



Ranch Hand II Epidemiology Study

Air Force Health Study



Air Force Health Study & Program Update

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Overview

Air Force Health Study

- **Background**
- **Special Studies**
- **Current & Pending Reports/Activities**
- **Major Findings**
- **Study Close-Out & Transition**



USAF Commitment

Air Force Health Study

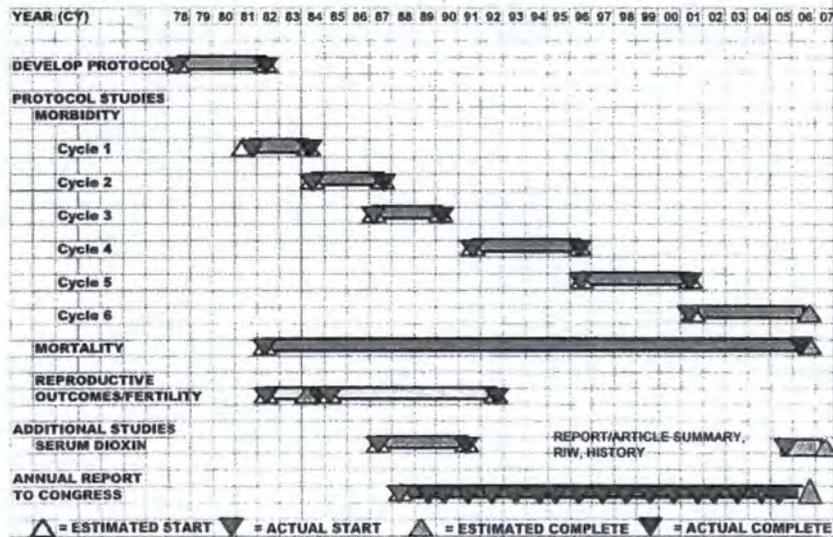
In 1979, the USAF committed to Congress & the White House to conduct an epidemiologic study with the purpose...

“To determine whether exposure to Agent Orange or its dioxin contaminant is related to adverse health in veterans of Operation Ranch Hand.”



Schedule [1978 – 2007]

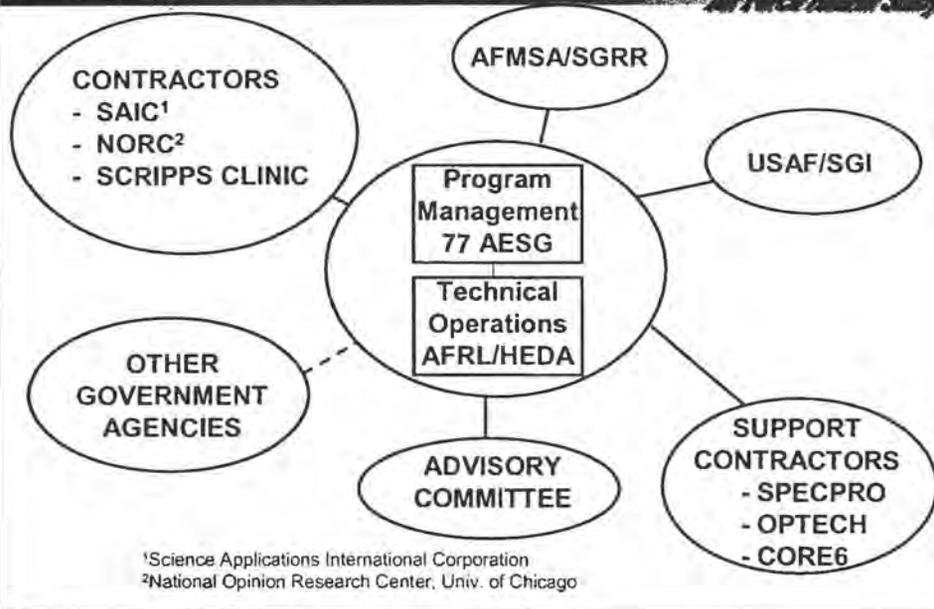
Air Force Health Study





Ranch Hand II Study Program Team

Air Force Health Study



Study Results Output

Air Force Health Study

- **Morbidity Reporting by Examination Cycle**
- **Mortality Reporting by Year**
- **Reproductive Outcomes Reporting**
- **Journal Articles**
- **Conference Presentations**



Productivity

Air Force Health Study

- 67 Journal Articles
- 13 Technical Reports
- 18 Annual Reports to Congress
- 4 Formal Congressional Hearings
- 7 HSVAC Staff Presentations
- > 40 Conference Presentations
- **Answers to Congressional Inquiries-TNTC***

*Too Numerous To Count



Interpretation of Results

Air Force Health Study

Repeating something in the news media does not make it true – even if it is repeated often.



