Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicide Orange
EPIDEMIOLOGIC INVESTIGATION OF HEALTH EFFECTS IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO HERBICIDE ORANGE

EPIDEMIOLOGY DIVISION
USAF SCHOOL OF AEROSPACE MEDICINE (AFSC)
BROOKS AFB, TEXAS
EXECUTIVE OVERVIEW
PROJECT RANCH HAND II

- OPERATIONAL BACKGROUND
- STUDY GOALS
- EPIDEMIOLOGIC STUDY DESIGN
- PRIMARY DATA COLLECTION METHODS
- STATISTICAL METHODOLOGY
- SUMMARY
PROJECT RANCH HAND II

PURPOSE OF THE STUDY: TO DETERMINE WHETHER LONG TERM HEALTH EFFECTS EXIST AND CAN BE ATTRIBUTED TO OCCUPATIONAL EXPOSURE TO HERBICIDE ORANGE
EPIDEMIOLOGIC STUDY DESIGN

COMPONENTS OF THE PROBLEM

Have there been, are there currently, or will there be in the reasonably foreseeable future, any adverse health effects among former ranch hand personnel caused by repeated occupational exposure to 2,4,5-T herbicide and its contaminant, TCDD (dioxin)?
GOALS OF STUDY

PREMISE: GOALS ARE INTERDEPENDENT

1. ASSESS HEALTH EFFECTS
   IDENTIFY INDIVIDUALS WITH ADVERSE HEALTH EFFECTS (PHYSICAL AND PSYCHOLOGICAL) FROM TCDD EXPOSURE, AND IDENTIFY OTHERS AT INCREASED RISK

2. SATISFY SOCIAL CONCERN FROM LAY AND POLITICAL SCIENTIFIC COMMUNITIES

3. CLARIFY COMPENSATION ISSUE
OPERATING ASSUMPTION

OPERATION RANCH HAND PERSONNEL WERE PROBABLY EXPOSED TO 2,4,5-T AND TCDD TO A SIGNIFICANTLY GREATER DEGREE THAN US ARMY GROUND PERSONNEL

IMPLYING THAT RANCH HAND PERSONNEL WOULD DEVELOP MORE ACUTE/CHRONIC CLINICAL SYMPTOMS FROM THE EXPOSURES AND WOULD MANIFEST THEM SOONER THAN THE US ARMY PERSONNEL
<table>
<thead>
<tr>
<th>STUDY PHASE</th>
<th>METHODS</th>
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<tbody>
<tr>
<td>MORTALITY STUDY</td>
<td>PERSON TRACKING, RECORD REVIEWS</td>
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<tr>
<td>MORBIDITY STUDY</td>
<td>BASELINE QUESTIONNAIRE, PHYSICAL EXAM</td>
</tr>
<tr>
<td>FOLLOW-UP STUDY</td>
<td>ADAPTIVE QUESTIONNAIRES, PHYSICAL EXAMS</td>
</tr>
</tbody>
</table>

THREE PHASE APPROACH REQUIRED
Epidemiologic Study Design

Classic Approach:
- Literature Review
- Pilot Study
- Nonconcurrence Prospective Study
- Retrospective
- Cross-Sectional
- Prospective

Project Ranch Hand II:
- Literature Review
- Mortality
- Morbidity
- Follow-Up
RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN
GROUP SELECTION, RATIONALE

PRIMARY EXPOSED GROUP

C-123 RANCH HAND; CREW+SUPPORT

CONTROL GROUP

C-130, CREW+SUPPORT

- STUDY REQUIREMENT
  - HIGH RELATIVE EXPOSURE TO HERBICIDE ORANGE (H.O.)
  - POPULATION IDENTIFIABLE

- NO JOB EXPOSURE TO H.O.
  - LARGE N, TIGHT MATCHING FEASIBLE
  - SIMILAR COMBAT STRESS AS C-123 CREWS
  - LIFESTYLE AND PERSONALITY SIMILAR TO C-123 CREWS

- ATTEMPT TOTAL ASCERTAINMENT OF BOTH GROUPS TO CONTROL HIDDEN MORTALITY EFFECTS
EPIDEMIOLOGIC STUDY DESIGN

- ANCILLARY STUDY GROUPS
  - DRUM HANDLERS
  - SECONDARY MAINTENANCE PERSONNEL
  - ARMY OBSERVERS
  - HELICOPTER CREWS
  - EXPERIMENTAL SPRAY UNITS
  - ALL OTHERS

- FACTORS
  - NUMERATOR: VOLUNTEER BIAS
  - DENOMINATOR: POPULATION AT RISK; UNKNOWN
  - CONTROL GROUP: MOOT

- PLAN
  - ALL DATA SUBSETTED, ANALYZED SEPARATELY
  - DATA AND INTERPRETATIONS, IF ANY, ANECDOTAL
RANCH HAND PERSONNEL

POTENTIAL FOR EXPOSURE

PILOTS, CO-PILOTS, NAVIGATORS  LOW

CREW CHIEFS, MAINTENANCE PERSONNEL  MODERATE

CONSOLE OPERATORS  HIGH
EXPOSURE INDEX CONSTRUCTION

SIMULANT STUDIES WITHIN AIRCRAFT (RICKENBACKER AFB OH)

