affairs Committee with annotations about where the testimony is in error. I hope that the annotations are sufficient for you.

The briefing materials also contain a copy of the Institute of Medicine's assessment of the data collected by the Environmental Support Group, under the direction of Col. Christian. This report corroborates the utility of this data, and raises the important point that we have been emphasizing over and over: we can label the III Corps personnel as to likelihood of exposure, and, *another* cohort, in II Corps, for example, or offshore, could have and should have been assembled to carry out an appropriate study. [It is also simply shameful that the IOM has never released this report -- it somehow appeared on my desk -- and, in fact, is sitting on 10 other reports on the project.]

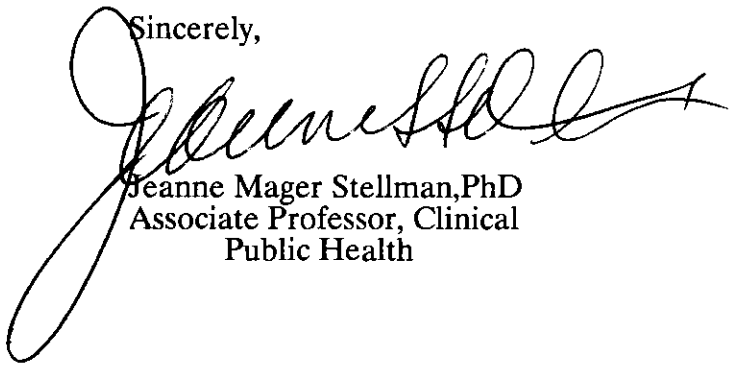
Included is another copy of the unpublished CDC report on their early analysis of these valuable data tapes. They knew what they had -- and didn't want to use it.

Finally, I've included a little factsheet on the Selected Cancers Study that I wrote for the Legion and which they published in their wire service to their departments. It may be of interest.

I will try to send out to you tomorrow some more materials on the issue of "Why the veteran's cup is always half empty" - or why the CDC and the Ranchhand people are continually calling positive results negative.

Please call me for clarifications, additional information, etc. and let me know if, and when and where you would like me to meet you in Washington. I could come in the day before, if that would be useful.

Sincerely,



Jeanne Mager Stellman,PhD
Associate Professor, Clinical
Public Health

Document 2

IOM Report on Selected Cancers Study

Testimony of Donald Whorton, MD, MPH

Accompanied by Michael A. Stoto, PhD

Representing the:

Institute of Medicine
National Academy of Sciences

Advisory Committee on the Centers for Disease Control
Study of the Health of Vietnam Veterans

Presented to the:

Committee on Veterans Affairs
U. S. House of Representatives

Cannon House Office Building, Room 335

April 4, 1990

INTRODUCTION

In May 1985, James Mason, then Acting Assistant Secretary of Health, requested that the Institute of Medicine (IOM) 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, and represent a large and complex effort to determine the possible long-term health effects of Vietnam veterans exposure to herbicides, including Agent Orange (the Agent Orange Study, AOS), the possible long-term effects of military service in Vietnam (the Vietnam Experience Study, VES), and the risk of selected cancers (the Selected Cancers Study, SCS). In September 1985, the CDC contracted with the IOM (1) to advise on the conduct of these three studies, (2) to advise on the interpretation of the data collected, and (3) to provide prepublication review of the CDC reports presenting analyses of these data. Extensive work to obtain reliable exposure data demonstrated that the AOS study was not scientifically feasible. The IOM oversight has therefore been primarily directed to consideration of the VES and SCS studies.

To fulfill the CDC contract, the IOM appointed a broadly expert committee to review the VES cohort study. Eleven reports were prepared and submitted to the CDC to complete the three tasks identified above. On completion of the study by the CDC, VES results were published in three articles in the Journal of the American Medical Association[1] and the original IOM committee was disbanded.

In 1988 the IOM appointed the Selected Cancers Study committee to advise the CDC on its study of the association between certain cancers and Vietnam service. A list of the committee members is attached. The primary objective of the SCS is to determine whether there is an association between service in Vietnam and the risk of developing any of six types of cancer -- Hodgkin's disease, non-Hodgkin's lymphoma (NHL), soft tissue and other sarcomas, nasal cancer, nasopharyngeal cancer, and primary liver cancer. The IOM committee has examined the study protocols, methods, and techniques used in obtaining and analyzing the data in this population-based case-control study. The first report of the committee, a review of the study design and analysis plan, was completed in October 1988. The committee also reviewed and discussed preliminary analyses of the data. The committee's second report reviewing the preliminary analyses of the NHL data was completed in April 1989, its third report on the preliminary analysis of the Hodgkin's disease and sarcoma data was completed in July 1989, and its fourth report on the other cancers and plans for presentation of the final results was completed in January 1990. On March 13, 1990 the committee met with the CDC staff to review a draft of the CDC's final reports on the SCS. Draft reports on (1) non-Hodgkin's lymphoma, (2) soft tissue and other sarcomas, and (3) the other cancers along with a draft executive summary were distributed to the committee in advance. At the meeting, members of the IOM committee and the CDC staff reviewed the findings and their presentation in the draft reports. The committee's conclusions are based on these materials, materials provided at earlier meetings, and its discussions with the CDC staff. The committee has not seen the ultimate CDC reports on the CDC study.

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[1] Health Status of Vietnam Veterans (3 papers). Vol. 259(18):2701-2719, May 13, 1988.

CONCLUSIONS

Based on its discussions with the CDC staff and the material it has reviewed, the committee believes that the Selected Cancers Study makes a useful and important contribution to understanding the relationship between Vietnam experience and the cancers under study. It has been a difficult undertaking, and the IOM committee commends the CDC staff on their efforts and progress. The staff have carefully gathered a very large amount of data under difficult circumstances and performed statistical analyses with diligence and resourcefulness.

The recommendations based on the committee's first four meetings are summarized below. At the final meeting the committee reviewed these recommendations with the CDC staff and found that the CDC had been responsive to the committee's concerns, and had made changes as appropriate. Because the committee has not seen the final report, it is unable to judge the CDC's responsiveness to the issues raised at the last meeting.

Study plan

In its earlier reports, the committee found the study plan to be a good one. The number of cases in the study gives it good power to study the relationship between Vietnam service and the development of non-Hodgkin's lymphomas and soft tissue sarcomas and adequate power for primary liver cancers. The committee notes that the original power calculations were performed assuming that nasal and nasopharyngeal cancers would be analyzed together, and the sample was projected to have adequate power under that assumption. Because these cancers were appropriately separated in the final analysis, the power is not as high as originally planned, but is sufficient to detect four-fold increases in risk (similar to those that have been reported in other studies.

The committee is satisfied with the rationale for selection of the six cancers chosen for study, and feels that the geographical distribution of the tumor registries and the method of selecting them was satisfactory. The committee accepts the appropriateness of using random digit dialing (RDD) for the selection of controls in the various geographical regions of the study. The committee also feels that the requirement for submission of histological specimens of each tumor for confirmation of pathological diagnosis is very valuable and adds to the validity of the study's results. The committee reviewed the data showing that dioxin in the serum of Vietnam-era veterans is generally at background levels and is not correlated with reported exposures. For this reason, and because it was not feasible to gather the necessary serum from the cases and controls in the SCS study, the committee concurred with CDC that serum dioxin measures should not be used.

