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DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF THE SECRETARY
WASHINGTON, D.C. 20201

August 1, 1980

Honorable Stuart Eizenstat
Assistant to the President
for Domestic Affairs and Policy
The White House
Washington, D. C. 20500

Dear Mr. Eizenstat:

I am forwarding the fourth report of the Interagency Work Group to Study the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants. Enclosed is the progress report for the months of June and July by the Chair of the Group's Scientific Panel, Dr. John Moore. During June and July the Work Group considered the Air Force protocol for the Ranch Hand study, the state of scientific knowledge on Agent Orange, and the format for a public meeting to be held in the near future.

I am also forwarding to you today under separate cover the Work Group report and recommendations with respect to the Ranch Hand study. The Work Group has recommended that the Ranch Hand study designed by the Air Force be conducted, and that the Air Force be the entity conducting the study. The Work Group's recommendations are fully detailed in the separate transmittal, which includes a report of the Scientific Panel on the Ranch Hand study.

In the third Work Group report to you, I noted that the Work Group had asked the Scientific Panel to report on the state of current scientific knowledge on Agent Orange. A copy of the memorandum to me from the Scientific Panel in response to that request is also enclosed.

The memorandum notes that some study results will be available in the near future. Results of a study to determine whether exposure of male mice to Agent Orange causes birth defects in their offspring or reduces fertility among the exposed mice will be released in early August. Additionally, results of health evaluations of workers in West Virginia and Arkansas who were exposed to 2,4,5-T and TCDD during manufacturing accidents are anticipated in late August. These studies are expected to shed light on the persistence of clinical findings and symptoms many years after exposure.

Specifically as to cancer, the Scientific Panel evaluated four Swedish papers and one German paper on the carcinogenicity of chemicals that were constituents of Agent Orange. A memorandum from the Panel on its evaluation is enclosed as an attachment to

the Panel's progress report. The Panel concluded that, despite the studies' limitations, they do show a correlation between exposure to phenoxy acid herbicides and an increased risk of some forms of cancer.

Additionally, results from a cancer bioassay on TCDD, the dioxin contaminant contained in Agent Orange, have been released by the National Cancer Institute. The results confirm earlier reports that TCDD is carcinogenic in laboratory animals.

Given the research already under way or being planned by the Federal Government and others, and with the exception of the above studies, the Scientific Panel has concluded that it is unlikely that our scientific knowledge about the long-term health effects of Agent Orange will significantly increase in the next six months and that two to three years longer will be required. The Work Group believes that longer term studies should be aggressively pursued.

A major stumbling block continues to be an inability to identify a population of ground troops the nature and extent of whose exposure to Agent Orange can plausibly be reconstructed or documented with any degree of reliability. The Ranch Hand study results will not permit the establishment of a quantitative risk for ground personnel because exposure among Ranch Hand personnel is estimated to have been much greater.

Further, neither the Ranch Hand study nor any future studies of ground troops will be able to be used to determine whether Agent Orange is the cause of particular health decrements of Vietnam veterans, particularly if the studies do not identify any rare or unique diseases associated with Agent Orange exposure. Moreover, many of the adverse health effects about which concerns have been raised by veterans and others are already known to be found in the general population as the result of other causes. However, the Ranch Hand study and studies of ground troops (if a population can be identified whose nature and extent of exposure can be documented) can define an association between exposure to Agent Orange and an increased risk of health effects.

It remains the opinion of the Scientific Panel that certain health decrements may be present in the veterans population that are a consequence of Vietnam service and not directly associated with Agent Orange. Taken together with the difficulty in reliably determining the nature and extent of individual exposures, the Scientific Panel believes that additional studies should be considered which focus on the health status of Vietnam veterans, so as to determine whether service in Vietnam, rather than solely Agent Orange exposure, may have placed Vietnam veterans at higher risk of suffering certain health decrements.

Consistent with this belief, the Scientific Panel has recommended that a study be initiated to determine if an increased risk of cancer is associated with service in Vietnam.

We believe that the judgments of the Scientific Panel as to the state of scientific knowledge about Agent Orange are of interest and importance to the public. Therefore, the Work Group has decided to make this information one subject of a public meeting to be scheduled in the near future. The purpose of the meeting will be to transmit information to the public on the results of the group's efforts to date as well as to receive information and answer questions from the public.

Sincerely,


Joan Z. Bernstein
General Counsel

Enclosures:

- (1) Progress Report from the Scientific Panel
- (2) Memorandum from the Scientific Panel on Agent Orange

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOR IMMEDIATE RELEASE
Friday, August 1, 1980

John Blamphin (202) 245-6343

The Interagency Work Group to Study the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants today made public its fourth progress report to the White House on the state of scientific knowledge about Agent Orange.

Agent Orange, a mixture of the herbicides 2,4-D and 2,4,5-T, which included the manufacturing contaminant tetrachlorodibenzo-dioxin (TCDD), was used extensively in Vietnam.