- SKIN EXPOSURE 5:1 (CONSOLE OPERATOR VS PILOT)
- RESPIRATORY EXPOSURE
  PARTICLES 5:1 (CONSOLE OPERATOR VS PILOT)
  VAPOR 3:1 (CONSOLE OPERATOR VS PILOT)
RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN
SOME KNOWN/ESTIMATED POPULATION PARAMETERS

<table>
<thead>
<tr>
<th>EXPOSED GROUP (C-123)</th>
<th>CONTROL GROUP (C-130)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE RANGE:</strong></td>
<td>28-62</td>
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<tr>
<td><strong>SEX:</strong></td>
<td>ALL MALE</td>
</tr>
<tr>
<td><strong>RACE:</strong></td>
<td>OFFICER: ~ 100% WHITE</td>
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<tr>
<td></td>
<td>ENLISTED: ~ 10-14% BLACK</td>
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<tr>
<td><strong>CURRENT ACTIVE DUTY:</strong></td>
<td>25%</td>
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<tr>
<td></td>
<td>OFFICER: SENIOR MANAGEMENT</td>
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<tr>
<td></td>
<td>ENLISTED: MIDDLE MANAGEMENT</td>
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<tr>
<td><strong>PAST SERVICE EMPLOYMENT:</strong></td>
<td>AEROSPACE INDUSTRY</td>
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<tr>
<td><strong>Socioeconomic:</strong></td>
<td>SIMILAR TO CONTROL</td>
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<td><strong>General Lifestyle:</strong></td>
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<td>SIMILAR TO STUDY</td>
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</table>
RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN
RATIONALE FOR MATCHING PROCEDURE

MATCHING PROCEDURE RATIONALE:

- EACH EXPOSED PERSON WILL HAVE A SET OF TEN CONTROLS, SELECTED ON BEST FIT BASIS
- ALLOWS STATISTICAL INTER-GROUP TESTS WITHOUT MAJOR ADJUSTMENTS
- PROVIDES BETTER FLEXIBILITY FOR MULTIVARIATE TESTING
RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN

EXPOSED GROUP
C-123

MATCHED 1:10

CONTROL GROUP
NOT EXPOSED TO H.O.
C-130

PRIORITIZED MATCHING VARIABLES: RATIONALE

• AGE, ±6 MONTHS: CONTROLS FOR ANY AGE-DEPENDENT EFFECTS

• AFSC: CONTROLS OFFICER-ENLISTED, RATED-NONRATED STATUS, ETC. (FIVE CATEGORIES) I.E., SOCIOECONOMIC MATCH

• LENGTH OF RVN TOUR ±6 MONTHS: CONTROLS COMBAT MORBIDITY/MORTALITY AND NEURO-PSYCH EFFECTS

• RACE, CAUCASIAN/NON-CAUCASIAN: CONTROLS DISEASE RATES, CULTURAL BACKGROUND
AGE DISTRIBUTION OF RANCH HAND AND CONTROL POPULATIONS

MEAN AGE, RANCH HAND AND CONTROL = 40.8
COMPUTER MATCHING
RANCH HAND TO CONTROL, 1:10

- 48% EXACT MATCH, BIRTH MONTH, JOB (5), TIME IN RVN, RACE, SEX
- 87% MATCH, ± ONE YEAR BIRTH, ALL OTHERS EXACT
- 95% MATCH PREDICTED, ± 18 MONTHS BIRTH, ALL OTHERS EXACT
### Selection of the Control Cohort for the Mortality Analysis

#### Exposed Control Cohorts

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<th>GROUP</th>
<th>1</th>
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SELECTION PROCEDURE FOR THE QUESTIONNAIRE, PHYSICAL EXAMINATION, AND FOLLOW UP STUDY

CONTROL INDIVIDUALS

LIVING RANCH HAND INDIVIDUAL

RANDOMLY SELECTED MORTALITY CONTROLS

† † DEAD
— — UNWILLING
※ ※ VOLUNTEER
※※ REPLACEMENT CANDIDATES
STUDY DESIGN SCHEMATIC

CONTROL UNIVERSE
N = 25K

CONTROL POPULATION
N = 12K BEST FIT

EXPOSED UNIVERSE
N = 1200

NO SUBSAMPLING

EXPOSED
N = 1200

1:1 MATCHED PAIR

MORBIDITY ANALYSIS
N = 1200

MORBIDITY ANALYSIS: QUESTIONNAIRE & RECORD REVIEW

MORBIDITY ANALYSIS: VOLUNTARY PE/INDEPTH INTERVIEW

ADAPTIVE QUEST & PEs: 1st 5YR FOLLOWUP

ALL OTHER INDICATED 5YR FOLLOWUP PERIODS

MORTALITY ANALYSIS
N = 6000

REPLACEMENT

(RANDOM)
PURPOSE OF THE REPLACEMENT STRATEGY

- CORRECT EXPECTED SELECTION BIAS

- ENHANCE STATISTICAL POWER
EFFECT OF RANDOM LOSS TO STUDY IN THE CONTROL POPULATION

- NO ADVERSE EFFECT (BIAS) OTHER THAN LOSS OF STATISTICAL POWER FROM SMALL N.
EFFECT OF NON-RANDOM LOSS TO STUDY IN THE CONTROL POPULATION

