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Young

**EPIDEMIOLOGIC INVESTIGATION OF THE
HEALTH EFFECTS DUE TO**



EPIDEMIOLOGY DIVISION USAFSAM

**HERBICIDE ORANGE EXPOSURE IN
AIR FORCE PERSONNEL**

PEER REVIEW BRIEFING

30 AUG 1979

EXECUTIVE OVERVIEW

PROJECT RANCH HAND II

- PEER REVIEW PROCESS
- PURPOSE OF STUDY
- OPERATIONAL BACKGROUND
- LITERATURE SYNOPSIS
- STUDY GOALS
- EPIDEMIOLOGIC STUDY DESIGN
- PRIMARY DATA COLLECTION METHODS
- STATISICAL METHODOLOGY
- RECOGNIZED STUDY DIFFICULTIES
- SUMMARY

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PROJECT RANCH HAND II

PEER REVIEW PROCESS

- UNIV OF TX, SCH PUBLIC HEALTH JUNE
- AF SCIENTIFIC ADVISORY BOARD AUGUST
- AFEB AUGUST
- NAS SEPTEMBER ?
- VA COMMITTEE SEPTEMBER ?

INDEPENDENCE OF PEER REVIEWS

MODIFICATION OF PROTOCOL, PRN, BETWEEN REVIEWS

3 0 AUG 1979

PROJECT RANCH HAND II

OBJECTIVES OF PEER REVIEW PROCESS

- **ENHANCE SCIENTIFIC VALIDITY**
- **IMPROVE CREDIBILITY, LAY & SCIENTIFIC**

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PROJECT RANCH HAND II

PEER REVIEW MECHANICS

- WRITTEN PROTOCOL, KEY REFERENCES PROVIDED BY AF
- BRIEFING FOR AMPLIFICATION DIALOGUE: COPY PROVIDED BY AF
- WRITTEN RESPONSE TO PROTOCOL BY REVIEW GROUP ~ 1 WK
- AF RESPONSE TO CRITIQUE, PRN, ~ 1 WK
- WRITTEN REBUTTAL BY REVIEW GROUP, PRN, ~ 1 WK
- UNRESOLVED ISSUES PRESENTED AT NEXT PEER REVIEW

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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

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BACKGROUND

AIR FORCE INVOLVEMENT

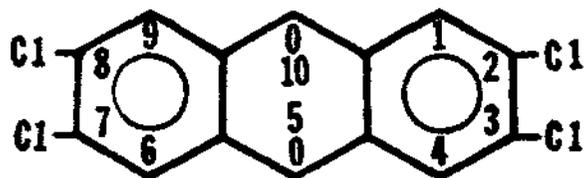
- **1940's RESEARCH AND DEVELOPMENT**
- **OPERATION RANCH HAND: VIETNAM EXPERIENCE**
 - **1962-65 HIGH CONCENTRATION TCDD (PURPLE)**
 - **1965-70 LOW CONCENTRATION TCDD (ORANGE)**
- **OCT 1969 - USE RESTRICTED TO NON-POPULATED AREAS**
- **APR 1970 - ALL USES OF ORANGE HALTED**
- **FEB 1971- PACER IVY- HERBICIDE REMOVED FROM VIETNAM**
- **1977-PACER HO-STOCKS INCINERATED AT SEA**

HERBICIDE ORANGE

N-BUTYL ESTER	2, 4-D	49.4%
FREE ACID	2, 4-D	0.1%
N-BUTYL ESTER	2, 4, 5-T	48.8%
FREE ACID	2, 4, 5-T	1.0%
BUTYL ALCOHOL AND ESTER MOIETIES		0.7%
MEAN TCDD CONTENT OF FORMULATION (500 SAMPLES)		2 PPM
RANGE OF TCDD CONTENT		< 0.02 - 15 PPM

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2, 3, 7, 8-TETRACHLORODIBENZO-p-DIOXIN (TCDD)



- **MOLECULAR WEIGHT** 321.8935
- **MELTING POINT** 303-305°C
- **DECOMPOSITION POINT** 980-1,000°C
- **SOLUBILITY, GRAMS/LITER**

ORTHO-DICHLOROBENZENE	1.40
CHLOROBENZENE	0.72
ORANGE HERBICIDE	0.58
BENZENE	0.57
CHLOROFORM	0.37
ACETONE	0.11
METHANOL	0.01
WATER	2×10^{-7}

INTRODUCTION TO ANIMAL STUDIES

COMPARISON OF STUDIES IS DIFFICULT DUE TO VARIATIONS IN EXPERIMENTAL DESIGN

SPECIES

AGE

SEX

LEVEL, ROUTE, & LENGTH OF EXPOSURE

PURITY OF CHEMICALS

CRITERIA MEASURED

TIMING OF DATA COLLECTION

NEVERTHELESS, ANIMALS HAVE SHOWN A WIDE RANGE OF TOXIC EFFECTS THAT MUST BE ANTICIPATED IN THE DESIGN OF HUMAN STUDIES

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PHARMACOKINETICS OF PHENOXY HERBICIDES

(IN HUMANS)

- RAPID ABSORPTION AND COMPLETE DISTRIBUTION
- BIOLOGICAL HALF-LIFE: 2,4-D - 33 HOURS
 2,4,5-T - 18 HOURS
- MAJORITY EXCRETED UNMETABOLIZED VIA URINE
- ACCUMULATION AFTER REPEATED LOW DOSES IS UNDOCUMENTED

PHARMACOKINETICS OF 2,4,5-T

- MARKED VARIATIONS IN PHARMACOKINETICS IN LITERATURE SECONDARY TO SPECIES, AGE, DOSE LEVELS, ROUTE OF ADMINISTRATION AND CHEMICAL FORMULATION
- GENERALLY, READILY ABSORBED AND DISTRIBUTED
- EXCRETION IS PRIMARILY VIA THE KIDNEYS, MAJORITY UNMETABOLIZED
- CLEARANCE RATE IS QUITE VARIABLE AND DOSE -DEPENDENT
- TISSUE ACCUMULATION OCCURS WITH REPEATED LOW DOSES

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PHARMACOKINETICS OF TCDD

- MOST DATA DERIVED FROM ANIMAL MODELS
- ABSORBED RELATIVELY COMPLETELY IN INTESTINES
- MAJORITY REMAINS UNMETABOLIZED IN LIVER MICROSOMES
- LIVER AND ADIPOSE TISSUE ACCUMULATE THE MAJORITY OF TCDD
- BIOLOGICAL HALF-LIFE RANGES FROM 12 TO 24 DAYS (INDIRECT MEASURE)
- MAJOR ROUTE OF EXCRETION IS THE FECES (>> URINE)

IMPLICATIONS

- IF LOW DOSES ARE THE MAJOR MODE OF TOXICITY, THEN A DELAYED RECRUDESCENCE OF TCDD FROM ADIPOSE TISSUE WITH WEIGHT LOSS COULD POSSIBLY RESULT IN A DOSE-RESPONSE PARADOX
- THE LIVER IS THE ORGAN WHERE DIRECT EFFECTS OF TCDD WOULD BE MOST LIKELY TO OCCUR (HIGH-DOSE EFFECTS)

PROPOSED MECHANISMS OF ACTION OF TCDD

INDUCTION OF MICROSOMAL ENZYMES

- CUTANEOUS PORPHYRIA
- CARCINOGENESIS/TUMORIGENESIS
- PROTECTION AGAINST ENDOCRINE TUMORS
- NEUROPATHY
- CHLORACNE

DIOXIN "INTERCALATION" WITH DNA

- MUTAGENIC
- TERATOGENIC
- CARCINOGENIC
- CHLORACNE

TOXICITY

- CELLULAR POISONING
- IMMUNE SUPPRESSION

SUMMARY OF 2,4-D, 2,4,5-T, AND TCDD ANIMAL STUDIES

	2,4-D	2,4,5-T	TCDD
LD ₅₀ RANGE (ACUTE)	100-1000 mg/kg	100-1000 mg/kg	1-1000 μg/kg
CHRONIC TOXIC DOSE	APPROACHES ACUTE RAPID CLEARANCE	<1/2 ACUTE VARIABLE CLEARANCE	MARKEDLY LOWER ACCUMULATION EFFECT
SIGNS OF ACUTE/ CHRONIC TOXICITY	ANOREXIA	ANOREXIA	WEIGHT LOSS
	WEIGHT LOSS	ATAXIA	INVOLUTION OF THYMUS
	MUSCULAR WEAKNESS	G.I. INJURY	ALOPECIA
	IRRITATED G.I. TRACT	LIVER CONGESTION	EPITHELIAL CHANGES
	MINOR LIVER INJURY	KIDNEY CONGESTION	LIVER LESIONS (VARIABLE)
	MINOR KIDNEY INJURY		HYPOTHYROIDISM
	MINOR LUNG CONGESTION		

SUMMARY OF 2, 4-D, 2, 4,5-T, AND TCDD ANIMAL STUDIES (CONT)

	2,4-D	2,4,5-T	TCDD
EMBRYO TOXIC DOSE	APPROACHES TOXIC MATERNAL LEVELS	APPROACHES TOXIC MATERNAL LEVELS	MARKEDLY BELOW TOXIC MATERNAL LEVELS
TERATOGENICITY	QUESTIONABLE	*LOW INCIDENCE ONLY IN MICE (CLEFT PALATES & DILATED RENAL PELVIS)	SPECIES VARIATIONS YES MICE NO RATS
CARCINOGENICITY	QUESTIONABLE WEAK AT BEST	ONE STUDY YES NUMEROUS STUDIES NO	EPITHELIAL CHANGES IN PRIMATES; YES IN RATS

*TCDD CONTAMINATION OF 2,4,5-T HAS BEEN SHOWN TO BE A CONTRIBUTOR TO TERATOGENIC EFFECT IN MICE

CLINICAL SYNDROME IN NONHUMAN PRIMATES

EXPOSED TO TCDD

QUANTITATIVE DIFFERENCES: ACUTE HIGH-LEVEL VS CHRONIC LOW-LEVEL

SEQUENCE

- LOSS OF BODY WEIGHT
- CUTANEOUS SYNDROME
- ACNEFORM ERUPTIONS AND BLEPHARITIS
- KERATINACEOUS FILLING OF EXTERNAL AUDITORY CANAL

CLINICAL SYNDROMES (CONT)

- SKIN DRY AND SCALY; LOSS OF NAILS
- PROGRESSIVE WEAKNESS, BUT ALERT
- CHRONIC, NON-LETHAL EXPOSURES CAUSE REPRODUCTIVE DIFFICULTIES IN FEMALES
- FEMALES AND NEONATES MORE SENSITIVE
- IN MOST SPECIES, ORGANS SHOW COMMONALITY OF LESIONS

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CLINICAL SYNDROMES (CONT)

- CUTANEOUS AND GASTROINTESTINAL LESIONS SPECIFIC TO MONKEY
- MONKEY RETAINS MORE DOSE IN SKIN
- EXCRETION VIA KIDNEY HIGHER IN MONKEY THAN RAT
- TISSUE DESTRUCTION INSUFFICIENT TO CAUSE DEATH
- IMMUNE SYSTEM LESIONS MAY CAUSE SECONDARY DISEASE SYNDROME

ENVIRONMENTAL FATE

	<u>HERBICIDE ORANGE</u>	<u>(TCDD)</u>
1. WATER SOLUBILITY	LOW (ESTER) MODERATE (ACID)	NEGLECTIBLE
2. VOLATILIZATION	RAPID (HOURS)	RAPID (HOURS)
3. PHOTODEGRADATION	SLOW (DAYS)	RAPID (HOURS)
4. SOIL PERSISTENCE	T $\frac{1}{2}$ = 1-3 MONTHS	T $\frac{1}{2}$ = 1-3 YEARS
5. PLANT-ABSORPTION	RAPID (HOURS)	NEGLECTIBLE
6. PLANT-METABOLISM	RAPID (DAYS)	NEGLECTIBLE
7. ANIMAL- ABSORPTION	READILY ABSORBED	BIOACCUMULATION IN FAT/LIVER
8. ANIMAL-METABOLISM	T $\frac{1}{2}$ = 2-10 DAYS (METABOLIZED & EXCRETED)	T $\frac{1}{2}$ = 3-16 WEEKS (METABOLIZED?)

