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

Ranch Hand Advisory Committee
February 27, 2006
Rockville, Maryland

Record of the Proceedings

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ATTACHMENT 1

List of Participants

RHAC Members
Dr. Michael Stoto, Chair
Dr. Paul Camacho
Dr. Ezdihar Hassoun
Dr. David Johnson
Dr. Sanford Leffingwell
Dr. Ronald Trewyn

FDA/NCTR Representatives
Dr. Leonard Schechtman
RHAC Executive Secretary

Ms. Kimberly Campbell
Management Specialist

U.S. Air Force Representatives
Ms. Denise Bruce
Col. Karen Fox
Mr. William Murray
Lt. Col. Julie Robinson

U.S. Air Force Contractors
Mr. Manuel Blancas
Operational Technologies Corporation

Dr. William Grubbs
Science Applications International 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. Shannon Middleton
The American Legion

Ms. Jaclyn Petrello
Exponent, Inc.

Dr. David Tollerud
University of Louisville

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

RANCH HAND ADVISORY COMMITTEE MEETING
February 27, 2006
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 February 27, 2006 at FDA, 5630 Fishers Lane in Rockville, Maryland.

Opening Session

Dr. Michael Stoto, the RHAC Chair, called the meeting to order at 8:46 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 February 27, 2006 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. Camacho requested an additional change to highlight an issue in Chapter 16 of the AFHS Comprehensive Study report. The problem is related to Simpson's paradox in which effects of an AFHS subgroup disappeared. The language that Dr. Camacho submitted to USAF contractors to address this issue will be added to the minutes in a footnote.

Dr. Stoto entertained a motion to approve the minutes as modified; a motion was properly made and seconded by Drs. Camacho and Hassoun, respectively. With no further discussion, the November 18, 2005 RHAC Meeting Minutes were unanimously approved with the changes submitted into and noted for the record.

Report of the AFHS Disposition Study

Dr. David Tollerud, of the University of Louisville, chaired the Institute of Medicine's (IOM) AFHS Disposition Committee (AFHSDC). He explained that his presentation would primarily cover the organization of and recommendations in the report because the IOM (a component of the National Academy of Sciences) provided RHAC with regular updates on AFHSDC's charge, membership, process to gather data and interim report.

The key sections of the AFHS disposition study report focus on the AFHS background and data holdings; the ability of outside researchers to access the data; USAF protocols to collect, process and store specimens; obstacles and limitations to future use of the data; the scientific merit of retaining and maintaining the data; and AFHSDC's recommendations and other options for further study.

In general, Dr. Tollerud reported that AFHSDC concluded that the medical records, data, and biological specimens collected in the study, which is scheduled to close on September 30, 2006, are a trove of valuable research material. The committee recommended that--after the Air Force Health Study's scheduled end--these assets be made available to researchers through a custodian that takes an active role in fostering their use. In particular, he summarized AFHSDC's key findings, conclusions, recommendations and options.

- The limitations of the AFHS research assets should be addressed, including a small cohort that is unrepresentative of other in-theater veterans; a lack of biomarkers of herbicide exposure other than TCDD; potential herbicide exposures in comparison populations; AFHS's flawed design and execution; and privacy, security, ethical, legal and social issues related to the database. However, these weaknesses should not serve as barriers to retaining, maintaining and conducting further studies with the AFHS research assets.
- The AFHS research assets should be used in the future to take advantage of newer information, more recent science and more sophisticated analytical techniques. These technologies could be applied in expanding the study period or re-analyzing AFHS medical records, biological samples and health outcomes of subjects.