- If control losses are ill, a spurious effect is attributed to herbicide exposure.
- If control losses are well, a true/valid health effect is diluted.
REPLACEMENT STRATEGY

EXPOSED

PRIMARY CONTROLS

LOSSES

MATCHED FOR HEALTH STATUS

REPLACEMENTS

(dead controls not replaced)
RATIONALE OF REPLACEMENT

DILUTIONAL BIAS

CONDITIONAL PROBABILITIES:

P(L/W) > P(L/I)

P(L/W)>> > P(L/I)

L = LOSS
W = WELL
I = ILL
CONTROL REPLACEMENT FOR THE MORBIDITY AND FOLLOW UP STUDIES

EXPOSED

1000

YEAR 0

YEAR 1

YEAR 2

YEAR 3

YEAR 4

YEAR 5

YEAR 6

CONTROL

1000

● QUESTIONNAIRE DATA

○ RECONSTRUCTED DATA

★ LOSS TO STUDY

☆ PHYSICAL EXAMINATION DATA
ESTIMATED IDENTIFICATION/PARTICIPATION OF THE RANCH HAND POPULATION

RANCH HAND POPULATION

UNACCOUNTABLE
≤ 1%

ACCOUNTABLE

NON-PARTICIPANTS
DEAD/MORIBUND 10%
UNWILLING 25%

NON-PARTICIPANTS
40%

NON-PARTICIPANTS
20%

NON-PARTICIPANTS
20%

RESPONSE ESTIMATE

ESTIMATED NUMBER OF PARTICIPANTS

99%
1200

65%
772

60%
463

80%
371

80%
297
RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN
FOLLOW-UP STUDY

OVER 5 YEAR PERIOD; RENEWABLE 5 YEAR OPTIONS

"ADAPTIVE" QUESTIONNAIRE
"ADAPTIVE" PHYSICAL EXAMINATION

IN YEARS 3 AND 5
PARTICIPATION SCHEMATIC FOR A GIVEN SUBJECT
BY DATE AND STUDY PHASE

1:5
MORTALITY
STUDY

1:1
MORBIDITY
STUDY

1:1
FOLLOW UP
STUDY

MONTH


Q QUESTIONNAIRE
AE ADAPTIVE EXAMINATION
AQ ADAPTIVE QUESTIONNAIRE

E PHYSICAL EXAMINATION
ADDITIONAL 5 YR FOLLOWUP PERIODS
INFORMATION SOURCES

- NATIONAL PERSONNEL RECORD CENTER, ST LOUIS
- AIR FORCE HUMAN RESOURCE LABORATORY
- MILITARY PERSONNEL RECORD CENTER
- AIR FORCE RESERVE/AIR NATIONAL GUARD
- UNIT HISTORIES AND PERSONAL REFERRALS
METHODS OF ASCERTAINMENT

NPRC

- MORNING REPORTS 1961-1966

- MILITARY PERSONNEL RECORDS
  - ALL VETERANS
    - UNITS OF ASSIGNMENT BY TIME/PLACE/STATUS
    - AIR FORCE SPECIALTY CODE (JOB) BY TIME
    - COMBAT FLYING HOURS
    - CUMULATIVE COMBAT MISSIONS

- MEDICAL RECORDS
  - INPATIENT/OUTPATIENT
    - VETERANS & DEPENDENTS

- PRESENT STATUS
  - RETIRED, RESERVES, DECEASED, VA CLAIM
  - ADDRESS AT TIME OF SEPARATION
DATA COLLECTION OVERVIEW

- MORTALITY DETERMINATION
- QUESTIONNAIRE
- RECORD REVIEWS
- PHYSICAL EXAMINATION
MORTALITY DETERMINATION

- MILITARY PERSONNEL RECORDS
- VETERANS ADMINISTRATION DEATH BENEFITS
- SOCIAL SECURITY ADMINISTRATION
- OTHER SOURCES: FAMILY, FRIENDS, SOCIAL ORGANIZATIONS, ETC.
QUESTIONNAIRE

PURPOSE

- Collect health data that can be analyzed for health effects due to herbicide exposure
- Capture data that would be lost through low physical examination compliance rates

QUALITY

- Development consultation contract
- Interviewer quality control
- Pretest

VALIDITY

- Questions restricted
- Verifiers/bias indicators
- Cross ref to MR, PE, and interview
- Development of question phrasing
SECTIONS OF QUESTIONNAIRE

