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

SAM/CC

Herein the principal investigators of the Air Force Protocol: "Epidemiological Investigation of Health Effects in Air Force Personnel Followup Exposure to Herbicide Orange," respond to the National Academy of Sciences (NAS) Panel Critique of that protocol. The Air Force protocol was issued to the NAS panel members on ~~December~~ 28 November, 1979; formally reviewed on the panel for three hours on December 19, 1979; and the NAS Panel report and attending press release was issued to the Air Force and public on May 6, 1980. This response is organized into General, Specific, and Summary Comment Sections for ease of review.

General Comments:

Although the NAS Panel report, pg ii, cites that panel members. . . "were chosen for their special competences and with regard for appropriate balance," the absence of the panel biostastician seems to contravene this claim. It is axiomatic that the central issues of any epidemiologic study focus on the biostatistical considerations of experimental design and data capture, analysis, and interpretation. The lack of a biostastician on the NAS Panel, and resulting lack of substantive discussion on biostatistical concepts during the 19 December review, led to considerable undervaluement of a strength of the Air Force Protocol. Further, it is noted and can be verified, that during the 19 December formal review, the majority of panel questions dwelled upon aspects of the Mortality Phase of the study - a study phase

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acknowledged by the majority of previous peer panelists to be the least important aspect of the whole epidemiologic study. In addition, it is noted that Dr. IAN ~~Jan~~ T. Higgins, University of Michigan Medical Center, was not present at the 19 December Panel Review as cited, pg iii, in the NAS Panel Report.

In introduction of the NAS Panel Report, pg 1, it is asserted that the Air Force made "extensive modifications" of the scientific protocol following their previous peer reviews. This assertion is not founded upon fact. Each of the previous independent reviews, to be sure, helpfully contributed to the detailed scope of the comprehensive study but in terms of proportional adjustments, not in terms of major study element deletions or additions.

Within the NAS Panel description of the proposed study, pg 2, incorrect reference is made to the Air Force investigator's development of "three independent study goals." Clearly within the protocol, the study goals are hallmarked as interdependent. This basic misperception by the NAS Panel is perhaps responsible for the tenuous thrusts and conclusions found later in the report on pages 4, 6, 8, 10, 11, 12. To reiterate, the "goals" are interrelated, to wit: The primary issue (goal) is health; are there adverse health affects and if there are, can they be causely attributed to occupational exposure to Herbicide Orange? The cause for this health study is political (Politikos, Gr = citizen) in that thousands of people (veterans and scientists) are alleging and promulgating ~~Promagating~~ that attributable adverse health effects in fact exist.

The issue of compensation to veterans is a spinoff, ancillary consideration. Compensation is referenced within the Air Force protocol for two significant reasons: 1) Possible future compensation to exposed study subjects, but not to unexposed control subjects, constitutes an extremely powerful positive bias that must be acknowledged by profound scientific care (as may be found within the protocol), and 2) from a governmental perspective, if compensation to veterans is to be conditional upon scientific evidence, then the epidemiologic study design must be broad-based and comprehensive to incorporate the wide spectrum of veteran complaints, and must be conducted as quickly as reasonable to provide whatever scientific interpretations the data permit. Clearly, the United States Government and its Veterans Administration have prudently opted to await additional scientific evidence, from any reputable scientific groups worldwide, before awarding compensation. It is already within the statutory power of the Veterans Administration to award compensation to veterans today, and without one shread of scientific evidence from any epidemiologic study. Thus, the Government is not awarding instant compensation and apparently for two reasons: 1) The alleged health issue may be a substitute for the social issue of society's benign neglect of Vietnam veterans following an unpopular war, and, therefore, not reason for "Health Compensation," and 2) the award of health compensation without substantive scientific input may be precedent setting with respect to other equally troubling environmental exposure issues. It is obvious that data from any scientific study on herbicide health effects will be used by both proponents and opponents of the compensation issue.

The Air Force investigators have never tauted the protocol as "definitive" or solely capable of answering the Herbicide Orange health question, much less answering a compensation question that the Government can already decide without further study. The investigators have, however, in light of the Governement's apparent decision to withhold compensation, designed an epidemiologic study to be properly comprehensive and rapid in order to provide a data platform from which other collabrative or independent studies may be placed in proper cause-effect perspectives. 4) For these reasons, it must be clear that the Air Force cited study "goals" are inextricably intertwined - interdependent - and cannot be sorted out independently for cursory review.

