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**Author** Shy, Carl M.

**Corporate Author** Panel of the Proposed Air Force Study of Herbicide Ora

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# NATIONAL ACADEMY OF SCIENCES

OFFICE OF THE PRESIDENT  
2501 CONSTITUTION AVENUE  
WASHINGTON, D.C. 20418

May 6, 1980

Murphy A. Chesney  
Major General, USAF, MC  
Director, Medical Plans and Resources  
Office of Surgeon General  
Bolling Air Force Base  
Washington, D.C. 20332

Dear General Chesney:

I am pleased to transmit five copies of the report of a distinguished Panel on the Proposed Air Force Study of Herbicide Orange. The report is a review of the U.S. Air Force Protocol entitled "Epidemiological Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicide Orange."

The panel recognizes the desirability of an extensive, in-depth study designed to ascertain and appraise the health effects of Herbicide Orange on Vietnam veterans. However, a major conclusion of the present report is that, as designed, the proposed study probably would not identify adverse health effects due to exposure to the herbicide, primarily because of the relatively small size of the group to be studied and the relatively short time for which it is proposed to follow the health of the group. Specific suggestions concerning expansion of the scope and duration of the study, intended to increase the likelihood of obtaining definitive understanding, are offered by the panel.

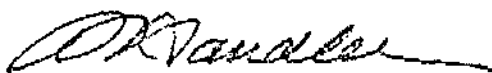
The panel has also expressed concern with respect to an issue extending beyond the scientific review they were asked to undertake. The panel is concerned that--given the temper of the times and the sense of diminishing public trust in the institutions of American society--were the ultimate report of the forthcoming study to contain equivocal conclusions and findings, questions concerning the impartiality and credibility of the report might be raised if the study were

Murphy A. Chesney  
May 6, 1980  
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conducted internally by the Air Force. Thus, the panel suggests that the Air Force give consideration to this question of public perception. In making these comments, the panel does not mean to imply that the Air Force lacks the appropriate resources and qualified investigators to conduct the proposed study.

We are pleased to be of assistance to the Department in its deliberation on this very vexing question.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "P. Handler", written in dark ink.

Philip Handler  
Chairman, National Research Council  
President, National Academy of Sciences

Enclosure

Review of U.S. Air Force Protocol:

Epidemiological Investigation  
of Health Effects in  
Air Force Personnel  
Following Exposure to  
Herbicide Orange

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Panel on the Proposed Air Force  
Study of Herbicide Orange



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Committee on Toxicology

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Board on Toxicology and Environmental Health Hazards

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Assembly of Life Sciences

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REVIEW OF U.S. AIR FORCE PROTOCOL:  
EPIDEMIOLOGICAL INVESTIGATION OF HEALTH EFFECTS IN  
AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO  
HERBICIDE ORANGE

Panel on the Proposed Air Force Study of Herbicide Orange  
Committee on Toxicology  
Board on Toxicology and Environmental Health Hazards  
Assembly of Life Sciences/National Research Council

NATIONAL ACADEMY OF SCIENCES  
Washington, D.C., May 1980

## NOTICE

The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the panel responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The work on which this report is based was performed pursuant to Contract No. NQ0014-80-C-0161 with the Office of Naval Research.

## PANEL ON THE PROPOSED AIR FORCE STUDY OF HERBICIDE ORANGE

Dr. Carl M. Shy, Chairman  
Institute for Environmental Studies  
University of North Carolina  
Chapel Hill, N.C.

Dr. Leon Gordis  
Department of Epidemiology  
School of Hygiene and Public Health  
Johns Hopkins University  
Baltimore, Md.

Dr. Ian T. Higgins  
University of Michigan Medical Center  
School of Public Health  
Ann Arbor, Mich.

Dr. Leonard T. Kurland  
Department of Medical Statistics  
Epidemiology and Genetics  
Mayo Clinic  
Rochester, Minn.

Dr. Philip Landrigan  
Division of Surveillance  
Hazard Evaluations and Field Studies  
National Institute for Occupational Safety and Health  
Cincinnati, Ohio

Dr. Raymond Seltzer  
Department of Epidemiology  
School of Hygiene and Public Health  
Johns Hopkins University  
Baltimore, Md.

Dr. Gordon W. Newell, Staff Officer  
National Research Council/National Academy of Sciences  
Washington, D.C.

Mrs. Frances M. Peter, Editor  
National Research Council/National Academy of Sciences  
Washington, D.C.