Because of potential gaps and errors in the U. S. Army and Joint Services Environmental Support Group (ESG) efforts to gather Vietnam-era military service records for subjects who reported Vietnam service, the committee recommended that CDC develop an *a priori* plan for handling discrepancies between the self-reported and the ESG data, taking into account the expected strengths and weaknesses of each data source.

The committee also recommended that the CDC continue to refine its measures of potential sources of exposure to dioxin outside of Vietnam, in addition to potential exposures through herbicides and pesticides.

Analysis

At its first meeting, the committee urged a rigorous, detailed analysis of the confounding factors and variables other than the Vietnam experience that might show an association with the individual cancers selected for study in order to answer key questions about service in Vietnam and at the same time yield information concerning the risk factors for the development of these cancers.

The committee discussed the rationale for the approaches to data analysis, such as the use of conditional vs. unconditional logistic regression models and their strengths and weaknesses. It suggested that the CDC use conditional logistic regression models where appropriate for studying confounded potential risk factors, but also present basic descriptive data in simple graphical and tabular form. The committee concurs with CDC's plan to calculate exact confidence intervals for odds ratios when possible and use approximate confidence intervals only when exact results are not available, such as for conditional multivariate logistic regression analyses.

The committee feels that decisions about which covariates to include in multiple logistic regression analyses to adjust odds ratios should employ prior knowledge and scientific judgment, and should not rely solely on a statistical procedure such as stepwise regression. Given the nature of the study and the lack of definitive information on all of the potential causes of soft-tissue cancers, the committee felt that the CDC efforts to identify "data-based" confounding variables are appropriate as long as they are limited to those variables for which, *a priori*, there is some information to indicate a potential causal relationship with the selected cancers or some other definite reason for consideration.

The committee recommended that a consistent policy be developed for presenting odds ratios in conjunction with cross tabulations of cases and controls by study variables and that a consistent wording be used for reporting statistical results that are suggestive of an association but not statistically significant. Odds ratios should generally be accompanied by an appropriate confidence interval, except in reporting the result of a sensitivity analysis.

The presentation of contingency tables or odds ratios as measures of association for multiple subsets of the data can sometimes be informative. However, because there are a large number of variables under investigation, many of the odds ratios in such small subgroups can take on very large or very small values solely because of chance fluctuations. Thus, in journal articles and in CDC's report to Congress, the committee recommended that the CDC develop a systematic approach to the presentation of subset analyses that gives as much information as possible but tends to avoid the presentation of large effects that are probably due to chance.

After reviewing a number of alternative data presentation formats for journal articles and its report to Congress, the committee recommended that CDC present the results of its comprehensive analyses of the main effects of Vietnam exposures on cancer risk and of possible

interactions with age and other potential modifiers. When in its judgment there is some evidence that the effects of exposure may differ in different subgroups, subgroup data in the form of 2x2 tables should be presented also so that the reader can see the basic data. This approach has the advantage of taking into account the multivariate complexity in the data as well as avoiding the problems of presenting many small tables.

The committee could not identify a general preferred solution to potential problems of misclassification, selection bias, and so on. Rather, the committee recommended that sensitivity analyses be performed, that is, statistical analyses should be carried out under a number of different assumptions related to the possible biases. If the final results of the analyses are similar despite the different assumptions, the problems can be regarded as minor; if the results differ markedly, the problem needs further analysis and discussion.

Despite the need for these sensitivity analyses, the committee feels that for the final presentation it is important to have a set of decision rules for handling these matters that is as consistent as possible across all of the studies and analyses. Therefore, the committee recommended that the CDC make every effort to develop consistent rules, including, for each disease under study, a common rule regarding the subjects that should be used for all statistical analyses. These rules would form the basis for the sensitivity analyses.

In this light, the committee reviewed the inclusion criteria for the nasal, nasopharyngeal, and primary liver cancers. In the preliminary analyses of both the nasal and nasopharyngeal cancers, the CDC had included a small number of cases of cancer of the nose and the nasopharynx that are not of epidermal origin, including a few cases of lymphoma. Because most of the information on risk factors on which the hypotheses were developed and the covariates were selected relate to epidermoid cancers per se, not the broader group, the committee recommended that the basic statistical analyses use the epidermoid cancer data alone.

In the case of primary liver cancer, however, the available epidemiological evidence does not suggest any difference between the known and suspected risk factors for the two major kinds of primary liver cancer: hepatocellular carcinoma and cholangiocarcinoma. Because there is no evidence of any epidemiological difference, and because pooling the data would increase the power of the statistical tests, in this instance the committee recommended that both kinds of primary liver cancer cases be included in the statistical analyses.

The committee agreed with the CDC that it is preferable to exclude from the statistical analysis those men not eligible to serve in Vietnam by virtue of having resided outside the United States just as non-eligible subjects are excluded from a randomized trial. However, to test the sensitivity of the results to this decision, the committee suggested that, in addition to the primary analysis, the CDC perform multivariate statistical analyses on the full data set (that is, including those not eligible to serve) appropriately controlling for eligibility variables.

Similarly, because the etiology of AIDS and non-AIDS lymphomas are likely to be very different, the committee feels that it is best to exclude subjects reported to have AIDS from the primary analysis. However, to test the sensitivity of the results to this decision, the committee

suggested that the CDC perform multivariate statistical analyses on the full data set (that is, including both the AIDS and non-AIDS subjects) appropriately controlling for AIDS status. The committee further recommended that the CDC carefully examine the "never married" and "intravenous drug use" variables because they might be associated with unidentified AIDS cases.

The committee reviewed the statistics on the self-reported use of malaria prophylaxis by veterans stationed in or off the coast of Vietnam, and agreed that the figures were probably too low, given what is known about military policies during the Vietnam era. As part of a sensitivity analysis, the committee recommended that the CDC carry out two sets of statistical calculations: one assuming that all men stationed in or off the coast of Vietnam were taking malaria prophylatics and another accepting the data at face value.

The committee also reviewed the CDC's plans for detailed analyses of the non-Hodgkin's lymphoma data, taking into account the branch of military service in which the men served, and addressed the issue of what would be an appropriate reference group. The committee feels that CDC has to go back to the original hypotheses to answer such a question. The primary hypothesis is that Vietnam service is associated with each of the cancers under study, so therefore the appropriate primary reference group should be men who did not serve in Vietnam, regardless of other military service.

For this and other purposes, however, the committee feels that there is value in having multiple reference groups and thus the committee recommended that the CDC further explore the effect of branch of military service *and other factors* using two other reference groups: (1) men with military but not Vietnam service, and (2) men with no military service.

General comments

The committee commends the CDC staff for their efforts in the design of the study and the analysis of its results. The staff have been extremely responsive to the committee's recommendations. Epidemiologic studies always require difficult judgments and face many constraints. The committee feels that the CDC staff has carried out the best study possible under the circumstances. In the committee's judgment, their work meets the highest professional standards.

The data collected in the Selected Cancer Study are a valuable resource for other than studying the health effects of Vietnam service. As a large-sample case-control study with careful pathological confirmation and extensive reported exposure data, the data constitute an extremely valuable resource for exploring the full range of occupational and environmental exposures that might be related to the six cancers under study. Furthermore, a comparison of the distribution of cell types for AIDS-related and the other NHL's might reveal important new information about the pathology of AIDS. Thus the committee recommends that, after the completion of the current study, resources be made available for further analysis of the SCS data by CDC staff and their collaborators and eventually by others.

