

RANCH HAND ADVISORY COMMITTEE MEETING
October 19-20, 2000
Hilton Palacio del Rio
San Antonio, Texas

The meeting of the Ranch Hand Advisory Committee (RHAC) was called to order by Dr. Robert W. Harrison, Chairperson, at 8:10 a.m., Thursday, Oct 19, 2000.

I. Attendees:

Committee members: Dr. Michael Gough, Dr. Paul Camacho, Dr. Steve Selvin, Dr. Robert Sills, and Dr. Michael Stoto.

Consultants, Air Force personnel, and staff: COL. Harry E. Marden, D.O., Consultant, LTC Bruce Burnham, LTC Karen Fox, M.D., (Brooks AFB); Dr. Joel Michalek, Principal Investigator (Brooks AFB); Debbie del Junco, UTSPH/Houston, Dr. Judson Miner and Manuel A. Blancas, Program Management Support; Mr. William Jackson; Meghan Yeager and Dr. William Grubbs, SAIC; Mr. Ronald Coene, Committee Executive Secretary; Ms. Barbara Jewell, NCTR, Committee Staff.

Observers: MAJ. Jack Spey (Ret.) Ranch Hand Vietnam Association

II. Ranch Hand study overview.

Dr. Michalek presented a description of the study, methods, and summarized results to date. Such information is to be made available on the web page. The official name of the study is *The Air Force Health Study*. Ranch Handers call it The Ranch Hand Study; and in the federal budget, the line item for this study is *Ranch Hand II Epidemiology Study*. The overall goal of the program was and is to ascertain whether any harm had been inflicted on US Ranch Hand veterans in any way (where 'any way' is defined as health, mortality and reproductive outcomes) as a result of their spraying of the herbicide.

The information reviewed included:

- A. Historical background
- B. Study objectives
- C. Study design and protocol (and its peer review)
- D. Participation (veterans and scientists)
- E. Epidemiologic template applied
- F. Summary of physical examinations (control and exposed groups)
- G. Exposure level comparisons (and assay methods applied)
- H. Program support
- I. Costs

Other specific topics addressed included:

- A . Reliability of the dioxin measurement (coefficient of reliability = 96%)
- B . Dioxin half-life data ($t_{1/2}$ = approximately 7.6 years)
- C . Means of exposure of Ranch Handlers to the herbicide
- D . Results of Ranch Handlers' responses to a questionnaire
- E . Informed consent issues
- F . Body burden (skin, fat) of dioxin and elimination rate
- G . Statistical analysis models
 - Model 1. Comparison of all Ranch Handlers with all controls; contrasts of Ranch Hands and Comparisons with each of three occupational strata (officers, enlisted flyers, enlisted ground personnel).
 - Model 2. Initial Dioxin Analysis- Extrapolation of Vietnam dose to Ranch Handlers from those with present high body burdens
 - Model 3. Dioxin Category Analysis - Contrasts of three Ranch Hand exposure cohorts (background, low, high) with comparison
 - Model 4. Evaluation of the relationship between dioxin body burden and health status irrespective of the source or amount of dioxin
- H . Quality control of data entry
- I . Specimen collection and storage (urine, serum, adipose tissue, semen); approximately 50,000 samples frozen
- J . Ethical issues; IRB informed consent and confidentiality issues
- K . Computer system, data capture, scanning of medical and military records

III. Study observations to date – Air Force Report (Dr. Joel Michalek)

- A. A significant adverse relation between reported health and dioxin body burden, and an increased risk of reporting fair-to-poor health in the high dioxin-exposed category
- B. No significant relationship between any measure of exposure and cancer
- C. A significant and adverse relationship between peripheral neuropathy and dioxin body burden
- D. A significant and adverse relationship between reduced short term memory loss and dioxin body burden
- E. A consistent and adverse relationship between certain liver enzymes such as GGT and dioxin body burden
- F. No evidence of a relationship between liver disease and dioxin body burden
- G. An overall 25 percent increase in cardiovascular disease in the Ranch Hand group
- H. Average platelet count and average mean corpuscular increased with dioxin body burden
- I. An adverse relation between diabetes and dioxin
- J. No detectable adverse relation between any measure of exposure and immune function
- K. An adverse relation between dioxin body burden and mild bronchial obstruction in Ranch Hand officers
- L. No dermatological evidence of chloracne
- M. No relationship between any measure of exposure and impairment of renal function