The Interagency Work Group was established by the White House last December. It oversees all Federal research efforts regarding the possible health effects of herbicides such as Agent Orange, and is charged with reporting to the public the results and implications of this research. The Work Group is chaired by Joan Z. Bernstein, General Counsel of the Department of Health and Human Services. It includes representatives of the Departments of Health and Human Services and Defense and the Veterans Administration. Representatives of the Environmental Protection Agency, the Departments of Agriculture and Labor, the White House Office of Science and Technology Policy, and the Congress' Office of Technology Assessment also participate as observers.

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The Work Group's fourth progress report, sent to the White House Domestic Council, reviews research activities already under way or being planned by Federal agencies and other research organizations, and includes a detailed report from its Scientific Panel.

State of Scientific Knowledge

The Scientific Panel's report concluded that, with the exception of several recent studies which will be available this summer, an additional two to three years of research will be required to expand significantly scientific knowledge about the long-term health effects of Agent Orange. The Scientific Panel also noted that current scientific knowledge does not permit unequivocal judgments as to the health risk associated with each of the wide spectrum of health effects alleged to have resulted from exposure to herbicides or their dioxin contaminants.

In addition, the Scientific Panel reported that recently released results of a National Toxicology Program cancer bioassay of TCDD, confirm earlier reports that TCDD is carcinogenic in laboratory animals.

The Panel reported on its review of five research papers by European scientists on the carcinogenicity of chemicals found in Agent Orange. The Panel concluded that despite the studies' limitations, they do "show a correlation between exposure to phenoxy acid herbicides and an increased risk of some forms of cancer." In this regard, the Panel's report notes that "Independent verification would further validate these studies."

The Panel further reported that several additional studies are nearing completion and will be reported later in the summer. In one, scientists of IHS' National Toxicology Program are studying the effect of exposure to Agent Orange on the fertility of male mice and the incidence of birth defects in their offspring. And scientists at the University of Cincinnati and the Environmental Sciences Laboratory of the Mt. Sinai School of Medicine in New York, are independently completing evaluations of the health of workers who were exposed during manufacturing accidents to 2,4,5,-T and TCDD.

Additionally, the Panel reported that in its opinion "certain health decrements may be present in the Veteran population that are a consequence of Vietnam service and not directly associated with Agent Orange. Taken together with the difficulty in reliably determining the nature and extent of individual exposures, the Scientific Panel believes that additional studies should be considered which focus on the health status of Vietnam veterans, so as to determine whether service in Vietnam, rather than solely Agent Orange exposure, may have placed Vietnam veterans at higher risk of suffering certain health decrements."

The parent Work Group's fourth progress report notes the limitations on scientific research caused by the inability to

(More)

reconstruct or document with any degree of reliability the nature and extent of exposure of ground troops to Agent Orange. It also discusses the limitations caused by the fact that many of the health effects which veterans believe were caused by exposure to Agent Orange are also known to be found in the population at large as a result of other causes. The report cautions that studies which focus exclusively on Agent Orange will only be able to determine whether a veteran who has been exposed to Agent Orange has a greater chance of developing a particular health disorder, but not whether a particular veteran's disorder is, in fact, a direct result of exposure to Agent Orange.

Ranch Hand

One study which will examine the possible health effects of Agent Orange, however, is the epidemiologic study of "Ranch Hand" personnel designed by the Air Force. "Ranch Hand" was the project title for the herbicide aerial spray project in Vietnam. Air Force personnel who prepared the aircraft or were involved with spraying are a defined population believed to have had a heavy exposure to Agent Orange.

In a separate letter to Stuart Eizenstat, Assistant to the President for Domestic Affairs and Policy, the Work Group today recommended that the Air Force proceed with its planned study

of the health effects of Agent Orange on Air Force "Ranch Hand" personnel. Its recommendation is based on the Scientific Panel's conclusion that, despite inherent statistical limitations in the proposed study, the study should be conducted because the "Ranch Hand" population is the only identifiable population the nature and extent of whose exposure to Agent Orange can plausibly be documented with any degree of reliability.

The Work Group also recommended that the Air Force itself conduct the study and that the strength of the study be increased by planning and ensuring government support for a significant period of follow-up beyond five years. Because of the complexity of the issues and the public concern about Agent Orange, the Work Group suggested that an independent peer review committee, comprised of representatives from the Work Group, scientists from the private sector and academia, and persons with scientific backgrounds nominated by veterans organizations, monitor the conduct of the study. "This action, together with the quality of the scientific expertise which the Air Force will bring to the study, can and should assure a high quality, unbiased study," the Work Group said.

The group also recommended that the study should be performed by the Air Force because of the substantial likelihood that significant delays in beginning the study will result if some other entity must be chosen to do the work. The Work Group said that such delays must be avoided in light of the seriousness and sensitivity of veterans' health concerns.

