viewed or altered by the National Institute of Building Sciences. The Council's focus, which distinguishes it from other Government projects which have conducted research on building technology without implementing the technologies in actual construction, will be on approving new technologies for use and assisting Federal agencies in including them in construction projects so that they can be evaluated by the Council and then implemented on a more widespread basis.

The members of the Council shall be named by the Secretary of Housing and Urban Development and shall be representatives of the nationwide building community with extensive experience in the building industry. The Council membership should include but not be limited to product manufacturers, health, safety, and fire hazard experts, architects, professional engineers, and representatives of consumer groups. The Secretary shall ensure that they are persons of exceptional talent, who are commited to the development and implementation of new technologies.

The cooperation between the Council and those Federal agencies involved in building construction and rehabilitation is the key to the success of this program. The results of this cooperation can be significant cost savings for the Federal Government and a substantial improvement in our ability to construct affordable housing. I believe the Advanced Building Technology Council will make a significant contribution to our national search for a way to make housing more affordable. I look forward to seeing the work of the Council implemented by the participating Federal agencies.

In addition to developing more affordable housing for the future, we must confront the homelessness problem which exists in this country today. Too many Americans do not have a safe, clean, affordable place to live, too many Americans are living in overcrowded shelters, in cars, and on the streets. The amendments to the McKinney Act included in this bill are vitally important to our war against homelessness. I am particularly pleased with emphasis in this bill on assisting homeless persons and families to make the transition from shelters to permanent housing.

Last year I introduced the Homelessness Prevention and Housing Rehabilitation Act, S. 772. I am pleased that key concepts behind that legislation have been included in the homelessness provisions of this bill. One of the new available transition programs, which I am particularly pleased was included in this 1990 Housing legislation, is a Security Deposit Grant Assistance Program which pays the security deposit and first month's rent for those homeless people who can pay a monthly rent but do not have the savings necessary to make the required downpayment on a permanent place to live. This Security Deposit Assistance Program is modeled on a program which has been very successful in Connecticut. In its first 2 years, the Connecticut program has enabled more than 2,000 homeless persons and families to move into permanent housing. Using only a small amount of money, security deposit assistance grants can make a critical difference in enabling many homeless families to leave shelters forever and find permanent homes.

I am pleased also that this bill recognizes the importance of rehabilitation and the opportunity it provides to develop permanent affordable housing, in many cases more quickly and at less cost than new construction. Rehabilitation is not only an effective way to create affordable housing, it is very important to the revitalization of neighborhoods now filled with abandoned buildings.

I commend my colleagues Senators CRANSTON and D'AMATO for their dedication to enacting this legislation this year. It is a great stride forward in American housing policy.●

U.N. TREATY AGAINST TORTURE

● Mr. SARBANES. Mr. President, I want to express my strong support for Senate ratification of the U.S. Convention Against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment and to thank Chairman PELL for his strong efforts to ensure that the Convention was ratified at the close of the 101st Congress. As a member of the Senate Foreign Relations Committee, I supported reporting the Convention to the full Senate. In light of the U.S. involvement in the early stages of developing the Torture Convention, it was time for this body to act placing the United States among the ranks of the more than 50 nations that have ratified the Convention.

At the outset I want to commend the chairman of the Senate Foreign Relations Committee, Senator CLAIBORNE PELL, for his leadership, not only this year, but even before the convention was adopted by the United Nations, in focusing attention on the need for his international agreement. I recall his strong support back in 1984 when he coauthored the joint resolution, which passed the Congress reaffirming the oposition of the United States to torture and restating its commitment to combating the practice of torture.

On December 10, 1984, the U.S. General Assembly adopted the Convention Against Torture and other Cruel, Inhuman or Degrading Treatment or Punishment by unanimous agreement. By the beginning of this year, 50 countries had ratified the Convention and 22 others had signed it. Adoption of the Convention by the United Nations as a significant event following more than a decade of international effort to eliminate the heinous practice of torture. The United States played a creative role in developing the Convention and insisted that it include provisions making torture a punishable offense.

The history of the ratification process of the Torture Convention is instructive. The Reagan administration submitted the Convention to the Senate in May of 1988 for its advice and consent and included 19 separate conditions with its submission. After careful review by a number of human rights organizations as well as the American Bar Association, these groups decided to oppose the Reagan conditions based on their concern that they limited U.S. participation in the implementing process and reduced its effectiveness.

Again Senator PELL played a key role by urging the newly elected Bush administration to review the conditions and to expedite consideration of the Convention. This was done, and the Convention was resubmitted to the Senate with 12 conditions.

The Senate Foreign Relations Committee held a detailed hearing on the Torture Convention in January of this year soon after the revised conditions were submitted to the Senate. This Convention was the product of 7 years of intensive international negotiations. It codifies international law as it has evolved in the post World War II era with regard to torture and inhuman treatment and punishment and is comprehensive in its treatment of the problem of preventing and combating the practice of torture.

Mr. President, our Nation has rightly claimed to be a leader among nations in the struggle for human rights. Ratification of the U.N. Convention Against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment places us in the company of all other permanent members of the U.N. Security Council and gives further impetus and credence to our role as a defender of human rights throughout the world.●

AGENT ORANGE UPDATE

● Mr. CRANSTON. Mr. President, as chairman of the Committee on Veterans' Affairs, I take this opportunity to update my colleagues and the public on the status of current scientific research concerning agent orange. This update includes reviews of the Centers for Disease Control's [CDC] study entitled "The Association of Selected Cancers With Service in the U.S. Military in Vietnam"; a recent scientific review commissioned by the American Legion, the Vietnam Veterans of America, and the National Veterans Legal Services Project entitled "Human Health Effects Associated With Exposure to Herbicides and/or Their Associated Contaminants—Chlorinated Dioxins"; the "Report to the Secretary of the Department of Veterans Affairs on the Association Between Adverse Health Effects and Exposure to Agent Orange" by Adm.

Elmo R. Zumwalt, Jr.; and the recommendations made by VA's advisory committee on environmental hazards to the Secretary of Veterans Affairs concerning possible associations between exposure to agent orange and either non-Hodgkins lymphoma [NHL] or soft-tissue sarcoma [STS].

Since agent orange first came to public attention in the late 1970's, I have been working to resolve the concerns raised about possible adverse health effects arising from veterans' exposure to this herbicide in Vietnam. These are very emotional and controversial issues, and the inability to resolve them completely undoubtedly has contributerd to a feeling on the part of some Vietnam veterans that they have not been treated fairly by the Nation for which they fought.

Mr. President, I am proud to have authored legislation that provided VA health care eligibility for Vietnam veterans exposed to agent orange and mandated comprehensive epidemiological studies of the health of Vietnam veterans. But I feel that we must continue to work to ensure that all appropriate efforts are made to try to find answers to the questions that have been raised regarding the long-term health effects of agent orange exposure, and to ensure that veterans exposed to that herbicide are treated fairly and compassionately.

To that end, I coauthored, with Senators DASCHLE and KERRY, a bill to compensate these veterans for NHL, STS, or chloracne and to create a mechanism to consider the basis for establishing presumptions of service connection for diseases determined to have positive association with exposure to agent orange or other herbicides in Vietnam and to provide for further independent study of this issue. The Senate has passed this legislation twice. First, on August 3, 1989, the Senate passed S. 1153 after a motion to table the measure failed by a vote of 92-8 and second, on October 3, 1989, as title VIII of S. 13 as incorporated into H.R. 901. Very similar provisions were reported by our committee this session as title I-C of S. 2100. Unfortunately, due to objections raised by two Senators, the Senate was unable to consider S. 2100. As I noted in a statement on the Senate floor on October 17, 1990, I intend to introduce this legislation in the 102d Congress and will do all I can to move it through committee and to the Senate as quickly as possible. The House passed similar legislation, in H.R. 5326, on October 15, 1990.

SELECTED CANCERS STUDY

Mr. President, the third element of the efforts of the Centers for Disease Control to carry out the agent orange and Vietnam-experience studies, mandated by Public Law 96-151 as amended by Public Law 97-72, was the selected cancers study. This study was designed to determine whether there is an increase among Vietnam veterans in the incidence of several serious, but relatively rare cancers that some studies have suggested might be linked to dioxin exposure. The report of the selected cancer study was released in March 1990.

In letters dated May 22, 1990, the chairman and ranking minority members of the House and Senate Committees on Veterans' Affairs requested a review of this study, with particular emphasis on the scientific methods and criteria used by the authors in the study as well as the validity of their analyses and conclusions, from the Office of Technology Assessment [OTA], the National Acadmey of Sciences [NAS], the White House Domestic Policy Council's Agent Orange Task Force [AOTF] and VA's Advisory Committee on Environmental Hazards.

Mr. President, I ask that the responses received be printed in the RECORD at this point.

The material follows:

CONGRESS OF THE UNITED STATES,
OFFICE OF TECHNOLOGY ASSESSMENT,
Washington, DC, September 27, 1990.

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

DEAR ALAN: Enclosed is a review of the Center for Disease Control's study on "The Association of Selected Cancers With Service in the U.S. Military in Vietnam," which you and your colleagues requested in your letter of May 22.

OTA approved the protocol for this study in February 1984, in accordance with the mandate of Public Laws 96-151 and 97-72. We find the "Selected Cancers Study"(SCS) to be well designed, conducted, and analyzed. We note that a modest increase in the risk of contracting one of the six cancers studied, non-Hodgkin's lymphoma, was found. There is no obvious explanation for the cause of this excess, but the pattern of risk among the services suggests strongly that it is not related to Agent Orange exposure (see attachment).

You asked specifically about whether any follow-up studies were warranted based on the results of the SCS. We do not see the need for new studies, but it would be valuable for the Department of Veterans Affairs to continue following the pattern of causes of death among Vietnam veterans, as they have been doing in their proportionate mortality study. In addition, while CDC has analyzed the SCS data for all appropriate military related variables, it is a rich source for analysis for many other factors, e.g., occupational and other exposures reported in the interviews. The data should be further analyzed by CDC, or some provision made to ensure that it is adequately accessible to independent researchers. Much of the value of the data will be lost if this is not done.

I hope this review is useful to you and your Committee. If you have any questions about it, please do not hesitate to contact me, or call Hellen Gelband or Clyde Behney in the OTA Health Program (at 8-6590).

Sincerely,

JOHN H. GIBBONS.

OTA REVIEW OF: THE ASSOCIATION OF SELECTED CANCERS WITH SERVICE IN THE U.S. MILITARY IN VIETNAM

(By the Centers for Disease Control Selected Cancers Cooperative Study Group)

(Background paper prepared by Hellen Gelband, Health Program, Office of Technology Assessment, U.S. Congress, September 1990.)

(The views expressed in this background paper do not necessarily represent the views of the Technology Assessment Board or its individual members.)

INTRODUCTION

The "Selected Cancers Study" (SCS) was one of three studies proposed by CDC to respond to the mandates of Public Laws 96-151 and 97-72, after responsibility for the studies had been shifted by interagency agreement from the Veterans Administration to the Department of Health and Human Services. The Vietnam Experience Study was completed in 1988, and the Agent Orange Cohort Study was canceled after extensive military records research and the laboratory-based "validation study" provided convincing evidence that the majority of ground troops had relatively little direct exposure to Agent Orange in Vietnam. By mandate of the two laws, OTA reviewed the study protocols for scientific validity and responsiveness to the laws. The SCS protocol was approved by the OTA Director in February 1984.

DESCRIPTION OF STUDY

The SCS is actually six separate case-control studies of the following cancers: non-Hodgkins's lymphoma (NHL), soft tissue and other sarcomas (STS), Hodgkin's disease, nasal cancer, nasopharyngeal cancer, and primary liver cancer. These cancers were chosen, on the basis of literature available when the study was planned, to include cancers that might plausibly be associated with exposure to phenoxy herbicides and their contaminants (mainly 2,3,7,8-tetrachlorodibenzo-p-dioxin, 2,3,7,8-TCDD, or dioxin). From the outset, the primary purpose of the study was to determine whether serving in Vietnam placed men at a higher risk of developing these cancers than if they had not gone. It was also planned, however, to include an analysis using some Agent Orange exposure rating to see whether there might be a correlation between level of exposure and cancer risk. As it turned out, the procedure envisioned to accomplish this was not acceptably reliable (this was not the same tracking procedure that was used in the "validation study," which examined the relationship between exposure estimates based on military records and blood dioxin levels of veterans), and there was no reasonable alternative. According to CDC, they asked the cancer registries participating in the study whether blood dioxin analyses could be added to the study. This was rejected by physicians treating the cancer patients, many of whom understandably felt it not in their patients' best interests to remove blood from them unnecessarily.

In a case-control study, a group of individuals with cancer ("cases") is identified, and another group is identified ("controls"), who are as similar as possible to the cases, expect that they do not have cancer. For the SCS, cases and controls were identified, contracted, and interviewed by eight population-based cancer registries around the country, according to a protocol drawn up by CDC and approved by OTA. The study included males born between the years 1929 and 1953, and first diagnosed with cancer between December 1, 1984 and November 30, 1988. Controls were identified by random digit dialing, and frequency matched to the lymphoma cases according to 5-year date of birth interval. Deceased controls were identified for cases who died before they could be interviewed.

In analyzing a case-control study, a determination is made for all individuals in the study concerning the "risk factors" of in-

terest. In the SCS, the main risk factor was whether the men served in Vietnam. Using appropriate statistical analysis, an "odds ratio" is arrived at, in this case signifying the odds of getting the particular cancer after serving in Vietnam versus the odds of getting the disease without service in Vietnam. (For relatively rare diseases, such as the cancers in this study, the odds ratio is nearly equivalent to another measure, the "relative risk.") An odds ratio of one (or a number near one, allowing for chance departures) connotes no excess risk.

In practice, a great deal of information, not just on particular risk factors, is gathered on each participant, much of it from personal interview (or from interviewing a surrogate, for those who have died). In addition to using this information directly in the analyses, it is used to adjust for differences (e.g., in demographic characteristics) that may exist between the cases and controls. The analyses and the ways in which the information was used in the SCS were appropriate and in accordance with good scientific practice.

In addition to interview information, CDC also collected information from military records and verified the diagnoses of cases by having pathologists review tissue specimens.

RESULTS

In all, there were 1,157 men with NHL, 342 with STs, 310 with Hodgkin's disease, 48 with nasal carcinoma, 80 with nasopharyngeal carcinoma, and 130 with primary liver cancer. A pool of 1,776 controls was for each cancer-specific analysis. These numbers make for a relatively powerful (in a statistical sense) study. The power to detect a relative risk as low as 2 (a relatively modest risk) for an association of service in Vietnam with non-Hodgkin's lymphoma, soft tissue sarcomas, or Hodgkin's Disease was well over 90%. For the rarer Cancers (nasal carcinoma, nasopharyngeal carcinoma, and primary liver cancers), the power was lower, but still adequate to detect relative risks of 5 or more. It is worth noting that for rare diseases, even a doubling of risk may amount to a very small number of extra cases.

The study found a modest excess risk of NHL among Vietnam veterans, about 1.5 times the risk for men who were not in Vietnam, and this finding was statistically significant at the conventionally-accepted 5 percent level. For the other cancers, no excess risk was seen for Vietnam veterans.

One of the puzzling aspects of this elevated risk for NHL is that it appears to be greatest among "blue water Navy" veterans, who were not actually stationed in Vietnam but were on ships off the coast, for men who actually were stationed in Vietnam, there is no statistically significant excess risk. CDC points out that this pattern of risk is not consistent with the hypothesis that the cancers were associated with exposure to Agent Orange. No obvious explanation has been put forth to explain these results. It is possible that the observed excess risk is an anomaly due to some unknown "confounding variable," something associated independently both with getting the cancer and with having served in Vietnam. It could be a chance finding. It could also represent a real risk arising from some common feature of serving "in Vietnam," which would have to encompass serving in the blue water Navy, as well as on land.

NEED FOR FOLLOW-UP

The results of the SCS do not suggest the need for more studies. However, it would be valuable for the Department of Veterans Affairs to continue following the pattern of causes of death among Vietnam veterans, as they have been doing in their proportionate mortality study. In addition, while CDC has analyzed the SCS data for all appropriate military-related variables, it is a rich source for analysis of many other factors, e.g., occupational and other exposures reported in the interviews. The data should be further analyzed by CDC, or some provision made to ensure that it is adequately accessible independent researchers. Much of the value of the data will be lost if this is not done.

NATIONAL ACADEMY OF SCIENCES,
Washington, DC, June 14, 1990.

Hon. ALAN CRANSTON,
Chairman, Senate, Washington, DC.

DEAR MR. CHAIRMAN: In response to your request for comments on the Centers for Disease Control (CDC) study of selected cancers in Vietnam Veterans, I enclose the summary report of our advisory committee to the Public Health Service (PHS.) An earlier version was presented to the House Committee in testimony in April.

The Institute of Medicine of the National Academy of Sciences convened our committee at PHS request to review the conduct of the CDC study and the interpretation of the data. The committee met with agency representatives on five occasions and reviewed the final reports.

Based on its discussions with the CDC staff and the material it has reviewed, the committee believes that the Selected Cancers Study makes a useful and important contribution to understanding the relationship between Vietnam experience and the cancers under study. In the committee's judgment, the CDC's work meets the highest professional standards.

The committee also believes that the data collected in the Selected Cancers Study are a valuable resource for other than studying the health effects of Vietnam service. Thus the committee recommends that, after the completion of the current study, resources be made available for further analysis of the Selected Cancers Study data by CDC staff and their collaborators and eventually by others.

If the Institute of Medicine and the Academy can be of further assistance, please don't hestitate to call on us.

Yours sincerely,

FRANK PRESS,
President.

SELECTED CANCERS STUDY: ADVISORY COMMITTEE ON THE CENTERS FOR DISEASE CONTROL STUDY OF THE HEALTH OF VIETNAM VETERANS

(Review of CDC Draft Reports, SUMMARY REPORT, Institute of Medicine, National Academy of Sciences, April 25, 1990)

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

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

The Institute of Medicine was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of appropriate professions in the examination of policy matters pertaining to the health of the public. In this, the Institute acts under both the Academy's 1863 congressional charter responsibility to be an adviser to the federal government and its own initiative in identifying issues of medical care, research and education.

This study is supported by the Centers for Disease Control under contract number 200-88-0951. 2101 Constitution Avenue, N.W. Washington, DC. 20418. (202) 334-3300.

ADVISORY COMMITTEE ON THE CDC STUDY OF THE HEALTH OF VIETNAM VETERANS

Board of Health Promotion and Disease Prevention

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

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

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

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

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

Institute of Medicine

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

INTRODUCTION

In May 1985, James Mason, then Acting Assistant Secretary of Health, requested that the Institute of Medicine (IOM) establish a committee to assist the Centers for Disease Control (CDC) in its conduct of epidemiologic studies on the health of Vietnam veterans. These studies are mandated by public laws 96-151 and 97-22, and represent a large and complex effort to determine the possible long-term health effects of Vietnam veterans exposure to herbicides, including Agent Orange (the Agent Orange Study, AOS), the possible long-term effects of military service in Vietnam (the Vietnam Experience Study, VES), and the risk of selected cancers (the Selected Cancers Study, SCS). In September 1985, the CDC contracted with the IOM (1) to advise on the conduct of these three studies, (2) to advise on the interpretation of the data collected, and (3) to provide prepublication review of the CDC reports presenting analyses of these data. Extensive work to obtain reliable exposure data demonstrated that the AOS study was not scientifically feasible. The IOM oversight has therefore been primarily directed to consideration of the VES and SCS studies.

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

In 1988 the IOM appointed the Selected Cancers Study committee to advise the CDC on its study of the association between certain cancers and Vietnam service. A list of the committee members is attached. The primary objective of the SCS is to determine whether there is an association between service in Vietnam and the risk of developing any of six types of cancer—Hodg-

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

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

CONCLUSIONS

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

The committee's recommendations are summarized below. Based on its discussions with the CDC staff at the fifth committee meeting and a review of the final CDC reports, the committee feels that the CDC has been responsive to the committee's concerns, and had made changes as appropriate.

Study plans

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

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

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

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

Analysis

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

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

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

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

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

After reviewing a number of alternative data presentation formats for journal articles and its report to Congress, the committee recommended that CDC present the results of its comprehensive analyses of the main effects of Vietnam exposures on cancer risk and of possible interactions with age and other potential modifiers. When in its judgment there is some evidence that the effects of exposure may differ in different subgroups, subgroup data in the form of 2x2 tables should be presented also so that the reader can see the basic data. This approach has the advantage of taking into account the multivariate complexity in the data as well as avoiding the problems of presenting many small tables.

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

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

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

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

The committee agreed with the CDC that it is preferable to exclude from the statistical analysis those men not eligible to serve

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

Similarly, because the etiology of AIDS and non-AIDS lymphomas are likely to be very different, the committee feels that it is best to exclude subjects reported to have AIDS from the primary analysis. However, to test the sensitivity of the results to this decision, the committee suggested that the CDC perform multivariate statistical analyses on the full data set (that is, including both the AIDS and non-AIDS subjects) appropriately controlling for AIDS status. The committee further recommended that the CDC carefully examine the "never married" and "intravenous drug use" variables because they might be associated with unidentified AIDS cases.

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

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

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

Presentation of results

Based on its review of the draft final reports and its discussions with the CDC staff, the committee developed the following recommendations about the presentaton and interpretation of the results:

First, the committee recommends that CDC should more fully note the history of the SCS study in the introduction and discussion sections of the reports. This would include an acknowledgement of the study's original focus on Agent Orange and a discussion of the reasons for not using physical measures of dioxin exposure or more detailed exposure measures based on self-report or military records.