III. Demographic data

A. Mortality

1. Increased risk of death from cardiovascular disease among enlisted ground crew (first noted in 1991)
2. No evidence of an exposure effect on overall mortality (published in 1998)
3. The mortality study can adjust for date of birth, race, and military occupation but cannot adjust for dioxin body burden or risk factors, such as smoking and drinking.
4. Relative risk of death from digestive diseases of 1.7 but unable to adjust for alcohol consumption

B. Reproductive Outcomes

1. No evidence of a relationship between exposure and reproductive effects
2. Little or no evidence of a relation between paternal dioxin level and birth defects was found, however there was an increased number of children with spina bifida fathered by Ranch Hands with the high dioxin levels.

C. Diabetes

1. New software has been developed that permits matching on medical histories of Ranch Handers and family members and other parameters (e.g. body fat, date of birth, race, military occupation, etc.)
2. Individuals with higher levels of body fat have an increased risk of diabetes
3. Analysis of the dioxin elimination rate vs. diabetes in the Ranch Hand cohort is being conducted
4. There have been approximately 300 Ranch Hand study subjects with Medically confirmed diabetes who have had dioxin measurements in all four physical exam years plus medically-verified diabetes
5. The association between diabetes and dioxin has been speculated as being caused by the relation between body fat and the dioxin elimination rate
6. An estimation of the elimination rate without knowledge of the initial dose can be done by means of a statistical model. Two covariance assumptions were studied:
 - a. Auto-regressive Order 1
 - b. Toeplitz
7. The Seveso data (to be presented at the next RHAC meeting by Dr. Michalek) appears to validate the first order model
8. No relationship between the elimination rate and diabetes was found in the Ranch Hand cohort
9. Average non-diabetic Ranch Hand insulin levels are significantly higher than the average non-diabetic comparison insulin levels
10. Adjusting for triglycerides did not alter the relationship between diabetes and dioxin; this does not support the hypothesis that dioxin binds differentially to triglycerides
11. A significant and positive relationship between the area under the curve (AUC) and diabetes in the Ranch Hand group (after adjustment for such factors as age, body fat, personality type) was found

D. Peripheral Neuropathy

1. A significant increase in the risk of peripheral neuropathy is observed in diabetics compared with non-diabetics (about 30 times greater the risk than non-diabetics)
2. This suggests that an adverse relationship between Ranch Hand veterans' exposure to dioxin and peripheral neuropathy was found.

V. Contract/Program management overview

- A. Dr. Miner presented an overview of program/management functions and contract management
- B. His office oversees the prime contractor, SAIC, in all aspects of the study including deliverables
- C. Personnel: The study uses 25-27 onsite contractor personnel at present.
- D. Contracting
 - 1. Primary contractor/sub-contractor arrangement established as of cycle 2
 - 2. SAIC- primary contractor for cycles 2-5
 - 3. Contract for cycle 6 will require advanced development of the statement of work
 - 4. FAR and RFP issues were discussed; contract award to be fixed-price
 - 5. Contract award for cycle 6 is set for June, 2001; May 2002 is the start date for the new contract

VI. Review of minutes of previous meeting

- A. Corrections and changes to the minutes for the previous meeting were noted
- B. Minutes were to be amended per committee member suggestions, modifications, additions and editing
- C. Minutes, as amended, were accepted by voice vote