Throughout the NAS Panel report, its introductory letter, and in the NAS press release, constant use is made of the phrase "as designed," which apparently is meant to connote the lack of a better or more appropriate design by the Air Force. It is reiterated that the circumstances of the study have been imposed by the history of events. The Air Force study can only be observational in nature and not experimental in design. There is no way to increase the number of exposed aircrews to coincide with academic perfection and to idealistic power concerns. The NAS Panel's notion (discussed in detail on pg. ________) to "integrate" other conceivably exposed groups as a solution to power problems, coupled with their complete misperception of the followup study phase, reveal a disturbing lack of appreciation of the complex vagaries attending a nonconcurrent

prospective study. Thus, in a scientific context, the NAS Panel phrase of "as designed" is bankrupt. And in light of the introduction of the NAS Panel press release of 6 May 1980, "Citing 'major weaknesses' in design. . .," it is clear that NAS has disturbingly misled the American public to the detriment of the issue itself.

Specific Comments:

Because of the detailed comments of the NAS Panel majority and minority on three broad critique areas, specific response will be made to commentary within each area as well as to the summary recommendations.

I. Statistical Power of the Study

A.	NAS Majority	NAS Minority	AF Response
	Little chance of detecting mortality effect within follow-up period (pg 5)	Nonconcur (Appendix pg 1,2)	Nonconcur

AF Commentary:

This majority comment presupposes that the mortality effect of the herbicide is low, if existent, in the age ranges of the study cohorts, a notion which is a question of the study; this concept receives cogent review by the minority. Both majority and minority comments, however, reflect misperception of the length of the followup cited within the protocol. It is clearly stated (Protocol pages _____) and thoroughly intended by the principal investigators that followup study phases be projected in five year renewable blocks, subject to the advice of an outside monitoring agency and to the appropriate review by the Air Force Surgeon General. Five year blocks were chosen because the Air Force attempts to project resource requirements five years in

advance of usage. Intuitively, a minimum of 2 five-year periods past the initial followup phase would be required to observe the study cohorts in a period of the highest death rate (mean age projected, 65). These facts were emphasized verbally to the NAS Panal during the review but were apparently discarded.

B.	NAS Majority	NAS Minority	AF Response
	Panel conceived that study with limited followup would be incorrectly interpreted (pg 5)	No Comment	Non concur

AF Commentary:

Since the followup phase is not limited to exactly five years as perceived, the issue is moot. Further, no reputable scientific group would allow such an elemental error either in the literature or lay press.

C.	NAS Majority	NAS Minority	AF Response
	Conduct additional power calculations at several Beta levels (pg 6)	No Comment	Concur

AF Commentary:

More detailed power calculations are in progress. It is noted that since study is observational and uses the maximum number of exposed study members, power calculations cannot be used to ideally adjust the number of exposed participants. Thus, the NAS majority statement, pg 5, "Since statistical power is crucial to the flexibility of the study. . ." is incorrect.

D.	NAS Majority	NAS Minority	AF Response
	(Find larger cohort) or follow study cohort for 20-30 years Post exposure (pg 6)	Concur (pg 3, Appendix)	Concur

AF Commentary:

Exposure to Herbicide Orange in the Ranch Hand Group occurred 10-18 years ago. At the completion of the first follow-up five year block, postexposure will range from 16-24 years. As previously stated herein, additional five-year periods of follow-up have been contemplated and incorporated within the protocol.

E.	NAS Majority	NAS Minority	AF Response
	Mortality analysis could not determine if AF personnel are at increased risk to cancer, etc (pgs 5, 6)	Nonconcur .(Appendix pg 2,4)	Nonconcur

AF Commentary:

The NAS majority conjectures that the herbicide effect, if it exists, is weak and therefore will not be detected with the current limited study population. The strength of the herbicide effect, if it exists, is, in fact, the subject of scientific inquiry. Further, the NAS majority notion ignores unusual career clustering that may be observed following environmental exposures, and considerabley undervalues the prospective collection of both morbid and mortality data. The Air Force protocol well describes the overall power boundaries of the study, a fact parodoxically receiving the panel's commendation

"for careful consideration" (pg 7). Concepts of "increased risk" to both common and rare health events must await conduct of the study in order to be placed in proper perspective. It will obviously be a responsibility of the investigators to cite power calculations, confidence limits, etc., for all key study observations so that every scientist may make his own interpretation of the data. To be sure, cases clinical endpoints will be difficult to ascertain unless case clustering or broad based relative risks emerge, but this is an irreceivable circumstance imposed by nature and not by the design of the study.