- Compliance with the Federal Records Act and retention of data for further research purposes should be strongly considered when evaluating the disposition of AFHS hard-copy records.
- The National Archives should serve as the federal decision-maker, evaluator and retainer of the AFHS research assets.
- All AFHS hard-copy records should be converted to an electronic format and then destroyed unless otherwise directed by the National Archives.
- Original electrocardiograms should be maintained because current technologies are not sufficient to transform these records into readily accessible or usable digitized data.
- Guidance should be solicited from the National Institute of Dental and Craniofacial Research about the future research value and disposition of videotapes on the teeth of AFHS subjects.
- A research entity should be identified and charged with managing and disseminating the existing AFHS research assets; continuing passive data collection on subjects; or conducting or facilitating further active data collection.
- The possibility of collecting additional data and specimens should be explored as well.
- The AFHS repository of biological specimens and other data should be maintained together and linked to generate the most value from these assets.
- A new AFHS custodian should be identified through a competitive process to manage and distribute AFHS epidemiologic data in the future or several existing infrastructures should be considered as options, including USAF, the National Archives, Department of Defense, Department of Veterans Affairs (VA), National Institutes of Health (NIH), Centers for Disease Control and Prevention, and the IOM Medical Follow-Up Agency (MFUA).
- MFUA, the Massachusetts Veterans Epidemiology Research and Information Center (ERIC), and the Seattle ERIC should be viewed as strong candidates to serve as the AFHS custodian. All three entities have demonstrated track records in conducting veteran's health studies; collecting, storing and disseminating epidemiologic data to independent researchers; maintaining quality control; and publishing results in the peer-reviewed literature. However, additional funding needs, potential disinterest in serving as the AFHS custodian and other limitations with these entities should be considered.
- The AFHS custodian should demonstrate existing abilities and a commitment to satisfy operational requirements for supervising and providing access to the research assets. This expertise should include capacity to oversee, maintain, retain and foster research on the data assets; provide external researchers with access to the data; market the

availability of the data assets to the scientific community; and address ethical, legal, social, privacy, security and confidentiality issues related to the management of biological specimens and epidemiologic records.

- USAF should implement a two-tiered informed consent process prior to the AFHS termination date. All subjects should be notified about the new custodian and their legal right to withdraw from AFHS at any point or refuse the transfer of their data. Each individual who continues to participate in AFHS should be informed about potential uses of the data and biological samples.
- The successor custodian should obtain new informed consent from AFHS subjects that covers a variety of areas, such as conducting new studies and collecting health data from children.
- An independent oversight and advisory board should be established and maintained to ensure transparency of the overall process and advise the custodian on proposals submitted for future research studies. The multi-disciplinary board should be represented by scientists, military officials, experts in ethical, legal and social issues, and other relevant stakeholders.
- The custodian should develop and implement strategies to provide input to subjects on new study results generated by AFHS data.
- Costs to maintain and provide access to AFHS data and conduct research on the assets should be thoroughly considered. These estimates include $150,000-$300,000 annually to support the custodian's data management responsibilities, $\geq$$200,000 annually to properly maintain the biological specimens, and additional costs to conduct new research depending on the scope, size and magnitude of the study.
- Congress should allocate a minimum of $250,000 annually for three years up front. These funds should be used to market the availability of the AFHS data assets to the external research community and award small grants to investigators to conduct secondary data analyses and pilot projects. However, these funds should not be diverted from other existing or planned research studies on the health of Vietnam veterans.
- The oversight and advisory board or another group should be convened five years after the custodian assumes responsibility to conduct an external and independent evaluation. This review should focus on the potential value and relevance of providing further support to retain, maintain and provide access to the AFHS research assets.

Dr. Tollerud made additional remarks to guide RHAC's discussion on the AFHS disposition study report. During a briefing on February 23, 2006, USAF announced that virtually all of the recommendations outlined in AFHSDC's interim report would be accomplished by the AFHS termination date. The National Cancer Institute (NCI) web site now contains recommendations on standards, procedures and protocols for all of its

funded biological specimen repositories. NCI also established a separate office specifically to address ethical, legal, social and other issues related to biological specimen repositories. The NCI model may become the federal standard in this area.

Groups that have received briefings on the report to date have expressed both enthusiasm for the scientific value of the AFHS research assets and caution about the funding aspects. AFHSDC has emphasized during the briefings that only a time-limited and relatively small investment will be needed to transition and advertise the AFHS data to the scientific community and provide outside investigators with access to the research assets.

Dr. Tollerud noted that the AFHS disposition study report reflects the outstanding efforts, valuable contributions and extensive participation of the ten AFHSDC members and consultants. He also thanked USAF staff and contractors for facilitating an extremely open and transparent process for AFHSDC to develop the report. USAF provided assistance to AFHSDC by answering a wealth of questions, hosting a site visit, and including the members in a specific analysis to determine the accessibility of data.

Dr. David Butler, of the Institute of Medicine/National Academy of Sciences (NAS), announced that briefings on the report have been provided to several groups, including VA staff, the House and Senate VA Committees, Congressman Christopher Shays, veteran's service organizations and MFUA. The VA was asked to brief the Massachusetts and Seattle ERICs as well.

Dr. Butler will seek permission from NAS leadership to provide RHAC with the full list of individuals and groups that have been briefed on the report. The entire report was submitted to Congress and the VA Secretary and is now available to the public on the National Academies Press web site (http://www.nap.edu/catalog/11590.html). The executive summary and full report were also distributed to RHAC.