RANCH HAND II

SUMMARY CHARACTERISTICS OF VETERANS CLAIMS SUBMITTED AS OF 30 APRIL 1979

TOTAL NUMBER OF REVIEWED CLAIMS: 361

SEX: 100% MALE (64% IDENTIFIED)

MEAN AGE: 34 YEARS (96.1% IDENTIFIED)

MEAN NUMBER OF SYMPTOMS PER VETERAN: 2.3

BRANCH OF SERVICE: (66.8% IDENTIFIED)

US ARMY	66.4%
US MARINE CORPS	17.4%
US AIR FORCE	11.2%
US NAVY	5.0%

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RANCH HAND II

PERCENT OF VETERANS SUBMITTING CLAIMS BY SIGN/SYMPTOM CATEGORY AS OF 30 APRIL 1979

CATEGORY	PERCENT
DERMATOLOGIC	48.9
PSYCHIATRIC	27.6
EAR, NOSE & THROAT	14.4
CANCER	13.8
PERIPHERAL NEUROPATHY	12.1
ASTHENIA	11.2
GASTROINTESTINAL	10.9
REPRODUCTIVE	10.1
OTHERS	< 10

N = 361 - 13 = 348 CLAIMS

NOTE: 13 CLAIMS ALLEGED "EXPOSURE" ONLY

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SUMMARY OF COMPLETED CASE AND EPIDEMIOLOGICAL STUDIES

	<u>SCOPE/FINDINGS</u>	<u>COMMENTS</u>
BERKLEY AND MAGEE (1963)	NEUROPATHY FOLLOWING EXPOSURE TO 2,4,-D	• 1ST DESCRIPTION OF NEUROPATHY
BRANDT (1971)	HERBATOX POISONING	• EXCELLENT LITERATURE REVIEW • GOOD EXAMPLE OF TYPICAL SYMPTOMS
JIRASEK, ET AL (1973,1974)	ACNE CHLORINA AND PORPHYRIA	• GOOD HISTORICAL REVIEW • 78 CASES ARE PRESENTED IN DETAIL
BLEIBERG (1964)	INDUSTRIALLY ACQUIRED PORPHYRIA	• 1ST DISCUSSION OF PORPHYRIA TO EXPOSURE
CROW (1978)	CHLORACNE: THE CHEMICAL DISEASE	• EXCELLENT REVIEW OF CHLORACNE
OLIVER (1975)	TOXIC EFFECTS OF TCDD	• ALLEGED SYSTEMIC SYMPTOMS WITHOUT PRIOR CHLORACNE
POLAND, ET AL (1971)	A HEALTH SURVEY OF WORKERS IN A 2,4-D/2,4,5-T PLANT	• ASSOCIATED ABNORMAL MMPI SCORE WITH EXPOSURE • CHLORACNE DISCUSSION

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SUMMARY OF COMPLETED CASE AND EPIDEMIOLOGICAL STUDIES

(cont.)

	<u>SCOPE/FINDINGS</u>	<u>COMMENTS</u>
KRAMER (1970)	HEALTH OF EMPLOYEES EXPOSED TO 2, 4, 5-T	• NO LONG TERM HEALTH EFFECTS ATTRIBUTABLE TO EXPOSURE
EPA (1979)	ALSEA OREGON STUDY	• ANALYSIS OF EARLY ABORTIONS IN OREGON • FOUND ASSOCIATION BETWEEN 2,4,5-T USE AND INCREASED INCIDENCE OF HOSPITALIZED ABORTION • SUBJECT OF SEVERE SCIENTIFIC CRITICISM
HOMBERGER (1979)	THE SEVESO ACCIDENT	• NO LONG TERM SYSTEMIC HEALTH EFFECTS DESPITE HIGH LEVEL EXPOSURE AND CHLORACNE • NO INCREASE IN SPONTANEOUS ABORTIONS OR MALFORMATIONS
ALDRED (1978)	CONGENITAL ANOMALIES STUDY (AUSTRALIA)	• NO MALFORMATIONS ATTRIBUTABLE TO HERBICIDE USE

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SUMMARY OF COMPLETED CASE AND EPIDEMIOLOGICAL STUDIES

(cont.)

	<u>SCOPE FINDINGS</u>	<u>COMMENTS</u>
TUNG (1973)	LIVER CANCER IN VIETNAM	<ul style="list-style-type: none">• ABNORMAL INCREASE IN PRIMARY CARCINOMA OF THE LIVER• INSUFFICIENT DATA FOR VERIFICATION
HARDELL & SANDSTROM (1978)	SOFT TISSUE SARCOMAS AND CHLOROPHENOL EXPOSURE	<ul style="list-style-type: none">• SIX-FOLD INCREASE IN SOFT TISSUE SARCOMAS• STATISTICAL METHODS WEAK• NO CONTROL OF CONFOUNDING IN THE ANALYSIS
POCCHIARI et. al. (1979)	SEVESO PROGRESS REPORT	<ul style="list-style-type: none">• CHLORACNE• POSSIBLE INCREASE IN NEUROPATHY

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SUMMARY OF MAJOR EPIDEMIOLOGIC STUDIES IN PROGRESS

SCOPE

SEVESO, ITALY

DERMATOLOGICAL STUDY OF 32,000 CHILDREN AND CLINICAL STUDIES OF 1,024 PERSONS (ALL AGES, BOTH SEXES) EXPOSED TO TCDD IN JULY 1976.

NITRO, WEST VIRGINIA

FORTY-YEAR FOLLOW-UP OF 228 PEOPLE (WORKERS & FAMILIES) EXPOSED TO TCDD IN 1949.

DOW CHEMICAL COMPANY,
MIDLAND MICHIGAN

LONG TERM HEALTH STUDY OF 204 MALE EMPLOYEES OF 2,4,5-T PLANT

DOW CHEMICAL COMPANY,
MIDLAND MICHIGAN

FERTILITY/REPRODUCTIVE STUDY OF WIVES OF WORKERS IN 2,4,5-T PLANT

CZECHOSLOVAKIA

TEN YEAR STUDY OF 80 MALES OCCUPATIONALLY EXPOSED TO TCDD IN 1965-68.

NATIONAL CANCER INSTITUTE

CASE CONTROL STUDY (MORTALITY) OF 4,500 NON-AGRICULTURAL PESTICIDE APPLICATORS IN FLORIDA

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SUGGESTED ATTRIBUTABLE SYMPTOMS OF HERBICIDE/TCDD IN HUMANS

2,4-D	2,4,5-T (+TCDD)	TCDD
		• CHLORACNE
	• PORPHYRIA	• PORPHYRIA
	• HYPERPIGMENTATION	• HYPERPIGMENTATION
• ASTHENIA	• ASTHENIA	• ASTHENIA
• PERIPHERAL NEUROPATHY	• PERIPHERAL NEUROPATHY	• PERIPHERAL NEUROPATHY
• SWEATING/FEVER		
• CARDIAC DISTURBANCE	• CARDIAC DISTURBANCE	• CARDIAC DISTURBANCE
• RENAL DYSFUNCTION		
• LIVER DYSFUNCTION	• LIVER DYSFUNCTION	• LIVER DYSFUNCTION
• GI DISTURBANCE	• GI DISTURBANCE	• GI DISTURBANCE
• HEADACHE		
• PNEUMONITIS		
		• HYPOTHYROIDISM
• CSF PROTEIN ABNORMALITIES		• HEARING/SMELL DISTURBANCES
• CONVULSIONS		

COMPONENTS OF SELECTED HUMAN SYMPTOM/SIGNS FOLLOWING EXPOSURE TO PHENOXY HERBICIDES AND/OR TCDD

NEURO-PSYCHIATRIC ABNORMALITIES

ASTHENIA

ANXIETY
DEPRESSION
FATIGUE
APATHY
LOSS OF DRIVE
LIBIDO
IMPOTENCY
SLEEPLESSNESS
EMOTIONAL INSTABILITY
ANOREXIA
DIZZINESS
↓ LEARNING ABILITY

PERIPHERAL NEUROPATHY

HYPOREFLEXIA
WEAKNESS
PARESTHESIAS
EXTREMITY NUMBNESS
MYALGIA
GAIT DISTURBANCE
"MILD" PARESIS

DERMATOLOGIC DISEASE

CHLORACNE
PORPHYRIA CUTANEA TARDA
HYPERPIGMENTATION
HIRSUTISM (BODY)
ALOPECIA OF THE SCALP

COMPONENTS OF SELECTED HUMAN SYMPTOM/SIGNS FOLLOWING EXPOSURE TO PHENOXY HERBICIDES AND/OR TCDD (CONT'D)

OTHER DISORDERS

HEPATIC DYSFUNCTION

CHOLESTEROL
SGOT , SGPT, LDH

RENAL DYSFUNCTION

PROTEINURIA
OUTPUT
TUBULAR DEGENERATION
GLOMERULAR DEGENERATION
RENAL GLUCOSURIA

GI DISTURBANCE

NAUSEA
VOMITING
DIARRHEA
GASTRITIS
ABD PAIN
FLATULENCE

CARDIAC DISTURBANCE

BRADYCARDIA
TACHYCARDIA
ATRIAL FIBRILLATION

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) ?

SCIENTIFIC PREMISE

THE SCIENTIFIC THRUST OF PROJECT RANCH HAND II IS TO DEFINE THE NATURAL HISTORY OF DISEASE, IF ANY, AND ITS SPECTRUM OF ILLNESS, BY DIRECT AND INDIRECT METHODOLOGY.

