

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
National Center for Toxicological Research**



Ranch Hand Advisory Committee Meeting
November 18, 2005
Rockville, Maryland

Record of the Proceedings

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH**

**RANCH HAND ADVISORY COMMITTEE MEETING
November 18, 2005
*Rockville, Maryland***

Meeting Minutes

The Department of Health and Human Services and the Food and Drug Administration (FDA) National Center for Toxicological Research convened a meeting of the Ranch Hand Advisory Committee (RHAC). The proceedings were held on November 18, 2005 at 5630 Fishers Lane in Rockville, Maryland.

Opening Session

Dr. Michael Stoto, the RHAC Chair, called the meeting to order at 8:34 a.m. and welcomed the attendees to the proceedings. He opened the floor for introductions; the list of participants is appended to the minutes as Attachment 1.

Dr. Leonard Schechtman, the RHAC Executive Secretary, read a statement into the record to confirm that no RHAC members had any financial or other conflicts of interests with any of the topics listed on the November 18, 2005 meeting agenda.

Review of Previous Meeting Minutes. Dr. Stoto announced that the previous meeting minutes were distributed to RHAC for review and comment. The current draft reflected technical comments, editorial changes and other revisions submitted by Dr. Stoto and the U.S. Air Force (USAF). Dr. Trewyn requested that the sentence under the "Cancer" section on page 10 be changed to "a review of medical records or death certificates."

Dr. Stoto entertained a motion to approve the minutes as modified; a motion was properly made and seconded by Drs. Leffingwell and Hassoun, respectively. With no further discussion, the June 10, 2005 RHAC Meeting Minutes were unanimously approved with the changes submitted into and noted for the record.

ATTACHMENT 1

List of Participants

RHAC Members

Dr. Michael Stoto, Chair
Dr. Paul Camacho
Dr. Ezdihar Hassoun
Dr. David Johnson
Dr. Sanford Leffingwell
Dr. Kwame Osei
Dr. Ronald Trewyn
Dr. Robert Sills

FDA/NCTR Representatives

Dr. Leonard Schechtman
RHAC Executive Secretary

Ms. Kimberly Campbell
Management Specialist

Mr. Anthony Graves

U.S. Air Force Representatives

Col. Karen Fox
Lt. Susan Levy
Ms. Julie Robinson

U.S. Air Force Contractors

Mr. Manuel Blancas
Operational Technologies Corporation

Dr. William Grubbs
Science Applications International
Corporation

Dr. Judson Miner
Operational Technologies Corporation

Dr. Maurice Owens
Science Applications International
Corporation

Dr. Marian Pavuk
SpecPro, Inc.

Ms. Meghan Yeager
Science Applications International
Corporation

Guest Presenters and Members of the Public

Dr. David Butler
National Academy of Sciences

Ms. Sonia Cheruvillil
National Academy of Sciences

Ms. Jennifer Cohen
National Academy of Sciences

Ms. Amy O'Connor
National Academy of Sciences

Dr. Mary Paxton
National Academy of Sciences

Ms. Jaclyn Petrello
Exponent, Inc.

Mr. Rick Weidman
Vietnam Veterans of America

Update on the Air Force Health Study (AFHS) Disposition Study

Dr. David Butler, of the National Academy of Sciences (NAS), covered the following areas in his status report. The Department of Veterans Affairs (VA) was mandated by Congress to conduct the AFHS disposition study and allocated funds to NAS to address five specific components. The NAS formed the Air Force Health Study Disposition Committee (AFSHDC) to respond to the Congressional charge. An interim letter was released addressing two segments of the committee's charge.

For component 2 of the AFHS disposition study, AFHSDC identified any potential obstacles to retaining and maintaining medical records, laboratory specimens and other data collected in the course of the AFHS. AFHSDC addressed this charge by convening meetings, holding workshops, visiting the AFHS research facilities, posing questions to AFHS staff, and reviewing AFHS data and laboratory specimens.