Mr. William Murray, of the USAF Surgeon General's Office (SGO), reported that SGO is extremely concerned about the AFHS transition process from a funding perspective. Because Congress will allocate FY'07 appropriations after the September 30, 2006 termination date, USAF must make an unfunded request in the next few weeks to provide SGO with an opportunity to use year-end FY'06 dollars to support the AFHS transition. A custodian must also be identified within the next two months to receive the initial funds.

Mr. Murray added that SGO needs guidance from RHAC within the next two months to facilitate the AFHS transition. This time-line will provide SGO with at least six months to formulate the AFHS transition process and collaborate with Congress in developing a

funding strategy and specific recommendations for the FY'07 appropriation. If these actions are not immediately taken, no funds will be available to transition AFHS.

RHAC extensively discussed its role in responding to the AFHS disposition study report and potential next steps in light of the September 30, 2006 termination date. RHAC was particularly concerned that responsibility for the AFHS transition has not been designated to any entity at this point.

Based on the AFHS disposition study report, concerns expressed and other issues raised during the discussion, Dr. Stoto proposed the following next steps for RHAC to consider.

- Dr. Stoto, as the RHAC Chair, will write a letter to the HHS Secretary to emphasize the following points.

- RHAC previously communicated with the HHS Secretary expressing support for and urging that actions be taken to retain and maintain AFHS specimens and other data. The value of the AFHS research assets will be emphasized in the letter.

- TIME IS OF THE ESSENCE because AFHS is scheduled to end on September 30, 2006 and no funds are available to continue the study after this date. RHAC is immediately responding to the IOM report of the AFHS disposition study.

- A USAF SGO representative attended RHAC's meeting on February 27, 2006 and strongly emphasized that decisions on transferring the AFHS specimens and other data and paying for the retention and maintenance of these research assets must be made within the next two months.

- RHAC endorses two major points in the AFHS disposition study report. First, "there is scientific merit in retaining and maintaining the medical records, other study data and laboratory specimens collected in the course of the AFHS after the study's currently scheduled termination date." Second, "further study of the AFHS medical records, other study data and laboratory specimens should be accomplished by making these materials available for research via a custodian that takes an active role in fostering use of the assets." These statements are consistent with RHAC's position as noted in its previous meeting minutes and letters to the HHS Secretary. To ensure these recommendations are implemented, RHAC urges the HHS Secretary to also endorse these two points and take

proactive steps with regard to funding and designating an entity with responsibility for AFHS transition activities.

- The AFHS disposition study report identifies several potential custodians and outlines specific criteria under which the custodian should operate. RHAC is not prepared to make recommendations about the custodian at this time, but is willing to collaborate with the VA, USAF and other relevant governmental agencies to review plans and options. RHAC will undertake this effort in a timely manner given the urgency of the matter.

Dr. Trewyn formalized the proposal by placing a motion on the floor for RHAC to take the action steps as described by Dr. Stoto. The motion was seconded by Dr. Camacho and unanimously approved by RHAC.

Dr. Stoto will draft the letter on FDA letterhead, circulate the document to all RHAC members for review and comment, and revise the letter based on any comments received. He strongly emphasized that the review and revision process must be completed in the next two days in order to send the letter to the HHS secretary on March 2, 2006 (Appendix 1 and 2).

RHAC suggested that copies of the letter be widely distributed to Congressional staff, veterans' organizations, the USAF Surgeon General, VA Secretary and other relevant groups.

Updates on AFHS Activities

Response to the IOM Interim Recommendations. Col. Karen Fox, the AFHS Principal Investigator, described USAF's ongoing and future activities to respond to the IOM recommendations outlined in the AFHSDS interim report.

- "Create a comprehensive inventory of master data files organized by cycle." USAF has completed this task for Cycles 1-5. The inventory for Cycle 6 is 90% complete.
- "Create a comprehensive inventory of variables contained in the master data files." USAF hopes to complete this task in its entirety by the AFHS termination date. Inventories have been completed for Cycles 5 and 6 and efforts are underway to finish inventories for Cycles 2 and 4.
- "Create a master data code book containing the name of every data variable represented anywhere in the AFHS database." USAF will not be able to accomplish this task due to time constraints and other factors.

