DEPARTMENT OF HEALTH AND HUMAN SERVICES

and

FOOD AND DRUG ADMINISTRATION
NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

convene the

RANCH HAND ADVISORY COMMITTEE MEETING

Rockville, Maryland
April 30, 2004

RECORD OF THE PROCEEDINGS

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FOOD AND DRUG ADMINISTRATION
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RANCH HAND ADVISORY COMMITTEE MEETING
April 30, 2004
Rockville, Maryland

Meeting Minutes

The Department of Health and Human Services (HHS) and the Food and Drug Administration (FDA) National Center for Toxicological Research (NCTR) convened a meeting of the Ranch Hand Advisory Committee (RHAC). The proceedings were held on April 30, 2004 at FDA's Washington Operations Office, 5600 Fishers Lane in Rockville, Maryland.

Opening Session

Dr. Michael Stoto, the RHAC Chair, called the meeting to order at 8:19 a.m. He welcomed the participants to the meeting and opened the floor for introductions. The following individuals were present for the deliberations.

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
Committee Management Specialist

U.S. Air Force Representatives
Col. Daniel Berry
Dr. Joel Michalek
2Lt. Margaret Montgomery
Lt. Col. 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

Ms. Meagan Yeager
Science Applications International Corporation

Guest
Dr. Richard Atkinson
MedStar Research Institute

Approval of Previous Meeting Minutes. Dr. Stoto announced that the previous meeting minutes were distributed to RHAC for review and comment; the draft was revised based on changes submitted by Drs. Michalek and Stoto. Dr. Stoto entertained a motion to approve the previous meeting minutes as modified; a motion was properly made and seconded by Drs. Trewyn and Leffingwell, respectively. The January 21, 2004 RHAC Meeting Minutes were unanimously approved as modified with no further discussion.

Update on the Long-Term Studies Meeting

Dr. Joel Michalek, the Air Force Health Study (AFHS) Principal Investigator, reported on a meeting he and Dr. Stoto recently attended. The meeting was sponsored by the U.S. Medicine Institute and focused on the value of long-term studies. The participants included experts in the field, Congressional staffers, and high-ranking officials from the Army and Department of Veterans Affairs (VA). The participants expressed enthusiasm and showed support for long-term studies and also made positive comments about the AFHS. Most notably, the Surgeon General of the Army mentioned that the AFHS and similar studies should be incorporated into the Department of Defense's (DoD) regular routine of business.

Proposal for Future Use of Biological Samples

Col. Daniel Berry, the Aeromedical and Medical Information System Division Chief, oversees the AFHS in the USAF Human Systems Program Office. He was pleased to announce that the AFHS has a higher follow-up rate and more data points than the Framingham study and is recognized as the world's premier epidemiological study. The AFHS is a well-operated program and is based on solid science. Most notably, the AFHS was one of only 24 research and development studies that met or exceeded program goals out of a total of 187 projects. Over the past 21 years, $125.9 million has been allocated to the AFHS to cover 13,183 physical examinations, 42,953 records, 26,500 x-rays and 66,597 specimens. The final AFHS physical examinations were successfully completed on May 5, 2003.

Despite this success, the value of the AFHS is not widely recognized. Participants are extremely concerned about the termination of the AFHS and the possibility of data and specimens being lost or destroyed (specimens are perishable even with refrigeration). Congress is now attempting to identify a suitable location to house the AFHS data and specimens and has asked the National Academy of Sciences (NAS) to conduct a study in this effort. However, the NAS study will only focus on the disposition of the AFHS data and will not address the issue of the stored specimens and the use of the data. If no practical purpose can be identified for the data or specimens before the AFHS terminates on September 30, 2006, the likelihood of using these valuable study resources in the future will significantly decrease. Moreover, if no actions are taken regarding the AFHS data and specimens prior to being warehoused, they risk being put in indefinite storage, in which case the samples will eventually deteriorate and chances are that funding for such storage will eventually be discontinued. Such a scenario will result in study materials that will never be used again and will never benefit other similar research activities.