## COMMITTEE ON TOXICOLOGY

Dr. Joseph F. Borzelleca, Chairman  
 Medical College of Virginia  
 Health Sciences Division  
 Virginia Commonwealth University  
 Richmond, Va.

Dr. David Axelrod  
 Commissioner of Health  
 New York State Department of Health  
 Albany, N.Y.

Dr. Lawrence Fishbein  
 National Center for Toxicological  
 Research  
 Jefferson, Ariz.

Dr. Ian T. Higgins  
 University of Michigan Medical Center  
 School of Public Health  
 Ann Arbor, Mich.

Dr. Wendell W. Kilgore  
 Department of Environmental Toxicology  
 University of California  
 Davis, Calif.

Dr. Howard I. Maibach  
 Department of Dermatology  
 University of California  
 School of Medicine  
 San Francisco, Calif.

Dr. H. George Mandel  
 Department of Pharmacology  
 George Washington University  
 School of Medicine  
 Washington, D.C.

Dr. Roger O. McClellan  
 Inhalation Toxicology Research  
 Institute  
 Lovelace Biomedical and Environmental  
 Research Institute  
 Albuquerque, N.M.

Dr. Charles F. Reinhardt  
 Haskell Laboratory for  
 Toxicology and Industrial  
 Medicine  
 E.I. Dupont de Nemours and  
 Company  
 Newark, Del.

Dr. Joseph V. Rodricks  
 Food and Drug Administration  
 Rockville, Md.

Dr. Ronald C. Shank  
 Department of Community and  
 Environmental Medicine  
 College of Medicine  
 University of California  
 Irvine, Calif.

Dr. Carl M. Shy  
 Institute for Environmental  
 Studies  
 University of North Carolina  
 Chapel Hill, N.C.

Dr. Peter Spencer  
 Institute for Neurotoxicology  
 Albert Einstein College of  
 Medicine  
 Bronx, N.Y.

Dr. Phillip G. Watanabe  
 Dow Chemical U.S.A.  
 Midland, Mich.

Dr. Gordon W. Newell, Project Director  
 National Research Council/  
 National Academy of Sciences  
 Washington, D.C.

Gary R. Keilson, Staff Scientist  
 National Research Council/  
 National Academy of Sciences  
 Washington, D.C.



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REVIEW OF U.S. AIR FORCE PROTOCOL: EPIDEMIOLOGICAL INVESTIGATION  
OF HEALTH EFFECTS IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO  
HERBICIDE ORANGE

The U.S. Air Force has been developing a protocol for an epidemiological investigation of health effects in Air Force personnel following exposure to "Herbicide Orange," a 50:50 mixture of the n-butyl esters of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), which contains parts per million quantities of the contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Early versions of the study protocol were reviewed by faculty of the School of Public Health at the University of Texas in Houston, by a committee of the U.S. Air Force Scientific Advisory Board, and by the Armed Forces Epidemiological Board. After making extensive modifications as a result of these reviews, the Air Force asked the National Academy of Sciences to conduct yet another review. In response, a panel of epidemiologists was established under the aegis of the Academy's standing Committee on Toxicology.

As a first step, the Air Force investigators provided panel members with a complete study protocol for review. Subsequently, on December 18, 1979, the panel met with representatives of the Epidemiology Division of the School of Aerospace Medicine of the U.S. Air Force.

Specifically, the panel was asked to consider the following questions:

1. Is the study adequately designed to address the scientific issues related to toxicology, epidemiology and statistics, data collection, and health studies?

2. Are there ways to improve the scientific validity of the study?
3. Are there additional techniques that could be used to reduce the number of anticipated biases?
4. Are there additional statistical procedures that could be added to determine whether detected associations are real or spurious?

This report reflects the agreement of the majority of panel members. A separate minority statement, which was prepared by one of the panel members, is appended to this report.

#### DESCRIPTION OF THE PROPOSED STUDY

The stated purpose of the proposed Air Force study is "to determine whether long-term health effects exist and can be attributed to occupational exposure to Herbicide Orange." To accomplish this, the investigators developed three independent study goals:

Health goals: "to identify veteran or active duty Air Force personnel who manifest adverse health effects attributable to herbicide exposure or who are at risk of developing future adverse health effects."

Political goals: "to satisfy the social concern for proper investigation voiced by lay and scientific communities."

