D E P A R T M E N T O F T H E A I R F O R C E

UNITED STATES SENATE

SUBJECT: Agent Orange

STATEMENT OF: MAJOR GENERAL ALEXANDER M. SLOAN
Deputy Surgeon General
United States Air Force

12 May 1988

NOT FOR PUBLICATION UNTIL RELEASED
BY THE COMMITTEE ON VETERANS' AFFAIRS
UNITED STATES SENATE

Major General (Dr.) Alexander M. Sloan is deputy surgeon general, Headquarters U.S. Air Force, Washington, D.C.

General Sloan was born Jan. 29, 1934, in Clarksburg, W.Va., where he graduated from Washington Irving High School in 1951. He graduated from the University of Maryland with a bachelor of science degree in 1955. The general attended West Virginia Medical School from 1955 to 1957, transferring to the University of Pennsylvania Medical School where he earned a doctor of medicine degree in 1959.

After serving a rotating internship at the Philadelphia General Hospital from July 1959 to July 1960, General Sloan entered the U.S. Air Force. He attended the primary course in aerospace medicine in September 1960 and was assigned as a flight surgeon at Kelly Air Force Base, Texas. In July 1963 he returned to the University of Pennsylvania for an Air Force Institute of Technology-sponsored Internal Medicine Residency and Neophrology Fellowship.

In July 1966 General Sloan was assigned to the U.S.. Air Force Hospital at Tachikawa Air Base, Japan. He served initially as chief of the Medicine Division and chief of the Dialysis Unit. In June 1968 he was named director of hospital services and deputy commander.

General Sloan returned to the United States in July 1969 and served as chief of renal service at Malcolm Grow USAF Medical Center, Andrews Air Force Base, Md. While there he became chief of internal medicine services in 1970 and chairman of the department of medicine in 1972.

In July 1976 the general transferred to the Air Force hospital at Keesler Air Force Base, Miss., as director of hospital services and deputy commander. From 1978 to 1980, he commanded the hospital at Keesler with the additional duty of director of base medical services. In May 1980 he was assigned as deputy director for medical plans and resources, Office of the Surgeon General, and became director in June 1981. He assumed his present duties in August 1985.

The general is a fellow of the American College of Physicians. He is a member of the American Society of Nephrology, International Society of Nephrology, national Kidney Foundation, American Academy of medical Directors, Aerospace Medical Association, Association of Military Surgeons of the United States, Air Force Association, Federal Health Care Executives Institute Alumni Association and the Society of Medical Consultants to the Armed Forces. He is a past treasurer, member of the board of governors and president of the Society of Air Force Physicians. In June 1968 he was certified by the American Board of Internal Medicine, recertified in October 1980 and in October 1974 General Sloan was certified by the American Board of Internal Medicine in his subspecialty of nephrology. He is a consultant to the Air Force surgeon general in his subspecialty of nephrology and is licensed to practice medicine in the state of Pennsylvania.

General Sloan is a chief flight surgeon. His military decorations and awards include the Legion of Merit, Meritorious Service Medical with one oak leaf cluster, Air Force Commendation Medal with one oak leaf cluster, National Defense Service Medal and Vietnam Service Medal.

He was promoted to major general Dec. 1, 1985, with date of rank Dec. 1, 1982.

General Sloan is married to the former Carol Ann Berger of Newark, N.J. They have three daughters: Barbara, Amy and Deborah.

Thank you for the opportunity to present an update on the progress of the Air Force Health Study of personnel exposed to herbicides in Southeast Asia.

In 1978, the United States Air Force responded to Congressional and veteran's interest in the Agent Orange issue and began work on an epidemiologic study of the possible health effects of exposure to herbicides and their 2,3,7,8-tetrachlorodibenzo-p-dioxin (referred to dioxin or TCDD) contaminants. Our study focused on Air Force veterans who served in the Ranch Hand defoliation operation during the Vietnam conflict.