To address these concerns and illustrate the value of using the AFHS data in the future, Col. Berry suggested that a small "demonstration study" be conducted and ideally designed as follows. AFHS data would not be destroyed or depleted. Information stored on computers and maintained in participants' records would serve as the primary data source. The majority of each specimen would be preserved since only a small fraction of a given specimen would be needed. According to Col. Berry, the study would appeal and be of value to veterans, the military, Congress and society. Concerns expressed by participants would be addressed since the AFHS data would be maintained and not lost or destroyed. The demonstration project would be supported by private dollars or Congress rather than AFHS funding.

Col. Berry proposed a specific example of such a demonstration project: using the AFHS data to address the worldwide obesity epidemic. Obesity has now surpassed smoking as the number one cause of preventable death. Since 1980, the prevalence of obesity in the United States has doubled in adults and tripled in children. This trend is continuing to rise because ~31% of all U.S. adults are now obese with a body mass index (BMI) of 30 kg/m^2. The epidemic also affects military personnel and veterans since more federal dollars are now allocated to health care for obesity-related problems. Of $100 billion annually spent on this issue in the United States, $51.6 billion is in direct health care costs. The long-term implications of obesity include cardiovascular problems, diabetes, cancer and other adverse health effects.

The rapid rise in the prevalence of obesity is not limited to the United States. China, England, Panama, Paraguay and Sweden have also seen dramatic increases in obesity over the past 10 to 20 years. Factors associated with obesity include over-consumption

of food, lack of exercise, stress, neurotransmitters, eating disorders, genetics and sedentary lifestyles. However, studies have shown that individuals with reduced food intake and increased exercise eventually begin to regain weight after the body's metabolism adjusts to the new conditions. The irregular pattern of obesity does not appear to be completely explainable based upon behavioral patterns, but may be compatible with an infectious etiological model.

Col. Berry then presented such an infectious etiological model to consider as it contemplates use of a demonstration project. Of seven adenoviruses known to produce obesity in animals, four cause damage to the central nervous system and three have been shown to cause obesity. According to Col. Berry, preliminary evidence suggests that a peripheral mechanism of action may exist. The SMAM-1 is an avian adenovirus that produces obesity in chickens and is also associated with obesity in humans. Human adenovirus-36 (Ad-36) has been shown to increase adiposity and paradoxically reduce serum cholesterol and triglycerides in chickens, mice and monkeys. Human studies have demonstrated that persons with Ad-36 antibodies are heavier and have lower serum lipids. Other research has shown that the prevalence of Ad-36 antibodies was 30% in obese individuals in the United States and 22% in obese persons in Australia. Only 10% of non-obese subjects in the United States were found to be antibody-positive for Ad-36. In two pairs of twins who were discordant for Ad-36 antibodies, the antibody-positive twins were heavier and fatter than the antibody-negative twins.

According to Col. Berry, a retrospective study with rhesus monkeys used an informational database of serum specimens similar to the AFHS database. After seven years of measuring weight and drawing blood every six months, all monkeys became Ad-36 positive. The weight decreased 0.04 kg in the year prior to seroconversion, but increased 1.8 kg from baseline after seroconversion. Serum cholesterol increased ~5 mg/dL in the year before seroconversion and decreased 35 mg/dL afterwards. Since an injection of Ad-36 causes infection and weight gain in animals, an ethical research design must be applied to demonstrate effects in humans. The human study would test for Ad-36 antibodies to ensure that no subjects had prior Ad-36 infection. The height and weight of the eligible cohort would be measured to calculate BMI. Blood samples would be taken every few years to identify subjects who acquired Ad-36 infection by natural means. Positive Ad-36 antibody tests would be used to compare weight gain among infected and non-infected subjects.