AF Commentary:

The investigators acknowledge that improvements in the fertility analysis are indicated and desirable. Questionnaire aspects on fertility and reproductive outcomes are being appropriately expanded.

H.	NAS Majority	NAS Minority	AF Response
	Integrate other exposed populations (Marines) into a coordinated study (pgs 6, 8, 9)	Nonconcur (pg 2, 4)	Nonconcur

AF Commentary:

The NAS majority, through persistent overconcern on statistical power, fell into the trap of proposing the "integration" or addition of other "exposed" individuals (Marines) to the Ranch Hand group as a simplistic solution to suboptimal study power. This problem, which was well acknowledged by the NAS minority, merits significant discussion from several perspectives in order to highlight this surprising and sophistic proposal.

The Marine data cited by the NAS Panel (pg 9) were probably extracted from the Government Accounting Office Report (GAO) #FPCD-80-23, 16 Nov 79, "U.S. Ground Troops in South Vietnam were in Areas Sprayed with Herbicide Orange." These data represent approximations of Marine strengths within distance and time parameters of Ranch Hand mission profiles (Herbs Tapes). Designation of exposure to Herbicide Orange for any given marine is highly tenuous for the following reasons:

GAO methodologies to obtain these data have not been verified.

1) The acknowledged geographic crudeness of the Herbs Tapes in citing C-123 mission parameters for a four minute aerial drop under combat circumstances, 2) the lack of knowledge of the location of any given Marine, while in combat, in relation to the C-123 spray path, 3) the environmental fate (absorption; photodegradation, proportion of spray reaching the ground, etc.) of the Herbicide components has been totally ignored in the concept of "exposure," and 4) the understandable ground troop confusion in "observing" the C-123 Ranch Hand aircraft versus the more frequent C-123 Malathion spraying aircraft. These considerations underscore the fact that either by objective independent allocation or by subjective (use of Marine histories) allocation, overwhelming misclassification will occur in the marine population with respect to "exposed, or not exposed categories." If objective allocation is used true misclassification will occur and will dilute any causal relationship if it exists. Alternatively, if subjective allocation is attempted, a strong positive bias will probably occur due to the compensation carrot. These concerns coupled with the stock reality of misclassification within marine control groups "outside" spray areas, suggest that profound pitfalls await any investigator of the Marine population. With objective allocation of the marines, "integration" of this misclassified group into the Ranch Hand population will dilute out any substantive causal relationship if it exists, and in essence, will fulfill the now incorrect prophesies of the NAS majority for low herbicide effect, study power, and credibility.

The NAS majority's fascination with larger numbers and theoretically higher study power in the marine population also raises the issue of "degree of exposure." It is clear that a minimum estimate of one order of magnitude difference exists between exposure of the Ranch Hand population (exposed massively, via skin and respiratory routes, on a twice daily basis) and the probabilistic rare event exposure of the marines. From a three dimensional perspective, degree or magnitude of exposure must play the key role in power considerations. Hence, from the exposure context, the Ranch Hand population provides the most powerful opportunity to ascertain health impacts if they exist and erases the numeric advantages of the marine population.

In short, because of potentially overwhelming misclassification of the marine population, the substantial differences in degree of exposure, and the significant differences in host factors between the populations, they are clearly noncommensurable. To combine or "integrate" the two populations into a ~~simple~~ single study, as proposed by the NAS majority, would constitute incorrect epidemiology.

OVERALL IMPRESSION IS THAT THIS DOCUMENT WILL NEVER LEAVE SAM. WHO WILL WRITE THE NAS REPORT? WE DON'T KNOW HOW TO PLAY POLITICS - THE TONE OF THIS RESPONSE WILL ~~BE~~ PROBABLY TOTALLY REMOVE THE Epidemiology Division from this program. I HOPE THIS IS A TOTAL CATHARSIS - WHEN DO WE GO TO WORK ON THIS RESPONSE?

