

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
January 21, 2004***

RECORD OF THE PROCEEDINGS

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Meeting Minutes

The National Center for Toxicological Research (NCTR), Food and Drug Administration (FDA), Department of Health and Human Services (DHHS), convened a meeting of the Ranch Hand Advisory Committee (RHAC). The proceedings were held on January 21, 2004 at FDA Headquarters, 5630 Fishers Lane in Rockville, Maryland 20857.

Opening Session

Dr. Robert Harrison, the RHAC Chair, called the meeting to order at 8:14 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. Robert Harrison, Chair
Dr. Paul Camacho
Dr. Michael Gough
Dr. Sanford Leffingwell
Dr. Kwame Osei
Dr. Michael Stoto
Dr. Ronald Trewyn

FDA/NCTR Representatives

Dr. Leonard Schechtman, RHAC Executive Secretary
Ms. Kimberly Campbell, Management Specialist

U.S. Air Force Representatives

Col. Karen Fox, M.D.
Lt. Margaret Montgomery
Dr. Joel Michalek
Lt. Col. Julienell 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
Mr. William Murray, ANSER
Dr. Maurice Owens, Science Applications International Corporation
Dr. Marian Pavuk, SpecPro, Incorporated
Ms. Meagan Yeager, Science Applications International Corporation

Guests

Dr. David Butler, National Academy of Sciences
Dr. Ezdihar Hassoun, University of Toledo
Dr. David Johnson, Florida Department of Health
Ms. Pat Phibbs, Bureau of National Affairs
Ms. Elizabeth Skillen, Agency for Toxic Substances and Disease Registry

Current RHAC Business

Approval of Previous Meeting Minutes. Dr. Leonard Schechtman, the RHAC Executive Secretary, confirmed that the November 14-15, 2001 meeting minutes were distributed to the members, revised based on RHAC's comments, and approved and finalized with the Chair's signature. The March 13, 2003 meeting minutes were circulated to the members for review and comment; NCTR is now seeking RHAC's approval on this document as well.

Dr. Stoto expressed concerns about the process of generating meeting minutes. He suggested that draft minutes be made available to the committee members in a more timely manner. He explained that, in his opinion, rather than the meeting minutes being a condensed version of a verbatim transcript, it was preferable to have the document summarize the essence of the deliberations, organize presentations and discussions by subject, and highlight key decisions.

Dr. Schechtman indicated that actions had already been taken to address these issues and that a new science writer had been contracted to produce verbatim transcripts, to work with NCTR in developing quality minutes, and to provide those minutes to the members more promptly. Regarding the minutes of the previous March 13, 2003 meeting, the RHAC members agreed to submit their comments and editorial changes to the draft distributed previously via email, as requested by Dr. Schechtman.

RHAC Membership. Dr. Schechtman informed the committee members of attempts to obtain a special exception to DHHS policy that limits the service of advisory committee members, pointing out that the language in the original 1981 charter stated that members would be invited to serve for the duration of RHAC. Furthermore, he asserted that because of the approaching (September 30, 2006) termination of the Ranch Hand Study (RHS), the RHAC efforts that would be involved in completing its review of the study results would be most efficiently carried out if the committee remained intact with its current knowledgeable, experienced membership. He stated that the significant turnover in membership at this time could very likely impose a hardship on the efforts of the RHAC that could jeopardize its efficiency and productivity and impede the review process as it moves towards closure and resources are no longer available.

Despite this reasoning, Dr. Schechtman regrettably announced that the Department had rejected the waiver request for Drs. Gough and Harrison because both of these members have served on RHAC for periods that far exceeded the limit imposed on currently allowable advisory committee terms of service. However, Dr. Schechtman was pleased to report that DHHS had approved additional two-year terms for Drs. Camacho, Osei and Sills from February 1, 2004 through January 31, 2006. These three members have not exceeded the limit on advisory committee terms as outlined in DHHS policy. In consideration of his experience on the committee and his familiarity with the RHS, Dr. Stoto was requested to replace Dr. Harrison as the RHAC; Dr. Stoto has accepted the position.

Because the attempts at obtaining a waiver approval were unsuccessful, nominations for new members were forwarded to DHHS on November 20, 2003. The two nominees who will fill the vacancies left by Drs. Gough and Harrison are Dr. Ezdihar Hassoun, University of Toledo and Dr. David Johnson, Florida Department of Health; they are currently awaiting confirmation.

