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Author

Corporate Author Epidemiology Division, United States Air Force School of

Report/Article Title Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicide Orange

Journal/Book Title

Year 1980

Month/Day June 17

Color ☐

Number of Images 77

Description Notes See items 1521 and 1532 for earlier versions.

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

- STATISICAL 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 PERSONNNEL 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 ━━━━━━━━━━━━━━━ HEALTH

   INDENTIFY 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

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

AIR FORCE PROJECT RANCH HAND

EPIDEMIOLOGIC APPROACH

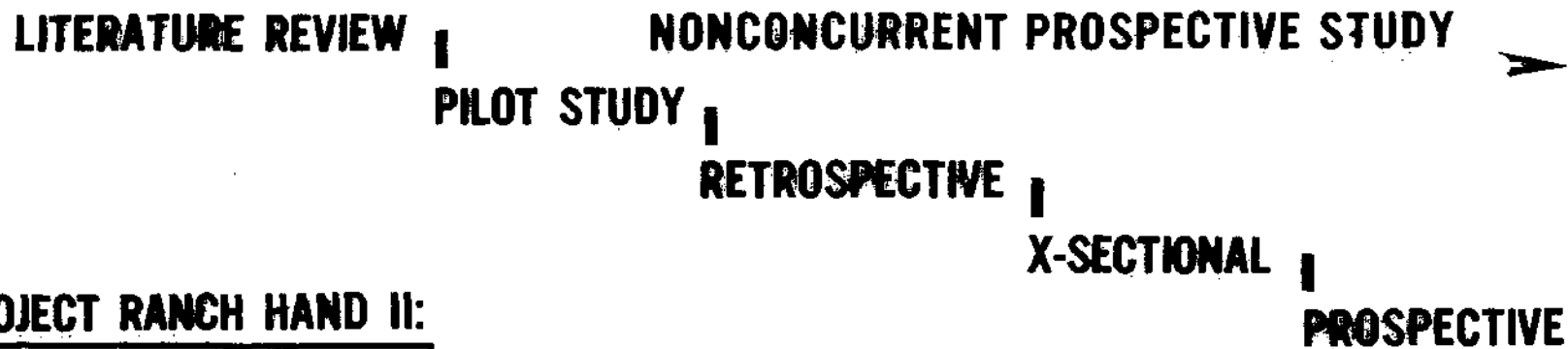| STUDY PHASE	METHODS
• MORTALITY STUDY	PERSON TRACKING, RECORD REVIEWS
• MORBIDITY STUDY	BASELINE QUESTIONNAIRE, PHYSICAL EXAM
• FOLLOW-UP STUDY	ADAPTIVE QUESTIONNAIRES, PHYSICAL EXAMS

THREE PHASE APPROACH REQUIRED

# EPIDEMIOLOGIC STUDY DESIGN

CLASSIC APPROACH:

LITERATURE REVIEW ▪   NONCONCURRENT PROSPECTIVE STUDY ➤

PILOT STUDY ▪

RETROSPECTIVE ▪

X-SECTIONAL ▪

PROSPECTIVE ▶

PROJECT RANCH HAND II:

LITERATURE REVIEW
▪
MORTALITY
▪
MORBIDITY
▪
FOLLOW-UP ▶
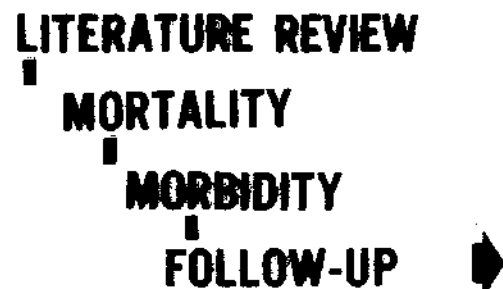
RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN
GROUP SELECTION, RATIONALE

PRIMARY EXPOSED GROUP

CONTROL GROUP
NOT EXPOSED TO H.O.

| C-123 RANCH HAND; CREW+SUPPORT | ←→ | C-130, CREW+SUPPORT |
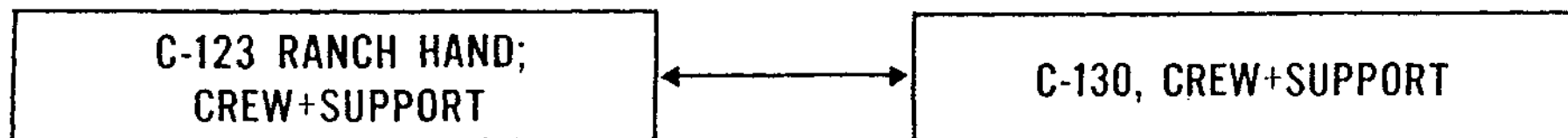
- •• STUDY REQUIREMENT

  - • 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)