Legal goals: "to clarify the question of compensation awards to the VA [Veterans Administration] claimants."

The Air Force proposes a complex study design consisting of a retrospective cohort mortality study, a questionnaire and physical

examination study of morbidity in Air Force personnel, and a 5-year prospective followup study of participants in the morbidity component.

The exposed cohort is identified as a group of 1,200 "Ranch Hand" personnel--those servicemen who flew and serviced the C-123 aircraft that sprayed the herbicide over Viet Nam between 1962 and 1970. This group represents the total exposed cohort of Air Force personnel. An individually matched cohort of aircrew members and support personnel would serve as unexposed controls. This group of 25,000 Air Force veterans was on active duty in Viet Nam between 1962 and 1970. Ten of the control personnel would be matched with each member of the Ranch Hand cohort. From this pool, five control veterans would be randomly selected as controls for each Ranch Hand in the mortality analysis and one as a control for each Ranch Hand in the morbidity and followup surveys. Members of the study group would range in age from 28 to 58 years, as of 1979. Controls would be individually matched with exposed personnel for age, race, Air Force Specialty Code (job title), and length of time in Viet Nam.

All selected participants would be asked to respond to a comprehensive personal and family health questionnaire by telephone. The questions would pertain to dermatological and neuropsychiatric conditions, history of fertility, malformations in offspring, sensory defects, personality factors, and general medical history. The investigators anticipate that there would be a 65% response rate. Participants would be subjected to a general physical examination, routine hematological and other clinical chemistries, and special examinations of dermatological conditions and of neuropsychiatric,

reproductive, and hepatic functions. A 40% response rate to this component of the study could be expected.

In the followup study a health questionnaire would be administered and a condensed version of the initial physical examination would be conducted 3 and 5 years after the initial morbidity survey.

In their protocol, the investigators place considerable emphasis on the replacement of nonresponding controls from the pool of eligible controls and to the analysis of potential selection biases. They explore in detail methods to derive quantitative estimates of exposure to Herbicide Orange among Ranch Hand personnel and address a number of potentially confounding factors. Moreover, they consider the adequacy of sample sizes for each phase of the study and provide a detailed discussion concerning statistical analysis of results.

The protocol calls for all phases of the study to be conducted by U.S. Air Force personnel. It identifies the principal and co-investigators as either armed services or civil service staff from the School of Aerospace Medicine or the Air Force Human Resources Laboratory, both of which are located at Brooks Air Force Base, Texas.

#### CRITIQUE OF THE STUDY

The majority of the panel believes that the study has major weaknesses that would preclude attainment of the stated study goals. The panel's critique is focused on three issues: (1) the statistical power of the study to detect an adverse effect of exposure to Herbicide Orange, if an effect truly exists, and the interpretation that may consequently be given to the results; (2) the large number of health

indices selected for study in the morbidity component (questionnaire and physical examination) of the protocol; and (3) the credibility of the results if the study is conducted by Air Force personnel.

#### STATISTICAL POWER OF THE STUDY

In the mortality component of the proposed study, the mortality experience of the 1,200 Ranch Hand personnel would be compared with that of the 6,000 unexposed aircrew and support personnel controls. Because the age of the subjects in the mortality analysis ranges from 28 to 58 years, and because of the relatively short time, i.e., 10 to 18 years, that has elapsed since the subjects were exposed to Herbicide Orange, there would be little likelihood of detecting a mortality effect attributable to Herbicide Orange within the followup period proposed by the investigators. According to the investigators' calculations, the study could detect as statistically significant only a doubling of total mortality. For the more common cancers, such as lung, prostate, or colon-rectum cancers, only a 3- to 5-fold or greater relative risk might be detected among the Ranch Hand study group. Effects of this magnitude would be very powerful and are infrequently observed as a result of exposure to environmental agents.

The panel is also concerned that a study with so low a probability of detecting an effect within this limited followup period would be incorrectly interpreted to mean that no cancer mortality or other specific cause of death can be attributed to exposure to Herbicide Orange. Since statistical power is crucial to the feasibility of the study,

the panel recommends that the investigators provide a table displaying the magnitude of the relative risk that can be detected as significant for each cause of death (e.g., all causes, all cancers, selected site-specific cancers, cardiovascular disease, etc.) at several levels of beta error (e.g., beta errors of 0.10, 0.20, 0.30). For these calculations, the investigators should assume a sample size of 1,200 exposed Ranch Hand personnel, which is indicated in the protocol.