GOALS OF STUDY

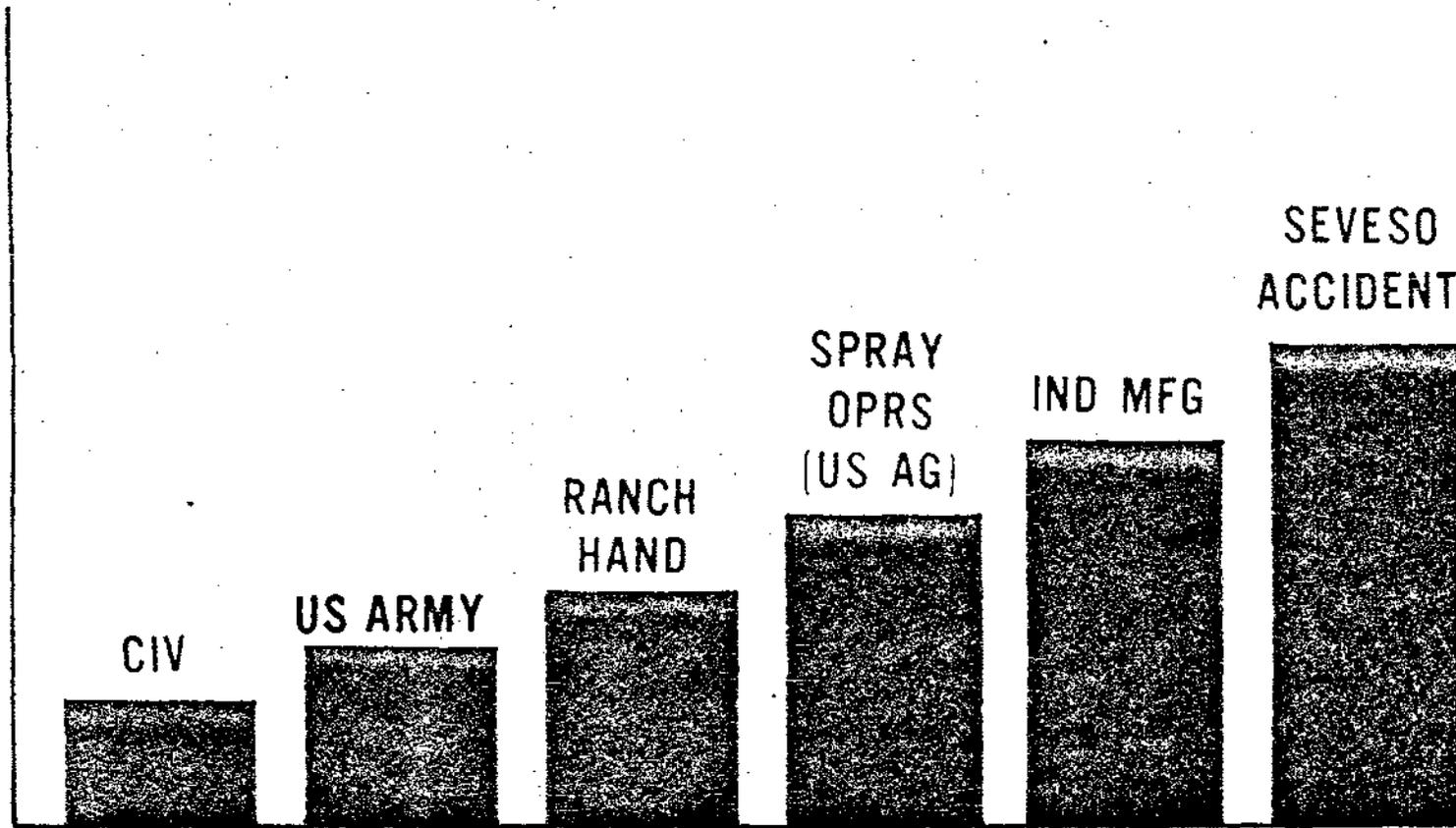
PREMISE: GOALS ARE INTERDEPENDENT

1. ASSESS HEALTH EFFECTS — — — — — HEALTH
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 — — — — — LEGAL

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ANTICIPATED DOSE-RESPONSE RELATIONSHIP BY POSSIBLE STUDY POPULATIONS

PROBABLE
ADVERSE
HEALTH
EFFECTS
ACUTE
CHRONIC



PROBABLE EXPOSURE TO TCDD



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OPERATING ASSUMPTION

- OPERATION RANCH HAND PERSONNEL MAY HAVE BEEN EXPOSED TO 2,4,5-T AND TCDD TO A HIGHER DEGREE THAN US ARMY GROUND PERSONNEL

IMPLYING THAT RANCH HAND PERSONNEL SHOULD DEVELOP MORE ACUTE/CHRONIC CLINICAL SYMPTOMS FROM THE EXPOSURES, AND SHOULD MANIFEST THEM SOONER THAN THE US ARMY PERSONNEL

EPIDEMIOLOGIC APPROACH

● "RETROSPECTIVE" PHASE

● PROSPECTIVE

● CROSS-SECTIONAL STUDY

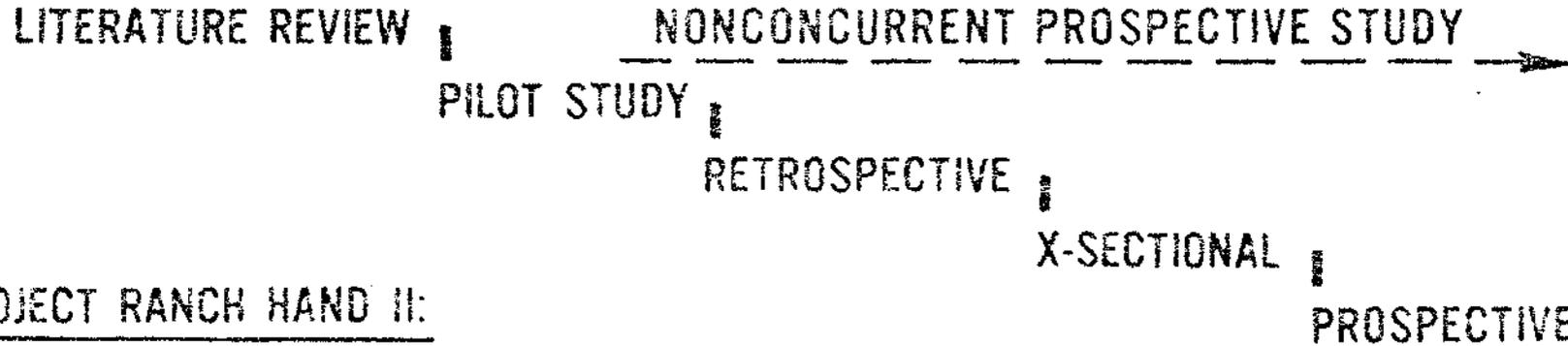
"NONCONCURRENT"
PROSPECTIVE STUDY

THREE PHASE APPROACH REQUIRED

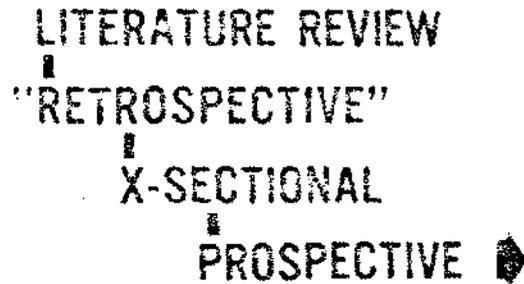
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EPIDEMIOLOGIC STUDY DESIGN

CLASSIC APPROACH:



PROJECT RANCH HAND II:



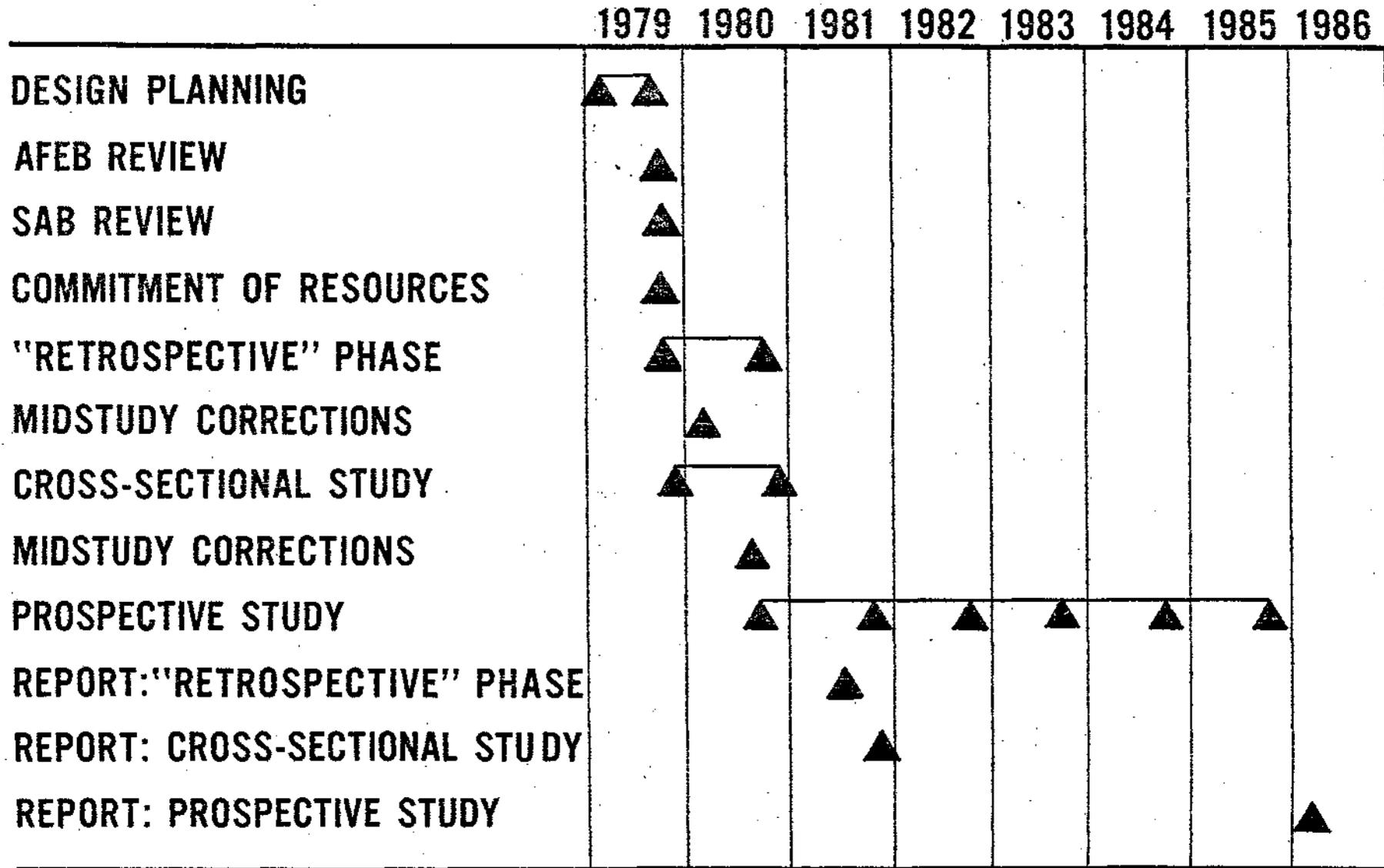
PROBLEMS:

- TIME COMPRESSION OF STUDY ELEMENTS
- DISEASE STATE, IF ANY, NOT DEFINED
- BIASES

REQUIREMENTS:

- "MEANINGFUL DATA" IN 1 YEAR
- START DATE: 15 OCT 79
- ID OF ALL PERSONS SIGNIFICANTLY AT RISK
- PE OF ALL PROBABLE/ACTUAL "CASES"

PROJECT RANCH HAND ANTICIPATED TIMING



RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN
GROUP SELECTION, RATIONALE

PRIMARY EXPOSED GROUP

**C-123 RANCH HAND;
CREW+SUPPORT**



CONTROL GROUP
NOT EXPOSED TO H.O.