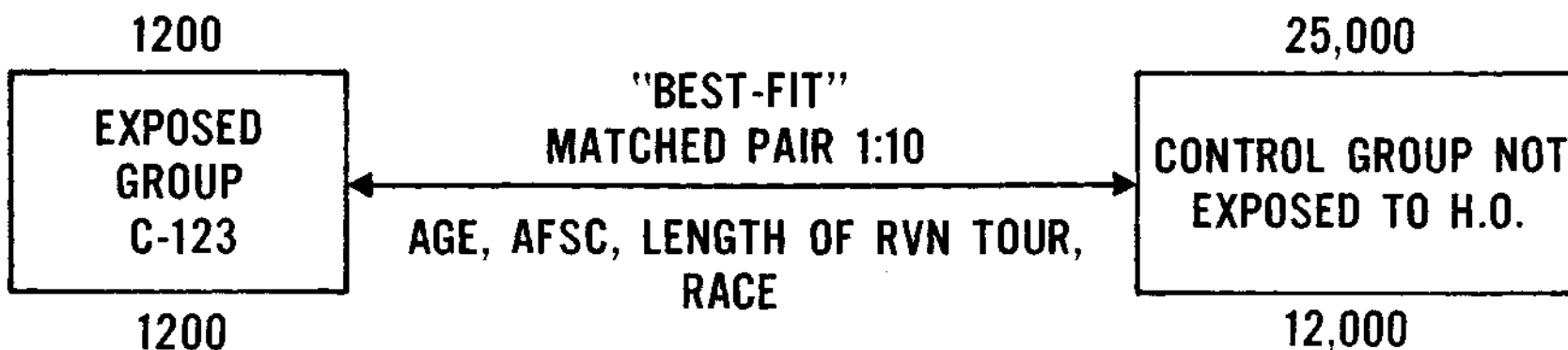- SKIN EXPOSURE 5:1 (CONSOLE OPERATOR VS PILOT)

- 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

	EXPOSED GROUP (C-123)	CONTROL GROUP (C-130)
AGE RANGE:	28-62	25-65
SEX:	ALL MALE	ALL MALE
RACE:	OFFICER: ~ 100% WHITE	~ 100% WHITE
	ENLISTED: ~ 10-14% BLACK	~ 10-14% BLACK
CURRENT ACTIVE DUTY:	25%	20-25%
	OFFICER: SENIOR MANAGEMENT	SENIOR MANAGEMENT
	ENLISTED: MIDDLE MANAGEMENT	MIDDLE MANAGEMENT
PAST SERVICE EMPLOYMENT:	AEROSPACE INDUSTRY	AEROSPACE INDUSTRY
SOCIOECONOMIC: GENERAL LIFESTYLE:	SIMILAR TO CONTROL	SIMILAR TO STUDY

RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN
RATIONALE FOR MATCHING PROCEDURE

1200

25,000

EXPOSED GROUP C-123	"BEST-FIT" MATCHED PAIR 1:10 ◄──────► AGE, AFSC, LENGTH OF RVN TOUR, RACE	CONTROL GROUP NOT EXPOSED TO H.O.

1200

12,000

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 MULTVARIATE 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
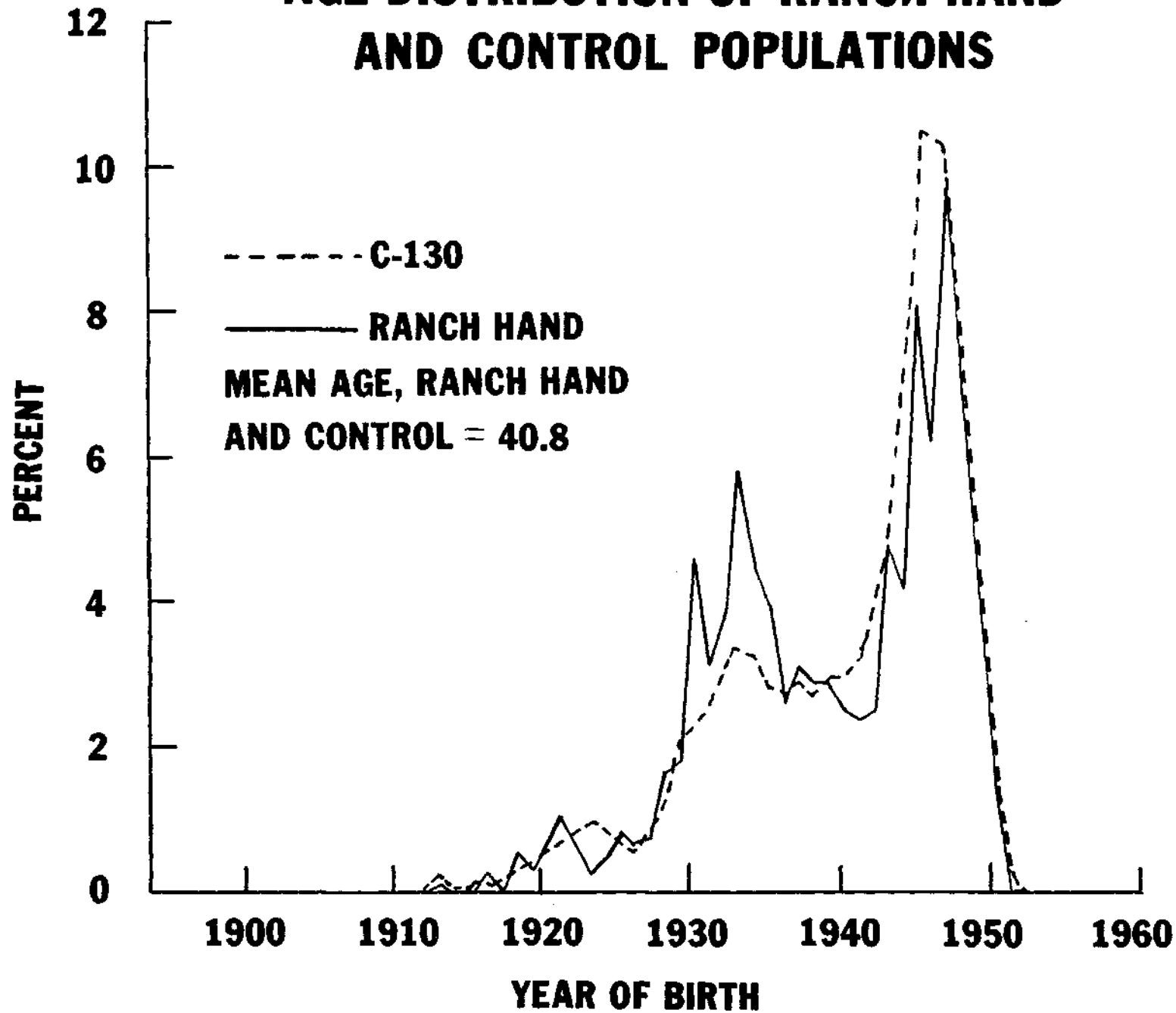
COMPUTER MATCHING
RANCH HAND TO CONTROL, 1:10

