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Al — Be sure to read the mouse-fertility data! Bill

DICWUCH

DEPARTMENT OF THE AIR FORCE
WASHINGTON 20330

OFFICE OF THE ASSISTANT SECRETARY

August 7, 1980

MEMORANDUM FOR AF/SG

SUBJECT: Ranch Hand Study Participation

As you know, it is absolutely crucial to the success of our Ranch Hand Study that we have the fullest possible participation from the former members of the Ranch Hand group. It will not suffice to merely enlist their involvement at the outset of the study, but we need to ensure that their active and wholehearted participation is sustained for the entire duration of the study. To a similar but somewhat lesser extent, the same would apply to the control group.

At the recent meeting (August 1) in Mr. Zengerle's office, which General Chesney and Florence Madden attended, we discussed this matter at some length although we did not arrive at any firm decision. This is to request that an options paper be prepared for my review and approval, and then for presentation to Mr. Zengerle. The paper should outline your thoughts and suggestions, with their associated advantages and disadvantages, on alternative approaches available to the Air Force to meet the goal of ensuring full sustained participation by the subjects in the Ranch Hand Study.

Please consider such issues as compensation for loss of pay during the period subjects have to be away from their jobs; compensation for time needed to answer the questionnaire; whether medical information should be guaranteed confidential (and if so, how); whether medical information which could lead to disqualification from certain jobs, e.g. flying, public safety, etc., should be divulged to the employer; if so, whether the Air Force should indemnify participants in the study against such loss of career, and if so, by what mechanism; whether active duty personnel should be treated the same as, or differently from, those in retired and veteran status in regard to the above issues; should participation by active duty personnel be voluntary or compulsory; if compulsory, how will continued participation after the subject separates be ensured?

for the maintenance of adequate inventory levels and for the effective financial management of the revolving supply fund.".

TITLE VI—EFFECTIVE DATES

SEC. 601. (a) Except as provided in subsections (b) and (c) of this section, the amendments made by this Act shall take effect on the date of the enactment of this Act.

(b) The provisions of titles I, II, and III and section 401 (b)(2), (c) (2) and (3), and (d)(2) shall take effect on October 1, 1980.

(c) The amendments made by section 506 shall be effective retroactively to October 1, 1979.

(The following statement occurred later in the day and is printed at this point in the RECORD by unanimous consent.)

Mr. CRANSTON. Mr. President, earlier today the Senate acted on H.R. 7511, the Veterans' Disability Compensation bill, by inserting it in the text of S. 2649 as reported. As chairman of the Committee on Veterans' Affairs, I am delighted with this action and thank the distinguished majority leader for his help in expediting action on this vital measure.

H.R. 7511/S. 2649, "VETERANS' DISABILITY COMPENSATION AND HOUSING BENEFITS AMENDMENTS OF 1980"

Mr. President, I rise in support of S. 2649 as reported, the proposed Veterans' Disability Compensation and Housing Benefits Amendments of 1980. The bill as reported would provide, effective October 1, 1980, for a 14.3 percent cost-of-living increase in service-connected disability compensation and dependency and indemnity compensation—DIC—benefits and make certain improvements in Veterans' Administration housing, medical, insurance, and educational assistance programs.

BACKGROUND

Mr. President, on May 2, I introduced S. 2649 at the request of the administration. As introduced, the bill provided for a 14.4-percent increase in the rates of disability compensation and dependency and indemnity compensation.

Previously, on February 4, 1980, our very able ranking minority member, the Senator from Wyoming (Mr. SIMPSON) introduced S. 2254, to authorize the VA to remove certain restrictions on land previously conveyed to Cheyenne, Wyo.; and on February 26, 1980, my distinguished colleague on the committee, the Senator from Georgia (Mr. TALMADGE) introduced S. 2330, to provide for the confidentiality of Veterans' Administration medical-care quality assurance records.

On June 12, 1980, with the cosponsorship of six committee members, I submitted amendment No. 1888 to S. 2649, to provide for limited specially adapted housing grants for certain very severely disabled veterans, to authorize the VA to guarantee certain refinancing loans at interest rates lower than the rates under the original loans, to provide for increases in the maximum amounts for VA home-loan guarantees, and to clarify the circumstances under which disclosures of certain information are permitted in conjunction with the management of the VA home-loan programs.

On June 17, 1980, Senator TALMADGE, at my request, held hearings on S. 2649, amendment No. 1688, S. 2330, and certain other bills pending before the committee.

On June 19, 1980, the committee held oversight hearings on the role of educational incentives in the All-Volunteer Force.

On June 27, 1980, I introduced administration-requested bills to provide for an expansion of the class of beneficiaries to whom assignments of certain VA life insurance proceeds may be made—S. 2897—and to amend the Post-Vietnam Era Veterans' Educational Assistance Act of 1977 to improve participation in the program established under that act—S. 2898. On July 24, 1980, I introduced S. 2960, an administration-requested bill to modify the VA's authority with regard to the operation of the revolving supply fund.

After reviewing the testimony received during the June 17 and June 19 hearings, the committee met in open session on July 30, 1980, to consider S. 2649, amendment No. 1888, and other related bills and amendments, and by a unanimous 10-to-0 vote ordered reported and reported S. 2649 with an amendment in the nature of a substitute—derived in part from the provisions of amendment No. 1888, S. 2254, S. 2330, S. 2897, S. 2898, and S. 2960—and a title amendment.

HIGHLIGHTS

Mr. President, S. 2649 as reported—which I will refer to as the committee bill—would provide for a 14.3-percent cost-of-living increase in compensation benefits for our Nation's service-connected disabled veterans and dependency and indemnity compensation—DIC—benefits for the survivors of those who gave their lives for our country. The 14.3-percent increase is the same rate of increase provided to social security and VA pension beneficiaries effective June 1, 1980. Our committee believes that the increase for these most deserving groups of veterans and survivors should be no less than the increase provided under the indexed social security and VA pension programs. Our committee, in its March budget views and estimates report, recommended this increase, and we have worked hard to assure that the levels in the budget resolution for function 700, veterans' benefits and services, would be adequate. Thus, I am pleased to note that the Veterans' Affairs Committee's allocation under the first budget resolution for fiscal year 1981—House Concurrent Resolution 307—allows for this increase, which would benefit more than 2,271,000 disabled veterans and 360,000 survivors of those who gave their lives in the service of our country.

Mr. President, the committee bill would also provide for limited specially adapted housing grants for certain very severely disabled veterans, authorize the VA to guarantee certain refinancing loans at interest rates lower than the rates under the original loans, provide for increases in the maximum amounts for VA home-loan guarantees, and clarify the circumstances under which disclosures of certain information are permitted in connection with the management of the VA home-loan programs.

These are important, needed improvements in VA housing programs. The provisions relating to refinancing would benefit more than 36,000 veterans who were caught in the high-interest-rate credit crunch this past winter and spring. H.R. 7458, a bill containing similar provisions, was passed by the House on July 28.

Mr. President, the committee bill also contains provisions designed to enhance the post Vietnam-era veterans' educational assistance program—VEAP—under chapter 32 of title 38, United States Code, and to modify the 1989 termination date for GI bill educational assistance applicable to the current Vietnam-era GI bill under chapter 34 of title 38. These amendments are designed to enhance the attractiveness of participation in the chapter 32 contributory-matching VEAP program and encourage the recruitment and retention of high caliber men and women in our Nation's All-Volunteer Armed Forces. The provisions were developed in close consultation and cooperation with the distinguished Senators from South Carolina (Mr. THURMOND), Hawaii (Mr. MATSUNAGA), and Virginia (Mr. WARNER).

In addition, the committee bill would provide needed protection to VA medical-quality assurance records in order to help assure the effectiveness of VA programs for the review of VA health-care activities and, consequently, to help maintain the quality of care in VA facilities.

SUMMARY OF PROVISIONS

Mr. President, I would like to summarize very briefly the provisions of the committee bill. The committee bill contains six titles: Title I, Veterans' disability compensation benefits; title II, survivors' DIC benefits; title III, special home adaptation grants for certain severely disabled veterans; title IV, Veterans' Administration home-loan program amendments; title V, miscellaneous amendments; and title VI, effective dates.

Title I, veterans' disability compensation benefits, and title II, survivors' DIC benefits, would amend chapters 11 and 13, respectively, of title 38, United States Code, to provide, effective October 1, 1980, a 14.3-percent increase—the same increase provided to social security and VA pension beneficiaries effective June 1, 1980—in disability compensation benefits for service-connected disabled veterans and DIC benefits payable to the surviving spouses and certain children of veterans whose deaths were service connected.

AGENT ORANGE: UPDATE

Mr. President, as chairman of the Committee on Veterans' Affairs, I would like to bring my colleagues up to date on the issue of agent orange. I know that all Senators share my view that finding the answers to the questions that have been raised about that defoliant, which was used in great quantity in South Vietnam during the war, particularly as those questions relate to Vietnam vet-

...ms. is—and should be—a very high ...iority for the Congress and for the Federal Government.

Mr. President, last Friday, August 1, 1980, the President's task force—the Interagency Work Group to Study the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants (the IAG)—submitted its fourth progress report to the White House. The report includes discussion of currently available scientific findings on dioxin—the toxic chemical contaminant in agent orange—including the IAG's assessment of five epidemiological studies of workers exposed to dioxin in Sweden and West Germany.

One important point raised by the IAG is that none of the studies now planned "* * * 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." Thus, the IAG recommends that the VA study mandated by Public Law 96-151 be expanded to include a focus to determine whether service in Vietnam, as opposed to exposure only to agent orange, may result in increased risk of Vietnam veterans developing certain health problems.

The implications of this recommendation are provocative, to say the least. However, the IAG does not make clear the full dimensions of this recommendation and what such an expansion of the VA epidemiological study would entail. I will be in contact with the IAG and the VA to clarify this point.

In addition, Mr. President, the IAG submitted to the White House its review—which I requested during a February 21 oversight hearing on the agent orange issue—of the Air Force protocol for the proposed study of ranch hand personnel. My colleagues will note that, although the IAG points out that the proposed design contains several inherent limitations, the IAG's assessment is that the design is "* * * a reasonable and appropriate approach to this kind of study * * *", and that, in order to preclude further delay in this very important study of a group of U.S. personnel whose exposure to agent orange can be quantified, the Air Force should conduct the ranch hand study, and that the conduct of the study should be monitored by an independent peer review committee—comprised of representatives of the science work group of the IAG, private sector scientists, academic scientists, and other persons with scientific backgrounds nominated by veterans' organizations—to assure that, to the greatest extent possible, the findings will be accepted as objective and valid.

On Friday the IAG also released a copy of a recently completed national toxicology program 20-week study of male mice exposed to heavy doses of agent orange and of nearly 5,000 offspring of those male mice. The results of this study are important because the male mice were exposed for 8 weeks—more than a complete spermatogenic cycle in mice—to the same mixtures of 2,4-D, 2,4,5-T, and dioxin that were contained in the agent orange sprayed over South Vietnam and no significant harm to fertility or reproduction was found and there was no evidence that paternal exposure to agent orange affected, in any way, the development or survival of offspring.

In this connection, it is important to note that the Center for Disease Control in Atlanta has begun a 2-year case-control epidemiological study of human birth records in the Atlanta area—which is also commented on in the IAG's progress report—in order to determine if Vietnam veterans are experiencing a high rate of specific birth defects in their children.

Although these studies will not resolve the agent orange matter, I am hopeful that, taken together, they will shed some light on one of the most troubling questions related to agent orange exposure—that of the possible effect such exposure could have on a veteran's children or on a veteran's ability to have children.