VII. Action items/considerations/issues from last meeting

- A. A need for updating each study's tour dataset to include the geographical locale of each tour of duty so that on-ground exposures can be addressed better (Dr. Trewyn)
- B. Data sources for "normal" ranges used should be cited
- C. Residential and employment histories of veterans; possible exposures within the U.S.; hot-spots in the U.S. (Dr. Favata) was discussed
 - 1. Residential history data are available (life-long), including residential address, latitude and longitude (Dr. Michalek)
 - 2. Area pollution; proximity to factories
 - 3. Employment histories available for all participants
 - 4. A standard coding system for data capture was used
- D. Other procedures discussed
 - 1. Invasive procedures- generally risky and logistically difficult
 - 2. Sigmoidoscopy- performed as a medically-indicated follow-up (Dr. Camp)
- E. Tour data will be updated (see A above), and employment exposures will be assessed (see C above). Invasive procedures will not be used.

VIII. Mechanisms for Additional/New Research

- A. Biological specimens
 - 1. Approximately 55,000 biological specimens have been collected and kept in freezers.

2. Additional specimens will be collected from physicals conducted in the year 2002
 3. Maintenance of specimens beyond the end of the Ranch Hand study
 - a. Specimens viewed as valuable research resource
 - b. Specimens should not be made available for other research purposes until the Agent Orange studies have been completed (Dr. Michalek)
 - c. Recommendation for seeking NIH funding for this purpose has been submitted to the Secretary of HHS (Dr. Harrison)
 - B. Parallel NIH study to assess the possible leeching of mercury from dental amalgam and its effect on neurological endpoints
- IX. Study Completion
- A. The study is due to end in 2006
 - B. The specimens, data, and medical information are valuable resources for additional studies and, if at all feasible, should be protected beyond the completion of the study.
 - C. A legal determination is needed about the future possible uses of the collected materials and records.
 - D. Recommendations (Dr. Harrison)
 1. Creation of a study group to address post-study-completion issues
 2. A statement to be inserted into the minutes proposing future efforts by the Air Force to address this problem (Drs. Camacho and Sills)
 3. The Air Force does not plan to fund any activities beyond 2006 (Dr. Miner)
 - E. A contract with the National Agricultural Library was funded to scan, catalogue, and restore a collection of over 300,000 Ranch Hand documents, photographs, index cards, now in storage
- X. Potential research projects to be added to the 2002 physical exams
- A. Six research proposals will be considered by the RHAC
 1. Collection and storage of whole blood samples at the 2002 exam
 - a. Purpose: to study AH receptor polymorphisms
 - b. Biological assays will be deferred until the technology to perform such a study matures
 2. Electrophysiological measurements (Dr. J. Albers) may serve to clarify peripheral neuropathy. RHAC decision is needed to determine whether such measurements are beneficial to the study; consideration to be given to using consulting reviewers (Dr. Harrison)
 3. A significant and adverse relation between carotid wall intima thickness and dioxin body burden has been identified and extension of those measurements to all participants in the 2002 exam will be considered.

4. A caffeine breath test applicable to the measure of dioxin activity in the liver has become available (Dr. George Lambert, University of North Carolina) and Dr. Michalek proposed adding this test to the 2002 exam.
5. Research Proposal (Dr. D. del Junco) to assess:
 - a. Possible genetic susceptibility
 - b. Genes susceptible to dioxin
 - c. Phenotypic expression of those genes induced by dioxin exposure
 - d. Genetic polymorphisms
 - e. Possible correlation between phenotypic expression of the genes and TCDD levels may be evaluated

B. External review of some of these proposals may be considered to supplement the RHAC activities

XI. Other concerns expressed to and by the RHAC

- A. Anticipated vs. actual cost to conduct a given test
- B. Trust and privacy issues regarding genetic testing
- C. Relevance and appropriateness of proposed tests and clinical measurements
- D. Potential contribution of such tests to the study
- E. Preservation of white blood cells
 1. Information to be sought regarding cost, logistics
 2. Relevant information to be obtained from Dr. Jeffrey Cheung, NIH

Adjournment: 5:00 p.m.

