

Item ID Number 01835

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Report/Article Title Memorandum with several attachments: from Chairman, Science Panel, AOWG, to Members of the Science Panel, AOWG, with subject Meeting of the Science Panel, dated February 5, 1985.

Journal/Book Title

Year 0000

Month/Day

Color

Number of Images 12

Description Notes Alvin L. Young filed this item under "Vietnam Veterans Twin Study." Memo gives notice of a science panel meeting scheduled for February 21, 1985 with the purpose of reviewing the VETS II protocol. Attachments include inquiries about the possibility of a female Vietnam veterans study, and the minutes of the November 29, 1984 meeting of the Science Panel of the Agent Orange Working Group.



Memorandum

Date February 5, 1985

From Chairman, Science Panel, AOWG

Subject Meeting of the Science Panel

To Members of the Science Panel, AOWG

This is to announce that there will be a meeting of the Science Panel of the Agent Orange Working Group at 9:30 a.m., February 21, 1985, in room 729G of the Hubert Humphrey Building, Washington, D.C.

The purpose of the meeting will be to review the protocol for the Veterans Administration Twin Study (VETS II). You will (or will have) receive(d) a copy of this protocol under separate cover. I am enclosing some comments made by a special review group last summer for your information. Please bring your written comments to the meeting and we will summarize our review at that time.

We have also received additional congressional correspondence concerning female Veterans' needs. It appears that we are now being requested to recommend what, if any, studies of the health of female Vietnam veterans should be done and to examine proposed studies in that light. I am enclosing appropriate materials and we will discuss this at our meeting.

In addition, please find enclosed the minutes of our last meeting (November 29, 1984) for your approval.

A handwritten signature in cursive script that reads "Carl Keller".

Carl Keller, Ph.D.

ALAN K. SIMPSON, WYOMING, CHAIRMAN

STROM THURMOND, SOUTH CAROLINA
ROBERT T. STAFFORD, VERMONT
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ARLEN SPECTER, PENNSYLVANIA
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JONATHAN R. STEINBERG, MINORITY CHIEF COUNSEL/
STAFF DIRECTOR

United States Senate

COMMITTEE ON VETERANS' AFFAIRS

WASHINGTON, DC 20510

January 23, 1985

Honorable Charles Baker
Chair
Cabinet Council Agent Orange
Working Group
Department of Health and Human Services
Humbert Humphrey Building, 614-G
200 Independence Avenue, S.W.
Washington, D.C. 20201


Dear Mr. Baker,

I have long had a strong interest in the issue of how the Federal Government might conduct research to investigate the possible health effects in female Vietnam veterans of their exposure to Agent Orange. Enclosed is a copy of an October 16, 1984, letter to me on this subject from Dr. James O. Mason, the Director of the Centers for Disease Control.

It is my understanding that the draft protocol outline mentioned in Dr. Mason's letter is pending in the Agent Orange Working Group and may be considered during the Group's next meeting, which is scheduled to take place in early February. I believe that it is extremely important that research be undertaken on this issue, and I strongly urge that the Working Group undertake its review of the protocol outline as expeditiously as possible. It is my strong hope that the members of the Working Group will be able to report favorably on the possibility of a study of female Vietnam veterans, either by endorsing the protocol outline as developed by CDC or by suggesting whatever changes to the outline the members believe are needed in order for a study to go forward.

Thank you for your attention to my views on this issue. I would appreciate hearing from you on this matter as soon as possible after the Working Group's February meeting.

With best wishes,

Sincerely

Alan Cranston
Ranking Minority Member

Enclosure

JAN 7 10 47 AM '85

United States Senate

WASHINGTON, D.C. 20510

January 4, 1985

The Honorable Margaret M. Heckler
Secretary
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Heckler:

I write regarding the government's epidemiological study on Agent Orange being conducted by the Centers for Disease Control (CDC).

As a member of the Senate Veterans' Affairs Committee, I am very concerned that CDC's study fails to include women who served in Vietnam. Approximately 20,000 women served there as members of the military or as civilians employed by service organizations. Many of these women are now suffering from health problems that may be associated with Agent Orange.

It is my sense that research is needed to assess the problems among women who were in Vietnam to avoid excluding them from Agent Orange compensation programs.

I urge that this omission be rectified by the Health and Human Services Administration. Your consideration of this request is greatly appreciated.

Sincerely,



Arlen Specter

AS:gfs

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**Memorandum**

Date December 20, 1984

From Director, Center for Environmental Health

Subject Possible Study of Female Vietnam Veterans

To Dr. Carl Keller
Chair, AOWG Science Panel

At the Agent Orange Working Group (AOWG) Meeting of December 4, 1984, Dr. Brandt requested that the Centers for Disease Control (CDC) and the AOWG Science Panel discuss what additional information the Science Panel would need to assess the scientific utility of a study of female Vietnam veterans.