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL TOXICOLOGY PROGRAM

TO : Chair, Interagency Work Group on Phenoxy Herbicides and Contaminants **DATE:** July 16, 1980

FROM : Chair, Scientific Panel

SUBJECT: Progress Report

The Scientific Panel continued to give priority consideration to activities relevant to health consequences of Herbicide Orange exposure. A status report on Herbicide Orange, which summarizes current knowledge, major ongoing activities, and the perceived utility of these data, has been prepared (attachment 1). Two major points that were presented in the report are:

- a. Attempts to identify an adequate population upon which to conduct studies on a broad range of health indices have, to date, been unsuccessful. An inability to document Herbicide Orange exposure in a population of sufficient size remains and completely frustrates these studies. This led the Scientific Panel to emphasize that large scale epidemiology studies should focus on determining if service in Vietnam is a causal factor in the development of adverse health effects. The use of a variety of other herbicides, drugs, and chemicals in Vietnam are compelling reasons for developing a broader etiologic focus.
- b. A number of studies will be completed in the next one to six months; additional data on the possible toxic effects of Herbicide Orange will not be realized for approximately two years.

Other specific activities of major interest are summarized below:

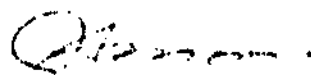
1. Review of the Proposed Epidemiologic Study of Air Force Personnel Following Exposure to Herbicide Orange (Ranch Hand Study).

The Scientific Panel considered the utility of this proposed study as well as the responsiveness of the Air Force to the comments contained in the four peer reviews of the proposed protocol. The Panel recommended that the study, as designed by the Air Force, be conducted. The Ranch Hand personnel represent the only population whose time and duration of exposure to Herbicide Orange is known. The detection of adverse health effects in this heavily exposed group would provide a focus as to the type of health effects that may occur in other personnel (ground troops) exposed to Herbicide Orange. The complete report of the Scientific Panel Review is attached (attachment 2).

2. Evaluation of five scientific papers on the carcinogenicity of chemicals that were constituents of Agent Orange. The opinion of the Panel on these papers which deal with human exposures were transmitted in a memorandum to you on June 25 (attachment 3).

The Panel previously recommended that human birth records data maintained for the Metropolitan Atlanta area be utilized for a case control epidemiology study to determine if Vietnam Veterans are siring children with an increased incidence of specific malformations. This study has been initiated and the Scientific Panel will review a detailed protocol that is currently being developed.

The Scientific Panel expects to receive a final report on the effects of the constituents of Herbicide Orange on fertility and offspring of treated male mice on August 1. It also is communicating with scientists in England and Czechoslovakia to ascertain if there is additional information on the long-term health consequences of accidental occupational exposures to the dioxin contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). It also remains in contact with the two medical groups that are conducting studies on the health of the Nitro, West Virginia, worker population. We are informed that these data may be available to the Panel by the end of the summer.



John A. Moore, D.V.M.

Attachments:

1. Herbicide Orange Status Report
2. Proposed Epidemiologic Investigation of Health Effects of Air Force Personnel Following Exposure to Herbicide Orange (Ranch Hand Study)
3. Evaluation of Five Scientific Papers on the Carcinogenicity of Chemicals that were constituents of Agent Orange

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL TOXICOLOGY PROGRAM

TO : Chair, Interagency Work Group on Phenoxy Herbicides
and Contaminants

DATE: July 30, 1980

FROM : Scientific Panel

SUBJECT: Herbicide Orange Status Report

The Scientific Panel has given priority attention to the concern of Vietnam Veterans as to possible long-term health effects as a consequence of exposure to Herbicide Orange. Current scientific knowledge does not permit unequivocal judgments as to the health risk associated with each of the wide spectrum of health effects alleged to have resulted from exposure to these phenoxy acids or their dioxin contaminants. It is our opinion that, with few exceptions, a significant increase in our knowledge is not likely to be realized for several years. The status of current knowledge, difficulties inherent in defining studies to enhance that knowledge, and the utility of pertinent studies whether planned or in progress are summarized in this report.

In an issue of this type the preferred course for gathering scientific knowledge is to identify an exposed population and conduct the appropriate medical studies. Attempts to identify a population from ground troops who served in Vietnam have not been successful. This completely frustrates any study whose objective is to define what risk, if any, is associated with Herbicide Orange exposure. To embark upon a study without accurate knowledge as to actual exposure results in errors of misclassification and jeopardizes the accurate interpretation of results. The Scientific Panel is aware of current Department of Defense efforts to identify a ground troop population of battalion size whose exposure to Herbicide Orange can be plausibly documented. The results of these efforts will be known in September.

The Air Force Ranch Hand personnel, who applied Herbicide Orange, constitute a population, whose dates of service and frequency and duration of exposure are documented. The Scientific Panel has recommended that studies of the health status of this group as designed by the Air Force be conducted. Their phenoxy acid herbicide exposure may equal or exceed that of the more exposed domestic applicators of these herbicides. The detection of adverse health effects in this study should provide a focus as to the type of health effects that may possibly occur in other (ground troop) personnel. Because their exposure is estimated to be much greater than ground troops, the data would not permit an establishment of quantitative health risk for ground personnel. The Ranch Hand population numbers (1160) imposes definite limitations on the level of confidence that can be placed on failure to detect an increased incidence of a variety of health effects.