INSTITUTE OF MEDICINE

Selected Cancers Study

Advisory Committee on the CDC Study
of the Health of Vietnam Veterans

Board on Health Promotion and Disease Prevention

Leon Gordis, Professor and Chairman, Department of Epidemiology, The Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland

Earl Philip Benditt, Professor, Department of Pathology, School of Medicine, University of Washington, Seattle

Norman E. Breslow, Professor and Chairman, Department of Biostatistics, University of Washington, Seattle

Paul Stolley, Herbert C. Rorer Professor of Medical Sciences, University of Pennsylvania, School of Medicine, Philadelphia

M. Donald Whorton, Executive Vice President and Chief Medical Scientist, ENSR Health Sciences, Alameda, California

INSTITUTE OF MEDICINE

Gary B. Ellis, Director, Division of Health Promotion and Disease Prevention
Michael A. Stoto, Study Director
Donna Thompson, Secretary

Document #3

Testimony of William L. Roper
Centers for Disease Control
April 4, 1990
Before the House Committee on Veterans' Affairs

Annotations:

Page 2: In describing the review processes for the CDC studies, Roper fails to note that when the Agent Orange study was abandoned, a new protocol and a new review for the Selected Cancer Study was needed, since that study was contingent upon the Agent Orange Study for its exposure measure.

Page 3: Roper alludes to the 'indirect' measurement of Agent Orange exposure, but fails to note that the CDC had already found in their Birth Defects study that these indirect measures were unreliable.

Page 3: Roper's statement on "inconsistent results" in other studies is incorrect. As our earlier analysis of these studies shows, most were without statistical power to detect an effect or, like the Selected Cancer Study, had no exposure measure.

Page 4: Roper describes how the study was of military service in Vietnam and just slides over the fact that this was not the hypothesis that was to be tested, nor does he explain what military service in general has to do with exposure to phenoxyherbicides in particular.

Page 5: Roper goes on to do precisely what the Institute of Medicine cautioned that the CDC not do: present analyses to Congress on subgroups in the population. The IOM warned that associations which were observed or failed to be observed could only be attributed to chance. This entire discussion is without epidemiological meaning, as discussed in the Background paper.

Page 6: "We found no evidence that the increased risk of NHL might be related to exposure to Agent Orange in Vietnam." He should have said " We didn't look". The rest of the presentation is a posteriori.

Page 7-8: This is a misleading review of the literature. It equates studies that have no power to detect an effect with positive studies. We have already reviewed these cancer studies in a separate report. The CDC should certainly be aware that the National Academy of Sciences long ago concluded that the Ranchhand study could not detect an increased rate of NHL because of insufficient numbers.

Page 9: Presenting the data on the other cancer sites is extremely misleading. Roper fails to state that only 2 nasal cancers, 3 nasopharyngeal carcinomas and 8 primary liver cancers were found in Vietnam veterans. The numbers in parentheses are the confidence intervals. Confidence intervals that include the value of 1.0 are not statistically significant. As you can see, these intervals are very wide. It is preposterous to be making a statement to the Congress about such a small number of cases. Furthermore, if the CDC wanted to they could also have said that their data are consistent with risks as great as 2.68 for primary liver cancer, 1.77 for nasopharyngeal carcinoma and 1.58 for sarcomas, since these are the upper limits of the confidence intervals.

Incidentally, it is absolutely unclear why the sarcomas, other than soft tissue sarcomas, have been thrown into this pot, unless it was to increase the very small number of cases accrued. No one has hypothesized a relationship between phenoxyherbicides and all sarcomas.

Pages 10 - 11: This testimony reiterates the inaccuracies about military records. See Document 5, the unpublished Institute of Medicine report to the CDC on these military documents, which attests to their utility and quality. Comments ont the blood measurements have already been submitted under separate cover.

Page 12-18: The Vietnam Experience Study -- Annotations will follow

Page 19 - The grandiose conclusion that Vietnam veterans do not differ from other veterans and other members of society is true, for the entire group, as far as most studies have shown. But, as all studies, except the CDC study which didn't differentiate, have shown -- Vietnam veterans who experienced combat, are significantly different from non-combat vets. And, now that the latency period is being passed, they appear to be suffering from Agent Orange related problems as well.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
Atlanta GA 30333

FOR RELEASE ONLY UPON DELIVERY

Testimony of

William L. Roper, M.D., M.P.H., Director

Centers for Disease Control

U.S. Public Health Service

Department of Health and Human Services

before the

COMMITTEE ON VETERANS' AFFAIRS

HOUSE OF REPRESENTATIVES

9:00 a.m.

Wednesday, April 4, 1990

Room 334, Cannon House Office Building

In May 1983, CDC completed and submitted a draft research protocol for scientific review and comment by four groups: the Congressional Office of Technology Assessment (OTA), the Science Panel of the Cabinet Domestic Policy Council Agent Orange Working Group (AOWG), the HHS Advisory Committee on Special Studies Relating to the Possible Long Term Effects of Phenoxy Herbicides and Contaminants (the Ranch Hand Panel), and CDC's own Ad Hoc Review Panel. CDC received comments from these groups by September 1983.

The final protocol for these studies was published by CDC in November 1983. The protocol incorporated modifications suggested by the scientific reviews and stated that the studies were designed to allow for the addition of procedures or questions based on interim analyses of the data or data from sources outside these studies. Three independent, but related, studies comprise the CDC's Agent Orange Projects:

1. The Vietnam Experience Study: a study of the effects of military service in Vietnam.

2. The Agent Orange Study: a study of the long-term health effects of exposure to herbicides in Vietnam.

3. The Selected Cancers Study: a study to determine the risks of specific cancers among Vietnam veterans. This study was designed because the number of these malignancies in the above two studies would not be sufficient to arrive at any valid conclusions.

I will first summarize the results of the Selected Cancers Study, the final study in CDC's investigations. I will then summarize the status of the other originally planned studies.

RESULTS OF THE SELECTED CANCERS STUDY

The Selected Cancers Study (SCS) is a population-based, case-control study, which examined the risk of (1) non-Hodgkin's lymphoma, (2) soft tissue and other sarcomas, (3) Hodgkin's disease, and (4) nasal, (5) nasopharyngeal, and (6) primary liver cancer among Vietnam veterans. These malignancies were chosen because of published studies suggesting an association with phenoxyherbicide exposure. Because of the difficulty in estimating Agent Orange exposure in individual veterans, we only indirectly evaluated Agent Orange exposure. We focused our analysis, instead, on the association of Vietnam service and cancer. Other studies on the risk of these cancers in association with Vietnam military service or with nonmilitary exposure to phenoxyherbicides have produced inconsistent results.