For the further information of my colleagues, I would note that today the VA Advisory Committee on Health-Related Effects of Herbicides is holding a meeting with a very busy agenda.

Finally, Mr. President, I believe that my July 31 letter to the Administrator of Veterans' Affairs regarding several agent orange-related matters that I raised early in June would be informative to all Senators. Therefore, Mr. President, I ask unanimous consent that the IAG's progress report, the IAG's assessment of the ranch hand protocol, the male mouse study, the VA Advisory Committee's agenda for August 6, and my July 31 letter be printed in the RECORD.

There being no objection, the material was ordered to be printed in the RECORD, as follows:

DEPARTMENT OF HEALTH AND HUMAN SERVICES,
Washington, D.C., August 1, 1980.

Hon. STUART EIZENSTAT,
The White House, Washington, D.C.

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 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 to 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.

MEMORANDUM

To Chair, Interagency Work on Phenoxy Herbicides and Contaminants.
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 casual 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.

MEMORANDUM

To Chair, Interagency Work Group on Phenoxy Herbicides and Contaminants.
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 casual 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

...miologic study of the Air Force Ranch ...nd personnel includes fertility assessment. ...he results of this study will not be available ...or 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 increases 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 populations 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.

MEMORANDUM

To Chair, Interagency Work Group on Phenoxy Herbicides and Contaminants.
From 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. Eardell 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 E. 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 6.6 (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-tetracholorodibenzo-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,
Washington, D.C., August 1, 1980.

Hon. STUART EIZENSTAT,
Assistant to the President for Domestic Affairs and Policy, the White House, Washington, D.C.

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 speical 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 conducting 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.

MEMORANDUM

To Chair, Interagency Work Group on Phenoxy Herbicides and Contaminants.
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.
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 number 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 noncomparable 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 spe-

the 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" and "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.

LIST OF ATTENDEES, SCIENTIFIC PANEL MEETING, JUNE 17, 1980

Name, organization, and telephone number

Terrie Gale, HHS–OGC, 245–7542.
Walter Rogan, NIEHS, 629–4578.
Phillip 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, 697–8573
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.
Phillip 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, NICED, 496–1711.
Don Barnes, EPA, 755–4362.
Barclay Shepard, VA, 389–2241 or 2331.

REPRODUCTION AND FERTILITY IN TREATED MALE MICE AND EVALUATION OF CONGENITAL MALFORMATIONS IN THEIR OFFSPRING

(By James C. Lamb IV, John A. Moore and Thomas A. Mraks)

ABSTRACT

This study was undertaken to determine the effects of mixtures (simulated Agent Orange) of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on reproduction and fertility of treated male mice.

Male C57B/6 mice were given feed containing varying concentrations of 2,4-D, 2,4,5-T and TCDD such that daily doses of approximately 40 mg/kg 2,4-D, 40 mg/kg 2,4,5-T and 2.4 μg/kg TCDD (Group II) or 40 mg/kg 2,4-D, 40 mg/kg 2,4,5-T and 0.16 μg/kg TCDD (Group IV) or 20 mg/kg 2,4-D, 20 mg/kg 2,4,5-T and 1.2 μg/kg TCDD (Group III) would be achieved. Controls (Group I) were given a diet with only the corn oil vehicle added to the feed. In the treated animals, dose-related liver and thymus toxicity were found and body weight gain was significantly reduced. Liver and thymus toxicity showed significant or complete recovery when the mice were returned to a control diet. Sperm concentration, motility and percent sperm abnormalities were evaluated and no significant effect was noted during or after the dosing period.

At the conclusion of an eight week dosing period treated males were mated to untreated virgin females (three per male per week for eight weeks). Mating frequency, average fertility, percent implantation and resorption sites and percent fetal malformations were all measured in relation to the treatment. No significant decrement in fertility or reproduction was noted in the study. There was evidence of germ cell toxicity. Survival of offspring and neonatal development were apparently unaffected by paternal exposure to the simulated mixtures of Agent Orange.

INTRODUCTION

Chlorinated phenoxyacetic acid compounds are used extensively as herbicides in forestry and agriculture. The Department of Defense tested and used a number of different herbicides containing chlorinated phenoxy acids in Vietnam as defoliants; these included Herbicide Orange, Herbicide White, Herbicide Purple, Herbicide Pink and Herbicide Green (Young et al., 1978). The herbicide most extensively used was Herbicide Orange, a 1:1 mixture of the n-butyl esters of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). It has been estimated that 107 million pounds were sprayed with the majority used in the years 1967 to 1969 (77% of total herbicide sprayed) (Young et al., 1978).

During the synthesis of 2,4,5-trichlorophenol (TCP) and subsequently 2,4,5-T, but not 2,4-D, a highly toxic contaminant is formed. This contaminant, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), has been found in Herbicide Orange at an average concentration of 2 ppm with individual analyses of up to 47 ppm reported (Young et al., 1978). Occupational or environmental exposure to humans to TCDD has been associated with a number of clinical disorders (Firestone, 1977; IARC, 1978). The heaviest exposures have involved industrial accidents which occurred in plants synthesizing TCP. The most consistently documented clinical manifestation has been chloracne, a severe form of pustular folliculitis which is most frequently observed on the face, neck and upper extremities. Other less common clinical findings following TCDD exposure include porphyria cutanea tarda, central and peripheral nervous system disorders, depression and irritability, hepatic dysfunction and altered serum lipid concentrations (Firestone, 1977; IARC 1978; Young et al., 1978).

A number of Vietnam Veterans have expressed concern as to health effects that may have resulted from exposure to Herbicide Orange either through application of the herbicide or through inhabiting defoliated areas (Holden, 1979; Rawls, 1979). A particular concern is that Herbicide Orange exposure may be related to reported decreases in both libido and fertility (low sperm counts and abnormal sperm forms) and that it may also be responsible for birth defects observed in offspring sired by veterans who were exposed to Agent Orange (Bogen, 1979; Holden, 1979).

The toxicity of TCDD and the phenoxy acids 2,4-D and 2,4,5-T has been studied in some detail. The biological effects of these chemicals are well documented in a number of mammalian test systems (Gehring and Betso, 1978; Moore, 1978). 2,4-D, 2,4,5-T and TCDD have all been investigated for teratogenicity and fetotoxicity when given to pregnant females. 2,4-D acid and 2,4-D esters show signs of fetotoxicity and embryotoxicity in hamsters and rats at high dose levels, but it is unclear whether the compounds are actually teratogenic (Collins and Williams, 1971; Khera and McKinley, 1971; Schwetz et al., 1971). Exposure of mice to 2,4,5-T during pregnancy results in congenital malformations (Courtney and Moore, 1971; Neubert and Dillman, 1972; Hood et al., 1979). Studies in rats (Sparschu et al., 1971) and monkeys (Dougherty et al., 1975), indicate that the teratogenicity of 2,4,5-T may be a species-dependent phenomenon, since gestational exposure to this compound produced fetotoxic but not teratogenic effects (Gehring and Betso, 1978).

Early studies with 2,4,5-T samples which are contaminated with 30 ppm of TCDD indicated that the herbicide was teratogenic in rats (Courtney et al., 1970). Subsequent studies by Courtney and Moore (1971), using purified 2,4,5-T, showed that both 2,4,5-T and TCDD were teratogenic in three strains of mice but in rats only TCDD was fetotoxic and possibly teratogenic. TCDD has been shown by other laboratories to be teratogenic and/or embryotoxic in mice at levels above 0.1 μg/kg/day (Smith et al., 1976) and rats at 0.125–2.0 μg kg/day (Sparschu et al., 1971).

Although fetotoxicity and teratogenicity associated with gestational exposures to these compounds have been extensively studied, there is a paucity of data as to the effects of male exposure on fertility and development of their offspring. Investigations in male rats undertaken to determine whether dominant lethal mutations could be caused by TCDD were negative. However, the incidence of fertile matings was decreased but it was not determined whether this was due to the systemic toxicity of TCDD or a direct effect on reproduction (Khera and Ruddick, 1971). Other studies that have considered reproductive competence in males have generally been multigeneration studies of animals treated during their entire lives with one of

the compounds of interest. In those studies neither 2,4-D (Hansen et al., 1971) nor 2,4,5-T (Smith et al., 1978) significantly reduced fertility when males and females were given feed containing the herbicides. Three-generation studies with TCDD demonstrated that ingestion of levels greater than 0.1 μg/kg/day decreased fertility and litter survival in the f_1 generation; exposure to 0.01 μg/kg/day decreased fertility in the f_1 and f_2 generations, but not the f_0 generation (Murray et al., 1979). In that case, an increase in the percentage of resorbed implantation sites could be related to female exposure to TCDD, but not to male exposure (Murray et al., 1979).

The consequences of chemical toxicity on male reproductive capabilities might include loss or decrease in fertility, abnormal sperm morphology, decreased sperm concentration and/or motility, or lesions in the reproductive tract and accessory sex glands (Gomes, 1970; Manson and Simons, 1980). In addition to effects on reproduction or fertility, chemical exposure might cause genetic mutations in the male germ cells which could be expressed in the offspring as an inherited anomaly, or embryo and fetal death (Jolle, 1979; Manson and Simons, 1980). Another mechanism to explain fetal effects via the male would be that the chemical might actually be transmitted to the female in the seminal plasma which could then result in a direct exposure of the ova.

The dominant lethal (Epstein, 1973; Generoso, 1973) and sperm morphology (Wyrobek, 1979) assays, used routinely in mice to evaluate potential chemical mutagenicity in male germ cells, were employed in this study. Both of these test systems involve chemical exposure followed by fertility testing or sperm evaluation of the animals for the duration of the spermatogenic cycle (approximately 35 days in mice). This approach is necessary since male germ cells are constantly dividing and differentiating during transit from spermatogonia to spermatozoa with each developmental stage varying in its sensitivity and susceptibility to chemical toxicity or mutagenicity. Experimental designs which are directed at determining male germ cell toxicity must consider this sperm maturation process to assure that all stages of development are tested.

The following investigations were undertaken to determine if composite exposure to 2,4-D, 2,4,5-T plus TCDD (ie., Herbicide Orange), could affect reproductive function in male mice.

* * * * *

MATERIALS AND METHODS

Test chemicals and purity

2,4-dichlorophenoxyacetic acid (2,4-D) (AGR 171114, 98.5 percent pure) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (AGR 133711, 98.7 percent pure) were supplied by the Dow Chemical U.S.A., Midland, Michigan. Both samples were analyzed by Dow Chemical for TCDD contamination who reported no TCDD or other dioxin detected in the samples (Tables 1 and 2).

The free acid was used to eliminate the volatility problem associated with the butyl ester which would compromise quantification of dose administered and pose an exposure risk to laboratory personnel. The free acid form is readily absorbed from this gastro intestinal tract.

TABLE 1.—ANALYSIS OF 2,4-D SAMPLE FOR DIOXINS

	Concentration	Detection limit
2,3,7,8-Tetrachlorodibenzo-p-dioxin	Not detected	1 ppb.
[illegible]-dibenzo-p-dioxins	Not detected	1 ppb.
[illegible]-dibenzo-p-dioxin	Not detected	20 ppt.
[illegible]-dibenzo-p-dioxin	Not detected	5 ppb.

TABLE 2.—ANALYSIS OF 2,4,5-T SAMPLE FOR DIOXINS

	Concentration	Detection limit
2,3,7,8-Tetrachlorodibenzo-p-dioxin	Not detected	0.5 ppb.
Hexachlorodibenzo-p-dioxins	Not detected	0.03 ppm.
Octachlorodibenzo-p-dioxin	Not detected	0.3 ppm.

2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) was synthesized by the Environmental Chemistry Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. The TCDD was reported to be of greater than 98% purity by gas chromatographic analysis performed by NIEHS. The principal contaminate was 2,3,7,-trichlorodibenzo-*p*-dioxin.

