

**RANCH HAND ADVISORY COMMITTEE MEETING**  
**August 26-27, 1999**

Parklawn Building, Conference Room K  
Rockville, Maryland

The meeting was called to order by chairperson Dr. Robert W. Harrison at 8:30 a.m., Thursday, August 26, 1999. Other committee members present were: Dr. Turner Camp, Dr. Irene Check, Dr. Delores Shockley, Dr. Michael Stoto, and Dr. Ronald Trewyn; consultants Dr. Robert Delongchamp and Dr. Sonia Tabacova, NCTR; Mr. Ronald Coene, Committee Executive Secretary and Ms. Barbara Jewell, Committee Staff.

Air Force participants were COL Harry E. Marden, M.D., Consultant; LTC Julie Robinson and LTC Bruce Burnham, former and present Chief of Population Research and Dr. Joel Michalek, Principal Investigator of Brooks AFB.

Observers were: Bob Gardner, VFW; Dick Christian, Agent Orange Coordinating Council; George Claxton, VVA; Weihsueh Chiu, GAO; Maurice Owens, SAIC, Program Manager; Dr. Jay Miner, Program Management Support; Manuel Blanca, Program Management Support; MAJ Kyle Snedden, Program Manager; Meghan Yeager, SAIC; Bill Grubbs, SAIC; John Oppenheim, GAO; Kwai-Cheung Chan, GAO; Peter Mazzella, Director, Office of Veterans Affairs; Clark Brooks, San Diego Union-Tribune; Tracy Underwood, American Legion; Dr. Linda Schwartz, Yale School of Nursing; Michael Keating, Vietnam Veterans of America; and M. Porter, Vietnam Veterans of America.

Dr. Harrison introduced himself and noted that there were a large number of non-committee observers present. Dr. Camp suggested that all present in the meeting room introduce themselves for the record. The Chair noted that Dr. Stoto would join the group in the afternoon, and that Dr. Favata, who was unable to attend in person participated by telephone.

Approval of the October 1998 minutes was requested by Dr. Harrison. Some minor corrections were noted by Air Force staff. Dr. Harrison expressed an interest in seeing certain grammatical conventions followed in Minutes of future meetings. Noting there were no gross errors in the Minutes as presented, Dr. Harrison felt that with certain cosmetic changes to be done by Mr. Coene, they were approvable. The committee agreed.

Mr. Coene informed the group that VA handouts to the committee were available as computer data files.

Dr. Harrison asked for any suggested changes or additions to the agenda. He put forth the idea of allowing very short public comment speeches immediately following the discussion of the Minutes, and there was no objection.

Noting that LTC Robinson was rotating off the Air Force study, Dr. Harrison felt the committee should add to tomorrow's agenda a discussion about the lack of a biologist being involved "near the helm" of the study. There was no objection.

Dr. Harrison then asked Dr. Michalek to take some time on Friday to discuss the availability of the datasets underlying the study, and also to review publications from the study.

Dick Christian, Vice Chairman of the Agent Orange Coordinating Council, representing Admiral Zumwalt, made some remarks to the committee about the study's use of the exposure index, and Dr. Harrison asked Dr. Michalek to address that issue on Friday.

The chair then turned the floor over to the Air Force staff. Dr. Michalek said he would provide thumbnail sketches of the chapters one by one, then opening the floor for discussion of each chapter in succession, which they proceeded to do.

## **REVIEW OF THE AIR FORCE HEALTH STUDY CYCLE 5 DRAFT CHAPTERS**

Dr. Michalek, using overheads, proceeded to discuss Chapter 1, the Introduction.

In response to an inquiry from Mr. Brooks (San Diego Union-Tribune), Dr. Michalek said that summaries of findings throughout the study cycles are located at the front of the clinical chapters, and the latest findings will be shown in the executive summary, to be available in October. Reference was also made to the concluding chapter of the book, which is an expanded executive summary, listing everything the study has produced.

Dr. Michalek emphasized that the framework of the report is based on a statement of work developed in 1995, which in turn is derived from the protocol. He said this review is leading up to public release of the final report on Cycle 5 in January 2000.

Discussing the study, Dr. Michalek explained that four models are used in analyzing the data, and conversationally described each to Dr. Harrison. He also explained what the study looks for and the role that covariates play.

Dr. Michalek says the study has produced hard statistical evidence between the Ranch Handers' exposure to dioxin in Vietnam and their current body burden. Also, a significant association between dioxin body burden and the loss of short-term memory has been shown,

as well as a relation between loss of short-term memory and days of skin exposure in Vietnam.

