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REPLY TO  
ATTN OF: EK

6 JUN 1980

SUBJECT: Response to the NAS Report Re: The Air Force Study of Personnel Exposed to Herbicide Orange

TO: USAFSAM/CC

1. The National Academy of Sciences (NAS) Panel report of 6 May 1980 on the USAF Herbicide Orange protocol has been reviewed with interest by our working group.

2. The central scientific point of the NAS review appears to be that the Air Force Ranch Hand cohort and matched controls are too small a study population to allow detection of selected adverse health effects (e.g., cancer, birth defects), assuming that any herbicide effect is low and that there is no clustering. We wholeheartedly share the NAS concern on suboptimal statistical power, as it is reflected quantitatively within the protocol. Since the protocol calls for the comprehensive study of all the exposed Ranch Hand population and a substantial control group, we note that the statistical power issue is due to the historical circumstance of exposure in Vietnam, i.e., there are no more Ranch Handers to study, nor are there appropriate alternative highly exposed Air Force populations to substitute or add. The problem of suboptimal power, therefore, is not related to the epidemiologic design, but to the vagaries of history.

3. The NAS Panel cited three helpful mechanisms by which statistical power might be improved, all of which merit comment.

The proposal to expand the Follow-up study phase unfortunately appears to stem from lack of protocol clarity and resulting misperceptions. The Air Force investigators have, from the beginning, proposed and briefed that the Follow-up phase will be conducted in five-year renewable blocks, subject to the advice of an outside scientific monitoring agency and approval of the USAF Surgeon General. The investigators have always assumed that at least two five-year renewal blocks past the initial Follow-up would be required to observe the cohort in the steepest slope of the mortality curve; thereby providing substantive age specific person-years of observation.

The NAS Panel's suggestion that the Marine population be integrated or added into the Ranch Hand study in order to gain numeric advantages is an appealing one. However, the Marine proposal presents some formidable issues: allocation of the Marines into "exposed, not exposed" categories will produce a dilutional result or a positive bias depending upon the method of allocation; the Marine group probably received an herbicide exposure three orders of magnitude less than the Ranch Hand cohort, and this would generate overall dilutional representations; and the significant differences in host factors further renders these groups noncommensurable. Thus, from a statistical power perspective considering exposure burdens, the Ranch Hand population constitutes the best military population, albeit of suboptimal size, from which to attempt health assessment. This is not to deny the potential wisdom of studying the Marine cohort; in fact, the Marines may best be studied independently

or as an adjunct to the Ranch Hand effort, or in collaboration with the current Australian study of their ground troops.

The NAS Panel recommendation to increase the study/control ratio from 1:5 to 1:25 is of indeterminate merit. The gain in progressing from a 1:1 study to a 1: infinity study is to halve the variance in the statistic under consideration. Eighty percent of that gain is already realized by the current 1:5 design. It is unclear whether the small fraction of additional power is worth a five-fold increase in expense, particularly if, as the Panel predicts, the endpoints of concern will be difficult to measure.

4. We concur with the NAS Panel that many health indices are contemplated for study. Exhaustive literature reviews, tabulations of current veteran complaints, and additives from previous peer reviews lead us to believe that these measurements are indicated and doable. Within an appropriate biostatistical framework, they are readily manageable. It would be remiss not to account for veterans' complaints and confirmed physical findings, particularly chloracne, the hallmark of dioxin exposure.

5. The USAF Medical Service has recognized the wide spectrum of credibility perceptions in this project since the outset. The investigators have been open and forthright in the science presentation and have solicited extensive peer reviews. Our purpose has been to design a comprehensive epidemiologic study that can identify adverse health effects, if present, within acknowledged limitations, and to provide a rapid data platform from which other less ideal collaborative or independent studies of military populations may be placed into proper cause-effect perspectives. It is difficult to reckon how the concrete science issues of exposure and finite population size can be altered by an outside contractor or financially independent investigator. We believe that ultimate credibility will be found in the scientific community when the effort is established in the literature; credibility with the American public will naturally follow. Our belief to "care for our own" remains intact and is relevant to the study setting. Nonetheless, the issue of how and when this study is to be conducted has been referred to the Inter-agency Work Group to Study the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants for additional review and consideration.

6. We are appreciative of the helpful minority report comments on the merits of the protocol. The spice of commentary from all scientists who have engaged in the Herbicide Orange arena provide ample testimony to the degree of difficulty in its science and to the degree of resulting societal concern. We acknowledge the entire Academy's participation in helping us.



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