In the interest of addressing the concerns of veterans, the Air Force Health Study (AFHS) was based on a scientific approach to the Agent Orange issue. The Air Force developed a protocol for a study including all 1267 members of the Ranch Hand unit serving from 1962 to 1971 and a group of matched comparisons. The comparison group was selected from the population of Air Force veterans who served in C-130 aircraft units stationed in Southeast Asia during the same time period. They were matched to the Ranch Hand group by age, race and job (pilot or copilot officer, officer navigator, non-flying officer, flying enlisted and ground enlisted). It was assumed that the comparisons were not exposed to herbicides or dioxin in Southeast Asia.

The protocol was subjected to extensive review by scientific peer groups including the University of Texas School of Public Health, the Air Force Scientific Advisory Board, the Armed Force Epidemiologic Board, the National Academy of Science and the Science Panel of the Agent Orange Working Group.

The protocol was approved in February 1981 and the first questionnaires were administered in October of that year. The baseline physical examinations were begun in January 1982 by a civilian contractor. Since that time, we have published four mortality reports and two morbidity reports. The study is a planned 20 year research effort.

What is the probability of this study to detect group differences? Power is the probability of detecting a group difference, usually expressed as a relative risk or a shift in mean values. This study has good power to detect relative risks of two or three when the disease rate in the comparison population is 5% or more. Similarly, the study has good power to detect a mean shift of 5% or more. For rarer diseases, our power is decreased. The power should improve with the passage of time since the basic disease rates should increase as the group ages.

A comprehensive clinical evaluation will be performed throughout the study with examinations by internal medicine, neurology and dermatology specialists. Psychological and

laboratory testing will also be included. Participation in the study has been excellent with 87% of the invited Ranch Hands and 75% of the invited comparisons taking part in the initial evaluation; 93% of those who participated in the initial study have returned for the follow-up evaluations.

The Morbidity Report published in October 1987 found that there were some differences in subjective measures of general health in the enlisted ground personnel, but these findings were not confirmed by more objective measurements. On balance, the assessment of general health did not reveal any reason for concern in this clinical area.

No significant differences between the Ranch Hand and the comparison groups were seen in the 1987 report for skin or systemic cancers. However, when overall lifetime basal cell carcinoma rates were adjusted for risk factors involved in the cause of such cancers (e.g. geographic area of residence, skin color, skin reaction to sun) Ranch Hands had a statistically significant higher number of basal cell carcinomas than the comparisons. This type of skin cancer is the most common neoplasm in the white population in the United States, is not prone to distant spread and is usually rapidly cured with simple treatment. These cancers were found in sun exposed areas of the body.

There were no unadjusted group differences for systemic lifetime cancer in the 1987 report. However, when occupation was considered, there was a significant increase among the Ranch Hand enlisted flyers for systemic cancer. These results may be unstable since they are based on only 5 cases of cancer and even one or two additional cases would alter these findings, which do not correlate with our estimated exposure index. These men are not in the group that we think had the heaviest exposure to the herbicides in Southeast Asia. A better understanding of the relevance of this observation must await the results of the serum dioxin testing.

During the interval between the two evaluations, a single case of soft tissue sarcoma and one case of non-Hodgkins lymphoma occurred in the Ranch Hand group. Earlier similar cases were found in the comparison group. This makes the incidence of these two conditions equal in both groups.

The neurologic assessment of cranial nerve function, peripheral nerve function and central nervous system coordination, did not reveal any consistently significant group differences in the 1987 report, although abnormalities tended to aggregate in the Ranch Hands. The Babinski reflex (found adverse in the Ranch Hands at the 1982 Baseline examination) was equal in both groups at follow-up. Age, alcohol and diabetes showed classical effects with many neurological measures.

Extensive psychological testing was conducted. In general, while statistically significant differences in some portions of the testing were seen, they were quite variable in nature and their clinical relevance is unknown. Post traumatic stress disorder was evaluated and only 1% in either group had this condition. There were no group differences for current or past neuroses or psychoses. Age, educational level, and alcohol history showed strong and expected effects on the psychological measures.

