



Ranch Hand Advisory Committee Final Briefing

7 Sep 2006

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Principal Investigator

Air Force Health Study



Discussion Topics



- **Summary of Dioxin 2006 presentations**
- **Summary of technical reports and manuscripts**
- **External collaborations**
- **Summary of transition activities**
- **Comprehensive report**



Dioxin 2006



- **Posters**

- Mortality in USAF Veterans of Operation Ranch Hand (Previously presented to RHAC)
- Viability of Stored Serum Specimens (Previously presented to RHAC)

- **Oral Presentations**

- AFHS Overview (Previously presented to RHAC)
- PCDDs, PCDFs, and PCBs in Serum of 800 USAF Veterans in 2002 (Previously presented to RHAC)



Technical Reports & Manuscripts

Since 27 Feb 06



- **Technical Reports**

- AFHS Compliance Report: (Previously reported)
- Third-source Causation: An Alternative Explanation for the Check Mark Pattern (Previously reported)
- A Matched Analysis of Diabetes Mellitus and Herbicide Exposure in Veterans of Operation Ranch (Previously reported)
- Post-Service Mortality of Air Force Veterans Occupationally Exposed to Herbicides during the Vietnam War: Final Report (Previously reported)



Technical Reports & Manuscripts

Since 27 Feb 06



- **Manuscripts Contracted with SAIC**
 - Serum Dioxin and Memory Among Veterans of Operation Ranch Hand
 - Author: Dr Cary
 - Submit to peer-reviewed journal
 - Nerve Conduction Study Data Verification and Review Report
 - Author: Dr Albers
 - Submit as a technical report
- Dr Pavuk will now summarize both manuscripts



Serum Dioxin and Memory among Veterans of Operation Ranch Hand

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William Jackson³, Marian Pavuk⁴

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2. SAIC, Falls Church, VA, USA

3. Air Force Research Laboratory, Brooks City-Base, TX, USA

4. SpecPro Inc., San Antonio, TX, USA



Background



- At the 1982 examination Ranch Hand veterans in the high category scored significantly lower than the Comparison veterans on the immediate and delayed recall trial of the Wechsler Memory Scale (WMS) Logical Memory subtest (Barrett et al., 2001)
- No substantial differences were reported for the Visual reproduction (immediate and delayed) and Associate learning subtests of the WMS in 1982



Memory Assessment 2006



- We have reanalyzed memory assessment data from 1982
 - 94 veterans added with dioxin measurement made in 2002 who participated at 1982 memory assessment
- Analyzed memory assessment data from the 2002 examination
- Compared results for 1982 and 2002



Demographic Characteristics at the 1982 and 2002 Examinations



	Comparison	Ranch Hand		
		Background	Low	High
Sample size^a				
1982	1,107	403	271	274
2002	1,172	351	210	213
Dioxin [median, range]^b				
1982	4.1 (0.4-55)	5.7 (0.4-10)	65.3 (32-117)	243 (118-4222)
2002	3.7 (0.4-32)	5.7 (0.4-10)	64.8 (33-117)	251 (119-4222)
Age (years) [mean (SD)]				
1982	43.9 (7.7)	44.6 (7.4)	45.2 (7.6)	40.9 (7.2)
2002	63.0 (7.0)	64.1 (7.0)	64.5 (7.0)	60.1 (6.8)

a. Sample size for 1982 is based on 2,055 veterans who had a dioxin measurement and either a Verbal Paired Associates, Logical Memory or Visual Reproduction subtest score from the 1982 examination; sample size for 2002 is based on 1,946 veterans who had a dioxin measurement and either a Verbal Paired Associates, Logical Memory or Visual Reproduction subtest score for 2002 examination

b. Measured (in ppt) in 1987, 1992, 1997, or 2002 in comparison and Ranch Hand background categories, extrapolated to end of service in Vietnam in Ranch Hand low and high categories.



Logical Memory Immediate Recall 1982



Memory Scale	Comparison	Ranch Hand		
		Background	Low	High
Logical Memory Immediate Recall				
Sample Size	1,044	379	254	252
Adjusted Mean ^a	6.56	6.41	6.38	6.12
Difference of Adjusted Means	0	-0.15	-0.18	-0.44
95% Confidence Interval		-0.49,0.20	-0.57,0.21	-0.85,-0.04
P-value		0.40	0.37	0.03

a. Adjusted for body mass index at time of the dioxin blood draw, military occupation, age, race, combat exposure, drink-years, marital status, education, organic psychotic conditions, other psychoses, neurotic personality and other nonpsychotic disorders, substance abuse, and use of psychotropic medications.