In the study, the case group was restricted to men who would have been between the ages of 15 and 39 in 1968, at the peak of U.S. troop strength in Vietnam. All men who were diagnosed in a 4-year period (late 1984-late 1988) as having any of the six cancers and who lived in the geographic areas covered by eight tumor registries were eligible for this study. Thus choice of study period allows us to include men whose cancers developed 15-15 years after service in Vietnam (a likely latency period). The eight participating areas, encompassing three states (Connecticut, Kansas, and Iowa) and five large metropolitan areas (Miami, Detroit, San Francisco, Seattle, and

Atlanta), included about 10% of the U.S. population. The comparison group of controls was scientifically drawn from households with telephones and included men of the same age, in the same geographic areas, who did not have any of the six cancers.

Information on military service in Vietnam, along with relevant medical and occupational history was collected from both case and control subjects via a telephone interview using a standardized questionnaire. Interview participation rates were high both for men with cancer (87%) and for controls who completed the selection process (83%). Cancer diagnoses were confirmed by a panel of pathologists who are experts in each of the six cancers. The panel members were unaware of the military service status of the men whose diagnoses were reviewed. The U.S. Army and Joint Services Environmental Support Group, of the Department of Defense, attempted to verify reported military service in Vietnam. The group was unaware of the case or control status of the subject whose record was being reviewed.

For several of the six cancers, the SCS is the largest such study ever conducted on men in this relatively young age range that has included confirmation of diagnosis by a review pathologist panel and extensive collection of data through a standardized interview.

The strength of the association between military service in Vietnam and each of the sites and types of cancer was assessed by the odds ratio (OR), an estimate of the relative risk. This method estimates whether cancer is more likely to develop in men who served in Vietnam than in men who did not.

We found an increased risk of non-Hodgkin's lymphoma (NHL) among Vietnam veterans relative to men who did not serve in Vietnam, but no increased risk for the other five cancers. After taking into account other factors that might influence the development of NHL among Vietnam veterans, we found these men to be at a roughly 50% increased risk for NHL (OR = 1.47). This is a statistically significant increase ($p = 0.01$), with the 95% confidence interval ranging from 1.09-1.97. When we restricted the comparison population to men who had served in the military, but not in Vietnam, or further restricted it to those who had served during the time of the Vietnam conflict, we found little change in the estimate of 50% increased risk. Thus, the increased risk appears to be specific to Vietnam veterans, rather than being associated with military service in general.

The data suggested a higher relative risk for veterans who had served a longer time in Vietnam, although the result was not statistically significant ($p = 0.10$). An examination of several characteristics of Vietnam military service, however, provided no evidence that NHL was more likely to develop in one group of Vietnam veterans than in another. In particular, the risk differed only slightly by dates of service, age at entry on duty in Vietnam, rank, or type of unit the veteran served in (combat, combat support, or support). Differences in risk by branch of service (with risk higher for the Navy and Marines than for the Army or Air Force) were not statistically significant. Viewed by itself, however, the increased risk for men who served in the Navy in Vietnam was statistically significant (OR = 1.89, 1.11-3.24). Further, the relative risk was slightly

higher (OR = 2.17) among the 84% of all Navy men who had served on ocean-going ships.

We found no evidence that the increased risk of NHL might be related to exposure to Agent Orange in Vietnam. The pattern of risk among subgroups of Vietnam veterans seemed to be the opposite of the pattern of use for Agent Orange in Vietnam: Navy veterans who served on ocean-going vessels tended to be at higher risk than Vietnam veterans based on land, and Vietnam veterans who served in III Corps, the region of heaviest Agent Orange use, tended to be at somewhat lower risk than Vietnam veterans who served in other regions. Furthermore, no greater risk was associated with serving in Vietnam during the period of heaviest spraying, 1966 to 1969. Only 1 of the 99 Vietnam veterans with NHL reported that he had handled equipment or containers used with Agent Orange, and none reported having sprayed defoliants. These data, along with evidence from other studies regarding the likelihood of Vietnam veterans' exposure to Agent Orange, make it quite unlikely that the increased risk of NHL among Vietnam veterans results from exposure to herbicides. In our study we did not identify any other factor as being responsible for that risk. Most known and suspected risk factors for NHL (immunodeficiency, the use of drugs to prevent malaria, and use of intravenous drugs, for example) were examined and none explained the increase in risk for Vietnam veterans. We were unable to determine why these men are at higher risk for NHL.

Compared with the other malignancies under investigation in the Selected Cancers Study, previous studies of Vietnam veterans more strongly support an association with NHL. In a proportionate mortality study including 50,000 deceased Vietnam-era veterans, Breslin et al. observed a twofold increase in

the proportion of deaths due to NHL among Marines who served in Vietnam compared with Marines serving elsewhere. In a historical cohort study of Army Vietnam veterans conducted by the CDC, investigators used a combination of self-report, medical record review, and information from death certificates to identify men with NHL. .Although several of the latency periods were short, and it is possible that these cases were not due to service in Vietnam, seven cases of NHL were found among Vietnam veterans vs. only one case among similarly aged veterans who did not serve in Vietnam. Furthermore, examination of death certificates of 19,000 Australian troops who served in Vietnam also suggested an increased risk for NHL although the confidence interval for this estimate was very wide, ranging from 0.4 to 8.

In contrast, other investigators have found no association between military service in Vietnam and NHL. Although Breslin et al. observed a significantly increased risk for NHL among Marine veterans, men who served in the Army (representing four-fifths of all Vietnam veterans in the study) in Vietnam tended to be at decreased risk, with a proportionate mortality ratio of 0.81. (In the current study, the risk of NHL among Vietnam veterans who served in the Army was lower than that among Marines, but the variation across branches was not statistically significant.) Proportionate mortality studies in West Virginia and Wisconsin did not find an increased number of deaths from NHL among Vietnam veterans, and a similar analysis of Vietnam veterans in New York did not find an association with all lymphoma (NHL and Hodgkin's Disease combined) deaths. However, none of these latter studies examined causes of death according to branch of service in Vietnam. Only one man with NHL has been identified among members of Operation Ranch

Hand, the group that sprayed defoliants from fixed-wing aircraft; the group is, however, too small for definitive analysis of the risk of NHL.

Although a risk of this magnitude may be due to unrecognized bias or uncontrolled confounding, an examination of several recognized potential sources of bias or confounding produced little evidence that these factors had an appreciable effect on our results. For example, the lack of an association between Vietnam service and any of the other malignancies limits the likelihood that the observed asaociation with NHL is due to underascertainment of Vietnam veterans in the control group. Since we studied all cancers simultaneously using the same design and an identical group of control subjects, several biases concerning selection and information quality should have similarly affected the risk estimate for each of the six cancers.

The risk estimate identified in our study is not high. It is, however, of the order of size the study was designed to be able to detect. The possibility that our finding is entirely explained by chance can never be completely ruled out, but it is highly unlikely. There is a 1 in 100 likelihood that the study result for NHL is due to chance, if this result is viewed by itself. While our study was designed to examine the associations between military service and six malignancies, whether or not to adjust for multiple comparisons is controversial. When multiple comparisons are considered, the probability of observing one or more associations of the magnitude observed for NHL by chance alone is at most 7 in 100.