Interpretation of Results

Air Force Health Study

- Information Bias
- Statistical Significance
- Multiple Testing Artifact
- Relative Risks
- Dose-Response
- Plausibility
- Can't Prove Safety



Study Strengths

Air Force Health Study

- Compliance
- Dioxin Measurement
- Length of Follow-Up
- Medical Record Verification
- Rigorous Quality Control
- Peer Review
- Two-Tiered Management Structure



Study Limitations

At Face Health Study

- Findings cannot be generalized to all Vietnam veterans.
- Small sample size for rare outcomes.
- Dioxin measured long after service ended.
- Possible incomplete adjustment due to unknown confounding factors.



In-House & Special Studies

At Face Health Study





Post-Service Mortality: Final Report

Air Force Health Study

- **Contrasted cumulative post-service mortality rates through December 31, 2003.**
 - Ranch Hands (N=1,263) versus Comparisons (N=19,080).
- **Used proportional hazards models & computed:**
 - Relative risks (RR), 95% confidence intervals (95% CI) and p-values.
 - Analyses adjusted for year of birth and military occupation.
- **Analyses with veterans who participated at physical examinations were adjusted for additional covariates (shown in tables).**



Cause-Specific Mortality to 31 December 2003

Air Force Health Study

Cause	Ranch Hand	Comparison	RR	95% CI	p-value
All Causes	240 (19.0)	2734 (14.3)	1.25	1.1-1.4	<0.001
Infection	2 (0.2)	29 (0.2)	1.0	0.8-1.4	0.96
Cancer	68 (5.4)	854 (4.5)	1.1	0.9-1.4	0.39
Endocrine	7 (0.6)	46 (0.2)	2.2	1.0-4.9	0.05
Circulatory	89 (7.0)	874 (4.6)	1.4	1.1-1.8	0.001
Respiratory	10 (0.8)	126 (0.7)	1.1	0.6-2.1	0.74
Digestive	12 (0.9)	101 (0.5)	1.7	0.9-3.0	0.10
Ill-Defined	10 (0.8)	92 (0.5)	1.8	0.9-3.4	0.09
Accident	31 (2.4)	370 (1.9)	1.2	0.9-1.8	0.26
Suicide	5 (0.4)	113 (0.6)	0.7	0.3-1.6	0.38
Homicide	3 (0.2)	27 (0.1)	1.8	0.5-5.8	0.36

Analyses adjusted for year of birth and military occupation.



All Causes Mortality to 31 December 2003

Air Force Health Study

Stratum	RH N (%)	Comparison N (%)	RR	95%CI	p-value
Officer Pilots	79 (17.9)	826 (15.7)	1.2	0.9-1.5	0.17
Administrators	7 (26.9)	57 (20.1)	1.8	0.8-4.0	0.15
Enlisted Flyer	46 (22.0)	493 (17.4)	1.0	0.7-1.3	0.86
Enlisted Ground	108 (18.4)	1,358 (12.7)	1.4	1.1-1.7	0.001

Analyses adjusted for year of birth.



Circulatory Disease Mortality to 31 December 2003

Air Force Health Study

Stratum	RH N (%)	Comparison N (%)	RR	95%CI	p-value
Officer Pilots	26 (5.9)	254 (4.8)	1.3	0.9-2.0	0.60
Administrators	2 (7.7)	18 (6.3)	1.6	0.4-6.8	0.72
Enlisted Flyer	12 (5.7)	149 (5.3)	0.8	0.5-1.5	0.58
Enlisted Ground	49 (8.3)	453 (4.2)	1.8	1.3-2.4	<0.001

Analyses adjusted for year of birth.



Mortality Analysis by Dioxin Category

Air Force Health Study

Analyses of 2,551 US Air Force veterans

- Valid dioxin assay results;
- Attended at least one physical examination.