Logical Memory Delayed Recall 1982



Memory Scale	Comparison	Ranch Hand		
		Background	Low	High
Logical Memory Delayed Recall				
Sample Size	1,067	386	266	259
Adjusted Mean ^a	4.51	4.55	4.24	4.16
Difference of Adjusted Means	0	0.05	-0.27	-0.34
95% Confidence Interval		-0.28,0.37	-0.63,0.10	-0.73,-0.04
P-value		0.77	0.15	0.08

a. Adjusted for body mass index at time of the dioxin blood draw, military occupation, age, race, combat exposure, drink-years, marital status, education, organic psychotic conditions, other psychoses, neurotic personality and other nonpsychotic disorders, substance abuse, and use of psychotropic medications



Logical Memory Immediate Recall 2002



Memory Scale	Comparison	Ranch Hand		
		Background	Low	High
Logical Memory Immediate Recall				
Sample Size	1,165	350	209	211
Adjusted Mean ^a	20.74	20.75	21.44	20.76
Difference of Adjusted Means	0	0.02	0.71	0.02
95% Confidence Interval		-0.76,0.80	-0.23,1.64	-0.94,0.98
P-value		0.96	0.14	0.97

a. Adjusted for body mass index at time of the dioxin blood draw, military occupation, age, race, combat exposure, drink-years, marital status, education, organic psychotic conditions, other psychoses, neurotic personality and other nonpsychotic disorders, substance abuse, and use of psychotropic medications



Logical Memory Delayed Recall 2002



Memory Scale	Comparison	Ranch Hand		
		Background	Low	High
Logical Memory Delayed Recall				
Sample Size	1,164	350	209	211
Adjusted Mean ^a	15.32	15.48	16.06	15.79
Difference of Adjusted Means	0	0.16	0.74	0.47
95% Confidence Interval		-0.69,1.02	-0.29,1.76	-0.58,1.53
P-value		0.71	0.16	0.38

a. Adjusted for body mass index at time of the dioxin blood draw, military occupation, age, race, combat exposure, drink-years, marital status, education, organic psychotic conditions, other psychoses, neurotic personality and other nonpsychotic disorders, substance abuse, and use of psychotropic medications



Differences between Paired Standardized 1982 and 2002 Scores - Logical Memory (I)



Memory Scale	Comparison	Ranch Hand		
		Background	Low	High
Logical Memory Immediate Recall				
Sample Size	806	295	187	189
Adjusted Mean Difference Score ^{a,b}	0.08	0.10	0.02	-0.09
Difference of Means ^c	0	0.02	-0.06	-0.17
95% Confidence Interval		-0.13,0.17	-0.22,0.11	-0.34,0.00
P-value		0.79	0.50	0.05

a. Adjusted for BMI at time of the dioxin blood draw, military occupation, date of birth, race, and combat exposure.

b. The mean difference score is determined by subtracting the 2002 standardized score from the 1982 standardized score and taking the arithmetic average of these differences.

c. Difference of means is the difference of the adjusted mean difference score from the adjusted mean difference score for comparisons. A positive difference of means indicates an adverse effect to Ranch Hands relative to comparisons.



Conclusions



- Reanalysis confirmed findings of earlier reports of small memory deficits in the immediate and delayed logical memory in the high exposed veterans although some results were no longer statistically significant
- The results of the 2002 examination data did not show any of the deficits observed in 1982 data
- Comparison of standardized memory scale scores between 1982 and 2002 showed no indication of memory function deterioration in Ranch Hands relative to the Comparison veterans
- Results in the enlisted ground crew Ranch Hand, the highest dioxin exposed group, are consistent with the results of other Ranch Hands



Conclusions



- The results of this study indicate that Agent Orange-exposed Ranch Hand veterans are functioning normally in regards to immediate and delayed memory
- While the 1982 examination found small memory deficits in the highest exposed veterans, the 2002 examination indicates that the memory deficit is no longer apparent
- The specific neurological mechanisms (e.g., structural, neurochemical, or other) related to the cause of the 1982 deficits in memory are unknown



Nerve Conduction Study Data Verification and Review Report

William Grubbs¹, James W. Albers², Marian Pavuk³

1. SAIC, Falls Church, VA, USA
2. NeuroBehavioral Resources, Inc., Ann Arbor, MI?
3. SpecPro Inc., San Antonio, TX, USA



Introduction



- Data collected in 1992 and 1997 indicated a statistically significant increased odds of *probable peripheral neuropathy* and *diagnosed peripheral neuropathy* among Ranch Hands with higher dioxin levels (Michalek et al., Neurotoxicology 2001)
- **Goal:** To use nerve conduction study results to confirm the presence of the peripheral neuropathy among 60 AFHS participants with clinically evident peripheral neuropathy



Results of NCS Interpretation and Classification



Generalized peripheral neuropathy	56
Sensorimotor	55
Sensory only	1
Participants with no evidence of generalized peripheral neuropathy – additional (superimposed) electrodiagnosis	4
Normal examination	1
Ulnar mononeuropathy (not further localized)	3



Results of NCS Interpretation and Classification



Characteristics of the generalized peripheral neuropathy	
Any motor conduction slowing < lower limit of normal	46
Both motor nerves recordable (n = 38) and abnormal	11
One of two recordable motor nerves abnormal	22
Only recordable motor nerve (n = 18) abnormal	13
Motor conduction slowing sufficient to suggest a possible "membranopathy"	14
Motor conduction slowing suggesting acquired demyelination	5
Additional (superimposed) electrodiagnosis	
Median mononeuropathy at the wrist	12
Ulnar mononeuropathy (not further localized)	4
Possible radiculopathy	6