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

HELICOPTER CREWS

SECONDARY MAINTENANCE PERSONNEL

EXPERIMENTAL SPRAY UNITS

ARMY OBSERVERS

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

EPIDEMIOLOGIC STUDY DESIGN
COMPARISON OF THE STUDY GROUP TO POSSIBLE CONTROL
GROUPS BY KNOWN AND ESTIMATED FACTORS

<u>KNOWN FACTORS</u>	<u>STUDY GROUP</u>		<u>POSSIBLE CONTROL GROUPS</u>	
	<u>RANCH HAND C-123</u>	<u>NONRANCH HAND C-123</u>	<u>C-7</u>	<u>C-130</u>
POPULATION SIZE	800-1200	3000	1200	20,000- 25,000
OFFICER/ENLISTED CREW RATIO	2:1	2:1	2:1	3:2
AIRCRAFT FUEL (AV-GAS)	YES/NO*	YES	YES	NO (JP-4)
OCCUPATIONAL HERBICIDE EXPOSURE	YES	YES/NO**	NO	NO
<u>ESTIMATED FACTORS</u>				
OCCUPATIONAL INSECTICIDE EXPOSURE	2+	1+ TO 4+	0	0
COMBAT HAZARD	4+	3+	3+	2+
RVN-IN COUNTRY ASSIGNMENT	4+	4+	4+	2+

* IN 1968, AIRCRAFT MODIFIED WITH JP-4 BOOSTERS

** CONTAMINATED AIRCRAFT FREQUENTLY RECONFIGURED FOR TRANSPORT USE BY NONRANCH HAND CREWS.

RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN
SOME KNOWN/ESTIMATED POPULATION PARAMETERS

	<u>EXPOSED GROUP (C-123)</u>	<u>CONTROL GROUP (C-130)</u>
AGE RANGE:	28-58	25-65
SEX:	ALL MALE	ALL MALE
RACE:	OFFICER: ~ 100% WHITE ENLISTED: ~ 10-14% BLACK	~ 100% WHITE ~ 10-14% BLACK
CURRENT ACTIVE DUTY:	25% OFFICER: SENIOR MANAGEMENT ENLISTED: MIDDLE MANAGEMENT	20-25% SENIOR MANAGEMENT MIDDLE MANAGEMENT
PAST SERVICE EMPLOYMENT:	AEROSPACE INDUSTRY	AEROSPACE INDUSTRY
SOCIOECONOMIC:	SIMILAR TO CONTROL	SIMILAR TO STUDY
GENERAL LIFESTYLE:		

FEASIBILITY FOR IDENTIFYING AIRCRAFT MAINTENANCE PERSONNEL (TOTAL POPULATION) EXPOSED TO HERBICIDE ORANGE

TIME	PRIMARY MAINTENANCE PERSONNEL ¹	SECONDARY MAINTENANCE PERSONNEL ²
JAN 1962 - JUL 1964	YES	NO
AUG 1964 - DEC 1966	YES/NO	NO
JAN 1967 - APR 1970	YES	NO

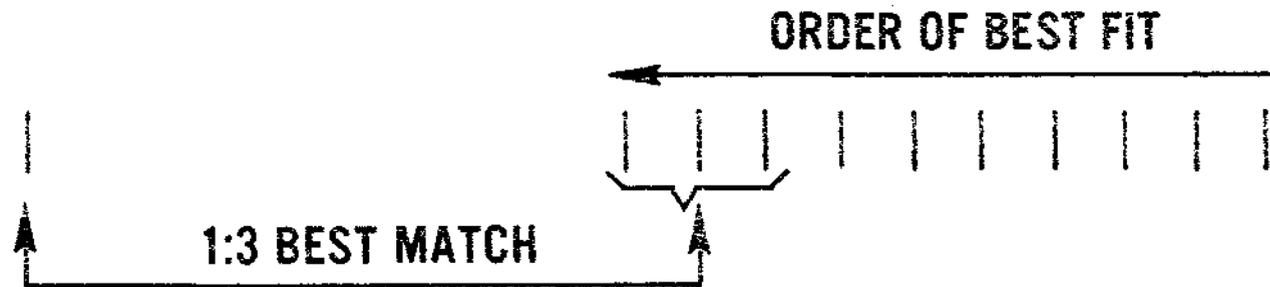
¹ INDIVIDUAL ASSIGNED TO RH; DENOMINATOR KNOWN

² INDIVIDUAL NOT ASSIGNED SPECIFICALLY TO RH, ALTHOUGH MAY HAVE SERVICED THE AIRCRAFT; DENOMINATOR NOT ASCERTAINABLE

SELECTION PROCEDURE FOR MORTALITY ANALYSIS

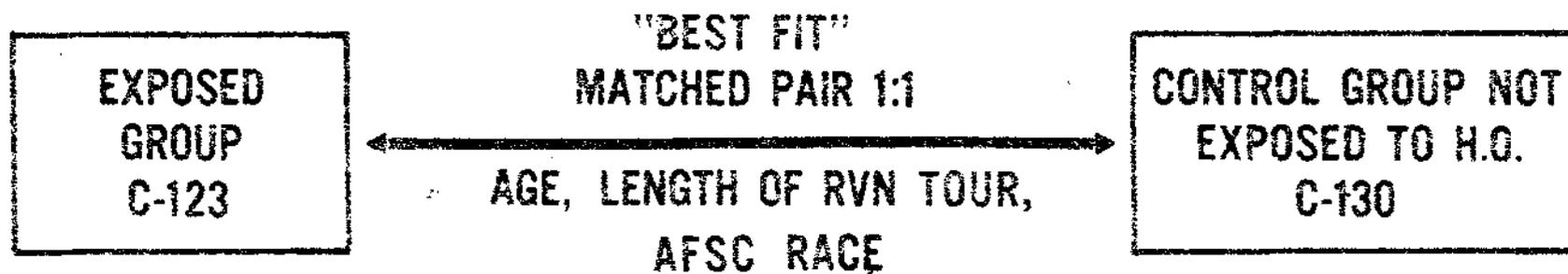
RANCH HAND INDIVIDUAL

CONTROL INDIVIDUALS



RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN
RATIONALE FOR MATCHING PROCEDURE

INTER-GROUP COMPARISON:



◆ **MATCHING PROCEDURE RATIONALE:**

- EACH EXPOSED PERSON WILL HAVE A RANKED SET OF POSSIBLE CONTROLS, SELECTED ON BEST FIT BASIS: CONTROL REPLACEMENT
- ALLOWS STATISTICAL INTER-GROUP TESTS WITHOUT MAJOR ADJUSTMENTS
- PROVIDES BETTER FLEXIBILITY FOR MULTIVARIATE TESTING

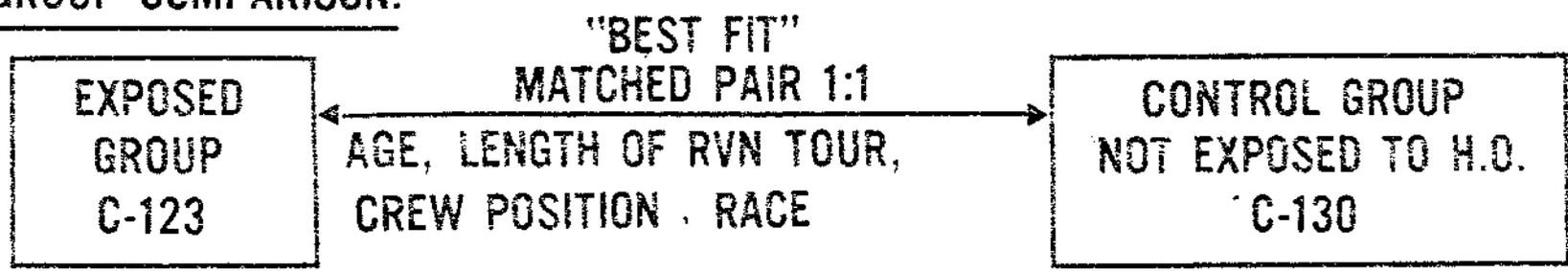
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RANCH HAND II

EPIDEMIOLOGIC STUDY DESIGN

RATIONALE FOR MATCHING PROCEDURE

INTER-GROUP COMPARISON:



PRIORITIZED MATCHING VARIABLES: RATIONALE

- AGE CLOSEST MONTH CONTROLS FOR ANY AGE-DEPENDENT EFFECTS
- AFSC: CONTROLS OFFICER-ENLISTED RATED-NON RATED STATUS.
I.E., SOCIOECONOMIC MATCH
- RACE: CAUCASION/NON-CAUCASION : CULTURAL BACKGROUND, SKIN RASH DX, ETC.
- LENGTH OF RVN TOUR (FLYING HOURS): CONTROLS COMBAT MORBIDITY/MORTALITY AND NEURO-PSYCH EFFECTS

INTRA-GROUP COMPARISON:

UTILIZE LENGTH OF TOUR (FLYING HOURS) + PRE-POST 1965 (CONC. OF TCDD 100-FOLD CHANGE) TO CONSTRUCT EXPOSURE INDEX VARIABLE FOR COMPARISON WITH HEALTH EFFECTS IN EXPOSED GROUP

VIETNAM EXPOSURE INDEX (E_I)

INTRAGROUP COMPARISON

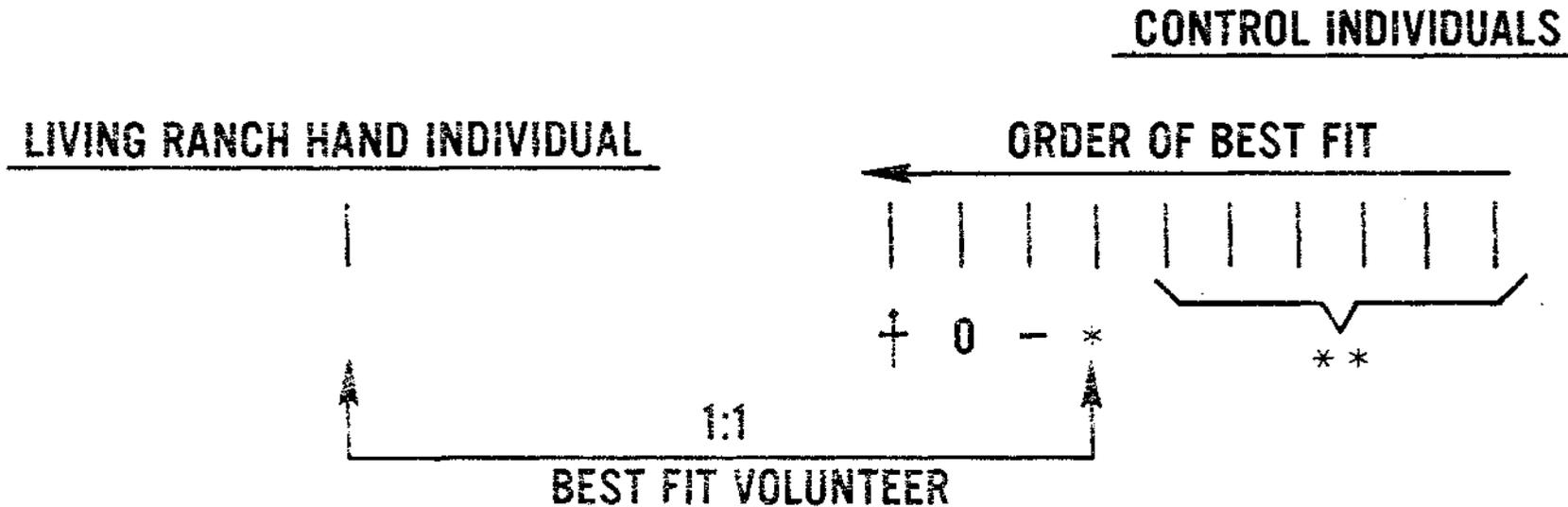
$$E_I = (\text{TIME IN VIETNAM} \times \text{MEAN TCDD CONC. [YR ADJ]}) \times \\ (\text{EXPOSURE EST. BY CREW POSITION}) (\text{EXPOSURE ROUTE SCORE}) \times \\ (\text{EXPOSURE HISTORY [QUEST.] SCORE})$$

PLAN: NORMALIZE STATISTIC

CONDUCT REGRESSION/STRATIFICATION TESTS TO HEALTH
EFFECTS DATA

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SELECTION PROCEDURE FOR THE QUESTIONNAIRE, PHYSICAL EXAMINATION, AND PROSPECTUS

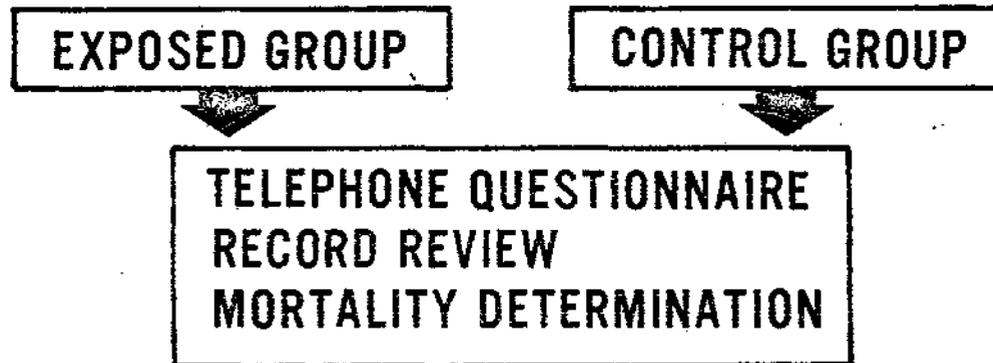


- † DEAD
- 0 UNACCOUNTED
- UNWILLING
- * VOLUNTEER
- * * REPLACEMENT CANDIDATES

RANCH HAND II

EPIDEMIOLOGIC STUDY DESIGN

RATIONALE: DATA COLLECTION, SELECTION PROCEDURES



PROCEDURES :