Dr. Trewyn saw a problem with the terms herbicides, herbicide Orange and dioxin being used interchangeably throughout the introduction. Dr. Michalek said this occurred because the study measures the contaminant, not the herbicide.

Dr. Trewyn spoke of cases where exposure to herbicide was ignored because of a lack of correlation to dioxin, and Dr. Michalek asked him to supply the references.

A discussion ensued among committee members regarding making written critiques immediately available to the public.

Dr. Michalek then went to Chapter 2, which concerned dioxin measurements, and the use of a biomarker. Dr. Trewyn raised a concern about lab handling of blood samples, but Dr. Check stated that the samples were being handled according to standard lab procedures.

Dr. Delongchamp inquired about the looking at a specific isotope versus a sum of all of them, and Dr. Michalek explained that the study looks at only one, a "smoking gun" for dioxin. Dr. Michalek agreed with Dr. Harrison that pooled material could be used for making multiple analyte measurements.

Proceeding to Chapter 3, Dr. Michalek described questionnaire methodology, and the PC-based CAPI system. He discussed the use of types of data obtained with the questionnaires. Dr. Favata, through written comments, suggested the addition of several questions, which Dr. Michalek said could be considered in developing the next questionnaire. He and Dr. Harrison then discussed ethical problems created by handling certain types of information about a patient.

Chapter 4 is a discussion of Physical Examination Methodology. Dr. Michalek stated all physicals were done at the Scripps Clinic in 1985 and stated they use a complicated scheduling process that, in itself, can be developed into a discussion. He described a sub-study, obtaining a fat sample to try to determine if there is a biological connection between dioxin and diabetes. Another piece of the physical, new to the study, was an ultrasound measurement of the thickness of the carotid artery. Dr. Check suggested changing the tables in terms of grouping the information.

The committee discussed some lab tests, like ESR, and suggested that it could prioritize inquiries into the data in its advisory capacity to the study. Dr. Delongchamp argued that he wouldn't want to get rid of an observed correlation in the data just because he didn't

understand it. He inquired about the use of certain exams, and Dr. Michalek told him that these get thoroughly IRB-reviewed both at his lab and at the Scripps Clinic.

Dr. Harrison talked about the longitudinal nature of the study, and that a lot of its value would be lost if tests were changed between cycles; and the point of maintaining consistency. Adding to Dr. Check's earlier suggestions, laboratory test results could be grouped more logically.

Study Selection and Participation, Chapter 5, was then discussed by Dr. Michalek. Issues addressed here are population composition and compliance; dealing with possible bias in selection. Dr. Michalek stated that bias calculations that were done at baseline are still applicable today, and they are choosing not to continue detailed bias calculations in the report. Dr. Harrison asked about the study's use of the terms hostile and active in classifying individuals identified for the study. Dr. Michalek noted that the study tries to present as much data as possible in its reports to allow anyone to do a bias calculation if they are interested. The wording of the consent form was discussed, along with recruitment practices.

The afternoon session began with a discussion of Chapter 9, General Health. The relationship between body fat and dioxin concentration in the body was explored. The self-perception of health by the Ranch Handers was discussed.

Dr. Trewyn observed that too heavy a focus on discovering causal correlations with dioxin will mask the involvement of other agents. What the Ranch Handers were possibly told when handling dioxin in Vietnam was discussed.

Dr. Harrison expressed semantic discomfort with the term, general health assessment, and said it ought to be general appearance assessment. Dr. Michalek said he would consider renaming the chapter. There was further discussion about rearranging the presentation of the data, summarizing what is in other chapters along the lines of a "general physical evaluation." "General impression of health" was also suggested as a title.

Dr. Michalek reviewed the trends in the Ranch Hand group's self-perceptions of health, and how their knowledge of dioxin exposure may have affected that perception.

The committee discussed the concentrations of dioxin in lipids versus adipose tissue, starting with a CDC paper saying that they were basically the same. A relationship between

triglyceride levels in blood and dioxin levels in blood was discussed.

Chapter 6, Quality Control: The reviewers felt high marks were in order for the study group on quality control.

Chapter 7, Statistical Methods. Dr. Michalek noted that through committee review and the preference of journals, main effects are being reported in papers while interaction models are being removed. Some covariates have changed from Cycle 4 to Cycle 5.

There was an extensive discussion of the BMI relationship to body fat and dioxin levels, and extrapolating the dose to Vietnam, and dealing with models to handle repeated measures on the outcome and on the dose.