The Ranch Hand Study (or studies of ground troops if a population with documented exposure is identified) will only define an association between exposure to Herbicide Orange and increased risk of observed health effects. Assuming that a rare or unique disease is not identified, extrapolation of these data to each veteran will require a policy determination as to how the diagnosis of a disease which is seen with some frequency in a "general" population is to be interpreted as to plausible service connection.

It remains the opinion of the Scientific Panel that certain health decrements may be present in the Veteran population that are a consequence of Vietnam service and not directly associated with Herbicide Orange exposure. Since the nature and degree of Herbicide Orange exposure is apparently impossible to ascertain, it is our opinion that a prudent approach is to design and conduct studies that indicate service in Vietnam as the causal factor. We also note that the Australian investigation of Vietnam Veterans acknowledges that contact with other herbicides or chemicals may possibly be associated with adverse health effects.

The alleged Herbicide Orange health effects can be subdivided into four major areas which are discussed below:

Birth Defects and Fertility

The principal issue is that male veterans allege and fear that they are at increased risk of siring malformed children years after exposure to Herbicide Orange. It is known from toxicology studies that exposure of female rats and mice to 2,4,5-T or 2,3,7,8-TCDD (a constituent and a contaminant of Herbicide Orange, respectively) can produce malformed offspring, fetal toxicity or fetal death. One cannot predict male effects from results obtained through studies of female exposure. Logic dictates that ability to sire malformed offspring years after Agent Orange exposure could plausibly occur only if there was permanent genetic damage (mutation) to the spermatogonial cells. Current data on the mutagenicity of the Herbicide Orange components, 2,4-D, 2,4,5-T, and 2,3,7,8-TCDD, are judged to be inadequate. These chemicals are being retested using the best current techniques. The first results are available and more will be forthcoming the next year.

A direct method of securing relevant toxicology data is through the administration of the constituents of Herbicide Orange to male laboratory animals and examining their sperm, ability to fertilize untreated females, examination of offspring for viability and malformations. Such a study in mice is completed with results scheduled for release in early August.

A third approach is to study and evaluate human birth records data. The Scientific Panel evaluated the potential utility of a birth defects registry that has been maintained since 1968 in the metropolitan Atlanta area. The Panel recommended that a case control epidemiological study be conducted using this registry. The Panel felt that such a study would have a good probability of determining

if Vietnam Veterans are siring an increased incidence of specific malformations. Detailed planning of this study is underway and is expected to require two years to complete. The study is unlikely to be able to indicate that Herbicide Orange was responsible for increased incidence of malformations should such a phenomenon exist. This latter point is not of major concern from a policy standpoint since the precept of veterans compensation rests on service connection effect rather than specific knowledge as to etiology.

In summary the ongoing mutagenicity tests and the male mouse studies should provide data in the next few months that will permit a reasoned opinion as to whether there is a scientific basis for the concern that Herbicide Orange exposure may pose a risk of males siring malformed offspring. The case control human birth records study should buttress the toxicology findings and additionally indicate if there were other factors or circumstances that resulted in Vietnam Veterans fathering an increased incidence of children with specific congenital malformations.

Fertility assessment is a major parameter being studied in the mouse reproduction study to be released in August. Further, the epidemiologic study of the Air Force Ranch Hand personnel includes fertility assessment. The results of this study will not be available for 2-3 years.

Cancer

Veterans are concerned that cancer (death, illness, or an increased risk) is associated with Herbicide Orange exposure,

TCDD was found to cause an increased incidence of cancer in three studies involving rats and in one study of mice. Additional experiments have clearly indicated that TCDD is also a potent cancer promoter,

i.e., ability to enhance the development of cancer due to exposure to other carcinogens. In addition, several recent case control epidemiology studies suggest that there is an increased risk of developing soft tissue tumors or malignant lymphomas as a consequence of exposure to phenoxy acids. These latter studies would be further strengthened by independent verification.

While these studies do establish a cancer risk from TCDD and possibly phenoxy acid exposure, the data do not lend themselves to the establishment of quantitative risk for veterans exposed to Herbicide Orange. To determine if "risk" is resulting in tumor occurrence, the veteran population should be studied directly. As previously stated, an exposed Herbicide Orange population cannot be identified; therefore, the results are unlikely to indicate if an increased cancer incidence is directly related to Agent Orange; it should provide evidence that increased risk of cancer is associated with Vietnam service, i.e., that the risk is service connected. A valid scientific criticism of such a study conducted at this time is that the study may be premature and prone to a false negative result given that the time elapsed since exposure in Vietnam is less than the 15-20 years that is typically required for excess cancer incidence to become manifest. However, the perception of cancer risk is a current concern, and in some instances excess cancer may appear in a population 10 years after exposure. Therefore, such a study should be initiated. The rationale for this recommendation is:

1. A negative finding would allay the current and possible increasing fear that Herbicide Orange or Vietnam service already is resulting in excess cancer deaths.
2. A positive finding would establish service connection and permit appropriate and rational policy decisions with respect to service connected disability and right to compensation.