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? COVER LETTER ? OF NECESSARY WE ARE PROBABLY THE ONLY ONES CONCERNED AT THIS TIME -

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General Comments:

TONE IS ABRASIVE

Although the NAS Panel report, pg ii, cites that panel members. . . "were chosen for their special competences and with regard for appropriate balance," the absence of the panel biostastician seems to contravene this claim. It is axiomatic that the central issues of any epidemiologic study focus on the biostatistical considerations of experimental design and data capture, analysis, and interpretation. The lack of a biostastician on the NAS Panel, and resulting lack of substantive discussion on biostatistical concepts during the 19 December review, led to considerable undervaluement undervaluation of ~~a~~ the strength of the Air Force Protocol. Further, it is noted and can be verified, that during the 19 December formal review, the majority of panel questions dwelled upon aspects of the Mortality Phase of the study - a study phase

STRENGTH

RESPONSE TO NAS

GENERAL:

MAJORITY	MINORITY	AF RESPONSE
1. GOALS INDEPENDENT	NO COMMENT	NONCONCUR
2. STUDY WEAKNESSES "AS DESIGNED"	NONCONCUR (AP, PGS 1, 4)	NONCONCUR
3. EXTENSIVE MODIFICATIONS IN PROTOCOL AS RESULT OF PEER REVIEW (PG 1)	NO COMMENT	NONCONCUR

RESPONSE TO NAS

MAJORITY	MINORITY	AF RESPONSE
4. LITTLE CHANCE OF DETECTING MORTALITY IN FOLLOW-UP PERIOD (PG 5)	NONCONCUR (AP. PG 1,2)	NONCONCUR

RESPONSE TO NAS

STATISTICAL POWER:

MAJORITY	MINORITY	AF RESPONSE
5. FOLLOW STUDY COHORT 20-30 YRS EXPOSURE (PG 6)	CONCUR (AP. PG 3)	CONCUR - IN PROTOCOL

RESPONSE TO NAS

STATISTICAL POWER:

MAJORITY	MINORITY	AF RESPONSE
6. STUDY WITH LIMITED FOLLOW-UP WOULD BE INCORRECTLY INTERPRETED (PG 5)	NONCONCUR (AP, PG 4)	NONCONCUR

RESPONSE TO NAS

MAJORITY	MINORITY	AF RESPONSE
7. DO MORE POWER CALCULATIONS AT SEVERAL LEVELS (PG 6)	NO COMMENT	CONCUR

RESPONSE TO NAS

STATISTICAL POWER:

MAJORITY	MINORITY	AF RESPONSE
8. MORTALITY STUDY CANNOT DETERMINE INCREASED RISK OF CANCER, ETC. (PGS 5, 6)	NONCONCUR (AP, PGS 2, 4)	NONCONCUR

RESPONSE TO NAS

STATISTICAL POWER:

	MAJORITY	MINORITY	AF RESPONSE
9.	DIFFICULT TO JUSTIFY COMPENSATION BASED ON STUDY RESULTS (PG 6)	NONCONCUR (AP. PG 4)	NONCONCUR

NAS RESPONSE

STATISTICAL POWER:

MAJORITY	MINORITY	AF RESPONSE
10. INADEQUATE PROVISION FOR ASSESSMENT OF REPRODUCTIVE OUTCOMES (PGS 9, 10)	CONCUR	PARTIALLY CONCUR

RESPONSE TO NAS

STATISTICAL POWER:

MAJORITY	MINORITY	AF RESPONSE
11. INTEGRATE (ADD) OTHER EXPOSED POPULATIONS (MARINES) INTO A COORDINATED STUDY (PGS 6, 8, 9, 12)	NONCONCUR (AP· PGS 2, 4)	NONCONCUR

RESPONSE TO NAS

STATISTICAL POWER:

MAJORITY	MINORITY	AF RESPONSE
12. IN MORTALITY STUDY INCREASE STUDY/CONTROL RATIO FROM 1:5 TO 1:25 (PG 12)	NONCONCUR (AP. PG 1)	NONCONCUR

RESPONSE TO NAS

STATISTICAL POWER:

	MAJORITY	MINORITY	AF RESPONSE
13.	NO COMMENT	LEVEL OF EXPOSURE IN MARINES RELATIVELY LIMITED IN EXTENT AND DURATION (AP, PGS 2, 4)	CONCUR

RESPONSE TO NAS

STATISTICAL POWER:

MAJORITY	MINORITY	AF RESPONSE
14. ESTABLISH BASELINE VALUES IN EXPOSED AND CONTROL GROUPS AND REPEAT IN 10 - 20 YEARS (PG 8)	NO COMMENT	NONCONCUR

RESPONSE TO NAS

HEALTH INDICES:

MAJORITY	MINORITY	AF RESPONSE
15. EVALUATION OF TOO MANY HEALTH INDICES, FOCUS TO 3-4 (PG 9)	NONCONCUR (AP. PG 3)	NONCONCUR

RESPONSE TO NAS

HEALTH INDICES:

MAJORITY	MINORITY	AF RESPONSE
16. DUBIOUS VALUE TO LOOK FOR PORPHYRIA OR CHLORACNE (PG 9)	NONCONCUR (AP. PG 3)	NONCONCUR

RESPONSE TO NAS

HEALTH INDICES:

MAJORITY		AF RESPONSE
17. EVALUATE SELECTIVE ENDPOINTS WITH MORE SENSITIVE TECHNIQUES (PG 10)	NO COMMENT	CANNOT COMMENT

RESPONSE TO NAS

CREDIBILITY:

MAJORITY	MINORITY	AF RESPONSE
18. ISSUES COULD BE RESOLVED IF STUDY CONTRACTED OUT (PG 11)	CONCUR (AP, PG 5)	NONCONCUR

RESPONSE TO NAS

CREDIBILITY:

MAJORITY	MINORITY	AF RESPONSE
19. STUDY AS DESIGNED HAS SO LOW A PROBABILITY OF DETECTING AN EFFECT, EVEN IF ONE EXISTS (PG 10)	NONCONCUR (AP. PG 1,2,4)	NONCONCUR

RESPONSE TO NAS

CREDIBILITY:

	MAJORITY	MINORITY	AF RESPONSE
20.	INAPPROPRIATE FOR USAF OR DOD PERSONNEL TO COLLECT THESE DATA THEMSELVES IF PROGRAM PART OF ATTEMPT TO PROVIDE SCIENTIFIC BASIS FOR AWARDING COMPENSATION TO VA CLAIMANTS (PG 11)	CONCUR? (AP. PG 5)	NONCONCUR

RESPONSE TO NAS

UNADDRESSED MINORITY COMMENTS:

MAJORITY	MINORITY	AF RESPONSE
21. NO COMMENT	MAJORITY REPORT MAY CAUSE LONG DELAY IN STUDY AND NOT RESULT IN ANY MAJOR IMPROVEMENT IN DESIGN OF THE STUDY (AP. PG 1,4)	CONCUR

RESPONSE TO NAS

UNADDRESSED MINORITY COMMENTS:

MAJORITY	MINORITY	AF RESPONSE
22. NO COMMENT	IF STUDY PRODUCES NO EVIDENCE OF SERIOUS DISEASE, EXPOSED INDIVIDUALS WOULD BE REASSURED (AP. PG 3)	CONCUR

RESPONSE TO NAS

UNADDRESSED MINORITY COMMENTS:

	MAJORITY	MINORITY	AF RESPONSE
23.	NO COMMENT	GROUP RESPONSIBLE FOR STUDY APPOINT AN ADVISORY COMMITTEE OF STATISTICIANS AND EPIDEMIOLOGISTS TO REVIEW DESIGN AND DATA ANALYSIS (AP. PG 5)	CONCUR - IN PROTOCOL

RESPONSE TO NAS

MAJORITY CONCLUSIONS AND RECOMMENDATIONS:

PGS 11-12

MAJORITY	MINORITY	AF RESPONSE
1. STUDY SHOUD BE REDESIGNED TO INCLUDE CONSIDERABLY LONGER FOLLOW-UP	CONCUR	CONCUR - IN PROTOCOL

RESPONSE TO NAS

MAJORITY CONCLUSIONS AND RECOMMENDATIONS:

PGS 11-12

	MINORITY	MAJORITY	AF RESPONSE
2.	IF STUDY REDESIGNED EVALUATE A LIMITED NUMBER OF MORBIDITY ENDPOINTS, EACH IN GREATER DETAIL	NONCONCUR	NONCONCUR

RESPONSE TO NAS

MAJORITY CONCLUSIONS AND RECOMMENDATIONS :

PGS 11-12

	MAJORITY	MINORITY	AF RESPONSE
3.	ANY REVISIONS OF STUDY SHOULD BE SUBJECTED TO OUTSIDE PEER REVIEW	CONCUR	CONCUR

RESPONSE TO NAS

MAJORITY CONSLUSIONS AND RECOMMENDATIONS:

PGS 11-12

	MAJORITY	MINORITY	AF RESPONSE
4	EXAMINE CREDIBILITY ISSUE IN VIEW OF PUBLIC PERCEPTION AND STATED STUDY GOALS	CONCUR	NONCONCUR
4A	CONSIDER ADDING LARGER COHORTS (MARINES) OF EXPOSED AND UNEXPOSED TO THE RANCH HAND PROJECT	NONCONCUR	NONCONCUR