Dr. Delongchamp talked about the relative merits of the models being used, stating a preference for Model 1.

Dr. Michalek next discussed Covariate Associations, covered in Chapter 8, displaying the relationships between covariates and the endpoints in the study; covariates versus dioxin. The committee pointed out reporting of Ranch Hands' pre-Southeast Asia exposures to herbicide, in addition to their post, as the questionnaire had been structured to capture posts, Southeast Asia exposure only. Dr. Michalek said he would track it down.

Moving to the chapter on Psychology, Dr. Michalek said that there was "not much going on here." The committee discussed various measures that were available, and results.

Gastrointestinal chapter. Model 4 produced findings in hepatic conditions. A comprehensive and well-written chapter, in the opinion of one reviewer.

The Committee meeting continued in the same location on August 27, 1999, being called to order by Chairperson Harrison at 8:30 a.m.

## **REVIEW OF THE AIR FORCE HEALTH STUDY CYCLE 5**

Dr. Robert Harrison identified the reviewers for Chapter 15, Hematology, as Dr. Harrison and Dr. Sonia Tabacova.

Dr. Joel Michalek used overheads to display increased dioxin levels in Hematology, but stated that no evidence of overt disease was found despite these changes, and that this was the only consistent finding.

Dr. Harrison did not disagree with the chapter findings, but offered two suggestions on the chapter. He noted that the background and references did not reflect the present state of the literature, and that the references seemed to have been closed off in the late '80s or early 90s. Dr. Harrison suggested that newer articles on the effects of dioxin should be included, and cited '97 and '99 reviews. He questioned the use of normalized numbers and was answered by Dr. Michalek; he then asked about a marginally significant difference, which was answered by Dr. Michalek and Dr. Stoto.

Dr. Harrison also suggested the inclusion of a new table for this and other chapters. The table would summarize the conversion of significant findings into nonsignificant findings (and the reverse) by correction or adjustment. Several participants liked the idea but had concerns about time and money. Dr. Camp suggested they call for a vote on the recommendation, and Dr. Stoto disagreed. Dr. Michalek pointed out that they were constrained by a fixed price contract and had a fixed deadline for the report. Dr. Harrison stated that they would make formal recommendations later, and Dr. Camp quoted from the Committee charter emphasizing the advisory role of the Committee, and agreed with the decision.

Dr. Harrison stated that the reviewers for Immunology were Dr. Check and Dr. Shockley. Dr. Michalek credited Dr. Irene Check with contributing to the design of the chapter.

Dr. Check stated that her input into the design was to decrease the number of purely speculative tests that are no longer done in clinical practice. She noted that there were many results and the magnitude of the changes was very small, for example in CD16 positive and CD56 positive natural killer cells, so that the interpretation of a few extra such cells is not based on much substance. Dr. Check suggested renaming the lupus panel to an autoantibody panel. She pointed out that in the antinuclear antibody test 50 percent of the controls are abnormal because of the desire to count all positives, but suggested a level of quantity measure for the next study.

Dr. Dolores Shockley noted that there had been difficulties with the test details, and flawed results, but praised the explanation of the changes in instrumentation and relating it to the previous results. She stated since the autoantibody test was expensive, the subjects were randomly selected. Dr. Shockley commented that even though very few results were positive, the studies contributed to epidemiological views. She stated that this was the first time she'd seen physical exercise as one of the covariants.

Dr. Harrison's concern that substantial changes were being suggested in the way the chapter was written to de-emphasize, but Dr. Check indicated that word changes in the interpretation portion would suffice, and volunteered to send them via e-mail. Dr. Camp asked if there were any relationship between the increase in lymphocytes and the sedimentation rate. Dr. Shockley stated that it possibly indicated an inflammatory response. Dr. Check added that red cells changes would contribute more to the ESR than a small number of lymphocytes. Dr. Harrison compared proteins in gel exclusion chromatography to red cells. Dr. Check pointed out that fibrinogen concentration and serum were bigger predictors of sed rate, but that no one measures fibrinogen. Dr. Harrison stated that the increased sed rate might not be due to inflammation, and Dr. Shockley reiterated that there was no clinical evidence of current inflammation.