The risk estimates for the other five cancers were 1.14 (95% CI, 0.71-1.83) for Hodgkin's disease, 1.00 (0.63-1.58) for soft tissue and other sarcomas, 0.66 (0.15-2.91) for nasal carcinoma, 0.53 (0.16-1.77) for nasopharyngeal carcinoma, and 1.16 (0.50-2.68) for primary liver cancer. None of the estimates were significantly different from 1.0, the value indicating that the risk among Vietnam veterans is identical to that among men who did not serve in Vietnam. Of particular interest is our finding of no increased risk for sarcoma, a group of cancers that has been of great concern among Vietnam veterans; restricting the cancer group to soft tissue sarcoma yielded a relative risk of 0.94. We found no indication that any particular subclass of sarcoma was increased after Vietnam service or that any subgroup of Vietnam veterans was at increased risk of sarcoma. As with NHL, we found no indication that the pattern of distribution of sarcoma among the 26 Vietnam veterans with sarcoma was related to the pattern of Agent Orange use in Vietnam.

I have limited my testimony primarily to the results of the Selected Cancers Study. However, for completeness, the status of the other originally planned studies, the results of which were previously presented to the committee, are summarized briefly in this testimony.

STATUS OF THE AGENT ORANGE STUDY

The Agent Orange Study (AOS) was designed to evaluate the possible health effects of exposure to Agent Orange in Vietnam veterans. Implementation of the AOS depended on development of a scientifically valid herbicide exposure

index based on information contained in military records. As cautioned in the 1983 protocol, many of the proposed assessments were necessary before a final decision could be made to proceed with a full-scale study.

As a result of intensive work between 1983 and 1986 by the U.S. Army and Joint Services Environmental Support Group (ESG) and CDC, a Science Subpanel of AOWG concluded in June 1986 that a "scientifically valid study based on military records was not possible without an independent method of exposure verification." During 1986 CDC began to develop a new laboratory method utilizing blood to measure current body burdens of dioxin as an indicator of previous exposure to dioxin-containing substances such as Agent Orange. The CDC scientists were successful with this new method as a more feasible approach for testing groups of individuals than previous methods because dioxin is measured in serum rather than adipose tissue. A protocol for a "Validation Study Comparing Military Records-based Estimates of the Likelihood of Exposure to Agent Orange with Current Serum Levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)" was developed by CDC and approved by the AOWG and OTA in October 1986.

The results of the Agent Orange Validation Study (AOVS) were released in July 1987. The results of the AOVS were published in The Journal of the American Medical Association (JAMA) in September 1988. A detailed monograph on the background methods and results of the AOVS was also published by CDC in January 1990. Copies of these reports have been previously submitted to the Committee. The results showed no association between serum TCDD levels and several different military records-based estimates of the likelihood of

Agent Orange exposure. Also, there was no meaningful association between TCDD levels and self-reported exposure obtained directly from the veterans. Among the 646 Vietnam veterans for whom TCDD levels were obtained, the median TCDD level was 2.8 parts per trillion (ppt), with a range from less than 1 to 45 ppt. The median TCDD level for the 97 non-Vietnam veterans was also 3.8 ppt, with a range from less than 1 to 15 ppt. Two Vietnam veterans had levels above 20 ppt, one with 25 and another with 45 ppt; no non-Vietnam veterans had levels above 20 ppt. The veterans with a level of 45 ppt reported no exposure (military or civilian) to herbicides; the veteran with a level of 25 ppt reported 180 days of indirect military exposure (defined as walking through, or clearing vegetation in, a previously sprayed area), plus one day of home use, but no other exposure. During the telephone interview, both of these men reported their health as "excellent," with no health problems perceived as a consequence of exposure to Agent Orange.

We concluded that a scientifically valid study of Agent Orange exposure could not be done based on military records and it was not feasible to establish the cohorts based upon serum TCDD analysis.

While the AOVS was underway, CDC was also measuring TCDD levels on a group of Air Force Health Study participants (which consists of Ranch Handers and a comparison group). Of the 147 Ranch Handers studied, 25 had current TCDD levels of between 50-100 ppt, 16 between 100-200 ppt, and 5 over 200 ppt; all but one of the 49 veterans in the comparison group had TCDD values less than 10 ppt. The Air Force/CDC Half-life Study, a National Institute of Occupational Safety and Health (NIOSH) Pilot study of herbicide production

workers, and the New Jersey Pointman Project have all detected substantially elevated TCDD levels in occupationally exposure individuals whose last known exposure occurred 15 or more years ago.

The VA and the Environmental Protection Agency (EPA) have recently released results of a collaborative effort measuring levels of 2,3,7,8-TCDD in 3 groups (40 Vietnam veterans, 80 non-Vietnam veterans, and 80 civilian men, all born between 1936 and 1954). The mean levels of dioxin were not significantly different between the 3 groups. They concluded that "the study results suggest that heavy exposure to Agent Orange for most Vietnam veterans was very unlikely and that there is no readily available and reliable indirect method of assessing exposure to Agent Orange for Vietnam veterans," (Reference 1, listed at the end of the testimony).

STATUS OF THE VIETNAM EXPERIENCE STUDY (VES)

The VES was designed to evaluate possible health effects of the "general Vietnam experience" by comparing the health status of a cohort of male U.S. Army veterans who served in Vietnam with a cohort of male U.S. Army Vietnam-era veterans who served elsewhere. This study was initially designed with three main components: a mortality assessment, telephone interviews, and medical and psychological examinations. Based on interim analyses of the data and the experience of the Ranch Hand Study (related to acquisition of birth records), CDC added to the VES a birth outcome validation component and a semen analysis component.

I will describe the general findings ofthe VES, starting with the Mortality Assessment component, which was published in February 1987. Then, I will address the morbidity findings which were published in The Journal ofthe American Medical Association (JAMA) on May 13, 1988. These results have also been published in a detailed series of monograph in January 1989. These reports have been submitted previously to the committee.

Mortality Assessment Component of the VES

The VES used a random sample of military records to find 9,324 male U.S. Army veterans who served in Vietnam and 8,989 Army veterans who served in Korea, Germany, or the United States during the same period. All of these men had been discharged alive with a rank of E1-E5 after a single enlistment starting between 1965 and 1971.

For the entire follow-up period (from discharge through December 1983), total mortality among the Vietnam veterans was 17% higher than for the other veterans.

The excess mortality occurred mainly in the first 5 years after discharge from active duty, when the death rate among Vietnam veterans was about 45% higher than the rate of non-Vietnam veterans.

Most of the increased mortality was from external causes, such as motor vehicle injuries, suicide, and homicide. After the first 5 years, mortality

among Vietnam veterans was similar to that of non-Vietnam veterans, except for drug related deaths, which continued to be elevated.

The overall finding of excess postservice mortality due to external causes among Vietnam veterans was similar to that found among men returning from combat areas after World War II and the Korean War.

Morbidity Findings of the VES

I will discuss the findings of the telephone interview, the medical and psychological examination, and the reproductive and child health components of this study. Since there are no comparable morbidity data from previous wars, it is not possible to compare morbidity data from the VES with data on veterans of previous wars.

Telephone Interview:

In the telephone interview, about 18,000 veterans (whose addresses on their military records date from the late 1960s) were traced. In 1985-1986, we located 94% of the Vietnam and 92% of the non-Vietnam veterans. Of the men located 93% of the Vietnam and 91% of the non-Vietnam men were interviewed, a tribute to their extraordinary spirit of cooperation.