- DEMOGRAPHIC DATA
- MEDICAL PROBLEMS
  - IDENTIFICATION IN RELATION TO TIME
  - ICDA CODES
- PERSONAL HISTORY
- MARITAL HISTORY
- PROGENY
- OTHER EXPOSURES
  - OCCUPATION
  - HOBBIES
  - RESIDENCES
- VIETNAM EXPERIENCE HISTORY
RECORD REVIEW

- MEDICAL RECORDS (AF, VA, CIV)
- PERSONNEL RECORDS
- DEATH CERTIFICATES/AUTOPSY REPORTS
- BIRTH CERTIFICATES ON OFFSPRING
DATA REPOSITORY

• COMPUTER INTEGRATION OF:
  • ALL QUESTIONNAIRES (DIRECT ENTRY)
  • PSYCHOLOGICAL TESTING
  • PHYSICAL EXAMINATION
  • MEDICAL RECORDS
  • HISTORICAL AND NATIONAL PERSONNEL RECORD CENTER DATA
  • DEATH CERTIFICATES
  • BIRTH CERTIFICATES

• MASTER FILE ON EACH STUDY AND MATCHED CONTROL

• CONFIDENTIALITY WILL BE ASSURED

• RETRIEVAL
  • MOMENTARY RECALL
  • DATA ANALYSIS
POSSIBLE DIAGNOSTIC INDICATORS OF HERBICIDE/DIOXIN TOXICITY
SOURCES OF INFORMATION

• ANIMAL STUDIES
• HUMAN CASE REPORTS
• EPIDEMIOLOGIC STUDIES
• VA CLAIMS / VA REPOSITORY
• VETERANS' CONCERNS
## Suggested Attributable Symptoms of Herbicide/TCDD in Humans

<table>
<thead>
<tr>
<th></th>
<th>2,4-D</th>
<th>2,4,5-T (+TCDD)</th>
<th>TCDD</th>
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<tbody>
<tr>
<td><strong>Symptoms</strong></td>
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<td></td>
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</tr>
<tr>
<td>Asthenia</td>
<td>•</td>
<td>• ASTHENIA</td>
<td>• CHLORACNE</td>
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<tr>
<td>Peripheral Neuropathy</td>
<td>• PERIPHERAL NEUROPATHY</td>
<td>• PERIPHERAL NEUROPATHY</td>
<td>• PORPHYRIA</td>
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<tr>
<td>Sweating/Fever</td>
<td>•</td>
<td>• PERIPHERAL NEUROPATHY</td>
<td>• HYPERPIGMENTATION</td>
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<td>Cardiac Disturbance</td>
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<td>Renal Dysfunction</td>
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<td>• RENAL DYSFUNCTION</td>
<td>• PERIPHERAL NEUROPATHY</td>
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<tr>
<td>Liver Dysfunction</td>
<td>•</td>
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<td>GI Disturbance</td>
<td>•</td>
<td>• GI DISTURBANCE</td>
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<td>Headache</td>
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<td>• HEADACHE</td>
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<tr>
<td>Pneumonitis</td>
<td>• CSF PROTEIN ABNORMALITIES</td>
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<td>• CONVULSIONS</td>
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<td>• HYPOTHYROIDISM</td>
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<td>• HEARING/SMELL DISTURBANCES</td>
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SUBJECTIVE SIGNS AND SYMPTOMS

ANXIETY
DEPRESSION
FATIGUE
APATHY
LOSS OF DRIVE

DECREASED LEARNING ABILITY
PARESTHESIAS
DECREASED LIBIDO
SLEEP DISTURBANCES
ANOREXIA
EPIDEMIOLOGIC STUDIES

- HARDELL AND SANDSTROM (1978)
  CASE CONTROL STUDY OF SARCOMA PATIENTS

- TUNG (1973)
  INCREASES IN THE DIAGNOSIS OF PRIMARY LIVER CANCER

- ALSEA, OREGON (1979)
  SPONTANEOUS ABORTIONS IN SPRAYED AREAS OF OREGON

- AUSTRALIA AND NEW ZEALAND (1978)
  BIRTH DEFECTS IN SPRAYED AREAS

- SEVESO, ITALY (1976)
  HUMAN EFFECTS FOLLOWING AN INDUSTRIAL ACCIDENT
PRELIMINARY RESULTS OF THE SEVESO STUDIES

• ACUTE AND SUB-ACUTE EFFECTS:
  • CHLORACNE
  • IDIOPATHIC NEUROLOGICAL CONDITIONS
  • IDIOPATHIC HEPATOMEGALY

• NO EVIDENCE TO DATE OF:
  • IMMUNOLOGIC DISTURBANCES
  • CYOGENETIC ABNORMALITIES
  • FETOTOXICITY
  • TERATOGENICITY
  • CARCINOGENICITY
GENERAL EVALUATION