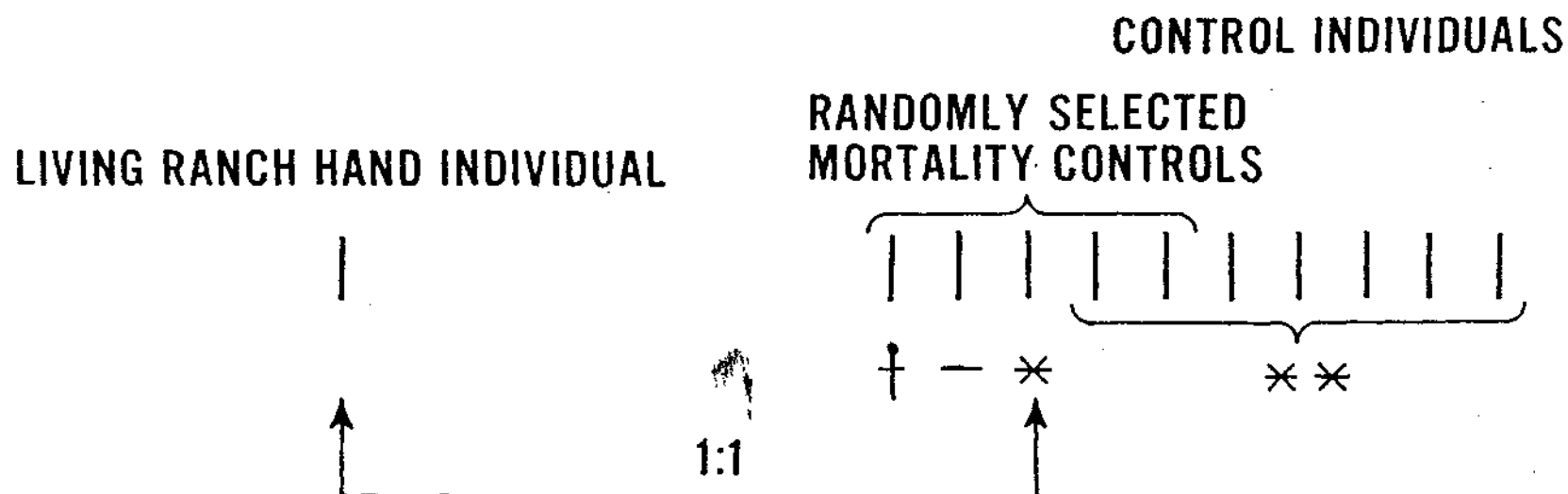- 48% EXACT MATCH, BIRTH MONTH, JOB (5), TIME IN RVN, RACE, SEX

- 87% MATCH, $\pm$ ONE YEAR BIRTH, ALL OTHERS EXACT

- 95% + MATCH PREDICTED, $\pm$ 18 MONTHS BIRTH, ALL OTHERS EXACT

SELECTION OF THE CONTROL COHORT
FOR THE MORTALITY ANALYSIS

EXPOSED GROUP	CONTROL COHORTS									
	1	2	3	4	5	6	7	8	9	10
R_1	$C_{1,1}$	$C_{1,2}$	$C_{1,3}$	$C_{1,4}$	$C_{1,5}$	$C_{1,6}$	$C_{1,7}$	$C_{1,8}$	$C_{1,9}$	$C_{1,10}$
R_2	$C_{2,1}$	$C_{2,2}$	$C_{2,3}$	$C_{2,4}$	$C_{2,5}$	$C_{2,6}$	$C_{2,7}$	$C_{2,8}$	$C_{2,9}$	$C_{2,10}$
R_3	$C_{3,1}$	$C_{3,2}$	$C_{3,3}$	$C_{3,4}$	$C_{3,5}$	$C_{3,6}$	$C_{3,7}$	$C_{3,8}$	$C_{3,9}$	$C_{3,10}$
•	•	•	•	•	•	•	•	•	•	
•	•	•	•	•	•	•	•	•	•	•
•	•	•	•	•	•	•	•	•	•	•
R_j	$C_{j,1}$	$C_{j,2}$	$C_{j,3}$	$C_{j,4}$	$C_{j,5}$	$C_{j,6}$	$C_{j,7}$	$R_{j,8}$	$C_{j,9}$	$C_{j,10}$