Dr. Schechtman reminded the members that he had circulated an e-mail message to RHAC on November 19, 2003 to inform them of these events regarding committee membership. He thanked Drs. Gough and Harrison for their exceptional efforts and valuable input while serving on RHAC and noted that they and their energies will be sorely missed. He confirmed that at a later date, DHHS will formally acknowledge the outstanding contributions of the two members with a letter of recognition and plaque.

Program Management Update

Dr. Judson Miner, Research Director of Operational Technologies Corporation, covered the following items in his status report. First, a contract will be awarded to the University of California-Davis to continue with adipose tissue studies and glucose transport mechanism studies. Second, Program Management has received its budget authority and is not under a continuing resolution. Third, Science Applications International Corporation (SAIC) is satisfactorily fulfilling the terms of its contract by revising draft health study chapters based on U.S. Air Force (USAF) comments and delivering the documents to Program Management on a timely basis. Dr. Miner confirmed that initial draft chapters with USAF comments, resolved comments and final draft chapters will be distributed to RHAC for review.

Vietnam Veterans Health Studies at the National Academies

Dr. David Butler, Senior Program Officer of the National Academy of Sciences (NAS) Institute of Medicine (IOM), explained that NAS was chartered by Congress in 1863 to serve as an independent non-governmental institution and advise federal agencies on scientific issues. IOM was chartered under NAS in 1970 to specifically focus on medical and public health issues. To fulfill its charge, NAS developed a rigorous study process. The NAS Governing Board Executive Council must review and approve each study. A committee of volunteer experts is formed to prepare reports based on findings from literature reviews, public hearings, workshops, written testimony and other information. Final reports must undergo external peer review before being publicized.

With respect to veterans' health, the Agent Orange Act of 1991 instructed the U.S. Department of Veterans Affairs (VA) Secretary to contract with NAS to conduct research on Agent Orange related

issues. In fulfilling this mandate, NAS has produced ten exposure assessments and herbicide health effects reports among Vietnam veterans since 1994. These studies are available to the public on the National Academies Press web site. The most recent effort by NAS related to Vietnam veterans is the Veterans Benefits Act of 2003 that was signed into law in December 2003. The new legislation requested that the VA Secretary contract NAS to conduct a study on the disposition of the RHS; the language also contained five elements for NAS to address in this research.

First, the scientific merit of retaining and maintaining medical records, laboratory specimens and other RHS data beyond the termination date of the RHS in 2006 should be evaluated. Second, privacy concerns of veterans, informed consent and other potential barriers to retaining and maintaining RHS data should be noted. Third, the need to provide independent oversight of RHS data should be assessed and a mechanism to provide the oversight, if appropriate, should be developed. Fourth, the need to extend the RHS should be evaluated in terms of its potential value, relevance, cost and the best entity to continue the research. Fifth, the feasibility of making RHS data available for independent study should be assessed in terms of the potential value, relevance and cost of the research.

Dr. Butler pointed out that the RHS disposition study is speculative at this point because the NAS Governing Board has not yet approved the project. However, the project is expected to be approved and NAS will then sign a contract with the VA. A study protocol and time-line that are consistent with the VA's Congressional mandate will be negotiated and outlined in the contract. NAS will then follow its standard study process by forming a committee, holding public meetings, and gathering information from RHAC, the VA, veteran service organizations, individual veterans and other interested sources. NAS will also post progress reports about the study on its web site.

Several RHAC members noted issues for NAS to consider while the RHS disposition study is being conducted. Dr. Gough advised NAS to consult with the National Institutes of Health (NIH) National Institute of Aging (NIA). Because the RHS is the longest and largest longitudinal study of racially-mixed males ever conducted, NIA will be extremely interested in the disposition of these data. Dr. Stoto added that other NIH institutes will also be interested in the RHS since the research has led to important findings on the environment, diabetes and other issues. He urged NAS to publicize the potential availability of the RHS data and materials to NIH and the broader scientific community. These agencies can serve as funding sources for scientists to explore additional research in the future. Overall, Dr. Stoto remarked that RHAC will be pleased to provide input to and interact with NAS on the RHS disposition study.

Dr. Trewyn suggested that NAS consider Drs. Gough and Harrison as either members of the RHS disposition study committee or resources in other areas of the project due to their extensive service on the RHAC and wealth of knowledge about the RHS. Dr. Osei inquired whether NAS will provide an opportunity for other private institutions to compete in conducting the RHS disposition study. Dr. Butler clarified that the only role that NAS will play in the project will be to provide advice on the disposition of the RHS by addressing the five elements outlined in the legislation. In general, NAS neither conducts primary research nor provides funding to support studies performed by other institutions. However, NAS may consider a role for organizations to manage RHS samples and other data.