Animals and husbandry

Four week old male and 10 week old female C57BL/6 StCr/BR inbred mice (Cesarean-Originated, Barrier Sustained) were purchased from the Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Upon arrival the mice were eartagged and housed in plastic cages with stainless tops (males, one per cage; females, ten per cage). Absorb-dri hardwood bedding (Barnes Supply, Durham, N.C.) was used, and cages were cleaned once each week. The animals were kept in constant temperature (20±2°C) and humidity R.H. 50±10%) on a fixed cycle of 12 hours light-12 hours darkness. The mice were allowed food and water *ad libitum*. The powdered diet was open formula NIH-31 prepared by Zeigler Bros. Co. of Gardners, Pa.

Preparation of diets

Stock solution of the test chemicals were prepared in a corn oil vehicle. The calculated and analytical values are given in Table 3. The test diets were prepared each week for 8 weeks by adding the appropriate stock solution into the feed (2% vol/wt). The concentration of chemicals in the feed was not changed during the 8 week exposure period study. Feed consumption (gm/mouse) was measured once a week. Approximate dose levels were projected using consumption of 5 gm feed/day by a mouse weighing 25 gm. The controls (Group I) were given a diet containing 2% corn oil. Group II consisted of mice that received about 40 mg/kg/day of 2,4-D, 40 mg/kg/day of 2,4,5-T and 2.4 μg/kg/day of TCDD for a total dose of 2.24 gm/kg of 2,4-D and 2,4,5-T each and 0.13 mg/kg of TCDD over the entire 8 weeks. Group III mice were treated at a rate of 40 mg/kg/day of 2,4-D and 40 mg/kg/day of 2,4,5-T (same as Group II), but received only 0.16 μg/kg/day of TCDD; the total dosages of 2,4-D and of 2,4,5-T were 2.24 gm/kg and 0.009 mg/kg of TCDD. The mice in Group IV received 20 mg/kg/day of 2,4-D, 20 mg/kg/day 2,4,5-T, and 1.2 μg/kg/day of TCDD, resulting in a total 8 week exposure of 1.12 gm/kg of 2,4-D and of 2,4,5-T and 0.067 mg/kg of TCDD. After the 8 week exposure period all mice were fed standard pelleted NIH 31 diet.

TABLE 3.—2,4-D, 2,4,5-T AND TCDD CONCENTRATIONS IN STOCK CORN OIL SOLUTIONS[1] AND PROJECTED DOSAGES IN FEED

Treatment group	2,4-D[2]			2,4,5-T[2]			TCDD[4]		
	Ppm[3]	Mg/kg/day[3]		Ppm[3]	Mg/kg/day[3]		Ppb[3]	μg/kg/day[3]	
I (Control)	0	(0)	0	0	(0)	0	0	(0)	0
II	10,000	(9,380)	40	10,000	(9,590)	40	600	(595)	2.4
III	10,000	(5,310)	40	10,000	(5,480)	40	40	(39)	.16
IV	5,000	(4,880)	20	5,000	(4,830)	20	300	(271)	1.2

[1] Calculated prepared concentrations and in ( ) amounts detected by analysis.
[2] Samples of oil collected for 2,4-D and 2,4,5-T analyses were extracted with ethyl ether, derivatized with diazomethane, extracted with hexane and analyzed on an electron capture gas chromatograph (ECGC) by the Midwest Research Institute.
[3] Dose levels based on ideal concentrations in feed and an average feed consumption of 5 gm feed per day per 25 gm mouse.
[4] Samples of oil collected for TCDD analysis were saponified in ethyl alcohol and potassium hydroxide, then extracted with hexane and analyzed with an ECGC by the Midwest Research Institute.

Experimental design

Two hundred male mice were weighed and sorted (by weight) into eight groups (25 per group). One half of the male mice (4 groups of 25 each) were used for toxicity evaluation, while the other half (4 groups of 25 each) were used for fertility and reproductive studies.

All males were then acclimatized on NIH-31 laboratory chow for three weeks before the chemical exposures were begun. Chemical exposure began when the males were eight weeks old. Body weights and food consumption were recorded on a weekly basis. The males were assigned to experimental and control groups such that weight differences between groups were minimized. The mice were then treated with one of the four treated or control diets for eight consecutive weeks.

Toxicopathology

One hundred of the mice were studied during and after the 8 week feeding period. Four animals from each of the four dose groups were killed by decapitation at 1, 4, 5, 6, 12 and 16 weeks after first receiving treated feed. Each mouse received a gross autopsy examination; body and organ (brain, liver, spleen, kidney, thymus and testis/epididymis) weights were measured. These organs as well as lung, duodenum, ear, prostate, seminal vesicle, coagulating gland and urinary bladder were fixed in 10% neutral buffered formalin, dehydrated, and embedded in paraffin blocks. Six μm histologic sections were prepared and stained with hematoxylin and eosin. The tissues were examined for evidence of histopathologic change.

Also at sacrifice, the vas deferens were removed and spermatozoa milked into a 1.0 ml volume of 0.9% saline. The concentration of sperm per vas deferens was estimated with a hemocytometer immediately after collection. Additionally, the percent motile (any movement vs. no movement) sperm was enumerated. The sperm sample was then stained with 0.25% eosin Y for 30 minutes. The sperm were evenly distributed within the staining solution using a Pasteur pipette and four slide preparations were prepared from each sample. The smears were allowed to air dry, were cover slipped and were examined at 400 X. Three hundred sperm were studied for each sample and sperm were classified as normal or abnormal using the criteria of Wyrobek and Bruce (1975) and Soares et al (1979).

Fertility and reproduction

Fertility and reproduction assessments were conducted on the remaining 100 mice (four groups of 25).

After the male mice had been treated with the test chemicals for eight weeks they were returned to control feed. Beginning the next day, each male was housed with three virgin female mice (fourteen weeks of age) for up to 5 days each week for eight weeks. Each female was examined each morning for evidence of mating by detection of a vaginal plug (Day 0 of pregnancy). Each mated

male was removed from the cage, weighed and placed in a cage with other mated females in that group. Females which did not appear to have mated during the 5-day cohabitation period were observed for three more weeks to permit detection of possible pregnancies for which vaginal plugs were not observed. Apparent failure of a female to mate or conceive was verified three weeks after cohabitation by killing the animal, removing the uterus, and staining it with ammonium sulfide to better identify implantation sites (Kopf et al., 1964).

For each weekly mating trial one female bred to each male was put in a group to be sacrificed on day 18 of pregnancy for teratology examination. A second bred female from each male was placed in a group which was allowed to deliver her offspring. All remaining dams found to have plugs were placed in a "teratology backup group" to be subjected to teratological evaluation if the dam selected for day 18 sacrifice was found not to have any live fetuses. The above pregnant mice were systematically distributed to the teratology, postnatal or "backup" groups such that no one group was biased with dams which mated first, second or third. However, if less than three dams had mated, priority was generally given to the teratology group. All mated dams were weighed on days 0, 7, 11, 15 and 18 of gestation.

On day 18 of gestation, the dams designated for teratology examination were coded to permit identification only by number so that laboratory personnel conducting the teratogenic analysis did not know the test group. The mice were killed by cervical dislocation of their reproductive status was determined. Implantation sites in each uterine horne were counted and the general condition of each conceptus was recorded. The detection of implantation sites in the uteri of apparently nonpregnant females was achieved through use of ammonium sulfide (Kopf et al., 1964). Live fetuses were weighed individually, sexed internally (surgical incision below navel), and examined for external malformations. Live fetuses weighing <0.5 g. or weighing less than two-thirds the mean of their larger littermates, were designated as being "stunted". At least one-half of the fetuses of each litter, all "stunted" fetuses and fetuses having external malformations, were examined for visceral alterations (Staples, 1974). The bodies of all fetuses were then processed for skeletal examination (Staples and Schnell, 1964). The heads of each fetus subjected to visceral examination (with the exception of any fetuses which had external head malformations) were cut off at the base and examined by the free-hand sectioning technique described by Wilson (1965).

The remaining dams (postnatal groups) were allowed to deliver their litters. Live and dead offspring as well as birth weight were recorded (day 0). The pups were reweighed on days 4, 7 and 21 and viability also was recorded. The dams and their offspring were killed on day 21.

The above procedures were repeated weekly for eight weeks resulting in a total of eight sets of data. Four weeks after the conclusion of the breeding study, (week 20 of the experiment), the male mice were killed and autopsied in a manner identical to that described for the males sacrificed for toxicopathologic evaluation.

Statistical evaluation

Statistical evaluations of possible pairwise treatment-control differences in food consumption, body weights, organ weights, fertility, mating efficiency, and sperm number, motility and abnormalities were made by Dunnett's test (Miller, 1966). Analyses of variance procedures were employed to assess the significance of differences among groups, week-to-week variability, and week by group interactions. Analyses of abnormalities among the offspring were carried out employing pairwise comparison of control versus treated groups with the Mann Whitney U test. The analysis of malformations considered the average percent malformed fetuses per litter as the experimental unit.

RESULTS

Feed consumption and body weight

The projected food consumption of 35 gm/week (5 gm/day) proved to be a conservative estimate in all groups throughout the period of chemical exposure. Lower food consumption for all groups is indicated in week-2 because only a fraction of the week (5 days) was measured. The addition of 2,4-d, 2,4,5-T or TCDD did not significantly decrease feed consumption during the full eight week dosing period in any treatment group, as compared to the controls. Statistically significant changes in feed consumption were only found in sporadic cases and no general trend of decreased feed consumption could be attributed to the addition of either phenoxy acids or TCDD.

Body weight and weight gain, however, showed significant reductions in the treated animals when compared to controls. This reduction in body weight was most pronounced in group II (2.4 μg TCDD/kg/day and 80 mg phenoxy acid/kg/day) from weeks 3 through 8 of the study. The Group II animals recovered most of their weight deficit when returned to control diet.

Generally all of the mice appeared healthy throughout the course of the study. Only two animals died during the twenty weeks, one in group IV at 5 weeks and one in group II at 19 weeks. Their death did not appear to be treatment-related.

Organ weights and histopathology

Statistically significant increases in liver weight (Figure 4) were observed in all treated groups and was positively correlated with the amount of TCDD exposure (i.e., 2.4 > 1.2 > .16 μg/kg TCDD/day, groups II, IV and III respectively). After conclusion of exposure the liver weight returned toward normal, although Groups II and IV continued to show significantly elevated values even at week 20. The livers of treated mice were enlarged, lighter in color than normal and mottled. The thymus was decreased in weight, which also appeared to be a function of the level of TCDD rather than phenoxy acid exposure. Although the thymus weights were significantly ($p < .01$) reduced in Groups II and IV relative to controls throughout the treatment period (weeks 1-8), thymic recovery appeared complete and weights were not statistically different from the controls by 4 weeks after the last exposure. No significant treatment-related effects were observed in the spleen, testis, kidney or brain. Histopathological evaluation showed no treatment-related changes in any organs, with the exception of the liver. Even the thymus, which had decreased in size to as much as one-third that of the control thymus, appeared histologically normal. The mild toxic effects observed in the liver included hepatocellular swelling, scattered single cell necrosis, increased numbers of mitotic figures, excess extramedullary hematopoiesis, and leukocytic infiltration. These changes were most apparent in group II (2.4 μg/kg/day TCDD; 80 mg/kg/day phenoxy acids) and least apparent in Group III (0.16 μg/kg/day TCDD; 80 mg/kg/day phenoxy acid). These signs of toxicity diminished substantially by the end of the twelfth week of the study (four weeks after chemical exposure was concluded).