Both the interval and lifetime history of liver disease were equal in both groups, as was a lifetime history of peptic ulcer disease in the 1987 report. Of the 11 laboratory tests performed to evaluate liver function, only two showed significant differences in the average values in the Ranch Hand and Comparison groups. However, the number of men who had abnormally high levels was not different in the two groups. The uroporphyrin test, which is the best indicator of porphyria cutanea tarda, was normal in the Ranch Hands. The comparisons had significantly higher levels of uroporphyrin, but this is considered to be of no clinical relevance.

In the 1987 dermatological assessment, not one case of chloracne was diagnosed on examination, nor was historical acne anatomically distributed in a pattern that suggested past chloracne in the Ranch Hand group. Exposure and comparison with the results of the 1984 report were also unremarkable.

The 1987 cardiovascular evaluation showed that when heart disease of all types was considered, the frequency of disease reached statistical significance. However, there were no group differences for hypertension or heart attacks, the types of heart disease we worry about the most. Other assessments of cardiac function by blood pressure measurements and electrocardiogram did not reveal any meaningful group differences.

Evaluation of peripheral pulses by the more accurate Doppler technique revealed group equivalence in marked contrast to the Baseline examination, which found significant pulse deficits in the Ranch Hands by manual measurement. As well, the effect of tobacco was controlled by restricting smoking for four hours prior to the measurement of the pulses. Overall, the groups were remarkably similar in cardiovascular health.

The 1987 assessment of eight hematological measures showed no significant group differences. In fact, the groups were more similar at the follow-up examination than at the Baseline examination. Age, race, and smoking were significant risk factors for most hematological measures.

The groups did not differ significantly in reported kidney disease, in the 1987 report, although the Baseline questionnaire noted such in the Ranch Hands. Five laboratory measures of renal

function were similar between groups in the unadjusted analyses. No pattern of results suggested a detriment to either group in the adjusted analyses.

For endocrine function, TSH and testosterone means were significantly higher in the Ranch Hands, in the 1987 report, but these results were within the normal range. Impaired glucose tolerance tests revealed an excess in the comparison group. Examination results for past thyroid disease, thyroid and testicular abnormalities, and additional tests for cortisol level and T3 % uptake were similar in both groups. Age, race, occupation, percent body fat, and personality type were taken into account as pertinent variables. Overall, the endocrine health status was comparable in both groups.

Comprehensive immunological tests, composed of six cell surface marker studies and three functional stimulation studies showed no significant group differences in the unadjusted analyses. Age, smoking, and alcohol usage were accounted for in the analysis. The assessment of delayed hypersensitivity by skin testing was declared invalid because of excessive reader variation and shifting diagnostic criteria.

The pulmonary assessment, in the 1987 report, consisting of past history, physical examination, and x-ray results did not indicate any consistently different disease patterns in the two

groups. Age and lifetime smoking history were important risk factors for most pulmonary measures.

The exposure index analyses, which were stratified by occupation, revealed sporadic differences between exposure levels; however, there were no consistent dose-response relationships that supported an herbicide effect for any clinical area.

Comparisons between the 1984 study and the 1987 findings were conducted for 19 variables, and 5 showed significant differences in the changes of the groups between the Baseline and follow-up examinations. Of these 5 variables, one (sedimentation rate) was believed to be related to a change in laboratory methods, and the other four (Babinski reflex, depression, platelet count, and manual all pulse index) were attributed to true changes over time for the groups. In comparing all results between the examinations as well as the formal longitudinal analyses, we see a subtle, but consistent decrease in group differences over the three year period.

In summary, the 1987 morbidity report concludes that there is insufficient evidence to support a cause and effect relationship between herbicide exposure and adverse health in the Ranch Hand group at this time. The study has revealed a number of minor medical findings that require continued surveillance. In full context, the results of this study are encouraging evidence that, at this time, the current state of health of the Ranch Hand

participants appears unrelated to herbicide exposure in Southeast Asia. However, we still cannot exonerate the herbicide at this time.

