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Report/Article Title Memorandum: From Robert W. Miller, Chairman, Advisory Committee, Ranch Hand Study, to Don M. Newman, Chairman, Agent Orange Working Group (AOWG), regarding Report of Visit to Review the Ranch Hand Study, dated November 9 ,1987

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Memorandum

Date November 9, 1987

From Robert W. Miller, M.D.
Chairman, Advisory Committee, Ranch Hand Study

Subject Report of visit to review the Ranch Hand Study

To Don M. Newman
Chairman, Agent Orange Working Group

A site visit was made on September 9, 1987 to the headquarters of Science Applications International Corporation (SAIC) in McLean, Virginia, to review an 1163-page report on the second cycle of medical examinations of Air Force Ranch Hand personnel. SAIC is under contract to prepare the report based on medical examinations conducted at the Scripps Clinic in La Jolla, California, under a separate contract.

In attendance, as shown in Appendix A, were 5 non-government members of the Advisory Committee, its chairman, executive secretary, and a consultant in statistics from the National Cancer Institute, the 2 principal investigators and 2 members of their staff from Brooks Air Force Base in San Antonio, and the 4 SAIC staff members involved in the data analysis and preparation of the report.

Cancer, chloracne and porphyria

The meeting began at 9 a.m. with an overview by Dr. William H. Wolfe of the recent clinical studies. Cooperation was excellent: 93% participated, 1016 Ranch Hands and 1293 in the comparison group. The forms of cancer previously associated with exposure to dioxin did not occur excessively. There has been one soft-tissue sarcoma and one lymphoma in each group. Personal histories of basal cell skin cancer continued to be more frequent among the Ranch Hands than the comparisons (relative risk = 1.56), but there was no difference between the groups in the interval since the first cycle of examinations. Other known effects of dioxin, chloracne and porphyria cutanea tarda, were not seen.

TCDD: blood levels and half-life

The most dramatic finding concerned new data on the body burdens and the half-life of dioxin, based on 30 blood samples obtained recently as compared with samples that had been stored since 1982 on some of the same men. The average half-life was 7.1 years (range = 3-30 years). In this pilot study the average body burdens of dioxin among a sample of 22 comparison subjects was 5.6 ppt (range = 3-9 ppt), as compared with 53.6 ppt (range = 3-314 ppt) for the sample of 51 Ranch Hands believed to have been heavily exposed. Serum dioxin levels under 10 ppt were found for all of the comparison sample and for 30% of the Ranch Hands. These results show that the Ranch Hand group was exposed about 20 years ago to substantial levels of dioxin, as compared with ground troops, whose levels were the same as for the military that did not serve in Vietnam.

The next step is to complete the preliminary study of bloods from 150 Ranch Hands and from 50 comparison subjects. The results of this collaboration with CDC will be published in two parts. The Air Force will have senior authorship for one which will describe the TCDD blood levels in the two groups. CDC will have senior authorship for the other which will describe the half-life.

After that, the TCDD blood levels will be determined for all Ranch Hands and an equal number from the comparison group (about 1000 each). The health effects can then be analyzed with respect to current body burden. The Committee stressed the importance of also analyzing the data according to the old exposure criteria, so comparisons can be made from one examination cycle to the next. Also, the 15 Ranch Hands with body burdens of dioxin that fell in the normal range (under 10 ppt) should not be regarded as non-exposed. They may be fast metabolizers of dioxin, and no longer have an increased body burden. An explanation for the low levels should be sought through a case-control study of these men as compared with the majority who had high levels after similar exposures.

(NIOSH has since found that in a small sample of workers at two factories in New Jersey, the dioxin blood levels averaged 110 ppt; ie, twice as high as the average for the sample of heavily exposed Ranch Hands.)

There was considerable discussion about determining the TCDD levels for all 1000 men in the comparison group rather than a representative sample. About half of the committee members were in favor of the whole group (at \$1000/specimen), and the remainder were neutral.

By-product research

No differences attributable to dioxin exposure were found with respect to abnormalities of other organ systems or in the battery of psychological tests. Although the immunological test-results show no differences attributable to dioxin exposure, it was pointed out, as at previous meetings, that by-product research on the relationship of immunological perturbations to alcohol and/or tobacco use or to diabetes mellitus would be of great interest. Also, the normal values for the Ranch Hands and their comparison group could be compared against those from the Scripps Clinic. Attention to outlying laboratory values was once again urged, particularly with respect to familial occurrence and implications for prevention; eg, high blood cholesterol levels. Also, as the interval histories reveal the occurrence of illnesses, the previous medical examinations can be evaluated to see how well they predicted the illnesses.