According to Col. Berry, an Ad-36 research project on humans would require several years after initiation, but data already gathered during the AFHS could be used for the demonstration study. Laboratory data could be reviewed to determine the height and weight of AFHS participants and a small scraping of fresh frozen plasma specimens could be tested. The study would be designed to assay for virus antibodies from all

AFHS time periods; correlate changes in weight, serum lipids and other variables maintained in the database; and leave the AFHS data intact for future studies.

The importance and benefits of an Ad-36 study would be significant for various stakeholders. From a research perspective, the project will most likely lead to an Ad-36 vaccine development program if the findings conclusively demonstrate that Ad-36 causes obesity in infected persons. From a military perspective, an Ad-36 vaccine could potentially prevent or reduce obesity induced by Ad-36 among military personnel, improve military readiness, reduce the cost of weight management programs funded by the military, and decrease the need for taxpayer dollars to support military health care costs directly related to obesity. From a societal perspective, the study would positively impact the non-military population since obesity is also a growing problem that affects a large portion of adults and children in the United States. From an AFHS perspective, the Ad-36 research project would be extremely rewarding to participants because their data will be used to benefit other groups. The study would also demonstrate the value of applying the AFHS data/specimens to other health studies and increase the likelihood that specimens will be maintained/preserved for use in the future studies instead of being destroyed or eternally stored and forgotten.

Col. Berry announced that expertise has already been identified for the Ad-36 demonstration project. Dr. Richard Atkinson, of MedStar Research Institute, is a leading researcher in the field of Ad-36 and obesity. He has expressed a willingness to design the study and collaborate with USAF in implementing the demonstration project. SpecPro is an Alaska Native corporation with a successful track record in obtaining Congressional funding and has already requested support for the study from Congress. SpecPro has an established relationship with the AFHS through its history of coding AFHS data.

During discussions with members of the Brooks City-Base Institutional Review Board (IRB), Col. Berry received favorable feedback on obtaining approval of the study protocol for the Ad-36 demonstration project. Additional support was being sought in the form of RHAC approval for the USAF to proceed with the study.
Dr. Stoto made clarifying remarks to guide the RHAC discussion of the proposal to use AFHS data for the Ad-36 demonstration project:

1. As a scientific advisory committee, the RHAC members should only focus on the scientific merits of the proposal and not lobby for or against any particular study.
2. The RHAC's role is limited to advising the HHS Secretary; and members should review the charter to compare the RHAC's charge to regarding its role with respect to the NAS's Congressionally mandated study on the disposition of AFHS data.
3. The members should carefully consider whether the RHAC is now in a position to endorse, support or approve the Ad-36 demonstration project as the best

mechanism for using the AFHS data in the future. In particular, several complex issues have not yet been resolved, such as informed consent, appropriate sample size, viability of the hypothesis, benefits beyond the military population, and the value of the study to the scientific community.

4. The members should consider funding sources other than Congress in this effort. For example, specimens and other AFHS data could be made available to researchers to make a compelling and scientific case to the National Institutes of Health (NIH), other funding agencies and research organizations to support the Ad-36 demonstration project.

Dr. Leffingwell requested additional details on the fraction of scrapings from the AFHS specimens that would contain stored plasma. Dr. Atkinson replied that the assays could be conducted with a minimum of 300 microliters of plasma, but 500 microliters would be ideal. If the project is funded, however, an assay will be developed that will require smaller quantities of plasma or serum in the range of 10-20 microliters.

Dr. Michalek expressed full support for the proposal, but he cautioned the RHAC that actions must be taken prior to the termination of the study on September 30, 2006. Civil service employees, military personnel and contractors with a wealth of knowledge, experience and expertise in the AFHS will not be available after the project is concluded. Informed consent will also play an important role in the time-line of the study. For example, two years were required to obtain questionnaire responses from 600 AFHS participants. Dr. Michalek emphasized that the impending termination date of the AFHS is becoming a source of anxiety in regards to initiating any new research. The ability to apply the AFHS data to another research project will be less realistic from a scientific perspective if no actions are taken over the next few months.