The interviews revealed a broad similarity between the two groups in terms of current demographic and social characteristics, such as education, income, employment rates, and marital status. However, the Vietnam veterans

reported more current limitations in activities, more current use of prescription drugs, and a greater prevalence of many types of disease and somatic and psychological symptoms. Also the two groups reported a similar, total number of physician-diagnosed cancers though the number is too small to draw any conclusions. The Vietnam veterans reported more problems with impaired fertility, yet both groups reported fathering the same average number of children.

Medical and Psychological Examinations:

In the examination component, we invited a random subsample of about 42 percent of interviewed men for comprehensive physical, psychological, and laboratory examinations. Physical and laboratory examinations showed few current differences between the two groups, despite the many differences elicited by telephone interview.

For example, there were large differences in skin problems reported during the telephone interview, but on examination all skin conditions, including scars from possible past chloracne, were found with similar frequency.

Overall, hundreds of physical health items and laboratory assays were evaluated as part of the examinations. For most items no statistically significant differences were found between the two groups. The most noteworthy differences were high frequency hearing loss (9.4% versus 6.2% for both ears), stool occult blood (1.3% versus 0.5%), evidence of past infection with Hepatitis B (14.1% versus 11.1%), lower sperm concentrations

(15.9% versus 8.1% below reference range), and lower average proportions of morphologically "normal" sperm cells (15.9% versus 11.4% below reference range). Nevertheless, the average number of children fathered per veteran in each cohort after assignment to primary tour of duty was identical--1.6 children.

Psychological evaluation of the men who were examined was done through standardized interviews and questionnaires. Although most men in both groups fell within normal limits in these evaluations, current psychological problems [primarily alcohol abuse or dependence (13.7% versus 9.2%), anxiety (4.9% versus 3.2%), or depression (4.5% versus 2.3%)] were more prevalent among Vietnam than non-Vietnam veterans.

About 15% of the Vietnam veterans reported experiencing symptoms which met diagnostic criteria for combat-related Post Traumatic Stress Disorder (PTSD). Combat-related psychological symptoms diminished over time, but 2.2% still experienced episodes of PTSD during the month before examination or 15 or more years later.

Reproductive Outcome Findings of the VES

Vietnam veterans reported more birth defects and other health problems among their children than non-Vietnam veterans during the telephone interview. However, the children of Vietnam veterans were no more likely to have birth defects recorded on hospital birth records than were children of non-Vietnam veterans. These results are consistent with the findings of three

epidemiologic studies (the Australian birth defects study, the CDC Birth Defects Study, and the U.S. Air Force Ranch Hand Study) conducted since 1981 on the relationship of Vietnam service and birth defects in children of male veterans.

NIOSH Production Workers Study

NIOSH is currently conducting a cohort mortality study and maintains a registry of approximately 7,000 workers who were employed at 14 plants in the production of chemicals that were contaminated with 2,3,7,8-TCDD. The NIOSH study is designed to identify effects of exposure to TCDD on reproductive, hepatic, neurologic, immunologic, and psychologic disorders.

In addition, NIOSH is doing a cross-sectional morbidity study of workers from 2 of these 14 plants. This study will include data from interviews of approximately 350 production workers with occupational risk of high exposure and from physical examinations of about 275 of the workers interviewed. Blood concentrations of TCDD were measured to determine the probable extent of exposure to TCDD. TCDD levels were also measured on the comparison group of unexposed individuals.

Conclusions

The results of our series of studies suggest several conclusions:

1. Vietnam veterans appear to be at increased risk of developing non-Hodgkin's lymphoma. The increased risk does not appear to be due to exposure to Agent Orange. There was no increased risk for the other cancers under investigation, specifically, soft tissue and other sarcomas, Hodgkin's disease, nasal cancer, nasopharyngeal cancer, and primary liver cancer.

2. Some conditions, such as post traumatic stress disorder (PTSD), alcohol abuse or dependence, anxiety and depression, are somewhat more prevelant among Vietnam veterans. About 15% of the Vietnam veterans experienced combat-related PTSD at some time during or after military service, and 2.2% had an episode of the disorder during the month before examination, 15 to 20 years after leaving Vietnam.

3. It is unlikely that most Vietnam veterans absorbed measurable amounts of dioxin and Agent Orange, unless they handled or sprayed herbicides as part of their job in the military.

4. Vietnam veterans appear to have lower sperm concentrations and lower mean proportions of morphologically "normal" sperm cells. Despite these differences in sperm characteristics, Vietnam and non-Vietnam veterans have fathered similar numbers of children.

5. Vietnam veterans do not appear to have overall increased risks of fathering babies with birth defects.

6. Vietnam veterans appear to have a somewhat higher rate for hearing loss and past infection with Hepatitis B, both not unexpected, given the combat conditions and location of the conflict, and

7. Veterans of the Vietnam era, whether they served in Vietnam or not, are similar to veterans of other wars. The vast majority are productive members of society.

This concludes the series of the Centers for Disease Control's Congressionally mandated epidemiologic studies to determine if exposure to Agent Orange or other characteristics of service in Vietnam have caused long-term adverse health effects in Vietnam veterans. We will continue to cooperate with other agencies involved with studies of veterans' health, such as the U.S. Air Force's Ranch Hand Study, to further assess the possible adverse health effects of exposure to dioxin and herbicides.

REFERENCES

1. Kang H., et al. Dioxins and Dibenzofurans in Adipose Tissue of U.S. Vietnam Veterans and Their Controls, as reported at the Meeting of the Society for Epidemiologic Research, Birmingham, AL, June 14, 1989.

Document 4

Unpublished IOM Assessment of Military Documents Abandoned by CDC / Agent Orange Study

Site Visit to the U.S. Army
Environmental Support Group

March 7, 1986
Washington, D.C.

Advisory Committee on the CDC Study
of the Health of Vietnam Veterans

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FOR CIRCULATION TO COMMITTEE ONLY
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Introduction

At the January 31, 1986 meeting of the Advisory Committee on the CDC Study of the Health of Vietnam Veterans, Mr. Richard Christian of the Environmental Support Group (ESG) invited the committee to visit his operation. The ESG is responsible for locating troops and spray paths in Vietnam. On March 7, a subset of this committee (Drs. Becker, Greenhouse and Weiss) conducted a site visit to the ESG; they were accompanied by Rita Schinnar (consultant to the Committee), Heather Miller (IOM Program Officer), and Professor Wesley Yates (University of California, Davis), an agricultural engineer and recognized expert in herbicide drift who has agreed to serve as an advisor to the committee on issues relating to herbicide spray. This report summarizes the March 7th site visit.

Those attending this site visit (hereafter referred to in this document as the subcommittee) heard a brief description of a pilot study now in progress at ESG that will be completed by early May. The objectives of the pilot study were (1) to identify problems in implementing strategies to locate troops and fixed wing sprays (Ranch Hand sprays) in Vietnam, and (2) to determine whether or not a sufficient number of veterans with possible exposure to Agent Orange can be identified using these methods.

The subcommittee was also shown a video tape of actual rotary wing and ground spray activities in Vietnam as well as Ranch Hand

of perimeter sprays, and about the factors which affect spray concentration and, therefore, exposure (thickness of foliage, sun, wind drift, temperature, season, droplet concentration). ESG estimates (from Services Herbs and Ranch Hand Tapes) that approximately 10% of all Agent Orange used in Vietnam was applied by ground sprays, the remainder having been applied through Ranch Hand missions. Dr. Bricker of ESG estimated that only about 30% of the herbicide reached the ground when there was foliation coverage. He added that perimeter sprays applied the herbicide on previously sprayed areas where growth was sparse and ground more accessible to the herbicide.

