



# Health and Scientific Research on Dioxins and Agent Orange: Past, Present, and Future

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## Intent of this talk

- Introduce the National Academies and the Institute of Medicine.
- Describe
  - **past** involvement of the National Academies in Agent Orange and dioxin health and science research,
  - the **present** status of IOM efforts, and
  - **future** plans and research opportunities for outside investigators.
- Summarize the conduct and content of the Air Force Health Study, a source of epidemiologic information on a cohort of Vietnam veterans.



# The National Academies

- Chartered by the U.S. Congress in 1863 as an independent non-governmental institution.



- “[T]he Academy shall, whenever called upon by any department of the Government, investigate, examine, experiment, and report upon any subject of science or art ....”

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# The Institute of Medicine

- Component of the National Academies.
- Chartered in 1970 “to enlist distinguished members of the medical and other professions in the study of problems that affect the public’s health.”



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## The National Academies study process

- Committee of volunteer experts formed.
- Reports written on the basis of
  - systematic literature reviews
  - public hearings and workshops
  - written testimony and other information
- Final report subjected to external peer review.

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## The Past



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# The “Effects of Herbicides in South Vietnam” study

- study initiated December 1970; published in February 1974.
- 17 committee members, 30 consultants, 8 Academy personnel carry out the work.
- 1500 person-days spent in Vietnam conducting research between September 1971 and late 1972.
- final report includes 19 working papers, primarily regarding the ecological impact of spraying and non-health impacts on Vietnam civilians.



## 1974 NAS study health effects findings

- “TCDD is extremely toxic to some laboratory animals.... [It] apparently decays very slowly under normal environmental conditions, indicating that its potential hazards may be very persistent.”
- “The Committee could find no conclusive evidence of association between exposure to herbicides and birth defects in humans. ... [It] recognizes however that the material is not adequate for definite conclusions.”





## 1974 NAS study health effects findings

- “Reports of Highlanders ... on death and illness caused by herbicides are so consistent that despite the lack of medical and toxicological evidence for such effects they cannot be dismissed out of hand and should be followed up ... by intensive studies....”



## The Present



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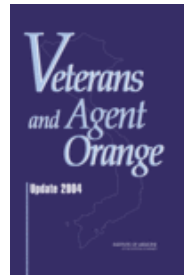
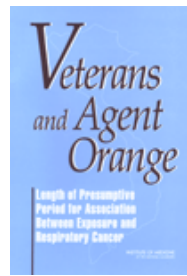
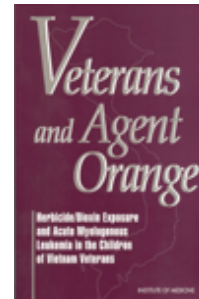
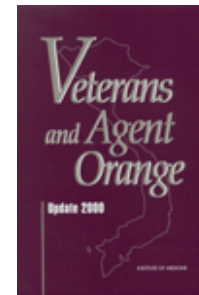
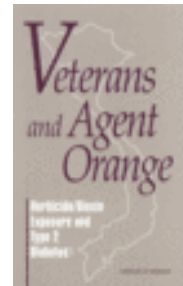
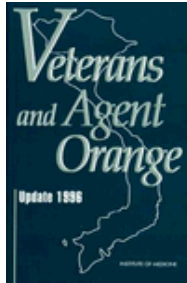
## The *Veterans and Agent Orange* reports

- Initiated by the Agent Orange Act of 1994.
- The statutory charge directs the National Academies to
  - “... review and summarize the scientific evidence, and assess the strength thereof, concerning the association between exposure to an herbicide used in support of the United States and allied military operations in the Republic of Vietnam during the Vietnam era and each disease suspected to be associated with such exposure.”

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## The *Veterans and Agent Orange* reports



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## *Veterans and Agent Orange - Update 2006*

**Summary of findings:  
the association between specific health outcomes  
and exposure to herbicides**

*Sufficient evidence of an association*

- Soft-tissue sarcoma (including heart)
- Non-Hodgkin's lymphoma
- Chronic lymphocytic leukemia (CLL)
- Hodgkin's disease
- Chloracne



## *Veterans and Agent Orange - Update 2006*

### **Summary of findings: the association between specific health outcomes and exposure to herbicides**

#### *Limited or suggestive evidence of an association*

- Laryngeal cancer
- Cancer of the lung, bronchus, or trachea
- Prostate cancer
- Multiple myeloma
- AL amyloidosis
- Hypertension
- Early-onset transient peripheral neuropathy
- Porphyria cutanea tarda
- Type 2 diabetes (mellitus)
- Spina bifida in offspring of exposed people