In addition to the morbidity analyses, periodic evaluations of the death (mortality) experience of the Ranch Hand and comparison groups have been conducted and reported. Analyses have been directed at total and cause-specific death rates with adjustment for year of birth, race, rank and occupation. All reports have contrasted survival of all known Ranch Hands who had not died in combat while in Vietnam, 1257, with 6171 matched comparisons. As of December 31, 1984, the overall mortality of the Ranch Hand group (4.4%) was nearly identical to that of the comparison group (4.6%). Ranch Hand officers have experienced fewer deaths than comparison officers while more Ranch Hand enlisted personnel have died than their matched comparison, but none of these differences are significant. As of December 31, 1985, the overall Ranch Hand and comparison mortality were 4.7% and 5.1% respectively. Due to the small number of deaths that occurred during 1985, an abbreviated mortality report was published in 1986. The 1988 mortality update is currently underway and is expected to be published this summer. This analysis will include the death experience of 20,000 men (all of the Ranch Hands and all men assigned to C-130 aircraft units in Southeast Asia between 1962 and 1971.)

Recently a follow-up evaluation of the 1984 baseline morbidity report (United States Air Force Personnel and Exposure to Herbicide Orange by Richard Albanese, M.D.) evaluates the relationship between the findings of the 1984 study and a literature review of the toxicology of dioxin. The results of subsequent follow-up clinical examinations, released in October 1987, were not included in this reevaluation. Variables from 11 clinical areas were selectively evaluated in the report: weight loss, malignant disease, birth defects, neurological disease, psychological problems, liver diseases, the presence of chloracne, heart disease, immunological function, endocrine status and death. The review highlighted six clinical areas warranting more in-depth evaluation in the future. Although this report used another approach to analyzing the 1984 data, the conclusions were essentially the same as in previous reports. We can neither definitely establish nor refute a link between dioxin and disease.

There has been much controversy concerning the relationship between herbicide exposure and birth defects in children. Initial evaluation of fertility and reproductive systems found there was a significant disparity between groups for reported birth defects. We incorrectly concluded that group differences were confined to minor skin conditions. The baseline findings of overall group differences in reported birth defects is being reinvestigated with full medical record verification of the birth defects reported on all children fathered by study participants. Over 6,000 medical records are under review. We expect to complete this analysis next summer.

Exposure Index

The initial study protocol developed an estimated exposure index that reflects the best calculation of the effective number of gallons of herbicide to which the airmen was exposed. It is based on an estimate of gallons of herbicide sprayed per month (1962-1971), the levels of dioxin contamination and the number of men assigned each month.

Individual exposure measurements could not be made. While the method used to establish the exposure index was state-of-the-art, several assumptions concerning individual work habits and circumstances had to be made.

In mid 1986, strong evidence was demonstrated by the Centers for Disease Control (CDC) and other institutions that dioxin levels could be measured in blood as well as fat tissue. The CDC demonstrated that blood levels and fat tissue appear to be equivalent. The Air Force recently concluded a collaborative study with the CDC to validate the study and estimate the half-life of dioxin in humans. This pilot study of 200 serum samples confirms clear and meaningful dioxin exposure did occur in the Ranch Hand group. The range of dioxin exposure in the Ranch Hand group (3-314 parts per trillion) is significantly higher than the control group (3-21.3 parts per trillion). A part per trillion is equivalent to one second in 32,000 years.

The distribution of dioxin levels for Ranch Hands confirms our belief that many members of this group had significant exposure to dioxin as compared to the general U.S. population and our comparison group. The serum dioxin measurement will quantify actual dioxin body burden and provides an individual exposure assessment.

The ability to improve the estimated exposure index with the serum dioxin test is a major opportunity in the scientific evaluation of the Agent Orange issue. This new serum dioxin assay will provide an accurate measure of the current body burden of dioxin. It should also be possible to estimate the half-life of dioxin in humans. Initial calculations indicate that the dioxin half-life in humans is approximately 7 years. Serum has been collected and stored from 2,010 study participants.

Within the next two years another morbidity report on the 1987 examination results, mortality reports and an expanded birth defects analysis will be completed.