- "Create a document describing the contents, format and location of the AFHS collection of materials." USAF expects to complete this task by the AFHS termination date.
- "Develop a plan to prepare electronic files for transmittal to the National Archives." USAF is undertaking this effort, but will be unable to transfer the files in a rich-text format as requested by the National Archives. USAF and the National Archives will discuss whether the current SAS format will be useful.
- "Re-inventory all laboratory specimens, verify the location, and ascertain the number, volume and type." USAF is continuing this ongoing activity and expects to complete this task by the AFHS termination date.
- "Compile all information regarding specimen history into a single reference database. Compile all protocols regarding the receipt, maintenance, dispersal and return of specimens into a single reference document." USAF expects to complete these tasks by the AFHS termination date.
- "Document the status of all laboratory specimens sent to outside investigators." USAF reintegrated, segregated and documented returned specimens in the AFHS database instead of disposing of the data. USAF is now sending letters to all external investigators who have not returned or disposed of specimens.
- "Perform currently planned re-assays to aid in the evaluation of specimen stability and condition." USAF conducted a viability study in response to this recommendation.

Viability Study. Dr. Marian Pavuk, of SpecPro, Inc. presented results of the viability study. The research was conducted to assess whether AFHS frozen samples will be viable for use in future studies by other investigators and determine if the multiple analyte profile (MAP) technology can be applied to assay biochemical parameters of AFHS frozen samples. Of >70,000 archived samples, some of have been stored for >24 years. High-density quantitative immunoassays panels developed by the Rules Based Medicine Laboratory (RBML) were used to perform the analysis.

Five AFHS subjects who participated in the first five physical examinations and had multiple serum samples stored were randomly selected for the viability study. One sample from all five subjects for each of the five physical examinations was chosen for a total of 25 serum samples for the analysis. Each serum specimen was analyzed for 177 analytes, including 78 specific serum antigens, 43 autoimmune serologies and 56 infectious disease serologies. AFHS repeatedly measured 16 analytes in at least two examination cycles. These analytes were included in RBML's human MAP panel for comparison.

Quantitative assays included alpha-1 antitrypsine, C3 complement, creatine kinase, immunoglobulins A and M, prostate-specific antigen, thyroid-stimulating hormone, and aspartate aminotransferase. Of 177 analytes examined, 170 provided measurable results with the MAP technology and seven provided results that could not be measured on the standard curve. These analytes are typically absent or present in extremely low amounts of serum of relatively healthy subjects.

Of the 16 comparison analytes, eight had continuous measured levels with normal laboratory set ranges and eight had positive or negative findings in the AFHS for hepatitis, mitochrondial and thyroidal microsomal antibodies. The analysis of the 16 comparison analytes showed a high degree of consistency between the AFHS examinations and RBML's human MAP panel for assays in stored frozen serum samples.

Of the 177 analytes, 147 provided complete results for all samples analyzed across all five cycles. Results below the standard curve appeared to be related to the subject rather than the examination cycle or storage time. The analysis did not indicate that older samples were less preserved than more recent ones. Inter-person variability was found to be more prevalent.

The viability study also demonstrated that the biochemical integrity of the samples appeared to be well preserved and sensitive immunoassay-based analyses were successfully performed. RBML's human MAP panel appears to be a useful tool in analyzing stored frozen samples, particularly when serum is available and the analysis of a large number of analytes is required. Results of the viability study suggest that the stored AFHS samples will serve as a rich source of well-preserved scientific data.

Dr. Tollerud urged USAF to quickly publish the viability study results in the scientific literature. The exciting and impressive findings will play a significant role in marketing the AFHS data assets to outside researchers. RHAC fully supported Dr. Tollerud's suggestion to USAF.

Mortality Study. Dr. Pavuk reported that the current mortality study contrasts cumulative post-service mortality rates for 1,263 Ranch Hand veterans through December 31, 2003 and rates for 19,080 comparison veterans. The study excluded 22 Ranch Hand and 109 comparison veterans who were killed in action because these deaths were not caused by herbicide exposure. Relative risks, 95% confidence intervals and p-values were calculated with proportional hazards models. The analyses were adjusted for year of birth and military occupation because the majority of comparison veterans did not attend the physical examinations. Analyses with veterans who participated in physical examinations were adjusted for additional covariates.

Of the entire cohort of 20,343 veterans, 6% were black. Analyses adjusted for year of birth and military occupation showed a statistically significant elevated risk in mortality from all causes. Other major or significant increases were seen in a small number of Ranch Hand cases for heart, digestive, ill-defined and endocrine diseases. Analyses by military occupation showed statistically significant increases in mortality from all causes and atherosclerotic disease in enlisted ground crew. Small elevations were also seen for cerebrovascular, hypertensive and other circulatory diseases. Small or no elevations were observed in officers or enlisted flyers.