Birth defects

The study of birth defects is a bit ahead of schedule. Review was to be made of the medical records of children under age 18 years whose parents reported them to have no anomalies, and 626 whose parents reported anomalies. Of 3275 reviewed to date, 448 (13.7%) have birth defects. The Committee pointed out that this proportion was far above that of major anomalies reported in other studies. The definition of a birth defect in the Ranch Hand study apparently includes many minor anomalies, such as birth marks. The classification of birth defects used by CDC should be evaluated for its use in the Ranch Hand study. Checking the records will be completed by November 1988. Analysis of the results and the writing of the report are expected to be completed by August 1990.

The third round of medical examinations, which began in May 1987, will be analyzed during the same interval. The fourth round of examinations is scheduled to begin in June 1992.

Publication plans

A 52-page manuscript prepared as a report on the initial examinations made in 1983 is near completion and will be sent soon to the Advisory Committee for review. The 1163-page report of the second cycle examinations is ready for publication as a book. A summary report will be prepared for the open literature. The Committee stressed again the importance of publications in the open literature, because scientists at large will not have access to in-house Air Force publications where the reports have appeared to date. Peer review for publication in journals, preferably those with wide audiences, will further strengthen the credibility of the publications.

Statistical analyses in the future

Some concern was expressed about the criteria for determining and reporting statistical interactions. In particular, loosening the stringent P-value criteria from $P=0.05$ to $P=0.01$ would allow readers to evaluate better the various factors under study. The statisticians replied that they would consider this change for future reports.

The Advisory Committee, which included five seasoned university-based scientists who are not given to hyperbole, were impressed by the performance of the Air Force investigators and their three contractors.

Recommendations

1. First and foremost, there is an urgent need to publish in widely read peer-reviewed medical journals to assure dissemination of the study results with the imprimatur of peer review.
2. A report on dioxin (TCDD) levels now being determined from blood samples of 150 Ranch Hands and 50 controls should be the first of these publications.
3. For quality control a small sample of the 200 men should be retested to learn if both results are in close agreement.
4. The body-burdens of TCDD, now being determined for each study participant, should be the basis for analyzing effects in relation to exposure.
5. The body-burdens of TCDD should be studied for their correlation with the previously used Air Force Exposure Index.
6. In the next analysis, the Exposure Index should also be used to allow comparisons with the results of the first two examinations.
7. Men with histories of heavy exposure should not be regarded as misclassified. They may instead be fast metabolizers. If so, the study should show if they are more or less susceptible to TCDD abnormalities, should any be found. Perhaps a simple test of metabolic clearance rates can be made.

8. A case-control study of these men as compared with others having high TCDD blood levels may explain the difference; eg, dissimilar body weight.
9. An attempt should be made to create a composite health profile to determine the frequency of medical abnormalities per person.
10. Consideration should be given to classifying birth defects as CDC does, which in addition to other benefits will allow easier comparison with CDC's findings.
11. The P-value criteria should be changed in future reports to $P=0.01$ instead of $P=0.05$.
12. By-product studies should be undertaken for the valuable new information that may be gained:
 - a. Immunologic findings should be studied in relation to tobacco and/or alcohol use, and to diabetes mellitus.
 - b. Persons with reproducible outlying laboratory values (eg, high cholesterol levels) should be studied in detail to determine the cause, and advice given on prevention, early detection of disease and the desirability of family studies.
 - c. Consider a study to relate new illnesses to the findings on past medical examinations as a measure of their predictive value.
 - d. As suggested before, consider having a graduate student in history prepare an account of the Ranch Hand Study, as a dissertation topic.
 - e. Consider having a medical and/or statistical Fellow undertake a by-product study as part of his/her science education, involving perhaps a collaboration between the University of California in San Diego, the Scripps Clinic and the Air Force.
13. Postpone the next major reanalysis of mortality until TCDD levels are available for the 2000-member Ranch Hand group under study.

Robert W. Miller
Robert W. Miller, M.D.,
for the Advisory Committee