We have analyzed the results of the first 5 years of our 20 year research study looking at the herbicide health question. Nearly 100 government, academic and industry scientists have guided and contributed to the study since its inception.

Our studies have not been able to establish a definitive adverse cause-effect relationship between adverse health and Herbicide Orange exposure. However, our studies identified some issues that require further evaluation.

Comments on Proposed Legislation

The Air Force and the Department of Defense object to presumption of causality in cases of lung cancer, non-Hodgkins lymphoma and certain immunosuppresent disabilities as a result of exposure to agent orange. Both S. 1787 and S. 1692 would disregard the research effort to evaluate the health effects of herbicides. Early data from the Air Force Health Study does not support the presumptions made in S. 1787 and S. 1692 of non-Hodgkins lymphoma, lung cancer and immune system suppression of significance from herbicide exposure in Vietnam.

This legislation appears to be based on a Veteran's Administration mortality study and a study of non-Hodgkins lymphoma among agricultural workers in Kansas. The scientific methods used in the VA study severely limited the ability of the study to reach any conclusions concerning causal relationships between disease and exposure. The investigators noted an increase in lung cancer cases in Marines but not in Army personnel. However, they did not take into account the effect of smoking, the primary cause of lung cancer. Their assumption that the observed deaths from malignant conditions were due to

herbicide exposure is not reasonable in light of serum dioxin levels found in Vietnam veterans. A recent study by the CDC, could not demonstrate a difference in blood dioxin levels between soldiers who were exposed to herbicide in Southeast Asia and those who never served in Southeast Asia. Nor were the blood dioxin levels of the two groups significantly different from those in the general U.S. population. This finding would suggest that the exposure of most soldiers in Vietnam was not significant.

Similarly, a cause and effect relationship between non-Hodgkins lymphoma and specific chemical exposure could not be made in the Kansas study. This study used the case-control approach and has an ill-defined exposure assessment. Allegations that herbicides cause immune system suppression in humans are not supported by scientific evidence. The CDC has reevaluated the skin testing data from residents of Missouri, and found that there were no differences in immune response when quality control of the testing was applied. The Air Force has included an extensive and comprehensive evaluation of the immune system in its study and has found no differences in immune function between the Ranch Hand and Comparison groups. This equivalence in immune function is of added importance when the results of serum dioxin testing in a subset of the study group are considered. Testing of Ranch Hands and comparisons revealed a significant increase in the mean serum dioxin level in the Ranch Hand group.

Conclusions which are applicable to the Vietnam veterans cannot yet be drawn from the scientific literature. Premature conclusions or conclusions contrary to available data undermine the credibility of the research effort and its scientists. The Air Force Health Study is a necessary part of the research now being done on herbicides. The Science Panel of the Agent Orange Working Group, Domestic Policy Council, has concluded that the two studies which are most likely to answer the question of possible health effects of phenoxy herbicides are the Ranch Hand Study and the National Institute of Occupational Safety and Health Study of occupationally exposed workers.

Although the National Academy of Sciences has the competency to conduct a literature review, such an undertaking would be redundant. The Veterans Administration, through research contracts, already sponsors a continuing annual review. The VA contractor reviews all articles published anywhere in the world on the herbicides which were used in Vietnam. The tenth volume in this continuing series was published in May 1987. A new review would be a needless expenditure of government funds.

The Air Force Health Study is the premier federally funded herbicide-related study underway. Its findings are important to our veterans and to their families. With your continued support, our work will continue. I will be happy to answer any questions at this time.

DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health
National Cancer Institute

Memorandum

Date January 13, 1988

From Chairman, Advisory Committee on Phenoxy Herbicides

Subject Evaluation of the report of the 1983 examinations, Air Force Health Study

To William H. Wolfe, M.D.

This memorandum extends the comments I made by telephone individually to Drs. Wolfe and Michalek in December.

The data are cold, having been issued almost four years ago. Reviewers and editors are likely to deem the findings outdated and already reported. On pages 3-4, for example, with reference to the measures of exposures, it is said that group exposures must be used because there is no indicator of individual dose. We now know that TCDD can be and is being measured in the blood.