Dr. Atkinson also commented on the short time-line in the context of the suggestion to consider NIH as a funding source. NIH's grant application deadlines are February 1, June 1 and October 1 of each year. If the RHAC tables a decision on the Ad-36 demonstration project until its September 2004 meeting, a proposal could not be submitted to NIH until February 1, 2005 because the October 1 deadline would not be feasible. The proposal would be reviewed in June or July 2005, but less than 20% of NIH grant applications are approved in the initial review. Dr. Atkinson acknowledged that a distinct possibility exists for the AFHS to be terminated on September 30, 2006 before NIH approves the grant application for the Ad-36 demonstration project. As a result, he agreed that other agencies should also be considered as funding sources.

Mr. Maurice Owens, of Science Applications International Corporation (SAIC), reported that the Veterans Benefits Act of 2003 directed the VA Secretary to contract NAS or a similar entity to conduct a study on the disposition of the AFHS data 60 days after the legislation was signed. The awarded contractor would be given 120 days thereafter to

produce a report. According to this time-line, a report of the findings is due by June 16, 2004 because the legislation was signed on December 16, 2003. However, the VA Secretary has not formally contracted NAS to conduct the study and has not allocated funds for this effort to date.

Dr. Camacho announced that he recently learned NAS maintains Science and Technology Boards for both the Army and Air Force. Bruce Braun is the Director of the Army Board and Michael Clark serves in this capacity for the Air Force. Because Mr. Braun has expressed a great deal of interest in housing the AFHS data, Dr. Camacho encouraged USAF to follow up on this contact as a potential source. Dr. Stoto committed to contacting Dr. Rick Erdtmann, the new Director of the Medical Follow-Up Agency. The agency is housed in the NAS and maintains databases of veterans' health for epidemiological studies.

Several RHAC members endorsed and expressed support of using the AFHS data for the Ad-36 demonstration project as proposed by Col. Berry. Based on comments by the members during the discussion, Dr. Stoto confirmed that the RHAC will take the following actions. First, Dr. Stoto will draft a letter on behalf of the RHAC to HHS Secretary Tommy Thompson, with a copy to VA Secretary Anthony Principi and Congressional staffers. Several points will be covered in the letter. USAF made a presentation to the RHAC on potentially using the AFHS data for an Ad-36 demonstration project. The members agree that the proposal is extremely promising, but the RHAC is not in a position to make a judgment about the project, due to its role as a federal advisory committee. Congress has asked NAS to conduct a study on the disposition of AFHS data, but no funding has been provided for this effort to date. The RHAC urges the HHS Secretary to communicate with the VA Secretary to allocate the funds soon. The draft letter will be circulated to the RHAC membership for review, comment and approval, finalized and placed on FDA/NCTR letterhead to be forwarded to the HHS Secretary. [Following the meeting, Dr. Stoto determined that it would be more appropriate to invite Secretary Principi to send a representative to the September meeting to discuss these issues. A copy of that letter is attached for the committee members' information.]

Second, the RHAC charter, NAS charter and other relevant briefing materials will be distributed to the members prior to the next meeting to assist the RHAC in its decision-making on the proposal for the Ad-36 demonstration project. Third, efforts will be made to invite an NAS representative to the next meeting to provide an update on the AFHS disposition study. The speaker will be asked to discuss funding to maintain the AFHS samples, necessary staff and other relevant issues.

Review of Chapter 1: Introduction

Dr. Stoto announced that the remainder of the meeting would be devoted to RHAC's first of three chapter reviews from the AFHS physical examinations in 2002. RHAC will primarily focus on background chapters during the first round and will review results chapters during the second and third rounds. Due to time constraints, he asked the members to limit the discussion to substantive issues and submit written editorial comments to Lt. Col. Julie Robinson of the USAF.

Drs. Trewyn and Camacho were charged with the review of Chapter 1. Their comments along with recommendations by other RHAC members are outlined below.