- PHYSICAL EXAMINATION
- URINALYSIS
- ELECTROCARDIOGRAM
- CHEST X-RAY
- VDRL/FTA
DERMATOLOGIC

• THOROUGH EXAMINATION FOR CHLORACNE: ACTIVE OR RESIDUAL LESIONS

• URINE PORPHYRINS AND PORPHOBILINOGEN

• SERUM STORED FOR SUBSEQUENT PORPHYRIN STUDIES AS TECHNOLOGY IMPROVEMENTS PERMIT

• PHOTOGRAPHS OF LESIONS

• DELTA ALA
HEPATIC/NEOPLASTIC

- PHYSICAL EXAMINATION
- CHOLESTEROL/HDL CHOLESTEROL
- TRIGLYCERIDES, SGOT, SGPT, GGTP, LDH

ANA AND HEPATITIS ANTIGENS AND ANTIBODIES
IF HEPATIC FUNCTION IS IMPAIRED
NEUROLOGICAL/PHYCHOLOGICAL

- THOROUGH NEUROLOGICAL EXAMINATION
- NERVE CONDUCTION VELOCITIES
- CPK
- PSYCHOLOGICAL BATTERY
  - MMPI
  - WAIS
  - WRAT
  - WECHSLER MEMORY SCALE I
  - CORNELL INDEX
  - HALSTEAD-REITAN
IMMUNOLOGIC/HEMOPOIETIC

- CBC
- SEDIMENTATION RATE
- PLATELET COUNT
- RBC INDICES
- SERUM ELECTROPHORESIS

IMMUNOELECTROPHORESIS, SKIN TESTING, AND QUANTITATIVE IMMUNOGLOBULIN DETERMINATIONS IF INDICATE BY HISTORY
ENDOCRINE/REPRODUCTIVE

- PHYSICAL EXAMINATION
- SEMEN ANALYSIS: NUMBER, MOTILITY, MORPHOLOGY
- LH, FSH, TESTOSTERONE
- FASTING AND 2 HOUR POST PRANDIAL SERUM GLUCOSE
- DIFFERENTIAL CORTISOL
- THYROID PROFILE (RIA)
- COMPLETE REPRODUCTIVE HISTORY

KARYOTYPING IF INDICATED BY HISTORY
ENHANCEMENT OF DATA QUALITY

- SINGLE CENTER
- BLIND ASSESSMENT
- FULLY QUALIFIED PERSONNEL
- COMPLIANCE WITH EXAMINATION PROTOCOL
- ON-SITE MONITOR
- STRICT LABORATORY QUALITY CONTROL
PROJECT RANCH HAND II

STATISTICAL METHODOLOGY
STATISTICAL METHODOLOGY - THRUSTS/GOALS

1. FULLY DEFINE STUDY POWER AND OPTIMIZE

2. ANALYZE BIAS SOURCES

3. INTERPRETATION
**INTERPRETATION OF HORIZONTAL COMPARISONS**

<table>
<thead>
<tr>
<th>OVERT EFFECT</th>
<th>SUBCLINICAL</th>
<th>OVER-REPORTING</th>
</tr>
</thead>
<tbody>
<tr>
<td>( M_R &gt; M_C )</td>
<td>( M_R = M_C )</td>
<td>( M_R = M_C )</td>
</tr>
<tr>
<td>( S_R &gt; S_C )</td>
<td>( S_R = S_C )</td>
<td>( S_R &gt; S_C )</td>
</tr>
<tr>
<td>( F_R &gt; F_C )</td>
<td>( F_R &gt; F_C )</td>
<td>( F_R = F_C )</td>
</tr>
<tr>
<td>( F_{RS} &gt; F_{CS} )</td>
<td>( F_{RS} &gt; F_{CS} )</td>
<td>( F_{RS} &lt; F_{CS} )</td>
</tr>
<tr>
<td>( F_{RS} &lt; F_{CS} )</td>
<td>( F_{RS} = F_{CS} )</td>
<td>( F_{RS} = F_{CS} )</td>
</tr>
</tbody>
</table>

**MORTALITY/SYMPTOM/SIGN REGRESSION ON EXPOSURE**

- **SIGN REGRESSION ON EXPOSURE**
- **NO REGRESSION ON EXPOSURE SEEN**

\[ F_R = F_{RS} S_R + F_{RS} (1 - S_R) \]
INDIVIDUAL EXPOSURE INDEX ($E_j$)

$$E_j = t_j \sum_{i} \left( f_{ij} \ c_{ij} \ p_{ij} \right) + h_j$$

FOR THE $i^{th}$ MISSION:

$f_{ij} = \text{FRACTION 2,4,5-T SPRAYED}$

$c_{ij} = \text{DIOXIN CONCENTRATION}$

$p_{ij} = \text{CREW POSITION}$

$t_j = \text{AVERAGE MISSION DURATION}$

$h_j = \text{SPECIFIC EXPOSURE HISTORY}$
MORTALITY ASSESSMENT

- THREE CATEGORIES: ALIVE, DEAD, UNACCOUNTED
- WILL MAINTAIN UNACCOUNTED $< 1\%$
METHODS FOR MORTALITY ANALYSIS

1. ESTIMATE STANDARDIZED MORTALITY RATIO (SMR) USING ARMITAGE APPROACH.

2. ESTIMATE SMR USING BRESLOW AND DAY MULTIPLICATIVE MODEL.

3. LOGISTIC MODELS (WALKER AND DUNCAN).

4. SURVIVAL MODELS (COX).

5. NONPARAMETRIC MATCHED PAIR SURVIVAL ANALYSIS (WEI).
(Armitage, 1971)

### Ranch Hand

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Person Years</th>
<th>Deaths</th>
<th>Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( P_{11} )</td>
<td>( m_{11} )</td>
<td>( r_{11} )</td>
</tr>
<tr>
<td>2</td>
<td>( P_{12} )</td>
<td>( m_{12} )</td>
<td>( r_{12} )</td>
</tr>
<tr>
<td>3</td>
<td>( P_{13} )</td>
<td>( m_{13} )</td>
<td>( r_{13} )</td>
</tr>
<tr>
<td>( k )</td>
<td>( P_{1k} )</td>
<td>( m_{1k} )</td>
<td>( r_{1k} )</td>
</tr>
</tbody>
</table>

### Controls

<table>
<thead>
<tr>
<th>Person Years</th>
<th>Deaths</th>
<th>Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{21} )</td>
<td>( m_{21} )</td>
<td>( r_{21} )</td>
</tr>
<tr>
<td>( P_{22} )</td>
<td>( m_{22} )</td>
<td>( r_{22} )</td>
</tr>
<tr>
<td>( P_{23} )</td>
<td>( m_{23} )</td>
<td>( r_{23} )</td>
</tr>
<tr>
<td>( P_{2k} )</td>
<td>( m_{2k} )</td>
<td>( r_{2k} )</td>
</tr>
</tbody>
</table>

\[
M = \frac{\sum_{j=1}^{k} m_{ij}}{\sum_{j=1}^{k} P_{ij}} \times 100
\]

\[
SMR = M \times 100
\]
• \( \lambda_{ijk} = \theta_i \phi_j \psi_k \)

• MAXIMUM LIKELIHOOD
LOGISTIC MODEL

\[ p = \frac{e^Z}{1 + e^Z} \]

\[ Z = \alpha + \beta_1 A + \beta_2 T + \beta_3 R + \beta_4 E + \beta_5 AE + \ldots. \]

A = AGE

T = TOUR LENGTH

R = RACE INDICATOR

E = EXPOSURE INDEX
## CONTROLS

<table>
<thead>
<tr>
<th>RANCH HAND PERSONNEL</th>
<th>DEAD</th>
<th>ALIVE</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEAD</td>
<td>a</td>
<td>b</td>
<td>a+b</td>
</tr>
<tr>
<td>ALIVE</td>
<td>c</td>
<td>d</td>
<td>c+d</td>
</tr>
<tr>
<td>TOTAL</td>
<td>a+c</td>
<td>b+d</td>
<td>n</td>
</tr>
</tbody>
</table>

$$X^2 = \frac{(b-c)^2}{b+c}$$
COX SURVIVAL MODELS

\[ \lambda = \lambda_0 e^{\beta \cdot x} \]
## WEI Mortality Method

<table>
<thead>
<tr>
<th>AGE AT EVENT</th>
<th>MATCHED CONTROL</th>
<th>GEHAN/WEI SCORE</th>
<th>SIGN TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXPOSED PERSONNEL</td>
<td>MATCHED CONTROL</td>
<td>GEHAN/WEI SCORE</td>
<td>SIGN TEST</td>
</tr>
<tr>
<td>56</td>
<td>62</td>
<td>-4</td>
<td>-1</td>
</tr>
<tr>
<td>59</td>
<td>60 *</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>53</td>
<td>58</td>
<td>-4</td>
<td>-1</td>
</tr>
<tr>
<td>57 *</td>
<td>55</td>
<td>1</td>
<td>+1</td>
</tr>
</tbody>
</table>

- $W_n$ has known distribution for large $n$
- Test more powerful than Sign Test
QUESTIONNAIRE DATA

- FOUR DATA TYPES: DICHOTOMOUS, POLY TOMOUS, COUNT, CONTINUOUS

- FOR CATEGORICAL RESPONSES USE LOG-LINEAR MODELS

- FOR ORDERED CATEGORICAL RESPONSES USE REGRESSION MODELS OF MCCULLAGH

- FOR CONTINUOUS RESPONSES USE GENERALIZED LINEAR MODELS
<table>
<thead>
<tr>
<th>AGE CATEGORY</th>
<th>RANCH HAND PERSONNEL</th>
<th>CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISEASE CATEGORY</td>
<td>1 2 3 4</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>1</td>
<td>x 111 x 112 x 113 x 114</td>
<td>x 211 x 212 x 213 x 214</td>
</tr>
<tr>
<td>2</td>
<td>x 121 x 122 x 123 x 124</td>
<td>x 221 x 222 x 223 x 224</td>
</tr>
<tr>
<td>3</td>
<td>x 131 x 132 x 133 x 134</td>
<td>x 231 x 232 x 233 x 234</td>
</tr>
<tr>
<td>4</td>
<td>x 141 x 142 x 143 x 144</td>
<td>x 241 x 242 x 243 x 244</td>
</tr>
</tbody>
</table>