The panel perceives the proposed mortality study as an epidemiological investigation intended to determine if the experience of Air Force personnel after exposure to Herbicide Orange indicates that such exposure presents a serious risk of disease. To accomplish this, the Air Force must either find a larger cohort of exposed persons (and this may not be possible) or follow this small cohort for at least 20 to 30 years after initial exposure. At this time, mortality analysis must be regarded only as an interim, preliminary evaluation of disease risk. As proposed, such an analysis could not be used to determine if Ranch Hand personnel are at increased risk of any organ-specific cancer or of other delayed and infrequent disease occurrences. Hence, it would be difficult to justify compensation awards to claimants on the basis of results of this study as currently designed.

Nevertheless, the investigators estimate that they will be able to use the morbidity data to detect a 2% relative increase in effect (relative risk = 1.02) for health indices that are continuously distributed, e.g., blood pressure, serum cholesterol, and other clinical chemistries. When there is a dichotomous distribution

of the health end points, the statistical power of the study depends on the proportion of the population having the disorder. The investigators estimate that if the effect of the herbicide is as large as the effect of aging on the occurrence of cardiovascular disease, this study would have sufficient statistical power to detect an effect of Herbicide Orange on more prevalent diseases. For less prevalent diseases, such as cancer, the investigators note that the study would be less sensitive, i.e., there would be a greater than 20% chance of overlooking effects from the herbicide that are smaller than or equal to those from aging.

Therefore, the study as designed would not be likely to produce results that would permit the scientific community to draw conclusions about the effect of Herbicide Orange on risk of cancer or birth defects. Similarly, the study lacks the statistical power to uncover an effect of moderate strength, such as the uncommon disorders mentioned in the complaints of veterans. Because of the limited sample size available to the investigators, the study apparently would be able to detect only differences in physiological and biochemical indices for the most common diseases that are or are not known to be associated with the toxic properties of the herbicide.

The panel commends the investigators for their careful consideration of statistical power and assessment of the limitations of their sample size. However, it believes that the overall study, including the morbidity and mortality components, is seriously limited by the insufficient sample size. Congress and the public are concerned



about the risk of disease, especially cancer, other disorders in exposed military personnel, and birth defects in their offspring. The stated health, political, and legal goals of this study relate largely to these infrequent disorders. The inadequacy of the sample size makes it highly unlikely that these goals could be addressed adequately within the limited time frame proposed for the study.

The panel recognizes that there may be other reasons for conducting a comprehensive medical examination of the exposed Air Force personnel. It may be "politically" desirable to offer medical services to any of the Ranch Hand personnel manifesting compromised health, independent of a possible relationship with exposure to the herbicide.

From an epidemiological viewpoint, it would be desirable to establish baseline values in exposed and control groups. These values could be compared with results of examinations repeated in 10 to 20 years, at which time more definite results might be obtained if a true effect of the herbicide does exist.

All panel members agree that the study should be redesigned to include a considerably longer followup period in order to meet the stated objective of evaluating whether long-term health effects can be attributed to exposure to Herbicide Orange.

The limitations in study design and the size of the exposed population (maximum of 1,200) give rise to the question of whether other exposed populations can be identified and whether they can be integrated into a coordinated study that has a reasonable expectation of producing meaningful results within a few years.

Among the exposed military personnel is a large but ill-defined group in the U.S. Army. Because service records do not provide the minimum requirements for identifying this exposed group, follow-up is not indicated.

From January 1, 1966 to December 31, 1967 approximately 5,900 (2.7%) marines were assigned to units in Viet Nam within 0.5 km of areas sprayed with Herbicide Orange the same day. Approximately 16,000 (7.4%) marines were assigned to units within 0.5 km of areas that had been sprayed within the previous 4 weeks. These were among approximately 218,000 marines then on assignment in Viet Nam. Similar assignments and backgrounds could be identified in the unexposed group to provide a sizable control group for comparison with the presumably exposed marines.

#### HEALTH INDICES SELECTED FOR STUDY

The panel believes that the Air Force investigators are attempting to evaluate too many health indices. It also believes that the design of the morbidity survey, including the questionnaire and physical examination, is too diffuse and should instead be focused on several pathophysiological alterations. In the panel's opinion, particular attention should be given to reproductive outcomes, liver function, the nervous system, and, possibly, the immune system. At this late date it may be of dubious value to search for manifestations such as porphyria or chloracne.