All Causes Mortality to 31 December 2003 by Dioxin Category

Air Force Health Study

Stratum	No. of deaths (%)	RR ¹	95%CI	p-value
Comparison	161 (10.6)	1.0	Ref.	--
Background	51 (11.3)	1.0	0.8-1.4	0.81
Low	38 (13.2)	1.2	0.8-1.7	0.35
High	35 (12.1)	1.3	0.9-2.0	0.12

Analyses adjusted for year of birth, military occupation, smoking, drinking and family history of heart disease. ¹p – for trend = 0.07



Cancer Mortality to 31 December 2003 by Dioxin Category

Air Force Health Study

Stratum	No. of deaths (%)	RR ¹	95%CI	p-value
Comparison	64 (4.2)	1.0	Ref.	--
Background	21 (4.6)	1.0	0.6-1.7	0.95
Low	11 (3.8)	0.8	0.4-1.5	0.42
High	8 (2.8)	0.9	0.4-1.9	0.74

Analyses adjusted for year of birth, military occupation, smoking, reaction to sun exposure and eye color. ¹p – for trend = 0.66



Circulatory Disease Mortality to 31 December 2003 by Dioxin Category

Air Force Health Study

Stratum	No. of deaths (%)	RR ¹	95%CI	p-value
Comparison	47 (3.1)	1.0	Ref.	--
Background	14 (3.1)	1.0	0.6-1.7	0.96
Low	18 (6.3)	1.9	1.1-3.3	0.02
High	18 (6.3)	2.3	1.3-4.0	0.005

Analyses adjusted for year of birth, military occupation, smoking, and family history of heart disease; ¹p – for trend = <0.001



Post-Service Mortality: Final Report Conclusions

Air Force Health Study

Analysis of All AFHS Participants

- Adjusted only for year of birth and military occupations.
- All causes mortality & mortality due to circulatory diseases.
 - Statistically significantly increased in Ranch Hand veterans – primarily enlisted ground crew.
- All causes mortality increase mostly due to increases in mortality from circulatory diseases.
- Mortality increases from digestive, ill defined or endocrine diseases.
 - Small number of cases.
 - Statistically significant only for endocrine diseases.



Post-Service Mortality: Final Report Conclusions

Air Force Health Study

Analyses by Dioxin Category

- Adjusted for possible confounding factors.
- Increased risk due to circulatory death found in low & high dioxin category.
- Dose-response relationship & significant test for trend observed.
- All causes mortality was elevated but was not statistically significant.
- No increase in risk for deaths due to cancer.



Mr. Shurway... is
Time for your
blood sample



Viability of Stored Frozen Serum Samples

Are Air Force Health Study frozen samples viable for use in future studies?

- Over 80,000 stored archived biological specimens.
- Some stored for over 24 years.



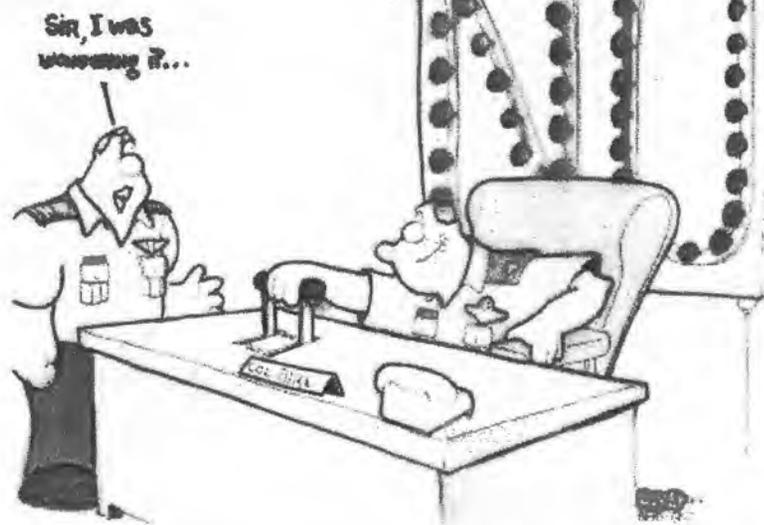
Viability of Stored Frozen Serum Samples

Air Force Health Study

- Randomly chose five AFHS veterans:
 - Participated at the 1982, 1985, 1987, 1992, and 1997 PEs;
 - Multiple serum samples stored.
- One sample per examination per participant selected.
- Total of 25 serum samples were analyzed.
- Results: There was no indication that older samples were less well preserved than more recent ones.