SELECTION PROCEDURE FOR THE QUESTIONNAIRE, PHYSICAL EXAMINATION, AND FOLLOW UP STUDY

CONTROL INDIVIDUALS

RANDOMLY SELECTED
MORTALITY CONTROLS

LIVING RANCH HAND INDIVIDUAL

1:1

† 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

(RANDOM)

N = 1200

←——— 1:1 MATCHED PAIR ———→

N = 1200 MORBIDITY ANALYSIS

N = 6000 MORTALITY ANALYSIS

REPLACEMENT

MORBIDITY ANALYSIS: QUESTIONNAIRE & RECORD REVIEW

MORBIDITY ANALYSIS: VOLUNTARY PE/INDEPTH INTERVIEW

ADAPTIVE QUEST· & PEs: 1st 5YR FOLLOWUP

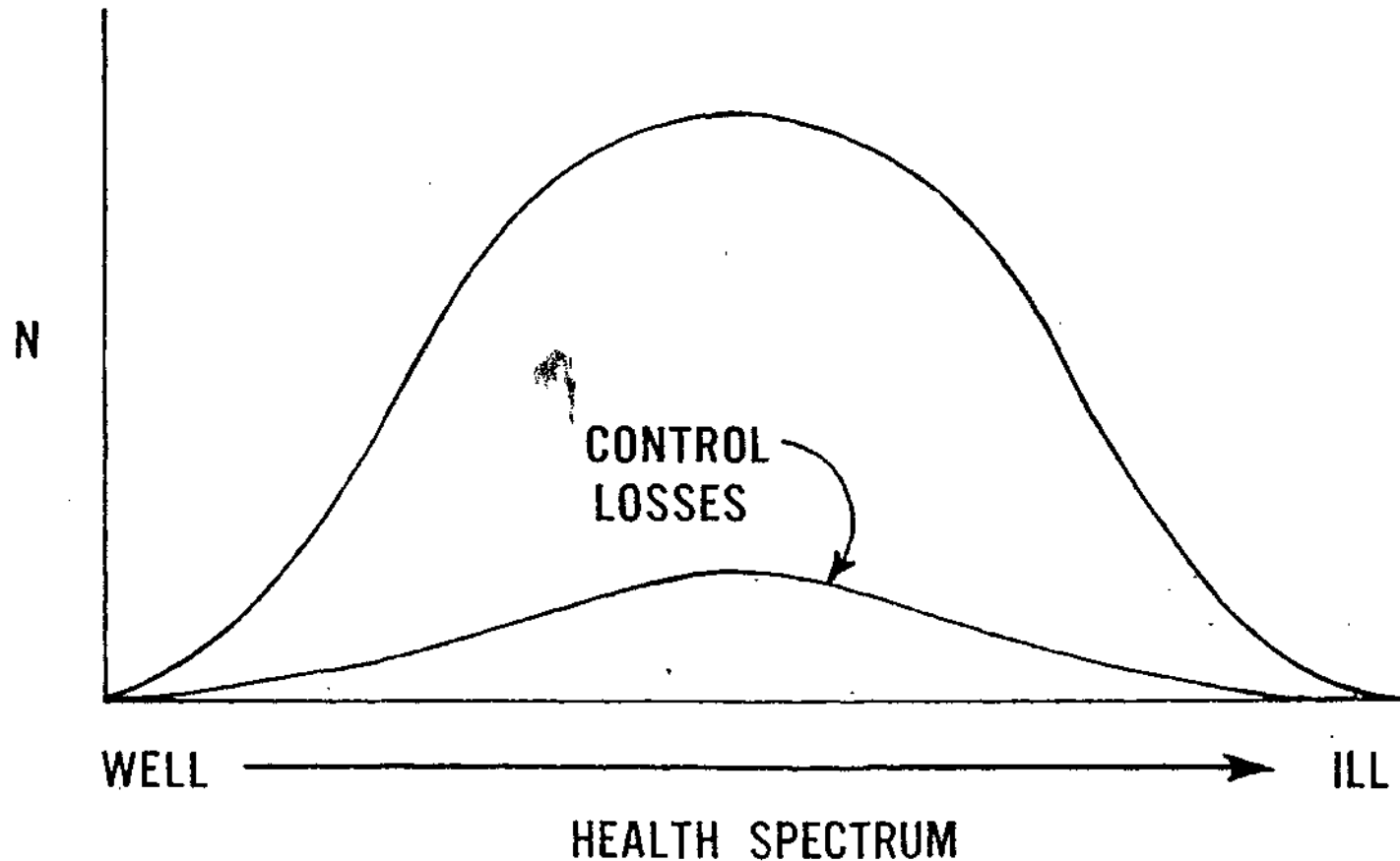| ALL OTHER INDICATED 5YR FOLLOWUP PERIODS |