As you know, CDC assessed the feasibility of a study of women veterans and described the possible study approach in a protocol outline dated June 25, 1984, copy attached. In that document and in the attached memorandum to Dr. Brandt from Dr. James Mason, CDC Director, responding to the Science Panel's initial critique of the protocol outline, CDC stated its belief that a comprehensive health assessment of female Vietnam veterans motivates the study, rather than any specific hypothesis. In addition, there are gender-specific issues that would not permit generalization of male data to the female veteran.

CDC has also clearly stated that the proposed study is a "Vietnam Experience" study rather than an "Agent Orange" study, per se. By that, I mean we believe it will not be possible to estimate individual female veterans' opportunity for exposure by relating their unit's location to herbicide spraying missions. Like the "Vietnam Experience" study being conducted in males, the study of female veterans would compare the health of Vietnam veterans to comparable veterans who served elsewhere. Any of the exposures women veterans experienced in Vietnam, (e.g. stress of caring for a high volume of combat casualties, parasitic diseases, whatever Agent Orange may have been ubiquitous in the Vietnamese environment, etc.) might influence the health of Vietnam veterans compared to other female veterans.

Page 2 - Dr. Keller

Given these two assumptions, that any health assessment of women Vietnam veterans should be as comprehensive as that in male Vietnam veterans, and that the study should look at all exposures in Vietnam, not exclusively at the opportunity for Agent Orange exposure, I believe that the study described in the protocol outline is appropriate. If the Science Panel can provide CDC with a list of specific hypotheses that will address the health concerns of female Vietnam veterans, I will request the resources to develop a protocol to study these hypotheses.

I look forward to hearing from you in the near future. Please do not hesitate to contact me if you have any further questions.


Vernon N. Houk, M.D.

Attachments

NOV 13 1984

Director
Centers for Disease Control

Possible Study of Female Vietnam Veterans

Edward N. Brandt, Jr., M.D.
Chair Pro Tempore
Cabinet Council Agent Orange Working Group

Thank you for the opportunity to review and respond to the Agent Orange Working Group Science Panel's critique of the protocol outline for a study of female Vietnam veterans. The Science Panel mentioned two issues which they felt must be carefully considered before proceeding further with development of the study:

- 1) "the great potential for confounding exposures both during and after Vietnam to teratogenic agents other than herbicides and their contaminants," and
- 2) "what a study of female veterans will contribute in the way of scientific information which is not already being obtained from the ongoing male studies."

CDC shares the Science Panel's interest in having a research plan which addresses potentially confounding exposures. In this regard, it is important to consider the purpose of the study. As stated in the protocol outline, the proposed study is similar to the Vietnam Experience Study of men currently being conducted. All the exposures unique to the Vietnam environment, from parasitic diseases, to psychological stress, to waste anesthetic gases may influence the health of the Vietnam veteran cohort. Agent Orange is only one of many exposures included in this experience.

For analyses of the effects of Vietnam service in general, exposure to excess waste anesthetic gases in field hospitals in Vietnam would not be a confounder of the association of Vietnam service with health outcomes. Rather, the anesthetic gases are but one of the many exposures that are part of the Vietnam Experience. On the other hand, for analyses focusing on specific exposures experienced in Vietnam, such as Agent Orange, waste anesthetic gas exposure might be a confounder. Such analyses would be expected to control for operating room experience in Vietnam. Occupational exposures, including waste anesthetic gases, experienced after military service might also be potential confounding factors since they could differ between the Vietnam and non-Vietnam female veterans. Again, these exposures would be considered in the analysis.

To respond to the general concern about confounding, CDC would deal with potentially confounding factors in this study with the same approach used in the recent Birth Defects Study and the ongoing study of male veterans.

Detailed information would be gathered from personal interviews and record reviews about potential confounders, e.g., demographic, occupational, or other risk factors for disease that might occur with differing frequencies among Vietnam and non-Vietnam veterans. In the analysis such factors would be controlled for, eliminating any actual confounding effect of these variables.

The second concern of the Science Panel related to the research questions unique to women that would be addressed in the proposed study. As stated above, the study is primarily designed to look at military service in Vietnam, in general, as the main exposure of interest, rather than estimates of Agent Orange exposure. Two caveats should be mentioned regarding the study of Agent Orange exposure, per se, in relation to the health of female Vietnam veterans. First, because of the duties of most women who served in Vietnam, their likelihood of exposure to Agent Orange may be less than that of male Vietnam veterans. Most women who served in Vietnam were stationed at military hospitals or headquarter units that were at some distance from the heaviest Agent Orange sprayings. Second, if, as speculated by some scientists, Agent Orange residues became ubiquitous throughout Vietnam, female Vietnam veterans may have been exposed through food supplies, drinking water, etc. However, these types of exposures could not be quantified by relating the proximity of the women's units to the Ranch Hand spraying missions or other applications of Agent Orange.