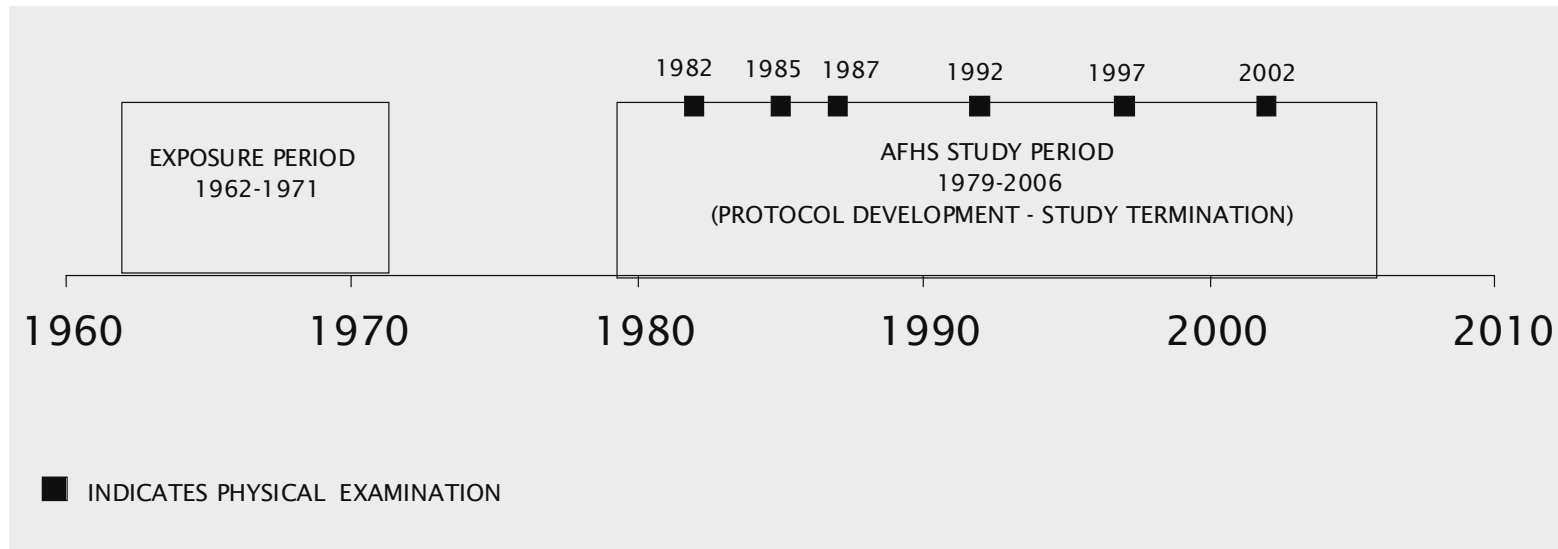


## The Air Force Health Study (AFHS)

- AFHS (popularly known as the Ranch Hand study) instigated by US Air Force (USAF) in June 1979.
- Protocol subjected to ten rounds of review and revision; final version (11) published in January 1982.
- Protocol called for a 20-year morbidity study with up to six physical examination cycles in years 1, 3, 5, 10, 15, and 20, plus companion mortality and reproductive studies.
- Total study cost (through FY 2006): ~\$143M



## AFHS timeline



Source: *Disposition of the Air Force Health Study*, Figure 2-1, p. 33 (IOM, 2006)





# AFHS morbidity study clinical examination health endpoints

- general health
- endocrine
- pulmonary
- immunologic
- neurologic
- renal
- gastrointestinal
- hepatic
- hematologic
- dermatologic
- psychiatric
- neoplasia (cancer)
- cardiovascular
- reproductive



# AFHS morbidity study clinical examination data gathering

- blood draws
- urine and semen collection
- skin and fat biopsies
- stool smears
- spirometry
- chest X rays
- electrocardiograms (ECGs)
- dermatology examinations
- peripheral vascular exams
- neurological assessments
- psychological testing
- many other clinical endpoints



# AFHS morbidity study questionnaire data gathering

- education
- employment
- income
- marital and fertility history
- spirometry
- child and family health
- health habits
- physical activities
- toxic substances exposure
- neurologic health
- military experience
- wartime herbicide exposure



## AFHS morbidity study data assets

- Detailed physical, mental, laboratory, and demographic data from 2,758 subjects who participated in at least one exam, including
  - ~15,000 chest X-rays
  - ~51,000 serum samples  
(~2,000 serum dioxin assays)
  - ~20,000 whole blood samples
  - ~7,000 urine samples
  - ~9,000 semen samples
  - ~300 adipose tissue samples



## AFHS reproductive outcomes study

- Comprehensive reproductive histories ascertained through interviews of current and former wives or partners.
- Medical records data gathered from partner and offspring health providers.
- Offspring followed through age 18.
- Medical data collected and verified for 9,921 conceptions and 8,100 live births.