* * * * *

Fertility

The average percent matings and overall fertility of the males through 8 weeks of the study are given in Table 4. There was a significant reduction in the mating frequency in males from group III (80 mg/kg/day phenoxy acid, 0.16 μg/kg/day TCDD). This effect was not observed in Group II whose phenoxy acid exposure was similar and whose TCDD exposure was 15-fold greater. Therefore, no dose-related effect could be attributed to this decrease. Also, the percent fertile matings and total fertility were not significantly reduced in Group III or in any group when compared to the control.

When fertility was evaluated on a week by week basis, no treatment-related changes were observed. Fertility was also studied on an individual per male basis and no significant changes were detected within treated males as compared to controls. At the conclusion of the study sperm concentration and motility and percent abnormal sperm were measured. These values were analyzed, on an individual male basis, to determine whether any correlation existed between low fertility performance (plug frequency, percent fertile matings and total fertility) and low values for sperm quality (concentration, motility, percent abnormal). In all groups there was no correlation between the parameters measured. This would indicate that, even though there was considerable variability within these parameters, variations in fertility could not generally be attributed to specific changes in sperm quality. The values for sperm concentration and sperm motility fluctuated considerably from week to week. Percent abnormal sperm were less variable. No treatment-related changes were observed in these parameters. The marked reductions in sperm concentration and increase in sperm motility which were observed from weeks 16 to 20 of the study might be at least partly explained by the fact that the males whose sperm were checked on week 20 had been through an 8-week intensive mating program whereas the males monitored in the earlier weeks were virgins.

TABLE 4.—FERTILITY AND MATING EFFICIENCY IN TREATED AND CONTROL C57Bl/6 MICE, 8-WEEK TOTAL

Treatment group[1]	Mating frequency[2]	Fertile matings (percent)[3]	Total[4] fertility (percent)
I (Control)	74.6±1.6	56.2±2.2	42.0±1.9
II (80; 2.4)	70.3±2.4	58.5±2.9	41.6±2.6
III (80; 0.16)	67.8±2.4	55.3±2.3	37.7±2.2
IV (40; 1.2)	72.6±2.0	60.8±2.9	44.2±2.3

[1] Calculated daily exposure is given in parentheses as total milligram phenoxy acids per kilogram per day; μg TCDD per kilogram per day.
[2] Percent plugs observed per total females housed with males.
[3] Percent fertile matings per females with plugs.
[4] Percent fertile matings per total females housed with males.
[5] $P < 0.05$ relative to controls.

Note: Values are mean plus or minus standard error of the mean, n equals 25 per group.

Teratological examinations

The results of the teratology examination of the dams mated with treated or control males for each group by week are detailed in Tables 5-8. A comparison of the tables indicates that the average number of implants per litter, average number of resorptions per litter or average number live fetuses per litter (Tables 5-8) were unaffected by the male's chemical exposures. For example, the mean values for control and Group II (most heavily exposed) were 7.1 vs. 7.4 implant sites per litter; also in Groups I and II there were 4.9 vs 5.0 live fetuses per litter and 2.15 vs 2.37 resorptions per litter. The average fetal weight was significantly ($p<0.05$) greater in all treatment groups as compared to controls. The total number of dead fetuses (i.e., offspring which weighed

more than 0.3 gm; offspring weighing <0.3 gm were listed as a resorptions) was 1 in Group I, 2 in Group II, 1 in Group III and 0 in Group IV for the entire 8 week study. The ratio of male to female fetuses was also determined; no treatment group exhibited any significant change ($p<0.10$) in this ratio as compared to the control.

Congenital malformations were not significantly increased in the offspring of treated versus control males (Tables 5–10). Visceral malfunctions were observed with less frequency than external and skeletal malformations in all groups. The incidences of the most frequently observed malformations are summarized in Table 9; eye defects (anophthalmia and microphthalmia), jaw anomalies (agnathia, micrognathia), were observed in 1.4 to 2.4 percent and 1.2 to 1.6 percent of the fetuses, respectively. Cleft palate and heart or major blood vessel anomalies were observed in all groups in somewhat lower incidences (Table 9). The total percent malformed fetuses (Table 10) ranged from 3.1 to 3.6 percent and the weekly percentage did not show any treatment-related increases in congenital malformations. A comprehensive listing of malformations observed during the study has been included (Appendix Table 1).

TABLE 5.—EFFECT OF 2,4-D, 2,4,5-T AND TCDD ON FETAL DEVELOPMENT, GROUP I CONTROL

	Week of study								
	1	2	3	4	5	6	7	8	Total, 8 weeks
Number of females examined	19	22	22	25	23	19	22	19	171
Maternal weight gain	13.1±1.0	12.6±0.7	12.7±0.7	12.0±0.8	10.0±0.7	10.1±0.7	11.4±0.8	12.1±0.6	11.6±0.3
Number of implants per litter	8.1±0.5	7.7±0.4	8.0±0.4	7.4±0.6	5.4±0.5	5.8±0.4	7.2±0.5	6.6±0.6	7.1±0.2
Number of resorptions per litter	2.15±0.38	2.41±0.32	2.16±0.32	2.16±0.25	2.29±0.25	2.16±0.33	2.27±0.3	1.68±0.30	2.18±0.1
Number of live fetuses per litter	5.9±0.7	5.3±0.5	5.9±0.5	5.2±0.6	3.0±0.5	3.7±0.4	4.9±0.5	4.9±0.6	4.9±0.2
Average fetal weight per litter	1.04±0.03	1.06±0.02	1.05±0.03	1.00±0.02	1.03±0.02	1.04±0.03	0.99±0.03	1.01±0.03	1.03±0.0
Male/female	59/52	47/68	63/64	69/60	38/32	32/38	52/53	42/52	404/419
Visceral malformations:									
Number of fetuses examined	60	62	68	73	39	39	62	52	455
Number with visceral malformations	0	0	0	1	1	0	0	0	2
Skeletal and external malformations:									
Number of fetuses examined	113	117	129	129	70	70	108	94	830
Number with malformations	2	3	4	4	4	0	4	5	26

Note: Values are mean plus or minus standard error of the mean.

TABLE 6.—EFFECT OF 2,4-D, 2,4,5-T AND TCDD ON FETAL DEVELOPMENT, GROUP II

	Week of study								
	1	2	3	4	5	6	7	8	Total, 8 weeks
Number of females examined	19	18	21	17	22	20	17	14	148
Maternal weight gain	14.1±0.5	12.7±0.9	12.2±0.8	11.5±1.0	10.8±0.7	10.4±0.9	12.6±0.5	12.0±1.0	12.0±0.3
Number of implants per litter	9.2±0.4	7.4±0.6	8.2±0.4	6.2±0.6	7.1±0.4	6.2±0.5	7.5±0.4	7.0±0.7	7.4±0.2
Number of resorptions per litter	2.37±0.27	1.94±0.37	2.71±0.40	1.76±0.22	2.55±0.36	2.30±0.45	1.88±0.38	3.43±0.71	2.37±0.1
Number of live fetuses per litter	6.6±0.3	5.5±0.7	5.6±0.5	4.5±0.7	4.5±0.4	3.9±0.6	5.6±0.6	3.6±0.7	5.0±0.2
Average fetal weight per litter	1.00±0.02	1.14±0.03	1.08±0.03	1.09±0.02	1.02±0.02	1.11±0.03	1.02±0.02	1.10±0.03	1.05±0.0
Male/female	62/67	39/60	61/48	36/39	45/54	43/34	42/54	28/20	356/376
Visceral malformations:									
Number of fetuses examined	66	53	61	42	54	42	47	28	393
Number with visceral malformations	0	0	0	0	0	0	2	0	2
Skeletal and external malformations:									
Number of fetuses examined	129	99	115	78	100	7	96	50	744
Number with malformations	2	6	2	0	5	7	7	1	26

Note: Values are mean plus or minus standard error of the mean.

TABLE 7.—EFFECT OF 2,4-D, 2,4,5-T AND TCDD ON FETAL DEVELOPMENT, GROUP III

	Week of study								
	1	2	3	4	5	6	7	8	Total, 8 weeks
Number of females examined	18	15	21	17	19	22	21	12	145
Maternal weight gain	12.9±0.9	12.9±0.9	11.8±0.7	12.0±0.9	10.7±0.8	10.9±0.8	10.2±0.6	12.2±1.1	11.6±0.3
Number of implants per litter	8.4±0.6	7.6±0.5	7.5±0.4	6.6±0.6	7.2±0.5	6.6±0.6	6.6±0.4	7.0±0.6	7.2±0.2
Number of resorptions per litter	2.65±0.58	2.27±0.44	2.14±0.35	1.65±0.29	2.84±0.37	2.14±0.34	2.05±0.30	2.33±0.72	2.26±0.1
Number of live fetuses per litter	5.7±0.7	5.4±0.6	5.3±0.5	5.0±0.5	4.3±0.4	4.5±0.5	4.8±0.4	4.7±0.7	4.9±0.2
Average fetal weight per litter	1.06±0.03	1.11±0.02	1.15±0.02	1.09±0.03	1.09±0.02	1.05±0.03	1.00±0.02	1.09±0.03	1.08±0.01
Male/female	47/50	41/39	58/53	33/50	46/35	51/47	51/45	25/26	356/349
Visceral malformations:									
Number of fetuses examined	53	44	60	44	47	56	56	32	394
Number with visceral malformations	1	3	0	0	0	0	0	1	5
Skeletal and external malformations:									
Number of fetuses examined	97	81	112	85	82	98	100	56	711
Number with malformations	2	1	4	2	5	0	5	1	20

Note: Values are mean plus or minus standard error of the mean.

TABLE 8.—EFFECT OF 2,4-D, 2,4,5-T AND TCDD ON FETAL DEVELOPMENT, GROUP IV

	Week of study								
	1	2	3	4	5	6	7	8	Total, 8 weeks
Number of females examined	18	23	20	24	21	21	18	15	160
Maternal weight gain	11.6±0.8	12.9±0.8	11.5±0.7	12.2±0.8	9.9±0.8	9.9±0.8	11.9±0.8	11.5±0.9	11.5±0.3
Number of implants per litter	8.9±0.7	7.3±0.6	7.0±0.6	7.6±0.5	6.0±0.5	6.5±0.5	7.5±0.6	5.5±0.7	7.0±0.2
Number of resorptions per litter	4.00±0.50	1.77±0.29	1.30±0.28	1.88±0.30	1.95±0.37	2.43±0.25	2.39±0.45	1.58±0.30	2.11±0.1
Number of live fetuses per litter	4.9±0.6	5.6±0.6	5.7±0.5	5.6±0.6	4.1±0.5	4.1±0.4	5.1±0.6	4.3±0.3	5.0±0.2
Average fetal weight per litter	1.12±0.04	1.16±0.03	1.09±0.02	1.11±0.02	1.10±0.03	1.07±0.02	1.05±0.03	1.02±0.03	1.10±0.0
Male/female	35/45	55/65	56/54	63/75	45/41	40/46	42/44	36/44	376/420
Visceral malformations:									
Number of fetuses examined	41	67	62	77	59	55	50	48	443
Number with visceral malformations	0	2	1	1	1	0	0	0	5
Skeletal and external malformations:									
Number of fetuses examined	78	125	113	129	85	85	82	82	899
Number with malformations	2	5	5	3	4	6	4	4	29

* Values not supplied.

Note: Values are mean ± standard error of the mean.