- Clearly describe the composition of the comparison group in Table 1-1 to differentiate between dioxin and herbicide exposures.
- Add language on line 95 to emphasize that an unexpected result of an increased risk of cancer with years spent in Southeast Asia (SEA) was found in the comparison group.
- Provide a breakdown of countries in Vietnam versus other locations where the comparison group served.
- Consider the possibility of using AFHS specimens from the 2002 physical examination to identify potentially significant health problems associated with exposure to non-dioxin-contaminated herbicides.
- Provide resources for the lay audience since the report is written at a highly technical level primarily for epidemiologists, clinicians and biostatisticians. For example, create a bibliography, develop a glossary of terms, and include a standard one-page summary at the beginning of each substantive chapter to explain that the definition of dioxin is "TCDD" and four different statistical methods were used. Use the "Introduction to Epidemiology" bibliography developed by Dr. Stoto as a resource in this effort.
- Incorporate text to reassure readers of the scientific integrity of the AFHS by describing quality control procedures, peer review and other actions that were taken.
- Insert new text into Section 1.1 to address concerns that may be raised by veterans, advocates and other interested groups in the future. For example, add language to document that the statistical models have been historically used and were also utilized in the AFHS for comparison purposes. Include a statement to explain that several findings on the comparison group were only recently discovered and the new information will be published in the future, such as years in SEA as a risk factor for cancer in the control group and no correlation between years in SEA and diabetes. Mention that the new publications are funded with AFHS

dollars. Repeat the new text in the "Future Directions" chapter and also cite the web site that lists the upcoming AFHS publications.

Dr. Michalek made follow-up remarks to the RHAC's comments on Chapter 1. The existing AFHS database cannot be used to develop an exposure index for non-dioxin-contaminated herbicides because day-to-day exposure records were not available in 1977 when AFHS was designed. The herbicide tapes are not specific to a particular base or individual. However, new and more detailed information with the actual date and base where an individual was stationed during the Vietnam War has been gathered. The data are currently being maintained by Dr. Jeanne Stellman of Columbia University and can be used to develop an exposure index for non-dioxin-contaminated herbicides for the first time. Because the new information is being used to study Army ground troops rather than Ranch Hands, Dr. Michalek is attempting to stimulate a discussion with Dr. Stellman about the benefits of applying these valuable data to the AFHS.

With respect to developing new material for the lay audience, Dr. Michalek explained that major revisions to the chapter format or any other changes in the scope of work will need to be considered and discussed by Program Management. He reminded RHAC that USAF is developing the report under a contract with SAIC.

Review of Chapter 2: Dioxin Assay/Appendix A

Dr. Hassoun was charged with the review of Chapter 2 and Appendix A. Her comments along with recommendations by other RHAC members are outlined below.

- Include a reference to inform readers that a detailed description of the method used for the serum dioxin assay can be located in the 1986 paper by Patterson published in *Annals of Chemistry*.
- Add a sentence to explain that Figure 2-4 illustrates no body burden among controls and a body burden among Ranch Hands, which suggests exposure to Agent Orange during years in Vietnam.

Review of Chapter 3: Questionnaire Methodology

Dr. Trewyn was charged with the review of Chapter 3; his comment is outlined below.

- Change the sentence on line 39 to "All participants were asked questions to update their medial histories since their last interviews and were reminded of information already reported."

Review of Chapter 4: Physical Examination/Appendix B

Dr. Johnson was charged with the review of Chapter 4 and Appendix B. His comments along with recommendations by other RHAC members are outlined below.