The mortality analysis by dioxin category included 2,551 USAF veterans who participated in at least one physical examination and had valid dioxin measurements. The high dioxin category contained a larger proportion of enlisted ground crew and younger veterans. Mortality from all causes was slightly elevated, but not statistically significant. No elevations were seen for cancer mortality. Adjustments for year of service or days of spraying did not change these results.

Elevations in circulatory disease mortality were seen in the low and high dioxin categories with a significant trend. This result was not observed in relation to dioxin in previous mortality reports because death certificates were used as the data source. Data were not available to adjust previous analyses for diabetes, but the magnitude or estimate of risk did not change in the current mortality study when adjustments were made for diabetes.

Key findings of the mortality study through December 31, 2003 are summarized as follows. Mortality from all causes and circulatory diseases showed statistically significant increases in Ranch Hand veterans in an analysis of all 20,343 AFHS participants. Increases in digestive, ill-defined and endocrine diseases represented a small number of cases and were statistically significant for endocrine diseases only. No significant decreases in risks of death were observed.

An increased risk of death from all causes and circulatory diseases was observed in enlisted ground crew. No substantial or statistically significant increases were seen in deaths from all causes, circulatory diseases or cancer in officers or enlisted flyers. Analyses by dioxin category showed an increased risk of death from circulatory disease in low and high categories. The test for trends was found to be significant. No increase in the risk of death due to cancer was observed. These analyses were adjusted for possible confounding factors.

The current mortality study strengthened the trend of an increased risk of death in Ranch Hand veterans observed in previous mortality studies. The trend of circulatory diseases is now stronger in all Ranch Hand veterans and Ranch Hand enlisted ground crew, the highest exposed group. Analyses by dioxin category supported this result and

found an increased risk of death due to circulatory disease in low and high categories. A dose-response relationship and significant test for trend were observed in these analyses.

Dr. Stoto pointed out that the current mortality study shows a new result in which the doubling of the circulatory disease mortality rate in a high proportion of the sample is due to factors independent of diabetes. He urged USAF to reexamine the role of diabetes in the current mortality study because more diabetes was found in dioxin-exposed groups.

Col. Fox made some clarifying remarks in response to Dr. Stoto's comments. The current analyses did not change the prevalence of diabetes, but showed a faster and stronger severity, onset and relative risk of diabetes in Ranch Hand veterans with high dioxin levels. Circulatory disease in enlisted ground crew in the high dioxin category was reported in USAF's previous mortality studies, but the new analyses show a stronger trend.

However, the overall results between the previous and current mortality studies did not change when adjustments were made for diabetes and other risk factors. Col. Fox noted that further research could be conducted with these data in the future to obtain more definitive answers about the stronger trends.

Comprehensive Study. Col. Fox announced that USAF awarded a contract to revise the comprehensive study report based on RHAC's previous comments at the last meeting held on November 18, 2005. The document is now being modified to reflect all of RHAC's recommendations with the following exceptions.

- Chapter 9-Endocrinology: "Use a bar graph to show incremental increases across cycles. Add relative risk, confidence intervals and the percentage of persons with diabetes." This task will require re-analysis because the scales of measurement change over cycles. Relative risk and confidence intervals will be reported in Chapter 4 only.
- Chapter 11-General Health Assessment: "Clarify lines 83-84 because the text can be misinterpreted to mean that dioxin can be consumed to maintain a youthful appearance." USAF will not change the sentence.
- Chapter 15-Neurology: "Provide information on peripheral neuropathy." USAF is not providing information on each disease, but will add a statement to clarify that none of the AFHS participants had acute or transient peripheral neuropathy.
- Chapter 17-Pulmonary: "Identify where malignant disorders are discussed." USAF addresses this issue in the neoplasia chapter.

- Chapter 19-Conclusions: "Move the VA list of Agent Orange-connected illnesses to the beginning of the report and use the list as a framework to present the results. Do not link all effects to dioxin." USAF will leave the VA list in its own chapter. The "check mark" pattern increases the difficulty in not linking all effects to dioxin.

Col. Fox added that USAF is attempting to leverage the expertise of a psychologist to thoroughly review Chapter 16-Psychology Assessment to address issues related to the ground crew. USAF will distribute the entire comprehensive study report to RHAC prior to publication, but the document will not be available for revisions.