October 20, 2000

The second day of the RHAC meeting was reconvened on Friday, October 20, 2000, at 8:30 a.m.

I. Current Statement of Work (SOW)

- A. Dr. Michalek presented an overview of the SOW.
- B. The SOW is performed under a government contract (fixed-price) with SAIC.
- C. The document serves as the basis for the entire contract effort: physical exam, travel, lodging, tracking, clinical activities, statistical analysis, and reporting
- D. Addendum A of the Air Force Health Study Examiner's Handbook presents the details of the last round of physical exams

II. Further RHAC concerns and discussion points

- A. Continuity across reports over time: the need to maintain consistency with respect to definitions, terminology, statistical analyses, models
- B. Capture and preservation of study data in electronic form
- C. Document deliverables under the contract

- D. Release of data to the public/file format: SAS files and flat files of the data will be made available for the public (Dr. Michalek); these are datasets that are identical to those used in the report, but have the case number replaced by a sequence number
- E. Study caretaker issues
1. The fate of the data and samples after the end of the study in 2006 is of major concern
 2. Archiving of study specimens and results
 - a. Drs. Sills and Camacho developed a short statement regarding the archiving of study samples and data beyond the end of the study
 - b. The statement reads:

The Advisory Committee is concerned about the termination of the Ranch Hand II Project in 2006. Consideration must be given for the development of an archive which will ensure the preservation of all pertinent data samples and other research materials associated with the project.

Given the high profile of the study materials, and the fact that the Ranch Hand study is one of the most comprehensive and well-organized studies with consistent successive samples from the same controls and exposed veterans, the Committee emphasized urgent need to maintain the funding of the materials and samples which are too valuable to place at risk.

So an initial estimation study should be developed which can assess the multiple factors, criteria for future access, and the accompanying costs involved for such an archive.
 3. An initial evaluation of all such factors and an estimation of related costs should be performed
 4. A designee or study group of the Advisory Committee will work with the study team to develop such an initial estimate, cost analysis, and/or an RFP for this endeavor
 5. Dr. Harrison is to compose a letter to the Secretary of the Air Force and to HHS Secretary Shalala concerning the preservation of the samples beyond the termination of the study in 2006
 6. Sources of funding for the archiving of data and samples beyond the end of the study
 - i. Drs. Camacho, Sills, Gough and Harrison will comprise a study group to assess this issue
 - ii. Dr. Camacho speculated that there may be funding sources outside of the Air Force and federal government
- G. Report for the next physical exam
1. RHAC recommends that individual specialists write literature review for each chapter
 2. RHAC recommends uniform reporting of the approximately 20 chapters
 3. RHAC to develop a process for the conduct of a peer review of the report chapters
 4. The Wechsler Memory Scale (included in the 1982 exam) will be included in the next exam
- H. Next meeting: the committee discussed possible December meeting dates

- I. Notification of veterans groups of meetings of the RHAC was discussed; mechanisms considered included use of the study's web page
- III. Open Public Session: Major Jack Spey (Ret.), a Ranch Hand veteran, made a statement about the project to the advisory committee.

Adjournment: 10:43 a.m.

_____/S/_____
 Robert W. Harrison, M.D.
 Chair, Ranch Hand Advisory Committee

_____/11/14/01_____
 Date

_____/S/_____
 Leonard M. Schechtman, Ph.D.
 Executive Secretary

_____/11/14/01_____
 Date

~~~~~  
 Complete details of the topics and discussion points addressed by members of the RHAC and summarized in these minutes are available from the transcript of the RHAC meeting [www.fda.gov/ohrms/dockets](http://www.fda.gov/ohrms/dockets) and select advisory committees. Complete study information is being made available to the public by the Air Force, by means of CD-ROMs and the web page. Downloadable datasets are in two formats, i.e. SAS and as flat files.  
 ~~~~~