The AFHSDC's general observations and findings on component 2 of the AFHS disposition study are as follows. Medical records, laboratory specimens and other data collected over the course of the AFHS were properly maintained at a level typical of most epidemiological research. AFHS staff were not tasked with rendering materials to be accessible to outside researchers, but the data are not currently organized and documented for easy understanding, evaluation, management or analysis by non-AFHS personnel. The current manner in which the data are documented and organized is an obstacle to retaining and maintaining the materials after the AFHS closure date.

The AFHSDC's specific recommendations to USAF on component 2 of the AFHS disposition study are outlined below.

- Reorganize and document the medical records, laboratory specimens and other data before the AFHS closure date in a form and format that can be easily understood, evaluated, managed or analyzed by non-AFHS personnel. Create comprehensive inventories of master data files and variables; a master data code book with the name of every data variable; and a document describing the contents, format and location of AFHS materials that have been scanned into pdf files.
- Compile medical records and other study data for all examination cycles into easily identified and definitive reference documents with uniform information content. Develop these documents as electronic and searchable pdf files.
- Update and create a single database for laboratory specimens.

- Compile all information on laboratory specimen histories into a reference database.
- Compile all protocols regarding the receipt, maintenance, dispersal and return of laboratory specimens into a reference document.
- Document the status of all laboratory specimens sent to outside investigators.
- Continue the ongoing re-inventory and physical reorganization of AFHS laboratory specimens because this effort will result in the reconciliation of existing inventories and the creation of a new database with the current location of all specimens and the volumes and types of biological materials stored for each AFHS participant.
- Perform the currently planned reassay to assist in evaluating the stability and condition of AFHS specimens.
- Add the examination cycle or data collection date to any vials that are not currently marked with this information if the reorganization is conducted.

The AFHSDC concluded that as the custodian of AFHS research materials, the USAF should ensure the proper documentation and organization of these data for both historical reasons and possible future use. AFHSDC further recommended that supplemental funding be provided to implement these activities in a complete and timely manner if available AFHS funds are not sufficient. AFHSDC's interim report on component 2 of the AFHS disposition study is available on the National Academies web site (<http://www.iom.edu/CMS/3793/24159.aspx>).

In terms of the entire AFHS disposition study, Dr. Butler announced that NAS solicited input from stakeholders throughout the data collection process and also consulted with the U.S. National Archives and Records Administration on the appropriate format to submit electronic data to this agency. The final report will include recommendations on the future home and ownership of the AFHS if the AFHS disposition study committee concludes that additional data analyses are appropriate. NAS expects to complete the final report by January 31, 2006 and will provide a copy to FDA for distribution to RHAC upon release to the public.

RHAC expressed support of AFHSDC's report on component 2 of the AFHS disposition study because the recommendations are consistent with RHAC's previous consensus advice to USAF to retain and maintain AFHS data. However, the voting members decided against placing a motion on the floor to formally endorse AFHSDC's report at this time and agreed to table further discussion and action on this issue until the next meeting. NAS will be asked to present the entire AFHS disposition study report to RHAC and the USAF will address whether additional funds can be allocated and time is

available to achieve all of NAS's recommendations. RHAC will then take a formal vote on the report in its entirety.

AFHS Specimen Viability Study

Dr. Marian Pavuk, of SpecPro, Inc., explained the purpose of the viability study is to examine the viability of >70,000 biological specimens archived over the course of the AFHS. Five AFHS veterans who participated in the 1982, 1985, 1987, 1992 and 1997 physical examination cycles and had multiple serum samples stored were randomly selected for the study. One sample from all five examination cycles was selected for two Ranch Hand and three comparison veterans for a total of 25 serum samples to be analyzed. A total of 177 analytes (78 specific serum antigens, 43 autoimmune serologies and 56 infection disease serologies) will be analyzed. This process will only require 100 μ l of serum from each specimen.