3. A positive finding would identify the types of cancer for which there is increased risk and the medical community could focus attention on specific surveillance for early detection of tumors with a possible attendant increase in successful treatment.

4. An appropriate cohort will have been registered that can and must be resurveyed at appropriate time periods to detect changes in major morbidity or cancer incidence.

Such a study could easily be included as part of the VA epidemiology study that is in the planning stage. Since results from this study are not expected for several years, other mechanisms should also continue to be explored. The proposed Air Force Ranch Hand Study will study cancer incidence; however, the limitation of study size dictates that a larger study also be planned.

Chloracne

The consensus is that the presence of this skin disorder in a veteran should, as a practical matter, be accepted as a priori evidence of Herbicide Orange exposure. Other chemicals are also known to cause this condition but the symptom is sufficiently unique to permit it to serve as a signal marker. The utility of its application has, to date, proven to be of limited value; the VA has identified but two veterans with this condition. The low prevalence may indicate lack of herbicide exposure; failure of the conditions of herbicide exposure to result in development of this condition despite its appearance in many people exposed to TCDD in occupational or accidental contaminations; the condition may have occurred and disappeared in the time period that has elapsed since herbicide exposure.

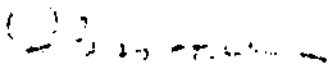
Other Clinical Findings and Subjective Symptoms

Studies of people associated with industrial and accidental contamination detected symptoms and clinical findings that include: enlarged liver or alterations in clinical chemistry indices or liver function; a decrease in the velocity by which nerves conduct impulses, altered lipid metabolism as evidenced by alterations in serum cholesterol or triglyceride levels, neuralgia, weight loss, muscle weakness, and psychiatric changes. The ability of a physician to determine that these symptoms or clinical findings represent a sequelae of Herbicide Orange exposure is very difficult given that each may result from a number of causative factors. Further, there is a paucity of data describing symptom appearance or persistence some years after exposure. An occupational exposure that has been extensively followed and reported in the scientific literature occurred in Czechoslovakia. Persistence of some of these symptoms and signs has been reported. Recent correspondence with these scientists reveals that two additional reports are to be published in the next 6-8 months. The Scientific Panel has also made similar inquiries in Great Britain where it understands a 10 year followup of an accidentally exposed population was recently performed. Reports on health evaluation of worker population in West Virginia and Arkansas are expected in late August, which should also provide information on the persistence of many of these clinical findings.

These new data which are expected to be released in the next few months, coupled with a review of the existing literature, constitute the information base from which to formulate policy as to their utility in the Vietnam veteran issue. Substantial additional data will not be available for several years. It is likely that these data can only be of relevant utility if an informed policy is established which states that the simultaneous presence of some portion of these nonspecific clinical findings or subjective symptoms will be

acknowledged as plausible cause for presumptive herbicide exposure. Such considered action would clearly represent a policy decision to arbitrarily augment imprecise medical or scientific knowledge.

The Scientific Panel is aware of several ongoing studies in the U.S. that are being conducted and financed by the private sector. The direct utility of these data to the Herbicide Orange issue can only be determined upon receipt of more complete details of the study designs or review of the completed reports.


John A. Moore, D.V.M.
Chair, Scientific Panel

DM : Scientific Panel, IWG

SUBJECT: Evaluation of Five Scientific Papers on the Carcinogenicity of Chemicals
that were Constituents of Agent Orange

The Scientific Panel is in receipt of 4 Swedish and 1 German paper.
They are:

1. L. Hardell and A. Sandstrom. Case Control Study: Soft Tissue Sarcomas and Exposure to Phenoxy Acetic Acids or Chlorophenols. British Journal of Cancer 39: 711-717 (1979).
2. M. Eriksson, L. Hardell, N. O. Berg, T. Moler, and O. Axelson. Case Control Study on Malignant Mesenchymal Tumors of the Soft Tissue and Exposure to Chemical Substances. Lakartidningen 76: 3872-3875 (1979). (EPA Translation)
3. L. Hardell, M. Eriksson and P. Lenner. Malignant Lymphoma and Exposure to Chemical Substances, Especially Organic Solvents, Chlorophenols and Phenoxy Acids. Lakartidningen 77(4): 208-210 (1980). (EPA Translation)
4. O. Axelson, L. Sundell, K. Andersson, C. Edling, C. Hogstedt, and H. Kling. Herbicide Exposure and Tumor Mortality; An Updated Epidemiological Investigation on Swedish Railroad Workers (Manuscript form 1980).
5. A. M. Thiess and R. Frentzel-Beyme. Mortality Study of Persons Exposed to Dioxin Following an Accident which Occurred in the BASF on November 13, 1953. Presented at the Fifth International Conference on Medichem, San Francisco, California, September 1977.