Dr. DeLongchamp asked a question about confidence intervals, and Dr. Michalek indicated that they were Wald intervals, but not in log units because of Committee preference. Further discussion on statistical methods of presentation (confidence interval vs. standard error) occurred. Dr. DeLongchamp corroborated that atomic bomb survivors had an increased sed rate, but noted that it was difficult to define a control group for these kinds of people. Dr. Schwartz suggested that the literature on chronic stress with post-traumatic stress disorder from the National Center of PTSD at Yale School of Medicine might be helpful. Dr. Shockley noted that they had excluded anyone who had been on anti-inflammatory drugs or was in any way immune compromised. Dr. Tabacova pointed out that free radicals were another possible common denominator with atomic bomb survivors. Dr. Harrison brought out that long-standing persistent changes were likely to be genetic changes. Some discussion of genetic information and the human genome project ensued, but it was decided that since someone else was going to make a proposal in that area, they would look at and discuss the proposal.

The reviewers for the Pulmonary chapter were Dr. Robert Trewyn and Dr. Favata. Dr. Favata provided her critique via speakerphone. Dr. Michalek started by saying that Pulmonary had produced few results; basically negative results and nothing consistent. The one finding is obstructive abnormality, mild versus none, increased in officers. Dr. Trewyn pointed out that there seemed to be a bias toward forcing a relationship with dioxin, rather than herbicide exposure. He expressed concern that the focus on dioxin tended to exonerate the Government if no causal relationship to dioxin was documented. Dr. Trewyn stated that although no significant adverse pulmonary outcomes were noted for the Ranch Hands, there were a higher percentage of thorax and lung abnormalities which should continue to be monitored.

Dr. Favata advised against discarding the marginally significant findings, and advocated continuing with the same diagnostic tests and statistical analyses for the 2002 evaluation. She pointed out an issue with covariates, and expressed concern about confusing a potential relationship with asbestos with that associated with dioxin. Dr. Favata suggested that further analysis be done in future cycles. She also asked about the dependent variable of observed FEV-1 to observed FEC, noted as an indicator of obstructive abnormality, and the separate obstructive abnormality dependent variable. Dr. Favata questioned whether both were needed. She also raised a question about the cause for hostile refusals, and asked if information could be gleaned from a previous hostile refusal group that had returned for the '97 exams. Dr. Favata asked for comments on the Chapter 3 questionnaire methodology, and Dr. Michalek suggested taking account of residential location (near or far away from Super Fund sites and sources of pollution). Dr. Favata suggested that for the 2002 cycle more detail be included, because it represents another potential source of exposure. She also noted that residential exposures included chemicals in the home as well as external chemical toxins and dioxin.

Dr. Joel Michalek presented data from three recent papers in the American Journal of Epidemiology 1998 - 1999. He stated that no overall increase in cancer was found. Ranch Handers actually had less prostate cancer on the average. Immunology was negative. Post-service mortality had an overall risk of 1.0, but there were increased cardiovascular deaths in the enlisted ground crew, SMR 1.5.

Dr. Michalek summarized a paper in Archives Environmental Health on acne and chloracne. A paper on diabetes in Epidemiology, 1996, showed a highly significant relation between diabetes and dioxin, with increasing prevalence with increased category of dioxin. There is increased insulin in non-diabetics, and earlier onset as well as increased severity with increased dioxin. The data had a "checkmark pattern" which caused interpretive difficulties, but was explained by Dr. Michalek. The checkmark pattern goes away if analysis is restricted to enlisted ground only.

Dr. Michalek also cited a recent paper in the Journal of Clinical Endocrinology and Metabolism that showed a very strong relation in alteration on the relation between sex hormone, total body globulin, and insulin with dioxin in nondiabetic veterans. Insulin increases with dioxin, but sex hormone and body globulin do not. Dr. Harrison asked whether all the veterans were non-insulin diabetics, and whether all were tested for C-reactive peptides. He expressed concern that they needed to show that all the subjects were



in the same category; if not, they would be combining two different categories of type diabetes with two different pathogeneses which would cause credulity problems regarding the basic cause of the diabetes. Dr. Michalek stated he would follow that up.

Dr. Camp cited conclusions from *Epidemiology* 1997 Volume 8, suggesting an adverse reaction between dioxin exposure and diabetes glucose mechanism. Dr. Michalek mentioned another *Epidemiology* article which showed a parallel relation between diabetes and dioxin in their comparison group. He confirmed that they had measured dioxin in the comparison groups.

