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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Members of the Science Panel

SUBJECT: Suggested Procedures for Review of CDC Protocol

The Science Panel has requested the assistance of the Ranch Hand Oversight Committee in the review of CDC's protocols of epidemiologic studies of the health of Vietnam veterans. Based on conversations with Dr. John Moore, it was agreed that the Science Panel would supply the Ranch Hand Oversight Committee with a list of concerns that would focus the Committee's attention on those issues which the Science Panel feels are most urgent, with the assumption that the individual committee members would be free to make any additional recommendations that they feel are appropriate.

The attached "Outline of Concerns" were drafted with the cooperation of Major Bob Capell (USAF), Dr. Phil Kearney (USDA), Jason Toth (EPA), and myself (EPA) after a telephone conference last Thursday, June 23. In addition, Dr. Carl Keller and Jason Toth, attended the Office of Technology Assessment's review of the CDC protocols on Friday, June 24, and felt it desirable to include a discussion of some of the more generic aspects of the protocol. At the same time, we do not want to discourage reviewers from missing this opportunity to comment on more specific aspects of the protocol.

We believe that our objective today should be to reach a consensus among ourselves as to which general concerns are most appropriately addressed by the Oversight Committee and what the format for such a review should be. We recommend that individual Science Panel members use this same outline in structuring their review of the protocols.

Donald G. Barnes

Donald G. Barnes, Ph.D.
EPA Representative to
Agent Orange Work Group
Chairman, Subcommittee on
Protocol Review

Outline of General Concerns

I. Background and Review of the Literature

Although the CDC literature review is relatively current and appropriately takes advantage of previous published comprehensive literature reviews, there is relatively little discussion of the clinical experience of the presently on-going Veterans studies. Recent Congressional testimony by Dr. Custis of the V.A. stated that there have been over 350,000 Agent Orange related outpatient visits, over 100,000 physical examinations, approximately 20,000 veterans who have received more than one exam and about 9000 Agent Orange related hospital admissions (May 1983). Although the physical examinations of veterans conducted by the V.A. represent a self-selected group, they nevertheless may provide a valuable data base from which to refine and modify physical examination protocols as well as providing reviewers with a basis for evaluating the relative merits of individual studies.

1. Do reviewers feel that it would be desirable to include a more thorough discussion of all relevant on-going epidemiologic studies of veterans in the final protocol, especially the V.A. Agent Orange Registry examinations and any preliminary findings of the Ranch Hand study?

II. Exposure Index

Accurately classifying Vietnam veterans with respect to herbicide exposure is the single most important aspect of this investigation, and CDC appropriately described several reasons as to why these obstacles have been a "formidable impediment to the accurate assessment of health effects related to herbicide exposure" thus far. Nevertheless, CDC feels that the "Herbs" tape and other available records are sufficient to make a reasonable determination of a veteran's potential exposure to Agent Orange. It is not clear however, how the CDC intends to validate this exposure index.

1. Do the reviewers have any specific recommendations for validating the exposure index proposed by CDC (such as crosschecking the pilot study sample against yet another source of data or using a sensitive biological marker of exposure)?

   The second major concern with respect to classifying veterans by potential exposure status is to investigate the influence of all confounding exposures, particularly combat experiences and insecticide exposure.

2. Do reviewers have any recommendations for minimizing the influence of confounding exposures?

3. Do reviewers have any concerns or suggestions relating to the sampling procedures and potential selection bias posed by the proposed scheme for selecting study participants? For instance, what are the potential consequences of randomly choosing one day of the week and then selecting study participants from company records? Would it be desirable to estimate quantitatively the influence of misclassification bias in several hypothetical scenarios and then recalculate power estimates?

III. General Study Design

With respect to the rationale and general study design, the case-control study of soft tissue sarcoma, the retrospective cohort mortality study, and the Vietnam experience study all represent needed additions to the current investigations of Vietnam veterans and appear to be relatively straight forward. However, the assessment of morbidity outcomes among Agent Orange exposed veterans is not as straight-forward as the above studies.

The utilization of a one-time physical examination and health questionnaire as the major instrument for assessing health status has certain limitations, such as: (1) missing those individuals whose overt manifestations related to Agent Orange exposure 15 years ago may not have persisted until the time of examination; (2) secondly, missing those individuals who currently have no apparent physical manifestations of disease but may nevertheless have subclinical metabolic changes of medical significance which may not be adequately investigated during the exam; (3) and thirdly, some veterans may not yet have had sufficient time to develop signs and symptoms associated with Agent Orange exposure.

1. What is the cumulative influence of these considerations on the liklihood of detecting a true adverse health effect attributable to Agent Orange exposure? Would it be desirable to follow a subset of individuals for a longer period of time, with periodic examinations and updated questionnaires such as in the Ranch Hand study?

2. A consistent recommendation made by the National Research Council, the University of Texas and the Department of Defense Armed Forces Epidemiological Board in review of the Ranch Hand study was that the physical and neuropsychological examinations should be more refined by "evaluating a limited number of morbidity endpoints, each in greater details." Do reviewers feel that the clinical examination should be expanded further to include more sophisticated tests such as nerve conduction velocity or should the clinical examination remain broad scoped unless physical findings indicate more refined tests? Do reviewers have any other suggestions for improving the clinical examination protocol?