Evaluation

Papers Nos. 1, 2, and 3 have a common design with L. Hardell appearing as first or second author. Each of the three studies appear to have been well executed although fairly permissive exposure criteria were utilized. Of particular interest to the Scientific Panel are the analyses which the authors defined as exposure only to phenoxy acid herbicides which identified a relative risk for soft tissue sarcoma of 4.3 (paper #1) or 6.8 (paper #2); and for malignant lymphoma 4.8 (paper #3). The phenoxy acid exposures in paper #1 are reported to be with 2,4,5-T and 2,4-D; thus the possible role of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) cannot be discounted. In paper #2 the authors suggested that the increased

risk may also be associated with phenoxy acids that do not contain TCDD. Paper #3 did not present separate data as a function of exposure to phenoxy acids with or without the TCDD contaminant.

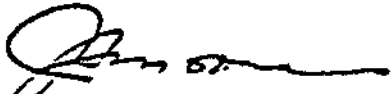
The similarity of design and involvement of at least one investigator in all three instances could permit the recurrence of an "unobserved bias" which weakens the Panel's acceptance that studies #1 and #2 represent a true independent verification of the findings.

In spite of the reservations that are generally associated with these case control epidemiology studies, i.e., permissive criteria for establishing "exposure" which varied between the studies; memory bias by patients or relatives that there was "exposure" because of a traumatic event such as cancer, the studies show a correlation between exposure to phenoxy acid herbicides and an increased risk of some forms of cancer. Independent verification would further validate these studies.

Paper #4 represents 348 persons which is small for this type of mortality study. The authors reported that the observed number of tumor deaths is higher than expected and that the causal relationship to specific agents (amitrol and phenoxy acids) are unclear. The interpretation of three stomach cancers is very tenuous due to the size of the population and the possible bias of familial or genetic relationship.

Paper #5 represents a study of 75 workers which should be considered as a clinical observation. Genetic or familial association of the three stomach carcinomas needs to be ascertained.

The full utility of small populations such as are represented in papers #4 and #5 can best be realized through the development of an International Registry which includes a number of such populations where the statistical power of such analyses can be substantially enhanced. The development of such a Registry is being actively pursued.


John A. Moore, D.V.M.
Chair, Scientific Panel

DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF THE SECRETARY
WASHINGTON, D.C. 20201

August 1, 1980

Honorable Stuart Eizenstat
Assistant to the President for
Domestic Affairs and Policy
The White House
Washington, D. C. 20500

Dear Mr. Eizenstat:

I am writing to advise you of the conclusions the Interagency Work Group on the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants has reached concerning the Epidemiologic Study of Ranch Hand Personnel designed by the Air Force.

The Work Group agrees that the study should be conducted and endorses the judgments and recommendations on study design of its Scientific Panel, which are set out fully in the attached memorandum to me from Dr. John Moore, Chair of the Scientific Panel. Recognizing that there are several inherent limitations in the study design which are outlined in Dr. Moore's memorandum, the Work Group nevertheless reached the consensus that the Air Force designed a reasonable and appropriate approach to this type of study.

However, the Work Group conditions its approval of the Ranch Hand study on an explicit recognition and commitment by the Executive Branch and the Congress that the evaluation may have to continue for a period of time much longer than five years -- perhaps up to 20 years -- in order to have a much better chance of detecting and validating latent or subtle effects. Although Ranch Hand and other studies can be expected to provide a substantially clearer health effects picture in a much shorter period, a serious effort must be made to insure that necessary resources will be available to conduct the Ranch Hand study for as long as necessary. In this regard, the Work Group recommends that the Administration take appropriate steps to insure support for this objective.

The Work Group noted that no peer review group questioned the ability of the Air Force scientists to conduct the study. However, the Work Group did consider whether the public would perceive the study's findings to be credible if the Air Force conducts the study. As you know, this issue was raised by the National Academy of Sciences (NAS) and other peer review groups in their reports on the Air Force protocol.


We recognize that the appearance of an organizational conflict of interest in the conduct of the study by the Air Force could affect the credibility of the study. While we understand the

reasoning that prompts this concern, we believe the concern can be properly and adequately addressed by independent review and monitoring of the study. Accordingly, the Work Group recommends that the conduct of the Ranch Hand study by the Air Force be overseen for at least the first five years by an independent peer review committee which could report to the White House Office of Science and Technology Policy or some other high-level entity. The peer review committee should be comprised of representatives of the Work Group, scientists from the private sector and academia, and persons with scientific backgrounds nominated by veterans organizations. The Work Group is prepared to devote special attention to defining more fully the nature of the independent peer review committee and the relationship between the committee and the Air Force. The independent peer committee, together with the quality of the scientific expertise which the Air Force will bring to the study, can and should assure a high quality, unbiased study.