Conclusions



- Review of the NCS results established a diagnosis of generalized peripheral neuropathy in 56 (93%) out of the 60 AFHS participants based on conventional criteria
- 46 (82%) of 56 AFHS participants having NCS evidence of a generalized peripheral neuropathy characterized by conduction slowing
 - Supports the possibility that participants with diabetes mellitus or pre-diabetes (impaired glucose tolerance) may be contributing causally to the pool of AFHS participants with clinically evident peripheral neuropathy
- The presence of substantial conduction slowing is in contrast to the findings associated with most forms of “toxic” neuropathy



Conclusions



- The influence of aging on the neurologic examination and NCS results is important as the mean age at the time of the NCS evaluation was 68.4 years (range: 54.0-87.7 years)
- Aging influences the results of the clinical neurological testing and NCSs, although the effects of “normal” aging on the peripheral nervous system are poorly understood



External Collaborations



External Collaborations



- External Collaboration Closure
 - Prior to Dr Michalek’s retirement reviewed list of collaborators
 - Dr Michalek indicated that all collaborations closed
- Letter sent to former collaborators
 - Notified of study’s closure and to return or destroy AFHS datasets or biospecimens
 - Reviewed by USAF legal advisors
 - Number of letters sent
 - Electronic datasets (45)
 - Specimens (4)
 - Non-respondents received a certified follow-up letter



External Collaborations



- Letter prompted response from
 - Gupta
- Additional collaborators that contacted AFHS
 - Gough
 - Boyle
 - DeVito
- Collaborative efforts
 - Gupta
 - Boyle
 - Gough



External Collaborations: Update



- Amit Gupta, MD, PhD UT-Southwestern Medical Center, et al
 - Anthropometric and Metabolic Factors and Risk of Benign Prostatic Hyperplasia: a Prospective Cohort Study of Air Force Veterans
 - *Urology*



External Collaborations: Update



- Steven Boyle, PhD Duke University Medical Center
 - The relation of hostility, anger and depression to 5-year increases in Lipids and Lipoproteins
 - *International Journal of Behavioral Medicine*
 - Hostility, Anger and Depression Predict Increases in C3 over a 10-year Period
 - *Brain, Behavior and Immunity*



External Collaborations: Update



- Haws, et al (Gough)
 - Are dioxin body burdens surrogates for other risk factors in associations between dioxin and diabetes?
 - *Dioxin 2006 abstract*
 - Evaluation of the Association between Serum Dioxin Levels and Type 2 Diabetes in Air Force Veterans Occupationally Exposed to Herbicides in Vietnam
 - *Environmental Health Perspectives*



External Collaborations: Update



- Frame L, et al
 - Three publications reviewed and cleared for publication
 - Previously reviewed with RHAC
 - Dr Frame unavailable for follow-up due to illness



Project Ranch Hand II Epidemiology Study

PE 0605306F

Program Management Update

7 September 2006



Team Status



- **Technical team**
 - All permanent civilian slots and technical contractor slots removed as of 30 Sep 2006
 - One “term” civilian slot to remain
- **Transition administrative team**
 - Contract for 6.5 FTE’s
- **Program management team**
 - Half-time PM; contract for 1.5 FTE’s



Contracting Efforts



- **Science Applications International Corp.**
 - Relational Information Warehouse
 - Air Force Health Study and Project Ranch Hand II Program History
- **SpecPro**
 - Transition Team (6.5 FTE's)
- **Core6 & OpTech**
 - Program Management (1.5 FTE's)



Funding



- **Congressional language identical for House and Senate FY 2007 direction and funding**
- **Contingency planning for possibility of “continuing resolution” budget process**
- **HQ USAF Program Element Monitor aware of funding disconnect until budget passed by Congress**



Wrap-Up



- **Political “hot potato” for most of study**
- **Managed \$139.6M budget over 26 years**
- **Managed 50 separate contracts over the course of conducting the study**
- **Logistics for 12,000+ person-trips to PE**
- **Integrated Product Team “Systems Approach” successful in completing the AFHS protocol as directed by the White House**



Transition Activities



- Disposition of AFHS scientific records
 - Hard copies
 - Medical records and other pertinent materials (2k+ boxes)
 - Stored in St Louis MO for 30 years then sent to
 - National Archives for permanent archiving
- Biological specimens
 - Completed reorganization of 80K+ specimens



Transition Activities (con't)



- Continue to construct electronic files per IOM recommendations (details previously briefed)
- Relational Information Warehouse
 - Structure completed and
 - Populating with specific AFHS databases



Transition Activities



- Participant notification
 - Transfer consent form and letter
 - Reviewed by USAF legal advisors
 - Locating ‘unlocatables’ and updating address database



Transition Activities



- House and Senate language requires retention of non-transferred records and biospecimens for a period of one year



Special Recognition

Leonard Schechtman and Kimberly Campbell