According to Dr. Pavuk, the viability study is designed to assess whether the multiple analyte profile (MAP) technology can be used to assay biochemical parameters in AFHS frozen specimens and determine if these samples are viable for use in future studies by other investigators. MAPs are high-density and quantitative immunoassay panels that allow biomarker patterns to be identified and provide a comprehensive evaluation of protein expression patterns indicative of responses to disease, drugs or environment. Rules-Based Medicine Laboratory (RBML) developed the MAP technology and was contracted to conduct this testing to analyze the AFHS samples.

The process of the MAP technology is summarized as follows. Bioassays, dyed microspheres, high-speed fluidics and digital signal processing are used. Specific dyes permeate the polystyrene microspheres and each microsphere set is covered with capture antibodies that react with the target protein. The microspheres pass single file past two lasers after the assay is complete. Results from the MAP technology can be obtained in three weeks.

According to Dr. Pavuk, the MAP technology is commercially available for use by other laboratories and investigators. RBML published studies to demonstrate that its technique and other immunoassays measure similar parameters. Moreover, the MAP technology can be applied to a broad range of areas, such as diagnostic testing and identification of disease profiles. The viability study is limited in its scope of only 25 specimens, but will still provide additional information on the uses and storage process of the AFHS samples. Efforts to complete contract activities with RBML are underway,

but samples for the viability study have been selected and are available to be shipped at this time.

RHAC commended USAF on developing a study that focuses on viability of the AFHS specimen. The members noted that this effort is extremely important and has the potential to provide useful information on whether to save the AFHS samples. Some members noted, however, that "viability" means more than whether the MAP technology can be used to analyze the specimens.

RHAC's suggestions to USAF to consider in further implementation of the viability study are outlined below.

- Expand the current focus beyond proteins to obtain data about the quality of DNA and RNA. Use this information to address important disease endpoints and other health issues among veterans in the future and strengthen the overall outcome of the AFHS.
- Test the 25 samples with non-MAP technologies to identify other aspects of viability.
- Obtain as much information as possible from the 25 specimens, but conduct follow-up studies due to the small sample size.
- Develop a rigorous protocol to identify the most important analytes to study because funding is not sufficient to analyze all 177.

USAF committed to providing RHAC with a comprehensive update on the AFHS specimen viability study when data is available.

AFHS Closure Activities

Ms. Julie Robinson, the AFHS Branch Chief, reported that some AFHS civilian personnel experienced a reduction in force (RIF) action last year. This required them to either retire or find another position. Personnel have elected to retire or have found other positions in preparation of the September 30, 2006 closure date of the AFHS. The effort to digitalize hard copy research records (medical records, microfiche) continues. The Armed Forces Institute of Pathology (AFIP) was contacted to determine if they could archive the biological specimens. Archiving non-AFIP research specimens is not in their charter.

USAF may not be able to address all of the AFHSDC's recommendations on component 2 of the AFHS disposition study prior to September 30, 2006; several

actions have already been taken to date in this effort. Specimens are being reorganized by participant. A single database is being developed that will show the exact number and type of specimen stored for each individual. The University of California-Davis and the Centers for Disease Control and Prevention (CDC) will return biological specimens to USAF to be archived. A data dictionary is being created.

Review of the AFHS Comprehensive Study Report

Col. Karen Fox, the AFHS Principal Investigator, reported that the comprehensive study is designed to document significant AFHS findings, reported in physical examination reports, USAF technical reports and publications.

Dr. Stoto announced that the draft AFHS comprehensive study report was distributed to RHAC prior to the meeting for review and comment. The members extensively discussed the document and committed to providing USAF with editorial changes in writing. RHAC commended USAF on its outstanding efforts in developing an extremely difficult document. RHAC's specific suggestions to USAF to consider in revising the draft report are outlined below.