The Work Group also believes the study should be conducted by the Air Force because it is convinced that significant delays in beginning the study -- and thus in obtaining even preliminary results -- will be caused if an entity other than the Air Force must conduct the study. It is the view of the Work Group that such delays must be avoided in light of the seriousness and sensitivity of the health concerns of Vietnam veterans. Indeed, it is imperative, in the judgment of the Work Group, that this important study be commenced as soon as possible.

In summary, the Work Group strongly recommends that the Ranch Hand study, with appropriate protocol modifications and with outside peer review and monitoring, be commenced by the Air Force as soon as possible.

Sincerely,


Joan Z. Bernstein
General Counsel

Enclosure

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL TOXICOLOGY PROGRAM

TO : Chair, Interagency Work Group on Phenoxy Herbicides and Contaminants DATE: July 14, 1980

FROM : Scientific Panel, IWG

SUBJECT: Proposed Epidemiologic Investigation of Health Effects of Air Force Personnel Following Exposure to Herbicide Orange (Ranch Hand Study)

The Scientific Panel has considered the utility of the proposed study in determining the Long Term Health Effects that may be associated with exposure to Herbicide Orange. It has also reviewed the responsiveness of the Air Force to the comments contained in the four peer reviews of the proposed protocol.

In conducting this task the Scientific Panel's expertise was augmented by the participation of six scientists that are knowledgeable in the design and conduct of epidemiology studies or in the toxicity associated with the constituents or contaminants of Herbicide Orange. These scientists are:

Dr. Aaron Blair, NCI
Dr. David Erickson, CDC
Dr. Carl Keller, NICHD
Dr. Renate Kimbrough, CDC
Dr. Phil Landrigan, NIOSH
Dr. Walter Rogan, NIEHS

The Scientific Panel requested and received the following documents from the Air Force:

1. Current Chronology of Herbicide Orange Events
2. Protocol: Project Ranch Hand II
3. University of Texas, School of Public Health Report
4. Air Force Scientific Advisory Board (SAB) Report
5. Air Force Response to the SAB Report
6. Armed Forces Epidemiological Board (AFEB) Report
7. Air Force Comments on the AFEB Report
8. National Academy of Sciences Report

The Scientific Panel met on June 17th and benefited from a briefing of several hours duration on the proposed study. A list of attendees is attached. The following areas were detailed during the briefing:

1. The nature of the Vietnam Ranch Hand operation and the "occupational exposure" experienced by Air Force personnel
2. A description of the epidemiological design
3. Methods of data collection and verification
4. The composition of the medical evaluation
5. Statistical methodology
6. A statistical comparison of data that would be realized from the Ranch Hand population, a theoretical group of U.S. Marines, and a composite analysis of both groups
7. The Air Force's response to the NAS Review of the Ranch Hand Protocol (memorandum of June 6 from Col. Lathrop to USAFSAM/CC was distributed at the meeting)
8. A variety of options that the Air Force has considered relative to the conduct of the proposed study.

The Scientific Panel is of the opinion that the Air Force did consider the suggestions and critical observations that were reported by the four peer review evaluations of its protocol.

The limitations of population size was identified in several reviews. The Air Force did examine the feasibility of expanding the populations and properly concluded that the result would be detrimental. The Ranch Hand population numbers 1160 which imposes definite limitations on the level of confidence that can be placed on failure to detect an increased incidence of a variety of health effects, i.e., lack of statistical power. This was a concern of the National Academy of Sciences and USAF Science Advisory Board panels that reviewed the Air Force protocol. Augmenting the Ranch Hand population with U.S. Marine or Army ground troops is not an acceptable means of increasing the study population. The Air Force presented convincing data which demonstrated that adding ground troops merely adds a non-comparable population whose exposure is uncertain and whose magnitude of exposure is significantly less than that of the Ranch Hand personnel, i.e., it dilutes the truly exposed cohort which diminishes the likelihood of detecting an untoward health effect.

Several peer reviews observed that the protocol was too comprehensive as to the spectrum of health parameters included in the health evaluation. However, there were no consistent recommendations as to which parameters should be deleted. The diffuse nature of the health indices reflects the lack of current knowledge as to which parameters are of principal importance in evaluating potential herbicide toxicity. It remains a legitimate concern that the substantial amount of time that an individual must commit in agreeing to participate in the study will seriously increase the risk of decreased participation. Reduction of the scope

of the health examination to reduce the time commitment would be an arbitrary choice but should be considered if it results in a substantive increase in participation.

The other consistent concern constantly raised by the peer reviewers was the issue of public perception of a credible study. The Scientific Panel notes this comment and defers the issue to the parent Interagency Work Group in the belief that this is not an issue restricted to science. It is to be noted, however, that none of the peer reviewers questioned the ability of the Air Force to conduct the study in a credible manner.

The Scientific Panel is of the opinion that the Ranch Hand personnel represent an occupational group that is unique from the standpoint of known time and duration of exposure to Herbicide Orange. Their phenoxy acid herbicide exposure may equal or exceed that experienced by other groups involved in some of the more intensive domestic uses of these herbicides. It is not aware of any other group that is likely to be identified whose exposure can be documented or was of similar intensity and duration.