ESG Operations

ESG has identified a total of 122 combat battalions which, between 1966 and 1969, operated in the III Corps tactical zone for at least a 1.5 year period. III Corps zone was the site of the most intensive Agent Orange spraying. From these 122 combat battalions, 65 were identified as having spent the longest period of time in that zone, and only these 65 will be included in the main Agent Orange Study (should it go forward). The main study will include 325 companies from these 65 battalions. ESG is charged with identifying the daily locations of operation for these companies from the last 3 months of 1966 through the first 3 months of 1969, using a hierarchical system of military record analysis to ascertain or infer the location of units. By relating information on unit location to information on location of Ranch Hand spraying of Agent Orange, ESG will classify the

companies as "exposed" or "not exposed" (i.e., either falling within or outside an exposure area). Finally, by reviewing military personnel files and identifying individual veterans serving in the respective companies, ESG expects to supply the CDC with the names of 8,500 subjects with "high" likelihood of exposure and 8,500 subjects with "no" or "little" likelihood of exposure. The CDC, in turn, expects to interview 12,000 subjects and conduct physical examinations on 4,000 of them.

To identify individuals with potential exposure to Agent Orange, the ESG is currently using the definition of "within 2 miles and 3 days" or "within 2 miles and 6 days" of a spray. ESG does not distinguish between "low" exposure and "no" exposure, but only attempts to determine whether or not a company was within the exposure area. The current study design calls for 2 cohorts, both to be selected from the III Corps tactical zone.

The pilot study includes 7 battalions (approximately 35 companies). These battalions were selected because they met the following criteria established by CDC:

(1) they had records available for the period October 1966 to March 1969;

(2) they had known "hits" and sizeable exposure to herbicide; and

(3) they required the least amount of record "gap" filling.

Some of the characteristics for battalions, such as "gaps" and "hits", were known from previous exercises in matching battalion locations with locations of sprays. A "gap" is defined as no location for 1 day

for 1 unit. If a unit had more than 60 gaps in a year, or if there were 30 consecutive gaps, that unit would be excluded from the study.

In the pilot study, the ESG makes reference to every military record possible to help track the locations of these companies. Each record is searched for location by grid coordinates, and each coordinate identified from records is verified by an artillery expert. The ESG told the subcommittee that its ability to make determinations on company locations has been hampered by CDC-imposed constraints. The ESG also pointed out that there is a considerable loss of numbers of veterans with potential exposure from the study because of CDC's stringent eligibility requirements. Specific examples of the ESG's objections to these requirements include:

(1) Inability to extrapolate location from non-grid data: the ESG believes that for companies with missing grid locations or with missing dates, one can reconstruct location from careful analysis of battalion daily journals and ORLL (Operation Reports - Lessons Learned) reports. Using what is referred to as "contextual analysis," the ESG employs a fixed algorithm to fill in gaps, and feels confident in its ability to fill in the gaps by interpreting the contents of these records. ESG is using the contextual approach in the pilot study, but thus far has not been authorized to do so in the main study.

(2) Selection of subjects: the ESG said that it could identify several cases where individuals had 10 or more exposures but were excluded from

the study because they do not meet another CDC eligibility criterion which specifies that subjects have 180 days of combat in a line unit within 1 year. If such subjects had 170 days of combat and were then moved into a headquarters unit they were not included in the study, regardless of the number of exposures which occurred prior to transfer.

(3) Selection of subjects:

All headquarters people are automatically excluded from the study. It has been presumed that one cannot keep track of the duties and activities of people on headquarters premises. However, the ESG believes (on the basis of personal observations and experiences of their personnel in Vietnam) that headquarters and firebase personnel may actually be more exposed than other field personnel due to repeated spraying of the perimeters of these bases by non-Ranch Hand operations. Ranch Hand operations were designed to drop 2-3 gallons of herbicide per acre, while perimeter sprays released 5-6 gallons per acre directly on previously sprayed areas with less dense vegetation. Perimeter sprays occurred approximately every 5 weeks. Another argument that the ESG presented which raises questions about the exposure of field troops involved the potential for exposure immediately after or during a Ranch Hand spraying. Fighter jets flew ahead of Ranch Hand planes to protect these slow, low flying aircraft from ground fire. It was well known that the fighters would occasionally have to strafe the spray path (approximately 260 feet wide, give or take 20 feet), thus decreasing the likelihood that Army

personnel would be located directly under a spray path.

(4) The ESG has instituted a quality control system. 5 percent of records abstracted in the morning and 5 percent of records abstracted in the afternoon are reviewed every day. When discrepancies or gaps were identified, a two person team worked out a solution to the problem. Because consensus among judges was used rather than assessment by a series of independent judges, the issue of interjudge reliability is moot. Quality control is also applied to gap filling and to keypunch operations. It should be noted, however, that when mistakes are corrected and gaps are filled, the ESG does not record the places or numbers of such occurrences. Hence, it is not possible to determine the proportion of data affected by quality control measures.

The following is a synopsis of the subcommittee's reactions to the pilot study and to other issues raised at the ESG site visit.

- The subcommittee is satisfied that the ESG is capable of determining locations and filling gaps using a contextual approach, and notes that the ESG exhibits a high degree of competence in recording data gathered from these activities.
- Although there is a significant amount of inference used to establish the locations of troops, the subcommittee was satisfied with the ESG's documented Standard Operating Procedure to fill in gaps, and was also satisfied with the methods used by teams or pairs to resolve questions which arose during contextual analysis.

- The subcommittee raised concerns about the degree of "blindness," on the part of individuals determining location, to a unit's level of exposure; however, they were assured by the ESG that location decisions are made independent of any information on exposure.
- The subcommittee was satisfied with the ESG's quality control program. However, they would like to see the ESG monitor the changes which occur from quality control measures in a more precise fashion.
- The subcommittee was concerned about the use of discrete categories to define exposure (e.g., exposure vs. non-exposure), and instead favors measuring exposure as a continuous variable. Indeed, the subcommittee favors the use of continuous variables whenever possible. The use of discrete categories in data collection stages essentially discards valuable information, and such data can be stratified for subsequent analyses.
- The subcommittee was perplexed about criteria established by CDC to select subjects, especially the 180 day cutoff for combat time and the exclusion of headquarters-based individuals exposed to perimeter sprays.
- The subcommittee strongly favors reinstituting the third cohort in the study (i.e., noncombat nonexposed veterans selected from areas in Vietnam outside the III Corps tactical zone) in order to have a comparison group of truly unexposed veterans. The subcommittee is less concerned about differences in samples imposed by selection of the third cohort from outside the III Corps tactical zone than it is

about the potential for exposure misclassification for individuals selected exclusively from within this zone.