Postnatal litter examinations

When females were allowed to carry their litters to term, the survival and development of their offspring were studied. The number of live pups and their mean body weight were compared in treated and control offspring (Tables 11–14). The lack of a toxic effect is graphically demonstrated by comparing values for control (Group I) animals to those for the animals exposed to the highest dose of phenoxy acid and TCDD (Group II). There was a marked reduction in the number of litters from day 0 to day 4 in all groups. In group I the number of litters fell from 80 to 44 and in group II from 90 to 60. This was accounted for in all groups by cannabalism by the mothers. After day 4, the loss of litters was greatly decreased. Other parameters show little difference between Groups I and II; on day 0, the number of live pups per litter were 4.40 and 4.19, number of dead pups per litter was 0.92 in both groups, and the average pup weights were 1.37 and 1.36. At day 21 the number of live pups per litter were 5.15 and 4.59 and the average pup weights were 7.48 and 7.50, respectively, for groups I and II. No effect on postnatal viability or growth could be attributed to the exposure of the adult male mice to phenoxy acids or to TCDD.

The pups were examined externally on day 0 for malformations (Tables 15 and 16). During the entire eight weeks the total malformation rate in these mice was between 2.9 and 4.4 percent. The only individual values which approach statistical significance are the malformation rates for week four group IV (40 mg/kg/day phenoxy acid, 1.2 ug/kg/day TCDD) (Table 15) versus control. In that case the control animals had no malformations and the treated had 13% malformations; all of these were either eye or jaw anomalies.

As seen in the prenatal evaluations, eye and jaw malformations accounted for the majority of the defects noted (Table 16). Anopthalmia or micropthalmia were seen in 1.7 to 2.6 percent of the pups and agnathia or micrognathia were seen in 1.3 to 1.9 percent of the pups for all treatment groups.

TABLE 9.—SUMMARY OF MOST FREQUENTLY OCCURRING DEFECTS IN FETUSES SIRED BY MALES TREATED WITH 2,4-D, 2,4,5-T AND TCDD

	Treatment group							
	I		II		III		IV	
Anopthalmia/micropthalmia	1.4	(12/830)	1.9	(14/744)	2.0	(14/711)	2.4	(19/805)
Agnathia/micrognathia	1.3	(11/830)	1.2	(9/744)	1.4	(10/711)	1.6	(13/805)
Cleft palate	.6	(5/830)	.7	(5/744)	.7	(5/711)	.7	(5/805)
Heart/vessels anomalies	.2	(1/455)	.5	(2/393)	1.0	(4/394)	.7	(3/443)

Note: Values are percent incidence of specific anomalies; number of specific malformations per number observed is given in parenthesis.

TABLE 10.—PERCENT MALFORMED FETUSES SIRED BY MALES TREATED WITH 2,4-D, 2,4,5-T AND TCD

Week	Treatment group							
	I		II		III		IV	
1	1.8	(2/113)	1.6	(2/125)	3.1	(3/97)	2.6	(2/75)
2	2.6	(3/117)	6.1	(6/99)	3.7	(3/81)	5.4	(7/129)
3	3.1	(4/129)	3.5	(4/115)	3.6	(4/112)	5.3	(6/113)
4	3.1	(4/129)	0	(0/76)	2.4	(2/85)	2.2	(3/139)
5	5.7	(4/70)	5.0	(5/100)	6.1	(5/82)	3.5	(3/86)
6	0	(0/70)	1.3	(1/77)	0	(0/98)	0	(0/85)
7	3.7	(4/108)	6.5	(8/92)	5.6	(5/105)	4.3	(4/94)
8	5.3	(5/94)	2.0	(1/50)	1.8	(1/56)	4.9	(4/82)
Total	3.1	(26/830)	3.6	(27/744)	3.2	(23/711)	3.6	(29/805)

Note: Values are percent malformed fetuses, number malformed per number observed is given no parentheses. No values are significantly different from controls ($p<0.05$).

TABLE 11.—EFFECT OF 2,4-D, 2,4,5-T AND TCDD ON POSTNATAL DEVELOPMENT OF OFFSPRING OF TREATED MALES, GROUP I CONTROL

	Week of study								Total, 8 weeks
	1	2	3	4	5	6	7	8	
Day 0:									
Number of litters	17	15	15	10	5	10	5	3	80
Number live pups per litter	3.94±0.70	4.67±0.80	6.00±0.62	2.60±0.85	4.00±1.10	3.70±0.91	5.40±0.51	5.00±2.51	4.40±0.32
Number dead pups per litter	1.47±0.43	1.33±0.45	0.20±0.20	1.10±0.41	1.00±0.78	0.44±0.18	0.20±0.20	1.33±1.33	0.92±0.16
Average pup weight	1.39±0.03	1.34±0.02	1.37±0.48	1.41±0.02	1.36±0.04	1.38±0.05	1.33±0.03	1.30±0.03	1.37±0.01
Day 4:									
Number of litters	8	5	10	4	4	6	5	2	44
Number live pups per litter	5.00±1.20	6.60±0.93	5.30±0.75	5.50±0.50	4.75±0.75	4.00±0.78	5.40±0.51	7.50±0.50	5.32±0.33
Average pup weight	1.87±0.10	2.22±0.19	2.04±0.15	2.43±0.10	2.71±0.24	2.32±0.26	2.35±0.19	2.25±0.29	2.22±0.07
Day 7:									
Number of litters	8	5	9	4	4	5	5	2	42
Number live pups per litter	4.25±0.95	6.60±0.93	5.76±0.64	5.50±0.50	4.75±0.75	4.00±0.95	5.40±0.51	7.50±0.50	5.32±0.31
Average pup weight	3.13±0.29	3.64±0.33	3.66±0.19	4.07±0.18	4.71±0.29	4.67±0.26	4.03±0.24	3.55±0.35	3.83±0.12
Day 21:									
Number of litters	8	4	9	4	4	5	5	2	41
Number live pups per litter	4.75±0.98	6.00±0.91	5.76±0.64	5.25±0.63	3.50±1.04	4.00±0.95	5.40±0.51	7.50±0.50	5.15±0.32
Average pup weight	6.43±0.51	7.02±0.75	7.34±0.32	8.74±0.21	8.62±0.54	7.71±0.65	8.07±0.51	6.41±0.12	7.48±0.21

Note: Values are mean plus or minus standard error of the mean.

TABLE 12.—EFFECT OF 2,4-D, 2,4,5-T AND TCDD ON POSTNATAL DEVELOPMENT OF OFFSPRING OF TREATED MALES, GROUP II

	Week of study								Total 8 weeks
	1	2	3	4	5	6	7	8	
Day 0:									
Number of litters	17	16	14	5	16	11	6	5	90
Number live pups per litter	4.76±0.53	4.83±0.68	5.29±0.72	2.80±1.20	3.56±0.59	1.55±0.72	3.50±0.92	4.00±1.41	4.19±0.2*
Number dead pups per litter	0.88±0.40	1.05±0.30	0.64±0.27	1.00±0.78	0.75±0.26	1.25±0.45	1.33±0.88	1.00±0.45	0.92±0.1*
Average pup weight	1.35±0.03	1.39±0.04	1.33±0.02	1.47±0.05	1.42±0.02	1.42±0.09	1.36±0.07	1.36±0.04	1.36±0.0*
Day 4:									
Number of litters	11	11	11	3	14	3	3	4	60
Number live pups per litter	4.63±0.46	5.25±0.56	5.36±0.61	4.67±0.67	4.64±0.56	4.50±0.50	3.67±0.33	4.25±1.44	4.79±0.25
Average pup weight	2.21±0.11	2.36±0.14	2.11±0.06	2.59±0.19	2.47±0.10	2.44±0.18	2.36±0.18	2.47±0.22	2.35±0.05
Day 7:									
Number of litters	11	11	11	3	14	3	3	4	60
Number live pups per litter	4.20±0.44	4.73±0.65	5.36±0.61	4.67±0.67	4.64±0.56	3.67±0.88	3.33±0.66	4.25±1.44	4.48±0.25
Average pup weight	3.61±0.19	3.65±0.25	3.55±0.10	4.12±0.25	4.09±0.44	3.83±0.90	4.19±0.23	4.04±0.24	3.96±0.09
Day 21:									
Number of litters	10	10	10	3	13	3	3	4	56
Number live pups per litter	4.60±0.48	5.00±0.58	5.10±0.64	4.67±0.67	4.92±0.56	3.67±0.88	3.33±0.66	4.25±1.44	4.59±0.25
Average pup weight	7.29±0.48	7.71±0.24	7.25±0.35	8.11±0.48	8.43±0.22	8.31±0.14	8.42±0.11	7.50±0.12	7.64±0.10

Note: Values are mean plus or minus standard error of the mean.

* Figures not supplied.

TABLE 13.—EFFECT OF 2,4-D, 2,4,5-T AND TCDD ON POSTNATAL DEVELOPMENT OF OFFSPRING OF TREATED MALES, GROUP III

	Week of study								Total, 8 weeks
	1	2	3	4	5	6	7	8	
Day 0:									
Number of litters	14	11	12	9	10	11	11	3	81
Number live pups per litter	5.64±0.52	3.91±1.01	5.67±0.85	6.11±1.03	3.80±0.88	2.73±0.75	3.82±0.89	1.67±1.67	4.44±0.32
Number dead pups per litter	0.57±0.34	1.55±0.45	0.27±0.14	0.11±0.11	0.60±0.34	0.50±0.27	0.90±0.41	1.00±0.58	0.67±0.13
Average pup weight	1.32±0.02	1.39±0.06	1.37±0.27	1.36±0.04	1.32±0.06	1.35±0.05	1.37±0.02	1.38	1.36±0.01
Day 4:									
Number of litters	12	3	8	4	8	5	7	1	48
Number live pups per litter	5.30±0.47	4.33±0.67	5.75±0.30	5.25±0.75	4.25±0.49	4.60±0.40	5.57±0.53	5.00	4.91±0.25
Average pup weight	2.03±0.05	1.76±0.89	2.15±0.16	2.25±0.16	2.50±0.10	2.75±0.08	2.73±0.07	2.32	2.37±0.06
Day 7:									
Number of litters	12	3	8	4	8	5	7	1	48
Number live pups per litter	5.00±0.44	4.33±0.67	5.13±1.04	5.25±0.75	4.25±0.45	4.60±0.40	5.57±0.53	5.00	4.92±0.24
Average pup weight	3.25±0.21	2.79±0.17	3.52±0.93	3.47±0.23	4.16±0.13	4.67±0.14	4.54±0.13	4.66	3.82±0.12
Day 21:									
Number of litters	12	3	7	4	8	5	6	1	46
Number live pups per litter	5.00±0.44	6.00±0.58	5.43±0.97	5.00±0.71	4.25±0.49	4.80±0.49	5.50±0.62	4.00	4.87±0.23
Average pup weight	6.83±0.22	7.43±0.64	7.12±0.37	8.39±0.75	8.15±0.18	7.66±0.24	8.55±0.28	10.31	7.67±0.15

Note: Values are mean plus or minus standard error of the mean.