Of particular concern to the panel is the inadequate provision for assessment of reproductive outcomes since the possibility of birth

defects following exposure of humans to dioxin is a major concern. To evaluate birth outcomes adequately requires the acquisition of a thorough family history and data on numbers of pregnancies, spontaneous abortions, stillbirths, abnormalities among live births, congenital defects reported after birth, and, possibly, an analysis of chromosomal patterns. In general, the panel believes that the study should be more selective of morbidity end points and should evaluate each one more thoroughly, in some cases with more sensitive techniques than stipulated in the protocol.

#### CREDIBILITY OF THE STUDY

In its proposal, the Air Force states that it has political and legal as well as health goals. The political goals refer to the social concern for a proper investigation, and legal goals to the question of compensation awards. The panel cannot claim special legal or political expertise, but as scientists they voiced strong concern over the issue of the public perception of the credibility of the study were it to be conducted by the Air Force. This concern was reinforced by the consideration that the study, as designed, has so low a probability of detecting an effect, even if one exists. The panel questioned whether the lay public and legal profession will interpret these negative results as showing that an agency that studies itself can only be expected to give itself a clean bill of health, especially when compensation claims are involved. In raising this issue, the panel does not mean to imply that the Air Force investigators are not qualified to conduct the proposed study.

These issues could be resolved satisfactorily if the Air Force or the DOD were to provide funding for another group to design and conduct such a study. The proposed mechanism of using several outside "peer reviews" for evaluation is not as effective as if impartial investigators were to design the study protocol.

There would appear to be valid legal reasons for the Air Force to conduct a large-scale examination of Ranch Hand personnel to identify those with adverse health effects. However, if this program is to be part of an attempt to provide a scientific basis for awarding compensation to Veterans Administration claimants, it is inappropriate for the Air Force or DOD personnel to collect these data themselves.

#### CONCLUSIONS AND RECOMMENDATIONS

The panel recognizes the concern of the public about potential adverse health effects of Herbicide Orange and supports a thorough followup study of exposed Air Force personnel. However, it believes that the Air Force's proposed epidemiological investigation, as designed, would be unlikely to achieve its stated goals. The major problems of small sample size and limited followup period would prevent the researchers from identifying even a moderately strong effect, should such an effect exist.

The panel offers the following recommendations:

1. The study should be redesigned to include a considerably longer followup period. (The investigators should not expect definitive results within the limited time frame proposed.)

2. If the study is redesigned, the investigators should evaluate a limited number of morbidity end points, each in greater detail.

3. Any revisions of the study should lead to a new proposal that again should be subjected to outside peer review.

4. The issue of public perception of the credibility of the study, were it to be conducted by the Air Force, needs to be examined in light of the stated political and legal goals.

If large cohorts of exposed and presumably unexposed marines could be identified and followed efficiently to determine mortality and, possibly, morbidity, the addition of this proposed group to the proposed Ranch Hand project should be considered. Also, consideration should be given to increasing the mortality study to include as controls all 25,000 Air Force personnel instead of the 6,000 planned. Moreover, the 22,000 marines presumed to have been exposed to the herbicide should be compared with the 218,000 unexposed marines known to have been in Viet Nam.

## APPENDIX

### Review of U. S. Air Force Protocol: Epidemiological Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicide Orange

#### MINORITY STATEMENT

of

Leonard T. Kurland, M.D., D.P.H.

I agree with the other panel members on many points; however, my disagreements are sufficiently serious to warrant a minority statement.

There is no controversy over the extreme importance and the need to clarify the long-term effects, if any, of the components of Herbicide Orange as used in Viet Nam. It is my opinion that the critique and conclusions of the majority report may, at the least, lead to a long delay before the necessary studies are conducted, and that the delay would not result in any major improvement in design of the study.

I believe that this study has scientific merit. It is well designed and should be launched with a few additions and modifications, which are described below. The results of such a study are expected to be important aids in determining whether or not serious long-term effects might be expected among those exposed to Herbicide Orange and among their issue.