Dr. Michalek noted three papers on reproductive outcomes (birth defects, gonadotropins, and low birth weight and infant death) that were co-authored by CDC in 1995 - 1997. He also cited a Letter to the Editor showing parallel relations in our data between diabetes, onset, and weight, a parallel study done in Sweden by Carlson published in *Epidemiology* in 1999. Dr. Michalek also discussed a methodology paper and statistics showing how to do a computer confidence interval and p value for the SMR, *American Journal of Epidemiology* 1998. He cited a Letter to the Editor on the checkmark pattern, *American Journal of Epidemiology* 1998, and another letter which questioned the relationship between diabetes, dioxin, and triglycerides. Dr. Michalek called out a half-life study paper in the *Journal of Toxicology and Environmental Health*, 1999, and one on statistical methodology for estimating the elimination rate in studies of persistent contaminants in people, *Environmetrics* 1998. He described the findings cited in a paper on TCDD exposure indices and dioxin, based on a questionnaire administered to all enlisted Ranch Handers, published in the *Journal of Exposure Analysis Environmental Health*, 1996. Dr. Michalek spoke briefly about other papers that addressed accuracy of CDC dioxin measurement, dioxin levels and comparisons, and half-life studies. He mentioned the two basic papers published in *JAMA* in 1990. Dr. Michalek noted a paper on the sex of children, and stated that the paper was noting dissimilar results from a Sevaso study and took a long time to get published. This sparked some discussion on the differences and reasons.

Finally Dr. Michalek provided brief summaries for a list of papers in submission to or revision for a variety of journals.

Dr. Stoto raised the question of how to bring the methodological sophistication represented in the papers into the standardized reports.

Dr. Harrison asked whether they subjected their published articles to analysis by something like the Science Citation Index, and Dr. Michalek answered in the affirmative.

## **OPEN PUBLIC SESSION**

Dick Christian, Vice Chairman Agent Orange Coordinating Council, representing Admiral Zumwalt, asked about peer review of published articles and Ranch Hand reports. He also asked about the weight of dioxin analysis that Ranch Hand applies to the CDC.

Dr. George Claxton, National Agent Orange Chair for Vietnam Veterans of America, critiqued the small size of the study and the focus on dioxin versus herbicides.

Dr. Linda Schwartz, Yale University School of Nursing, suggested questioning veterans about illegal drugs, and using peers to recruit subjects for the study. She also made a suggestion about displaying the results of each covariate, and cited the Women's Reproductive Outcome Study, the effects of prolonged stress caused by service in Vietnam, and concern about congenital anomalies in the children of Vietnam veterans.

Weihshueh Chiu, General Accounting Office, provided a short history of the study.

Clark Brooks, San Diego Tribune, criticized the lack of "openness" of the study. He also asked whether the relative risk of health outcomes for the Ranch Hands was greater than for the comparisons, and how many people had requested the data sets.

Dr. Claxton asked about notification of veteran's organizations and national organizations concerning open meetings.

Maj. Sneddon, Program Manager, commented on the program and its future.

Tracy Underwood, American Legion, suggested that they work more with service organizations on notification.

## **PLANS AND DATES FOR MEETING**

The Committee agreed to meet on October 14th and 15th.

## **PLANS FOR CYCLE 6**

Dr. Michalek showed two slides, one on data release and one on the plans for 2002. The

data release slide listed the clinical areas, and he explained that there was a related data set for each. All data that could link an individual to results has been removed or changed. He spoke about the process of verification prior to sending the data to NTIS. Dr. Michalek also provided information on plans to put the data on the Air Force Research Lab web site.

Dr. Michalek presented information on stopping the half-life studies, and the cost savings to be realized. He also discussed measuring the thickness of the carotid artery, which could be resumed if funding were available.

Dr. Stoto asked Dr. Michalek for bullet points for the discussion next time; Dr. Harrison agreed.

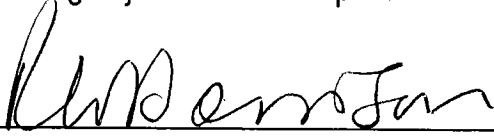
Dr. Michalek spoke about loss to follow-up prevention.

There was discussion about whether to provide a list of all proposed topics or just the new items, and about prioritizing the list.


Storage of blood samples was discussed, as well as good scientific use of them, considering the original purpose of the samples (ICDs), and suitability of potential reviewers. Some budget and contract processes were also discussed.

Several suggestions on presentation of data and the addition of summary table(s) were discussed. A concern with personnel changes and continuity was expressed.

The meeting adjourned at 2:38 p.m.

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

2/4/00  
Date

  
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Ronald F. Coene, P.E.  
Executive Secretary

2/10/00  
Date