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1. The review of the USAF Herbicide Orange protocol by the National Academy of Sciences panel has been studied with interest by our working group. A central scientific point of the <sup>NAS</sup> review appears to be <sup>the</sup> consideration that the Air Force cohort of 1200 exposed persons may be too small for detection of selected, epidemiologically significant, herbicide effects. We concur with this consideration. The USAF study is planned for five years with an option for renewal at the end of that period. Power calculations provided in the USAF protocol show that more than 1200 exposed persons must ~~be~~ <sup>be</sup> examined to detect a substantial herbicide effect on the incidence of a common cancer. Thus, even assuming that all 1200 exposed USAF personnel were followed to the point of death, a period well beyond the first 5 year check point, a significant herbicide orange cancer effect could be missed, unless the effect were very strong.

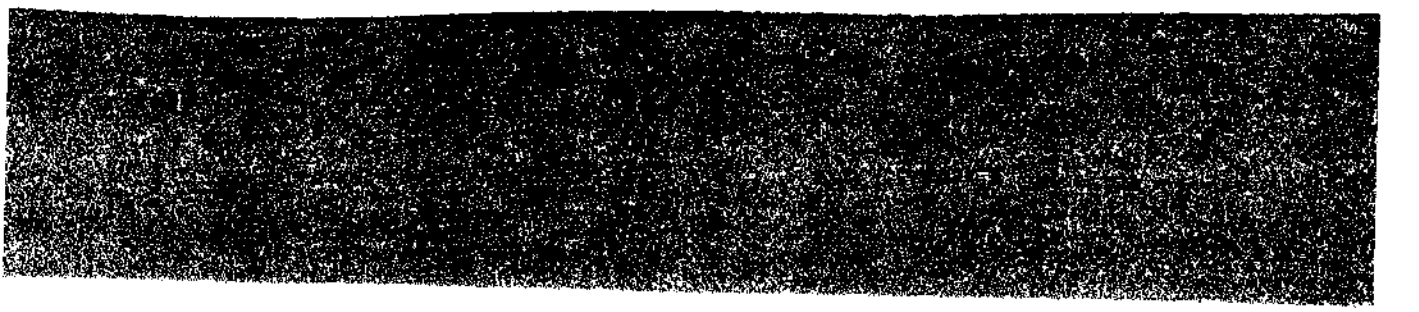
2. Outside the domain of neoplasia, the USAF protocol calculations show that the USAF proposed study may be very powerful in detection of a herbicide effect on cardiovascular disease, hypertension and other more common conditions. Further, the study is seen to be exquisitely sensitive in the detection of abnormalities in important clinical indicators such as the white blood cell count, blood pressure, nerve conduction velocity etc.

3. From the discussion above it is evident that a decision to implement a particular study is dependent upon a balancing of data requirements with proposed study capability, vis-a-vis other possible studies. In this context, the NAS suggestion to study a marine cohort is of great interest.

4. From the statistical study design standpoint it is not possible to combine the Ranch Hand and marine groups into a single consolidated epidemiological study since the exposure indices available for the groups are disjoint. Specifically, for the Ranch Hand flying personnel, a quantitative exposure index expressed as a total, time-integrated herbicide burden is calculated, while for the marines only a semi-quantitative positional measure of herbicide burden is available.

5. The NAS proposed marine study may be less powerful in the detection of herbicide orange effects than the USAF Ranch Hand study. This diminished capability results from the combined effects of (a) the lower herbicide burden imposed on the marines, and (b) the large variance in the marine positional exposure index. Remembering that relative risk falls precipitously with <sup>dose and with</sup> exposure misclassification due to exposure index variance, the large numbers of marines available may simply not be competitive with the Ranch Hand cohort.

6. The USAF protocol proposes a broad medical examination with in-depth review of reproductive, liver, nervous system and immune function. The large number of health indices examined reflects the broad spectrum of the veterans' medical complaints already reported to the Veterans Administration.



7. The NAS suggestion to employ 25000 C130 personnel as controls in the mortality phase of the Ranch Hand Study may not be appropriate. 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 this gain is already realized by going to a 1:5 design, and it is not clear that the remaining increase in power is truly worth the five-fold increase in expense.

8. In conclusion, <sup>detailed</sup> ~~brief~~ analysis of the NAS marine cohort suggestion would now appear necessary, providing a cost-benefit trade-off with the Ranch Hand effort. Our present opinion is that the Ranch Hand study is more powerful than the marine study and is of approximately equal cost. Performance of both studies along with further laboratory research would maximize the probability of understanding herbicide epidemiological effects.