Dr. Harrison acknowledged that NAS will need to address some important issues during the RHS disposition study. First, in research projects that must protect human subjects, obtaining consent from study participants to utilize samples and other materials after the data have been collected is often a challenge. Most notably, the rationale for maintaining data is difficult for many subjects to understand in retrospect. Second, no technology has been developed to date to maintain biological samples for an indefinite period of time. The RHS disposition study committee should be mindful of this issue during its deliberations. Dr. Joel Michalek, the RHS Principal Investigator, added that >90% of RHS participants expressed a willingness for their data to be maintained for future research purposes. Overall, Dr.

Harrison was pleased that NAS was asked to review the RHS and provide sound scientific guidance on the disposition of data.

Dr. Butler agreed that these issues are extremely important and will be considered by NAS. To assist in this effort, experts in the fields of bioethics, long-term management and maintenance of biological samples, and treatment of human subjects and materials will be asked to participate in the RHS disposition study.

RHS Update

Dr. Michalek summarized several components of the RHS to inform RHAC of recent findings.

Serum Dioxin and Four Biochemical Parameters of Adipose Tissue. Dr. Michalek announced that the study takes an unprecedented molecular epidemiologic approach and represents the first research on dioxin and gene expression in humans. The study is designed to understand whether dioxin is adversely associated with one or more components of the biochemical pathway leading to diabetes mellitus. The research is based on data collected during the 1997 physical examination. Following a factorial design, 650 subjects who were compliant at the cycle 4 examination in 1992 were randomly selected and asked to provide 12 grams of adipose tissue by liposuction at the cycle 5 examination in 1997. Of the 650 invited subjects, 313 volunteered and provided specimens.

The original sample size was reduced due to refusals, insufficient body fat, medications being taken, medical deferments and an inability to schedule subjects. Body fat, age and diabetic status were used as criteria to select subjects, while glucose transporter 4 (GLUT4), GSRC, NF κ B and C/EBP α were the biochemical parameters measured in the study. The median age of subjects at the baseline examination was 42 years. Subjects participating in the 1995 examination were classified as either diabetic or non-diabetic. However, the diabetic status of several subjects was reversed in this study to be consistent with the change in the American Diabetes Association's (ADA) definition of "diabetic" in 2002. GAPDH was used as a "housekeeping" gene for normalization to remove the effects of obesity on messenger RNA.

The study showed the following results. A significant increase was seen in GLUT4 expression among lean non-diabetics in the comparison group, but this change was not seen in the Ranch Hand group. GLUT4 increased with dioxin load among lean diabetics in the Ranch Hands group. Diabetic status was an important factor and influenced the value of measurements. Log transform values were negatively correlated with percent body fat at the time of adipose tissue sampling. This finding suggested that fat droplet size affected messenger RNA yield. The transformed GAPDH level was not significantly different between diabetics and non-diabetics. This result indicated that GAPDH would not introduce artifacts related to diabetes if the gene was used to normalize others.

Interactions prevented simple interpretations and an analysis of main effects. The small sample size of 313 subjects did not allow for a detailed path analysis. Path analyses are generally used for large data sets >1,000 subjects. Because a separate path is made and applied to the comparison group. This method would have reduced the cohort to ~120 subjects. Replicating the study with a different cohort is not possible. Error terms and other important parameters were not measured, but the study does account for medications and several other risk factors.

The study contained complete data for each subject, was performed under strict quality control and implemented solid follow-up procedures. The data suggest that dioxin may disrupt the normal diabetic pathway through an interaction with GLUT4, but additional research is needed to understand the complex regulatory mechanism of diabetes and other pathways. The study is currently being prepared for journal publication.

Dr. Gough pointed out that the study is based on animal data, but biochemical animal research with dioxin is performed at much higher doses than those used in human studies. He inquired about the study's ability to extrapolate from animals to humans and also questioned whether the complex methods and analyses will be informative. Dr. Michalek explained that the study animals were exposed to small dioxin doses of $<0.10 \mu\text{g}/\text{kg}/\text{body weight}$ because these ranges were compatible to those received by Ranch Hands in Vietnam.