Entire Report

- Move all "Chapter Structure" sections to the "Study Design" section in the main AFHS report and provide references to this document in the applicable chapters of the comprehensive study report.
- Provide detailed descriptions in the applicable chapters on extensive data available in the AFHS and methods used to control for diabetes, cardiovascular disease, peripheral neuropathy and other confounding factors.
- Streamline and focus the report to only document and explain significantly positive and negative results.
- Describe findings that were seen in breakdowns of AFHS participants by race/ethnicity, level of education, socioeconomic class and similar confounding variables.
- Include a new section to clearly outline the limitations of the AFHS.

Chapter 1: Introduction

- Add a disclaimer to clarify that the comprehensive study report covers the period from February 1982 to March 2005 and does not include adverse

health effects to AFHS participants following herbicide exposure prior to this time.

- Page 1-4: Emphasize that the five-year follow-up reports all use the same four statistical models, but journal articles often use different, often more sophisticated models.
- Line 16: Systematically discuss the published reports and journal articles that describe the findings of the entire study.
- Lines 19-20: Delete the text on the history of spraying herbicides in South Vietnam.

Chapter 3: Interpretive Considerations

- Clearly define the manner in which the term “statistically significant” is used throughout the chapter.

Chapter 4: Illnesses Presumptively Recognized as Agent Orange-Connected

- Clarify that USAF examined the medical records of AFHS participants and did not detect any cases of porphyria cutanea tarda, chloracne or transient peripheral neuropathy.
- Explain that the statistical power of the AFHS was not adequate to detect rare cancers among participants.
- Revise the title.
- Delete the word “presumptively” in the title.
- Expand and move Chapter 4 to the introduction or conclusions chapter. Describe the AFHS findings and relationship to the VA list of Agent Orange-connected illnesses.
- Add text to the beginning of the chapter to document that Ranch Hand veterans spent most of their Southeast Asia (SEA) service in Vietnam, while the SEA service in Vietnam among comparison veterans was <30% on average.
- Pages 4-5 - 4-6: Report relative risks and confidence intervals for prostate cancer, respiratory cancers, soft tissue sarcoma and type 2 diabetes.
- Line 73: Revise the sentence to clarify that chloracne has a typical pattern different than common forms of acne seen in teenagers.
- Lines 78-79: Modify the sentence to explain that chloracne “usually persists for a maximum of 2 to 3 years after exposure has ceased.”
- Line 167: Duplicate the sentence from Chapter 4, lines 179-180.
- Line 193: Select a few key indicators of diabetes to clearly make the case that these measures are supported by other related findings.

Chapter 5: Reproductive Outcomes

- Lines 18 and 128: Cite references for the “series of journal articles.”
- Lines 110 and 158: Emphasize the significance of the spina bifida results by duplicating the sentence from Chapter 4, Section 4.12, lines 188-191.

Chapter 6: Mortality

- Consistently report the mortality findings in terms of relative risks and confidence intervals throughout the chapter.
- Add a “conclusion” section to summarize the key mortality results.

Chapter 7: Cardiovascular Assessment

- Add text to the beginning of the chapter to clarify to non-technical audiences the importance of consistency. Cite the “Phil Goulding theory” in this effort.
- Add text to explain the rationale for the lack of consistency to support an association if a “statistically significant” result was found in one of the six physical examinations, but no others.
- Emphasize that several risk factors other than dioxin or service in Vietnam are known to be associated with cardiovascular disease and statistical models used in the AFHS were adjusted for these variables.
- Note that cardiovascular disease was controlled for diabetes.
- Page 7-3: Bold the X’s in the table to indicate results that were statistically significant in a particular physical examination.
- Line 112: Include language to clearly explain the co-morbidity and mortality associated with myocardial infarction among AFHS participants.
- Line 238: Revise the “Kidney, Urethra and Bladder (KUB) X-Ray Abnormalities” title and section to clarify that the KUB analysis was conducted to detect hardening of the arteries in the circulatory system.
- Lines 251-253: Revise the sentence to emphasize that the cause for the increase in the number of deaths from circulatory system diseases in Ranch Hand non-flying enlisted personnel is unknown, but this effect was found in the AFHS.
- Lines 252-253: Clarify the meaning of “does point to the possibility of an association with dioxin.”