- The subcommittee was impressed by several factors that were illustrated in the video tape on ground sprays. Airplanes and helicopters varied greatly in the precision of spray deposition of the herbicide. Spray from helicopters was often delivered through uneven-size holes crudely drilled into pipes attached to the helicopter or through equipment designed for insecticide application which produced much finer atomization which in turn carries a higher potential for drift. The equipment used in rotary wing sprays illustrated in the video tape represented technological improvisation - such devices were not designed for herbicide spraying; by contrast, fixed wing aircraft delivered standard size droplets (367 microns) from equipment specifically designed for this task. Leaks and crudely constructed equipment had the capacity to significantly vary the amount of herbicide delivered.

- The subcommittee was impressed by the contribution of wind to actual spray delivery. The video tape illustrated that, in the presence of wind, substantial horizontal deviation from the expected perpendicular spray path occurs. The subcommittee questioned the exposure of a person standing within 1 km of the spray path under windy conditions.

- The subcommittee was also impressed by the type of spraying that occurred from non-Ranch Hand delivery. Ground sprays used every conceivable type of vehicle and hand carried equipment. River banks, communication lines, and open

highways were regularly sprayed, as were the perimeters of headquarters and fire bases. The video tape clearly showed handlers of the herbicide who wore no protective garments, no masks, and sometimes not even a shirt. Individuals spraying from the back of trucks and men spraying from helicopters with open doors were visibly sprayed themselves as wind blew the droplets back on them. The ESG presented anecdotal data describing herbicide "spray fights," where men would hose each other down with Agent Orange or other substances just "for fun."

- The information on aborted missions also raised questions for the subcommittee. An aborted mission would dump up to 970 gallons of Agent Orange within a very small area. Data was presented on one aborted mission in which the dump occurred on a headquarters as the plane tried to land shortly after takeoff upon discovery of an engine malfunction. In at least one instance, headquarters personnel were exposed to the preponderance of 970 gallons of Agent Orange. There are 9 aborted missions on record which led to dumps plus 1 crash. The altitudes at which the dumps occurred varied from 150 feet to 5,500 feet.

The subcommittee met in closed session in the afternoon to summarize their impressions from the site visit. The subcommittee made the following observations:

* The subcommittee is concerned about the exposure which occurred though non-Ranch Hand sprays. While the Ranch Hand Study showed no significant increase in mortality or morbidity for men participating in fixed wing operations**, the subcommittee wondered about the risk for those who lived on the ground with low-dose chronic exposure from perimeter and other ground sprays. There was potential for exposure through air, water, dirt, food and "just clean fun." They expressed concern about the men who conducted the ground sprays and the ones who hosed each other for a good time. The subcommittee would like to see verification of anecdotal reports.

** [Ranch Hand Study summary from Michael Gough's "Dioxin, Agent Orange: The Facts:

The Ranch Hand Study compared the mortality statistics of the 1,269 men who participated in fixed wing Agent Orange spray missions to a cohort of other Air Force members who flew the same type of aircraft in Vietnam but who did not spray Agent Orange. To increase the power of the study, the non-Ranch Hand cohort was 5 times the size of the Ranch Hand cohort. The Ranch Hand cohort included men who shipped, handled and loaded Agent Orange, those who flew spray missions, and those who cleaned planed and equipment.

Overall death rates analyzed by race and occupation of subjects (i.e. pilot, navigator, flight engineer-enlisted, and other enlisted men) showed no statistically significant differences between the cohorts. Ranch Hand enlisted men,

has the same mortality rates as Ranch Hand officers. Mortality statistics by specific cause of death showed an increase in rates in Ranch Handers for homicide and digestive system disorders, but lower rates for cancer. No difference, however, was statistically significant.]

* The subcommittee expressed concern about the definitions currently used to determine exposure. Issues related to the use of continuous versus discrete variables to measure exposure as well as wind dispersion and distance covered by spray have already been discussed (above). However, there remain questions about time, including the relationship of troop location to spray location with respect to time, and the half-life of dioxin (dislodgeable from plant surfaces? on soil? in human tissue?). The committee questions how "time" and residues will be built into the determination of exposure.

* The subcommittee was impressed by the amount of information available to the ESG on issues related to spraying, including wind direction and velocity, temperature, time of spray, season, the specific substance sprayed, and type of aircraft used. However, there is some concern that such data appear "hard," and in fact, may be much "softer." It must be remembered that these data were collected under combat conditions and that accuracy remains a question.

* The subcommittee had questions about scoring individual exposures. The criteria used to define exposure and to define who will be included in the study seem arbitrary and

confusing. For example, if an individual was [illegible] from an aborted mission, he would be coded as having a single hit. However, the actual exposure he received might be very much higher than that experienced by an individual 1 kilometer from a flight path on a windy day (who would nonetheless receive the same exposure score). If the individual experienced the dump within the confines of a headquarters base, as was the case for the aborted landing mission, he would not qualify for inclusion in the study. The subcommittee concurred with the ESG that there appear to be many exposed individuals who will be excluded from the study as it is now designed. The subcommittee questions the rationale for excluding headquarters-based companies from the study. They would like an explanation on how combat and noncombat duty relate to exposure, given that both types of duty can occur in a combat zone, and that both appear to give an individual the potential for exposure. In addition, the ESG has data on 1,100 individuals in the chemical units that were attached to each battalion. Chemical units were responsible for herbicide supply, and for herbicide distribution in non-Ranch Hand sprays. It is not clear that only chemical unit personnel were involved in ground sprays; other personnel may also have been used. However, the subcommittee concurred with the ESG that some special examination of these individuals is important. The subcommittee concluded that there appear to be different kinds of exposure, and that individuals were exposed under a variety of conditions; these issues need to be addressed

more carefully. The subcommittee finds the current definition of exposure to be inadequate.

* The subcommittee feels that the range which exists in types of exposure makes a strong argument for reinstating the third cohort (noncombat, nonexposed) in the Agent Orange study, since it appears that everyone in the combat zone had the opportunity for exposure.

* The subcommittee is under the impression that, in the main study, the ESG will only be responsible for determining the locations of companies and spray paths. Dr. Carl Keller's Science Panel of the Agent Orange Interagency Working Group is currently trying to define "exposure." The subcommittee strongly believes that the ESG should only be responsible for providing CDC with the raw data on locations. There was considerable interest expressed by individuals at the ESG in participating in modeling exposure data. The ESG has two of its employees on Keller's exposure-definition group (Christian and Bricker). The subcommittee does not feel that the ESG is qualified to conduct such analyses, and suggests that CDC should be responsible for all data analyses.

* In addition, the subcommittee, upon examination of the membership roster of Keller's Science Panel, was concerned about the thinness of expertise in certain areas. They expressed interest in knowing exactly who will be responsible for defining exposure and what criteria they will use to make this determination. Staff cautioned the subcommittee that he who finalizes the definition of exposure will be the one to determine if the Agent Orange Study will go forward. Staff

role for this committee.

[In response to the concern of the subcommittee regarding the panel defining exposure, and to similar concerns expressed by the CDC, staff have made an appointment with Dr. Keller to discuss the process and progress of his group in defining exposure.]

* The subcommittee would like to ask the CDC to clarify why they dropped the third cohort, why they are using cutoffs to define exposure, and how it derived criteria for eligibility.
* The subcommittee concluded that the ESG appears to be doing a reasonable job of determining locations, and the subcommittee is of the opinion that the contextual approach improves the quality of the data. However, they would like to see the ESG record the number of gaps filled in by contextual analysis, as well as the number of times disagreements are found in the data.