The contents and format raise the question, is the audience expected to be specialists, professionals or the laity. It seems as if the laity is the target, for the statistical explanations are elementary. Professional journals are not likely to use their space for this purpose.

Combining the findings in the literature with the findings in this study under the section on Results is unusual and does not make for smooth reading. Several reviewers found this format unacceptable. Comparison of the present and past findings belong in the Discussion.

From the report the reader gets no feel for the nature of the study. Who did the interviewing, where, how and under what contract? The same for the medical examinations and analysis of the data. How was quality control maintained?

One option that should be seriously considered is to combine the findings of the first two medical examinations in one report, written in the standard fashion for a scientific journal, making it as succinct as possible. This course would provide contemporary data with a place for previously unreported data in a way that does not seem to exhume them. The easiest way to accomplish this is to draw heavily from the executive summary of the most recent report, supplemented by findings from the earlier report as needed for a more complete portrayal of the study and its results.

Enclosed are extracts of reviewers' comments which may be helpful to you. Several said that the text discouraged them from reading through the entire manuscript.

Robert W. Miller

Robert W. Miller, M.D., Dr. P.H.

Some of my comments are relatively trivial and some are substantial.

Page 2, last paragraph: "The Ranch Hand and comparison groups will be.... for the next ____ years". Do they mean until 2008? Why not give the actual year or specify a starting point? The next sentence needs changing, too: ".... examinations were scheduled to be offered to participants....."

Page 3, first paragraph: Omit the theoretical discussion about experimental vs. observational studies. The last half of this paragraph belongs in Discussion.

Page 3, last paragraph: Omit.

Page 4, third paragraph: Discussion.

Page 4, last paragraph: "Job category matching used five categories:" Here and elsewhere the unfortunate acronym AFHS is unnecessary. If they had had to write this out, they would have recognized its boring repetition and would have done something about it.

Page 5, third paragraph under "Questionnaire and physical examination": Limiting between-observer variability is relatively unimportant; what is important is to have insured that each observer saw Ranch Hands and Comparisons in proportion to their total numbers.

Page 8, first paragraph under Morbidity: Sentences need rephrasing to avoid starting them with numbers. E.g. lines 4-5: 99.5% were contacted; 1,174 (97%) of the Ranch Hand group.... The phrase about selection bias is hardly necessary.

Page 8; last paragraph: This belongs in Methods.

Page 9, line 1: Omit mispelled principal.

Page 9, last paragraph: Omit.

Page 10, first complete paragraph: Discussion.

Page 10, secodd paragraph: Discussion.

Page 10, third paragraph: Omit.

Page 11, first complete paragraph: Stick with "weight" since that was what was measured. Not necessary to switch to "fat".

Page 12, second sentence after table 4: Omit this sentence. It makes no sense to combine two disparate findings. It would help to give p values for the relative risks for skin cancer and for systemic caneer.

Page 13, line 1: "regressed" is jargon; say what was meant in ordinary English.

Page 13, line 6: Hamster

Page 13, lines 27-28: This sentence is too vague. What does uncertain mean?

Page 18, line 5: "Inconsistent" is too vague. Inconsistent with with?

Page 22, second paragraph: Convert these logarithmic units to something meaningful. Will readers know what degreasing chemical exposure is? Shouldn't this be commented upon fully or omitted as irrelevant?

Page 23, penultimate paragraph: "In none of the above analyses were adjustments'...."

Page 31, table 18: Either it should be noted that the two parts of the table are not mutually exclusive, or, <u>better</u>, it should be subdivided into four categories: Flying officers, flying enlisted personnel, ground officers, ground enlisted personnel.

Page 32, last sentence: This idea belongs in Discussion. Summary is probably a better word for this section than conclusion. The conclusion portions belongs in Discussion.

Page 34, lines 8-9: (d) is too succinct. For most readers, the implications of multiple comparisons on statistical tests will beed to be spelled out.