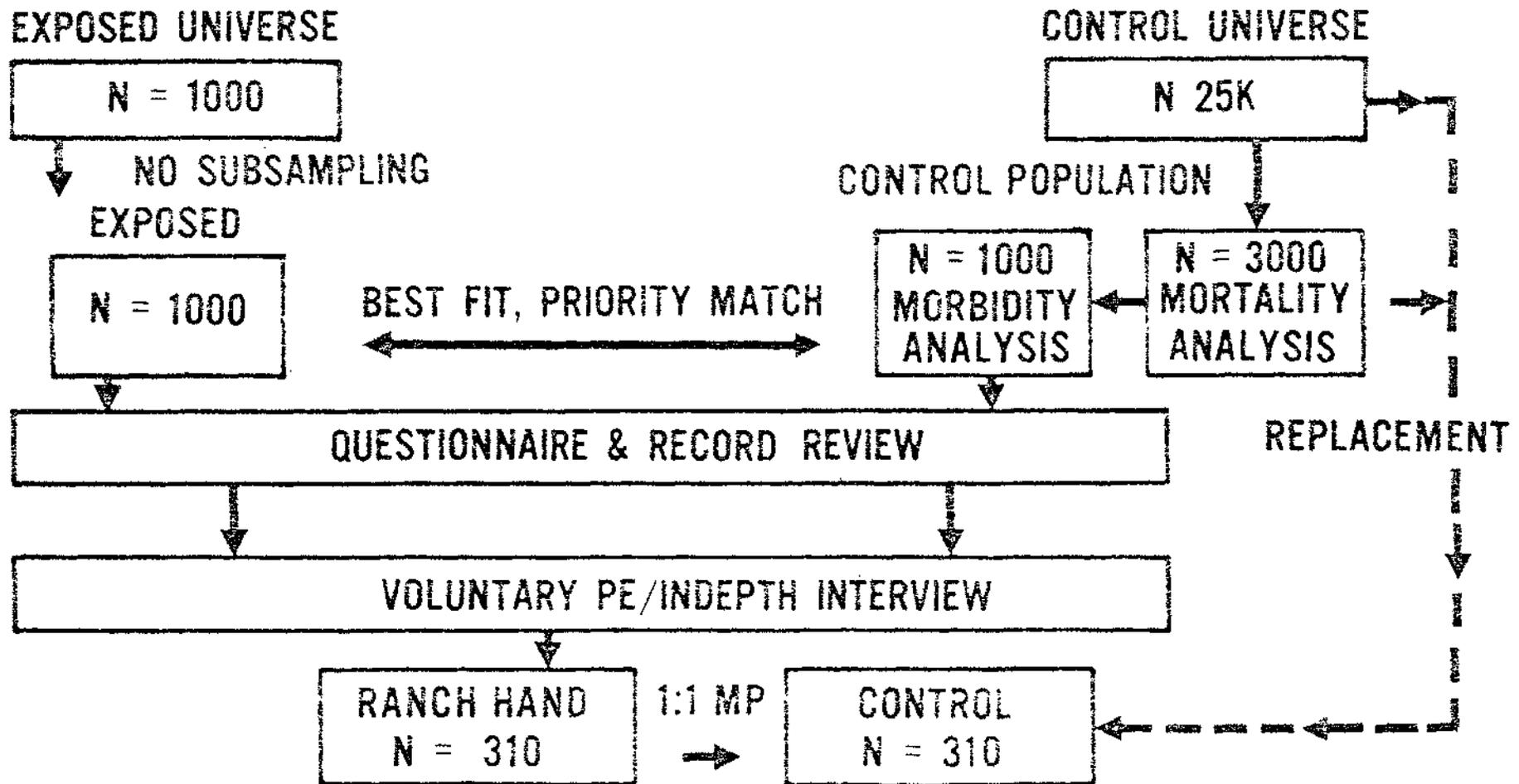
RATIONALE LITERATURE REVIEW: DEVELOP PROBABLE "DISEASE" SYMPTOM COMPLEX FOR CROSS REFERENCE

- **QUESTIONNAIRE : IDENTIFY HIGH RISK POPULATION AND/OR "DISEASE"**
 - TELEPHONE QUESTIONNAIRE : ATTEMPT TO CONTROL ± RESPONSE BIAS**
 - TRAINED INTERVIEWERS: ATTEMPT TO CONTROL OBSERVER VARIATION**
- **HEALTH RECORD REVIEWS: ATTEMPT TO CONTROL ± RESPONSE BIAS**
- **DEATH CERTIFICATE REVIEWS, BOTH GROUPS: DEFINE MORTALITY PARAMETERS, EACH GROUP**