Compliance Study. Col. Fox presented preliminary results of the compliance study. The study analyzed associations between AFHS compliance and group, race, age, dioxin level, military occupation and military commitment. Of all Ranch Hand veterans and original comparisons (OCs), 87.8% chose to participate in at least one examination. Of all Ranch Hand veterans and OCs eligible to attend all six examinations, 61.4% chose to participate in all six examinations.

Ranch Hand veterans had a higher compliance rate than OCs, while OCs had a higher compliance rate than replacement comparisons. Enlisted flyers had a higher compliance rate than enlisted ground crew. The compliance rate for officers was similar to enlisted ground crew at the beginning of the AFHS, but was closer to enlisted flyers by the end. Older veterans had a higher compliance rate than younger veterans. Retired veterans had a higher compliance rate than veterans who did not make the military their career. No associations were seen between compliance in race or dioxin.

Reasons for refusal included health reasons; dissatisfaction with USAF, the government, AFHS or previous examinations; fear of a physical examination; confidentiality issues; potential adverse impact on careers; and logistical reasons, such as a financial hardship, lack of interest or time, job commitments, length of travel or family concerns. USAF defined a "passive" refusal as the presence of a gatekeeper and two cancellations or failures to show for a scheduled examination. Of refusals at the 2002 physical examination, 28.6 were passive.

USAF initially classified "adamant" refusals during the 1992 examination as persons with no desire to be contacted by USAF ever. Of refusals at the 2002 physical examination, 23.3% of Ranch Hand veterans and 21.1% of comparison veterans were adamant. An analysis of the increase in non-compliance from the 1997-2002 physical examinations due to refusals for health reasons showed no association between refusing for health reasons and group or race. Older veterans refused more often for health reasons than younger veterans. The refusal rate for health reasons was greater

for enlisted ground crew than enlisted flyers and officers after adjusting for age. Enlisted ground grew was the youngest occupation on average.

An analysis of refusals for non-health reasons is underway. Preliminary results are now being examined on reasons for refusal due to dissatisfaction with USAF, AFHS, the U.S. government or previous examinations. Compliance at the most recent previous examination was found to be the best predictor of compliance at the current examination. Based on feedback USAF obtained during previous physical examinations, Col. Fox estimated that ~94% of AFHS participants would comply with the recommendations in the AFHS disposition study report.

External Collaborations. Col. Fox reported that USAF's collaboration with a researcher at the Texas Tech University Health Science Center has resulted in submissions of three papers to journals on the relationship between dioxin and sleep. In response to requests from two other investigators, USAF provided data to answer research questions on diabetes and dioxin in Ranch Hand veterans and psychological factors and the incidence of coronary heart disease.

Technical Reports. Col. Fox noted that USAF has provided briefings to RHAC on its papers on mortality through December 31, 2003, hypertension, the checkmark pattern, and a matched analysis of diabetes and herbicide exposure. USAF was unable to submit the papers to peer-reviewed journals for publication due to the limited time remaining in the AFHS. As a result, USAF will develop and publish the papers as technical reports to ensure these data are not lost.

Public Comment Period

Dr. Stoto opened the floor for public comments; no attendees responded.

Update on the *Nightline* Interview

Dr. Stoto announced that the transcript of the *Nightline* interview was distributed to RHAC for review. The interview focused on whether chemicals sprayed during the Vietnam War are now causing cancer in veterans. The interview aired on November 17, 2005 and featured Dr. Ronald Trewyn, a current RHAC member, and Col. Julie Robinson of USAF.

Dr. Stoto also noted that he received a letter in December 2005 from Lt. Gen. Claudius Watts, a USAF retiree and chair of the Ranch Hand Veterans Association. Lt. Gen.

Watts expressed concerns about remarks Dr. Trewyn made during the interview. Dr. Stoto responded to the letter in January 2006 and clarified that Dr. Trewyn's comments were made as an individual and not as an RHAC member. He further explained that he could not act on Lt. Gen. Watts' suggestions to communicate with the television station, contact other parties or ask Dr. Trewyn to apologize for his comments. Dr. Stoto emphasized that Dr. Trewyn is free to openly express his personal views as any other individual in this country.

Dr. Stoto explained the protocols for public communications for RHAC's future reference. As the RHAC Chair, Dr. Stoto serves as RHAC's designated spokesperson with the media. Questions about RHAC's procedural and operational issues should be directed to Dr. Schechtman as the RHAC Designated Federal Official.