| --- |

PURPOSE OF THE REPLACEMENT STRATEGY

- CORRECT EXPECTED SELECTION BIAS

- ENHANCE STATISTICAL POWER

EFFECT OF RANDOM LOSS TO STUDY IN THE CONTROL POPULATION

N

CONTROL
LOSSES

WELL ———————————————→ ILL

HEALTH SPECTRUM

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

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

WELL ————————————————————→ ILL

HEALTH SPECTRUM
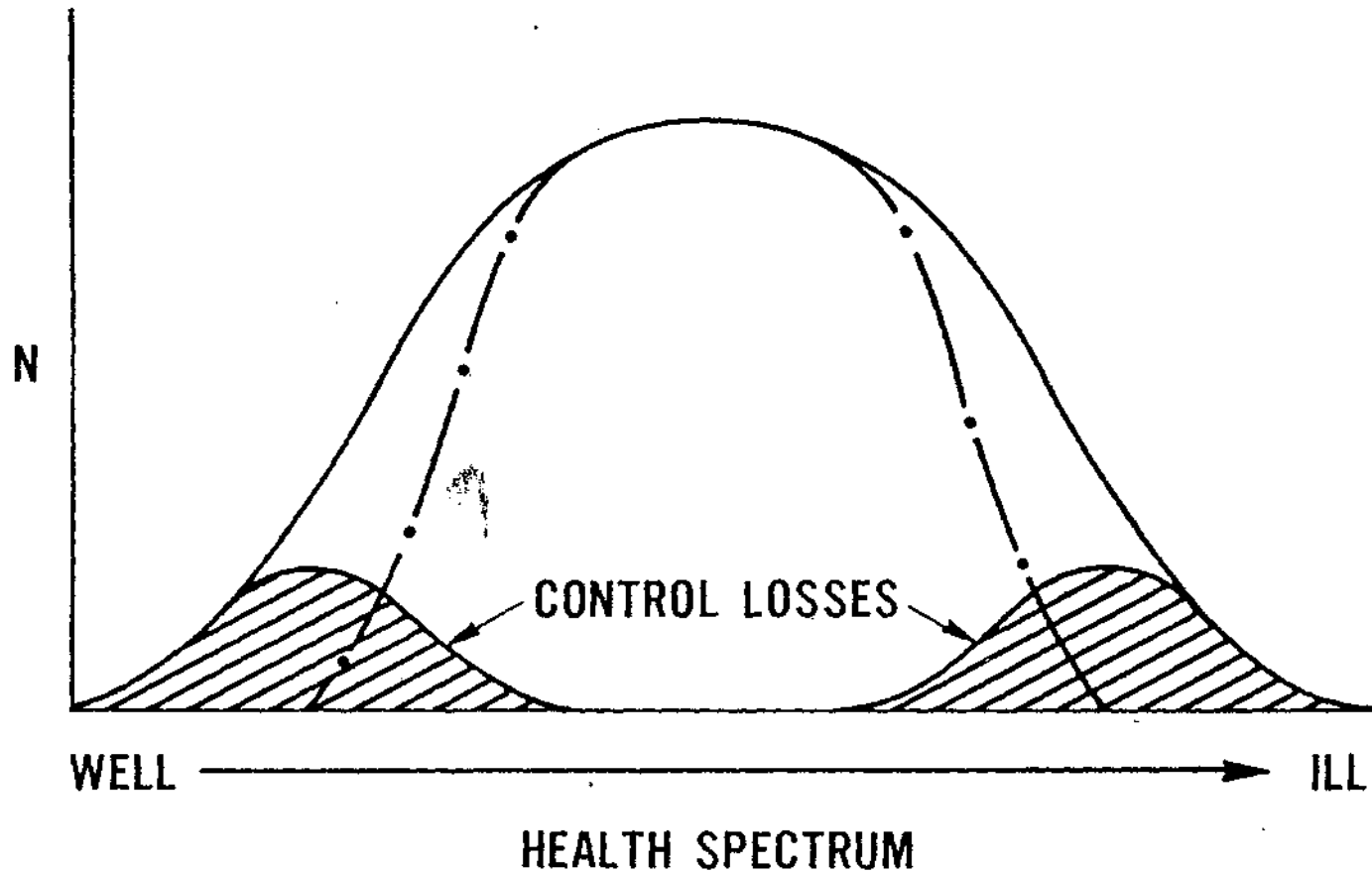
- IF CONTROL LOSSES ARE ILL, A SPURIOUS EFFECT IS ATTRIBUTED TO HERBICIDE EXPOSURE.

- IF CONTROL LOSSES ARE WELL, A TRUE/VALID HEALTH EFFECT IS DILUTED.