- Add a statement to clarify that all internists referenced in the report are "Board Certified Internists."
- Change "internist with subspecialty in pulmonary disease" in Table 4-1 to "pulmonologist" to be consistent with "radiologist" and "dermatologist."
- Revise Table 4-2 as follows: change "differential segs" to "segmental neutrophil;" change "cubic micra" to either "cubic micrometer" or "micron;" change "differential lymphs" to "differential lymphocytes;" place "absolute" in the left column under "T & B lymphocytes" with the list of other absolutes in the right column; and reformat the list of 137 laboratory tests to be consistent with the list of 83 laboratory tests in Appendix B.
- Include a statement to confirm that the physical examinations were properly administered despite errors in the *Examiner's Handbook*.
- Add language to clarify that the *Examiner's Handbook* was provided to SAIC and Scripps Clinic clinicians for guidance only; clinicians were actually trained in administering physical examinations with the biomedical test plan developed by SAIC. Include the biomedical test plan in Chapter 4 or reference the web site where the document can be located.
- Add language in parenthesis to the "chemistry" table on line 38 to explain whether the rapid plasma reagent card test, fluorescent treponemal antibody absorption test or both were conducted to detect syphilis.
- Expand "additional QC included the following elements" on line 63 to clearly describe standardized data and other quality control procedures clinicians used to verify results of the physical examinations. Include forms the clinicians used in Appendix B.
- Add language to clarify and expand on the following sentences: "Alcohol was prohibited for 24 hours before the first day of the examination" on line 86; "They were paid their stipends and reimbursed for travel at this time" on line 105;" and "On the first examination day, participants were asked to collect their first urine void of the day at the hotel" on line 107.
- Change the sentence on line 121 to "the Air Force was provided 35 cc of serum and 10 cc of whole."

Review of Chapter 17: Renal Assessment/Appendix F-9

Dr. Leffingwell was charged with the review of Chapter 17 and Appendix F-9. His comments along with recommendations by other RHAC members are outlined below.

- Clarify the "Statistical Methods" section with the following statements. Scheffe's method or a similar procedure is appropriate for a restricted setting, but is not suitable for the AFHS. A multiple comparison procedure is best used in a control clinical trial where primary endpoints and contrasts with placebo and control groups are required. Rothman and other current textbooks argue against using the Bonferroni method.
- Reformat Table 17-3 to illustrate positive findings only and place the remainder of the extensive analysis that shows no significant associations in an appendix or newspaper column.
- Provide percentages for the "born <1942 or ≥1942" dependent variable-covariate associations to illustrate the significant correlation with blood urea nitrogen.
- Replicate Dr. Leffingwell's "Table of Significant Results" in substantive chapters where numerical differences substantially add values beyond the p value. Create the tables as a separate handout or supplement to the major report.
- Revise line 247 as follows. Add language to clarify that the text refers to an empiric formula estimating creatinine clearance and is not an actual calculation. Include a citation to reference that the actual formula is from Cockroft-Gault.
- Revise lines 369-373 to note that age and weight may provide a different adjustment or additional information to estimate 24-hour creatinine generation or excretion as an independent variable. Tabular data suggest a positive correlation between race and weight or age.
- Correct the "Cockroft-Gault (52, 53)" citation on line 1088; the "References" section lists 52 and 53 as Coresh and Lam, respectively.
- Change the sentence on line 1096 to "The AFHS cutpoints for hematuria and pyuria (two cells per HPF) will miss few cases of disease, but may cause inclusion of more healthy subjects that would result in higher numbers."

Review of Chapter 9: General Health/Appendix F-1

Dr. Johnson was charged with the review of Chapter 9 and Appendix F-1. His comments along with recommendations by other RHAC members are outlined below.