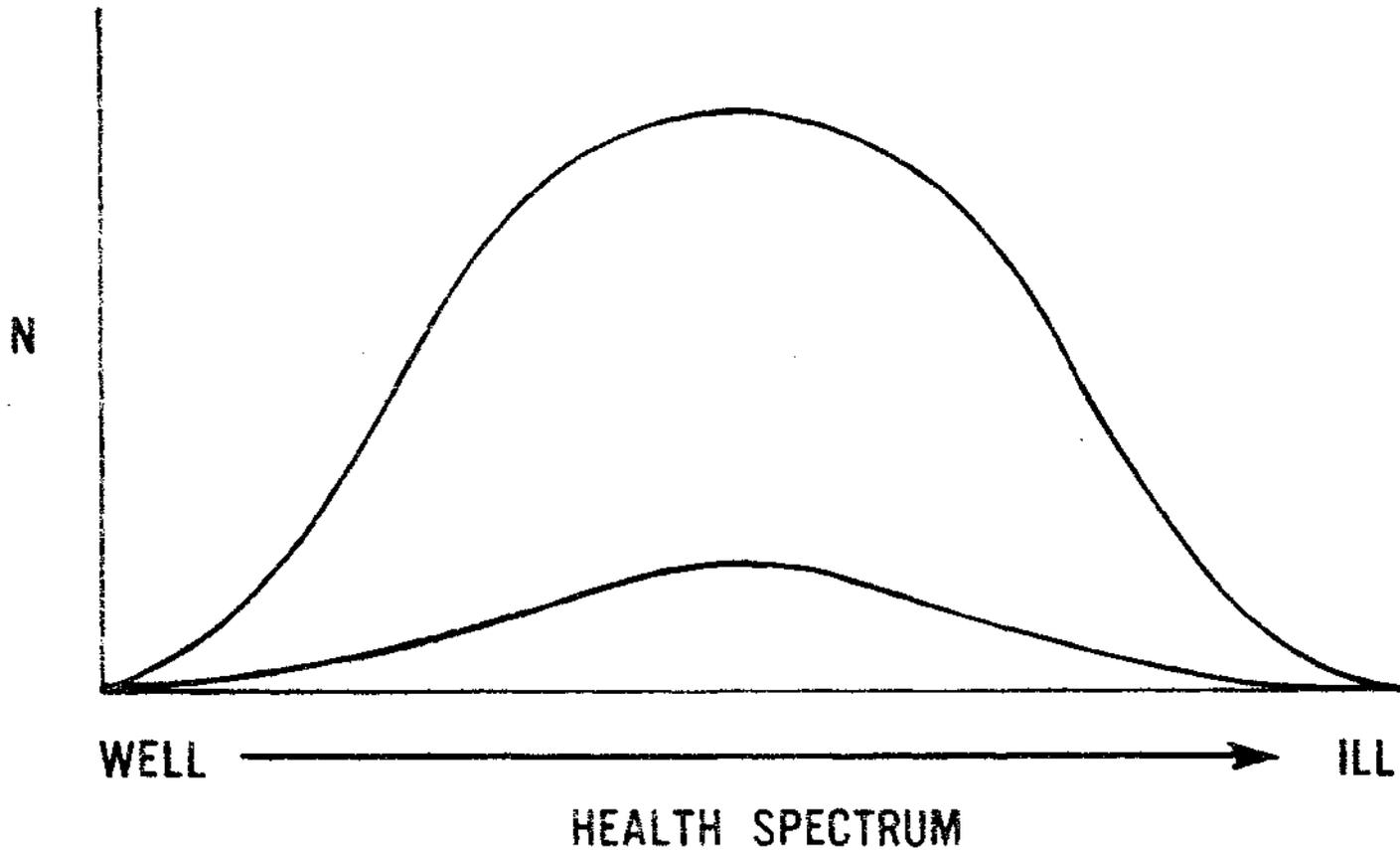
RANCH HAND II

EPIDEMIOLOGIC STUDY DESIGN

ESTIMATE AND MAINTENANCE OF SAMPLE SIZES

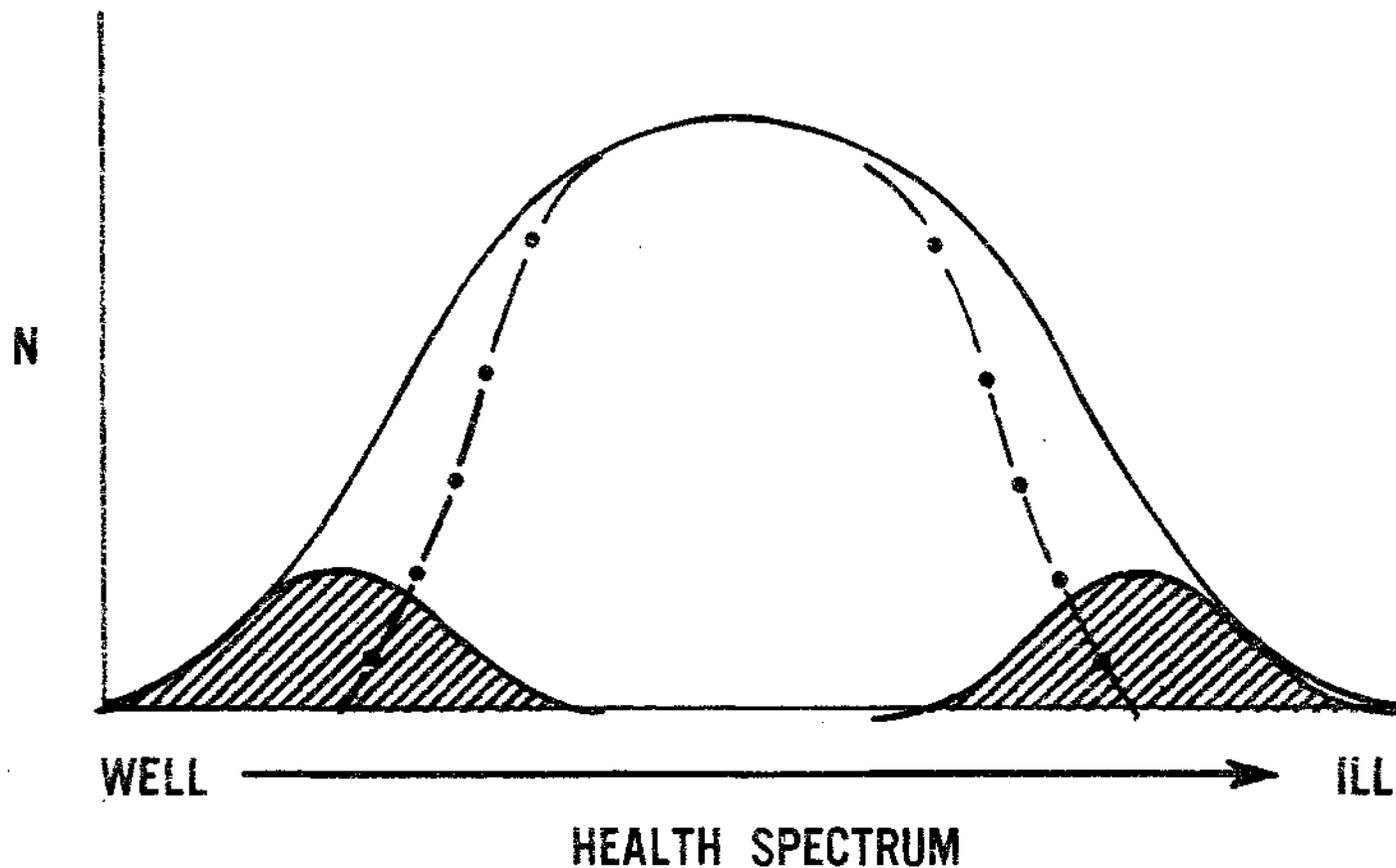


EFFECT OF RANDOM LOSS TO STUDY IN THE CONTROL POPULATION



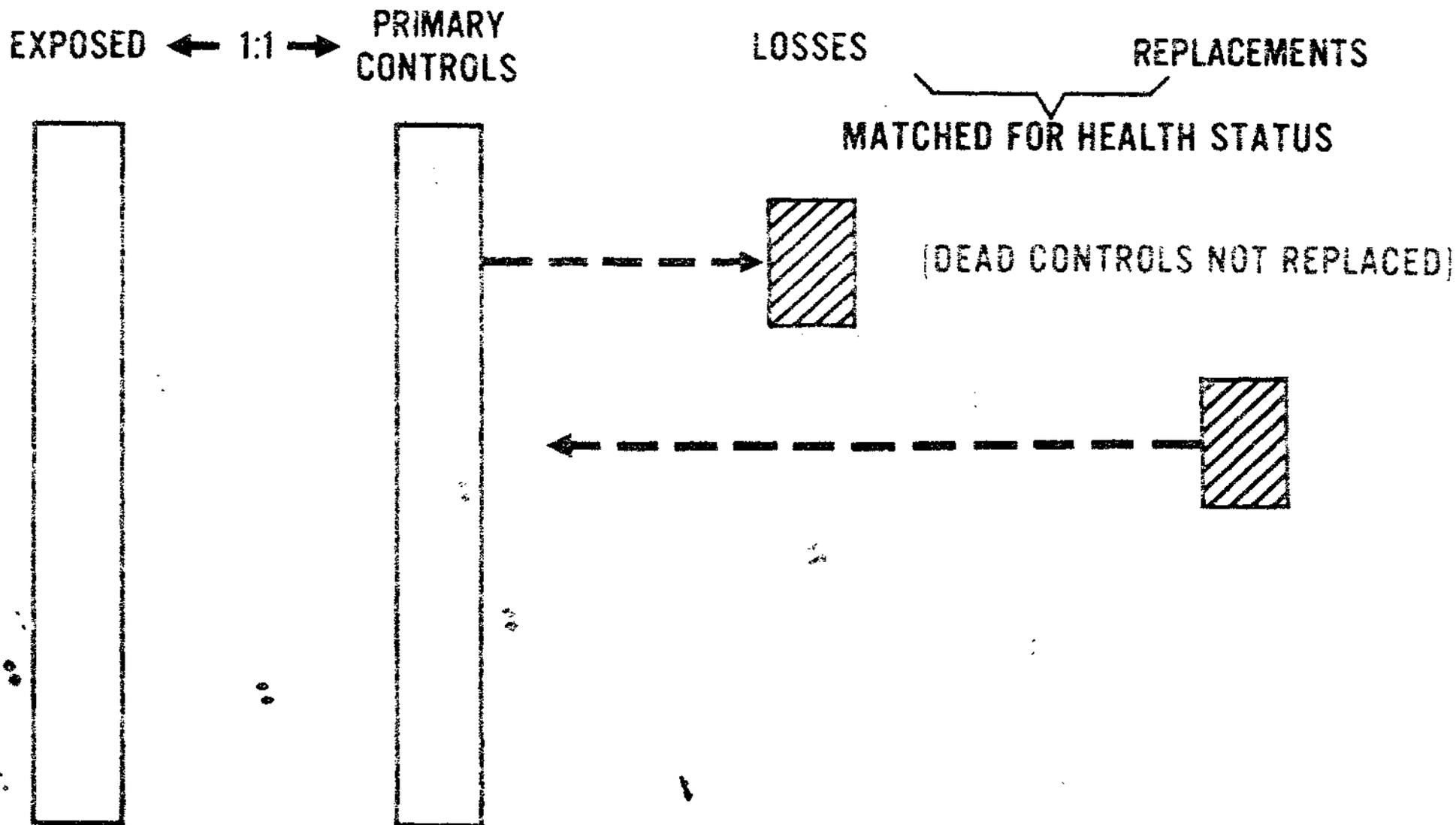
- NO ADVERSE EFFECT (BIAS) OTHER THAN LOSS OF STATISTICAL POWER FROM SMALL N.

EFFECT OF NON-RANDOM LOSS TO STUDY IN THE CONTROL POPULATION



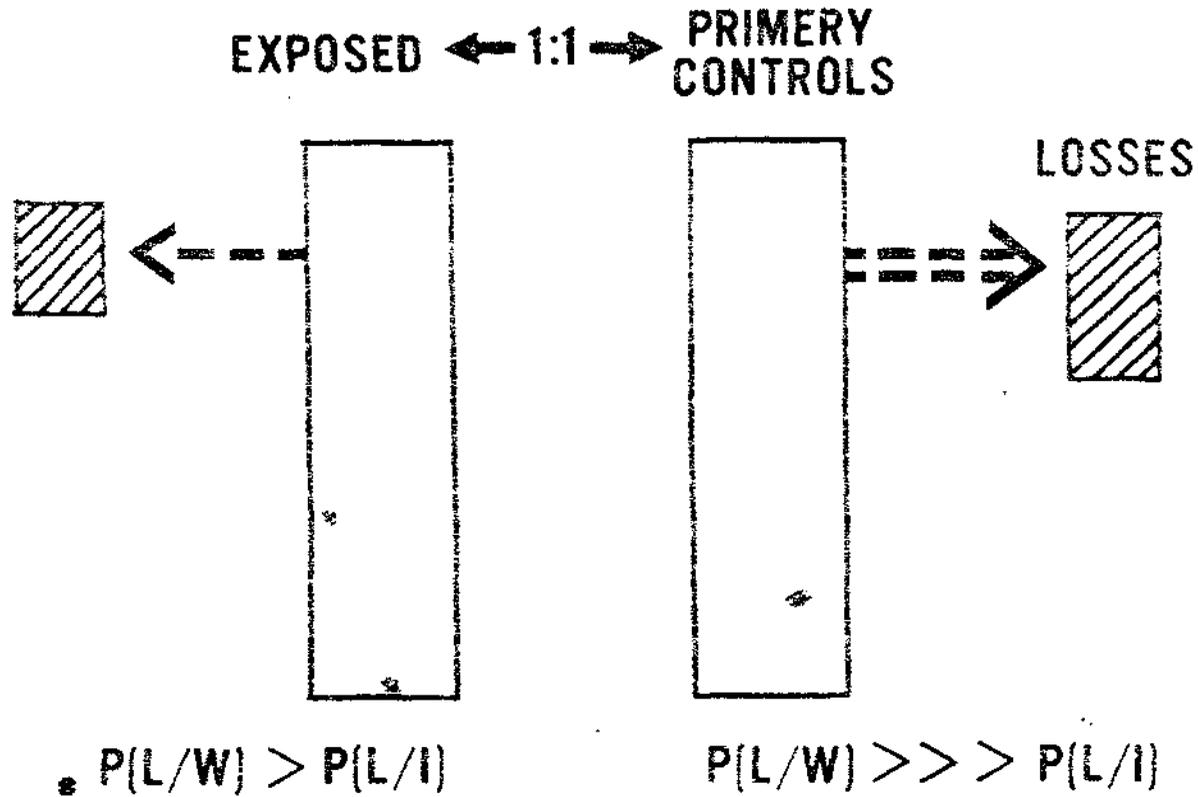
- IF CONTROL LOSSES ARE ILL, A SPURIOUS EFFECT IS ATTRIBUTED TO HERBICIDE EXPOSURE.
- IF CONTROL LOSSES ARE WELL, A TRUE/VALID HEALTH EFFECT IS DILUTED.

ANALYSIS OF REPLACEMENT SCHEME



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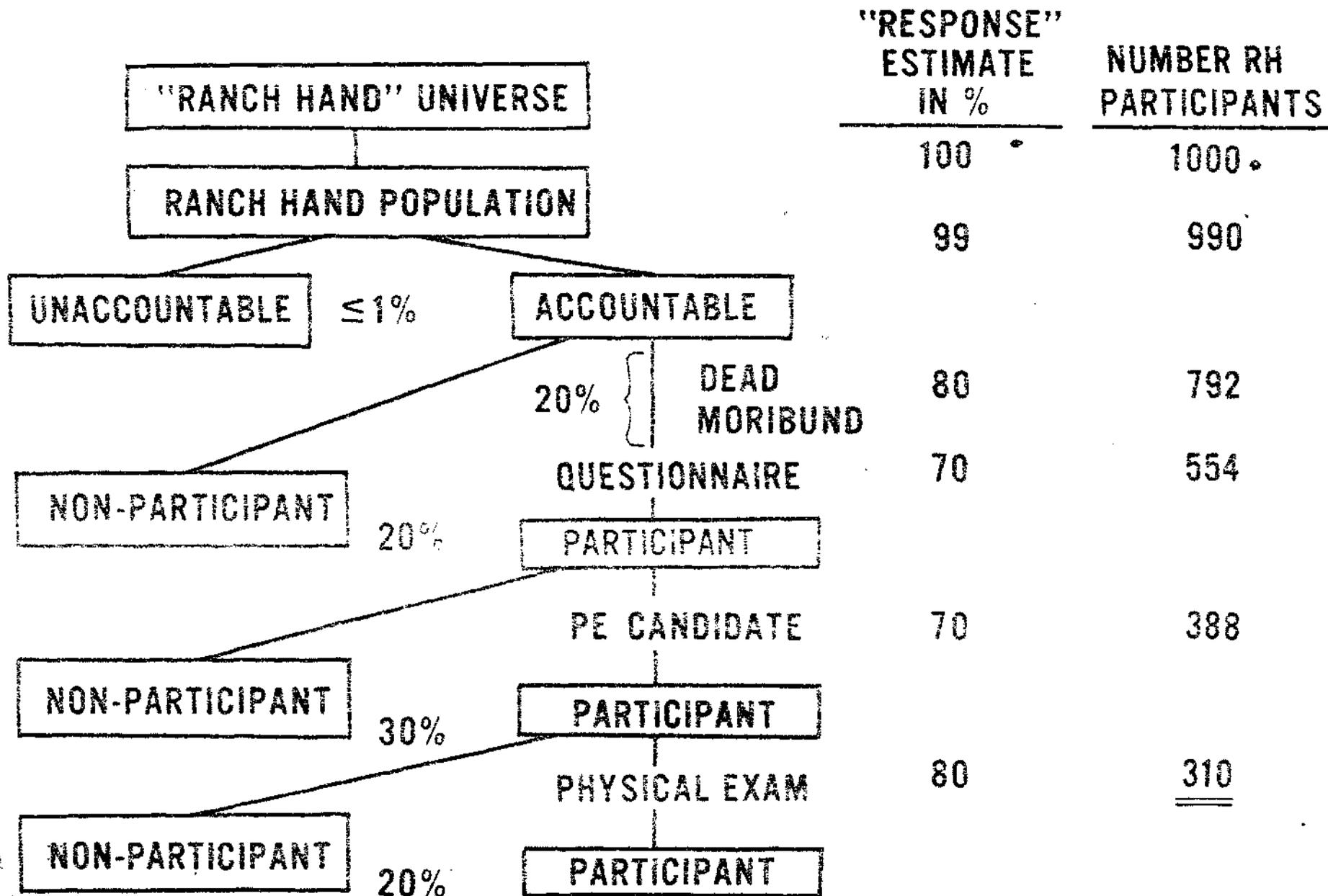
RATIONAL OF REPLACEMENT STRATEGY