Chapter 8: Dermatology Assessment

- Line 7: Change the sentence to, “Chloracne may persist for at most 2 to 3 years after discontinuation of exposure.”

Chapter 9: Endocrinology Assessment

- Create a bar graph to illustrate the diabetes results, such as the incremental prevalence from 1982-2002.
- Provide numbers throughout the chapter of the relative risk and percent of persons over time who developed diabetes.
- Link the diabetes results to the cardiovascular disease findings to show the relationship to dioxin.
- Lines 489-490: Change the sentence to "consistent adverse relation between dioxin levels and diabetes."
- Lines 499-500: Delete the entire sentence.

Chapter 10: Gastrointestinal Assessment

- Page 10-3: Bold "prior hepatitis B" and "prothrombin time" in the table.
- Page 10-3: List and specifically define the significant "other liver disorders" in the table and conclusion section.

Chapter 11: General Health Assessment

- Move the chapter to the beginning of the report.
- Lines 83-84: Clarify the sentence because the current text can be misinterpreted to mean that dioxin can be consumed to maintain a youthful appearance.

Chapter 12: Hematology Assessment

- Page 12-2: Bold "absolute neutrophils (bands)" and "absolute neutrophils (segs)" in the table.

Chapter 13: Immunology Assessment

- Lines 308-309: Revise the sentence to clarify that no consistent findings were seen to support the presence of an autoimmune disorder and the number of the tests had no relationship to antinuclear antibodies.

Chapter 14: Neoplasia Assessment

- Line 3: Replace "related to" with "caused by," "induced by" or "initiated and/or promoted by."
- Line 4: Change the sentence to, "Although herbicides have been determined to be carcinogenic in animal studies."
- Line 8: Delete the sentence, "Many studies have assessed the carcinogenic potential of dioxin in humans."
- Lines 8-9: Change the sentence to, "While the cumulative epidemiological data from human studies have not been entirely consistent."

- Lines 26-27, 31, 41-42 and 46: Delete the word “behavior” and change the text as follows. “In the AFHS examination reports, skin neoplasms were analyzed by diagnosis as malignant or benign. In particular, analysis was conducted on skin neoplasms according to the following four categories: Skin neoplasms of uncertain or unspecified nature.” “Systemic neoplasms were analyzed by diagnosis as malignant or benign. In particular, analysis was conducted on systemic neoplasms according to the following four categories: Systemic neoplasms of uncertain or unspecified nature.”
- Lines 309-311: Delete the entire sentence.
- Line 312: Strengthen the conclusion section to document that other potential risk factors were analyzed in AFHS results, journal articles and other publications; two papers showed cancer effects; and many cancers on the VA list of Agent Orange-connected illnesses are too rare to detect in the AFHS population.

Chapter 15: Neurology Assessment

- Add text to the introduction to clarify that adjustments were made for diabetes and other known causes of peripheral neuropathy.
- Include more information on peripheral neuropathy as an acute health effect and its relationship to diabetes in the conclusion section. Note that these findings were the most significant among AFHS participants in terms of neurological diseases.
- Page 15-4: Place X's under 1985, 1992 and 1997 on the “probable peripheral neuropathy” line in the table to be consistent with lines 364-365.
- Line 368: Delete “In a 2001 journal article.”

Chapter 16: Psychology Assessment

- Revise the chapter to consistently report findings between the individual sections and conclusion section. For example, “higher,” “increased” and “greater than average” results are documented throughout the chapter, but the conclusion section states no “clear evidence of disorders or syndromes that can be associated with exposure to herbicides and dioxin” appears to exist.