Air Force Health Study





Air Force Health Study Compliance Report

Air Force Health Study

Group/Examination	1982	1985	1987	1992	1997	2002
Ranch Hand Veterans Eligible to Participate	1,209	1,199	1,188	1,149	1,102	1,043
Ranch Hand Participants	1,046	1,017	996	953	870	777
Percentage of Ranch Hands Participation Relative to Those Eligible to Participate	86.5%	84.8%	83.8%	82.9%	78.9%	74.5%
Comparison Participants	1,223	1,292	1,298	1,280	1,251	1,174
Total	2,269	2,309	2,294	2,233	2,121	1,951



Air Force Health Study Compliance Report

Air Force Health Study

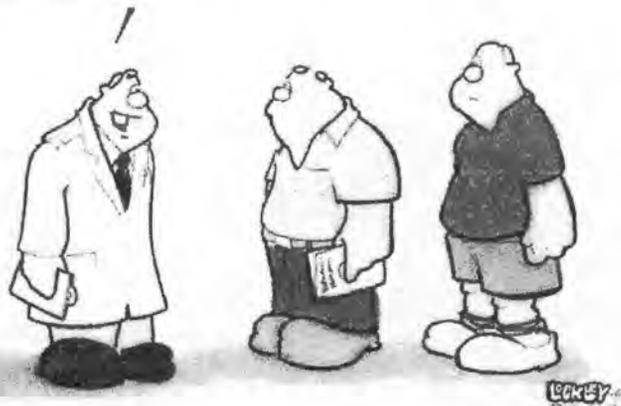
- **Ranch Hands significantly more compliant than Comparisons.**
 - Higher for enlisted flyers than enlisted groundcrew.
- **Compliance rates similar for 1982, 1985, 1987 & 1992 PEs.**
- **Large decrease in compliance noted for 1997 and 2002 PEs.**
 - Health and logistical reasons;
 - 1987 PE and later: age associated with health reasons.
- **The loss of power due to declining participation does not appear to have compromised the validity of the AFHS.**



CDC Dioxin Laboratory Study

Air Force Health Study

We're gonna have to hold off
on takin' your blood samples...
Our SUCTION PUMP IS ON THE
FRITZ ...



PCDDs, PCDFs, and PCBs in Serum of 800 US Air Force Veterans in 2002

Air Force Health Study

Goal: To measure levels of dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), mono-ortho and non-ortho substituted polychlorinated biphenyls (PCBs) in 800 randomly selected participants of the 2002 physical examination.

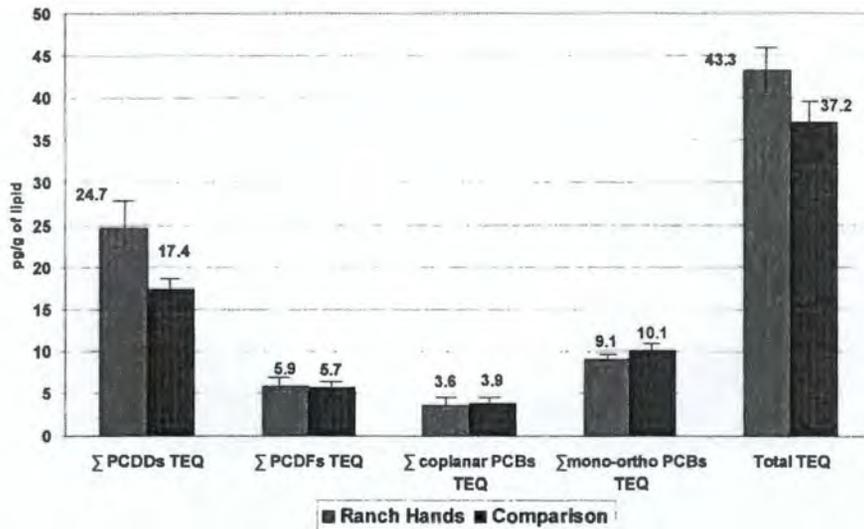
- **Contrasted Ranch Hand and Comparison levels with reference ranges from the US general population based on NHANES* 2001-2002 data.**