DILUTIONAL BIAS

ESTIMATED IDENTIFICATION/PARTICIPATION OF RANCH HAND POPULATION

55



**RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN
PROSPECTIVE PHASE**

- OVER 5 YEAR PERIOD; RENEWABLE 5 YR OPTIONS
 - "ADAPTIVE" QUESTIONNAIRE TO ALL, ANNUALLY
 - "ADAPTIVE" PE TO ALL PARTICIPANTS, Q 2 Y
-
- CONVERSION OF AN ASYMPTOMATIC RANCH HAND TO SYMPTOMATIC INITIATES IMMEDIATE ADAPTIVE PE TO THAT INDIVIDUAL
 - CONVERSION OF AN ASYMPTOMATIC CONTROL TO SYMPTOMATIC INITIATES IMMEDIATE ADAPTIVE PE TO THAT INDIVIDUAL

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METHODS OF ASCERTAINMENT

NPRC

- MORNING REPORTS 1961-1966
- MILITARY PERSONNEL RECORDS
 - ALL VETERANS
 - ADDRESS AT TIME OF SEPARATION
- MEDICAL RECORDS
 - INPATIENT/ OUTPATIENT
- DECORATIONS
 - PURPLE HEART, AIR MEDAL
- PRESENT STATUS
 - RETIRED , RESERVES, DECEASED, VA CLAIM

METHODS OF ASCERTAINMENT (CONT)

- AFHRL COMPUTER 1965-PRESENT
 - AFSC
 - DUTY LOCATION
 - DUTY ORGANIZATION
 - TRUNCATED M.P.R.
 - CURRENT ADDRESS

- UNIT HISTORIES 1961-DEACTIVATION WITH ACTIVE DUTY
 - NAMES
 - LOCATIONS
 - ORGANIZATIONS

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METHODS OF ASCERTAINMENT (CONT)

- USAFMPC ACTIVE DUTY PERSONNEL
 - MBR ON ACTIVE DUTY
 - CURRENT ADDRESS

- RANCH HAND PERSONAL REFERRALS (ALL TIME)
 - RANCH HAND ASSOCIATION
 - LETTER OF INQUIRY TO KNOWN RANCH HAND PERSONNEL
 - MEDIA ANNOUNCEMENTS

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RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN
METHODS OF POPULATION ASCERTAINMENT

EXPOSED GROUP, C-123

CONTROL GROUP, C-130

• **COMPUTER SEARCH (13M)**

AFSC

YES

YES

ORGANIZATION, RVN

YES

YES/NO

TYPE AIRCRAFT

YES

YES

TIME IN RVN

YES

YES

• **NATIONAL PERSONNEL RECORD CENTER**

YES

YES

• **UNIT HISTORIES**

YES

YES

• **REUNION RECORDS**

YES

NO

• **ADVERTISEMENTS**

YES

NO

• **CROSS LINKS TO VA, SS, IRS**

YES

YES

QUESTIONNAIRE

I. PURPOSE

- DEFINE THE "DISEASE"/SYNDROME/SYMPTOM COMPLEX

II. QUALITY

- CONTINUOUS REFINEMENT
- PRETEST

III. VALIDITY

- VERIFIERS/BIAS INDICATORS
- CROSS REF TO MR, PE, AND INTERVIEW
- QUESTION PHRASING/SEQUENCING

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

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DATA REPOSITORY

I. PURPOSE

- COMPUTER INTEGRATION OF
 - ALL QUESTIONNAIRES (DIRECT ENTRY)
 - PSYCHOLOGICAL TESTING
 - PHYSICAL EXAMINATION
 - MEDICAL RECORDS
 - HISTORICAL AND MIK MILITARY PERSONNEL CENTER DATA
 - DEATH CERTIFICATES
 - BIRTH CERTIFICATES
- MASTER FILE ON EACH STUDY AND MATCHED CONTROL
 - KEYED TO MULTIPLE IDENTIFIERS
- RETRIEVAL
 - MOMENTARY RECALL
 - DATA ANALYSIS

PHYSICAL EXAMINATION

A COMPREHENSIVE EXAMINATION WITH EMPHASIS ON SPECIFIC TARGET ORGAN SYSTEMS

DERMATOLOGIC
NEURO-PSYCHIATRIC

REPRODUCTIVE
NEOPLASTIC/LIVER

GENERAL

FBS, 2 HR PP

CBC AND ESR

CPK

U/A

PLATELET COUNT

ECG AND XRAY

BUN/Cr

RBC INDICES

CHOL /HDL CHOL

DIFFERENTIAL CORTISOL

VDRL/FTA

TRIG

THYROID PROFILE (RIA)

SERUM PROTEIN

ELECTROPHORESIS

DERMATOLOGIC

EXAMINATION

URINE PORPHYRINS/PORPHOBILINOGEN

NEURO-PSYCHIATRIC

NERVE CONDUCTION VELOCITIES

COMPLETE PSYCHOLOGICAL BATTERY

MMPI

WRAT

WAIS

WECHSLER MEMORY SCALE I

HALSTEAD -REITAN

CORNELL INDEX

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PHYSICAL EXAMINATION (CONTINUED)

A COMPREHENSIVE EXAMINATION WITH EMPHASIS ON
SPECIFIC TARGET ORGAN SYSTEMS

REPRODUCTIVE

EXAMINATION
SEMEN ANALYSIS
LH, FSH, TESTOSTERONE

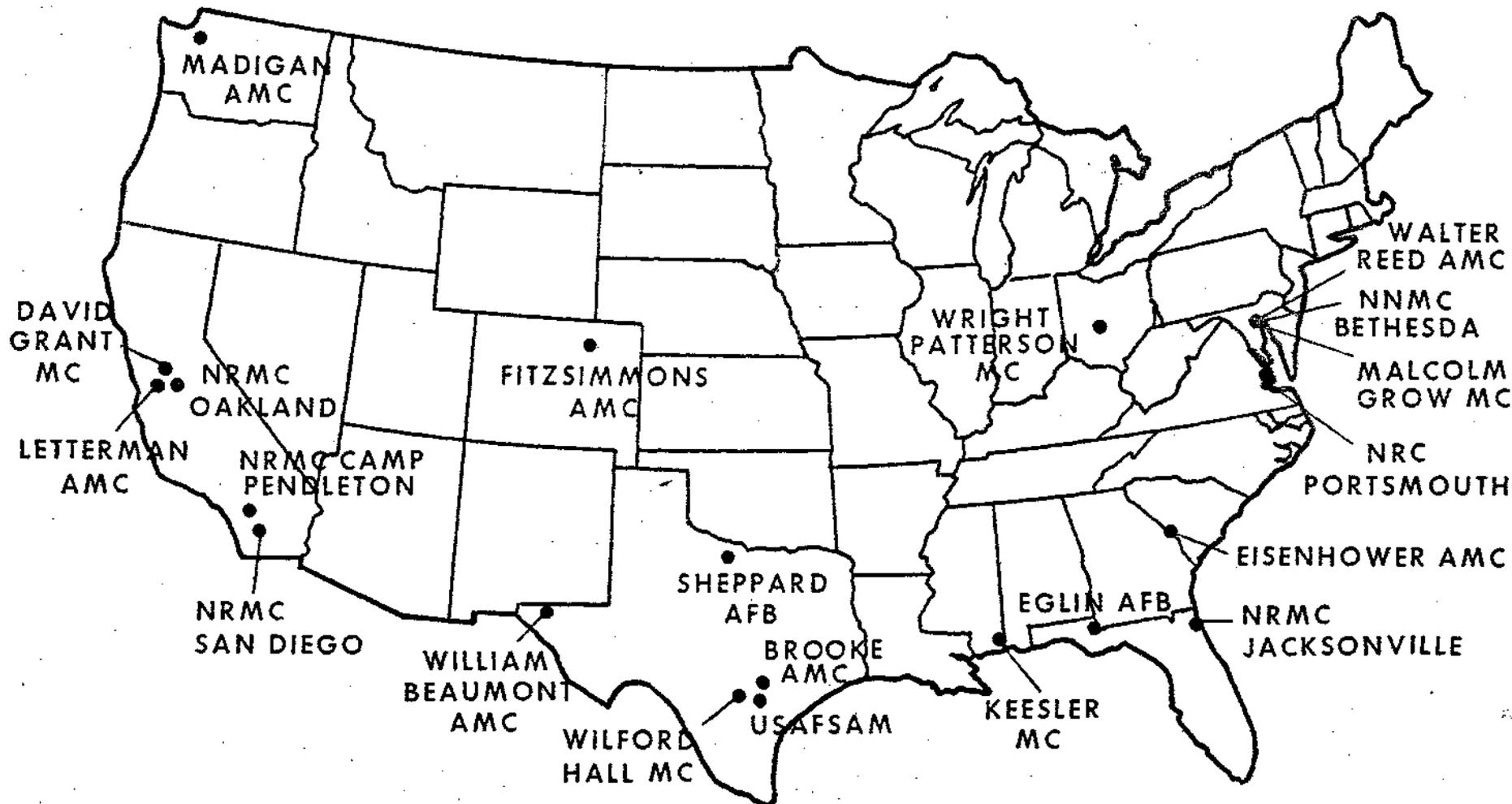
NEOPLASTIC/LIVER

PHYSICAL EXAMINATION	ALK PHOS
SGOT	GGTP
SGPT	LDH

ADDITIONAL STUDIES FOR INDIVIDUALS WITH ABNORMAL HISTORY AND/OR FINDINGS

KARYOTYPING	ANA
ADDITIONAL CONSULTATIONS AS REQUIRED	HEPATITIS ANTIGENS (A AND B)

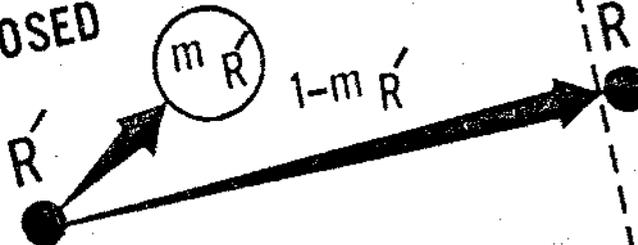
LOCATION OF DOD MEDICAL FACILITIES WITH CAPABILITY TO PERFORM RANCH HAND II PHYSICAL EXAMINATIONS



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DESIGN SCHEMATIC

EXPOSED



s_R (circled)

$1 - s_R$

RS

f_{RS} (circled)

RSF

$RS\bar{F}$

$R\bar{S}$

$f_{R\bar{S}}$ (circled)

$R\bar{S}F$

$R\bar{S}\bar{F}$

1:3 MORTALITY ANALYSIS

1:1 QUESTIONNAIRE

1:1 PHYSICAL EXAMINATION

s_C (circled)

$1 - s_C$

CS

f_{CS} (circled)

CSF

$CS\bar{F}$

$C\bar{S}$

$f_{C\bar{S}}$ (circled)

$C\bar{S}F$

$C\bar{S}\bar{F}$

CONTROL

m_C (circled)