Chapter 17: Pulmonary Assessment

- Lines 127-131: Repeat these two sentences in the individual sections that assess the various pulmonary conditions.

Chapter 18: Renal Assessment

- Lines 32-36: Revise the paragraph to clearly define the subgroups of “younger” and “older” AFHS participants.
- Line 54: Modify “more Ranch Hands had a higher average serum creatinine level” because the text is repetitive and redundant.

In addition to proposing revisions for each chapter of the AFHS comprehensive study report, RHAC also recommended that USAF consider the following organization and framework to strengthen the conclusions and overall document.

- Restructure the report in a newspaper style format in which the most important issues serve as the leading topics and are followed by the supporting data.
- Describe the tremendous amount of research that has been conducted on Agent Orange-connected illnesses by AFHS, the Institute of Medicine and broader scientific community.
- Point out areas where the AFHS and VA results are consistent.
- Emphasize that the AFHS was unable to address certain issues due to a small sample size or events occurring before the AFHS was initiated.
- Clarify that the AFHS analyzed conditions other than those on the VA list of Agent Orange-connected illnesses.
- Streamline each chapter to succinctly describe the AFHS activities, publications and results.
- Clarify Chapter 2, “Measures of Exposure,” to strongly emphasize that the AFHS broadly focuses on exposure to herbicides, but the comprehensive study primarily uses dioxin as a surrogate of exposure to Agent Orange.
- Move the VA list of Agent Orange-connected illnesses from Chapter 4 to the beginning of the report.
- Reformat Chapter 19, “Conclusion,” to include key points from the conclusion sections in each individual chapter.
- Structure the conclusion sections in each individual chapter to be consistent with this framework.

Public Comment Period

Mr. Rick Weidman, Director of Government Relations for Vietnam Veterans of America (VVA), emphasized the critical need for USAF to address NAS's recommendations on component 2 of the AFHS disposition study. Compiling the data into a standard format will preserve materials for the future and will also ensure that the integrity and custody of the specimens are maintained while NAS completes the AFHS disposition study and Congress makes its decision on the disposition of the AFHS. USAF is obligated to comply with NAS's recommendations because taxpayers have invested ~\$140 million in the AFHS. AFHS data belong to U.S. citizens and should be made available to reputable researchers, scientific groups and academic institutions throughout the country in the future for further analysis.

Mr. Weidman also noted that the conclusions in the AFHS comprehensive study report are not supported by data from previous AFHS documents. As a result, VVA will most likely take the position that the conclusions are untruthful and intended to deceive the public. He committed to providing RHAC and USAF with a list of these inconsistencies in writing. Dr. Stoto confirmed that RHAC will then determine its position on whether or not to formally support VVA's comments.

Report on the *Nightline* Interview

Dr. Ronald Trewyn is a RHAC member and was recently interviewed by *Nightline* to express his perceptions and observations on the AFHS. He stated during the interview that he made specific recommendations to USAF on the cancer chapter, conclusions and overall AFHS report, but many substantive changes were not made. As a result, he expressed his disappointment during the interview about USAF's failure to analyze the AFHS data in a different format. Dr. Trewyn pointed out that this strategy may have resulted in new findings and made a strong case to continue the AFHS.

Ms. Robinson clarified that the AFHS report summarized the findings of the Cycle 6 physical examinations. USAF included Dr. Trewyn's recommendations on journal articles in the introduction of the document and in the neoplasia chapter. The summary report that USAF is now preparing will be a comprehensive overview of all AFHS findings including cancer.

Program Management Update

Lt. Susan Levy, the AFHS Deputy Program Manager, covered the following areas in her status report. From AFHS's total projected cost of \$139.5 million from 1981 to September 30, 2006, participants have been provided with 13,177 physical examinations, travel, lodging and meals; data have been collected, stored and analyzed; and reports and journal articles have been completed.