Dr. Stoto remarked that the study provides valuable information in further understanding the causes of diabetes. However, he strongly emphasized the need to clearly delineate potential biases in the discussion section of the paper. For example, the study reflects complete data only for obese subjects who were not taking medication. The study also does not contain a sufficient sample of subjects with high dioxin levels to determine whether the outcome would have been different. Moreover, issues related to sample selection may complicate the interpretation of the findings, which are essentially third-order interactions.

Dr. Osei expressed concern about the reversals in diabetic status from 1995 to 2002. For example, the data show an increase in GLUT4, but the gene expression should actually decrease if dioxin produces diabetes. Exercise, medications or other variables that influence GLUT4 levels are most likely the cause for the change in diabetic status rather than the new 2002 ADA definition. He advised the investigators to consider these factors before conducting pathway analyses.

Dr. Harrison encouraged the investigators to make an additional correlation in the future. Intracellular feedback mechanisms lead to changes in messenger RNA levels that reflect changes in protein transcription or protein levels. The mechanisms then influence GLUT4 and reduce activity of the gene. He suggested that the investigators review E-Cell, a computer simulation of glucose metabolism in cells, because the technology may serve as an innovative and non-statistical mechanism to analyze data. Dr. Michalek confirmed that this issue has been addressed. A code was written to run a feedback loop from GLUT4 to PBF and from C/EBP α and NF κ B.

Cancer Prevalence in Comparisons. Dr. Michalek reported that the study focused on an unexpected trend in the comparison group discovered while assessing cancer incidence among Ranch Hands. The data showed that cancer prevalence is adversely related to years of service in Southeast Asia (SEA) and is not related to dioxin or Agent Orange. Cancer prevalence was determined through December 31, 1999; all cases were confirmed by record review. The comparison group included persons who were fully or partially compliant with any of the five physical examinations. Time to onset was measured from the end of the last SEA tour to the earliest occurrence of cancer, death or end of follow-up. Cancers that occurred within 15 years of the last SEA tour were not considered.

All cancer definitions used in the study were prescribed by the National Cancer Institute Surveillance Epidemiology End Results (SEER). The all-site SEER category includes all SEER cancers. Proportional hazards models were used throughout the study. All-site, respiratory, prostate, digestive system, and basal and squamous cell cancers were adjusted with specific risk factors, such as year of birth, race, military occupation, skin reaction to sunlight, eye color and pack-years of smoking. Of the 1,785 persons in the cohort, ~50% spent <2.1 years in SEA. Older age and smoking were strongly associated with increased years in SEA.

The study showed the following results. The risk of all-site SEER, digestive system and prostate cancers significantly increased in the comparison group based on increased years in SEA. No significant trends were seen for other cancers. The increases appeared to be unrelated to exposures to dioxin or dioxin-contaminated herbicides. The underlying cause is unknown because no biomarkers were measured except dioxin; detailed exposure histories are not accessible; and information on tour locations is not available at this time. However, the exposures may be related to water, food or other environmental media, insecticides or other chemicals, tropical diseases or medications.

A database is currently being developed to pinpoint the exact locations and dates of SEA tours from 1942-1982. Removal of the 15-year latency period from the data analysis resulted in increased statistical significance. Record reviews were conducted to verify all outcomes and determine dates of cancer onset. The study was performed under rigorous quality control and will soon be submitted to a journal for publication.

Dr. Stoto noted the significant difference in smoking among persons with long and short SEA tours. On the one hand, the study found digestive and prostate cancers to be significant, but these sites are not generally associated with smoking. On the other hand, a weak trend was seen for respiratory cancer, but this site is related to smoking. He raised the possibility of combining cancer sites that are most strongly associated with smoking to confirm these outcomes.

Dr. Leffingwell suggested that efforts be made to correlate cancers and sexually transmitted diseases received during Vietnam tours, such as prostate cancer and human papilloma virus or gonorrhea and hepatitis B and C. The analysis should be thoroughly considered, particularly if the liver is the site in the digestive system with a high rate of cancer. Dr. Marian Pavuk, an RHS investigator with SpecPro, Inc., reviewed the literature on this subject. He reported that of 26 digestive system cancers, one case of liver cancer, six cases of colon cancers, nine cases of rectum-to-stomach cancers, and three cases of pancreatic cancers were identified. Due to the small number of cases, the study could not definitively conclude that an unusual distribution of digestive system cancers occurred.