The retrospective cohort mortality study should be initiated as designed, since little additional power will be obtained by going beyond five controls per exposed subject. This reviewer takes issue with the statement (page 5, lines 10-12) that "...there would be little likelihood of detecting a mortality effect attributable to Herbicide

Orange...." This presumes that the effect of the herbicide on mortality is very small. However, the proposed study can show a difference between cases and controls: (a) if the effect is greater than currently expected, although the extent or existence of an effect is unknown and is the reason for the study; (b) if the sample size could be increased--but the study design utilizes the largest available significantly exposed group of U.S. personnel available; to do so with the U.S. Marines or Army introduces so much uncertainty of significant exposure that it would be far less likely to provide a successful result; or (c) if the followup can be extended to provide more person-years, particularly into the age periods of higher death rates--a step that I favor.

The majority report suggests that the followup period must be extended to at least 20 to 30 years, but does not provide supporting facts. If no trends are observed within 10 to 15 years after the exposure, it would not seem reasonable to extend the followup any further.

The majority of the panel recognizes that only a slight difference may be observed in the mortality study and that this difference may not be statistically significant, given the size of the study group. A twofold increase in total mortality and a three- to fivefold increase in specific cancer causes may be required to achieve statistical significance. Nevertheless, results obtained from a sample of the respectable size called for in this protocol can be far more useful than the "no data" state we are now in. Such results could indicate the length of time required for additional followup to produce a definitive result, if possible.

I believe that the measures to study possible adverse effects in the morbidity studies were carefully selected and reasonable. The great effort and high cost of bringing this cohort to examination justifies the extensive number of tests based not only on the published literature, but also on the complaints of veterans seeking compensation. The veterans' complaints must be pursued and clarified, particularly if they differ from effects described in the literature. I agree with the majority that the study should be altered so that more comprehensive details on reproductive outcomes can be obtained and that the study would be enhanced considerably by a longer period of followup.

If the study produces no evidence of serious disease or reproductive defects in the exposed cohort, the exposed individuals would be reassured. Moreover, there would then be a reasonable basis for taking action on the complaints received from veterans. If no detrimental effect is identified now, it is not likely to develop in another 10 or 15 years; but if it does, corrective action can be taken to assure that affected individuals are identified and compensated. If the findings are questionable or borderline, the proposed long-term followup would be necessary in an attempt to provide more definitive information. Therefore, plans should be developed to increase the length of followup.

For the morbidity studies, I believe that the projected response rates of 65% and 40% are unduly conservative. If the Air Force obtains the assistance of experienced public health groups doing similar health surveys with persons who can be motivated, results should be considerably better than those projected.



I disagree with the statement that the study may not be able "...to justify compensation awards to claimants...." (page 6, lines 19-20). The proposed study can provide the greatest possible in-depth evaluation of a large group with known exposure. Results-- both negative and positive--are certainly much more reliable than claims against the Veterans Administration that originate from exposed and unexposed veterans with complaints that are similar to those described in the lay press. The scientific community can be informed of results and of the strength of any observed association. Within such constraints, conclusions can be drawn as to the effect of Herbicide Orange on general mortality, specific causes of death, cancer, birth defects, etc.

The majority report discusses a larger potential cohort of U.S. Marines. However, the exposure of each individual in this group cannot be determined with certainty. In fact, the level of exposure is believed to have been comparatively limited in extent and duration. In view of the many other conditions that may have more serious effects on survival, I am not optimistic that relevant differences in mortality between the exposed and unexposed marines can be detected. However, a study of the death rates and causes of death in the two groups of marines should be undertaken if it can be conducted as an adjunct to the Ranch Hand Study, but not if it causes any further delay.

I conclude that the proposed study has scientific merit and can be conducted with the suggested modifications for the length of followup and with the additional study of birth outcomes and reproductive capabilities. With the modifications, this study offers a

reasonable opportunity for detecting the long-term detrimental effects produced by moderate exposure to Herbicide Orange.

The investigators' discussion of bias and sampling problems in the conduct of the study indicates that considerable thought has been given to these issues. However, the section of the protocol dealing with statistical methods does not make it clear that the investigators are sufficiently aware of the need to work with age-specific person-years of observation as the basis for comparison between the exposed individuals and the controls. I strongly recommend that the group responsible for the final design and conduct of this study appoint an advisory committee of statisticians and epidemiologists to review the study design and data analysis.

I agree with the majority statement pertaining to credibility and to the need for identifying an impartial scientific group that would provide the needed design modifications and would conduct the study.

Leonard T. Kurland, M.D., D.P.H.  
Professor and Chairman  
Department of Medical Statistics  
and Epidemiology  
Mayo Clinic, Rochester, Minnesota