- Revise the "Study Summary Results" throughout the chapter because these sections are filled with various facts and are difficult to read. Include language to explain that the summaries were extracted from previous reports.
- Clearly define the terms "direct," "positive," "inverse" and "adverse" in the "Results" section.
- Create a boilerplate with standard language to incorporate into each clinical chapter.
- Revise the tables to highlight significant p values in bold.
- Incorporate more text into the description of each model to clarify the following terms: "Ranch Hands-Initial Dioxin-Unadjusted," "analysis results for $\log_2$ initial dioxin," "adjusted relative risk," "adjusted for BMI," "relative risk for a twofold increase in initial dioxin," and "the p value is 0.314 for adjusted relative risk."
- Change the sentence on line 150 to "Apart from the AFHS examinations, only a few published reports other than those described above relate clinical laboratory indices to serum and adipose dioxin levels."
- Add "(>20 mm/hr)" after "erythrocyte sedimentation rate abnormalities" on line 168, but delete the phrase in the remainder of the chapter to avoid redundancy.
- Add text on line 181 to further explain "the (geometric) mean erythrocyte sedimentation rates did not differ significantly."
- Change the sentence on line 215 to "In general, body fat and erythrocyte sedimentation rate exhibited significant direct associations with initial dioxin."
- Change the sentence on line 234 to "In summary, with the exception of erythrocyte sedimentation rate, the data analyzed in the general health assessment did not reveal any direct association between adverse health effect and herbicide exposure or to body burden of dioxin."
- Change the sentence on line 270 to "Longitudinal analyses showed that Ranch Hands, particularly the two enlisted strata, had a higher percentage of abnormal erythrocyte sedimentation rates relative to comparisons."
- Change the sentence on line 273 to "This increased occurrence of elevated erythrocyte sedimentation rates in Ranch Hands raises the possibility of a subtle inflammatory, infectious or occult malignant disease process associated with the body burden."
- Include language to explain that "erythrocyte sedimentation rate" is not mentioned again after line 281 because the section was moved from the "General Health" to "Hematology" chapter in the 2002 physical examinations.
- List the "dependent variables" on line 285.

- Move “weight/(height)^2" on line 305 to the end of the sentence on line 306.
- Move “(118)” on line 309 to the end of the sentence on line 310.
- Incorporate text at the beginning of the “Dependent Variable-Covariate Associations” section to explain the rationale for the sentence on line 389: “The highest percentage of participants who perceived their health as fair or poor was among nondrinkers.” Clarify that this association was summarized rather than studied due to its importance in interpreting other results.
- Change the sentence on line 432 to “Model 2 explored the relationship between the dependent variable and the initial dioxin level at the time of potential exposure to dioxin when they began as a Ranch Hand.”
- Change the sentence on line 443 to “Model 3 created categories of Ranch Hands based on the initial dioxin levels and examined the relation between the dependent variables and these categories.”
- Add more descriptive language to the titles of all models in the tables, such as “Self-Perception of Health of Ranch Hands Versus Comparisons Unadjusted for Covariates” on line 476 and “Self-Perception of Illness in Ranch Hands Versus Initial Dioxin Unadjusted for Covariates” on line 478.
- Replace “0.10" with “0.05" on line 517 to be consistent with the remainder of the report and emphasize the “minimum p value.”
- Change the phrase on line 760 to “helped to clarify.”
- Change the sentence on line 773 to “However, during the course of the AFHS since 1982, self-perception of general health has shown mixed results.”
- Change the sentence on line 782 to “Officers more often perceived their health to be in the “excellent” or “good” categories” to clarify that the variation was across subjects and not over time.
- Change the term on line 784 to “various levels of education.”
- Revise the text beginning on line 796 to distinguish between the entire longitudinal study and the 2002 physical examination only.
- Make the following changes to dearly differentiate between other studies or prior follow-up examinations: “a finding similar to results reported in earlier phases of this study” on line 802 and “These results are generally consistent with earlier phases of this study” on line 818.
- Change the sentence on line 847 to “Therefore, more than one-third of AFHS participants are at risk for health complications associated with obesity.” Delete “significant” since the finding was not statistically evaluated and has no p value.

Review of Chapter 6: Quality Control/Appendix D

Dr. Camacho was charged with the review of Chapter 6 and Appendix D. His comments along with recommendations by other RHAC members are outlined below.