Dr. Gough indicated that efforts to correlate exposures to cancer excesses may be overwhelming since 25% of the population develops the disease and the cause is very rarely identified. Dr. Trewyn noted that chlordane was heavily used in SEA during the Vietnam War and may be related to the increased cancer risk. Dr. Pavuk mentioned that blood samples and other stored specimens may be analyzed for the Ranch Hands and comparison veterans to determine whether DDT, DDE, pesticides or other organochlorine compounds used in SEA are associated with the cancer trend observed in the study.

Cancer in Air Force Veterans of the Vietnam War. Dr. Michalek conveyed that the period of risk in the study was from end of service in SEA to December 31, 1999. All study outcomes were confirmed by record review, International Classification of Disease codes and SEER category definitions. The data were analyzed in two parts. The external analysis focused on cancer incidence and mortality versus SEER rates for U.S. males, while the internal analysis focused on prevalence by dioxin category. To isolate years in which Agent Orange was most heavily sprayed, both the external and internal analyses were stratified by presence or absence in Vietnam, amount of time spent in SEA and actual years in Vietnam.

In the control group, the data showed a trend and a median of two years in SEA. All-site SEER cancer, melanoma restricted to whites, and prostate cancer were the covariates used the study. When the data were stratified according to time served in SEA (with 2 years as the cutpoint), many Ranch Hands who were in SEA 100% of the time were included in the sample. The external sample of 2,965 excluded all persons with cancer before or during tours of duty, while the internal sample of 2,438 excluded all

persons with a missing dioxin measurement. The study was restricted to whites to allow a comparison with national rates. Compared to national rates, significant increases were seen in prostate cancer and melanoma. Close follow-up at Scripps Clinic in which Ranch Hands were examined by a dermatologist and doctor of internal medicine were suggested to account for the apparent increases observed.

To resolve this issue, efforts were made to identify cancers that were detected as a direct result of physicals at Scripps Clinic. A review of these data showed that Scripps Clinic physicals were responsible for four of 17 melanomas and some cases of prostate cancer in the comparison group. In the period of heaviest spraying, an increase was seen in prostate cancer among Ranch Hands and controls who were in SEA during that time. An increase was seen in melanoma only among Ranch Hands during the Agent Orange period. Using an analysis of Ranch Hands with 100% of SEA service in Vietnam and controls with 0% time in Vietnam (100%-0% analysis), standardized incidence ratios (SIRs) for both prostate cancer and melanoma increased even though the sample size decreased. The dioxin category was analyzed only for persons who were in SEA <2 years because the data showed that years in SEA was statistically a confounder.

Stratifying the data on time spent in SEA showed a significant pattern of increased risk and greater dioxin body burden among Ranch Hands. Relative risks in both high and low categories for all-site SEER cancers reached statistical significance as well. Using the 100%-0% analysis, a larger relative risk of all-site SEER cancers also reached statistical significance even with smaller sample sizes.

In the external analysis, melanoma increased among Ranch Hands and prostate cancer increased in both cohorts. In the internal analysis, all-site, melanoma and prostate cancers increased after adjusting for ≤2 years in SEA in the high category. All-site cancer increased using the 100%-0% analysis. The study will be published on February 11, 2004 in the *Journal of Occupational and Environmental Medicine* and has been selected for continuing medical education training as a model of good epidemiologic research.

Prostate Cancer and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in USAF Veterans of the Vietnam War. Dr. Michalek reported that the study was designed to specifically investigate a potential association between TCDD and prostate cancer among USAF veterans of the Vietnam war. Prostate cancer affects one of nine men ≥65 years of age and is the second leading cause of cancer-related deaths in men. TCDD is classified as carcinogenic in animals and humans, but the IOM has only found “suggestive/insufficient” evidence from animal and human studies to link TCDD to prostate cancer. Data and biological specimens were collected during six medical examinations from 1982-2002, while serum dioxin was measured during three physicals from 1987-1997.

Ranch Hands and comparisons who had serum TCDD measurements and were fully compliant to at least one examination were considered for the study. The study assumed that at least 20 years passed after initial exposure to TCDD and development of prostate cancer. In addition to dioxin level measurements, area under the curve (AUC) was computed beginning at the end of exposure in Vietnam. AUC is a metric used in animal studies that is proportional to the bioavailable dose. For purposes of this study, AUC was calculated using the average dioxin half-life of 7.6 years. Based on tertiles of the AUC comparison, Ranch Hands were assigned to low, medium and high categories. Veterans were excluded from the analysis on the bases of no TCDD measurement, <20 years of follow-up and non-white. The exclusion criteria resulted in a loss of 20 comparisons and eight Ranch Hands. Proportional hazards models were used to calculate hazard ratios and 95% confidence intervals.