$1 - m_C$

C

UNUSED

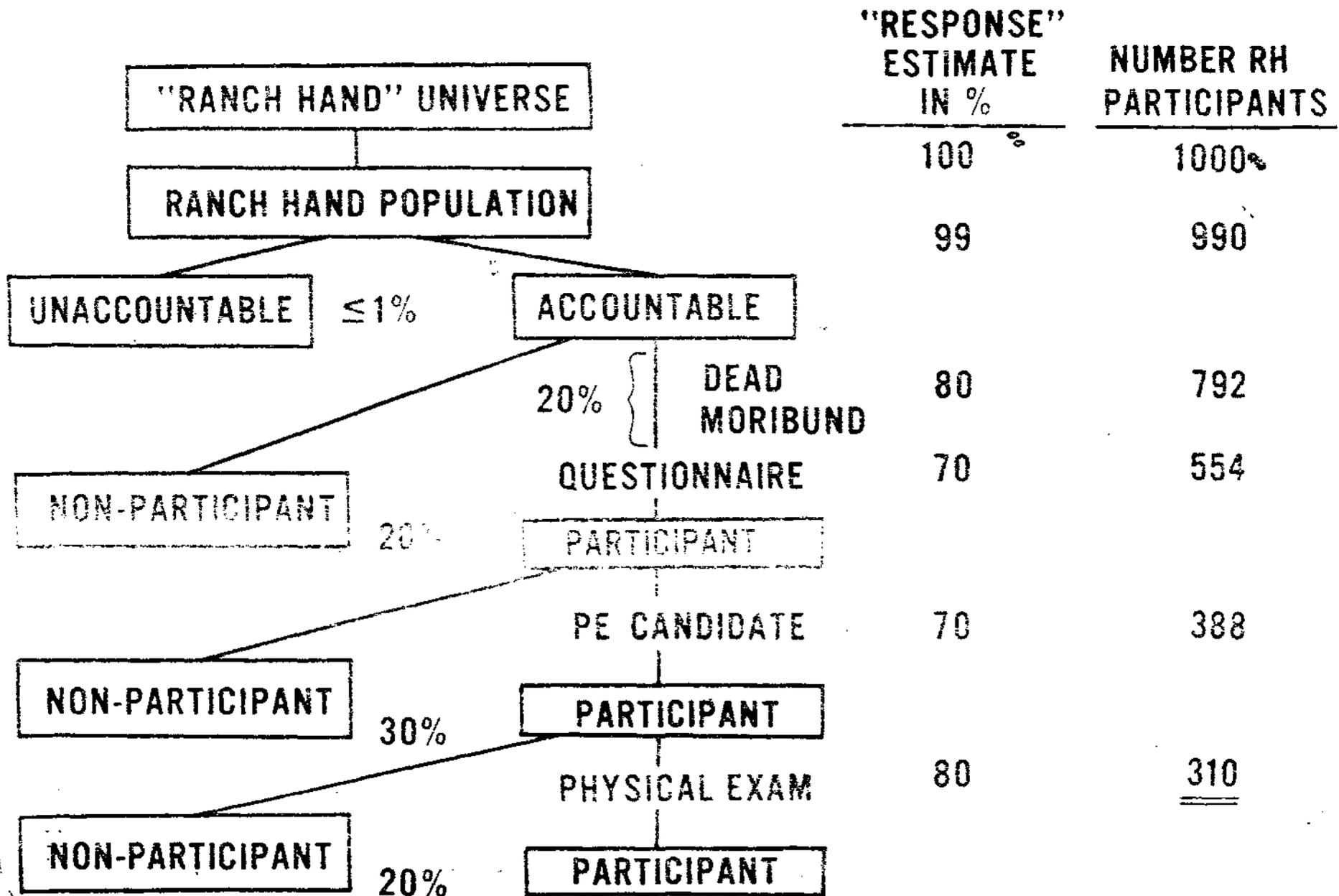
REPLACEMENTS
"BEST-FIT"

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66

ESTIMATED IDENTIFICATION/PARTICIPATION OF RANCH HAND POPULATION

55



MORTALITY ASSESSMENT

- THREE CATEGORIES: ALIVE, DEAD, UNACCOUNTED
- WILL TEST GROUPS FOR DIFFERENCES IN UNACCOUNTABILITY RATES
- MORTALITY ANALYSIS (1:3) WILL PROCEED IF THERE ARE LOW AND/OR COMPARABLE UNACCOUNTABILITY RATES

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METHODS FOR MORTALITY ANALYSIS

1. ESTIMATE PROPORTIONATE MORTALITY RATIO (PMR) USING ARMITAGE APPROACH.
2. ESTIMATE PMR USING BRESLOW AND DAY MULTIPLICATIVE MODEL.
3. LOGISTIC MODELS (WALKER AND DUNCAN).
4. SURVIVAL MODELS (COX).

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(ARMITAGE, 1971)

RANCH HAND

AGE GROUP	PERSON YEARS	DEATHS	DEATH RATE
1	P_{11}	m_{11}	r_{11}
2	P_{12}	m_{12}	r_{12}
3	P_{13}	m_{13}	r_{13}
⋮	⋮	⋮	⋮
k	P_{1k}	m_{1k}	r_{1k}

CONTROLS

PERSON YEARS	DEATHS	DEATH RATE
P_{21}	m_{21}	r_{21}
P_{22}	m_{22}	r_{22}
P_{23}	m_{23}	r_{23}
⋮	⋮	⋮
P_{2k}	m_{2k}	r_{2k}

$$M = \frac{\sum_{j=1}^k m_{ij}}{\sum_{j=1}^k P_{ij} r_{2j}}$$

$$PMR = M \times 100$$

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MORTALITY ASSESSMENT (CONT'D)

- USE LOG-LINEAR MODELS

$$\ln o = B_0 + B_1 A + B_2 T + B_3 R + B_4 P + B_5 E + B_6 AE + \dots \in$$

- IF LOG-LINEAR MODELS SHOW NO ASSOCIATION OF MATCHING FACTORS WITH THE EFFECT OF EXPOSURE, USE McNEMAR'S TEST

CONTROLS

RANCH HAND PERSONNEL	DEAD	ALIVE	TOTAL
DEAD	a	b	a+b
ALIVE	c	d	c+d
TOTAL	a+c	b+d	n

$$\chi^2 = \frac{|b-c|^2}{b+c}$$

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QUESTIONNAIRE DATA

- **FOUR DATA TYPES: DICHOTOMOUS, POLYTOMOUS, COUNT, CONTINUOUS**
- **FOR CATEGORICAL RESPONSES USE LOG-LINEAR MODELS
FOR CONTINUOUS RESPONSES USE GENERALIZED
LINEAR MODELS**
- **IF NO ASSOCIATION BETWEEN MATCHING FACTORS AND
GROUP DIFFERENCES THEN MATCHED PAIR
CONTINGENCY TABLE TESTING CAN BE PERFORMED**

PHYSICAL EXAMINATION DATA

- SAME DATA TYPES AS QUESTIONNAIRE
- TO VALIDATE QUESTIONNAIRE DATA
- TO ESTIMATE RATE OF OCCURENCE OF PHYSICAL FINDINGS
- TO EVALUATE RELATIONSHIP OF SYMPTOMS AND PHYSICAL FINDINGS
- ESSENTIALLY USE THE SAME STATISTICAL TESTS AS USED WITH QUESTIONNAIRE

AGE CATEGORY DISEASE CATEGORY	RANCH HAND PERSONNEL				CONTROLS			
	1	2	3	4	1	2	3	4
1	X 111	X 112	X 113	X 114	X 211	X 212	X 213	X 214
2	X 121	X 122	X 123	X 124	X 221	X 222	X 223	X 224
3	X 131	X 132	X 133	X 134	X 231	X 232	X 233	X 234
4	X 141	X 142	X 143	X 144	X 241	X 242	X 243	X 244

$$\ln m_{ijk} = u + u_1(i) + u_2(j) + u_3(k) + u_{12}(ij) + u_{13}(ik) + u_{23}(jk) + u_{123}(ijk)$$

POWER STUDY-CARDIOVASCULAR DISEASE SETTING

NUMBER OF PAIRS	$\gamma = \beta$		$\gamma = .8\beta$	
	POWER NEGLECTING PAIRING	POWER WITH PAIRING	POWER NEGLECTING PAIRING	POWER WITH PAIRING
100	.69	.93	.81	.82
160	.89	.98	.86	.87
200	> .95	> .995	.93	.95

$\alpha = 0.05$

POWER-CONTINUOUS VARIABLES

$$\alpha = 0.05, \quad \sigma_C / \mu_C = 0.1, \quad \gamma = \mu_{RH} / \mu_C$$

$$\text{POWER} = 1 - \beta$$

R	γ	POWER = 1 - β	
		n=180	n=450
.20	1.01	.20	.38
.20	1.02	.55	.88
.20	1.05	> .995	> .995
.70	1.01	.86	> .995
.70	1.02	> .995	> .995
.70	1.05	> .995	> .995

POWER-DICHOTOMOUS VARIABLES

p ₁	p ₂	REL. RISK	R	POWER = 1 - β				
				n= 160	n= 200	n= 250	n= 300	n= 350
.05	.01	5	0	.71	.78	.84	.89	.92
.04	.01	4	0	.56	.64	.72	.79	.84
.03	.01	3	0	.40	.45	.51	.57	.61
.10	.05	2	0	.54	.61	.69	.76	.81
.20	.10	2	0	.80	.86	.92	.95	.95

α = 0.50

.05	.01	5	.1	.65/.02	.82/.033	.89/.029	.94/.038	.96/.032
.04	.01	4	.1		.54/.020	.72/.033	.79/.029	.87/.038
.03	.01	3	.1			.38/.020	.55/.033	.68/.046
.10	.05	2	.1	.60/.058	.67/.054	.76/.055	.77/.036	.85/.048
.20	.10	2	.1	.81/.036	.92/.056	.94/.043	>.96/.038	>.98/.46

α AS INDICATED

STATISTICAL METHODOLOGY

NEXT STEPS

- ASSESS POWER OF TESTS PARTICULARLY AS APPLIED TO PHYSICAL EXAMINATION DATA
- DETERMINE APPLICATION OF FACTOR ANALYSIS AND CLUSTER THEORY
- EXAMINE MULTIVARIATE TESTING POSSIBILITIES
- DETAIL QUESTIONNAIRE VALIDATION CONCEPTS (BIASES)
- WORK SURVIVAL CURVE ANALYSES
- DEFINE ANALYTIC STEPS FOR INDICES:
 - EXPOSURE, RVN & US
 - ABORTION
 - FERTILITY ?

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

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PROJECT RANCH HAND II

RECOGNIZED STUDY DIFFICULTIES

- PRECEDENCE
- POLITICS
- BIASES

ACCOUNTABILITY, RISK TAKING, RESPONSE,
INTERVIEWER

- LOSS TO STUDY, STATISTICAL POWER
- VARIABILITY
- CONFOUNDING VARIABLES

PROJECT RANCH HAND II

CONCEPTUAL SUMMARY

- TOTAL ASCERTAINMENT STUDY AND CONTROL POPULATIONS
- 3-PHASE APPROACH: "RETROSPECTIVE," X-SECTIONAL, PROSPECTIVE
- TIGHT MATCHING: STUDY TO CONTROL
- QUEST. & PE TO ALL VOLUNTEERS: MAX POWER POSSIBLE
- EMPHASIS UPON STUDY PITFALLS AND CORRECTORS
- PRESET STATISTICAL FRAMEWORK
 - MAXIMUM VALIDITY WITHIN CONSTRAINTS OF THE STUDY

PROJECT RANCH HAND II

ONGOING/FUTURE ADDITIONAL TASKS

- REFINEMENT OF POPULATIONS (~ 13M RECORDS)
- COMPUTER MATCHING, STUDY: CONTROL
- START OF MORTALITY ANALYSIS
- MEDICAL DATA/RECORD CROSS LINKS
- FURTHER DEVELOPMENT OF INDEPTH INTERVIEWS (PE)
- STATISTICAL REFINEMENTS: INDICES, AND PROSPECTIVE PHASE
- COORDINATION/SELECTION PE SITES