- Incorporate language to clarify that the National Opinion Research Center (NORC) specifically developed and designed the computer-assisted personal interview system for the AFHS.
- Add another down arrow to Figure 6-2 to illustrate the exit.
- Include a statement in the "Data Completeness Checks" section to note that physicians performed the majority of quality control measures while participants were at Scripps Clinic, but participants were asked to return if necessary.
- Change the sentence on line 130 to "NORC schedulers telephoned the 15 participants who should have been asked these questions, but were not to collect that information."
- Use either lower case or capital letters to make the following titles consistent throughout the chapter: "field manager," "data collection task leader," "interviewer," "Air Force researchers" and "NORC designers."
- Add language in Appendix D-1 to clarify that lower numbers mean better quality control. Include sentences to explain that "high," "medium" and "low" refer to a laboratory quality control measure in which manufactured specimens are used to calibrate equipment.
- Revise "No participants felt that the experience was unsatisfactory" on line 193 to more strongly emphasize the overall clinic experience.

At the conclusion of the first round of chapter reviews, Dr. Stoto suggested that the two drafts for each chapter be clearly indicated in the future with "Draft 1" or "Draft 2" in the footer of the document. The RHAC also agreed that a global change should be made throughout all chapters by revising tables to replace phrases with complete descriptive sentences. Overall, the RHAC acknowledged the tremendous effort that has been devoted to the AFHS and commended USAF and SAIC for developing a well-written and evidence-based report.

Public Comment Period

The Chair called for public comments; no attendees responded.

RHAC Business

Dr. Stoto announced that the RHAC will conduct its review of the second set of chapters during the September 2004 meeting; those chapters will address psychology, hematology, immunology, cardiovascular disease, and study selection participation/statistical methods. If time permits, the endocrine chapter may be included in this round as well. For the second cycle, Drs. Stoto and Camacho will review the statistical methods chapter and Dr. Hassoun will review the psychology chapter. Ms. Kimberly Campbell, the Committee Management Specialist, will circulate an e-mail to the RHAC requesting the expertise of each member. A roster will be developed based on this feedback to assist Dr. Stoto in assigning chapters to members for the second review.

Dr. Trewyn suggested that before the RHAC reviews the cancer chapter, the USAF should revisit this section to determine whether a statistically significant health effect is present if the comparison group is divided by personnel stationed in-country versus those stationed out of country. Dr. Michalek confirmed that new findings to address this issue will be incorporated into the cancer chapter and will also be published soon. The new unpublished data show that an SEA effect on birth defects and diabetes was not seen in the control group. However, presence in Vietnam was found to be a risk factor for cancer in the control group and an extremely strong effect on the incidence of cancer was seen.

Dr. Stoto advised USAF to list the upcoming publications with the new findings in both the literature review and discussion sections of the report. Dr. Camacho urged USAF to take proactive measures in addressing concerns that may be raised by the community in the future. For example, the report could be revised to clarify that effects on birth defects and diabetes were not seen when personnel stationed in country and those stationed out of country were maintained as one comparison group.

Dr. Michalek summarized the RHAC charter in preparation for the members to make a decision during the next meeting on the proposal for the Ad-36 demonstration project. The charter states that the Assistant to the President for Domestic Policy directed the establishment of an interagency workgroup in December 1979 to study possible long-term health effects. The interagency workgroup recommended that USAF conduct the study in August 1980 and RHAC was formed in 1981.

The RHAC is charged with advising the Secretary and Assistant Secretary for Health about the oversight and conduct of the AFHS and providing scientific oversight of the VA Chemical Corps Vietnam Veterans Health Study and other studies in which the Secretary or Assistant Secretary for Health believes involvement by RHAC is desirable. In addition to the RHAC's purpose and structure, the charter also outlines appropriate

members to serve on RHAC; suitable qualifications of both the Chair and members; frequency and structure of meetings and public sessions; and honoraria, meeting minutes and the expiration date.

Closing Session

The next RHAC meeting is tentatively scheduled on September 22, 2004; several members had a conflict with the date of September 8, 2004 that was proposed during the previous meeting. NCTR will poll the members by e-mail to confirm the new date.

With no further discussion or business brought before the RHAC, Dr. Stoto adjourned the meeting at 12:59 p.m.

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

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

_____ _____

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

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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 and select advisory committees.

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