In comparing the two groups, age, height, weight, body mass index (BMI), pack-years of smoking and alcohol use were found to be similar. The Ranch Hands spent more time in Vietnam, while the comparisons spent more time in SEA. Increased dioxin levels were seen among the high AUC category; the full range of 24,569 ppt-years was <50% of exposures to U.S. chemical workers who made herbicides. An increase was also seen in cumulative TCDD levels by AUC category. The comparison

group showed a significant trend of increased prostate cancer risk based on years in SEA, but this trend was not seen in Ranch Hands. The trend in the control group was most likely due to the cut point of ≤ 2 years in SEA.

The study also focused on age and medical procedures among 47 prostate cancer cases in the comparison group and 33 cases in the Ranch Hands group. All of these subjects had prostate cancer more than 20 years after SEA tours. The analysis found no association between Gleason scores and AUC categories. The study showed the following results. Without accounting for time spent in SEA, no increase in prostate cancer risk was seen in the Ranch Hands TCDD categories. The length of time spent in SEA increased the risk of prostate cancer in the comparison group, but time spent in SEA was not associated with TCDD. A shorter stay in SEA of ≤ 2 years and higher TCDD levels increased the relative risk of prostate cancer in Ranch Hands. The incidence of prostate cancer was found to be elevated in both the comparison and Ranch Hands groups relative to the U.S. male population.

The study has been submitted to a journal for publication, but some aspects of the research may be modified in the future based on current efforts. Physiologically-based pharmacokinetic modeling is being introduced to accommodate half-life changes in the Ranch Hands cohort in terms of time, lipid content and body fat. The half-life modeling paper has been submitted to the *Lancet* and will eventually lead to the development of new initial dose estimates.

Dr. Pavuk further defined two terms used in the study. A "Gleason score" measures the stage of prostate cancer with a pathological examination of prostate tissue obtained through biopsy or surgery at the time of diagnosis. An "AUC" calculation reflects length of time of follow-up and from exposure to development of disease. AUC serves as a better estimate of cumulative body burden than a single measurement at one time point. Dr. Stoto clarified that IOM found "limited/suggestive" rather than "suggestive/ insufficient" data to link TCDD to prostate cancer.

Dr. Harrison questioned the methodology of extrapolating to the initial dose without data from the initial period. He pointed out that all measurements based on the new half-life study will appear after the initial slope is removed. Dr. Michalek agreed with these comments because when RHS data were combined with findings on the 1976 dioxin accident among males in Seveso, Italy, a linear pattern appeared within three months of initial exposure. However, a very rapid and highly significant non-linear decrease was seen before the three-month time period. Dr. Michalek acknowledged that the study he presented does not account for the non-linear pattern, but the new analysis will accommodate this finding.

Adjustments for Ethnicity and Cut Points. Dr. Michalek reported that the study was conducted in response to two questions submitted by Dr. Gough. The first issue related to whether the study results on melanoma would be different if an adjustment was made for ethnicity. In response to this question, the analysis assumed that blue-eyed and fair-skinned persons of Scandinavian or Danish descent would have a much higher risk of melanoma than individuals with darker skin. The study was adjusted for self-reported ethnicity in which persons were asked during physical examinations whether they considered themselves Scandinavian. The sample size of 2,965 persons reflected 1,189 eligible Ranch Hands and 1,776 eligible comparisons.

In the comparison, background, low and high categories, ~5% of persons considered themselves Scandinavian. To address these responses, a new covariate was created and introduced into the melanoma analysis in which "1" represented Scandinavian descent and "0" represented other ethnic groups. A large percentage of persons in the cohort self-reported their ethnic backgrounds as Irish or French. Overall, the original conclusions did not change when the covariate of ≤ 2 years in SEA was incorporated into the melanoma analysis.

Dr. Gough's second question focused on whether the study results would be different if the two-year cut point was changed. Based on quartile of years in SEA, the analysis showed trends in year of birth and pack-years of smoking among the comparison group. Similar changes were seen for these covariates in the Ranch Hands group as well. The two-year cut point was found to be important because ~6% of comparisons who were in SEA up to 2.1 years experienced cancer, but the rate was flat among Ranch Hands. The analysis was unable to explain the dynamic in the comparison group.