## AFHS mortality study

- Mortality data collected through periodic status queries to major databases: Social Security Administration, DVA, IRS, USAF, National Death Index.
- Date of death and reported primary and secondary underlying cause of death coded.
- Data collected and analyzed on ~20,000 subjects.



## The National Academies and the AFHS

- National Academies *Panel on the Proposed Air Force Study of Herbicide Orange* reviewed version 6 of the AFHS protocol, issuing their final report in 1980.
- AFHS results reviewed as part of IOM's *Veterans and Agent Orange* -series of reports from 1994 through the present.
- *The Veterans Benefits Act of 2003*—now Public Law 108-183, §602(c)—directed IOM to offer advice on the AFHS research assets.

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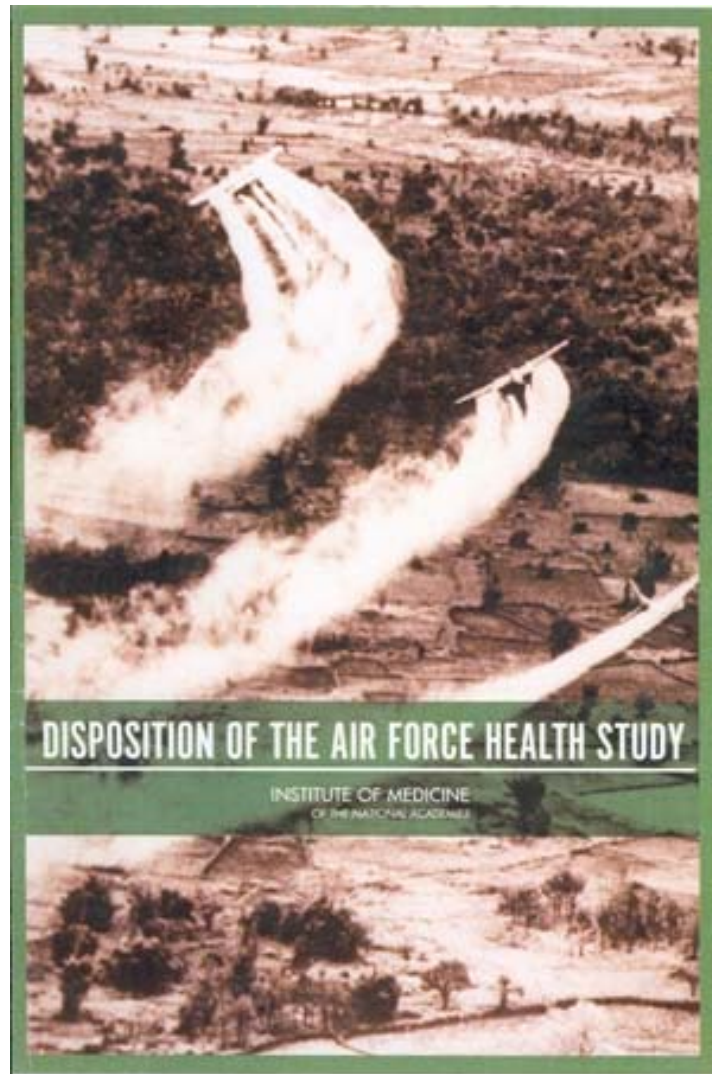


## IOM's response to the congressional charge

- *Committee on the Disposition of the Air Force Health Study* formed in 2004.
- Committee meetings, a workshop, and information gathering and analysis—including a site visit to the AFRL research facility and biorepository in San Antonio, TX—conducted in 2005.
- Interim letter report released in November, 2005; final report in February, 2006.







## Value of the research assets

### – conclusions –

- The AFHS data assets are unique: no other epidemiologic dataset on Vietnam veterans contains as detailed information over as long a time period.
- The data collected by the AFHS appear to be of high quality and the specimens appear to be well preserved.
- Analysis of the AFHS data assets has contributed to the literature addressing the health of Vietnam veterans.



## Value of the research assets

### – conclusions –

- It follows that there is scientific merit in retaining and maintaining these resources after the study's currently scheduled termination date.
- However, the AFHS dataset has weaknesses that limit its utility as a means of evaluating the health impacts of Agent Orange exposure.



## Weaknesses of the AFHS dataset

- Inherently small size of the cohort.
- Cohort is unrepresentative of in-theater veterans.
- Lack of biomarkers of herbicide exposure other than TCDD.
- Little information on subjects' wartime locations.
- Unavailability of detailed exposure histories.
- Possible herbicide exposures in the comparison population.