TABLE 14.—EFFECT OF 2,4-D, 2,4,5-T AND TCDD ON POSTNATAL DEVELOPMENT OF OFFSPRING OF TREATED MALES, GROUP IV

	Week of study								Total, 8 weeks
	1	2	3	4	5	6	7	8	
Day 0:									
Number of litters	19	23	14	11	15	10	11	5	108
Number live pups per litter	4.84±0.64	5.35±0.68	5.29±0.63	3.82±1.04	3.67±0.56	2.50±1.19	4.45±0.72	2.80±1.66	4.41±0.2*
Number dead pups per litter	0.95±0.29	0.74±0.20	0.79±0.38	1.09±0.52	0.73±0.28	1.50±0.56	0.27±0.14	0.80±0.45	0.84±0.1*
Average pup weight	1.36±0.02	1.35±0.03	1.39±0.03	1.44±0.05	1.35±0.03	1.43±0.05	1.33±0.03	1.43±0.06	1.39±0.0*
Day 4:									
Number of litters	10	10	8	4	9	4	8	3	56
Number live pups per litter	5.57±0.43	5.40±0.67	6.00±0.66	6.25±1.03	3.33±0.50	5.75±1.49	4.88±0.55	4.67±0.88	5.13±0.2*
Average pup weight	2.24±0.16	2.41±0.08	2.66±0.97	2.30±0.13	2.46±0.15	2.54±0.50	2.54±0.16	2.58±0.26	2.41±0.0*
Day 7:									
Number of litters	10	10	8	4	9	4	8	3	56
Number live pups per litter	5.00±0.47	5.40±0.67	6.00±0.65	6.00±1.08	3.33±0.50	5.75±1.49	4.88±0.55	4.67±0.88	5.04±0.2*
Average pup weight	3.28±0.31	4.08±0.15	4.06±0.18	3.86±0.24	3.96±0.41	3.80±0.33	4.24±0.25	3.95±0.46	3.94±0.1*
Day 21:									
Number of litters	10	10	8	4	9	4	8	3	56
Number live pups per litter	5.00±0.47	5.30±0.63	5.75±0.59	6.00±1.08	3.33±0.50	5.75±1.45	4.75±0.55	4.67±0.88	4.96±0.2*
Average pup weight	6.99±0.34	8.15±0.33	7.53±0.40	8.26±0.09	8.55±0.66	6.66±0.74	8.34±0.37	7.38±0.57	7.80±0.1*

Note: Values are mean plus or minus standard error of the mean.

* Figures not supplied.

TABLE 15.—SUMMARY OF MALFORMATION RATES (PERCENT) IN POSTNATAL STUDY[1]

Week	Treatment group							
	I		II		III		IV	
1	5.4	(5/92)	2.1	(2/95)	1.1	(1/87)	1.9	(2/105)
2	2.2	(2/90)	3.2	(3/95)	6.0	(3/50)	0	(0/145)
3	1.1	(1/93)	6.0	(5/83)	6.6	(5/76)	2.4	(2/83)
4	0	(0/37)	5.3	(1/19)	8.9	(5/56)	13.0	(7/54)
5	4.0	(1/25)	1.1	(1/85)	4.5	(2/44)	2.7	(2/73)
6	2.2	(1/45)	0	(0/32)	2.1	(1/48)	2.1	(1/47)
7	7.1	(2/28)	13.3	(4/30)	3.8	(2/53)	3.8	(2/52)
8	5.3	(1/19)	8.0	(2/25)	0	(0/8)	4.3	(1/23)
Total	3.0	(13/429)	3.8	(18/468)	4.4	(19/432)	2.9	(17/579)

[1] All fetuses (live or dead) were assumed to be at risk.

TABLE 16.—SUMMARY OF SPECIFIC MALFORMATIONS IN POSTNATAL STUDY

	I		II		III		IV	
Anopthalmia/micropthalmia	1.9	(8/429)	2.6	(12/468)	2.5	(11/432)	1.7	(10/579)
Agnathia micrognathia	1.4	(6/429)	1.3	(6/468)	1.9	(8/432)	1.4	(8/579)
Cleft lip/palate	.2	(1/429)	.4	(2/468)	0	(0/432)	0	(0/579)
All else	0	(0/429)	0	(0/468)	[1] .5	(2/432)	0	(0/579)

[1] 1 exencephaly; 1 clubbed right hind limb.

DISCUSSION

In these studies we have evaluated the toxicity of three combinations of 2,4-D, 2,4,5-T and TCDD, in combination, on reproduction in male mice. Mating frequency, fertility, germ cell mutagenesis, and fetal or postnatal development were all considered in the selection of toxicological endpoints. Male mice were continuously exposed to high doses of 2,4-D plus, 2,4,5-T mixed with 2 or 60 ppm TCDD in the phenoxy acid for 8 weeks. These TCDD levels represent average and high contamination levels within Herbicide Orange used in Vietnam (Young et al., 1978).

This study employed the free acids of 2,4-D and 2,4,5-T rather than the butyl esters which were components of Herbicide Orange because of the lower volatility of the acids. The esters are rapidly metabolized to the free acid in both plants and animals, and therefore, the systemic toxicity can be attributed to the free acid (Gehring and Betso, 1978) and should be comparable on a molar basis. The does levels employed exhibited moderate to low direct toxicity in exposed male mice as evidenced by decreased body weight gain, changes in thymus and liver weights and morphologic changes in the liver. The mortality, however, was quite low. The severity of these toxic effects appeared to be primarily related to the TCDD content of the simulated "Herbicide Orange" mixture.

Despite the use of continuous, moderately toxic, chemical exposures throughout the complete period of spermatogenesis, no significant increase in reproductive abnormalities in the 2,4-D, 2,4,5-T or TCDD exposed groups were observed. TCDD has previously been demonstrated to alter spermatogenesis in C57BL/6 mice (McConnell et al., 1978), however, that study used a single high (lethal range) does of TCDD. Additionally testicular lesions were only found in clinically ill animals, as opposed to those which

altered exposure to similar doses (McConnell et al., 1978). Altered spermatogenesis has also been reported in rats (Hoshiba et al., 1978), guinea pigs (McConnell et al., 1978), and monkeys and chickens (Norback and Allen, 1973), although these were again toxic exposures. In the present study, morphological changes were not observed in the testis of treated mice. Throughout this study testis weight was not affected, nor was sperm motility or percent abnormal spermatozoa. Mean sperm concentration, however, was slightly reduced after five and eight weeks of dosing, although the effect was not statistically significant ($p>0.10$).

The levels of TCDD chosen for this study were within the range that had already been shown to result in cleft palate and kidney anomalies when given to pregnant C57BL/6 female mice (Moore et al., 1973). Mixtures of phenoxy acids plus specific levels of TCDD were used in order to better mimic human exposures to Herbicide Orange. Additionally, previous investigators (Neubert et al., 1973), showed that adding as little as 0.1 μ/kg TCDD to 2,4,5-T increased the teratogenicity in mice of 2,4,5-T in offspring of exposed mothers above that expected by a simple additive effect. The dose of TCDD in this study is at or above the 0.1 μg/kg/day level. Also, it should be emphasized that human exposures involved mixtures of 2,4-D, 2,4,5-T and TCDD (Herbicide Orange).

Certain chemicals, when given to adult males, can cause fetal death or alter normal development in offspring sired by these males (Jolle, 1979; Manson and Simons, 1980), however, such signs of toxicity were not elicited in these experiments by exposing male mice to the 2,4-D, 2,4,5-T and TCDD mixtures. As evidenced by the numbers of implants and resorptions, neither embryo toxicity nor dominant lethal mutations could be attributed to exposure to these chemicals. The unaffected values for percent abnormal sperm, which is a test for mutagenicity (Wyrobek, 1979) also leads one to the conclusion that the chemicals, as given, were not mutagenic towards the male germ cells. This correlates well with previous multigeneration studies (Murray et al., 1979) and dominant lethal assays (Khera and Ruddick, 1971).

The values for percent malformed fetuses also indicated that 2,4-D, 2,4,5-T and TCDD had no influence on the offspring of exposed males. The study was designed such that, if the overall percent malformed fetuses (3%; see Appendix Table 1) was doubled in one of the experimental groups, there was a 90% chance that it would have been detected. There was a 70–80% chance of detecting a four-fold increase in congenital defects in any one week. For any specific malformation or class of malformations the corresponding powers would be somewhat less. For example, for visceral defects (background rate 0.44%; see Table 5) the experiment had approximately a 90% chance of detecting an overall rate as high as 3% in any particular treatment group. The only variation which we could find elevated in treated versus control offspring, in the entire study, was the incidence of fused sternebrae (Appendix Table 2). In that case, we observed a statistically significant ($p<0.05$) increase in fused sternebrae in Group III at week 3 and in Group IV at week 4. The incidence in the controls at those times, however, was unusually low (0 in both weeks 3 and 4). This type of skeletal variation has been described as occurring as often as 5–15% or more of offspring from untreated pregnancies in mice and although they are frequently observed, the incidence is apparently inconsistent and this anomaly is considered variation and not a malformation (Wilson, 1973).

APPENDIX TABLE 1.—SUMMARY OF ALL MALFORMATIONS OBSERVED IN FETUSES SIRED BY MALES TREATED WITH 2,4-D, 2,4,5-T AND TCDD

	Treatment group							
	I		II		III		IV	
Visceral malformations:[1]								
Heart/vessels anomalies	0.2	(1/455)	0.5	(2/393)	1.0	(4/394)	0.7	(3/443)
Kidney Agenesis	.2	(1/455)	0	(0/393)	.5	(1/394)	0	(0/443)
Liver—2 lobes only	0	(0/455)	0	(0/393)	0	(0/394)	.2	(1/443)
Lung—lobes ¾-normal size	.2	(1/455)	0	(0/393)	0	(0/394)	0	(0/443)
Right kidney—½ normal size	0	(0/455)	0	(0/393)	0	(0/394)	.2	(1/443)
Skeletal and external malformations:[1]								
Anophthalmia/microphthalmia	1.4	(12/830)	1.9	(14/744)	2.0	(14/711)	2.4	(19/805)
Agnathia/micrognathia	1.3	(11/830)	1.2	(9/744)	1.4	(10/711)	1.6	(13/805)
Cleft palate	.6	(5/830)	.7	(5/744)	.7	(5/711)	.7	(6/805)
Cleft lip/nose	0	(0/830)	0	(0/744)	.3	(2/711)	0	(0/805)
Open eye	.5	(4/830)	0	(0/744)	0	(0/711)	0	(0/805)
Exencephaly/hydrocephaly	.2	(2/830)	.4	(3/744)	.1	(1/711)	.2	(2/805)
No tongue	0	(0/830)	0	(0/744)	.1	(1/711)	0	(0/805)
Umbilical hernia	.1	(1/830)	.3	(2/744)	.3	(2/711)	.1	(1/805)
Ribs fused/missing	.1	(1/830)	.3	(2/744)	0	(0/711)	0	(0/805)
Spinal centra doubled/misaligned	.1	(1/830)	0	(0/744)	.1	(1/711)	0	(0/805)
Spinal arches fused	0	(0/830)	0	(0/744)	.1	(1/711)	0	(0/805)
Mandibles fused	0	(0/830)	0	(0/744)	.1	(1/711)	0	(0/805)
Skull bones missing	0	(0/830)	.1	(1/744)	.1	(1/711)	0	(0/805)
Eye bones missing	0	(0/830)	.1	(1/744)	0	(0/711)	0	(0/805)
Facial bones fused	.2	(2/830)	.5	(4/744)	.4	(3/711)	0	(0/805)
Kinked tail	.1	(1/830)	0	(0/744)	0	(0/711)	0	(0/805)
Total malformations[2]	5.2	(43/830)	5.8	(43/744)	6.6	(47/711)	5.7	(46/805)
Total malformed fetuses[2]	3.1	(26/830)	3.6	(27/744)	3.2	(23/711)	3.6	(29/805)

[1] Values are percent incidence of specific anomalies; number of specific malformations per number of observations is given in parentheses.
[2] Values are percent incidence of malformations or malformed fetuses; number of malformations per malformed fetuses per number of observations is given in parentheses.