\[ \ln mijk = u + u_1(i) + u_2(j) + u_3(k) + u_{12}(ij) + u_{13}(ik) + u_{23}(jk) + u_{123}(ijk) \]
<table>
<thead>
<tr>
<th>RANCH CATEGORY</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$n_{11}$</td>
<td>$n_{12}$</td>
<td>$n_{13}$</td>
<td>$n_{14}$</td>
</tr>
<tr>
<td>2</td>
<td>$n_{21}$</td>
<td>$n_{22}$</td>
<td>$n_{23}$</td>
<td>$n_{24}$</td>
</tr>
<tr>
<td>3</td>
<td>$n_{31}$</td>
<td>$n_{32}$</td>
<td>$n_{33}$</td>
<td>$n_{34}$</td>
</tr>
<tr>
<td>4</td>
<td>$n_{41}$</td>
<td>$n_{42}$</td>
<td>$n_{43}$</td>
<td>$n_{44}$</td>
</tr>
</tbody>
</table>
PHYSICAL EXAMINATION DATA

• Same data types as questionnaire

• To validate questionnaire data

• To estimate rate of occurrence of physical findings

• To evaluate relationship of symptoms and physical findings

• Essentially use the same statistical tests as used with questionnaire
POWER VERSUS RELATIVE RISK, 1:5 MORTALITY STUDY BY THREE DISEASE INCIDENCES
### Morbidity Study

#### Power – Dichotomous Variables

<table>
<thead>
<tr>
<th>$P_1$</th>
<th>$P_2$</th>
<th>REL RISK</th>
<th>$r$</th>
<th>$n = 250$</th>
<th>$n = 350$</th>
<th>$n = 450$</th>
</tr>
</thead>
<tbody>
<tr>
<td>.05</td>
<td>.01</td>
<td>5</td>
<td>0</td>
<td>.77</td>
<td>.82</td>
<td>.92</td>
</tr>
<tr>
<td>.04</td>
<td>.01</td>
<td>4</td>
<td>0</td>
<td>.61</td>
<td>.75</td>
<td>.85</td>
</tr>
<tr>
<td>.03</td>
<td>.01</td>
<td>3</td>
<td>0</td>
<td>.40</td>
<td>.51</td>
<td>.59</td>
</tr>
<tr>
<td>.10</td>
<td>.05</td>
<td>2</td>
<td>0</td>
<td>.61</td>
<td>.75</td>
<td>.85</td>
</tr>
<tr>
<td>.20</td>
<td>.10</td>
<td>2</td>
<td>0</td>
<td>.87</td>
<td>.94</td>
<td>.97</td>
</tr>
<tr>
<td>.05</td>
<td>.01</td>
<td>5</td>
<td>.1</td>
<td>.89/.029</td>
<td>.94/.032</td>
<td>.98/.064</td>
</tr>
<tr>
<td>.04</td>
<td>.01</td>
<td>4</td>
<td>.1</td>
<td>.72/.033</td>
<td>.87/.038</td>
<td>.88/.041</td>
</tr>
<tr>
<td>.03</td>
<td>.01</td>
<td>3</td>
<td>.1</td>
<td>.38/.020</td>
<td>.68/.046</td>
<td>.71/.077</td>
</tr>
<tr>
<td>.10</td>
<td>.05</td>
<td>2</td>
<td>.1</td>
<td>.76/.055</td>
<td>.85/.048</td>
<td>.88/.048</td>
</tr>
<tr>
<td>.20</td>
<td>.10</td>
<td>2</td>
<td>.1</td>
<td>.94/.043</td>
<td>.98/.046</td>
<td>.99/.057</td>
</tr>
</tbody>
</table>

- $\alpha = 0.05$
- $\alpha = \text{as indicated}$
MORBIDITY STUDY
POWER-CONTINUOUS VARIABLES

\[ \alpha = 0.05, \quad \sigma_C / \mu_C = 0.1, \quad \gamma = \frac{\mu_{RH}}{\mu_C} \]

\[ \text{POWER} = 1 - \beta \]