The analysis showed a decreased risk of cancer in the comparison group among those who were in SEA ≤ 2 years. The 100%-0% analysis was used in the study because years spent in SEA were considered to be a surrogate for length of time spent in Vietnam or other factors. An interaction model that included significant years by dioxin and group was found to be critical to reducing years in SEA. For purposes of this analysis, "group" was defined as Ranch Hands and controls. The model showed that the relationship between dioxin and SEER cancer changed with years in SEA and group, while the main effects model used in other research was found to be inappropriate for this study. When the cut point was changed, the adjustment disappeared and treatment effects in Ranch Hands were more difficult to detect.

The analysis showed the following results. The association between cancer and dioxin significantly changed with years served in SEA. The risk of cancer increased with years served in SEA among comparisons. Increasing the value of the two-year cut point attenuated the adjustment for confounding. Years served in SEA were a confounder and may be a surrogate for another factor in the comparison group, but confounding was controlled by stratification.

Dr. Stoto raised the possibility of applying another methodology in future studies of ethnicity. National rates can be reviewed to identify countries with relative high rates of melanoma, such as England, Ireland, Scandinavia or Scotland. The rates could then be grouped for a combined analysis rather than focusing on country data for Scandinavia only. Dr. Harrison noted that the ethnicity analysis relied on self-reported data, but this tool is not reliable in many instances.

Dioxin and Memory Loss. Dr. Michalek announced that the study was designed to determine whether dioxin and memory loss are adversely associated in Ranch Hands veterans. The Wechsler Memory Scale (WMS) was administered to 2,000 persons in 1982 and 2002 to test five components: immediate and delayed logical memory, associate learning, and immediate and delayed visual reproduction. The study was reviewed by NAS and published in *Neurotoxicology* in 2002, but the 2002 data are preliminary. Based on the WMS, the data showed a significant deficit in the high dioxin exposure category on immediate recall. Significantly lower scores among Ranch Hands in the highest exposure category relative to comparisons were statistically significant.

The study was adjusted for military occupation, age, race, years of drinking, marital status, combat exposure, organic psychotic conditions, other psychoses, neurotic personality, non-psychotic disorders, substance abuse and use of psychotropic medications. The study showed a significant decrease in delayed logical memory among the highest exposure category, but all other components of the WMS at baseline were not found to be significant. No significant deficits were seen in associate learning or immediate and delayed visual reproduction at baseline in any Ranch Hands category.

In the 2002 WMS data collected at cycle 6, one subject in the background category and 34 comparisons had missing data. Sample sizes at cycle 6 with complete data included ~1,170 comparisons and a range of 211-351 persons in the background, low and high categories. Of persons who completed the WMS at the cycle 6 physical, the mean age was ~60-65 years; dioxin levels ranged from 3.9-48; and BMI was ~30 for all categories. Education was obviously an important indicator of the ability of subjects to complete the WMS. In the comparison, background, low and high categories, the percentage of subjects who had at most a high school education ranged from 34%-68%. Education was also highly correlated with

officers versus enlisted personnel. No significant decrements were seen in immediate and delayed logical memory or associate learning when the analysis was repeated at cycle 6 and adjusted for age and education.

In comparing cycle 1 in 1982 and cycle 6 in 2002, 200 subjects in the high category had complete associate learning data at both cycles, while 846 comparisons had complete data at both cycles. No significant differences were seen among persons who were fully compliant with both cycles. The data analysis subtracted baseline values from cycle 6 values because the subjects were expected to have lower WMS scores in 2002 than 1982. The study has not yet been adjusted for covariates other than age, but the new data analysis will account for these factors. Efforts are currently being made to locate confounders, resolve the visual reproduction analysis and obtain serum dioxin measurements. At the present time, no evidence has been generated to support the hypothesis that dioxin is adversely related to memory deficits in Ranch Hands.

Several RHAC members noted that the demographics on education are unclear. For example, the data do not show whether subjects completed high school, attended college or received degrees. The current analysis combines all persons, such as those without a high school diploma and those who received a Ph.D. Dr. Stoto recommended that the demographics on education be clarified with a cut point of "high school or less." He also pointed out that the original findings may contain false-positives since the new data are not yet adjusted for years in SEA or other covariates.