RHAC Business

Dr. Stoto announced that the next RHAC meeting will be the last. RHAC should focus on providing guidance in response to the AFHS disposition study, particularly retaining and maintaining the specimens and other data. Dr. Stoto acknowledged that RHAC's role in this effort is unclear because specific transition activities are not discussed in the original AFHS mandate or RHAC's charter. Moreover, responsibility to transition AFHS after the September 30, 2006 termination is not designated to Congress, VA or any other agency.

Dr. Butler announced that NAS will be unable to support the participation of Dr. Tollerud or other AFHSDC members if the last RHAC meeting is held after April 30, 2006. Dr. Butler will attempt to use his personal time to attend the last meeting after this date. Dr. Schechtman pointed out that FDA may be able to provide these resources if the last RHAC meeting is held after April 30, 2006. Dr. Leffingwell suggested that every effort be made to convene the last RHAC meeting in April 2006. RHAC's letter to the HHS Secretary and wide dissemination of the document to various constituencies may facilitate actions to advance the AFHS transition process.

RHAC agreed to tentatively schedule the last meeting on April 10, 2006 to react to AFHS transition plans developed by any agency or group. RHAC will use the recommendations and options outlined in the AFHS disposition study report as the basis to provide input. The meeting will be rescheduled for a later date if no agency or group proposes an AFHS transition plan in March 2006.

Closing Session

Dr. Stoto thanked RHAC for its participation; USAF, IOM and AFHSDC for their diligent efforts in the AFHS disposition study; and FDA for its continued logistical support in convening meetings.

With no further discussion or business brought before RHAC, Dr. Stoto adjourned the meeting at 1:59 p.m.

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

9/7/06
Date

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

9/7/06
Date

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

Appendix 1

March 2, 2006

The Honorable Mike Leavitt
Secretary of Health and Human Services
200 Independence Ave. S.W.
Washington, D.C. 20201

Dear Secretary Leavitt:

I am writing to you in my capacity as chairman of the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants, a.k.a. the Ranch Hand Advisory Committee (RHAC), which reports to the Secretary of Health and Human Services and provides scientific advice regarding the Air Force Health Study (AFHS).

As my predecessor Robert W. Harrison, MD, wrote to Secretary Donna Shalala on April 5, 2001 and I wrote to Secretary of Veterans Affairs Principi on September 2, 2004, the RHAC has long been concerned that the national resource represented in the data and biological specimens collected in the Air Force Health Study will be lost when Air Force funding for the study runs out in September of this year. If this happens an investment of approximately $140 million, plus the time and energy of thousands of Vietnam veterans, will have been squandered.

Fortunately, in response to the *Veterans Benefits Act of 2003* (P.L. 108-183), and with support from the Department of Veterans Affairs (DVA), the National Academy of Sciences/Institute of Medicine (IOM) has recently completed a report entitled *Disposition of the Air Force Health Study* (http://www.nap.edu/catalog/11590.html). The report concludes that "There is scientific merit in retaining and maintaining the medical records, other study data, and laboratory specimens collected in the course of the Air Force Health Study after the study's currently scheduled termination date. Further study of the AFHS medical records, other study data, and laboratory specimens is advisable. This should be accomplished by making these materials available for research via a custodian that takes an active role in fostering use of the assets." While the RHAC did not have enough time between the report's release on Friday, February 24 and its meeting on Monday, February 27 to review all of the IOM's conclusions in detail, the statements that I quote are consistent with our understanding of the study's value, as well as the RHAC's views as expressed in the letters cited above. So, on this basis, the RHAC directed me to write in order to communicate our endorsement of the IOM conclusions quoted in this paragraph. Because time is of the essence, I am directing a similar letter to Secretary of Veterans Affairs R. James Nicholson, and enclose a copy for your information.

The IOM report goes on to identify some options regarding an appropriate custodian of the data and materials, including two DVA Epidemiological Research and Information Centers (ERICs) and the IOM's Medical Follow-up Agency (MFUA). Two agencies of the Department of Health and Human Services, the National Institutes of Health and the Centers for Disease Control and Prevention are also mentioned. The RHAC has not yet had time to study the IOM's recommendations, and consequently, is unable, as yet, to endorse any of them. However, we believe that we can most effectively fulfill our responsibility to provide scientific advice about the AFHS by offering our assistance to the Department of Veterans Affairs' and other agencies' in helping to identify a custodian for AFHS' assets. We recognize that a number of governmental and non-governmental entities might take on this role, but focus on the DVA as the Congressionally-mandated sponsor of the IOM study. We should not overlook the potential benefit of the massive information base that has been collected over the last 24 years; it now exceeds that collected for the Framingham study, which has been a cornerstone of preventive medicine for several decades. There has been no comparable study following young people through this phase of their lives. With new technology, the biological specimens might prove an invaluable resource for understanding development of disease processes and prevention of chronic disease.