*National Health and Nutrition Examination Survey



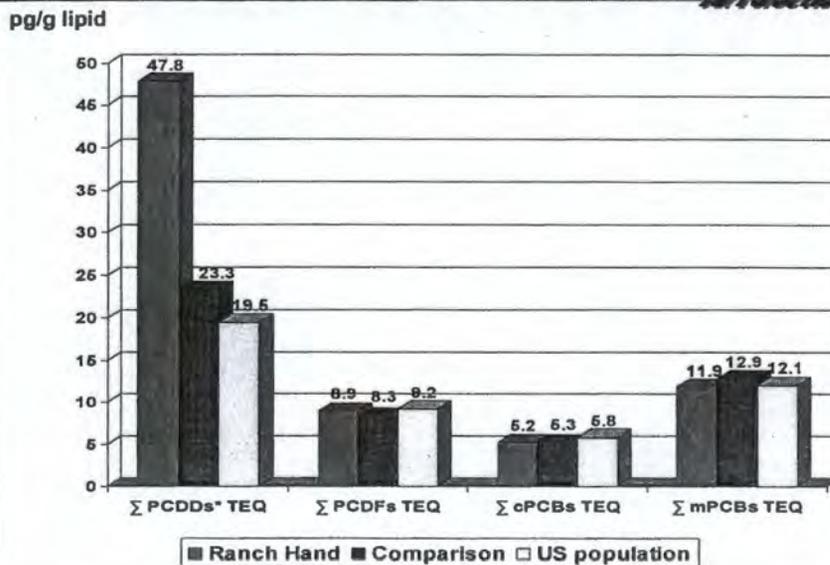
Means and 95% CIs of PCDDs, PCDFs, cPCBs and mPCBs TEQs (1998 TEFs)

Air Force Health Study



90th Percentiles of PCDD/F/c-mPCBs TEQs in 45-59 years old (1998 TEFs)

Air Force Health Study

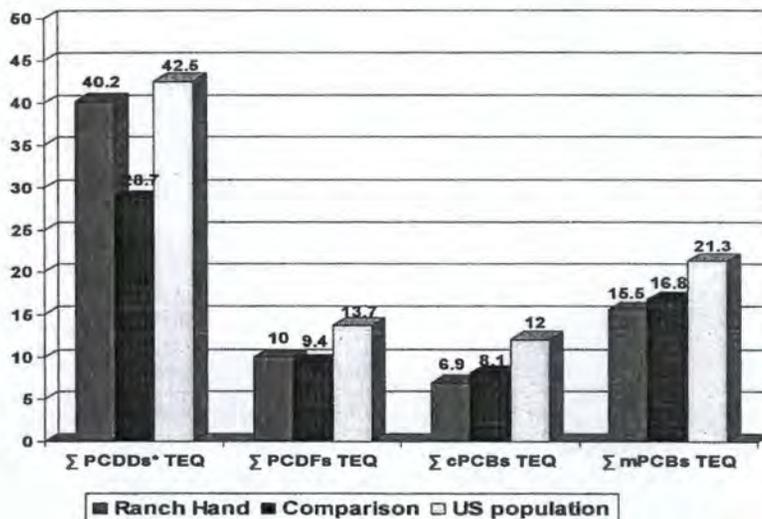




90th Percentiles of PCDD/F/c-mPCBs TEQs in 60+ years old (1998 TEFs)

Air Force Health Study

pg/g lipid



PCDDs, PCDFs, and PCBs in Serum of 800 US Air Force Veterans in 2002

Air Force Health Study

Conclusions

- Mean PCDDs TEQ higher in Ranch Hands than in Comparisons (24.7 pg/g lipid vs. 17.4 pg/g lipid).
- Reflected the difference in the mean TCDD levels (10.7 pg/g lipid vs. 3.2 pg/g lipid).
- As a result, Ranch Hands had higher total TEQ than Comparisons (43.3 pg/g lipid vs. 37.2 pg/g lipid, respectively).



Air Force Health Study



Serum Dioxin and Memory Among Veterans of Operation Ranch Hand

Air Force Health Study

- **Author: Dr Cary, Psychologist for 2002 Physical Examination.**

Method

- **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.**



Serum Dioxin and Memory Among Veterans of Operation Ranch Hand

AFHS Health Study

Conclusions

- 2002 examination data results did not show deficits observed in 1982 data.
- Findings in the enlisted ground crew Ranch Hand, the highest dioxin-exposed group, consistent with the results of other Ranch Hands.
- Results of this study indicate that Agent Orange-exposed Ranch Hand veterans are functioning normally in regards to immediate and delayed memory.