APPENDIX TABLE 2.—INCIDENCE OF FUSED STERNEBRAE IN FETUSES SIRED BY MALES TREATED WITH 2,4-D, 2,4,5-T AND TCDD

Week	Treatment group							
	I		II		III		IV	
1	0.9	(1/113)	1.6	(2/129)	1.0	(1/99)	1.3	(1/78)
2	1.7	(2/117)	3.0	(3/99)	3.7	(3/81)	1.6	(2/125)
3	0	(0/129)	.9	(1/115)	12.1	(8/112)	2.7	(3/113)
4	0	(0/129)	2.6	(3/115)	2.4	(2/85)	15.0	(21/139)
5	1.4	(1/76)	2.0	(2/100)	3.7	(3/82)	2.3	(2/88)
6	1.4	(1/70)	5.2	(4/77)	3.1	(3/98)	3.6	(3/85)
7	3.7	(4/108)	2.1	(2/96)	0	(0/100)	2.2	(2/92)
8	2.1	(2/94)	2.0	(1/50)	0	(0/56)	1.2	(1/82)
Total	1.3	(11/830)	2.3	(17/744)	2.8	(20/711)	2.6	(21/805)

[1] $p<0.05$ versus controls.

Certain anomalies are associated with embryotoxicity, not teratogenicity or mutagenicity. However, with chemical exposure only to the males, not pregnant females, embryotoxicity would not be expected in their offspring. If exposure of the embryo directly to the chemicals had occurred, via seminal plasma or sperm, one would expect to observe increased embryotoxicity in the first weeks of the study, when the chemical levels in the body (or ejaculate) were the highest. One would have also anticipated that during the first weeks of the teratology study germ cell toxicity would most likely have been detected, unless the spermatogonia were affected, because the spermatozoa that were evaluated in the first week of mating had been exposed to the chemicals throughout all stages of the spermatogenic process. If the spermatogonia had been affected by the exposure, the effect would have been most apparent in the last weeks of the mating, because at that time, we were evaluating spermatozoa which were spermatogonia during the entire 8 week dosing period and only began to proceed through the spermatogenic cycle near the end of chemical exposure.

Thus, there does not appear to be a residual or transient effect of 2,4-D 2,4,5-T and TCDD at the concentrations in this study, on the fertility of exposed male mice. In addition, exposure to these chemicals did not appear to influence the fetal or neonatal development or the viability of offspring sired by these mice.

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We thank Thomas Mangum for his valuable technical support during this study. We also wish to thank Melissa Marr and Pamela Fisher for performing the statistical analyses of the teratological and postnatal data. The technical assistance of Freida Gerling, Betty King, Loretta Langhoff, Barnes Ray, Lynn Smith and Vickie Wilson is gratefully acknowledged.

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ADVISORY COMMITTEE ON HEALTH-RELATED EFFECTS OF HERBICIDES

8:30 a.m. Call to Order and Opening Remarks, Barclay M. Shepard, M.D., Chairman.

8:35 a.m. Report on VA Activities:

Chloracne Task Force, Dr. Shepard.

Literature Analysis, Dr. Shepard.

Agent Orange Registry, Dr. Shepard.

Data Analysis, William F. Page, Ph.D.

Epidemiological Study, Lawrence B. Hobson, M.D.

9:00 a.m. VA Policy Coordinating Committee, Mr. Guy McMichael, General Counsel.

9:10 a.m. Environmental Protection Agency Hearings, Adrian Gross, Ph.D.

9:30 a.m. Comments from Chief Medical Director, Donald L. Custis, M.D.

9:45 a.m. Comments from Administrator of Veterans Affairs, Mr. Max Cleland.

10:00 a.m. Veteran Attitudes, Irving B. Brick, M.D., Mr. Ronald W. DeYoung, Mr. Charles A. Thompson.

10:30 a.m. Presentations and Discussions:

Follow-up on Industrial Exposure Data and Discussion on Swedish and West German Studies, Raymond R. Suskind, M.D.

Professor Ton-That-Tung's Latest Study, Walter J. Rogan, M.D.

Center for Disease Control Proposed Birth Defects Study, J. David Erickson, D.D.S., Ph.D.

NIOSH International Dioxin Registry, Pat Honchar, Ph.D.

AFIP Registry and Proposed Studies, Carolyn H. Hingeman, M.D.

Ranch Hand Study, Major Phillip G. Brown.

Department of Agriculture Activities, Phillip C. Kearney, Ph.D.

11:30 a.m. Questions and Answers, Dr. Shepard.

12:00 Noon, Adjournment.

COMMITTEE ON VETERANS' AFFAIRS
Washington, D.C. July 31, 1980.

Hon. MAX CLELAND,
Administrator of Veterans' Affairs,
Washington, D.C.

DEAR MAX: I am writing to follow up on your plans to deal with several Agent Orange related issues.

First, during a June 3 telephone conversation you had with several members of the Committee staff, you agreed that the VA must intensify its efforts to assure Vietnam veterans who are concerned about the possible health effects of exposure to Agent Orange, particularly those suffering from a disease or disability that they believe might be the result of such exposure, that they can receive a physical examination in a timely fashion and any necessary follow up at the nearest VA Medical Center.

In light of this agreement, I announced, during my remarks at the convention of the California Department of the Disabled American Veterans on June 5, the VA's intention to intensify its public information activities in order to assure Vietnam veterans that they can receive medical help from the VA for illnesses or disabilities they believe are caused by exposure to Agent Orange. On July 17, a pamphlet entitled "Worried about Agent Orange?" was made available to the Committee, and, on a very limited basis, all other members of Congress. I hope that this event indicates that the intensified outreach effort discussed during the June 3 telephone call will soon be fully underway. I would appreciate hearing from you at your earliest convenience about other aspects of this outreach effort that you have planned.

Second, I have received no indication about the VA's plans in response to my recommendation, which I also announced at the California DAV convention and about which you also were advised during the June 3 telephone call, that the management of the Congressionally-mandated epidemiological study being planned by the VA about the effects on human health of exposure to Agent Orange should be placed in the hands of an independent organization outside the Federal Government. As you know, I made this recommendation reluctantly after coming to the conclusion that the intensity of emotions surrounding the Agent Orange issue indicates that it is unlikely that the findings of a study managed by the VA would be acceptable to Vietnam veterans and the public. In my view, this is a very serious matter which deserves your immediate attention, and I would appreciate your response as soon as possible.

Third, I am enclosing copies of reports by the President's Interagency Work Group on Dioxin and the Office of Technology Assessment on reviews I requested of the four Swedish and the West German epidemiological studies of workers exposed to dioxin in those countries. The reports discuss the implications of those studies as they relate to possible effects on human health of exposure of dioxin—the toxic contaminant contained in Agent Orange. Specifically, Dr. John A. Moore, Chairman of the Scientific Panel of the Interagency Work Group (IAG), states that "In spite of the reservations that are generally associated with these case-control epidemiological studies . . . the studies show a correlation between exposure to phenoxy acid herbicide and an increased risk of some forms of cancer. Independent verification would further validate these studies."

OTA states that Dr. Richard Remington, Dean of the School of Public Health, University of Michigan, who reviewed the five studies, concluded that the three case-control studies carried out on Swedish workers are ". . . among the most carefully conducted investigations of their type that I have ever seen. In toto, the Swedish work is credible if not fully conclusive." OTA also indicates that these three studies would be very useful in the process of designing the mandated VA study.

I believe that these IAG and OTA reports strongly justify a reevaluation of the VA preliminary position regarding the validity and significance of these studies as set forth in an April 16, 1980, letter to Congressman David E. Bonior: "my scientific advisers . . . do not think the papers make a major contribution to answering the problem. . . .". Moreover, I believe that the VA must have a constructive response to the increased possibility evidenced in these three studies that soft-tissue sarcomas and malignant lymphomas are related to exposure to dioxin, keeping in mind, of course, the necessity for further studies before any positive conclusions about any cause and effect relationship can be made.

I urge your immediate consideration of these matters, Max, and look forward to hearing from you about them in the near future.

Thank you for your continued cooperation with the Committee.

With warm regards,

Cordially,

ALAN CRANSTON,
Chairman.

OFFICE OF TECHNOLOGY ASSESSMENT,
Washington, D.C., June 20, 1980.

Hon. ALAN CRANSTON,
Chairman, Senate Committee on Veterans' Affairs, U.S. Senate, Washington, D.C.

DEAR CHAIRMAN CRANSTON: Thank you for your letter of May 22, 1980, concerning five epidemiologic studies of phenoxyacid herbicides. Michael Gough of the Office of Technology Assessment Health Program had earlier reviewed these papers on an informal basis in response to a request from your committee staff. To obtain an expert outside review of the papers, we asked Dr. Richard Remington, Dean of the School of Public Health, University of Michigan to read and comment on the papers Dean Remington has, as you know, agreed to serve as chairman of the OTA Advisory Panel for the review of the VA Epidemiologic Study of Viet Nam Veterans.

Dean Remington's letter to Michael Gough and his review of the five papers are attached. I wish to bring your attention to two points made in the letter. The first is the high marks accorded to the three case-control studies carried out by the Swedish workers. Dean Remington cites those as ". . . among the most carefully conducted investigations of their type that I have ever seen. *In toto*, the Swedish work is credible if not fully conclusive." I would add a further reservation, because all of the Swedish case-control studies have some authors in common, a possibility exists that some unconscious, undetected bias colors all the studies. This is not to suggest that the work is less than excellent, but only to point out that verification of those studies by an independent investigation would remove that reservation. I understand that the Interagency Work Group on Phenoxyacid Herbicides has also concluded that the Swedish case-control studies have merit. Taken all together, these studies do suggest that health effects have resulted from exposure to phenoxyacid herbicides in forestry work.

The other point made by Dean Remington is that he now thinks " . . . that it would be possible using combined military experience to design a useful study of reasonable sensitivity . . ." He refers, of course, to the proposed VA study.

Thank you for this opportunity to aid you in your efforts to keep abreast of developments in this difficult area.

Sincerely yours,

JOYCE C. LASHOF, M.D.,
Assistant Director.

THE UNIVERSITY OF MICHIGAN,
Ann Arbor, Mich., June 19, 1980.

Dr. MICHAEL GOUGH,
Project Director, Office of Technology Assessment, Congress of the United States, Washington, D.C.

DEAR MIKE: I have now been able to review the five investigations into possible relationships between Agent Orange and human health and disease. My detailed critique of the individual studies is attached to this letter. Two of the studies are cohort or prospective investigations. The first of these involving the BASF workers exposed in 1953 is almost totally unhelpful. I do not believe it is even worth citing as evidence in one direction or the other. However, the four Swedish studies are generally good and do considerably raise the index of suspicion concerning possible carcinogenicity of phenoxy acid. The prospective study of Axelson et al. is small and suffers from some analytical dif-

...ies. The case control investigations are among the most carefully conducted investigations of their type that I have ever seen. In toto, the Swedish work is credible if not fully conclusive. Certainly this work would seem to justify further investigation.

I have also been able to review the critique by the NAS panel of the proposed Air Force "ranch hand" investigation. The critique is good and I generally agree with the views of the majority. However, Dr. Kurland raises important points in his minority report. I must frankly admit that my level of optimism concerning the possible utility of prospective epidemiologic investigations in this area has increased since studying these documents. I now believe that it would be possible using combined military experience to design a useful study of reasonable sensitivity to important health effects.

Thank you for your patience. See you soon. Best personal regards.

Sincerely,

RICHARD D. REMINGTON, Ph. D.,
Dean.

SPECIFIC SUMMARY CRITIQUE OF FIVE INVESTIGATIONS RELATED TO CONCERNS ABOUT AGENT ORANGE

(By Richard D. Remington)

1. "Mortality Study of Persons Exposed to Dioxin Following an Accident Which Occurred in the BASF on 13 November, 1953" by Thiess and Frentzel-Beyme.

This study reports on an average 20-year follow-up experience of 73 employees of the BASF in West Germany in 1953. A matched control group and three external control series, based on local and regional vital statistics were selected. The study purports to show an increased frequency of stomach cancer in the dioxin-exposed group.