Dioxin and Syndrome X. Dr. Michalek reported that the study resulted in a published case definition of "Syndrome X." The term is defined as three or more of the following conditions at the cycle 6 examination in 2002: a waist circumference of >102 cm; a triglycerides level of ≥ 150 mg/dl; a high-density lipoprotein cholesterol level of <40 mg/dl; high blood pressure or a diagnosis of hypertension; or a fasting glucose level of ≥ 110 mg/dl or a diagnosis of diabetes based on ADA criteria. The case definition was published in NIH's Third Report of the National Cholesterol Education Program.

The study focused on whether dioxin and Syndrome X are adversely associated in Ranch Hands. Recent data gathered by Scripps Clinic in 2002-2003 were used for the analysis. The sample size reflected 1,086 comparisons and 775 Ranch Hands. Of the total cohort, only 89 subjects were excluded due to missing dioxin measurements. Demographics on age, birth year, race, military occupation and pack-years of smoking were similar to other RHS data. Other covariates that were more important for this study were similar among comparisons and Ranch Hands: ~11 median years of drinking; a family history of diabetes of ~20%; a family history of hypertension of ~40%; and a remarkable risk of Syndrome X of ~42%. Similar to other RHS data, dioxin exposure increased in the high category.

The data showed a significant increase in the risk of Syndrome X in the high exposure category and a significant trend after adjusting for covariates. The study could not explain the cause for the significant deficits of Syndrome X and hypertension in the background category. Syndrome X was not adjusted for BMI since this variable is included in the model, but incorporating BMI into the hypertension analysis was found to attenuate the result. The study concluded that dioxin may be adversely associated with Syndrome X, but additional research in this area is needed; other confounders need to be considered and measured; and exposures need to be accurately classified.

Dr. Osei noted that the 42% rate of Syndrome X in the study is much higher than the national average of 25%. He indicated that the larger percentage is most likely due to the study population of males only.

Protocol Completion

Lt. Col. Julie Robinson, of the USAF, reiterated that the RHS protocol and funding will end on September 30, 2006. USAF has developed cost estimates and several options for the end of the RHS, including taking no further action or conducting another physical examination. USAF's entire time-line to complete the protocol by September 30, 2006 was distributed to RHAC, but Lt. Col. Robinson highlighted some of the key activities. The final Institutional Review Board report is scheduled for July 2006. USAF is requesting that RHAC review 12 chapters during its meetings in April, September and November 2004. The members will receive three documents for each chapter: an initial draft from SAIC to USAF; resolutions to comments by USAF and SAIC; and a revised second draft based on the comments. Some chapters will contain appendices for RHAC to review as well.

To date, RHAC has received two initial draft chapters, an instruction sheet, an explanation of the attachments, and contact information for Lt. Col. Robinson. USAF hopes to provide RHAC with a total of five of the 12 chapters by mid-February 2004 and will make every effort to distribute chapters to the members at least two months prior to meetings. Each chapter was written by lead and alternate writers who are all from Scripps Clinic; the list of writers was distributed to RHAC. The literature research was conducted by an SAIC subcontractor. USAF plans to submit articles to peer-reviewed journals up until January 1, 2006; any remaining reports will be transformed into USAF technical documents.

Dr. Stoto saw the benefit in prioritizing chapters for RHAC to review based on USAF need or other factors. Dr. Harrison advised RHAC to identify consultants with appropriate expertise to provide assistance in reviewing the chapters. Dr. Trewyn raised the possibility of using former RHAC members as consultants for the chapter reviews. Dr. Schechtman confirmed that he would contact the Committee Management Office to determine if former members can serve as consultants to advisory committees. He planned on reporting his findings to RHAC as soon as possible.

Public Comment Period

The Chair called for public comments; no attendees responded.

Closing Session

April 30, September 8 and November 3, 2004 were tentatively scheduled for the next three meetings; NCTR will poll the members by e-mail to confirm these dates.

Lt. Col. Robinson presented a certificate to Ms. Barbara Jewell, *in absentia*, to recognize her as an official member of the Air Force Health Study Crew. Prior to Ms. Jewell's recent retirement, she served as the RHAC Committee Management Specialist for 14 years and was extensively involved with RHAC and the RHS. She made outstanding efforts in coordinating RHAC meetings, developing agendas and providing other support. The certificate was given to Dr. Schechtman to be forwarded to Ms. Jewell.

With no further discussion or business brought before RHAC, Dr. Harrison adjourned the meeting at 1:27 p.m.

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

Date

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

Date

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

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.