We have been advised by the office of the Surgeon General of the Air Force that some action needs to be taken within weeks if the resources of the AFHS are to be saved. Thus we have scheduled the final meeting of the RHAC for Monday, April 10. In order to help us fulfill our responsibility to provide scientific advice about the AFHS most effectively, we respectfully request that you send a representative to discuss the Department of Health and Human Service's reaction to the IOM's recommendations about identifying a custodian for the AFHS's assets. Dr. Leonard Schechtman, the Executive Secretary of the Ranch Hand Advisory Committee, will be in touch with you regarding the specific time and place of the April 10 RHAC meeting.

Thank you for your resolute attention to this most urgent matter.

Sincerely,

Michael A. Stoto, PhD
Chairman, Ranch Hand Advisory Committee

Appendix 2

March 2, 2006

The Honorable R. James Nicholson
Secretary of Veterans Affairs
810 Vermont Ave. NW
Washington, DC 20420

Dear Secretary Nicholson:

I am writing to you in my capacity as chairman of the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants, a.k.a. the Ranch Hand Advisory Committee (RHAC), which reports to the Secretary of Health and Human Services and provides scientific advice regarding the Air Force Health Study (AFHS).

As my predecessor Robert W. Harrison, MD, wrote to Secretary of Health and Human Services Donna Shalala on April 5, 2001 and I wrote to Secretary Principi on September 2, 2004, the RHAC has long been concerned that the national resource represented in the data and biological specimens collected in the Air Force Health Study will be lost when Air Force funding for the study runs out in September of this year. If this happens an investment of approximately $140 million, plus the time and energy of thousands of Vietnam veterans, will have been squandered.

Fortunately, in response to the *Veterans Benefits Act of 2003* (P.L. 108-183), and with support from the Department of Veterans Affairs (DVA), the National Academy of Sciences/Institute of Medicine (IOM) has recently completed a report entitled *Disposition of the Air Force Health Study* (http://www.nap.edu/catalog/11590.html). The report concludes that "There is scientific merit in retaining and maintaining the medical records, other study data, and laboratory specimens collected in the course of the Air Force Health Study after the study's currently scheduled termination date. Further study of the AFHS medical records, other study data, and laboratory specimens is advisable. This should be accomplished by making these materials available for research via a custodian that takes an active role in fostering use of the assets." While the RHAC did not have enough time between the report's release on Friday, February 24 and its meeting on Monday, February 27 to review all of the IOM's conclusions in detail, the statements that I quote are consistent with our understanding of the study's value, as well as the RHAC's views as expressed in the letters cited above. So, on this basis, the RHAC directed me to write in order to communicate our endorsement of the IOM conclusions quoted in this paragraph. Because time is of the essence, I am directing a similar letter to Secretary of Health and Human Services Mike Leavitt, and enclose a copy for your information.

The IOM report goes on to identify some options regarding an appropriate custodian of the data and materials, including two DVA Epidemiological Research and Information Centers (ERICs) and the IOM's Medical Follow-up Agency (MFUA). The RHAC has not yet had time to study these recommendations, and consequently, is unable, as yet, to endorse any of them. However, we believe that we can most effectively fulfill our responsibility to provide scientific advice about the AFHS by offering our assistance to the Department of Veterans Affairs' and other agencies' in helping to identify a custodian for AFHS' assets. We recognize that a number of governmental and non-governmental entities might take on this role, but focus on the DVA as the Congressionally-mandated sponsor of the IOM study.

We have been advised by the office of the Surgeon General of the Air Force that some action needs to be taken within weeks if the resources of the AFHS are to be saved. Thus we have scheduled the final meeting of the RHAC for Monday, April 10. In order to help us fulfill our responsibility to provide scientific advice about the AFHS most effectively, we respectfully request that you send a representative to discuss the DVA's reaction to the IOM's recommendations about identifying a custodian for the AFHS's assets. Dr. Leonard Schechtman, the Executive Secretary of the Ranch Hand Advisory Committee, will be in touch with you regarding the specific time and place of the April 10 RHAC meeting.

Thank you for your resolute attention to this most urgent matter.

Sincerely,

Michael A. Stoto, PhD
Chairman, Ranch Hand Advisory Committee