Three broad groups of health outcomes would be studied in relation to Vietnam service: reproductive outcomes, psychologic outcomes, and general health outcomes for which women may experience different risks than men.

Reproductive outcomes would include fertility, spontaneous abortions, and congenital malformations as well as diseases of female reproductive organs. Pregnancy outcomes of the women are of particular interest since maternal exposures are more commonly associated with adverse effects than paternal exposures. Diseases of reproductive organs may be related to the influence of various stresses and insults to the delicate hypothalamic-pituitary-ovarian axis. Also of note in this regard, certain subclinical parasitic diseases, such as malaria and anebiasis, may become manifest during the stress of pregnancy.

Psychologic outcomes such as anxiety, depression, and Post Traumatic Stress Disorder and behavioral outcomes such as substance abuse and criminal activity may exhibit different patterns in male and female Vietnam veterans. With a large proportion of acute care nurses among female Vietnam veterans, special consideration would be given to possible stressful effects of caring for a large volume of combat casualties. The psychosocial component of the female study is also crucial to the complete evaluation and interpretation of the other clinical data to be collected, specifically in the determination of behavioral outcomes as a cause versus an effect of physical and biochemical disorders (e.g. hepatitis, cirrhosis, memory disorders).

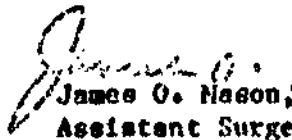
General health outcomes would include a variety of conditions of concern to female Vietnam veterans. These outcomes are similar to those being addressed in the ongoing study of male veterans. As was the case in the study of male veterans, there are few specific hypotheses based on previous scientific studies. CDC believes that a comprehensive health interview and physical examination would be needed to address the veterans' concerns thoroughly.

The statistical power of the proposed study for important health outcomes would be good. The interview phase of the study is designed to detect increases of about twofold in the relative risks for health outcomes occurring with the frequency of 0.5%, while the examination phase is designed to detect twofold increases in conditions that occur with a frequency of 1.5% or greater (power = 0.95, Alpha = 0.05, 1-tail). With that level of statistical power, most conditions that are of concern to women who served in Vietnam will be adequately addressed. Only relatively small increases in uncommon conditions would escape detection.

The intent of the study which CDC was asked to propose is to address the health concerns of female Vietnam veterans comprehensively and with sufficient statistical precision. That has determined the study design and sample size, rather than any single research hypothesis.

The cost of doing this study is significant. A decision to do this research, in a world of finite resources, may mean that money for other activities may not be available. We are neutral on doing the study. However, if a decision is made to proceed, we are confident that we can do a valid study, acceptable to the veterans groups, if we are provided the necessary resources.

We will be pleased to provide any further information you need.


James O. Mason, M.D., Dr.P.H.
Assistant Surgeon General

cc:
OD
CEH
CDC/W
ES/PHS
Tracer 85084; CDC ID D19247; CEH #B-59
10/19/84
CDC:CEH:CDD:AOP:PLayde:dd/doc

Minutes of the November 29, 1984 Meeting of the
Science Panel of the Agent Orange Working Group

The Science Panel of the AOWG met at 9:30 AM on November 29, 1984, in the offices of the United States Army and Joint Services Environmental Support Group (ESG) in room 210, Riddell Building, 1730 K Street, NW, Washington, D.C. Attendees were as indicated on the attached attendance sheet.

The purpose of the meeting was to review in depth the procedures to be used by the ESG to assign an Exposure Opportunity Index to individual Vietnam veterans identified from other sources. Since the procedures had been developed during the CDC Birth Defects Study, individual records of Vietnam veteran participants in that study were available for review. Several individual records were selected to illustrate the information available and the method and steps used to assign an estimate of the likelihood of exposure to Agent Orange while in Vietnam.

The method used in the CDC Birth Defects Study assigned a value from one to five to each veteran depending on the recorded proximity of his unit to an Agent Orange application while he was assigned to the unit. The value of the assigned index also took into account the particular job classification that the veteran had at the time. For example, a veteran whose job was either clerical, administrative or logistical would not be expected to be with his unit while on patrol away from the base, although he might be expected to serve guard duty on the base perimeter. If exposure consisted of a patrol approaching a Ranch Hand spray track, he would not be included, but if exposure consisted of base perimeter spraying, he could have been exposed.