Second, the committee recommends that the CDC explicitly acknowledge and discuss alternative explanations for the elevated relative risk associated with Vietnam service found in the NHL study. Specifically, the committee suggests that final CDC reports address the problem of multiple comparisons and possible misclassification of Vietnam service, as discussed below:

Third, the committee recommends that the CDC review the use of terms relating to statistical significance, definition of Vietnam service, and sensitivity analysis in the text, and make them as clear and consistent as possible.

General comments

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

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

PUBLIC HEALTH SERVICE,
Washington, DC, May 24, 1990.

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

DEAR MR. CHAIRMAN: When Dr. William Roper transmitted the Selected Cancers Study to the Ranking Majority and Minority Members of the Senate and House Veterans' Affairs Committees, he indicated that a Science Panel review of the study would follow within approximately 6 weeks. That review has been completed and is enclosed.

Identical letters are being sent to Senator Frank H. Murkowski; Congressman G.V (Sonny) Montgomery, Chairman of the House of Representatives Veterans' Affairs Committee; and Congressman Bob Stump, Ranking Minority Member of that committee.

Sincerely yours,
JAMES O. MASON, M.D., Dr.P.H.,
Assistant Secretary for Health.

PUBLIC HEALTH SERVICE,
CENTERS FOR DISEASE CONTROL,
Washington, DC, May 16, 1990.

MEMORANDUM

From: Assistant Director for Science, Center for Environmental Health and Injury Control.

Subject: Agent Orange Task Force/Science Panel Review of Selected Cancers Study.

To: Vernon N. Houk, M.D., Director, Center for Environmental Health and Injury Control.

In this memorandum, I will summarize the comments of the members of the Science Panel of the Agent Orange Task Force on the Selected Cancers Study.

The consensus of the Science Panel is that this was a very thorough and carefully conducted set of case-control studies of cancers which had been associated in the literature with exposure to phenoxyherbicides and chlorophenol. Although the study looked at exposure to Agent Orange, it emphasized the point that this was not a study of Agent Orange exposure but of service in Vietnam as a possible risk factor for these particular malignancies. Great care was taken in the design of the study, in confirmation of all cases of cancer included in the study by blinded pathological review of slides and tissues, and in validation of reported military service through the records of the Environmental Studies Group, Department of Defense. The papers were clearly written and the conclusions supported by the appropriate tables.

The Science Panel concurs with the conclusions of the Selected Cancers Study.

DANIEL A. HOFFMAN, Ph.D., M.P.H.

DEPARTMENT OF VETERANS AFFAIRS,
OFFICE OF THE GENERAL COUNSEL,
Washington, DC, September 11, 1990.

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

DEAR MR. CRANSTON: You had previously requested the views of the Veterans' Advisory Committee on Environmental Hazards on two reports: a study by the Centers for Disease Control, "The Association of Selected Cancers with Service in the U.S. Military in Vietnam" and a report by the Agent Orange Scientific Task Force entitled, "A review of the Scientific Literature on Human Health Effects Associated with Exposure to Herbicides and/or Their Associated Contaminants—Chlorinated Dioxins." The Committee considered those reports at its May, 1990, meeting. A copy of the minutes of that meeting is enclosed. (These topics are discussed at pp. 4 and 5 of the May 17, 1990, minutes.) I am also enclosing a copy of the transmittal memorandum to Secretary Derwinski which also discusses the report of the Agent Orange Task Force.

If I may be of further assistance, please let me know.

Sincerely,
FREDERIC L. CONWAY,
Executive Secretary,
Veterans' Advisory Committee
on Environmental Hazards.

DEPARTMENT OF
VETERANS AFFAIRS,
September 10, 1990.

MEMORANDUM

From: Executive Secretary, Veterans' Advisory Committee on Environmental Hazards.

Subject: Minutes of May 16-17, 1990, Meeting.

1. The Veterans Advisory Committee on Environmental Hazards met on May 16 and 17, 1990. (The minutes of that meeting are attached.) It reviewed the scientific literature relating to whether there is a significant statistical association between exposure to a herbicide containing dioxin and the subsequent development of a soft tissue sarcoma. After considering over 80 articles, the Committee concluded that the weight of the evidence was such that it was at least as likely as not that such an association existed. Committee members noted that work done in Sweden was strongly compelling for an association while studies done elsewhere not showing an association were also very strong. It was noted by Committee members that the positive studies tended to be confined to one geographic area of the world and that studies involving Vietnam veterans did not find such an association. Nevertheless, in keeping with the requirement that reasonable doubt be exercised in favor of an association when the evidence is in approximate balance, the Committee recommended that, in their opinion, there was a significant statistical association between expo-

sure to a herbicide containing dioxin and soft tissue sarcomas. Several Committee members noted, however, that they did not believe that the evidence demonstrated a causal association.

2. In the course of their review of the literature, the Committee considered the report of the Agent Orange Scientific Task Force. The Committee agreed with a review prepared by Dr. Whitlock. In his review, he noted that the studies cited by the Agent Orange Scientific Task Force contained one or more of the following shortcomings: (1) In most of the reports, exposure to phenoxyacetic acid and/or chlorinated dioxins was inferred, and not documented. (2) In some cases, the populations studied were also exposed to other chemicals. (3) In almost none of the studies was there an attempt to demonstrate a dose-response relationship between (presumed) exposure and an adverse health effect(s). The lack of adequate exposure data, in the Committee's opinion, made it difficult (if not impossible) to draw firm conclusions from these epidemiologic studies.

3. The Committee commented that while the Agent Orange Scientific Task Force also recognized this limitation on the inferences one could draw from the literature, it provided no new data or novel analyses that addressed the problem. The Committee also stated that the Task Force failed to document its approach to "synthesizing all of the available data to determine their overall or aggregate meaning." In the Committee's opinion, the absence of such documentation makes the Task Force's conclusions scientifically indefensible.

4. The Committee also noted that the Task Force implied that the possible adverse health effects of phenoxyacetic acids and/or chlorinated dioxins depended not only upon exposure to the compund of interest but also upon the genetic makeup of the individual and his/her exposure to other chemical substances. The Task Force provided no new data or information that addressed these issues.

5. The Task Force noted correctly that, for regulatory purposes, a chemical that causes cancer in animals should be considered a potential human carcinogen. However, the Committee commented, its classification as a potential carcinogen does not constitute evidence that 2,3,7,8-TCDD does, in fact, produce cancer in man. There is even evidence from animal studies (not cited by the Task Force) that 2,3,7,8-TCDD produces a protective (i.e., anti-carcinogenic) effect in animals subsequently exposed to carcinogenic polycyclic aromatic hydrocarbons [See Cohen, G.M., et al., *Cancer Res.* 39: 4027-4033 (1979); DiGiovanni, J., et al., *Cancer Res.* 40: 1580-1587 (1980)] By analogy, these observations raise the possibility that 2,3,7,8-TCDD may, under certain circumstances, produce a similar protective effect in humans. The Committee noted that this concept is not discussed by the Task Force in its report.

6. From a scientific standpoint, in the opinion of the Committee, the conclusions of the Task Force represent an over-interpretation of the inconclusive data and an oversimplification of a complex biological process. The Task Force presented only a selective review of the literature and its review appeared to be generally uncritical and lacking of any discussion of the strengths and weaknesses of a particular study.

FREDERIC L. CONWAY,
Executive Secretary.

MINUTES OF VETERANS' ADVISORY COMMITTEE ON ENVIRONMENTAL HAZARDS, MAY 17, 1990

When the Council resumed, it reviewed a paper by Milham, Samuel, "Herbicides, Occupation, and Cancer," *"Lancet,* June 26, 1982, p. 1464. Dr. Kurland, the primary reviewer, commented that the exposure assessment made by the author was indirect and somewhat uncertain. This was the same observation made by Dr. Whitlock in his written comment. Both reviewers characterized the paper as valid and inconclusive.

Next, the Council reviewed a paper by Bond, et al., "Medical and Morbidity surveillance findings among employees potentially exposed to TCDD," *Br. J. Industrial Med.* 40: 318-324 (1983). Dr. Kurland, the primary reviewer, though that the exposure assessment in this study was also somewhat uncertain. He commented to that while the study was negative for soft tissue sarcoma, it had inadequate power. Therefore, he characterized the study as valid but inconclusive. Dr. Whitlock, the secondary reviewer, made the same observations in his written comments.

Dr. Kurland served as primary reviewer for Smith, et al., "Soft Tissue Sarcoma and Exposure to Phenoxyherbicides and Chlorophenols in New Zealand," *JNCI* 73: 1111-1117 (1984). (See note 60.) It was noted that this paper had been previously reviewed in conjunction with a later paper by Smith (see note 61). It was agreed that taken together the papers should be described as valid and negative.

The next paper considered was Hoar, et al. "Herbicides and Colon Cancer," *Lancet,* June 1, 1985, pp. 1277-1278. Dr. Kurland, the primary reviewer, observed that the paper was valid with respect to colon cancer but that it was not pertinent with regards to soft tissue sarcomas.

The Council next took up a paper by Coggon, et al., "Mortality of workers exposed to 2 methyl-4 chlorophenoxyacetic acid," *Scan. J. Work Environ. Health* 12: 448-454 (1986). Dr. Kurland again served as primary reviewer. He noted that there was one death from soft tissue sarcoma in the exposed cohort compared with 1 death expected. He thought the study to be valid but inconclusive. Dr. Melvin, the secondary reviewer, agreed also commenting on the study's low power and observing that misclassification of tumor type could result in very different outcomes.

The next paper reviewed was by Bond, et al., "Evaluation of Mortality Patterns Among Chemical Workers with Chloracne," *Chemosphere* 16: 2117-2121 (1987). Dr. Kurland noted that while there was no significant difference between the observed and expected cases of soft tissue sarcoma (0 observed, 0.1 expected) the study lacked adequate power due to its small size. Consequently, he called the study valid but inconclusive. Dr. Melvin, the second reviewer, agreed.

A paper by Forcier, et al., "Mortality of Australian Veterans of the Vietnam Conflict and the Period and Location of Their Vietnam Service," *Military Medicine* 152: 117-123 (1987) was reviewed next. Dr. Kurland, the primary reviewer, observed that there was nothing in this paper with respect to soft tissue sarcoma. He called the study valid but inconclusive for soft tissue sarcoma.

The Council then considered two papers by Stellman, et al., "Combat and Herbicide Exposures in Vietnam among a Sample of American Legionnaires," *Environ. Res.* 47: 112-128 (1988) and "Health and Reproductive Outcomes among American Legionnaires in Relation to Combat and Herbicide Exposure in Vietnam," *Environ. Res.* 47: 150-174 (1988). The first paper was not considered to be pertinent to the issue of soft tissue sarcoma. Concerning the second paper, Dr. Colton referred to the observations of the authors that "(b)ecause of the low background rates of all types of cancer in a group with this age distribution, the present study does not have the statistical power to detect such effects. Also for the majority of the cohort, insufficient time has elapsed for the natural latency of the disease process to have passed." Dr. Kurland, the primary reviewer, agreed with this characterization. Dr. Melvin, the second reviewer, commented on the low response rate in this study to the questionnaire. Dr. Lathrop agreed that a low response rate could cause considerable problems particularly if there was a differential with respect to the cases and the control groups. Dr. Kurland noted he would generally dismiss a study as inconclusive if it had a response rate of less than 90% and the response rate in this study was of the order of 60 to 65%. Dr. Melvin commented that he thought that the benchmark response rate should be of the order of 75% or better.

Dr. Yanders observed that the first paper did not purport to produce evidence on soft tissue sarcomas and the second paper, in view of the authors' comments, also did not provide any pertinent information concerning soft tissue sarcomas. Council members agreed with this characterization.

The next paper reviewed was Hardell, et al., "Exposure to Hair Dyes and Polychlorinated Dibenzo-p-dioxins in AIDS Patients With Kaposi Sarcoma: An Epidemiological Investigation," *Cancer Detection and Prevention Supplement* 1:567-570 (1987). Dr. Kurland, the primary reviewer, commented on the fact that the cases in this study were interviewed in the outpatient department or in the hospital whereas the controls were interviewed over the telephone. He also noted that the study focused on Kaposi's sarcoma and asked whether that could properly be classified as a soft tissue sarcoma. There was a general consensus among Council members that it was not a soft tissue sarcoma. The paper was then thought not to be pertinent to the Council's consideration. Dr. Whitlock in his written comments said that the study design, the exposure assessment and the choice of the control were each inadequately described. For that reason, he thought the study to be invalid.

The Council then reviewed a paper by Tong, et al., "Elevated Levels of 2,3,7,8-TCDD in the Tissue of an Agricultural Sprayer of Herbicides: A Single Case Study," *Chemosphere* 18:469-476 (1989). Dr. Kurland noted that this was a single case report and did not think it to be pertinent. The Council also felt that the next paper was not pertinent: Centen, et al., "Coproporphyrinuria and Chronic Hepatic Porphyria Type A Found in People From Seveso (Italy) Exposed to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)," *Chemical Porphyria in Man,* Strik and Koeman, eds., Elsevier/North-Holland Biomedical Press, 1979, pp. 75-81.

The Council next considered a paper by Pazderova-Vejlupkova, et al., "The Development and Prognosis of Chronic Intoxication by Tetrachlorodibenzo-p-dioxin in Men," *Arch. Environ. Health* 36:5-11 (1981). Members commented on study's findings relative to prophyria cutanea tarda and the apparent high levels of exposure the workers experienced. Dr. Kurland noted that among the reported findings was the relatively good reproduction experience which suggested that exposure would not be expected to give rise to a genetic mutation. With regards to soft tissue sarcoma, it was believed

that the study population was too small thereby giving the study low power and the latency period of 18 years was thought to be very short. Dr. Bender said he characterized it as a series of case reports and that while the study was valid, it was not pertinent to soft tissue sarcomas.

The Council then reviewed a paper by Anderson, et al., "Wisconsin Vietnam Veteran Mortality Study: Proportionate Mortality Ratio Results; Standardized Mortality Ratio Results. Final Report," (1986). Dr. Lathrop served as the primary reviewer. He noted that Vietnam veterans had the same risk for soft tissue sarcoma when compared to non-veterans and non-Vietnam-Vietnam era veterans but an increased risk when compared to all other veterans. He thought this to be essentially a negative result. He commented, however, that this was a RMR type study. Dr. Colton, the secondary reviewer, said that the study, being a PMR study, lacked the analytic capability to detect an increased risk for either mortality or morbidity. It was noted that the Council had considered other PMR studies as either valid positive or negative so this study should be considered to be valid negative. Dr. Melvin observed that the study did not address the issue of exposure to dioxin contained in 2,4,5-T.

Dr. Yanders then reported that he had asked Dr. Bender and Dr. Melvin to serve as reviewers of one of the papers identified by Admiral Zumwalt as deserving of consideration. Bond et al., "Update of Mortality among Chemical Workers with Potential Exposure to the Higher Chlorinated Dioxins," *J. Occupational Med.* 31: 123–127 (1989). Dr. Bender observed that he would consider this as weak evidence of an association. Dr. Lathrop questioned this commenting that with one case observed versus an expected tenth of a case, that is virtually an equivalency of one. Dr. Bender thought it was suggestive because the case occurred among the group who had chloracne and that, therefore, the exposure assessment was very good. Dr. Lathrop agreed that this was an extremely exposed cohort but nonetheless very small. He thought that the small numbers involved, one observed, less than one expected, made it very difficult to subject it to appropriate statistical analysis. He said that he would characterize the study as valid but inconclusive. Admiral Zumwalt noted that it was a chemical company sponsored study and if the true facts were known it would be a positive study. He went on to contend that Dow had known for a number of years and failed to disclose that 2,4-D had a dioxin contaminant in it. He stated his opinion that a company which failed to make this disclosure should not be treated with respect with regards to a study it sponsored. Dr. Lathrop rejected this comment.

Dr. Melvin asked whether it has been indicated how 2,4-D had come to be contaminated, for example, has a vessel containing 2,4-D been previously used to produce 2,4,5-T? Admiral Zumwalt said he did not know. He offered to provide the document to the Committee.

Dr. Colton, in commenting on the Bond paper, agreed with Dr. Bender that it was a suggestive study and that it should be characterized as valid and inconclusive. He went on to note that this study, along with a number of other papers reviewed by the Council, had a common format of being a follow up mortality study of a group of people who were either clearly exposed or quite possibly exposed to dioxin. He raised the question of whether these studies were poolable so as to give them sufficient power to say something meaningful about mortality due to soft tissue sarcoma.

Dr. Bender made the additional comment about the Bond paper that with 12 to 13 years of follow up it may be just on the inside edge of a reasonable latency period and that with time, the observed findings may become more clearly significant.

Admiral Zumwalt then proferred the document to which he referred earlier which he contended evidenced Dow Chemical Company's less than forthright position concerning phenoxy herbicides. The document was headed "R&D Report, Dow Chemical U.S.A." and was dated October 1978. Admiral Zumwalt directed the Council's attention to the statement that shortly after the start-up of the 2,4-D process, "a new and unexpected class of nonacidic impurities were isolated in which two of the major components were tetrachloroxanthone and octochlorospirobixanthrene." He stated that he has been advised that these two impurities were dioxin-like substances and as lethal as TCDD. He made the observation that the fact that Dow Chemical had not made known this information for over 17 years should be taken into account in considering the value of their studies.

Referring back to the Bond paper, Dr. Kurland thought that given the findings as reported, the page should be considered to be valid and inconclusive. Council members agreed.

The Council then reviewed a paper by Eriksson, et al., "Exposure to Dioxins as a Risk Factor for Soft Tissue Sarcoma: A Population-Based Case-Control Study," *JNCI* 82: 486–490 (1990). Dr. Yanders commented on the inclusion in the exposed group of individuals who had exposure of only one day. While he questioned whether they should be considered to have been exposed, he did think that the study showed a valid positive association. Dr. Colton thought that the study was fairly strong with regard to case control methodology. He agreed with Dr. Yanders that it was a valid positive study. Dr. Lathrop commented that the authors had attempted to correct many of the deficiencies of their earlier work but he expressed surprise that they relied on self-administered questionnaires instead of utilizing trained interviewers. He agreed, however, that the study was valid and positive. Dr. Bender found it interesting that the trend analysis conducted by the authors was not significant for total duration of exposure to phenoxyacetic acids.

Dr. Lathrop asked whether the paper suggested that 2,4-D was contaminated with dioxin. Dr. Bender noted a statement appearing in the report that "2,4-D and dichlorprop are contaminated by dioxins other than 2,3,7,8-TCDD." Dr. Lathrop commented that his question was directed to Admiral Zumwalt's comments concerning the contamination of 2,4-D and noted that the compounds of interest were contaminated with a whole variety of chemicals that may or may not be related to the exact structure of 2,3,7,8-TCDD. Admiral Zumwalt stated that his comments were pointed toward the integrity of the company. Dr. Kurland observed that the concentration of the contaminants may have a bearing on whether their existence was known and that extremely small amounts, parts per trillion, may have no meaning in terms of exposure. Dr. Melvin noted that the compounds in the paper distributed by Admiral Zumwalt, Krumel and Arnold, "A Study of the Formation and Removal of Impurities in the Process of 2,4-D," Dow Chemical U.S.A., 1978, discussed compounds that were not polychlorinated dibenzodioxins (a dioxide) or polychlorinated dibenzofurans (a monoxide). He stated that while he recognized that they had been identified chemically and structurally, he was not aware of any studies in toxicology for these two compounds. He also noted that they were detected in an old building after the process had been moved to another building and that it was not known if they were looking at process-induced contamination or contamination from some other source.

Dr. Yanders suggested that further discussion of this paper be deferred until after the members had a chance to consider it in more detail.

The Council then reviewed a study by the Centers for Disease Control, "The Association of Selected Cancers with Service in the U.S. Military in Vietnam," 1990. Dr. Yanders served as the primary reviewer. He stated that the study was a carefully conducted case control study and that the authors clearly set forth their findings, the most important of which was the significant increase in risk for non-Hodgkin's lymphoma among Vietnam veterans. With respect to soft tissue sarcoma, he noted that it was negative. Because of the nature and manner of the study, he thought it should be characterized as valid and negative for soft tissue sarcoma. Dr. Colton, the secondary reviewer, agreed. He thought one of the strengths of the study was the confirmation of diagnosis. He felt that the study was very strong methodologically and that it was a valid negative study. With respect to Agent Orange exposure, however, the study was uninformative.

Dr. Colton observed that the Council had characterized case control studies conducted in Sweden as valid and positive and, he noted, they have been replicated in Sweden. On the other hand, case control studies conducted elsewhere tended to be negative.

Admiral Zumwalt criticized the Selected Cancers Study because it analyzed service in Vietnam and did not attempt to focus on those individuals who were truly exposed. He was also critical of the very narrow period of time in which diagnoses were made and commented that that may well have been before the period of maximum latency. He was also critical of the authors' assertion that blue water Navy personnel were not exposed to Agent Orange. He argued many in the blue water Navy served multiple tours in Vietnam, some also serving in the brown water Navy and therefore had significant opportunity for exposure. If these were removed from the unexposed category, he thought it would have the result of showing an increase among the land based personnel.

Dr. Colton noted that this effort was not the result of a sole effort on the part of the Centers for Disease Control. He observed that this study had undergone extensive peer review, including reviews by the Congressional Office of Technology Assessment and the Science Panel of the Agent Orange Working Group. Admiral Zumwalt stated that the fact that the study may have undergone extensive peer review had no bearing on whether the study properly classified people in terms of their exposures. He commented that he spoke with a person who served on a review panel and that he had not known about potential exposure of blue water Navy personnel. Dr. Colton stated that the study could not deal directly with Agent Orange exposure, a deficiency shared by many of the studies reviewed by the Committee. Admiral Zumwalt thought that a realistic exposed group could have and should have been obtained through the use of blood dioxin levels. Dr. Lathrop commented that that was not possible at the time the study was designed and conducted. He further noted that the Centers for Disease Control made no pretense that this was an Agent Orange study; it was a Vietnam

experience study and on that basis showed significant results.

Dr. Lathrop questioned how Admiral Zumwalt could accept the non-Hodgkin's lymphoma findings and refute the other findings of the study. Admiral Zumwalt stated that in the case of non-Hodgkins's lymphoma, even though there was significant dilution due to misclassification, if an exposed group had been looked at the results would have been even more significant. Dr. Lathrop suggested that Admiral Zumwalt might want to encourage research involving highly exposed persons. Admiral Zumwalt stated that Dr. Lathrop came at the problem from the viewpoint that there was no correlation whereas he came at it from the perspective that he thought there was. He thought that the Committee was finally getting a balancing of views. Dr. Colton took issue with Admiral Zumwalt's comments saying that Committee members came to the issue with an open mind and without any preconceived notions. Admiral Zumwalt stated that in reviewing the transcripts, it was his judgment that Dr. Lathrop often sought to characterize inconclusive studies as negative and positive studies as inconclusive. He thought that evidenced bias in the other direction from his own after having gone though all of the evidence. Dr. Lathrop stated he did not regard his opinions as bias but rather as based on where the data took him.

Mr. Meadows then commented that he had neglected to make it clear to Admiral Zumwalt the stucture of the Committee and the manner in which it operated. He pointed out that there was the full 15 member Committee and an 11 member Scientific Council. The Council was charged to look at the scientific literature and give its advice. When the Council met, the lay Committee members were permitted to observe and, when asked by the Council, to express an opinion. He noted that the lay members were not members of the Scientific Council. Admiral Zumwalt asked how many lay members made their views known. Mr. Meadows stated that the Council, from time to time, would permit lay members to ask questions or make comments. After the Council completed its review of the literature, every member of the Committee would be permitted to express his or her opinion and participate in the discussion of what recommendations to the Secretary were appropriate.

Dr. Yanders then asked if members wished to express any views on the Agent Orange Scientific Task Force Report. Dr. Colton suggested that Dr. Whitlock's comments be referred to as they were prepared prior to the meeting and would not have been tainted by any discussions occurring during the meeting. Dr. Yanders summarized Dr. Whitlock's comments, a copy of which had been provided to every member (see Attachment II). Dr. Whitlock had stated that the possible health effects, as delineated in the report, were complicated by: inadequate exposure data; the likelihood that environmental and genetic factors may influence susceptibility to the compounds; and the possibility that some of the compounds may exert a beneficial effect. He concluded that from a scientific standpoint, the conclusion of the Task Force was untenable. It represented, in Dr. Whitlock's opinion, over-interpretation of inconclusive data and an over-simplification of a complex biological process.

Dr. Yanders expressed the view that the Task Force presented a selective review of the literature and did not present any new material. Dr. Colton said the Task Force had apparently not understood what the Council had done in assessing the literature. He said that it appeared to him the Task Force had made an uncritical review of the literature whereas the Council had attempted to discuss the strengths and weaknesses of a study. Dr. Lathrop took exception to the Task Force's listing of subclinical findings and subjective conditions as being among those deserving of compensation. Dr. Bender also commented on the Task Force's lack of knowledge as to how the Council operated. He noted that while the Task Force was critical of the Council's procedures, it presented its own conclusions without stating how they were arrived at. He agreed with Dr. Lathrop's comments concerning the use of subjective symptoms and subclinical laboratory findings as the basis for any actions relating to compensation. He further stated that he thought that that issue was not an issue for consideration by the Committee. Dr. Neel observed that the Task Force report underlines the intensive scrutiny the Council's activities received and noted that it served to make more important the need to develop creative principles to aid the Council in its assessment of the literature.

Dr. Yanders invited lay members to comment. Admiral Zumwalt again commented on the use of chemical company studies which should be downgraded and the failure of the Council to look to animal studies as the Task Force did in issuing its report. He thought the Council to be very vulnerable and urged it to consider the approach he suggested earlier of referring studies to experts for their review and of establishing a series of criteria for analyzing and assessing the studies. Colonel Bonner commented that the Council was set up to look at the scientific evidence and she thought the Council had done that, noting that much time was required of Council members in preparing for a meeting which may not be reflected in the minutes. Mr. Conroy noted the wide spectrum of opinion expressed by the scientific community, ranging from dioxin as an innocuous substance, to dioxin as the most toxic chemical ever known. He did not think that the opinions expressed were necessarily the result of people operating with personal agendas but that they were sincerely arrived at and held. He did not think it served any purpose to question motivations of individuals for the opinions they held. He expressed the opinion that after 9 years of dealing with this issue he thought that political rather than a scientific resolution would be achieved. Mr. Meadows said that it would be well to remember that the Committee had been doing the best it could and that while it did not operate in the best of all worlds, it did try to provide the best advice it could to the Secretary.

Following a short break, Dr. Yanders reminded Council members of the standard to be applied in assessing the literature and asked whether it could make a recommendation as to whether there was a significant statistical association between exposure to a herbicide containing dioxin and soft tissue sarcoma. Dr. Kurland asked that the Council's assessment of the studies be provided. Dr. Yanders asked Mr. Conway to present the Council's findings. (These may be found in Attachment IV).

At the conclusion of the listing, Dr. Yanders stated the Council had three options: (1) find that an association was at least as likely as not; (2) find no such association; or (3) advise that there was not an association but such an association could not be ruled out.

Dr. Colton pointed out the difficulty he had in assessing the literature. He noted that the valid positive and valid negative studies had different study designs which would affect the weight to be given them. Also, there were differences in the certainty of exposure and the method and duration of exposure among the studies. He also queried how to bring to bear the results of the many inconclusive studies reviewed by the Council.

Dr. Lathrop noted that among the positive studies, most came out of Scandinavian countries. He wondered if that was suggestive of an environmental causative agent unique to a particular region of the world.

Mr. Conroy raised the question of latency, observing that many of the inconclusives were considered to be such because of short latency periods. Dr. Colton agreed that was a good point with respect to cohort studies. Dr. Yanders thought it applicable to case control studies also because, as the population ages, the more cases there would be to strengthen or weaken the association over time.

Dr. Neel suggested the Council tally the inconclusive studies to see in which direction they were going. Dr. Colton objected, saying that the Council would be doing what it had wrongly been accused of in the past. He did think that contemporary techniques of pooling ought to be looked at and see if they could be applied to this situation.

Dr. Lathrop proposed looking at the valid positive and valid negative studies in terms of the quality of their exposure data. If the negative studies tended to have poor exposure quality as compared to the positive studies, then far more credence should be given to the positive studies.

Dr. Colton suggested that the Council had made a first pass through the literature. What was required now was a more analytic approach to assess the relative strengths and weaknesses of each of the valid studies. Such an approach would take into account factors such as the quality of the exposure data, latency, and geographic location of the study. Dr. Lathrop, Dr. Neel, Dr. Bender and Dr. Yanders agreed. It was suggested that several members could work with a consultant to develop criteria for pooling studies and for assessing the quality of studies the Council reviewed. (It was subsequently decided to have a subcommittee of the Council meet and attempt to address this issue. A meeting was scheduled for July.)

The Committee then broke for lunch.

Upon returning, Mr. Conway again reminded Committee members of the standard to be employed in assessing the literature. Dr. Yanders then suggested it may be helpful to see how Council members generally felt about the issue and see whether there was a general consensus developing.

Dr. Lathrop began the discussion by stating it was his opinion, after reading and assessing the various valid positive and valid negative studies, that there was a significant statistical association. He stated that he thought there were now a series of articles that pointed towards a statistical association. He emphasized, however, that it was a statistical association that had been established and not a cause and effect association.

He also offered several additional comments. First, he noted that the majority of positive studies had come from one region of the world. He said he did not know if that was meaningful in terms of study methodology or of the population groups studied. Second, he noted that the disease being assessed was difficult to diagnose and encompassed over 100 separate cancers. He suggested that consideration be given towards not including mesothelioma associated with asbestos exposure and Kaposi's sarcoma associated with AIDS (Acquired Immune Deficiency Syndrome) among the soft tissue sar-

comas being associated with exposure to a herbicide containing dioxin. He indicated that while it did not seem reasonable to him that all of these tumors could arise out of a single environmental exposure, he thought that the evidence was strong enough to meet the at least as likely as not criteria to be applied by the Committee.

Dr. Bender agreed. He said that recent evidence demonstrated an association with phenoxy herbicides and, presumably, TCDD but he commented that the linkage was weak for any particular component. He also did not know what to make of the apparent geographic distribution of the positive versus the negative studies.

Dr. Kurland said he would prefer to get a better sense of the histologic types that could be regarded as associated in a positive way. He also would like to have had more information about the studies characterized as inconclusive as it was his sense that they tended to be more negative than positive. However, he said that the evidence was close and that applying reasonable doubt he would go in the direction of an association.

Dr. Colton said that he thought the Hardell studies were very strong and had no obvious flaws in them and that they were reinforced by the most recent study released in 1990. While he found the Swedish studies to be compelling for an association, he also found other negative studies equally compelling, referring for example to the CDC studies and the studies done in New Zealand. He would give the benefit of the doubt for finding an association.

Dr. Melvin agreed that there was a significant statistical association. He questioned whether Dr. Kurland's suggestion of considering the histological types would be helpful noting that when the biopsy was performed, where it was performed and who performed it could introduce a lot of variation in results. He would be hesitant to say that soft tissue sarcomas could be further subclassified with respect to their association with phenoxy herbicide exposure.

Dr. Neel said that while he shared the opinions expressed he was reluctant to make a final decision in the absence of a stronger statistical analysis. He referred particularly to the number of papers included in the inconclusive category. He did not think that they had not been looked at in a way designed to extract useful information from them.

Dr. Bender agreed with Dr. Neel about the need for a better way to articulate the analysis that he thought each member had gone through in an informal way. He again suggested that a more formal system was needed to document how the Council arrived at its conclusion.

Dr. Yanders cited reasons why he was initially uncomfortable with finding an association: first, there were a number of strong negative studies including some that involved Vietnam veterans; and second, the geographical distribution of the positive studies suggested that there may be some other factor involved such as a genetic component. Nevertheless, he would have to agree that it was at least as likely as not that soft tissue sarcomas were connected with exposure to a herbicide containing dioxin.

Dr. Neel thought the analysis to be too superficial and Dr. Colton agreed that a much more analytic assessment should be done. Dr. Lathrop also agreed but he commented that he was surprised that there was a consensus after the first pass for an association. Dr. Yanders said that he too was surprised that Council members independently arrived at essentially the same conclusion. He further noted that the members appeared to be uneasy about making a recommendation in the absence of a more detailed analysis. He indicated that he did not know how to develop this and not delay inappropriately any action the Secretary may wish to take. Dr. Lathrop suggested that he thought it sufficient that the Council had reached a consensus that could stand alone and not require a more rigorous analysis. He returned again to the earlier suggestion that several members of the Council be tasked with recommending appropriate matrix analyses the Council could employ for assessing the literature. Dr. Yanders agreed.

Dr. Bender suggested that the recommendation to the Secretary be qualified somewhat. He noted that studies of Vietnam veterans did not suggest an association with Vietnam service (unlike the situation with non-Hodgkin's lymphoma where the association was found with service in Vietnam). He thought it important to make it clear that the association was with exposure to a phenoxy herbicide containing dioxin. He thought that this would allay concerns that Vietnam veterans generally were at increased risk by virtue of their having served in Vietnam.

Dr. Lathrop asked whether there should be additional caveats. First, should there be a 5 year latency period in light of studies which begin to show an association after 10 years? Dr. Lathrop thought that it would be properly conservative to recommend a 5 year latency period. Second, he suggested that pleural or diaphragmatic mesothelioma associated with asbestos exposure not be included for compensation. And, third, he questioned whether it would not be appropriate to exclude Kaposi's sarcoma in the presence of an HIV positive antibody.

Dr. Kurland asked whether it would be practical to require a showing of an elevated dioxin serum level. Dr. Yanders suggested it would not be appropriate because all the Council was asked to address was whether there was an association with a herbicide containing dioxin and not whether dioxin was the particular causative agent. Dr. melvin noted that the question then would be at what level would a veteran be eligible for compensation. Dr. Bender asked how deceased veterans would be handled.

Dr. Colton noted that the Committee had not been asked to detail the requirements for compensation. It was his judgment that a 5 year latency period was rather arbitrary. He also did not think there was sufficient basis for adopting the exclusions suggested by Dr. Lathrop. After further discussion, it was the consensus that the Secretary should be advised of these concerns but the Committee had no recommendations with respect to them.

Dr. Yanders asked the lay members of the Committee if they had any comments. Admiral Zumwalt thought that the consensus that had been achieved was a fair one based upon the literature that the Committee had reviewed. Mr. Meadows thought that a statistical association had been demonstrated. He thought that was all the Secretary had to be advised of and that it should be left up to him what limitations he may wish to impose for determining service connection. Mr. Conway related Mr. Conroy's conclusion that there was a significant statistical association. (Mr. Conroy had to leave prior to this discussion.)

Dr. Neel said that he was very uncomfortable that the Council had not done a better job. He urged that the Council adopt a procedure for conducting a more rigorous analysis. Mr. Meadows asked whether that was really needed. Dr. Bender noted that in the radiation area such a scheme would be helpful. It was also noted that in the area of reproductive effects an approach as had been suggested could assist the Council in its review of the literature. Admiral Zumwalt agreed with the suggestion that the Committee adopt a more rigorous review process.

Dr. Yanders then took a formal poll of the Scientific Council members as to whether there was a significant statistical association between exposure to a herbicide containing dioxin and soft tissue sarcomas. The opinion expressed was unanimous for an association.

The Committee then addressed the issue of whether it had been provided with adequate administrative support. Mr. Meadows agreed to discuss this matter with the Secretary.

Dr. Colton asked whether it would be appropriate to restrict the Council's review to only those papers appearing in the peer review literature. It was thought by Council members to be important that it be perceived as willing to look at everything. Council members were reminded that a mechanism for looking at non-peer reviewed papers had been established: use of single reviewers who would bring to the attention of the Council those papers thought to be important and deserving of the Council's consideration.

Admiral Zumwalt asked what health effects the Committee would be taking up next. Among the effects identified were porphyria cutanea tarda, chloracne (whether the maximum period of 6 months following exposure was appropriate), birth defects, immunological disorders, and cancers other than those already considered by the Committee. Mr. Meadows said that the Committee would have to prioritize these issues to address those of most concern to the Secretary and to Vietnam veterans. Mr. Conway reminded the members that the radiation issue had to be addressed also, referring to the need for the Committee to review the BEIR V report.

After discussion, it was agreed that the next meeting of the Committee would be in the latter part of August. Among the issues to be addressed at that time would be the proposed regulation implementing the Committee's recommendation concerning soft tissue sarcomas; porphyria cutanea tarda; chloracne; and the BEIR V report.

Dr. Lathrop asked me to make a comment. He said that while he had the deepest respect for the distinguished military accomplishments of Admiral Zumwalt he took extreme exception to his statements of bias arising from industrial or governmental studies. He thought it most inappropriate to downgrade studies simply because they were performed by industry or government scientists. He noted that he intended to express his views very strongly to the Secretary and invited those members who shared his opinions to join him in his letter.

Admiral Zumwalt responded by stating he expressed his strongly felt views based on his reading of the research over a 7 month period. He felt his observations about governmental bias and misconduct were valid and justifiable. He further suggested that a Congressional investigation would show policy decisions had been made to change data derived from the CDC and the Ranch Hand studies.

Dr. Lathrop stated that these allegations were erroneous with respect to the Ranch Hand study. He noted that he could not speak to the CDC study but commented that if any study reviewed by the Committee were demonstrated to be tainted it would clearly be withdrawn from consideration. With respect to Admiral Zumwalt's allegations, Dr. Lathrop thought them not to be substantiated.

Dr. Colton agreed with Dr. Lathrop. He also went on to note that from his experi-

ence as a member of the Committee, he thought the VA had been totally supportive and exemplary. He said that there had been no attempt to influence him nor any other member. Dr. Bender seconded that as did Dr. Kurland.

Dr. Bender thought it important to note that the Committee, in changing its assessment, should not be considered as having been wrong in the past when it found the evidence wanting. Rather, additional evidence was forthcoming and the standard being applied changed. Second, he thought it inappropriate for the Committee to consider allegations and depositions arising out of court cases as they were not science.

Mr. Meadows again noted that the role of the Scientific Council within the Committee and he expressed appreciation for the Council's willingness to permit the lay members to participate.

He then asked for the full Committee to adopt the recommendation of the Council whereupon a unanimous vote was obtained.

The Committee then adjourned until August.

Approved:

OLIVER MEADOWS,
Chairman.

STANFORD UNIVERSITY
MEDICAL CENTER,
Stanford, CA, May 14, 1990.

Mr. FREDERIK L. CONWAY,
Department of Veterans Affairs, Washington, D.C.

DEAR MR. CONWAY: Enclosed are some general comments on the report entitled "Human Health Effects Associated with Exposure to Herbicides and/or Their Associated Contaminants—Chlorinated Dioxins", authored by the Agent Orange Scientific Task Force.

Please feel free to share these thoughts with the other members of the VA Advisory Committee on Environmental Hazards.

Sincerely,

JAMES P. WHITLOCK, Jr.,
Professor.

STANFORD UNIVERSITY
MEDICAL CENTER,
Stanford, CA, May 14, 1990.

MEMORANDUM

To: Mr. Frederick L. Conway, Executive Secretary, Veterans' Advisory Committee on Environmental Hazards

From: James P. Whitlock, Jr., M.D., Professor of Pharmacology, Stanford University School of Medicine

Subject: Comments on the Report Submitted by the Agent Orange Scientific Task Force, Dated April, 1990

The literature review entitled "Human Health Effects Associated with Exposure to Herbicides and/or their Associated Contaminants—Chlorinated Dioxins", compiled in April, 1990 by the Agent Orange Scientific Task Force (AOSTF) raises several scientific issues that illustrate the complexity of the Agent Orange problem and the difficulties involved in determining whether exposure to phenoxyacetic acids and/or chlorinated dioxins is associated with adverse health effects in humans.

HUMAN EXPOSURE DATA

In my opinion, the authors of the review have correctly identified the crux of the matter: "A major problem with the various epidemiologic studies of people exposed to phenoxyacetic acid herbicides is that there have not been many large populations with known exposures available for study and follow-up over long periods or, where such populations exist, like Vietnam veterans and the Vietnamese, these have not been adequately studied" (page 2, lines 6–11 of the review). Thereafter, the review cites reports of populations with "potential for exposure" (page 8, line 17), workers who were "potentially exposed" (page 9, line 2) or who had "potential exposure" (page 9, line 11), and veterans who had "higher opportunities for exposure" (page 14, line 18). In these and other reports cited by the AOSTF, the extent of exposure to herbicides and/or dioxins was not directly measured. Thus, the studies cited by the AOSTF contain one or more of the following shortcomings. (1) In most of the reports, exposure to phenoxyacetic acids and/or chlorinated dioxins was inferred, and not documented. (2) In some cases, the populations studied were also exposed to other chemicals. (3) In almost none of the studies was there an attempt to demonstrate a dose-response relationship between (presumed) exposure and an adverse health effect(s). The lack of adequate exposure data makes it difficult (if not impossible) to draw firm conclusions from these epidemiologic studies. Furthermore, as the AOSTF recognizes (pages 33–37), humans are also exposed to 2,3,7,8-TCDD from "background" sources. Thus, even when exposure to 2,3,7,8-TCDD is reasonably well-documented, the actual source of the chlorinated dioxin is not always certain. This fact further complicates the interpretation of epidemiologic studies. Therefore, by several important criteria, the epidemiologic data on exposure of humans to phenoxyacetic acids and/or chlorinated dioxins are inadequate. From a scientific standpoint, the inadequacy of the exposure data, which the AOSTF concedes (page 2, lines 6–11) weakens the inferences that one can draw from these epidemiologic studies. Although the AOSTF recognizes this issue in their review, they provide no new data or novel analyses that address the problem. In particular, the AOSTF fails to document its approach to "synthesizing all of the available data to determine their overall or aggregate meaning" (page 4, lines 1–3). In the absence of such documentation, the AOSTF's conclusions are scientifically indefensible.

GENETIC AND ENVIRONMENTAL FACTORS

The AOSTF notes correctly that, in humans, "there is great variability in individual responses in TCDD exposure" (page 18, line 20). The implication of this observation is that some individuals are more susceptible than others to the possible adverse health effects associated with exposure to phenoxyacetic acids and/or chlorinated dioxins. The factors that determine susceptibility are unknown; however, there are at least two possibilities. (1) One possibility is that an environmental factor(s) influences the human response to herbicides and/or dioxins. The AOSTF correctly points out that "dioxin . . . may well interact with other coexposures" (page 17, line 23); thus, additional environmental factors may influence the response to phenoxyacetic acids and/or chlorinated dioxins. For example, given the multi-step nature of carcinogenesis, if 2,3,7,8-TCDD were to act as a tumor promoter in humans, the affected individual would also require exposure to a second substance that acts as a tumor initiator. (2) A second possibility is that a genetic factor(s) influences the human response to herbicides and/or dioxins. For example, the AOSTF notes that phenoxyacetic acids and/or chlorinated dioxins may produce porphyria cutanea tarda (PCT) "most likely only in individuals with inherited uroporphyrinogen decarboxylase deficiency" (page 20, lines 3–5). The implication of this observation is that only a particular subpopulation is at risk for induction of PCT by herbicides and/or dioxins. In principle, the same situation may obtain for other effects that might be associated with exposure to these compounds.

Taken together, the above observations imply that the possible adverse health effects of phenoxyacetic acids and/or chlorinated dioxins depend not only upon exposure to the compound of interest but also upon the genetic makeup of the individual and his/her exposure to other chemical substances. Unfortunately, we do not know what these genetic and environmental factors are, and we are currently unable to identify human subpopulations who are particularly susceptible (or resistant) to the biological effects of phenoxyacetic acids and/or chlorinated dioxins. The AOSTF review provides no new data or information that addresses these issues.

ANIMAL DATA

In Appendix A, the AOSTF review notes correctly that, for regulatory purposes, a chemical that causes cancer in animals should be considered a *potential* (my emphasis) human carcinogen. In fact, 2,3,7,8-TCDD is regulated as a potential human carcinogen (and appropriately so). However, its classification as a potential carcinogen does not constitute evidence that 2,3,7,8-TCDD does, in fact, produce cancer in man.

Animal studies not cited by the AOSTF reveal that, in the skin of inbred mice, 2,3,7,8-TCDD produces (1) hyperkeratinization and other epidermal changes resembling human chloracne and (2) tumor promotion, and that it does so only in animals that have a homozygous recessive mutation at the hr (hairless) locus [see Knutson, J.C. and Poland, A. *Cell* 30:225–234, 1982; Poland, A., Palen, D., and Glover, E. *Nature* 300:271–273, 1982]. These observations support the concept, discussed above, that a genetic factor(s) influences the susceptibility of individuals to 2,3,7,8-TCDD and related compounds.

In other studies not cited by the AOSTF, 2,3,7,8-TCDD produces a protective (i.e., anti-carcinogenic) effect in animals subsequently exposed to carcinogenic polycyclic aromatic hydrocarbons, substances to which most humans are exposed [see Cohen, G.M. et al. *Cancer Res.* 39:4027–4033, 1979; DiGiovanni, J., et al. *Cancer Res.* 40:1580–1587, 1980]. By analogy, these observations raise the possibility that 2,3,7,8-TCDD may, under appropriate circumstances, produce a similar protective effect in humans. The concept that exposure to 2,3,7,8-TCDD could, in principle, be beneficial in some situations is raised infrequently in discussing the human health effects of phenoxyacetic acids and/or chlorinated dioxins. It is not mentioned in the AOSTF review.

SUMMARY

As outlined above, analysis of the possible health effects of human exposure to phenoxyacetic acids and/or chlorinated dioxins is complicated by

(a) inadequate exposure data,

(b) the likelihood that environmental and genetic factors influence susceptibility to these compounds, and

(c) the possibility that the compounds may exert a beneficial effect under some conditions.

Therefore, from a scientific standpoint, the "inescapable" (page 4, line 19) conclusion reached by the AOSTF is untenable. It represents over-interpretation of inconclusive data and oversimplification of a complex biological problem.

REVIEW OF SCIENTIFIC LITERATURE

Mr. President, a study sponsored by The American Legion, the Vietnam Veterans of America, and the National Veterans Legal Services Project, enti-

tled "A Review of the Scientific Literature on Human Health Effects Associated with Exposure to Herbicides and/or their Associated Contaminants—Chlorinated Dioxins" was released in April 1990. In letters dated May 21, 1990, the chairmen and ranking minority members of the Veterans' Affairs Committees, as well as the chairman and ranking minority member of the House Subcommittee on Compensation, Pension, and Insurance, requested a review of this report from OTA, the AOTF, and VA's Advisory Committee, with particular reference to the scientific methods used and the validity of the statistical analysis, as well as identification of any specific findings discussed in the report that warrant followup investigation or analysis.

Mr. President, I ask that the responses received from OTA and the AOTF be printed in the RECORD at this point. I note that the views of VA's Advisory Committee on this study appear in the material reprinted earlier.

The material follows:

CONGRESS OF THE UNITED STATES,
OFFICE OF TECHNOLOGY ASSESSMENT,
Washington, DC, September 21, 1990.

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

DEAR ALAN: Enclosed is OTA's review of the report "Human Health Effects Associated With Exposure to Herbicides and/or Their Associated Contaminants—Chlorinated Dioxins," which you and your colleagues requested in your letter of May 21. The report was written by the "Agent Orange Scientific Task Force," a group of seven scientists working with the American Legion, the Vietnam Veterans of America, and the National Veterans Legal Services Project. You asked specifically about the "scientific methods, criteria used by the authors . . . as well as the validity of their analyses and conclusions."

The authors of the report give no information about the methods they used to draw their conclusions. They state that the standard used was that of a "statistically significant association," the same used by the Department of Veterans Affairs Advisory Committee on Enviornmental Hazards, as specified by regulation. Neither group has stated an operational definition of the term, however: In judging any one study, a determination of statistical significance (at some prespecified level, most often, five percent) could be made, but there is no standard method for doing so for a body of literature. Since the Task Force described no such method, it cannot be critiqued.

It would not be appropriate to use the report as a guide to compensating veterans. It might be useful, however, for the Veterans Advisory Committee on Enviornmental Hazards to review the medical conditions (at least those of clinical significance) covered by the Task Force, including all pertinent studies, not only those showing a positive association with exposure to herbicides, as the Task Force did.

I hope you find this review useful to your Committee. Please do not hesitate to call on me if OTA can be of further assistance, or have your staff call Hellen Gelband in the Health Program (at 8-6590), who prepared the enclosed review.

Sincerely,

JOHN H. GIBBONS.

[A Review of the Scientific Literature prepared by the Agent Orange Scientific Task Force, April 1990]

OTA REVIEW OF HUMAN HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO HERBICIDES AND/OR THEIR ASSOCIATED CONTAMINANTS—CHLORINATED DIOXINS

(Background paper prepared by Hellen Gelband, health program, Office of Technology Assessment, U.S. Congress, September 1990.)

(The views expressed in this background paper do not necessarily represent the views of the Technology Assessment Board or its individual members.)

The Agent Orange Scientific Task Force consists of seven scientists working with The American Legion, the Vietnam Veterans of America, and the National Veterans Legal Services Project. The report, "Human Health Effects Associated With Exposure to Herbicides and/or Their Associated Contaminants—Chlorinated Dioxins," was prepared because the sponsoring groups "have been dissatisfied with the efforts of the VA and its Advisory Committee on Environmental Hazards" in their review of scientific literature concerning possible links between exposure to phenoxy herbicides and their contaminants and adverse health effects.

STANDARDS AND METHODOLOGY USED BY THE TASK FORCE

The report states that the standard used by the Task Force was one of "significant statistical association," with no further clarification on how they defined this term operationally. In judging any one study, a determination of statistical significance (presumably at the level of 5 percent) could be made, but the means for doing so for a body of literature is not standard. On this point, the section on "Methodology" states only that they did not follow what they report to be the methodology of the VA Advisory Committee. In referring to the VA Advisory Committee, the report states:

* * * the Advisory Committee simply classified studies as positive or negative and then tallied them, apparently under the theory that all studies are equal and can be viewed independently from all other knowledge on the subject.

This is not an accurate representation of what the Advisory Committee did, according to detailed minutes of the Advisory Committee's meetings. (Although the Advisory Committee did not develop a specific plan for synthesizing the evidence from all the studies, they informally gave varying weights to studies based on their overall reliability, potential biases, source of exposure information, etc.) There is no discussion of the method used by the Task Force to synthesize the information and come to a decision about whether a "significant statistical association" existed, so it cannot be critiqued.

The report states that the Task Force reviewed epidemiologic studies, because that is what the Advisory Committee had done, but it also criticizes the Advisory Committee for excluding animal studies from consideration, stating:

* * * there is an overwhelming scientific consensus that carcinogenicity data derived from well-designed animal studies can be extrapolated with confidence to predict human cancer risk.

This is a misinterpretation of the consensus on the value of animal studies. For *regulatory* purposes, evidence of carcinogenicity in animals is accepted as evidence of *potential* carcinogenicity in humans. The regulation of 2,3,7,8-TCDD is based on animal test data. However, only epidemiologic studies can determine whether phenoxy herbicides and dioxin are actually causing cancer in human beings. There is certainly no consensus that quantitative predictions can be drawn from animal data to cancer risks in humans.

REVIEWS OF EVIDENCE FOR POSSIBLE ADVERSE HEALTH EFFECTS

Most of the report consists of discussions of specific diseases and the studies that support an association of phenoxy herbicides and dioxin with each of them. Studies that do not support associations are rarely mentioned. As discussed above, no indication is given of how overall determinations of an association were made.

The report contains considerable criticism of certain individual studies, e.g., CDC's Selected Cancers Study and the Ranch Hand Study, and of the Government's decision to cancel the Agent Orange study. Many specifics of these discussions are incorrect. Examples are cited below:

1. Concerning the Selected Cancers Study, the report challenges CDC's interpretation that the study provides no evidence that the observed excess of non-Hodgkins lymphoma (NHL) is related to Agent Orange. The report states: "If the CDC data on veterans in I Corps and III Corps are taken together, they show an increased risk of both non-Hodgkin's lymphoma and soft tissue sarcoma." According to CDC, this is not true. In any case, since the Task Force did not have the raw data from CDC, they could not have made this calculation.

2. The report erroneously reports that the Agent Orange study was cancelled because CDC claimed that "it was not possible to determine exposure to Agent Orange from military records." They state further that CDC "concluded there was no correlation between exposure, as predicted by certain military records, and dioxin levels in tissue and serum samples of certain veterans." TCDD serum levels in the background range in veterans were not unexpected based on the military records, which had suggested strongly that even veterans who served in areas of heavy spraying were not directly exposed to a significant degree.

Some of the studies included in the report, e.g., the Columbia University-American Legion study, are of doubtful validity because of serious flaws in methodology or execution. The validity of other studies, particularly industry-sponsored studies, are called into question.

CONCLUSION

The report of the Task Force presents no new information. Their conclusion—that many adverse health effects, both clinically apparent and subclinical, are associated with exposure to phenoxy herbicides—are given with no explanation of how they were derived. It would not be appropriate to use this report as a guide to compensating veterans. It might be useful, however, for the Veterans Advisory Committee on Environmental Hazards to review the medical conditions (at least those of clinical significance) covered by the Task Force, including all pertinent studies, not only those showing a positive association with exposure to herbicides.

PUBLIC HEALTH SERVICE,
Washington, DC, July 17, 1990.

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

DEAR MR. CHAIRMAN: Thank you for your letter of May 21 to Secretary Sullivan requesting that the Domestic Policy Council's (DPC) Agent Orange Task Force review "Human Health Effects Associated with Exposure to Herbicides, and/or Their Associated Contaminants—Chlorinated Dioxins, A

Review of the Scientific Literature," prepared by the Agent Orange Scientific Task Force (AOSTF) commissioned by the American Legion, the Vietnam Veterans of America, and the National Veterans Legal Service Project.

Earlier I had requested that the Science Panel of the DPC Agent Orange Task Force assess this document. That has been completed and is enclosed.

The veterans groups' AOSTF concluded that the aggregate of the weight of evidence from available epidemiologic studies establishes a causal relationship between Agent Orange exposure and a range of cancers and other health outcomes among Vietnam veterans.

The members of the DPC's Science Panel concluded that the AOSTF review did not use generally accepted criteria for causality. The review cited an extensive list of elevated risks without acknowledging the limitations of the studies from which they were taken. The review gave undue weight to studies where exposure to Agent Orange was either unknown or poorly defined in order to draw a causal relationship between health outcomes and Agent Orange.

In summary, the Science Panel concluded that an objective, critical review of the literature would not support the conclusions of the AOSTF's evaluation.

Identical letters are being sent to Senator Frank H. Murkowski, Congressman G.V. (Sonny) Montgomery, Congressman Bob Stump, Congressman Douglas Applegate, and Congressman Bob McEwen.

Sincerely yours,

JAMES O. MASON, M.D., Dr. P.H.,
Assistant Secretary for Health.

PUBLIC HEALTH SERVICE,
CENTERS FOR DISEASE CONTROL,
Washington, DC, May 16, 1990.

MEMORANDUM

From: Assistant Director for Science, Center for Environmental Health and Injury Control.

Subject: Review of "Human Health Effects Associated with Exposure to Herbicide and/or Their Associated Contaminants-Chlorinated Dioxins, Agent Orange, and the Vietnam Veteran".

To: Vernon N. Houk, M.D., Chairman, Science Panel, Director, Center for Environmental Health and Injury Control.

I have reviewed and will summarize in this memorandum the comments of ten of the Science Panel members of the Agent Orange Task Force and three ad hoc reviewers (reviewers identified in Attachment A) on a document produced by the Agent Orange Scientific Task Force entitled "Human Health Effects Associated with Exposure to Herbicides and/or Their Associated Contaminants- Chlorinated Dioxins, Agent Orange and the Vietnam Veteran, A Review of the Scientific Literature". This paper was commissioned by the American Legion, the Vietnam Veterans of America, and The National Veterans Legal Services Project. The specific comments of the Science Panel members and ad hoc reviewers, minus their names and Agency affiliation, are provided as Attachments B through N.

BACKGROUND

The objective of the Agent Orange Scientific Task Force (AOSTF) was "—to review the scientific literature related to potential human health effects associated with phenoxyacetic acid herbicides and/or their associated contaminants (chlorinated dioxins)—." The review was specifically directed at assessing purported adverse health effects among Vietnam veterans which may be associated with exposure to Agent Orange. The literature review focused on epidemiologic studies of exposed humans and used as their measure of effect the "—significant statistical association—" to be consistent with the standard of causality used by the Veterans Administration Advisory Committee. The AOSTF emphasized the point that this may be an inappropriate standard because epidemiologic studies must have sufficient statistical power and sensitivity to detect the adverse effects of low levels of exposure. This requires large exposed populations followed for long periods of time. The AOSTF also made the point that, while they did not review the experimental animal literature, "—there is an overwhelming scientific consensus that carcinogenicity data derived from well-designed animal studies can be extrapolated with confidence (emphasis added) to predict human cancer risk."

ORANGE SCIENTIFIC TASK FORCE AOSTF

The AOSTF distinguished their review of the literature from that of the VA's Advisory Committee by stating that the latter "—simply classified studies as positive or negative and then tallied them, apparently under the theory that all studies are equal—." "This procedure was not followed by the Task Force (AOSTF)." One surmises from this statement that the AOSTF conducted a critical review of the literature in which all available data were examined on their merits and whether or not the studies followed generally accepted epidemiologic principles. This was not to be the case as will be discussed later in this review.

The AOSTF concluded from their review that "—the aggregate of all the evidence derived from available relevant epidemiologic studies establishes a causal (emphasis added) relationship between Agent Orange exposure and a range of cancers and chronic diseases." The cancers that the AOSTF linked to phenoxyacetic acid herbicides and/or their associated contaminants included non-Hodgkin's lymphoma and soft tissue sarcoma. The AOSTF also concluded that there is "—sound scientific evidence of an association with exposure to Agent Orange, but the evidence does not reach the level of formal statistical significance, for the following effects: leukemia, and cancers of the kidney, testis, stomach, prostate, colon, hepatobiliary tract and brain." Other medical conditions for which the AOSTF concluded that there was a significant statistical evidence for an association with exposure to Agent Orange were skin disorders/chloracne, subclinical hapatotoxic effects, and porphyria cutanea tarda.

GENERAL COMMENTS OF SCIENCE PANEL MEMBERS

The AOSTF presented a narrative review of selected literature which lacks the rigor or advantages of a systematic meta-analysis of the data. There is no systematic review of the data and the reader has no idea as to the completeness of the literature search. Although there is repeated reference to criteria for statistical significance, this is nowhere defined for the reader. No effort is made to systematically evaluate the various studies presented in terms of study quality. Studies, both rigorous and anecdotal, are treated with essentially equal weight. Although the AOSTF cites the need for studies to have adequate size and statistical power, they do not use these criteria in selecting the data cited in their report to support their opinions on the health effects of exposure to Agent Orange. Although the AOSTF states the important principles for evaluating scientific data, they don't always adhere to these principles in their review. The AOSTF review ignores the "negative" studies and instead concentrates on those studies which show an effect that supports their preconceived opinions on the health effects of Agent Orange exposure. There is no attempt at a balanced, critical evaluation of the literature.

In summary, the AOSTF review did not use generally accepted criteria for evaluating causality. The review cited an extensive list of elevated risks without acknowledging the limitations of the studies from which they were taken. Finally, the review gave undue weight to studies where exposure to Agent Orange was either unknown or poorly defined in order to draw a causal relationship between health outcomes and Agent Orange.

It should be mentioned that much of the data reviewed by the AOSTF has been extensively reviewed and published by other scientists (Fingerhut, 1986; Johnson, 1990; Lilienfeld and Gallo, 1989; and Harvard Study, 1990). These reviewers evaluated these studies and have generally concluded that definitive conclusions could not be drawn from the studies because of limitations such as exposure characterization, latency, and study size.

SPECIFIC COMMENTS—ASSESSMENT OF EXPOSURE

The AOSTF presented an innacurate picture of the Agent Orange exposure issue. They confuse opportunity for exposure with exposure itself, even though they were aware of the CDC feasibility study which demonstrated the inadequacy of that assumption. The results of the CDC study of serum 2,3,7,8-TCDD measurements on 646 veterans considered to be among the highest exposed of the Army ground troops on the basis of five exposure indices including self-perceived exposure showed a distribution of 2,3,7,8-TCDD levels which was almost identical to that in the 97 comparison veterans. It was concluded that the ground troops in Vietnam have body burdens of 2,3,7,8-TCDD similar to body burdens of the general population of the United States. Only the Operation Ranch Hand veterans had higher body burdens. The studies the AOSTF cited as showing an association between Agent Orange exposure and health effects relied on self-reported and unverified exposure data.

The AOSTF is inconsistent in their comments on the use of serum 2,3,7,8-TCDD levels as a measure of exposure. They criticize the CDC Selected Cancers Study for failing to use the assay (page 12) but refute its use as a measure of exposure in other places in the report. On page 38, they either confuse the 16% coefficient of variation (CV) for serum 2,3,7,8-TCDD assay with an error rate of 16%, or are purposely trying to mislead their audience. In fact, the CV reflects the degree of variability in the assay and not that 16% of the assays were unreliable, as implied by the authors.

The AOSTF does not address the issue of other possibly confounding exposures to potential carcinogens. They loosely refer to studies with strikingly different exposures in such a way that the reader could infer that the exposures are directly comparable; e.g., studies on Agent Orange, studies of industrial mishaps involving 2,3,7,8-TCDD, studies of contaminated areas in Missouri, and studies of occupational exposures.

CANCER

The AOSTF comments regarding non-Hodgkin's lymphoma (NHL) suggest a much clearer picture than actually exists. While a number of studies have found statistically significant associations between exposure to herbicides, farming, agricultural occupations, manufacture of herbicides, and NHL, two recently published independent reviews reached substantially different conclusions.

Johnson (1990) concluded that additional study was required before conclusions regarding this association could be reached. Bond et al. (1989) concluded that the evidence did not support a carcinogenic risk to humans. These reviewers cited methodologic problems in published studies. They noted that, in many studies, associations were found in occupations where exposure to herbicides might occur, but not with the compounds themselves. The AOSTF ignores these key points in their reveiw. They also cite studies in a misleading way. For example, they cite a 1989 report by Wiklund as showing an elevated risk of NHL. While technically true, the relative risk was 1.01 or a one percent increase in risk. Citing this estimate as being "increased" is misleading.

The AOSTF's review concerning soft tissue sarcoma, Hodgkin's disease, and other cancers suffers from similar problems. Again, other independent published reviews have reached opposite conclusions. Moreover, the AOSTF review apparently ignored important negative studies, for exampie the study of Hoar et al. (1986), which did not show an association between herbicide exposure and soft tissue sarcoma. For some cancers, like pancreatic cancer, significantly negative reports have been completely ignored. This again illustrates the lack of an even-handed approach in the AOSTF review.

On page 10, contrary to the implication of the AOSTF, the Environmental Protection Agency has not "* * * called for a reassessment of the Monsanto data with a goal of correcting tho erroneous estimate of the risk of cancer * * *"

REPRODUCTIVE EFFECTS

The conclusions of the AOSTF on the reproductive effects occuring among Vietnam veterans is misleading. Although there were differences in several of the sperm parameters, the mean number of pregnancies and the mean number of livebirths fathered by Vietnam and non-Vietnam veterans was the same.

Studies of the assoication between Vietnam service and the risk of miscarriage or early fetal loss are based on the veteran's report of his wife or partner's reproductive experience. Medical confirmaiton of the reproductive outcome was not done. Studies have shown that a man's recall of his wife's reproductive experience is poor and subject to selective biases. Thus, studies that are based solely on self-reported data should be interpreted with caution, something that the AOSTF review did not do.

OTHER CLINICAL EFFECTS

Although the AOSTF review cites the finding of anergy in the Quail Run Study, it did not cite the follow-up study by the same investigators which acknowledged the fact that the anergy disappeared on a second follow-up.

For the finding of porphyria cutanea tarda (PCT), this condition has been reported only twice among persons occupationally exposed to 2,3,7,8-TCDD in doses large enough to cause chloracne. PCT occurred in a Czechoslovakian chemical plant when hexachlorobenzene was also present. This chemical is recognized as a potent cause of PCT. Careful study of the occurrence of chloracne and PCT in the Diamond Shamrock chemical plant in New Jersey even more clearly related PCT to contact with hexachlorobenzene.

SUMMARY

In summary, the Science Panel felt that the AOSTF review was a biased, non-critical review of the literature on the effects of 2,3,7,8-TCDD on human health. The conclusions of the report were not supported by their evaluation of the research.

Daniel A. Hoffman, Ph.D., M.P.H.

REPORT TO THE SECRETARY

Mr. President, on May 5, 1990, Adm. Elmo R. Zumwalt, Jr., Special Assistant to Secretary of Veterans Affairs Ed Derwinski, submitted a report entitled "Report to the Secretary of the Department of Veterans Affairs on the Association Between Adverse Health Effects and Exposure to Agent Orange."

In letters dated July 13, 1990, the chairmen and ranking minority members of the Committees on Veterans' Affairs requested a review of this report from OTA and the AOTF, with particular reference to the report's methods and criteria in the context of generally accepted scientific practices and the validity of its analyses and conclusions.

Mr. President, I ask that the responses I have received thus far be printed in the RECORD at this point.

The material follows:

CONGRESS OF THE UNITED STATES,
OFFICE OF TECHNOLOGY ASSESSMENT,
Washington, DC, July 23, 1990.

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

DEAR ALAN: Enclosed is OTA's review of Special Assistant Admiral E.R. Zumwalt, Jr.'s "Report to the Secretary of the Department of Veterans Affairs on the Association Between Adverse Health Effects and Exposure to Agent Orange." This OTA review was requested by you and your colleagues in your letter to me of July 13, 1990.

Admiral Zumwalt's report gives a brief history of Agent Orange use in Vietnam; mentions early health studies related to phenoxy herbicides; reviews the history of compensation for Agent Orange-related health effects; discusses the work of the Department of Veterans Affairs (VA) Advisory Committee on Environmental Hazards; discusses various aspects of the Centers for Disease Control (CDC) validation study, and gives brief mention to some conclusions of the Selected Cancer Study; discusses some findings of the Air Force Ranch Hand Study; mentions some other studies of phenoxy herbicides exposure; and makes recommendations to the Secretary of Veterans Affairs for compensating Vietnam veterans for health conditions he believes are related to Agent Orange.

The report seems to take the form more of a legal brief than of a scientific review of evidence; it makes an argument for finding that Agent Orange is responsible for a wide range of health problems among Vietnam veterans. The argument depends in large part on Admiral Zumwalt's attempting to discredit the VA Advisory Committee on Environmental Hazards and various Government researchers.

Our review is limited to questions of substance, particularly in those areas in which OTA has been involved. Most prominently, this includes the CDC validation study and the military records research leading up to it. OTA's considerable involvement in these issues stems from its statutory responsibility (stated in Public Laws 96-151 and 97-72) for reviewing study protocols and monitoring the conduct of studies of Agent Orange and the Vietnam Experience. OTA has also followed the progress of the Ranch Hand Study and reviewed the major reports from that study, as well as a large number of other Government and private sector studies relating to the Agent Orange question, for the Veterans' Affairs Committees of Congress. However, OTA staff have not been involved in some of the areas covered by Admiral Zumwalt, e.g., the workings of the VA Environmental Hazards Committee, and no comments on those areas are offered.

Based on a review of the areas in which OTA has been involved, we conclude that many of the assertions made in the report supporting a conclusion that Agent Orange is responsible for a wide range of health problems among Vietnam veterans, are incorrect. These are not mainly matters of differing opinion, but matters of fact—what did or did not happen. For those aspects about which OTA staff have detailed knowledge, it appears that Admiral Zumwalt's arguments are based, in many instances, on faulty information or incorrect interpretation of data.

Please do not hesitate to contact me if you have any questions, or contact Hellen Gelband in the OTA Health Program (8-6590), who was responsible for the review. I hope you find this material helpful in sorting out these difficult issues.

Sincerely,

JOHN H. GIBBONS.

OTA REVIEW OF REPORT TO THE SECRETARY OF THE DEPARTMENT OF VETERANS AFFAIRS ON THE ASSOCIATION BETWEEN ADVERSE HEALTH EFFECTS AND EXPOSURE TO AGENT ORANGE, SUBMITTED BY SPECIAL ASSISTANT ADM. E.R. ZUMWALT, JR., MAY 5, 1990

(Background paper prepared by Hellen Gelband, Health Program, Office of Technology Assessment, U.S. Congress, July 1990.)

(The views expressed in this Background Paper do not necessarily represent the views of the Technology Assessment Board or its individual members.)

INTRODUCTION

On July 13, 1990 the Chairman and Ranking Minority Members of the House and Senate Committees on Veterans' Affairs asked OTA to review the "Report to the Secretary of the Department of Veterans Affairs on the Association Between Adverse Health Effects and Exposure to Agent Orange," submitted by Special Assistant Admiral E.R. Zumwalt, Jr. The report is reviewed in this OTA Background Paper.

Admiral Zumwalt's report gives a brief history of Agent Orange use in Vietnam; mentions early health studies related to phenoxy herbicides; reviews the history of compensation for Agent Orange-related health effects; discusses the work of the compensation for Agent Orange-related health effects; discusses the work of the Department of Veterans Affairs (VA) Advisory Committee on Environmental Hazards; discusses various aspects of the Centers for Disease Control (CDC) validation study, and gives brief mention to some conclusions of the Selected Cancers Study; discusses some findings of the Air Force Ranch Hand Study; mentions some other studies of phenoxy herbicide exposure; and makes recommendations to the Secretary of Veterans Affairs for compensating Vietnam veterans for health conditions he believes are related to Agent Orange.

The report takes more the form of a legal brief than of a scientific review of evidence; it makes an argument for finding that Agent Orange is responsible for a wide range of health problems among Vietnam veterans. The argument depends in large part on Admiral Zumwalt's attempting to

discredit the VA Advisory Committee on Environmental Hazards and various Government researchers.

This Background Paper concentrates on questions of substance, particularly those areas in which OTA has been involved. Most prominently, this includes the CDC validation study and the military records research leading up to it. OTA's involvement stems from its mandated responsibility (in Public Laws 96-151 and 97-72) for reviewing study protocols and monitoring the conduct of studies of Agent Orange and the Vietnam Experience. OTA has also followed the progress of the Ranch Hand Study and reviewed the major reports from that study, as well as a large number of other Government and private sector studies relating to the Agent Orange question, for the Veterans' Affairs Committees of Congress. OTA staff have been less involved with some of the topics covered by Admiral Zumwalt, e.g., the workings of the VA Environmental Hazards Committee, and no comments on those areas are offered.

CDC STUDIES

Admiral Zumwalt's characterization of the CDC studies contains many misstatements of fact. His analysis of the overall picture, suggesting serious wrongdoing by CDC, is built on much of this incorrect information. OTA was part of the process that led to canceling the Agent Orange study, and had reviewed progress along the way toward that decision. CDC provided OTA with interim reports at various points during the process, particularly when CDC proposed significant changes in study design; OTA commented on and approved or disapproved those changes, consistent with its statutory mandate. Most of Admiral Zumwalt's discussion concerns the "validation study," followed by a short discussion of the Selected Cancers Study.

Admiral Zumwalt states that, based on Congressional testimony, "the design, implementation and conclusions of the CDC [validation] study were so ill conceived as to suggest that political pressures once again interfered with the kind of professional, unbiased review Congress had sought to obtain."

The study is described by Admiral Zumwalt as "a study of the long-term health effects of exposures to herbicides in Vietnam * * * supposedly conducted to determine if exposure could, in fact, be estimated." The study was not a study of health effects; its purpose was to determine whether exposure estimates based on military records could be validated by a biological marker of exposure, dioxin levels in blood serum.

Admiral Zumwalt's report states:

"After four years and approximately $63 million in federal funds, the CDC concluded that an Agent Orange exposure study could not be done based on military records. This conclusion was based on the results of blood tests of 646 Vietnam veterans which ostensibly demonstrated that no association existed between serum dioxin levels and military-based estimates of the likelihood of exposure to Agent Orange."

It is true that CDC concluded that a study could not be done based on military records; OTA concurred in this. It is incorrect to suggest that $63 million was spent finding this out. Most of the money spent by CDC went to the successfully completed Vietnam Experience Study (a cohort study of about 17,000 men) and to the successfully completed Selected Cancers Study, a large case-control study. The more serious problem with this statement is the characterization of the validation study results. In fact, the blood tests *did* validate the exposure estimates from the military records, which suggested that few ground troops had significant exposure to Agent Orange. That initial finding, based on military records ably provided by the U.S. Army and Joint Services Environmental Support Group (ESG), that ground troops generally were not in or around areas during spraying or shortly afterward, was the reason OTA and others questioned the wisdom of going ahead with an Agent Orange study on the basis of exposure based on military records. The validation study was an attempt to see if, in fact, these men would have dioxin in their bodies suggestive of higher exposures than were suggested by the military records. They did not.

Admiral Zumwalt's report goes on to say that the validation study itself suffered from "a purposeful effort to sabotage any chance of a meaningful Agent Orange analysis." This is based on his erroneous contention that men in the study were tracked on the basis of the positions of their battalions, not on their company positions. Although at one point during the process, CDC considered using battalion locations, in the final study, the men were tracked by company locations, something OTA insisted on. This is stated clearly in the Journal of the American Medical Association paper (which is not cited in Admiral Zumwalt's report) in which CDC reported the results of the validation study:

"* * * the Environmental Support Group had abstracted company locations for 50 of the 65 identified battalions. For each day of the study and for each company in these 50 battalions, five exposure scores were computed from the dates and map coordinates of herbicide sprays and from military unit locations. Scores were then assigned to each Vietnam veteran by using the dates he served in various companies."

The report by Admiral Zumwalt next presents an interpretation of information from an interim report submitted by CDC to OTA, stating:

"* * * In a February 1985 report to the Congressional Office of Technology Assessment, the CDC reported that in analyzing 21 of 50 detailed computer HERBs tapes developed by the ESG on company movements that it was possible to correlate the exposure data to areas sprayed with Agent Orange with consistent results. Indeed, a peer reviewed study sponsored by the American Legion conclusively demonstrated that such computerized data could be used to establish a reliable exposure classification system essential to any valid epidemiologic study of Vietnam Veterans."

First, the CDC report discusses location data for 21 battalions, the only reference to "21" that is in the report. The "Herbs tape" is a computer tape prepared by the National Academy of Sciences giving the coordinates of Air Force Operation Ranch Hand spray missions; it contains no information on troop movements. A second tape with similar spray information for other types of herbicide application, e.g., ground-based, helicopter spraying, and others, called the "Services Herbs tape," was prepared by ESG; it also contains no troop movement data. The statement concerning correlations of exposure data to areas sprayed may be referring to the following statement in the CDC interim report:

"* * * there have been several attempts to validate the information on the [Herbs] tape. The latest validation studies were done in Australia and included a computer imaging of satellite photographs to analyze vegetation stress and its relationship to the data on the tape. These studies conclude that while the data appear to be consistent with the information available for validation, these sources are not sufficient to allow a definitive study."

The validation referred to in the CDC reports concerns only whether the data on the Herbs tape itself, documenting spray missions, are accurate; they do not refer to any troop movement data.

The American Legion study referred to by Admiral Zumwalt used a method of classification that appears to be even less valid than methods rejected by OTA as being unacceptable for use in an epidemiologic study. A copy of OTA's review of the American Legion study, which contains a detailed critique of the study methods, is attached.

The next issue taken up in Admiral Zumwalt's report is that of the eligibility criteria for veterans to be included in the validation study. He notes that the original protocol required nine months of service in Vietnam, subsequently reduced to six months; that the study was restricted to veterans with one tour of duty in Vietnam; and that the time period of eligibility was extended three months backward and three months forward from the period originally chosen. Admiral Zumwalt characterizes the effect of these criteria as "dilut[ing] the possibility that study subjects would have been exposed to Agent Orange, which in turn would impair any epidemiological study's ability to detect increases in disease rates."

In fact, the two changes (in length of service and calendar period of service) were made in an attempt to include more people who had been present during periods of heavy spraying in 1967 and 1968. As it turned out, some battalions that had been in or near areas that had received heavy spraying during 1967 had arrived in Vietnam in late 1966. Had the original criterion been retained, all the men in these battalions would have been excluded. The reduction in total amount of time spent in Vietnam was also an attempt to include men who had been in closest proximity to spraying on a large number of days, but who might not have spent nine months in Vietnam. The approximately 10,000 eligible men formed the pool from which men with the highest probability of exposure, based on the military records, were selected for the exposed group in the validation study. A dilution effect, as suggested by Admiral Zumwalt, would only operate if *all* the men were included, which was not the case. The restriction to men who had served one tour of duty was the original criterion proposed by CDC (not a change, as Admiral Zumwalt states) in an attempt to study men most representative of the majority of men who served.

Admiral Zumwalt states that CDC:

"determine[d] unilaterally that blood tests taken more than 20 years after a veteran's service in Vietnam were the only valid means of determining a veteran's exposure to Agent Orange."

The long-lived persistence of dioxin in the body had been known for many years, based on biopsies of fatty tissue of people heavily exposed. The development of the blood test by Swedish researchers and by CDC made measurement of body burden of dioxin a feasible approach to studying somewhat larger numbers of men than was feasible using fatty tissue. At the time CDC's validation study was planned, they had already conducted a study comparing blood serum dioxin levels with dioxin levels in fat in a population in Missouri exposed years earlier, and found a very good correlation between the two measures. The same laboratory tests, performed by the Swedish researchers, were used in a similar validation study of Vietnam veterans carried out by researchers at the New Jersey Agent Orange

Commission. More than 20 years after exposure, the Ranch Hands, as a group, still have significantly elevated levels of dioxin in their blood, so it was not unreasonable to expect ground troops with significant exposure would also have elevated levels.

The report goes on to state that:

"* * * Dr. Houk further "assumed" that the half-life for dioxin in the blood was seven years. [ref] When the underlying data for Houk's assumptions were recently reviewed, however, 11 percent of the blood tests were invalid * * * and the half lives of dioxin in the remaining study subjects ranged from a low of 2 to a high of 740 years!"

First, it should be noted that Dr. Houk was not the principal investigator for the study, so conclusions from the study cannot be attributed to him directly. The estimate of a seven-year half life came from measurements made on the blood (collected in 1972 and 1987) of 30 Ranch Hand participants. In the case of four Ranch Hands, the measurements were, as Admiral Zumwalt notes, higher in the larger measurement than in the former. Overall, however, among the entire group, there was a decline, and a half-life of about seven years was estimated from those data. As reported in the *JAMA* paper, CDC states, "Recent results suggest a TCDD half-life in humans of about seven years," consistent with the data that existed at that time. The four apparently anomalous measurements could have resulted from physiological changes in the participants, measurement error, or a combination of both. Admiral Zumwalt does not provide a reference for the range of 2 to 740 years he cites as half-life calculations for the remaining Ranch Hands. In its July 1987 provisional report to OTA on the results of the validation study, CDC provided the data for the half-life estimate; among the 26 remaining subjects (excluding the four with anomalous reading, half-life ranged from 2.9 to 26.9 years. Most of the results fell between 4 and 10 years. It has not been claimed by CDC that this test is infallible, or that measurements on individuals are definitive, but that, as an epidemiologic tool, highly exposed populations can be distinguished from populations exposed to a lesser degree, and this is true even after many years. Since the blood test was being suggested for use in an epidemiologic study, this seems to be appropriate.

Admiral Zumwalt goes on, concerning the blood test, to say:

"Such conclusions are especially suspect given the fact that scientists have consistently cautioned against the use of blood tests as the sole basis for exposure classification."

I am unaware of the particular cautions referred to here, and no references are provided. However, CDC was attempting to correlate blood test results with a variety of classification schemes based on military records, not to use them as a sole basis of classification. The premise was that, as a group some separation could be made of higher versus lower exposure, if that range existed among the ground troops in the study. Later in Admiral Zumwalt's report (page 42–4, footnote 84), he cites a paper discussion exposure assessment, noting that "a serum market for 2,3,7,8-TCDD [developed] by Kahn may provide the means of identifying persons who have been exposed." This appears to be an endorsement of a technique that is similar to CDC's for exposure assessment, with which he has found fault.

The details of the Selected Cancers Study are not discussed by Admiral Zumwalt, but he does comment on the way in which the findings were reported by CDC:

"Even though the CDC has previously stated that it believes exposure to Agent Orange is impossible to assess, it found no difficulty in reporting to the press upon the release of the Selected Cancers Study that exposure to Agent Orange does not cause cancer. This conclusion was reached despite the fact that the CDC made no effort to determine . . . if study subjects were, indeed, exposed to dioxins . . . In fact, according to scientists who have made preliminary reviews of the CDC's findings, the statistical power of any one cancer grouping, with the exception of non-Hodgkin's lymphoma, was so low as to make any conclusion virtually impossible."

The Department of Health and Human Services' press release on the Selected Cancers Study quotes Dr. Roper as saying, "The study did not find any evidence that the increased risk [of non-Hodgkin's lymphoma] might be due to Agent Orange exposure." It goes on to explain:

"The pattern of risk among subgroups of Vietnam veterans seemed to be the opposite of the pattern of use of Agent Orange in Vietnam: Navy veterans who served on ocean-going vessels off the coast of Vietnam tended to be at higher risk than Vietnam veterans based on land, and Vietnam veterans who served in III Corps, the region of heaviest Agent Orange use, tended to be at somewhat lower risk than Vietnam veterans who served in other regions."

We do not agree with Admiral Zumwalt's claims about the statistical power of the study as regards the ability to detect associations with service in Vietnam, which was the primary purpose of the study. This is discussed in the testimony attached, which was presented at the April 4, 1990 hearing before the House Committee on Veteran's Affairs.

THE AIR FORCE RANCH HAND STUDY

Admiral Zumwalt also discusses the Ranch Hand study. OTA has not had direct involvement with this study, but we have reviewed most of the major Ranch Hand reports for the House and Senate Veterans' Affairs Committees, and have kept up to date on its progress through the Agent Orange Task Force (formerly the Agent Orange Working Group) and through independent contacts with the Ranch Hand researchers. We comment here on particular errors of fact noted in the Ranch Hand section of Admiral Zumwalt's report.

Admiral Zumwalt notes that the report on the 1987 Ranch Hand examinations, dated February 23, 1990:

"described statistically significant increases in health problems among Ranch Handers including: all cancers—skin and systemic combined, both verified and suspected; skin cancers alone; hereditary and degenerative neurological diseases and other problems."

What the Air Force researchers reported was a statistically significant excess for the category "verified skin and systemic cancers combined" only in the analysis *unadjusted* for potentially important variables (e.g., demographic factors); the adjusted analysis showed no significant excess. The category "verified and suspected skin and systemic cancers combined" showns no significant excess, either in the adjusted or unadjusted analyses. The category of hereditary and degenerative neurological diseases was dominated by hereditary diseases, which, by definition, cannot be cause by exposures in adulthood, either to Agent Orange or to anything else.

Admiral Zumwalt states further that:

"* * * The Ranch Hand study is not, at this date, an Agent Orange study at all since dioxin exposure could not be determined reliably in the first place. In other words, the Air Force could just as easily have concluded that the health problems associated with the Ranch Handers were not necessarily related to eating beer nuts."

The Ranch Hands, as a group, were known to have been exposed to Agent Orange. The residual levels of dioxin in their bodies, as found by current blood tests, verifies this group exposure. The comparison group in the study did not have such exposure. In the best of all worlds, a more specific measure would be used. In fact, the Air Force researchers have been reanalyzing the data from the study using the newly available dioxin blood levels as more specific means of categorizing exposure. In an earlier portion of Admiral Zumwalt's report on health studies relating to phenoxy herbicides, he states:

"In 1974, for example, Dr. Lennart Hardell began a study which eventually demonstrated a statistically significant correlation between exposure to pesticides containing dioxin and the development of soft tissue sarcomas.

"In 1974, Axelson and Sundell reported a two-fold increase of cancer in a cohort study of Swedish railway workers exposed to a variety of herbicides containing dioxin.

"In 1980, another provocative mortality study of workers involved in an accident at an industrial plant which manufactured dioxin compounds suggested that exposure to these compounds resulted in excessive deaths from neoplasms of the lymphatic and hematopoietic tissues."

In none of these studies, or many others cited by Admiral Zumwalt was there any direct measure of dioxin exposure. Just as with the Ranch Hands, these were people *presumed* exposed because of their occupations. In many cases, exposures were not as well documented as they were for the Ranch Hands, even before dioxin blood levels were measured. If the Ranch Hand study is to be considered invalid because of this, so must these others.

SUMMARY

A major theme of Admiral Zumwalt's report is captured in the following quote:

"Unfortunately, political interference in government sponsored studies associated with Agent Orange has been the norm, not the exception. In fact, there appears to have been a systematic effort to suppress critical data or alter results to meet preconceived notions of what alleged scientific studies were meant to find."

Based on a review of the areas of Admiral Zumwalt's report in which OTA has been involved, it appears that many of the assertions leading to his conclusions are incorrect. These are not mainly matters of differing opinion, but matters of fact—what did or did not happen. For those aspects about which OTA staff have detailed knowledge, it appears that Admiral Zumwalt's arguments are based, in many instances, on faulty information or incorrect interpretation of data.

PUBLIC HEALTH SERVICE,
Washington DC, October 26, 1990.

HON. ALAN CRANSTON,
Chariman, Committee of Veterans' Affairs,
U.S. Senate, Washington, DC.

DEAR MR. CHAIRMAN: This is in further response to your letter of July 13 for an Agent Orange Task Force review of the "Report to the Secretary of the Department of Veterans Affairs on the Association Between Adverse Health Effects and Exposure to Agent Orange," by Admiral E.R. Zumwalt, Jr. dated May 5, 1990.

I asked the Science Panel of the Agent Orange Task Force to conduct such a

review. A copy of each Panel reviewer's findings and a list of the names of the reviewers are enclosed, along with a summary cover sheet prepared by the Panel. In general, the Science Panel found that the report "is not based on fact and is without scientific merit."

Identical letters are being sent to Congressmen Bob Stump and G.V. (Sonny) Montgomery, and Senator Frank Murkowski.

Sincerely yours,

JAMES O. MASON, M.D., Dr. P.H.,
Assistant Secretary for Health.

[Review by the Agency Orange Task Force Science Panel]

"REPORT TO THE SECRETARY OF THE DEPARTMENT OF VETERANS AFFAIRS ON THE ASSOCIATION BETWEEN ADVERSE HEALTH EFFECTS AND EXPOSURE TO AGENT ORANGE"

(By Admiral E.R. Zumwalt, Jr.)

Admiral Zumwalt's report takes more the form of a legal brief than a scientific review. The report cites unverifiable references. These include uncontested charges in a congressional hearing (pages 24 to 32), an anonymous review (page 22), extracts from personal letters (pages 5, 20-22, 36, 40), a "selection of papers" not otherwise characterized (page 22), citations from a veterans service organization (page 27, 29), unsupported statements by a legislator (pages 24, 32, 34, 35), charges presented in a legal brief (page 37), newspaper articles (pages 47, 48), and other sources not generally accessible for critical review (pages 12, 23, 34, 39).

Much of the "scientific" information contained in Admiral Zumwalt's report is a restatement of the Report of the Agent Orange Scientific Task Force commissioned by the American Legion, The Vietnam Veterans of America, and the National Veterans Legal Service Project. The problems contained in the American Legion report have been commented on before.

Admiral Zumwalt's report restates previously discussed issues with a very selective interpretation of historical information to support a particular point of view. Many of the inaccuracies are not matters of differing opinion, but of fact—what did or did not happen.

The Science Panel concludes that Admiral Zumwalt's report is not based on fact and is without scientific merit.

Copies of the individual members' review without identifying information are contained in Appendices A through M.

AGENT ORANGE TASK FORCE SCIENCE PANEL

CHAIRMAN

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MEMBERS

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Ms. Hellen Gelband, Analyst, Office of Technology Assessment, U.S. Congress, 600 Pennsylvania Avenue, S.E., 4th Floor, Washington, D.C. 20003, Phone: (202) 228-6590, Fax: (202) 228-6098.

Dr. Lawrence B. Hobson, Director, Environmental Medicine Office, Department of Veterans Affairs, 810 Vermont Avenue, N.W., Room 637, Washington, D.C. 20420, Phone: 373-4117 OR (202) 233-3604, Fax: 373-2807.

Dr. Han K. Kang, Director, Department of Veterans Affairs, Office of Environmental Epidemiology (10B/A02), 1825 K Street, N.W., Room 322, Washington, D.C. 20006, Phone: 634-4600, Fax: 634-4609.

Dr. Jeffrey Lybarger, Office of Health Assessment, Agency for Toxic Substances & Disease Registry, 1600 Clifton Road, N.E. (E-31), Atlanta, GA 30333, Phone: 236-0550 OR (404) 639-0550, Fax: 236-0569.

Dr. Robert W. Miller, Clinical Epidemiology Branch, National Cancer Institute, NIH, EPN-400, Bethesda, Maryland 20892, Phone: 496-5785 OR (301) 496-5785, Fax: (301) 496-1854.

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Dr. David E. Uddin, M.D., USN, Senior Policy Analyst for Medical Research, OASD Health Affairs, Room 3D366, The Pentagon, Washington, D.C. 20301-1200, Phone: 695-7116 OR (202) 695-7116, Fax: 694-3537.

Colonel William H. Wolfe, MC, USAF, Chief, Epidemiology Division, USAF School of Aerospace Medicine (AFSC), Brooks Air Force Base, Texas 78235-5301, Phone: (512) 536-2604, Fax: (512) 536-3219.

Dr. John F. Young, Director, Division of Reproductive & Developmental Toxicology, National Center for Toxicological Research, Food and Drug Administration, County Road #3, Jefferson, Arkansas 72709, Phone: 790-4304 OR (501) 541-4304, Fax: 790-4136.

STAFF

Anthony S. Fowler, Deputy Chief, Agent Orange Projects, Centers for Disease Control, 1600 Clifton Road, N.E. (F-16), Atlanta, Georgia 30333, Phone: 236-4460 OR (404) 488-4460, Fax: 236-4141.

APPENDIX A

MEMORANDUM

Date: August 7, 1990.

Subject: Report to the Secretary of the Department of Veterans Affairs on the Association between Adverse Health Effects and Exposure to Agent Orange.

To: Vernon N. Houk, M.D., Director, Center for Environmental Health and Injury Control (F29).

In general, this report rehashes previously discussed issues with a very selective use of historical information to support a particular point of view. I am particularly concerned that Admiral Zumwalt has taken a clearly anti-Government stance to the point that he does not cite Government sources when they support his position (e.g., the Selected Cancer Study conclusions on non-Hodgkin's lymphoma), cites preliminary proposals from the Centers for Disease Control (CDC) as final protocols (e.g., the 1985 interim report to the Institute of Medicine which was used for discussion in subsequent revision of protocols), and recommends the use of the serum dioxin test for all veterans after summarily dismissing the test's utility. In addition, the Admiral's lack of qualification as either an epidemiologist or a laboratory scientist is frequently evident by the nature of his presentation of data, notwithstanding his use of consultants who are either anonymous or known to be biased with regards to this topic. To draw the conclusions that he does, the Admiral should have done the carefully constructed meta analysis of the scientific information to quantitatively and critically assess the studies that address each of the issues that concern him. This simply was not done.

I will present specific comments below to issues as they appear in the report.

Page 17. The meaning of the phrase "at least as likely as not in a scientific study show a significant statistical association between a particular exposure to herbicides containing dioxins and a specific adverse health effect" has no practical meaning. Critically important is the fact that conclusions are often not based on statistical criteria, but rather a vagary about "at least as likely as not."

Page 19. It is not accurate to characterize Jeanne and Steven Stellman, as well as an anonymous reviewer, as impartial scientists.

Page 21. It is accurate to characterize the Stellman's report as representing a point of view rather than a careful assessment of the evidence. The Working Group has provided a critical review of the Stellman report previously.

Page 24. In response to allegations about the propriety and quality of the CDC study, it should be clearly reiterated that not only did CDC gather together an excellent group of scientists from both inside and outside the Government to conduct the Vietnam Veterans studies, but that the protocols for each of the studies were carefully reviewed both by the science panel of the Agent Orange Working Group and by an exceptionally talented and impartial group selected by the Institute of Medicine. Comments from these reviewers were sometimes critical and subsequently their suggestions were incorporated into both the study design and analyses conducted by the CDC staff. In short, it should be made clear that CDC did not act alone or in a vacuum, and that non-governmental experts were asked from the beginning to provide input and critique of CDC activities.

Page 25. Allegations which appear throughout such as "a purposeful effort to sabotage" are unfortunate and detracts from other elements of the report.

Page 27. Discussing Richard Christian's testimony is quite misleading. The 1985 report to OTA Expert Panel was preliminary and only dealt with the correlation amongst different exposure measures in predicting troop movements. That these might be correlated with each other has nothing to do with whether or not they may accurately predict exposure to Agent Orange.

In the second paragraph on page 27, CDC is criticized for various alterations in the CDC protocol. These alterations are, in fact, a series of efforts to increase the power of the study to draw significant statistical conclusions. The investigators examined the effect on study power of each of the changes described (e.g., minimum length of service.) The effect of these possible changes in design were then reviewed by the science panel and the IOM to ascertain what would be the optimal study size. It should be recognized that the basic critical parameters for retaining comparability of exposed and unexposed groups were never compromised. In addition, it should be re-

called that only in the validation study were any of these alternative methods employed since the actual Agent Orange Study was never conducted. It is quite common for scientists to look at alternative ways to design a study in order to balance things such as precision of estimates with power considerations.

Page 29. The decision to rely on a blood test was hardly unilateral. CDC had received frequent criticisms by the review groups for dependence upon Army records and, at the insistence of the external reviewers, had turned to the laboratory for more precise measures of exposure. As a result, the validation study was conducted, the design of which was reviewed by the science panel of the Agent Orange Working Group, the OTA Expert Panel, and an outside group of experts in laboratory science to assure the excellence of the laboratory procedures. The report of this study was reviewed by the science panel of the Agent Orange Working Group and OTA expert Panel (as well as reviewers for the Journal of the American Medical Association) before publication.

A footnote on page 29 reads, "that the senior statistician of the Agent Orange Project believed that the dioxin blood analysis was so flawed that there was a substantial likelihood that there was no correlation between exposure scores and blood levels." Based on a reading of a memorandum from the senior statistician to the Project Director (who, incidentally, was the most senior statistician in the Agent Orange Project) that summarize comments from a pair of outside experts. The reference was, in fact, to a comment by an outside consultant (not the CDC statistician) who was concerned that the exposure scores based on army records would not be correlated with adipose (not blood) measurements of dioxin. This consultant was in fact, most concerned about the precision of the exposure scores, not the blood tests. One could read that same memorandum and compliment the Agent Orange Study Group for their ability to seek out and utilize critiques from experts outside the Government.

Page 31. The report fails to note that Dr. Landrigan has subsequently stated that his comments were misconstrued and has apologized for any misunderstanding to Dr. Houk and others at CDC.

Page 32. The allegation that the CDC studies lack sufficient statistical power to detect increased risk is simply untrue. The studies were designed with particular statistical power to detect differences between cases and controls and that was the reason why this study took five years to complete. The Selected Cancer Study did not specifically look at exposure to Agent Orange, rather at Vietnam experience and did conclude there was an increased risk of non-Hodgkin's lymphoma based on this analysis. This, of course, led to the Veterans' Administration allowing compensation for this cancer. In the Discussion the CDC authors did note they could not specifically look at Agent Orange exposure because of limitations of available data. The various indicators of potential exposure which were delineated were not consistent with increased risk related to Agent Orange exposure. This is a common epidemiologic procedure when direct evidence is not available.

Page 34. The CDC birth defects study of the children of Vietnam veterans is criticized in the report on the grounds that it was limited to data available in the Atlanta area, that data were obtained only from birth certificates and not physician or hospital records, and that the study did not include a direct measure of Agent Orange exposure. the well recognized strengths of this large population-based study which offers the only feasible dataset upon which a study looking at veterans experience could be conducted in a reasonable number of years were not mentioned. The report also fails to mention the findings of the Vietnam Experience Study which did delineate specific effects on sperm of veterans of Vietnam not found in veterans from the United States or Germany. The Vietnam Experience Study, however, also showed the lack of difference in the occurrence of birth defects among Vietnam and non-Vietnam veterans.

Page 35. The last sentence of the page contains a gratuitous remark on the Ranch Hand Study which tries to minimize the efforts of the Air Force investigators with a comment about "beer nuts." Such comments detract from the authors' effort to present a reasoned argument.

Page 48. The immunological argument about the possibility of one molecule of a carcinogen could cause cancer presents a problem that has no solution. Obviously, in the day-to-day environment of any U.S. citizen, each of us is exposed to many more molecules of carcinogens. Given the "immunological argument," everyone could contact cancer within the next 5 to 10 years. Indeed, the presence of carcinogens in sidestream smoke of cigarettes would more than fulfill this prophecy.

Page 50. The CDC decision not to use the HERBS tapes is explicable and is based on sound scientific judgment, not only by CDC investigators, but by the Agent Orange Science Working Group Panel and the IOM Expert Panel.

Also, the first sentence in the last paragraph on page 50 states that, "science is now able to include with as great a likelihood as not that dioxins are carcinogenic . . ." is simply not based on the evidence.

The report suggests that all children with birth defects whose father served in Vietnam should be compensated. This may or may not be true as a compensation policy, but there is no basis upon which to derive this in relation to exposure to Agent Orange. Again, the causes of birth defects are such that you would not expect all types of birth defects to result from exposure to a particular mutagen or teratogen. It is also interesting to note that in both of the report's alternative proposals, blood tests for dioxin are recommended despite the criticism of these very tests in this report.

Page 52. The decision to compensate veterans with non-Hodgkin's lymphoma was based on the CDC Selected Cancers Study and this should be acknowledged.

APPENDIX B

AUGUST 8, 1990.

Subject: Review of Document.

To: Vernon N. Houk, MD, Director, Center for Environmental Health and Injury Control, Centers for Disease Control, Atlanta GA.

1. As you requested, I have reviewed the "Report to the Secretary of the Department of Veterans Affairs on the Association Between Adverse Health Effects and Exposures to Agent Orange" prepared by Admiral E. R. Zumwalt, Jr. I found the document to be very one-sided in its presentation of data. The Admiral uses a double set of criteria in his evaluation of scientific data; he is very uncritical of work that supports his strongly held opinions and is very critical of work that counters his position. He also makes extremely derogatory statements and personal attacks on the authors and scientists who disagree with him. The Admiral selectively cites results from scientific studies, often ignoring study design flaws and the lack of statistical significance of the data he presents. He also cites studies such as the Alsea Oregon miscarriage study while ignoring other work that renders their conclusions invalid. At other times, he takes quotes out of context (pages 30 and 39), distorting the actual intent of the author.

2. One of the most frustrating aspects of this report is the Admiral's unwavering position that mere presence in Vietnam equates to significant exposure to Agent Orange and that all Vietnam veterans are at risk of a wide range of diseases and health conditions caused by that exposure. This basic assumption is not based on fact. This assumption is based on outdated and erroneous estimations of the likelihood of exposure of most military personnel while serving in Vietnam. Policy decisions made in the late 1970's and early 1980's concerning the likelihood of exposure to combat troops in Vietnam have been superseded by new data on the actual body burden of dioxin in Vietnam veterans. Studies conducted in Massachusetts and New Jersey and at the Centers for Disease Control on both Army and Air Force personnel clearly demonstrate that significant exposure of military personnel only occurred for those men directly involved in the handling and application of the herbicides. None of these studies have found any other identifiable group of military personnel with elevated body burdens of dioxin. While this does not prove that other veterans were not exposed, it does indicate that significant exposure did not occur for the vast majority of troops in Vietnam.

3. The Admiral alleges that government scientists knew that Agent Orange was a hazardous mixture and that it was still used. This allegation is based largely on a letter from an "Air Force scientist" (Dr James R. Clary) and is not true. The use of herbicides in Vietnam was based on a 20-year history of use in forestry and agriculture. Problems were recognized in industrial populations but not among agricultural workers and other users of the end products. The Admiral repeatedly makes allegations of collusion and fraud by government and nongovernment scientists. He clearly feels that anyone who disagrees with his position on this issue is unethical. These allegations are unfounded, unjustified and inappropriate in a document that purports to be scientific. Admiral Zumwalt clearly does not understand the basic facts of laboratory science. On page 29, he cites what he feels are serious flaws in the laboratory determination of dioxin. These variations are normal and expected in the laboratory and are understandable to anyone knowledgeable in the management of laboratory work. Again, the Admiral appears to use any excuse to denigrate results he disagrees with. Contrary to the Admiral's statements, most scientists feel that serum or adipose tissue dioxin levels are the "Gold Standard" of exposure. It is also becoming increasingly clear that in studies of short duration exposure to potentially toxic substances, the determination of actual body burdens of the chemical of interest is vital to the validity and success of the study. Without such measurements, a valid study is virtually impossible to accomplish.

4. The Admiral's comments on the Ranch Hand study are distorted and in error. His allegation (page 32) that ". . . there has been a systematic effort to suppress critical data or alter results" is unfounded. The data from the Ranch Hand studies were never altered and the conclusions were not "substantially" changed. Air Force scientists did modify the text of the report as it went through the editing process to improve the clarity of the report and consistency of the conclusions with the data. The authors did not want to either overinterpret or underin-

terpret the data. Allegations that there was ". . . perpetration of fraudulent conclusions" are wrong.

5. The Admiral alleges that there has been management interference in the science of the Ranch Hand study by Air Force and White House staff. These allegations are untrue. There has been no interference. The Air Force scientists have informed the Air Force and White House management staff of study progress and results just prior to public release, but those managers have not influenced the scientific direction of the study, the scientific data or the study results.

6. Admiral Zumwalt criticizes the Air Force for the use of a calculated index of exposure based on the number of gallons of herbicide sprayed and the number of men assigned to each type of job each month. This approach was in accord with procedures used in occupational epidemiology studies at the time the protocol was prepared. Those approaches are still used today in most epidemiologic studies of occupational exposures. Even though the Air Force exposure index does not accurately assess exposure for the individual veteran, it is more accurate than the exposure metric suggested by the Admiral and others for studies of ground troops. The method suggested cannot be applied below the level of the combat company, thus it has little relevance to the individual soldier and does not permit the determination of actual contact with herbicides or dioxin.

7. The Admiral selectivity cites the findings of the Air Force study results, mentioning the increased risk of overall cancer and skin cancer but failing to cite the nonsignificant risk of systemic cancer and failing to mention that the increased risk for overall cancer was due to the increase in skin cancer. He also cites an increase in birth defects. This increase was in "reported" defects and was based on a preliminary and incomplete analysis. Only 60% of the positive reports of birth defects and none of the births reported to be normal had been verified at the time the draft report was prepared. Fully verified data on all of the children fathered by the study participants have been obtained and the report on those data is nearing completion and should be available by Spring 1991.

8. The Admiral's conclusions are greatly overstated. There is an association between service in Vietnam and non-Hodgkin's lymphoma (NHL), but there is no evidence that this disease in veterans is related to Agent Orange exposure. Similarly, skin disorders were common in Vietnam and persist in many veterans, but there is little evidence that they are related to Agent Orange. Porphyria and chloracne are related to dioxin exposure in industrial populations, but there is little evidence that these diseases among veterans are related to their exposure to Agent Orange. The Admiral lists 31 diseases or groups of conditions he feels are caused by exposure to Agent Orange, but there is little scientific support for an Agent Orange causation for most of these. Most of the valid scientific data presented in this report concerns NHL which is already a compensible disease.

9. Summary: Admiral Zumwalt's opinions are obvious in this report, but he presents little valid evidence from studies of humans to support his allegations of a link between disease and Agent Orange. He repeatedly denigrates all studies that reach conclusions counter to his personal beliefs and makes personal attacks on the integrity of the scientists concurring those studies. At the same time he blindly accepts the results of studies that agree with his opinions. On balance, this report contributes little to the Agent Orange issue. The Admiral clearly has a personal stake in the Agent Orange issue and it is unreasonable to expect him to provide the neutral and unbiased approach necessary to evaluate the scientific material concerning the effects of Agent Orange on the health of Vietnam veterans.

MEMO FOR RECORD

AUGUST 8, 1990.

To: Vernon N. Houk, MD, Director, Center for Environmental Health and Injury Control, Centers for Disease Control 1600 Clifton Road, NE (F29) Atlanta, GA.

This material contains my comments on Adm. Zumwalt's document. I am sorry it is not on letterhead stationary, but I have been on leave and TDY for most of the past 3 weeks. I will express mail a clean copy of the letter on official stationery on Friday. I hope this material will be helpful in preparing your response to the committees.

I have also found some background material on Dr. Clary, the Air Force "scientist" cited by the Admiral. He was an active duty captain working at Eglin AFB from 1969 to 1971. Al Young knew him at that time and says he (Clary) knew little about the herbicides and knew nothing about dioxin until 1971 when Al told him about it. He went on an extended TDY to Vietnam in 1970, most likely as part of the team that closed out the spraying operations and moved the remaining herbicides to Johnston Island.

The unnamed reviewer mentioned by the Admiral is Dick Albanese. At least he confined his criticism to the VA hazards committee and left us pretty much untouched.

APPENDIX C

AUGUST 15, 1990

VERNON N. HOUK, M.D.,
Assistant Surgeon General, Director, Center for Environmental Health and Injury Control, Centers for Disease Control Atlanta, GA.

DEAR VERNON: I regret that I did not respond sooner to your request for a review of Admiral E.R. Zumwalt's "Report to the Secretary of the Department of Veterans Affairs on the Association Between Adverse Health Effects and Exposure to Agent Orange." The Agent Orange Task Force was asked to review this report by the Senate and House Veterans Affairs Committees.

The Zumwalt Report is designed to establish a link between a list of health outcomes and exposure to Agent Orange. The standard he uses to establish this link—"that it is least as likely as not that there is a statistical association"—is a legally based standard, not an epidemiological or toxicological standard. Several recent reviews in the biomedical literature are much more circumspect about the relationship between Agent Orange (specifically 2,3,7,8-TCDD) and human disease (Lilienfeld and Gallo, 1989; Johnson, 1990). Given the high quality of these reviews—in fact, Lilienfeld and Gallo is even cited in the Zumwalt Report—I do not see the need to respond to the allegations made in the Zumwalt piece.

Sincerely,

REFERENCES

Johnson, E. (1990) Association between soft tissue sarcomas, malignant lymphomas, and phenoxy herbicides/chlorophenols: evidence from occupational cohort studies. Fundamental and Applied Toxicology, 14, 219-234.

Lilienfeld, D. and Gallo, M. (1989) 2,4-D, 2,4,5-T, and 2,3,7,8-TCDD: an overview. Epidemiologic Reviews, 11, 28-58.

APPENDIX D

JULY 28, 1990.

Re review of the "Report to the Secretary of the Department of Veterans Affairs on the Association Between Adverse Health Effects and Exposure to Agent Orange" prepared by Admiral E.R. Zumwalt, Jr.

DR. VERNON HOUK,
Chairperson, AOTF Science Panel, Director, CEHIC, Centers for Disease Control (F-29), 1600 Clifton Road, N.E., Chamblee, Building 27, Atlanta, GA.

DEAR DR. HOUK: What has happened to "scientific" evaluation of the literature? Is it vogue to present only one side of the issue? This is the second document that the Science Panel has reviewed lately that does a very thorough job of presenting the case of potential harm to the Vietnam Veteran from dioxin and/or Agent Orange. Has anyone taken the time to pull together only the negative data so that we can have separate documents for both sides of this issue?

I'm at a loss as to even how to approach critiquing this document. Admiral Zumwalt's list of health hazards to dioxin exposure on page 3 was amazing, to say the least! This must comprise every health issue that has ever been even mentioned in a dioxin article. Did he leave out any type of cancer? Admiral Zumwalt also concluded on page 3 that ". . . the Veterans' Advisory Committee on Environmental Hazards has not acted with impartiality in its review and assessment of the scientific evidence . . ."; it would seem that Admiral Zumwalt could be accused of a similar failure to exercise impartiality!

Quite a few of Admiral Zumwalt's references to documenting the health hazard of dioxin are from the 1970s when the knowledge base was mainly animal data. There is little disagreement, if any, that dioxin is very toxic in our laboratory animals in a variety of ways; it was this toxicity that initiated the extensive research effort in the 1980s, both in animals and humans. However, the subsequent human epidemiological published reports have not proven, when taken in total, that dioxin is as potent to humans as would be implied by the animal toxicity. Perhaps, as pointed out by Admiral Zumwalt, just enough time has not elapsed since the Vietnam conflict for the dioxin health effect to be properly assessed; but this lack of time-lapse does not justify inclusion of every effect mentioned in the '70s.

Admiral Zumwalt stated on page 12 that ". . . it can fairly be said that the general attitude both within and outside the scientific community was, and continues to be increasing concern over the mounting evidence of a connection between certain cancer illnesses and exposure to dioxins."; I'm just the opposite! With all the money and effort that has been expended on dioxin research and the proven animal toxicity at fairly low levels, I am amazed that more substantial findings have not been linked with human health hazards.

Admiral Zumwalt stated on pages 19-20 that he asked several "impartial scientists" to review the Advisory Committee transcripts. I am not familiar with the credentials and impartiality of Drs. Day and Hartzman; however, Drs. Jeanne and Steven Stellman have proven that they are anything but impartial with this issue. In fact their 1988 articles in Environmental Research read very much like this document in their one sided approach to the literature.

Admiral Zumwalt recommends that the Vietnam Veteran be compensated for a variety of illnesses that he has concluded are connected with Agent Orange and their

Vietnam service. I have no problem with compensating the Vietnam Veteran for any illness. I have no problems with decisions based on political considerations as they are beyond my sphere of influence or expertise. However, I do have problems with justifying that compensation based on the scientific evidence for and against dioxin or Agent Orange as the weight of the data is presently just not there.

Just once before I got off of the Science Panel, I would like to see a scientifically sound and unbiased review of the dioxin literature that the scientific community, the Vietnam Veterans organizations, and the politicians would embrace. However, I know that I am just being optimistic!

Sincerely,

———.

AUGUST 7, 1990.

Dr. Vernon N. Houk,

Chairman, Science Panel, AOWG, Center for Environmental Health and Injury Control, Building 27, Room 1213, Centers for Disease Control, 4770 Buford Highway, Chamblee, GA.

DEAR DR. HOUK: I am responding to your request that the Science Panel members review the "Report to the Secretary of the Department of Veteran Affairs on the Association Between Adverse Health Effects and Exposure to Agent Orange," by Admiral E. R. Zumwalt, Jr., dated May 5, 1990.

I was saddened by reading the document. It is not an impartial assessment of scientific studies. The document makes numerous charges of misconduct and fraud, citing comments from various individuals as evidence for the charges. Although the document expresses the author's reasons for recommending compensation for Vietnam veterans, the reasons are not based upon a critical evaluation of scientific studies relevant to the questions of exposure and health effects.

I have previously reviewed many of the relevant studies ("Epidemiology of Populations Exposed to Dioxins", M. Fingerhut et al. in Solving Hazardous Waste Problems: Learning From Dioxins, A.C.S. Symposium Series 338, American Chemical Society, Washington, D.C., 1987). I have also commented many times on the studies as a member of the Science Panel. Consequently, I have no additional comments to offer on the scientific issues.

Sincerely yours,

———.

APPENDIX F

MEMORANDUM

Date: July 27, 1990.

Subject: The Zumwalt Report on Agent Orange.

To: Vernon Houk, M.D.

The best, most comprehensive review of the effects of dioxin on the human is the book by Michael Gough, *Dioxin, Agent Orange: The Facts* (Plenum Press, 1986). Dr. Gough was the Director of Special Projects at the Congressional Office of Technology and Assessment, and oversaw its report on dioxin by an expert panel of university-based experts. He knows the subject as well as, if not better than anyone. His book is dispassionately scientific and in marked contrast to the report by Admiral Zumwalt, which does not cite the book.

It is difficult for someone who has not been deeply involved in a scientific subject, especially a non-scientist, to separate real from spurious findings on dioxin.

For example, the report states a preference for estimates of exposures to Agent Orange based on difficult-to-confirm military locations in Vietnam, instead of an objective laboratory measurement. There is no way to confirm exposure indices except by laboratory tests. If there was no exposure, there can be no effect. Until proven otherwise, the serum levels show no exceptional exposure of ground troops in Vietnam. The same tests clearly show elevations in levels of dioxin in Ranch Hand personnel. The report attempts to discredit the blood test, but it is Christian's exposure indices that cannot be substantiated.

The question of birth defects among the children of Ranch Hand personnel: the report prefers subjective information from parents to objective reports from medical records. It is well known that medical histories are more fully reported when the respondents are concerned about a particular exposure than when they have not been exposed. The Air Force will soon complete its study of birth defects recorded in the medical records of the children of Ranch Hand personnel. Until then, no statement can be made about the reality of an effect.

Page 3 of the report lists 30 health problems said to be related to Agent Orange exposure. The report fails to consider that a poorly documented claim of an effect must be distinguished from one in which causality is supported by a dose-response effect, exclusion of other possible explanations, biological plausibility, and/or replication of the finding by other investigators. Were these standard criteria applied, the list would evaporate, except for chloracne, porphyria and a few findings which are equivocal and still under study.

APPENDIX G

AUGUST 4, 1990.

Dr. VERNON HOUK,

Chairman, Science Panel, Agent Orange Work Group, Centers for Disease Control, Atlanta, GA.

DEAR DR. HOUK: Attached is my review of "Report to the Secretary of the Department of Veteran Affairs on the Association Between Adverse Health Effects and Exposure to Agent Orange", as requested in your letter of July 24, 1990.

As you are no doubt aware, the paper in question is not a scientific document, per se; rather, it is a policy recommendation that is supported by a technical discussion of the issue. The document is more akin to a legal brief than to a scientific paper. Consequently, the document is not amenable to a standard scientific review in the traditional sense.

As an advocacy piece, the document does a good job in mounting an argument for a particular point of view. However, as is often the case in such advocacy pieces, the paper is not a balanced, objective treatment of the scientific literature on the toxic effects of Agent Orange and/or 2,3,7,8-TCDD. Only selected facts are presented and often in a one-sided way. Interpretations of motives of individuals are intermixed with interpretation of data from experiments. In many instances there are alternative, competing interpretations—for both the motives and the data—which should be also considered by decisionmakers.

Sincerely,

———.

APPENDIX H

Memorandum for: Dr. Vernon N. Houk, Director, Center for Environmental Health and Injury Control, Centers for Disease Control.

Subject: Review of "Report to the Secretary of the Department of Veterans Affairs on the Association between Adverse Health Effects and Exposure to Agent Orange", prepared by Admiral E.R. Zumwalt, Jr.

I reviewed the subject document in my capacity as a member of the Science Panel of the Agent Orange Task Force. The following comments are provided:

Admiral Zumwalt concluded that the work of the Veterans' Advisory Committee on Environmental Hazards is "not sensible" and "rather unsatisfactory", has "little or no scientific merit", and contains "faulty conclusions, flawed methodology, and noticeable bias"; the CDC study "design, implementation and conclusions were so ill conceived as to suggest that political pressures once again interfered with the kind of professional, unbiased review Congress had sought to obtain"; conclusions of the Air Force Health Study were "altered"; studies conducted by independent reviewers are characterized by the same "deception, fraud and political interference that has characterized government sponsored studies".

There is no evidence presented to support these accusations other than the opinions of the "experts" drawn upon by Admiral Zumwalt. The paper is not an impartial review of the literature.

APPENDIX I

A REVIEW OF "REPORT TO THE SECRETARY OF THE DEPARTMENT OF VETERAN AFFAIRS ON THE ASSOCIATION BETWEEN ADVERSE HEALTH EFFECTS AND EXPOSURE TO AGENT ORANGE"

GENERAL COMMENTS

1. The paper in question is not a scientific document, per se; rather, it is a policy recommendation that is supported by a technical discussion of the issue. The document is more akin to a legal brief than to a scientific paper. There are many references made to testimony presented in court proceedings or at Congressional hearings (often citing the words of the legislators, rather than the technical experts), and in correspondence with the author, that are hardly the type of peer-reviewed sources to which scientists are comfortable in ascribing unalloyed scientific credibility.

Consequently, the document is not amenable to a standard scientific review in the traditional sense.

2. The criterion of "as likely as not" is generally unfamiliar for scientific inquiry and, consequently, is open to considerable interpretation. In any event, any assessment should rest on an integrated assessment of all of the data that are available on a topic, not simply a single study.

3. The document presents a strong advocacy position. However, there are alternative views of the same—and more extensive—information which should be considered by decisionmakers.

4. While the toxicity data are not definitive, EPA continues to take steps to reduce the exposure to chlorinated dibenzo-p-dioxins (CDDs) to the extent feasible.

SPECIFIC COMMENTS

1. The author is undoubtedly a man of considerable talent, who has contributed greatly to our country. His particular credentials for undertaking this scientific assessment, however, are unclear.

It is commendable that he consulted other workers in the area. However, the credentials and backgrounds of some of those experts are similarly unclear; e.g.,

a. The Stellmans have certainly published on this subject, but most often from an advocacy position on behalf of some of the parties in this dispute.

b. The comments (allegations) of the unnamed fourth expert are difficult to assess in the absence of a legitimate analysis.

2. P. 3:

a. ". . . at least as likely as not . . ." is an unfamiliar criterion for judgment in the scientific realm. At a minimum it implies the need to assess the *entire weight of the evidence*, rather than any particular study.

b. The conclusion that ". . . the Veterans' Advisory Committee on Environmental Hazards has not acted with impartiality . . ." is a serious one. However, without access to more information on the Committee's deliberative process, it is not possible to assess the merit of this serious charge.

3. P. 5 and elsewhere: James Clary is quoted as a former government scientist from Eglin Air Force Base. His letters and statements are given prominence in this report, while the more complete, peer reviewed studies of the Eglin Air Force experience and Ranch Hand studies are given limited exposure. It such imbalances throughout the paper that limits its usefulness as a comprehensive, analytical document.

4. P. 6: The contention is made that, despite acknowledging that "the bulk of Agency Orange herbicides . . . were reportedly sprayed from 'Operation Ranch Hand' . . . aircraft" . . . (,) (a) significant, if not major, source of exposure for ground forces was from non-recorded, non-Ranch Hand operations." The only basis given for this allegation is the author's awareness the AO "was frequently used on unrecorded missions". As stated, this is slim support, indeed.

5. P. 7, footnote 10: The Huong studies have been the subject of considerable interest for some time. However, the studies are limited by access to the original data, diagnostic techniques, etc. As I understand it, there have been only limited contacts between Federal scientists and the Vietnam workers. Perhaps this situation will change in the future.

6. PP. 10-11, Footnote 18: As both IARC and EPA noted in their assessments of the literature, human exposures to 2,3,7,8-TCDD (and related CDDs) are almost always often confounded by concurrent exposures to several other chemicals which might be of toxicological concern. Therefore, human data have been judged to be inadequate for assessing the carcinogenic potential of 2,3,7,8-TCDD in humans.

7. P. 11: There is no mention of the objections which have been raised about the interpretation of Alsea data. A balanced treatment would discuss these points.

8. P. 12: As a long time participant in the CDD issue, it is not at all clear to me that ". . . the general attitude both within and outside the scientific community was, and continues to be increasing concern over the mounting evidence of a connection between certain cancer illnesses and exposure to dioxins". Compared to the public and scientific prominence given to the "dioxin" in the days of the 2,4,5-T hearings, the "Swedish studies", Love Canal, Times Beach, etc. around 1980, both scientific and public concerns have generally become more informed and studied.

In my experience the "certain cancer illnesses" most often mentioned in connection with CDD have been soft tissue sarcomas and non-Hodgkin's lymphoma. Therefore, it is difficult for me to understand the basis of the author's statement on p. 53 that ". . . with a very high degree of confidence . . ." the list should include lip cancer, bone cancer, and lung cancer, as well as skin cancer (which might derive from an interpretation of the Ranch Hand data).

8. P. 16, footnote 31: The cause-and-effect criterion is reached through a variety of considerations, including dose-response consistency, consistency between multiple studies, biological plausibility, and over all weight-of-the-evidence (i.e., including consideration of negative, as well as positive, studies.)

9. P. 21: The statement about "valid negative" studies is a good one that could be pursued.

10. P. 24: a. As someone who have served on the Science Panel for more than a decade, it would hardly for me to characterize the relationship between the agencies as being in "collaboration", in its most derogatory connotation. In the early '80s there was almost more combat, than collaboration, between some of them; e.g., VA vs. CDC and VA vs. EPA vs. CDC.

b. The VA's problem was not "footdragging" as much as it was a problem of developing a study design that would past muster in front of various review boards, such as the National Academy of Sciences and the Science Panel.

11. P. 25 and following: This discussion suggests that the author is confused about the hypothesis of the CDC validation study and the implications of its results. As I recall, the study was first conceived by a subcommittee of the Science Panel and somewhat thrust upon the CDC by the Panel and by the Office of Technology Assessment. The study was peer reviewed by a number of different professional groups. The bottom line is that the distribution of blood levels amongst those with a "high opportunity for exposure" is indistinguishable from the distribution found amongst those with a "low opportunity for exposure". Therefore, to proceed with the study as designed would most likely lead to the null hypothesis, perhaps for the reason suggested by the author (dilution of any exposed personnel with those who were not exposed highly exposure), perhaps for the reason that the "highly exposed" were not. The "dilution hypothesis", however, is called into the question by the similarities in the tails of the two distributions; i.e., those people with high blood levels.

In any event the results (and the exposure of individual analyses) argue for conducting a study amongst a cohort of more likely exposed personnel, each of whose levels can be directly assessed. This has been the rationale for studying the Ranch Hand cohort so closely. Future reports from this study should be particularly revealing.

In addition, the about-to-be-released NIOSH study should shed additional light on the matter. Here is a large cohort (more than 5000 people), the exposure index for which has been validated (to some degree) by individual blood leel analyses.

12. P. 29: a. The "assumption" by CDC of a half life of 7 years is supported by data from several labs around the world. While individual studies (including a self-administered study in Europe) have suggested a range of values (generally from 5 to 10 years, as I recall), the value of 7 years is generally agreed upon in the scientific community.

b. Footnote 34: This statement appears to point to further confused understanding of the CDC study. The whole point of the validation study was to investigate a possible correlation between blood levels and exposure (opportunity) scores. The study found none. This conclusion certainly raises questions about the premise for conducting the ground troops study, in addition to whatever questions it might raise about problems in the blood analysis. The latter problems were addressed in a variety of peer reviews and found to have been generally well-addressed.

13. PP. 31-32: The Selected Cancer Study was always conceived of as a "Vietnam experience" study, not an Agent Orange study. Where elevated cancers were found; e.g., the blue-water Navy, the authors simply investigated whether an Agent Orange hypothesis seemed plausible. In their judgment, which is shared by many peer reviewers, this seems highly unlikely.

14. P. 33: It is not clear why or on what basis the Ranch Hand Advisory Committee being denigrated here. The purpose of the Committee was to be a highly qualified, highly respected group of scientific experts who could provide advice and a rigorous peer review. It appears that this is what they did. The only question to ask—which is not raised here—is "What was the basis for changes they recommended?" I understand that this information is fully available in the proceedings of the committee.

15. P. 34: The critical paragraph and footnote 64 (and the earlier cited notes 10 and 18) provide only weak substantive support for the strong assertion that ". . . it is very likely that the CDC's negative findings on birth defects were also vastly understated."

16. P. 35: The whimsical reference to beer nuts vis a vis exposure to "dioxin" suggests further confusion by the author. The Ranch Hand cohort was selected becasue of an assumed, but plausible, high likelihood of exposure to "dioxin", not beer nuts. Anecdotal evidence, visual records, personal testimonies, and some published blood levels support this assumption. As noted above, blood samples from the entire, cohort are being analyzed.

17. P. 37: The author cites plantiff's brief as the source of the ". . . conclusive evidence that the studies . . . were fraudulent." This is another instance of strong statement with weak support. In our system of jurisprudence such advocacy sources are not expected to be scientific and objective. It is only an error when they are regarded as such; cf., this document.

As I understand it, the basis for these allegations is being investigated at a variety of levels. However, and more to the point, the same cohorts are being restudied on an independent basis in the NIOSH study. Therefore, the information from these cohorts is being reassessed as a part of an even more powerful study.

18. P. 38 and following: The EPA has judged the cancer epidemiology evidence for 2,3,7,8-TCDD to be "inadequate". This judgement stems, in part, from an inability to distinguish the effects of 2,3,7,8-TCDD from the effects of other chemicals which are a part of many exposure situations. This judgement is similar to that reached by IARC.

Of course, this judgment and all other scientific judgments are subject to additional, new information which may become available in the future; hence, our continued interest in the NIOSH study, subsequent Ranch Hand reports, etc.

19. P. 40: Dr. Teitelbaum alleges containants in 2,4-D which have not been revealed to EPA. It is not clear what contaminants are referred to here. The basis for his information about the content of 2,4-D and his information about what the EPA does not know is similary unclear.

EPA conducted an extensive exercise in the mid-1980s relative to the presence of 1,3,6,8- and 1,3,7,9-TCDD in certain formulations of 2,4-D. The Agency continues to pursue activity a variety of issues associated with 2,4-D.

20. P. 41: The interesting Breslin proportionate mortality study has been commented on in the past by members of the Science Panel.

21. P. 42: The pulp and paper industry is associated with many different chemicals, among them CDDs. The risks posed by the CDDs are more directed at consumers of fish downstream from the plant than they

are to workers in the plants. It is not clear what in-part exposures to workers would present high risks from the CDDs.

22. P. 43, footnote 84: The development of such a validated proxy for exposure was the goal behind the CDC validation study. For just the reasons cited here, the CDC study indicated the inadvisability of proceeding with the ground troops study.

It is unclear why the author cites the serum marker work of Kahn to the exclusion of the comparable, more extensive work of CDC.

Again, there seems to be some confusion with regard to the 10 year latency period. The exposures of interest in Vietnam took place around 1970. Studies on that cohort published in the last decade (1980–90) would have a latency of at least 10–20 years.

23. P. 44: The citation and quotation from a 10-year old anonymous memo detracts from whatever strength and quality exists elsewhere in the document.

24. P. 45: As noted above, EPA's judgment that 2,3,7,8-TCDD is classified (in the Agency's scheme) as a "probable human carcinogen" is based upon sufficient evidence of carcinogenicity in laboratory animals and inadequate evidence in humans. The IARC determination is made on a comparable basis.

25. Pp. 46–47: The advocacy position of the sponsors of the "scientific task force" is noted. The identity of the participants in the task force is not. It is also not clear whether—and to what extent—the work of the task force received the benefit of any scientific peer review and whether it has—or will—be published as a part of the technical, peer-reviewed literature.

26. P. 48: The emphasis on immunotoxicity late in the paper is curious. Certainly, this is an effect elicited by 2,3,7,8-TCDD and has been the subject of considerable study for the past 1 years or so. However, this discussion is neither a complete, balanced, nor adequate treatment of a complex subject.

It is even more curious that the only citation to support the "one-hit" model of immunotoxicity (for which the author acknowledges less than unanimous agreement in the scientific community) is a court document.

27. P. 50: The author's suggestion to use blood testing as a means of assessing prior exposure is consistent with a wide range of scientific opinion. Questions of cost, logistics, and "human testing" also need to be addressed.

28. P. 51: a. The propriety of and the choice between policy alternatives are basically risk management decisions which are beyond the mandate of the Science Panel. However, it should be noted that "20 kilometers/30 days" criterion far exceeds the criterion used in the Exposure Opportunity Index, which itself has been criticized as possibly including too many unexposed individuals.

b. The document provides little scientific basis for concern about male-transmitted reproductive problems associated with 2,3,7,8-TCDD of the type that are being recommended for compensation here.

APPENDIX J

MEMORANDUM

Date: August 13, 1990.

Subject: The Zumwalt Report, May 5, 1990—Remarks on CDC's Study: Vietnam Veterans' Risks for Fathering Babies with Birth Defects (Birth Defects Study).

To: Vernon N. Houk, M.D., Director, Center for Environmental Health and Injury Control, CDC (F29).

The purpose of this memorandum is to set the record straight regarding two comments made in the Zumwalt Report about CDC's Birth Defects Study.

1. The Zumwalt Report states (page 34) that ". . . the original CDC birth defects study . . . merely examined birth defects as reported on bith certificates, rather than as reported by the child's parent or physician." In fact, the source of cases for the Birth Defects Study was CDC's Metropolitan Atlanta birth defects registry which uses multiple sources (of which birth certificates ae only one) to ascertain babies born with birth defects. For a baby to be included in the registry, his/her defect must have been *diagnosed by a physician* and recorded in a hospital chart. Moreover, during the course of the Birth Defects Study interviews, parents were questioned about the presence of defects in their babies.

2. The Zumwalt Report states (page 34) that "The CDC never recorded hidden birth defects, such as internal organ malformations and other disabilities that only became apparent as the child developed." In fact, the CDC Birth Defects Study included all types of major structural and chromosomal defects, including many types that could be termed "hidden;" not included were babies with disabilities such as mental retardation without an accompanying structural or chromosomal defect. Examples of "hidden" defects included in the study are many types of cardiovascular defects, lung defects, intestional tract defects, and urinary tract defects. Babies are included in the Atlanta registry if their defects are diagnosed any time during the first year of life.

APPENDIX E

JULY 30, 1990.

DR. VERNON N. HOUK,

Director, Center for Environmental Health and Injury Control, Building 27, Room 1213, Centers for Disease Control, 4770 Burford Highway, Chamblee, GA.

DEAR DR. HOUK: I received the request to review "Report to the Secretary of the Department of Veterans Affairs on the Association between Adverse Health Effects and Exposure to Agent Orange" by Admiral Zumwalt on July 27, 1990. My comments follow below.

This report reads more like an editorial, not a report; and as such diminishes its usefulness. The extraordinary amount of emotion which has entered into this contentious debate over Agent Orange will ensure that the only solution to the situtation will be political and not scientific. Admiral Zumwalt has spent a great deal of time discussing studies which support his conclusions. Much less time was spent in presenting information on those which ran counter to his view, or how the conflicting findings could be resolved, or discounted.

The current state of knowledge regarding the adverse health effects associated with Agent Orange exposure will likely remain fiercely debated for some time to come and is unlikely to change in the near future. The Secretary (of Veterans Affairs) has the authority to make the determination on the issue of compensation now. Rather than to continue the debate, and spend millions of more dollars in evaluating the situation, the time for an equitable compromise may be the most prudent course.

The list of compensable health effects which were suggested by Zumwalt are broad, without qualifications, and ignore the significant (and known) contributions from other environmental, genetic, and personal risk factors for the development of these diseases or conditions. Any proposal (for compensation) will no doubt serve to be another focus for debate as individuals will argue over whom should be compensated and how much. On the other hand, the continuation of the debate will consume tremendous amounts of time, energy, and money, and yet may not allow us to come to any consensus agreement over this divisive issue.

Sincerely,

APPENDIX L

COMMENTS ON REPORT TO THE SECRETARY OF THE DEPARTMENT OF VETERANS AFFAIRS ON THE ASSOCIATION BETWEEN ADVERSE HEALTH EFFECTS AND EXPOSURE TO AGENT ORANGE

(By Adm. E.R. Zumwalt, Jr.)

It is difficult to evaluate Admiral Zumwalt's Report as a scientific review and critique of the "numerous data relevant to the statistical association between exposure to Agent Orange and the specific adverse health effects manifested by veterans who saw active duty in Vietnam." Although the Report superficially resembles a scientific review, it lacks the balanced presentation of data, objective evaluation of the relative merits of various research efforts, and careful documentation of any conclusions drawn from them, features which characterize medical and scientific reviews. The Report appears to be an attempt to validate foregone conclusions through acceptance of any evidence whether scientific data, personal letters, undocumented opinions or legal charges that support these conclusions. Well accepted research that does not support them is ignored or presented only to attempt to rebut it. The use of prejudicial words and phrases is generally avoided in scientific papers. The Report, however, uses them repeatedly.

The Report presents attacks on work that tends to refute the occurrence of detrimental effects of Agent Orange at three times the space devoted to support for adverse effects. An attempt to disprove the research results of the Centers for Disease Control (CDC) occupies more space than is given to all citations accepted as supporting the herbicide's toxic effects. Such a distribution of effort is unusual in reviews of science in any field.

The Report cites unverifiable references both for and against adverse effects. These include contested charges in a Congressional hearing (pages 24 to 32), an anonymous review (page 22), extracts from personal letters (pages 5, 20 to 22, 36, 40), "a selection of papers" not otherwise characterized (page 22), citations from a veterans' service organization (pages 27, 29), unsupported statements by a legislator (pages 24, 32, 34, 35), charges presented in a legal brief (page 37), newspaper articles (pages 47, 48), and other sources not generally accessible for critical review (pages 12, 23, 34, 39). The citations may be valid and the data and opinions accurate. It remains impossible, however, for a reviewer to arrive at an independent opinion about the sources.

When citations are complete, a reviewer can check the accuracy of data and of conclusions in the original references. Errors in information from references are present throughout the Report where they can be checked. For example, the VA's mortality study is said to indicate 'a 110 percent higher rate of non-Hodgkins lymphoma in Marines—.' The study, however, reported a proportional mortality study which can only determine a ratio and not a rate. The Report also says L.B. Hobson "claims that TCDD 'presents no threat from the exposures experienced by the veterans and the public at large' and virtually accuses scien-

tists who find that such health effects do exist to be nothing more than witch doctors". The text, used in 1985, was "Witch hunts have been stopped in individual episodes when tempers cooled, discontented groups found peace, and the excesses of belief in the attendant black magic were seen for what they are. This seems to be happening now with the TCDD episode, largely as scientific evidence mounts that the compound really presents no threats from the exposures experienced by veterans and the public at large." No-one was "virtually accused" of being a witch doctor.

Over the years, VA's evaluations of research on Agent Orange, dioxin, and related subjects have paralleled the opinions expressed by independent, non-federal medical and scientific organizations such as the American Medical Association, the Universities Associated for Research and Education in Pathology, and the National Council of Safety and Health. The Royal Commission on the Use and Effects of Chemical Agents on Australian Personnel in Vietnam conducted a wide-spread, two year review of the scientific issues and other aspects, of Agent Orange. Their conclusions agreed with the VA's evaluations. Independent reviews by the Office of Technology Assessment of the U.S. Congress have not disagreed with the VA's evaluations of research results. The critical evaluations of the VA Advisory Committee on Environmental Hazards likewise have not been criticized by scientific organizations.

The Report, however, criticizes the Advisory Committee's actions, particularly at its November 1989 meeting when it discussed non-Hodgkin's lymphoma in association with Vietnam service. The discussion resulted from the judgement in *Nehmer vs. U.S. Veterans Administration*, 712 F. Supp. 1404 (N.D. Cal. 1989). The court directed the VA, in effect, to standardize the procedure by which the Advisory Committee arrived at decisions as to a "significant statistical association" between herbicide exposure and adverse health effects. Such a standardized procedure is a new concept in arriving at scientific decisions in so large and complex an area. The Advisory Committee, acting in public, attempted to develop the required methodology.

As with any pioneering effort, it is easy to find critics of the process and product. This appears to be true of some individuals whose criticism is cited, in part from private letters which do not reflect knowledge of the problems facing the Advisory Committee (pages 20 to 22). No detail is given as to why the criticism should be accepted nor how future difficulties can be avoided.

The most difficult to disprove of the Report's charges is the supposed political pressure to alter research results. Scientific papers undergo critical review by one or more scientists prior to submission for publication. The Ranch Hand Advisory Committee is an independent group of scientists, not as Senator Daschle has said operating under the White House Agent Orange Working Group (page 32). It reviewed the Ranch Hand documents and recommended changes to Ranch Hand reports on scientific, not political, grounds. There has been no credible evidence that CDC studies were altered, either in execution or reporting, by political influence as charged in the *Oversight Review of CDC's Agent Orange Study: Hearing Before the Human Resources and Interpovernment Relations Subcommittee* on March 9, 1990.

The Report's conjectures about the immune system and immunotoxity cannot be sustained and no data are offered to do so (pages 47 to 50). Insofar as immunological effects of phenoxy herbicides or dioxins are used as basis for concluding that the chemicals produce health effects, that basis is weakened scientifically rather than strengthened.

Scientific support for the Report's sections on "Compensation" and "Recommendations" is almost entirely lacking. Non-scientists bringing other training and experience to a review may come to conclusions different from those of scientists. Admiral Zumwalt has prepared a Report from an unscientific background and presented his opinions to other ends.

APPENDIX M

MEMORANDUM

Date: August 21, 1990.

Subject: Review of "Report to the Secretary of the Department of Veterans Affairs on the Association Between Adverse Health Effects and Exposure to Agent Orange".

To: Chairman, Agent Orange Working Group Science Panel P-23.

I reviewed the report entitled "Report to the Secretary of the Department of Veterans Affairs on the Association Between Adverse Health Effects and Exposure to Agent Orange" by Admiral E.R. Zumwalt, Jr. The author describes this report as a review of the scientific, political, and legal aspects of the health impact of agent orange and dioxin upon personnel serving in Vietnam.

Although the author describes the report as a review of scientific literature, he expresses his review and summarization in a biased manner. This report is more a reflection of his expression of concern for veterans compensation—providing multiple allegations of governmental conspiracy to misrepresent the scientific investigation or interpretation of the toxicity of dioxin.

My review of the Zumwalt report did not include a review of all references disclosed in the report, and therefore, I cannot comment on the validity of his interpretation of these references. I would, however, concur that dioxin constitutes an important health concern for persons who have served in Vietnam. Unfortunately, no definitively exposed population has been defined for evaluation other than the Ranch Hand Cohort. Although no definitive evidence for a causal association between dioxin exposure in Vietnam and adverse health effects has been demonstrated (with the exception of the Ranch Hand Studies) some indirect evidence of concern is described in his report. I find his report to be more of an argument attempting to impact public policy.

VA ADVISORY COMMITTEE RECOMMENDATIONS

Mr. President, on November 3, 1989, VA's Advisory Committee made recommendations to the Secretary of Veterans Affairs concerning a possible association between NHL and exposure to agent orange. On May 17, 1990, the Advisory Committee made recommendations to the Secretary concerning STS.

As chairman of the Veterans' Affairs Committee, in letters dated July 6, 1990, I requested that OTA and the Domestic Policy Council's Agent Orange Task Force evaluate the analyses and conclusions concerning these recommendations to the Secretary.

Mr. President, I ask that the responses I have received thus far be printed in the RECORD at this point.

The material follows:

CONGRESS OF THE UNITED STATES,
OFFICE OF TECHNOLOGY ASSESSMENT,
Washington, DC, September 24, 1990.

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

DEAR ALAN: As you requested in your letter of July 6, we have reviewed the recommendations made by the VA Advisory Committee on Environmental Hazards to the Secretary of Veterans Affairs concerning possible associations of non-Hodgkins lymphoma (NHL) and soft tissue sarcoma (STS) with exposure to Agent Orange. The attached memorandum to me from Hellen Gelband, who carried out the review, summarizes our findings.

As you know, at a meeting in November 1989, the Advisory Committee found no "statistical association," as defined by regulation, of NHL with exposure to dioxin-containing herbicides. At a meeting in May 1990, the Committee did find a "statistical association" of STS with exposure. In contrast, OTA's review of the detailed minutes of the meetings, supported by our prior review of many of the relevant studies, does not reveal a substantial difference in the quality of the evidence for an association with NHL and with STS, or any specific pieces of information that would explain the Committee's differing decisions on NHL and STS. Of course, all of these judgments are, to some extent, subjective, since there is no specific procedure, particularly not a quantitative one, that can be used to weigh the evidence.

I hope this analysis is helpful. Please do not hesitate to contact me if I may be of further assistance, or have your staff contact Hellen Gelband in the OTA Health Program (at 8-6590).

Sincerely,

JOHN H. GIBBONS.

OTA HEALTH PROGRAM, STAFF MEMORANDUM
SEPTEMBER 18, 1990.

To: Jack Gibbons.

From: Hellen Gelband, Health Program.

Re: Review of VA Advisory Committee recommendations.

As you requested, I have reviewed the recommendations made by the VA Advisory Committee on Environmental Hazards to the Secretary of Veterans Affairs concerning possible assocations of non-Hodgkins lymphoma (NHL) and soft tissue sarcoma (STS) with exposure to Agent Orange. My review is based on reading the detailed minutes of the meetings at which the VA Advisory Committee formulated these recommendations, and my previous knowledge of the epidemiologic studies on which the recommendations are based.

THE NHL MEETINGS

NHL was discussed at the November 2-3, 1989 meeting. At the beginning of the meeting, the Committee was instructed on the regulation that was to govern their assessment of the scientific literature. Mr. White from the Veterans Benefits Administration's Compensation and Pension Service explained that the Committee was to determine whether a "significant statistical association" existed between exposure to a herbicide containing dioxin and a given medical condition. According to the regulation, a significant statistical association exists when the relative weight of valid positive and valid negative studies permits the conclusion that it is "at least as likely as not" that the purported relationship between a particular type of exposure and a specific adverse health effect exists. The regulation also discusses criteria for judging whether a study is "valid."

The issue of validity, having to do with basic study design, the ways in which data are collected, potential biases, etc., is familiar to all experts in evaluating medical evidence. The Committee handled this professionally and competently, discussing each study put before them. They also had no problems in determining which studies were relevant to the question at hand. However, there is no specific procedure for considering the results of many different studies together and arriving at a conclusion as to where the weight of the evidence lies. The task becomes even more difficult when the endpoint is whether the association is "at least as likely as not" to exist, a term that does not lend itself to an objective definition. Any determination is bound to be somewhat subjective. The Committee discussed the issue of methods of arriving at a decision several times during both meetings, and considered various alternatives to assist in coming up with a final judgment, but did not adopt any formal procedure.

At the NHL meeting, the Committee reviewed 30 individual papers of relevance to the NHL question, characterizing 4 as valid and positive for an association of NHL; 12 as valid and negative; 10 as valid and inconclusive (mainly due to small sample sizes and consequent low power); and 4 as not valid because of severe defects in methodology or execution. Several others were dismissed as not germane to the subject. After the review of individual papers and the tally, the Committee further discussed the types of exposure in the studies, and how they might be differentiated, e.g., giving less weight to studies in which there was only the *opportunity* for exposure, and more to studies in which exposure was documented. They also discussed the "inconclusive" studies further to see if, as a group, they were more informative than they were separately.

In the end, the Committee members stated their own conclusions about the existence of a "statistical association," as they understood it to be defined by the regulation. They concluded that, while they could not rule out such an association, the evidence they reviewed did not support a conclusion that such an association existed.

THE STS MEETING

The meeting to review studies relating to STS, held on May 16 and 17, was conducted similarly to the NHL meeting. Before the review of individual studies began, however, Admiral Zumwalt, attending his first meeting as a Committee member, made a statement criticizing the previous work of the Committee and praising the work of the "Agent Orange Scientific Task Force," a group supported by the American Legion, the Vietnam Veterans of America, and the National Veterans Legal Services Project. Once again, after discussion of the individual papers, the idea of formalizing the process for coming to a conclusion was discussed. Some strong sentiments were expressed in favor of exploring such a process, but in the end, that was not done.

The tally of studies was: 8 considered valid and positive; 10 considered valid and negative; 27 considered valid and inconclusive; and 5 considered not valid. There was considerable discussion concerning the fact that most of the positive evidence came from studies in Scandinavia, and that similar studies elsewhere showed no such association. Eventually, the members of the Committee were polled, and the consensus was that a "statistical association" existed.

Throughout the meeting, Admiral Zumwalt injected skepticism about studies done by researchers in industry and in the Federal Government. He cited testimony in court cases challenging some of the industrial studies, and claimed that the Federal Government exerted influence over the results of Government studies. This was contested by several members of the Committee. It is not clear to what extent Admiral Zumwalt's accusations influenced the deliberations of the Committee.

CONSISTENCY OF THE RECOMMENDATIONS

From reading the meeting minutes and from my knowledge of the studies discussed, I do not find a substantial difference in the quality of the evidence for an association with NHL and with STS. I cannot identify any specific pieces of information that would explain the Committee's differing decisions on NHL and STS, though the Scandinavian studies, which provide most of the positive findings, seemed to be influential. In my own subjective judgment, the evidence is quite similar, taking into account the levels of risk detected in the positive studies, the potential biases in the studies, the sources of exposure information, the types of exposure involved, and other factors.

The Committee has been given very difficult questions to answer. There may be no single right answer, because the standard of evidence required to decide that a "statistical association" exists as defined by the regulation, cannot be defined precisely.●

MESSAGES FROM THE HOUSE RECEIVED SUBSEQUENT TO SINE DIE ADJOURNMENT

ENROLLED BILLS AND JOINT RESOLUTIONS SIGNED

Under the authority of the order of the Senate of January 3, 1989, the Secretary of the Senate, on October 29, 1990, subsequent to the sine die adjournment of the Congress, received a message from the House of Representatives announcing that the Speaker has signed the following enrolled bills and joint resolutions:

H.R. 3791. An act for the relief of Buelah C. Shifflett;

H.R. 4090. An act to authorize the establishment of the Glorietta National Battlefield in the State of New Mexico, and for other purposes;

H.R. 4299. An act to authorize a study of the fishery resources of the Great Lakes, and for other purposes;

H.R. 5872. An act to amend title I of the Employee Retirement Income Security Act of 1974 to require qualifying employer securities to include interest in publicy traded partnerships;

S.J. Res. 375. Joint resolution to designate October 30, 1990, as "Refugee Day"; and

S.J. Res. 388. Joint resolution waiving cerain enrollment requirements with respect to S. 2830, the Food, Agriculture, Conservation and Trade Act of 1990.

Under the authority of the order of the Senate of January 3, 1989, the enrolled joint resolution (S.J. Res. 388) was signed on October 29, 1990, subsequent to the sine die adjournment of the Congress by the President pro tempore [Mr. BYRD].

Under the authority of the order of the Senate of January 3, 1989, the remaining enrolled bills and joint resolution were signed on October 31, 1990, subsequent to the sine die adjournment of the Congress by the President pro tempore [Mr. BYRD].

ENROLLED BILLS SIGNED

Under the authority of the order of the Senate of January 3, 1989, the Secretary of the Senate, on October 30, 1990, subsequent to the since die adjournment of the Congress, received a message from the House of Representatives announcing that the Speaker has singed the following enrolled bills:

H.R. 3911. An act to amend title 5 of the United States Code to increase the allowance for services of attendants;

H.R. 5004. An act to amend the Wild and Scenic Rivers Act to designate certain segments of the Mills River in the State of North Carolina for potential addition to the wild and scenic rivers system;

H.R. 5433. An act to direct the Secretary of Agriculture to release on behalf of the United States a condition in a deed conveying certain lands to the Conservation Commission of West Virginia, and for other purposes; and

H.R. 5933. An act to provide for the temporary extension of the certain laws relating to housing and community development.

Under the authority of the order of the Senate of January 3, 1989, the enrolled bills, except the bill H.R. 5933, were signed on October 31, 1990, subsequent to the sine die adjournment of the Congress, by the President pro tempore [Mr. BYRD.].

Under the authority of the order of the Senate of January 3, 1989, the enrolled bill, H.R. 5933 was signed on October 31, 1990, subsequent to the sine die adjournment of the Congress, by the Vice President.

Under the authority of the order of the Senate of January 3, 1990, the Secretary of the Senate, on November 1, 1990, subsequent to the sine die adjournment of the Senate, received a message from the House of Representatives announcing that the House has passed the bill (S. 2343) to amend the Wild and Scenic Rivers Act by designating a segment of the Clarks Fork River in the State of Wyoming as a component of the National Wild and Scenic Rivers System.

The message also announced that the House has passed the following bill, without amendment:

S. 3084. An act to provide for the settlement of water rights claims of the Fallon Paiute-Shoshone Indian Tribes, and for other purposes.

The message further announced that the House agrees to the amendment of the Senate to the amendment of the House to the amendment of the Senate to the bill (H.R. 4009) to authorize appropriations for fiscal year 1991 for the Federal Maritime Commission, and for other purposes.

The message also announced that the House agrees to the amendment of the Senate to the bill (H.R. 4793) to amend the Small Business Act and the Small Business Investment Act of 1958, and for other purposes.

The message further announced that the House agrees to the amendment of the Senate to the bill (H.R. 4008) to encourage solar, wind, waste and geothermal power production by removing the size limitation contained