Intramural activities covered in the FY'06 budget include supporting Program Management operations; retrieving, storing, coding, scanning and analyzing data; maintaining medical records; developing, editing and finalizing the mortality analysis, journal articles and technical reports; providing briefings and reports to Congress; and disposing of medical records, laboratory specimens, computers, and other data or equipment in accordance with requirements of the Privacy Act and Health Insurance Portability and Accountability Act of 1996.

Extramural activities covered in the FY'06 budget include SAIC contract modifications for the longitudinal summary of Cycles 1-6, the outline of the AFHS history, MAP testing for specimen viability and the relational database. CDC's serum sample testing for dioxin congeners and other chemical measurements will also be supported by FY'06 extramural funds. Program Management will attempt to address as many of NAS's recommendations on the AFHS disposition study as its financial and time constraints will allow.

AFHS FY'06 Activities

Col. Fox covered the following areas in her update. USAF's October 6, 2005 briefing to the House and Senate VA Subcommittees on the AFHS summarized results of the 2002 physical follow-up examinations, five papers published since January 2004, presentations at scientific meetings, involvement with RHAC, actions taken to respond to NAS's recommendations on the AFHS disposition study, and future research activities.

The Ranch Hand Association held its annual reunion on October 8, 2005 in Ft. Walton Beach, Florida with 50 Ranch Hand veterans and their families. USAF presented the same information that was given during the Congressional briefing. The Ranch Hand Association anticipates a much larger turnout at the 2006 reunion because this event will represent a 40-year anniversary.

Results of the 2002 follow-up physical examinations were officially released on July 8, 2005. USAF responded to numerous inquiries about the report and posted the

document on its web site. SAIC was contracted to develop an outline of the AFHS history and expects to complete this activity in February 2006. The draft AFHS comprehensive study report was distributed to and extensively discussed by RHAC during the meeting. USAF will revise the document based on RHAC's comments and expects to publish the final report over the next two months.

In terms of external collaborations, USAF established new guidelines and time-lines for its previous and current partners to submit papers and complete other activities in preparation of AFHS's closure date on September 30, 2006. CDC's dioxin congeners study is underway. The University of California-Davis adipose tissue study was completed. The Texas Tech University Health Science Center submitted three papers for publication on the metabolic syndrome and dioxin, insomnia and dioxin, and a nested case-control study on the metabolic syndrome and chronic sleep loss. SAIC was contracted to write a compliance study report to identify factors that impacted the participation of AFHS subjects in the six physical examinations. A statistical analysis of existing AFHS data will serve as the basis of this effort. SAIC expects to complete the compliance study in February 2006.

However, USAF believes that most of NAS's interim recommendations can be implemented. USAF had planned to develop contracts to publish three papers on nerve velocity conduction, dioxin and memory, and dioxin and hepatic function. USAF will continue its internal research on AFHS mortality.

Dr. Trewyn advised USAF to analyze differences between Ranch Hand and comparison veterans based on days of spraying, amount of the time spent in SEA and calendar period of service in an effort to detect birth defects, reproductive outcomes or other adverse impacts beyond cancer.

Dr. Stoto recommended that USAF include in their compliance study propensity score methodology. This strategy will assist in adjusting the study for non-responses and determining whether different results would have been obtained if veterans did or did not participate in the AFHS.

Update on the Dioxin Congeners Study

Dr. Pavuk covered the following areas in his status report. The purpose of the study was to determine whether AFHS veterans were exposed to dioxin congeners other than

2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in Vietnam. The study was designed to provide a detailed assessment of personal exposure to TCDD by measuring levels of dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), and mono-ortho and non-ortho substituted polychlorinated biphenyls (PCBs) in AFHS subjects who participated in the 2002 physical examination and did not have a previous valid TCDD measurement. USAF undertook this effort after CDC provided the entire battery of measurements.