3. Do reviewers feel that it would be desirable for a more thorough discussion of the rationale for those tests whose purpose is not obvious, as well as a discussion of the criteria that will be used to evaluate the results of its pretests? Should the results of of the pretests be a major check point before proceeding with the rest of the investigation?

4. Do reviewers feel that the proposed timetable is overly optimistic?

5. What are the consequences on the power of study to detect potential adverse health outcomes if substantive modifications of the protocol are made during the course of the actual investigation?

6. Do reviewers feel that there needs to be a clearer delineation between the pilot study phase and the principal investigation?

IV. Specific Concerns

A. Sarcoma-Lymphoma Study

1. What is the effect of non-uniform histologic classification of soft tissue sarcoma, especially if non-SEER cancer registries are utilized?

2. Do reviewers have any suggestions for minimizing hypothesis testing problems posed by the simultaneous investigation of multiple cancer sites?

3. Are the power calculations of the ability to detect a statistically significant elevation of cancer risk based on appropriate data? For instance, does the protocol take into consideration the anticipated fraction of Vietnam veterans who were likely to have been exposed to herbicides between the years 1963-1969 and are now living within the boundaries of participating SEER registries?

4. Does the Committee have any recommendations concerning the selection of controls or minimizing recall bias among cases?

5. Could this study be conducted more efficiently and rapidly by closer collaboration with NCI and their investigations of soft tissue sarcoma? Alternatively, should all presently on-going case-control studies of soft tissue sarcoma utilize CDC's questionnaire for investigating Vietnam Agent Orange exposure?

6. What are the relative advantages and disadvantages of utilizing next-of-kin interviews of deceased cases, thereby offering the possibility of completing the study earlier than planned?

B. Vietnam Experience Study

1. Should this study be given more emphasis in view of its potential to investigate "many factors in addition to herbicide exposure which could have adversely affected those who served in Vietnam" as well as satisfying veterans' demands for an investigation of compensatable disabilities?

2. Do reviewers have any recommendations which could improve the ability of this study to investigate the morbidity of veterans who had combat experience but were not exposed to herbicides?

3. Do reviewers feel that there should be a discussion of how CDC's proposed Vietnam experience study relates to the "Vietnam Veterans Mortality Study" and the V.A. "Survey of Patient Treatment File for Vietnam Veteran In-Patient Care?" For instance, could the power of detecting conditions of low prevalence be improved by combining all three efforts?

C. Agent Orange Study

1. Do members of the Committee feel that the present on-going CDC investigation of birth defects, which is focused primarily on structural abnormalities, is sufficient to investigate all possible reproductive hazards? If not, would a more detailed questionnaire or spouse interview be sufficient to improve the investigation of reproductive hazards in the present study or would it be necessary to measure sperm count, morphology or sister chromatid exchanges to investigate adequately these endpoints?

2. Should there be a much more detailed discussion of the selection of tests for the neuro-psychologic examination? Would it be possible to describe a psychological syndrome or set of symptoms which have been reported most frequently by the V.A. examiners (and in the literature) and then investigate this "pattern" of symptoms more systematically?

3. Do the reviewers have any further recommendations that would improve the scientific validity of this study? For instance, does the Committee have any recommendations concerning the relative merits of CDC's efforts to balance misclassification bias against comparability of study participants?

4. Do the reviewers feel that the CDC is being realistic in their estimates of the number of physicals and specialist examinations that could be conducted by individual physicians? Is it absolutely necessary to examine all study participants at one or two centers, or could blood samples and test results be sent to a single laboratory for analysis, while at the same time examining many more veterans at multiple facilities? In order to minimize the inter-observer variation that multiple examining centers would present, would it be possible to develop strict clinical classification criteria or to document suspected cases of chloracne with photographs that could later be read by a panel of specialists?

5. Is there any way to include veterans who served multiple tours without compromising the comparability of the study participants or introducing too much selection bias?

V. Overall Objectives and Purpose of Investigation

It is clear that the major impetus for the current mandate by Congress (Public Law 96-151) to require the Veterans Administration to conduct an epidemiological investigation of U.S. veterans derives from the persistent and legitimate demands of veterans' organizations that the U.S. government investigate their claims for war related disability compensation. Although statements of purpose such as "to assess the possible health effects of exposure to herbicides and dioxin during the Vietnam experience" can certainly be understood to encompass the development of a data base from which such claims may be evaluated, the stated objectives of the CDC protocol do not reflect full cognizance of the potential problems of interpretation and litigation that are likely to follow a study of such complexity and controversy as this one. For instance, Representative Thomas A. Daschle has sponsored a special service-connected disability compensation bill which contains a sunset provision to retract the presumption of association for chloracne, porphyria cutanea tarda, and soft tissue sarcoma if data from the ground troops study does not confirm these associations. It would appear then that there are expectations, which although legitimate may be unreasonable, and it may be necessary to evaluate the objectives of the proposed studies within this context.

1. Do reviewers feel that the proposed studies, either individually or collectively, are sufficient to adequately resolve compensation issues? Are there potential modifications which could improve the ability of this study to resolve such issues?

2. With respect to the stated objectives, will the proposed studies contribute substantively to our understanding of the adverse health effects of 2,4,5-T and dioxin exposure among veterans?