## Value of the research assets – conclusions –

These limitations are not an intrinsic obstacle to retaining and maintaining the assets after the currently scheduled termination date.

Further study of the AFHS medical records, other study data, and laboratory specimens is thus advisable.



# Value of the research assets

## – conclusions –

The potential value and relevance of extending study of the data assets rest in taking full advantage of available information and in the application of the results of future research that could encompass:

- reanalysis of outcomes examined by the AFHS using different assumptions and approaches than have been applied to date,
- new analyses of the medical records and other study data that examine questions that were not addressed in the AFHS,



# Value of the research assets

## – conclusions –

The potential value and relevance of extending study of the data assets rest in ... future research that could encompass:

- new studies of the collected biospecimens that take advantage of advances in technology and science to conduct analyses that were not contemplated in the AFHS protocol,
- expansion of the study's period of analysis through follow-up of the cohorts using publicly available information, and
- additional follow-up of health outcomes in AFHS participants.



## Future of the AFHS research assets – conclusions –

- It is advisable to extend the AFHS by making the database and associated biospecimen collection available for study via a custodian that should take an active role in fostering research on the assets.
- It is advisable to allow for the possibility of collecting additional data and specimens.





## Establishing the AFHS assets as a resource for researchers

- The committee recommended that Congress allocate a minimum of \$250,000 per year for three years to cover the direct costs of small grants for secondary data analysis or pilot projects using the data assets of the AFHS. This allocation will provide seed money for one to three investigations each year.
- Research support beyond the seed money will be the responsibility of prospective researchers, who will need to obtain it from other funding sources.



## Future review of support for the AFHS assets

- A five-year commitment—that is, two years after the last small grants proposed above are made—should be sufficient to establish whether the AFHS resources have value and relevance as a resource.
- Therefore, five years after the chosen custodian assumes responsibility, a committee should be convened to evaluate the potential value and relevance of extending further support to the maintenance of access to the data or the biospecimens collected in the course of the AFHS.



## The Future



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## Events since the release of the 2006 IOM report

- Section 714 of the John Warner National Defense Authorization Act for Fiscal Year 2007 (Public Law 109-364) directed the Air Force to transfer custodianship of the AFHS's data and biospecimens to the Medical Follow-up Agency at the conclusion of the AFHS.
- AFHS sought permission from the Study cohort to transfer the data assets to MFUA; over 95% consented.
- AFHS transferred Study data to MFUA shortly before ceasing operations on 30 September, 2007.



# The Medical Follow-up Agency

- Founded shortly after World War II at the urging of Dr. Michael DeBakey, then a Colonel in the Office of the Army Surgeon General.
- Over 50 years of experience in researching the health of active-duty military personnel and veterans.
- Manages the MFUA Cohort Catalog—a collection of study populations of former military personnel assembled as part of proposed or completed research dating back to the 1940's—and makes their data assets available to researchers.

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## Events since the release of the 2006 IOM report

- Because MFUA does not have an in-house capability to maintain biospecimens, it sought an alternative location to securely store them; the Air Force Research Laboratory at Wright Patterson Air Force Base (Dayton, OH) agreed to assume this responsibility.
- AFHS biospecimens are currently being maintained at AFRL-WPAFB.



## Events since the release of the 2006 IOM report

Bills currently under consideration in the US Congress would allocate funding to support maintenance of the AFHS assets and provide seed money for new research

- H.R. 2681 – *To provide for the maintenance, management, and availability for research of assets of Air Force Health Study*
- S. 1315 – *Disabled Veterans Insurance Improvement Act of 2007* (§ 805)
- S. 2640 – *Veterans' Benefits Enhancement Act of 2008* (§ 805)



## MFUA's plans for the AFHS research assets

Once funding is provided, MFUA will seek to promote new and innovative research on the AFHS assets by ...

- soliciting proposals from qualified researchers,
- subjecting submissions to rigorous scientific and IRB review,
- seeking collaborative relationships with successful applicants,
- disseminating available support money to promising proposals, and
- promoting publication of research results.

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## Learning more about IOM's Agent Orange-related research initiatives

- Full text of *Disposition of the Air Force Health Study*:  
<http://www.nap.edu/catalog/11590.html>
- Links to the full text of almost all National Academies reports:  
<http://www.nap.edu>
- Information on the MFUA Cohort Catalog:  
<http://www.iom.edu/CMS/3795/4903.aspx>
- Email address of the AFHS cohort research project:  
[AFHS-study@nas.edu](mailto:AFHS-study@nas.edu)