A score of five (highly likely to have been exposed) was assigned to all individuals in a unit which was known to have been within two kilometers within 72 hours of an Agent Orange application and who held military occupational specialties (job classifications) implying that they should have been with their assigned unit on such a mission. A score of five was also assigned to all veterans known to have handled Agent Orange, such as Ranch Handers or chemical personnel. A score of one (very unlikely to have been exposed) indicated that the veteran was assigned to a unit which was neither known nor expected to have been near an application site. Scores of two to four indicated a range of possibility from probably not exposed to probably exposed.

Although the methods used to develop these procedures involved considerable subjective judgement on the part of the investigators, a description of the Vietnam experience contained in the records of veterans classified as "very unlikely to have been exposed" seems quite adequate to consider them as much less likely to have been exposed to Agent Orange than those classified as "highly likely to have been exposed". Members of the Science Panel unanimously agreed that the data and methods under consideration are adequate to classify many of the veterans into groups which were highly likely or very unlikely to have been exposed to Agent Orange while in Vietnam. Other methods for assigning intermediate values need to be completed and may best be adopted for specific studies where necessary.

Some of the implications of using the Exposure Opportunity Index as defined above were discussed as follows:

- 1) Some veterans cannot be classified because their records are not available or are incomplete. It is thought that this will be a small group if adequate search is undertaken.
- 2) Many veterans, such as would fall in groups two to four of the CDC Birth Defects classification system, cannot be unambiguously assigned to highly likely or very unlikely exposed categories. Several suggestions as to how to handle these were:
 - a) Classify them as unknown and drop them from further analysis. This would have rendered approximately one half of the Vietnam veterans in the CDC Birth Defects Study as unclassifiable.
 - b) Use five classes (as in the CDC Birth Defects Study) or one or more intermediate classes. This system, would retain larger numbers of classifiable study subjects, but may reduce the statistical power of a study due to missclassifications.
 - c) Attempt to classify all veterans with available records into likely or unlikely exposed groups. This is also almost certainly going to increase missclassification and therefore reduce statistical power.
- 3) The index as currently developed is intended to be a measure of the likelihood that any exposure took place and presents some problems during analysis since it is not a dose response statistic. Using the computer methods now available, there is the possibility for counting the number of encounters a given unit may have had and trying to estimate the intensity of exposure. There is some support for this since almost all of the encounters which a given unit has had may be recorded in the quarterly reports (at least in those units which have been specifically examined).
- 4) There is clearly an association between combat and Agent Orange exposure since combat operations are a major factor in determining opportunities for exposure at the individual as well as the unit level. This must be considered in the light of specific study needs e.g., it may not have been relevant for a Birth Defects Study, but may be important in a Mortality Study.
- 5) While the methods which have been developed do provide for an estimation of the number of opportunities for exposure, there has been no attempt to quantify the possible exposure amount. The index only assigns a value to the likelihood that a given veteran was within two kilometers within three days of an application of Agent Orange. Whether this constitutes an effective toxic dose cannot be determined from the records and is the subject of ongoing health effects research.

In order to assist in the usefulness of these methods for future research, a subpanel was assigned the task of developing guidelines for the application of these alternative methods to specific studies. The meeting adjourned at 1:30 PM, November 29, 1984.

Science Center Building 11000-

November 29, 1984

A+JSESG, Rm 210, 1730 K St. NW, Wash DC

Carl Keller
 Mike Rough
 Miriam Davis
 Riz Hague
 S S Mc Connell
 Dick CHRISTIAN
 Rob Lipaick
 Don HAKENSON
 LORRAINE D. Goodrich
 Leslie E. Halagy
 Peter E. M. Beush
 John Allen
 HAN KANG
 JOE MULINARE
 Lawrence B. Hobson
 CRAIG NIEDERPRUEM
 Barclay M. Shepard
 Dick Hilder
 Jerome G. Bucker
 Charles E. Broduski

MEAS
 OTA
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 EPA/ORD
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 MCRP/ESG
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 CCAOWG.
 ISG
 OSD/HA
 VA/AOPD
 CDC
 VA/AOPD
 U.S. ARMY, OTSAG
 VA/AOPD
 WSRAM
 OASD(HA), DoD
 Dept of State

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 245-6301
 382-5967
 FTS 629-3267
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 245-6156
 653-1522
 697-8978
 389-5534
 404-452-4080 (FTS-236)
 389-5534
 695-1700
 376-7528
 576-1418
 697-8975
 632-5337



**Veterans
Administration**

JAN 30 1985

In Reply Refer To: 10A7

Dear Colleague:

Enclosed is a copy of the latest version of the Vietnam Experience Twin Study Protocol. These are being distributed at the request of Dr. Carl Keller--he will be in touch with you in the near future to arrange a meeting to discuss his plans for reviewing the protocol.

Sincerely,

A handwritten signature in cursive script that reads "Barclay M. Shepard".

BARCLAY M. SHEPARD, M.D.
Director
Agent Orange Projects Office

Enclosure