Nerve Conduction Study (NCS) Data Verification and Review

AFHS Health Study

- Author: Dr Albers, NeuroBehavioral Resources, Inc., Ann Arbor, Michigan.
- 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 presence of the peripheral neuropathy among 60 AFHS participants with clinically evident peripheral neuropathy.



Nerve Conduction Study (NCS) Data Verification & Review

Air Force Health Study

- Review of NCS results established a diagnosis of generalized peripheral neuropathy in 56 (93%) out of 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 (diabetic status not evaluated).
- The presence of substantial conduction slowing is in contrast to the findings associated with most forms of "toxic" neuropathy.



Air Force Health Study





Air Force Health Study Summary Report

Air Force Health Study

- **Summary of Findings in Published Reports and Articles**
 - Includes the six physical examination reports, additional technical reports and peer-reviewed journal articles as of 31 December 2005.
 - By clinical group (endocrine, cardiovascular, neoplasia, etc.)

- **In draft; will be published as technical report.**



Adipose Tissue Study

Air Force Health Study

Molecular Epidemiological Evidence for Diabetogenic Effects of Dioxin Among Vietnam Veterans

By

**Phillip Fujiyoshi, Joel Michalek,
and Fumio Matsumura**



Adipose Tissue Study - Conclusion

Air Force Health Study

“We could obtain the definite molecular epidemiological evidence, indicating that dioxin is acting as a diabetogenic risk factor among Vietnam veterans even after many years from the time of exposure at such low levels of exposure.”

Dr. Matsumura



Amalgam Exposure & Neurological Function

Air Force Health Study

- **National Institute of Dental and Craniofacial Research.**
- **Examined 1663 AFHS Participants (677 RH, 986 C).**
- **Collected amalgam history and neurological measurements.**
- **Overall found no association between amalgam exposure and neurological signs or clinically evident peripheral neuropathy.**



Results

Air Force Health Study



Major Findings

Air Force Health Study

- **Diabetes**
 - Time to onset & severity dioxin dose-response.
- **Cancer**
 - Positive findings, but with complicated pattern;
 - More research required.
- **Spina bifida/anencephaly**
 - IOM determination.
- **Mortality (through 2003)**
 - Increase in all-cause mortality;
 - Circulatory disease death for enlisted ground crew significantly increased.



Wrap-Up

Air Force Health Study



Current Papers & Activity

Air Force Health Study

- **Summary of Findings in Published Reports and Articles**
 - Results from all TR's and peer-reviewed articles (approx 80).
- **Project Ranch Hand II/Air Force Health Study History**
 - Record process & “lessons learned”.
- **Relational Information Warehouse**



Transition Activities

Air Force Health Study

- **Disposition of AFHS Scientific Records**
 - **Hard Copies**
 - **Medical records and other pertinent materials (2k+ boxes).**
 - **Stored in St Louis MO, for 30 years.**
 - **Sent to National Archives for permanent archiving.**

- **Biological Specimens**
 - **Completed reorganization of 80K+ specimens.**



Hard-Copy Records

Air Force Health Study





Ready to Go

Air Force Health Study



Transition Activities

Air Force Health Study

Closure with External Collaborators

- Letters sent to all external collaborators holding:
 - AFHS datasets;
 - Biospecimens.
- Institutional Review Board/Legal Requirement



Transition Activities

Air Force Health Study

- **Defense Authorization Act for FY07**
 - Directs transfer AFHS electronic data and specimens.
 - Requires study participant notification and consent for transfer.

Transfer consent form & explanation letter completed & reviewed by legal.

Mailing underway by week of 8 October.



Transition Activities

Air Force Health Study

- **House and Senate language requires retention of non-transferred records and biospecimens for a period of one year.**
- **Non-transferred electronic records and biospecimens will be kept at Brooks City-Base and after the one-year period expires permanently destroyed.**



Last Civil Service Permanent Staff

Retired 30 September 2006

Air Force Health Study



Team Status

Air Force Health Study

- **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 FTEs.

- **Program Management Team**
 - Half-time PM;
 - Contract for 1.5 FTEs.



"THE ROAD TO VALOR IS BUILT BY ADVERSITY." - OVID

Air Force Health Study



<http://www.brooks.af.mil/AFRL/HED/hedb/defaultHEDA.htm>