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Page	Comment
9-10	The discussion on power is hard to understand. Specifically, an incidence of 1/1000 is not clear; what is the period during which the disease occurred? I assume that incidence here refers to cumulative incidence during the period of follow-up to date. This should be clarified.
11	Second paragraph, first line. `Toxicological´ is misspelled.
12	Given the concern about soft-tissue sarcoma, a statement should be made about the occurrence or lack thereof in these groups. It may be of interest simply to list the types of cancer for each group.

Comments on AF paper.

In general, I find the report verbose, unfocussed and poorly organized. This applies to all the sections. Specifically,

Methods - section needs on statistical analysis
describe the study in greater detail
what is a 'nonconcurrent prospective setting'
drop section on 'Influence', pp 3-4
Describe Tables 1 + 2 in the text. T. 2 is standard lab. procedures anyway.

Results.

p8 drop 2nd para
p9 drop 3rd para to end p 10. Include brief discussion of power in Discussion
Results should be only results
Drop lit. review throughout.
Table 6 is very problematic.
Why suddenly switch to pre- and post-SEA experience for this analysis? What is the rationale?
Pre-SEA is irrelevant. Just need to look at sig. & comparisons in post SEA exposures
Reduce the outcomes described to a few which are comparable to literature.
Could drop BD analysis since it is not complete. It raises more questions than are addressed here.

Conclusion: This is not a conclusion, but an unconclusion. Conclusions conclude & they go at the end.

Discussion: This is woefully inadequate. need to set the findings in perspective. What are the findings. What are the shortcomings, are the findings biologically plausible? Do they concur with the literature? If not, why not? What will you do NEXT?

Thank you for sending me the report on the recent site visit of the Ranch Hand Study and the manuscript summarizing the baseline morbidity and mortality data. While I agree that it is important that interim results of the Ranch Hand study be submitted for publication in a peer-reviewed journal, I am VERY concerned about the way this manuscript is written. I believe that the paper requires substantial revision prior submission for publication. I have concern about the tenor and organization of the manuscript in general as well as about the section on birth defects in particular.

First, the manuscript is too verbose and lacks focus. Most of the references to specific animal experiments and to anecdotal case reports of patients with dioxin exposure and one disease process or another can be eliminated in favor of a couple of references to recent reviews on dioxin toxicity. Mentioning each paper in one sentence blurs the critical details of these studies such as dosage, acute or chronic exposure, host susceptibility, etc. Moreover, although a few negative studies are cited, positive ones seem more likely to be mentioned. In any case, review of previous studies belongs in the introduction or discussion, not the results section.

Second, there is an unexplained inconsistency in the presentation of data. Why are confidence intervals for relative risks presented for dermatologic diagnoses and not for other outcomes such as neoplasms or birth defects? (Such confidence intervals should always be reported). Why is the Kolmogorov-Smirnov Test used for measures of immune function but not, for example, measures of liver function? What is the point of reporting things like differences in the slope of linear models of coproporphyrin-alcohol covariates when "the clinical relevance of these differences of slope is unclear"?

Third, Table 19 is extremely misleading. This table and the accompanying text suggest that important differences were found among Ranch Hands and comparisons in 6 of 11 endpoints studied. In fact, there were hundreds if not thousands of endpoints studied and most of the comparisons in each of the 11 groups of endpoints looked at in this paper showed no difference between Ranch Hands and comparisons. Moreover, many of the findings taken as supporting previous work do not in fact do so. For example, associations have previously been suggested between dioxin exposure and soft tissue sarcoma and lymphomas, not skin cancer. No association was seen in this study with soft tissue sarcoma or lymphoma, only with skin cancer. The previous work and the Ranch Hand study are not in agreement.

Fourth, the discussion is completely inadequate. A comparison of the Ranch Hand data and previous work should be made for each positive result. The issue of statistical significance needs to be discussed more thoroughly. Most of the differences reported in this paper have p values between 0.05 and 0.01. While it is true that the precise effect of multiple statistical testing is not well defined, it is certainly well known that spurious associations are more likely with multiple comparisons. The discussion should also include statements regarding the biological significance, if any, of differences in the slope of the regression of various laboratory measurements with age of a few percent or less per year.

I also find a number of important problems in the presentation of data on reproductive outcome. The methods section does not describe how these data were obtained (i.e, exclusively by interview, usually of spouses). Furthermore, it does not define "miscarriage", "physical handicap", "birth defect", or "learning disability", and many different definitions of these terms are in use. The method of adjustment for confounding variables is potentially misleading. For example, maternal alcobol use (during pregnancy?) was scored as a yes/no variable although the risk for fetal alcohol syndrome would be expected to be the same in women who drink one or two drinks a day as in women who do not drink at all; the risk is very different for women who drink 10 drinks a day. There is no adjustment for ethnic origin or socio-economic status although these factors are known to influence the risk of many adverse reproductive outcomes. There is also no consideration of what the specific birth defects observed were (apart from their severity) or of whether there was any pattern to the anomalies observed. Moreover, there is no indication of how many of the birth defects or physical handicaps have other identified causes. The most likely explanation for an increased frequency of minor birth defects among the offspring of Ranch Hands is more frequent reporting, given the concern that exists among families of veterans about the reproductive toxicity of Agent Orange. This possibility is not even mentioned in the discussion.

Bob, the Ranch Hand study is extremely important, and its results merlt publication in a widely-read peer-reviewed journal such as J.A.M.A. The investigators should be congratulated for their impartiality and diligence, but they should be encouraged to produce a more staight-forward and critical presentation of their preliminary data. It is not sufficient just to waffle, as they do in their discussion. The manuscript must be scholarly in the best sense of the word. The findings should be presented clearly and interpreted with great caution. Every conclusion made needs to be justified, and every major limitation clearly pointed out.

his offspring. He concluded that genetic damage to stem cells for spermatogonia is the only plausible means by which defects could be produced in conceptuses conceived long after the exposure. He pointed out that there is no strong evidence that Agent Orange or its components produce this type of an effect.

Chapman, D.E., and Schiller, C.M. 1985. Dose-related effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in C57BL/6J and DBA/2J mice. Toxicol. Appl. Pharmacol. 78:147-157

KEYWORDS: Acute toxic effects, Hepatic effects, Lethality, Mechanism of toxic action, Other toxic effect, Oral exposure, Chlorinated dibenzo-p-dioxins, Mouse

A study of body weight loss and lipid parameters in "responsive" and "non-responsive" strains of mice given a single oral dose of TCDD inidcates that lipid changes were not simply due to decreased feed consumption in this species.

Clark, D.A., Gauldie, J., and Sweeney, G. 1984. Dose response, time-course and mechanism for suppression of cytotoxic T cell generation by 2,3,7,8-tetrachlorodibenzo-p-dioxin. In Poland, A. and Kimbrough, R.D., eds. Banbury Report 18: Biological Mechanisms of Dioxin Action. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Pp. 421-434

KEYWORDS: Immunological effects, Mechanism of toxic action, Chlorinated dibenzo-p-dioxins, Review

The authors review studies performed in their laboratory of the immunosuppressive effects of TCDD in mice. Of specific interest is the suppression of cytotoxic T lymphocytes which the authors suggest is the result of promotion of suppressor T cells in the thymic epithelium. (20 references)

Commoner, B., Webster, T., and Shapiro, K. 1985. Environmental levels and health effects of PCDDs and PCDFs. Presented at the 5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, FRG (September 16-19, 1985) 1 page (abstract)

KEYWORDS: Cancer, Environmental exposure, Chlorinated dibenzo-p-dioxins, Human, Commentary, Abstract

This abstract of a symposium presentation suggests that "background" levels of polychlorinated dibenzodioxins and dibenzofurans in adipose tissues and human breast milk, possibly derived from municipal and industrial incinerators, may pose an unacceptable risk of cancer in the general population.

Constable, J.D., and Hatch, M.C. 1985. Reproductive effects of herbicide exposure in Vietnam: Recent studies by the Vietnamese and others. Teratogen. Carcinogen. Mutagen. 5:231-250