Of the 94 comparison veterans who participated in the 2002 physical examination and did not have a TCDD measurement, 61 did not attend any previous physical examination and 33 did not have a previous valid measurement. The study also included 12 Ranch Hand veterans without TCDD measurements. The cohort was not randomly selected.

CDC used high-resolution gas chromatography and high-resolution mass spectrometry to analyze dioxin-like compounds. Lipid adjusted measurements were presented in values of pg/g of lipid or parts per trillion for all congeners, but mono-ortho PCBs were reported in values of ng/g of lipid or parts per billion. Toxic equivalency factors (TEFs) established by the World Health Organization were used to calculate PCDD, PCDF and PCB toxic equivalencies (TEQs) and the total TEQ in pg/g of lipid or parts per trillion. Demographic characteristics of the Ranch Hand and comparison veterans were considered in the study as well, including age at qualifying tour, year of birth, body mass index, alcohol consumption in drink years, pack years of smoking, and occupation as an officer, enlisted flyer or enlisted ground crew.

The dioxin congeners study concluded as follows. Background levels of organochlorines observed in the general population were also found in both the Ranch Hand and comparison veterans. The reduction in mean TCDD levels of two to five times relative to the 1987 levels was consistent with decreases seen in the general population. The mean 2002 TCDD level in Ranch Hand veterans was ~3 times higher than in comparison veterans, but total TEQs were similar between the two groups. The sample size of the Ranch Hand veterans was too small to make definitive conclusions about the total TEQs.

CDC and USAF are currently performing a statistical analysis of 600 more samples to detect PCDDs, PCDFs, PCBs and organochlorine pesticides in randomly selected Ranch Hand and comparison veterans. Preliminary results on the new component of the study with 300 Ranch Hand and 300 comparison veterans show that the overall exposures are similar, but exposure in Vietnam caused a difference. This difference is seen in TCDD, but none of the other congeners.

RHAC questioned the relevance of the dioxin congeners study in light of AFHS's time constraints. The members generally agreed on the importance of obtaining more information on differences in TCDD levels between Ranch Hand and comparison veterans, but emphasized that the limited amount of time remaining in the AFHS can be used to address more critical issues.

RHAC also noted that the objective of the dioxin congeners study differs from the purpose of the AFHS to determine whether long-term health effects exist and can be attributed to occupational exposure to herbicides with specific emphasis on Agent Orange. RHAC's position was that the existing data set should be used to make solid and confident correlations of adverse health effects seen in AFHS participants. It was not clear to the committee how the introduction of new data from the dioxin congeners study at this time would lead to new and valid findings.

USAF recalled that RHAC previously criticized the AFHS for solely focusing on TCDD measurements rather than the entire battery of congeners.

RHAC Business

Dr. Schechtman announced that RHAC may be charged with participating in conference calls, reviewing additional information and conducting other activities if USAF obtains an extended funding period beyond AFHS's closure date on September 30, 2006. However, the agencies that support RHAC meetings and other activities have stated no additional funds will be allocated beyond the end of FY'06. As a result, FDA will also need more funding to support RHAC's activities beyond this time.

Closing Session

The next RHAC meeting will be held on February 27, 2006. A decision will be made at that time on a specific date for the following meeting in late summer 2006. Dr. Stoto thanked USAF for its informative presentations, RHAC for its valuable input and participation, and FDA for its continued support.

With no further discussion or business brought before RHAC, Dr. Stoto adjourned the meeting at 2:01 p.m.

I hereby certify that to the best of my knowledge, the foregoing Minutes of the proceedings are accurate and complete.

2/27/06

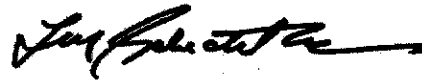
Date



Michael A. Stoto, Ph.D.
Chair, Ranch Hand Advisory Committee

2/27/06

Date



Leonard M. Schechtman, Ph.D.
Executive Secretary,
Ranch Hand Advisory Committee