The Scientific Panel recommends that the Epidemiologic Study of Ranch Hand Personnel as designed by the Air Force be conducted. The Ranch Hand personnel were heavily exposed to Herbicide Orange and should be provided information that indicates if they are manifesting adverse health effects or are at increased risk of developing future adverse effects as a result of this exposure.

The detection of adverse health effects also would provide a focus as to the type of health effects that may possibly occur in other personnel (ground troops) exposed to Herbicide Orange.

The Scientific Panel's recommendation is conditional based on the following points:

- That the study be undertaken with an explicit commitment that the evaluation period should continue much longer than five years-- possibly up to 20 years in order to optimize the chance of detecting late or subtle effects. A study of 5 years duration may be incapable of detecting long-term health effects.
- That a table be promptly prepared that displays the detectable relative risks for specific causes of death as well as for reproductive outcomes.
- Statistical power is an inherent limitation in the study. The only way to enhance the power is through a high rate of participation in the extensive questionnaire and health evaluation phases of the study. The Scientific Panel is concerned that a health evaluation that requires several days may result in poor participation which will jeopardize the entire study. Enhanced participation by aggressively insuring that participants experience no loss of income, or even through directed participation, should be seriously considered.

- The protocol be revised to succinctly outline the procedure to be utilized for assessment of reproductive outcome. Its diffuse identification throughout the protocol does not permit a clear evaluation.
- That the Ranch Hand personnel, the public, and the scientific community clearly understand that the stated health goal in the Air Force Protocol may not be fully realized. That goal is:

"to identify veterans 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"

This caveat does not imply flaws in protocol design; it is to emphasize the inherent limitation of study size which cannot be augmented--there are no more Ranch Hand personnel. Because of this, it needs to be clearly understood that failure to identify increased risk in a variety of health parameters is to be interpreted as inconclusive and not necessarily a true lack of effect.

A major criticism of the NAS report was that the study could not fulfill the other stated goals:

"to satisfy the social concerns for proper investigation voiced by the lay and scientific communities"

"to clarify the question of compensation awards to the VA claimants"

The Scientific Panel agrees with that observation; however, the Panel does have the perspective that the Ranch Hand study is but one segment of a larger effort. There are other studies that are also critical to the overall effort, some of which are: the U.S. Dioxin Registry; the proposed International Dioxin Registry; the Case Control Study of Human Birth Defects; the Health Evaluation of the Nitro, W. Va. worker population; the proposed VA Epidemiology Study; the "Agent Orange" male mouse study; and ongoing laboratory studies such as those which are assessing the potential of Herbicide Orange components to cause genetic damage (mutation). It is the sum of these activities that may result in the attainment of these goals.

John A. Moore, D.V.M.
Chairman

Attachment

LIST OF ATTENDEES

SCIENTIFIC PANEL MEETING - June 17, 1980

| <u>NAME</u> | <u>ORGANIZATION</u> | <u>TELEPHONE #</u> |
|----------------------------|----------------------|--------------------|
| Terrie Gale | HHS-OGC | 245-7542 |
| Walter Rogan | NIEHS | 629-4578 |
| Philip C. Kearney | USDA | 344-3533 |
| Alvin L. Young | USAF, Brooks AFB, TX | 512 536-2604 |
| Michael Gough | OTA | 224-4142 |
| Dave Erickson | CDC | 236-4035 |
| William Wolfe | USAF, Brooks AFB | 512 536-2715 |
| Joel Michalek | USAF, Brooks AFB | 512 536-3441 |
| R. A. Albanese | USAF, Brooks AFB | 512 536-3441 |
| George Lathrop | USAF, Brooks AFB | 512 536-2604 |
| Renate Kimbrough | CDC/HHS | 404 452-4176 |
| William S. Augerson | OASD(HA)/OSD | 697-8973 |
| Lt. Col. Ronald D. Burnett | AFSC/SGP | 981-5235 |
| Major Phil G. Brown | HQUSAF/SGES | 767-5078 |
| Bill Welch | USAF, Brooks AFB | 512 536-3705 |
| Carlos Stern | USAF/Pentagon | 697-9297 |
| Fredric Doppelt | AFSC/SG | 981-4562 |
| Gerald W. Parker | HQUSAF/SGH | 767-5050 |
| Patricia Moynahan | USAFSAM EKO | 512 536-2600 |
| Sherrill G. Laney | SAF/MIQ | 697-9297 |
| Philip J. Landrigan | NIOSH/CDC | 513 684-2427 |
| Lawrence B. Hobson | VA | 389-2616 |
| J. A. Moore | NTP | 629-3267 |
| Pat Honchar | NIOSH | 684-3593 |
| David Logan | OSHA | 523-9603 |
| Carl Keller | NICHD | 496-1711 |
| Don Barnes | EPA | 755-4362 |
| Barclay Shepard | VA | 389-2241 or 2331 |