<table>
<thead>
<tr>
<th>R</th>
<th>$\gamma$</th>
<th>(n=180)</th>
<th>(n=450)</th>
</tr>
</thead>
<tbody>
<tr>
<td>.20</td>
<td>1.01</td>
<td>.20</td>
<td>.38</td>
</tr>
<tr>
<td>.20</td>
<td>1.02</td>
<td>.55</td>
<td>.88</td>
</tr>
<tr>
<td>.20</td>
<td>1.05</td>
<td>&gt; .995</td>
<td>&gt; .995</td>
</tr>
<tr>
<td>.70</td>
<td>1.01</td>
<td>.86</td>
<td>&gt; .995</td>
</tr>
<tr>
<td>.70</td>
<td>1.02</td>
<td>&gt; .995</td>
<td>&gt; .995</td>
</tr>
<tr>
<td>.70</td>
<td>1.05</td>
<td>&gt; .995</td>
<td>&gt; .995</td>
</tr>
<tr>
<td>Number of Pairs</td>
<td>( \gamma = \beta )</td>
<td>( \gamma = 0.8 \beta )</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Power Neglecting Pairing</td>
<td>Power With Pairing</td>
<td>Power Neglecting Pairing</td>
</tr>
<tr>
<td>250</td>
<td>&gt; .99</td>
<td>&gt; .995</td>
<td>.93</td>
</tr>
<tr>
<td>300</td>
<td>&gt; .99</td>
<td>&gt; .995</td>
<td>.96</td>
</tr>
<tr>
<td>350</td>
<td>&gt; .99</td>
<td>&gt; .995</td>
<td>.97</td>
</tr>
</tbody>
</table>

\( \alpha = 0.05 \)
REPLACEMENT CONCEPT

- DERIVED FROM LIFE-TABLE METHODS EMPLOYING PERSON-YEAR
  DENOMINATORS FOR INCIDENCE COMPUTATIONS

MATANOSKI ET. AL., AMER. J. EPID., 101, 1975
SHEPS, MILBANK MEM. FUND., 44, 1966
ELVEBACK, JASA, 53, 1958

- ADDRESSES BIAS AND POWER CONCERNS

\[ P(X) = \alpha P_c(X) + \beta P_{nc}(X) \]
\[ M = \alpha M_c + \beta M_{nc} \]
\[ \text{BIAS} = M_c - M \]
REPLACEMENT CONCEPT: STEPS

1. **USE ALL DATA AVAILABLE ON NONCOMPLIANT INDIVIDUALS**

2. **DEVELOP DISCRIMINANT FUNCTION FROM THIS DATA**

   \[ D = (H_1, H_2, H_3; L_1, L_2) \]

   *"HEALTH FACTORS"*  
   *"LOGISTIC FACTORS"

   \( H_1 = \) SUBJECTIVE HEALTH ASSESSMENT  
   \( L_1 = \) TIME FROM HOME

   \( H_2 = \) CURRENT USE OF LONG-TERM HEALTH CARE  
   \( L_2 = \) TIME FROM WORK

   \( H_3 = \) ABSENTEEISM

3. **THE REPLACEMENT WILL HAVE SAME HEALTH PERCEPTION \((H_1)\) AS THOSE LOST TO STUDY**

4. **OTHER FACTORS \((H_2, H_3, L_1, L_2)\) WILL BE ASSESSED AFTER ENTRY INTO STUDY**
STUDY DESIGN CONSIDERATIONS

- LACK OF MULTIPLE CLINICAL MARKERS OR RECOGNIZED END POINTS
- STUDY BIASES (+ AND -)
- MULTIPLE HERBICIDE ENVIRONMENT; CONFOUNDING VARIABLES
- HERBICIDE ORANGE EXPOSURE NOT QUANTIFIED
- RESPONSE RATES TO QUESTIONNAIRES AND PEs
- PEs MAY DETECT DISQUALIFYING DEFECTS
- VARIABILITY OF DATA
AIR FORCE RANCH HAND STUDY

ACHIEVEMENTS TO DATE

- Comprehensive literature review (2,500)
- Contact established: All leading H.O. experts (5 visits)
- Endorsement by Ranch Hand Association
- 15 M records by computer; 37 K records, hand sort
- Ranch hand group fully identified
- Basic scientific protocol set
- Basic statistical formats and data repository set
UNIQUE FEATURES OF THE PHYSICAL EXAMINATION

- COMPREHENSIVE BY NECESSITY
  - LITERATURE REVIEW
  - VETERANS CLAIMS/CONCERNS

- ESSENTIALLY A STANDARD EXAMINATION WITH EXPANDED EVALUATION OF:
  - BIOCHEMICAL FUNCTION
  - NEUROLOGICAL AND PSYCHOLOGICAL STATUS

- DATA COLLECTED FOR SCIENTIFIC AS WELL AS CLINICAL CONSIDERATIONS
  - ASSESSMENT WITHOUT KNOWLEDGE OF EXPOSURE STATUS
  - STRICT ADHERENCE TO EXAMINATION PROTOCOL
  - HISTORY NOT TAKEN BY THE EXAMINER
  - DATA NOT ANALYZED BY THE EXAMINER
COMPONENTS OF THE MEDICAL EVALUATION

- Comprehensive Medical/Social/Occupational History including a Fertility History of the Subject and His Spouse (s)

- Comprehensive Physical and Laboratory Evaluation with Emphasis on the Target Systems/Conditions