Unfortunately, both the report and the investigation itself are inadequate and shed little light on the important questions under investigation. The case series is small and the risk of cancer of specific sites even over so long a follow-up period remains at a low level. Indeed, the number of stomach cancer cases in the exposed group is only four. All cause mortality in the exposed group is lower than that of one external comparison group and not different from the other two groups. It is somewhat higher than that of the internal control group. Inadequacies in the description of the investigation include (1) no age breakdown of the exposed population; (2) no description of the matching procedure beyond the global statement that matching by age and date of entry into the factory took place. Was the age matching to a single year, for example, or only to five-year age groups? Within what limits was date of entry controlled? (3) The comparison group is stated to have been selected "at random from the universe of all persons ever included in a cohort study until now." This description is unclear and inadequate. Did a formal randomization occur, i.e., using random number tables?

The authors select stomach cancer for particular attention, and this may not be unreasonable. However, they ignore other differences, for example, among violent deaths. Comparisons between mortality structure by cause with all four control groups reveals substantial variation. In fact, inspection of differences among the external control groups reveals some very large discrepancies, for example, in cardiovascular diseases, overall natural deaths, and all cause mortality rates. These differences themselves cast doubt upon other comparisons within the investigation.

Finally, tests of significance using the Poisson distribution produce estimated p values for the study. This is a "default" type of analysis. The authors seem to believe that use of the Poisson distribution is justified whenever one is inspecting small numbers of events. Nothing could be farther from the truth. The homogeneity assumption for individual event probabilities is almost certainly violated in these data, involving as they do a broad range of ages and other basic characteristics. This lack of homogeneity might well induce an appropriate model whose true variance is well in excess of that of the Poisson distribution.

In summary, this investigation really does not bear centrally on the question of Agent Orange's possible carcinogenicity. The study is inadequately described. The experience is limited. The analytical techniques are questionable. Thus, this investigation neither establishes nor excludes a possible association between dioxin and stomach cancer (or any other cause of death).

2. "Herbicide Exposure and Tumor Mortality: An Updated Epidemiological Investigation on Swedish Railroad Workers" by Axelson, Sundell, Andersson, Edling, Hogstedt, and Kling.

This updated epidemiologic investigation by Swedish railroad workers exposed to herbicides has been carefully conducted and is well described in the research report. A cohort of 348 individuals were followed through October 1976. Mortality ascertainment is very complete and the follow-up experience is excellent. The authors have included only individuals exposed to herbicides for more than 45 days during the period 1957 through 1972. This again is a strength of the investigation. In addition, they have subdivided exposure to amitrol from that to phenoxy acids, again a strength. Statistical significance is once again assessed by the Poisson distribution and earlier reservations apply here. Thus, estimated p values can only be taken as approximations.

The results of this investigation are suggestive. Overall tumor mortality to workers exposed to phenoxy acids appears to have been increased as does mortality due to stomach cancer. This would appear particularly to be true for workers exposed in the early years, although here the numbers appear to be inadequate to provide a breakdown into amitrol and phenoxy acid subgroups.

Once again, the numbers available to this study are inadequate to permit definite conclusions. However, the results of this careful investigation must raise the index of suspicion concerning possible carcinogenicity of phenoxy acids.

3. "Case-Control Study: Soft-Tissue Sarcomas and Exposure to Phenoxyacetic Acids or Chlorophenols" by Hardell and Sandstrom.

This case control study compares 52 living or deceased male patients with soft-tissue sarcomas admitted to the Department of Oncology in Umea, Sweden in 1970–77 with carefully selected matched controls. Aside from the intrinsic limitations of case control methodology, this is an excellent investigation. The authors are unusually careful to exclude questionable cases and controls and to detect and eliminate obvious sources of bias. Thus, their finding of a relative risk of 6.3 for exposure to phenoxyacetic acids must be taken seriously. Their statistical procedures are modern and carefully selected. Their attention to detail is exemplary.

The only misgiving concerning the study is a generic one. Case control studies are uniquely susceptible to hidden sources of bias of ascertainment, recall, and patient selection. The methodology, no matter how careful, cannot guarantee the absence of such biases. Even so, the findings of this particular investigation are suggestive and serve further to raise the index of suspicion concerning induction of soft-tissue sarcoma by exposure to phenoxyacetic acids.

4. "Case-Control Study on Malignant Mesenchymal Tumors of the Soft Tissue and Exposure to Chemical Substances" by Eriksson, Hardell, Berg, Moller, and Axelson.

This study is similar to No. 3 above but concentrates on experience in Southern Sweden. The results are generally similar to that of the earlier investigation and the methods virtually identical. Again, the results are consistent with the hypothesis that phenoxy acid exposure increases the risk of tumors of this type. Once again, the investigators have exercised unusual care to exclude biasing effects as far as they are able to do so. However, again, case control methodology is intrinsically susceptible to subtle and unmeasurable biases.

5. "Malignant Lymphoma and Exposure to Chemical Substances, Especially Organic Solvents, Chlorophenols and Phenoxy Acids" by Hardell, Eriksson and Lenner.

This case control study is by the same investigative unit responsible for references 3 and 4 above. This time a case control study of patients with malignant lymphoma was conducted using methodology similar to that in the earlier investigations of soft tissue sarcoma. Again, a substantial and statistically significant relative risk is found for this group of tumors. And again, phenoxy acid exposure is specifically incriminated. Earlier comments concerning the care these investigators have applied to the study are also appropriate here, and similar limitations of case control methods should be noted.

MEMORANDUM

To: Chair, Interagency Work Group on Phenoxy Herbicides and Contaminants.
From: 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. Moller, 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 No. 1) or 6.8 (paper No. 2); and for malignant lymphoma 4.8 (paper No. 3). The phenoxy acid exposures in paper No. 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 No. 2 the authors suggested that the increased risk may also be associated with phenoxy acids that do not contain TCDD. Paper No. 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 No. 1 and No. 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 No. 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 No. 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 No. 4 and No. 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 Registery is being actively pursued.

JOHN A. MOORE, D.V.M.,
Chair, Scientific Panel.

Mr. CRANSTON. Title III, special home adaptation grants for certain severely disabled veterans, would amend chapter 21 of title 38 to provide for limited specially adapted housing grants, up to a maximum of $5,000, and eligibility for direct VA home loans, to certain veterans who, as a result of service-connected disability, are totally blind or have lost or lost the use of both upper extremities.

Title IV, Veterans' Administration home-loan program amendments, contains amendments to chapter 37 of title 38 which would:

First, enable veterans who have used their VA loan-guaranty entitlement in obtaining a loan for the purchase of a conventional home, condominium, or mobile home to refinance such loan, under certain circumstances and at a lower interest rate, with a VA loan guaranty for the refinancing loan.

Second, increase, from $25,000 to $30,000, the maximum VA loan guaranty amount for a conventional home or condominium.

Third, increase, from $17,500 to $20,000, the maximum VA loan guaranty amount for a mobile home, mobile home lot, or mobile home and lot.

Fourth, authorize the VA to make certain disclosures of information pertaining to individual veterans as necessary in connection with the management of VA home-loan programs.

Title V, miscellaneous amendments, includes amendments which would:

First, amend chapter 57 of title 38 to make records and documents created by the VA as part of the agency's medical quality assurance program privileged and confidential and to bar disclosure of such records and documents except to specified recipients in specified circumstances.

Second, amend Public Law 89-345 to authorize the VA to convey to the city of Cheyenne, Wyo., free and clear of the park and recreational use restrictions established by the VA deed made pursuant to Public Law 89-345, which originally authorized the conveyance of the tract in question, with regard to a certain part of that tract needed by the city for the expansion and improvement of a roadway.

Third, amend chapter 32 of title 38 to make certain modifications in the way in which contributions are made to a servicemember's VEAP—account, namely: Lowering the minimum and raising the maximum permissible monthly contributions, making clear the Secretary of Defense's authority to make contributions on behalf of servicemembers, and permitting servicemembers to make lump-sum contributions.

Fourth, amend chapter 34 of title 38 to delete the December 31, 1989, termination date for the current GI bill—for which generally only persons entering service before 1977 are eligible—and provide that a veteran discharged from active duty on or after January 1, 1980, may use his or her entitlement to GI bill educational assistance only until: First, the expiration of 5 years after he or she begins a program of education following discharge, if he or she begins a program of education within 2 years of discharge; or second, December 31, 1989, whichever occurs later.

Fifth, amend chapter 19 of title 38 to expand the categories of persons to whom assignments, under very specific and limited circumstances, of National Service Life Insurance and U.S. Government life insurance proceeds may be made.

Sixth, amend chapter 81 of title 38 to allow VA revolving supply fund reimbursements to be based on the cost of recent significant purchases of the items involved and to provide for the return to the Treasury at the end of each fiscal year of only such amounts as the Administrator determines to be in excess of supply fund needs.

Mr. President, so that all Senators and the public may have a full understanding of the provisions of the committee bill, I ask unanimous consent that appropriate excerpts from our committee's report on S. 2649, S. Rept. No. 96-876, be printed in the RECORD at the conclusion of my remarks.

The PRESIDING OFFICER. Without objection, it is so ordered.

(See exhibit 1.)

CONCLUSION

Mr. CRANSTON. Mr. President, in closing, I would like to thank the distinguished ranking minority member of the committee, the Senator from Wyoming (Mr. SIMPSON), for his always excellent help and cooperation on the bill, the Senator from Georgia (Mr. TALMADGE) for his fine work and guidance, and all the other committee members who are all cosponsors of this measure and whose help was invaluable during our work on the bill, Senators RANDOLPH, STONE, DURKIN, MATSUNAGA, STAFFORD, THURMOND, and HUMPHREY.

In addition, I would like to thank members of the majority staff, especially our hardworking and devoted editor, Harold Carter, and his able assistants, James MacRae and Walter Klinger, and Mary Sears, Janice Orr, Babette Polzer, Bill Brew, Ed Scott, Jon Steinberg, Julie Susman, Molly Milligan, Ingrid Post, Terri Morgan, Julia Butler, and Becky Walker, and Senator TALMADGE's assistant, Bobby Avary, as well as members of the committee's minority staff—Garner Shriver, Ken Bergquist, and John Pressly—for all of their very hard and effective work in developing this important measure.

Mr. President, on behalf of the Veterans' Affairs Committee, I urge the Senate's favorable consideration of the committee bill.

EXHIBIT 1

DISCUSSION

TITLES I AND II: VETERANS' DISABILITY COMPENSATION AND DEPENDENCY AND INDEMNITY COMPENSATION BENEFITS

Background

Disability Compensation

The service-connected disability compensation program provides monthly cash benefits to veterans who have suffered disabilities during, or as a result of, their service in our Nations Armed Forces. This program ranks as the highest program priority of the Veterans' Affairs Committee.

The amount paid in individual instances is contingent upon the nature of the veterans' disability or combination of disabilities and the extent to which earning capacity is considered to have been impaired. Compensable disabilities are rated according to the VA's Schedule of Rating Disabilities on a graduated scale ranging from 10 to 100 percent. A totally disabled veteran is thus compensated at not less than the 100-percent rate. Higher monthly rates are payable to totally disabled veterans with certain specific, very severe disabilities and combinations of disabilities.

The Veterans' Administration disability compensation program currently provides benefits for 2,271,808 veterans who have service-connected disabilities. This number is composed of disabled veterans with the following periods of service: 31,900 World War I veterans; 1,206,300 World War II veterans; 230,600 Korean-conflict veterans; and 546,400 Vietnam-era veterans.

The following table shows average costs and caseloads for veterans and survivors: