



JUL 17 1990

Office of the Assistant Secretary
for Health
Washington DC 20201

The Honorable G.V. (Sonny) Montgomery
Chairman, Committee on Veterans' Affairs
House of Representatives
Washington, D.C. 20515

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 Alan Cranston, Senator Frank H. Murkowski, Congressman Bob Stump, Congressman Douglas Applegate, and Congressman Bob McEwen.

Sincerely yours,

James O. Mason
James O. Mason, M.D., Dr.P.H.
Assistant Secretary for Health

Enclosure

Memorandum

Date May 16, 1990

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."

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 include 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 hepatotoxic 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 inaccurate 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 review. 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 example 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 the erroneous estimate of the risk of cancer----" (see Attachment F).

REPRODUCTIVE EFFECTS

The conclusions of the AOSTF on the reproductive effects occurring 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 association 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 confirmation 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.

Attachments