REPLACEMENT STRATEGY

EXPOSED

PRIMARY
CONTROLS

LOSSES   REPLACEMENTS

MATCHED FOR HEALTH STATUS

(DEAD CONTROLS NOT REPLACED
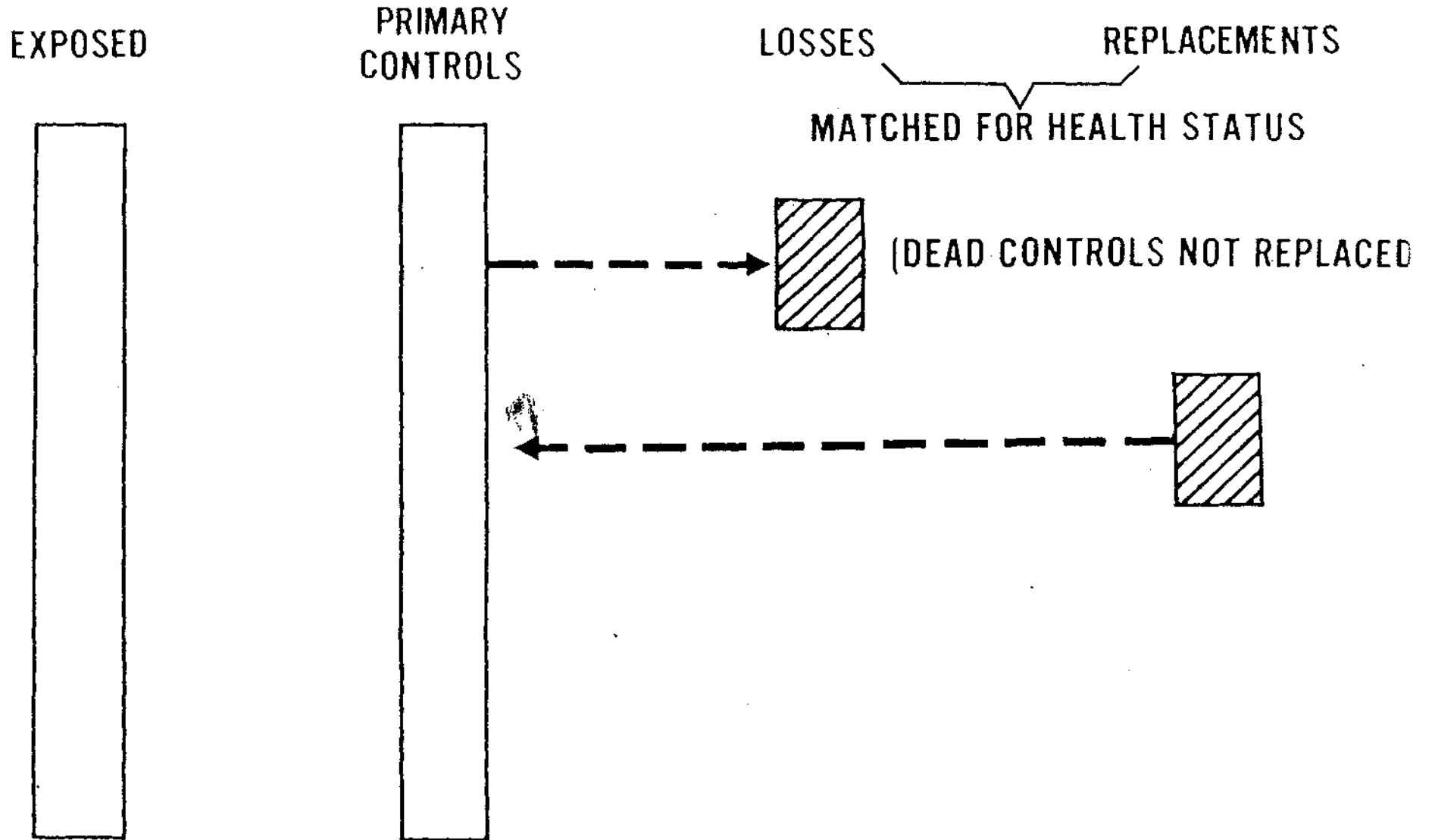
RATIONALE OF REPLACEMENT

DILUTIONAL BIAS

EXPOSED

PRIMARY CONTROLS

LOSSES

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

$$P(L/W) >>> P(L/I)$$
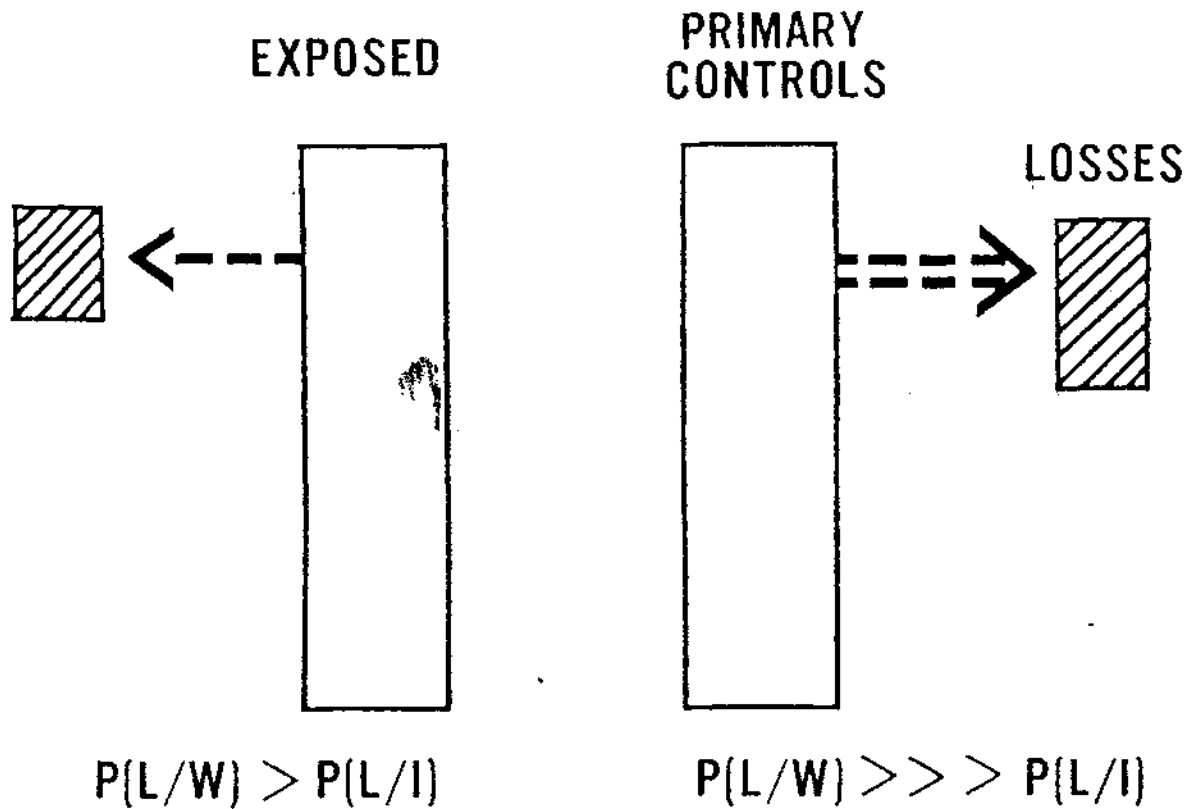
CONDITIONAL PROBABILITIES:

L = LOSS

W = WELL

I = ILL

CONTROL REPLACEMENT FOR THE MORBIDITY
AND FOLLOW UP STUDIES

ESTIMATED IDENTIFICATION/PARTICIPATION
OF THE RANCH HAND POPULATION

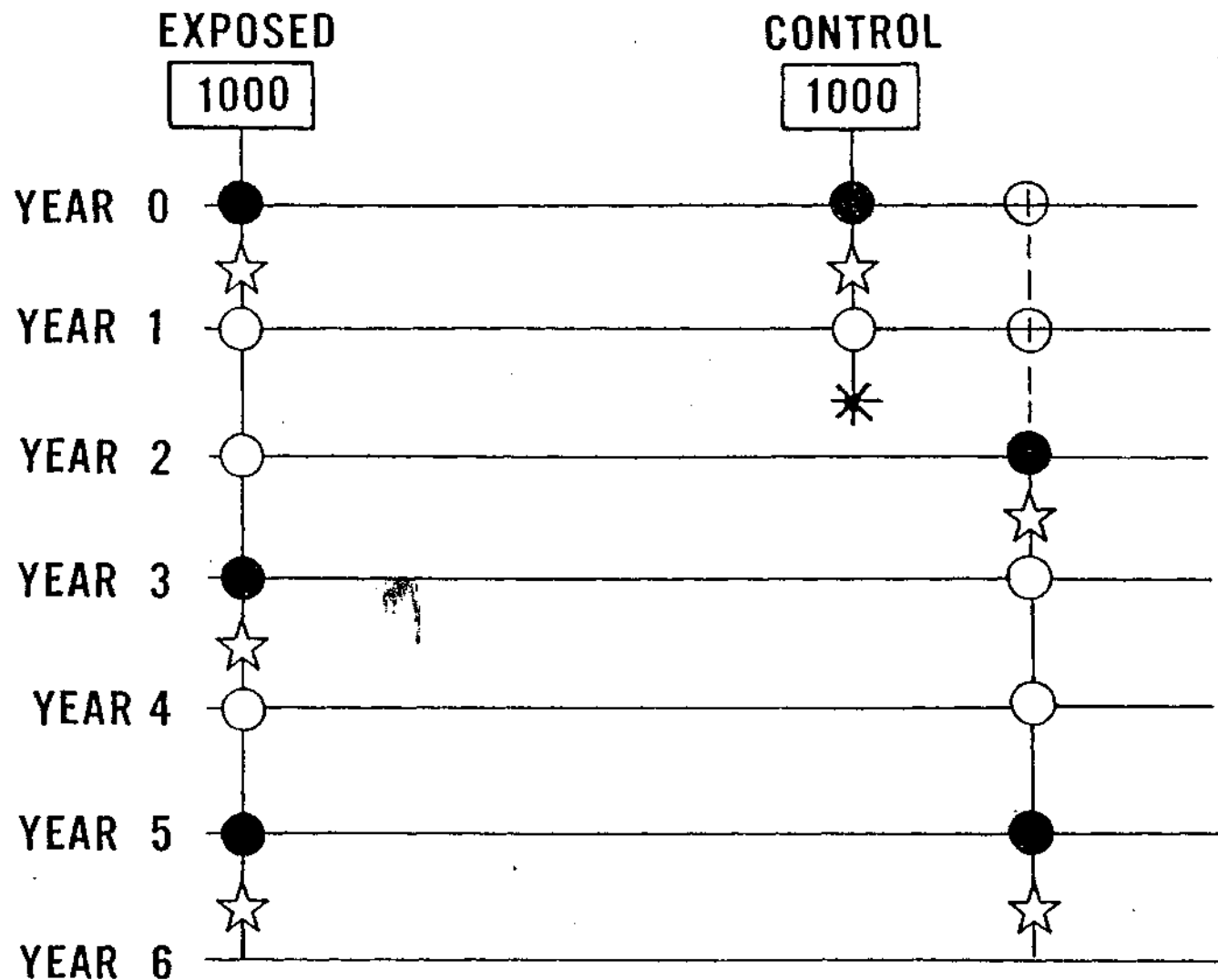|		RESPONSE ESTIMATE	ESTIMATED NUMBER OF PARTICIPANTS
RANCH HAND POPULATION		—	1200
UNACCOUNTABLE ≤ 1%	ACCOUNTABLE	99%	1188
NON-PARTICIPANTS DEAD/MORIBUND 10% UNWILLING 25%	QUESTIONNAIRE PARTICIPANTS	65%	772
NON-PARTICIPANTS 40%	BASELINE EXAM PARTICIPANTS	60%	463
NON-PARTICIPANTS 20%	1st FOLLOW-UP EXAM PARTICIPANTS	80%	371
NON-PARTICIPANTS 20%	2nd FOLLOW-UP EXAM PARTICIPANTS	80%	297
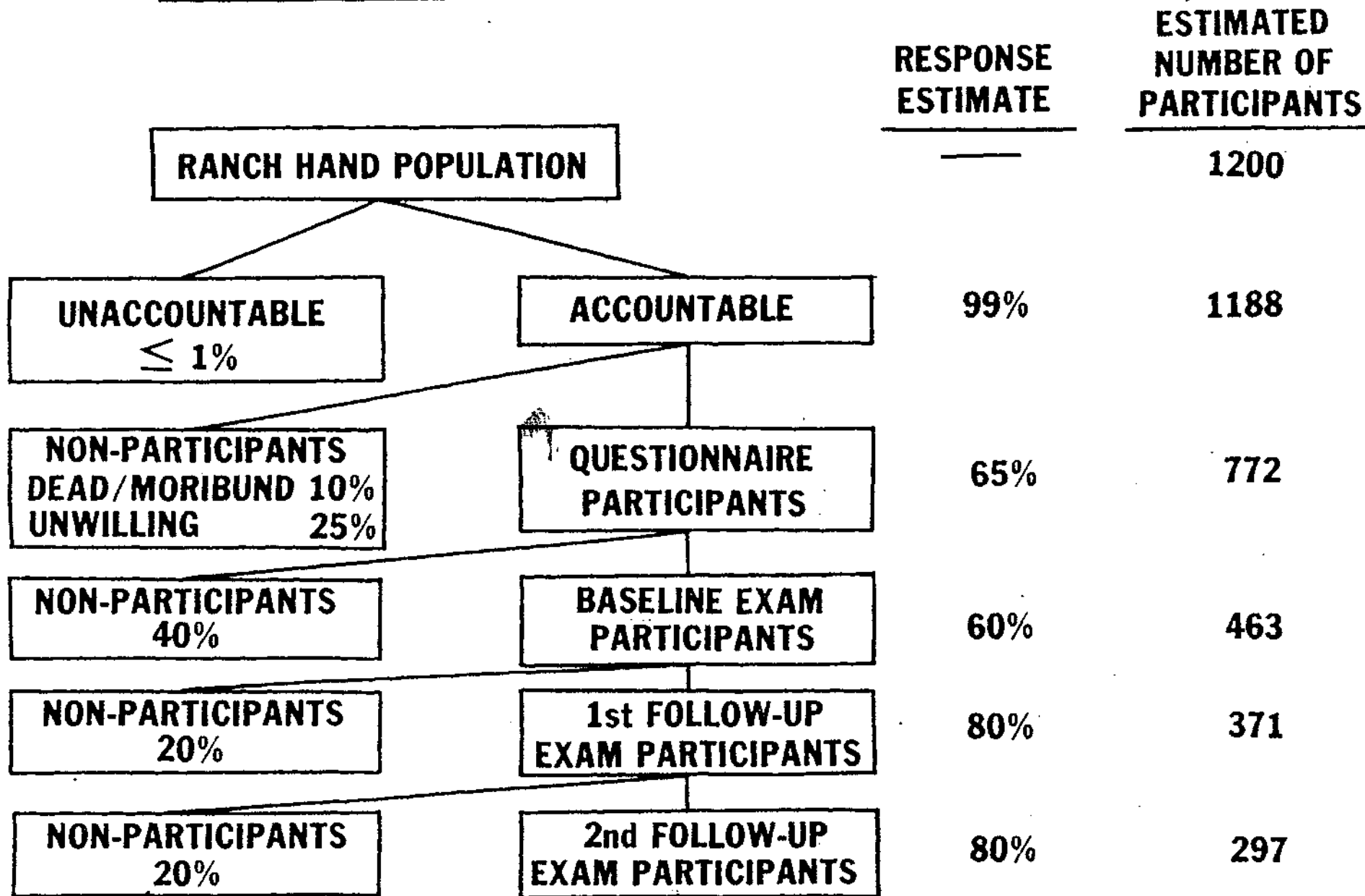
RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN
FOLLOW-UP STUDY

OVER 5 YEAR PERIOD; RENEWABLE 5 YEAR OPTIONS

"ADAPTIVE" QUESTIONNAIRE

"ADAPTIVE" PHYSICAL EXAMINATION
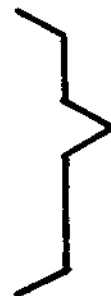
IN YEARS 3 AND 5

PARTICIPATION SCHEMATIC FOR A GIVEN SUBJECT
BY DATE AND STUDY PHASE

1:5 MORTALITY STUDY

1:1 MORBIDITY STUDY — Q, E

1:1 FOLLOW UP STUDY — AE, AQ

ADDITIONAL 5 YR FOLLOWUP PERIODS →

MONTH J A J O J A J O J A J O J A J O J A J O J A J O J A J O

CY 1980 1981 1982 1983 1984 1985 1986 >

Q QUESTIONNAIRE   E PHYSICAL EXAMINATION

AE ADAPTIVE EXAMINATION   AQ ADAPTIVE QUESTIONNAIRE
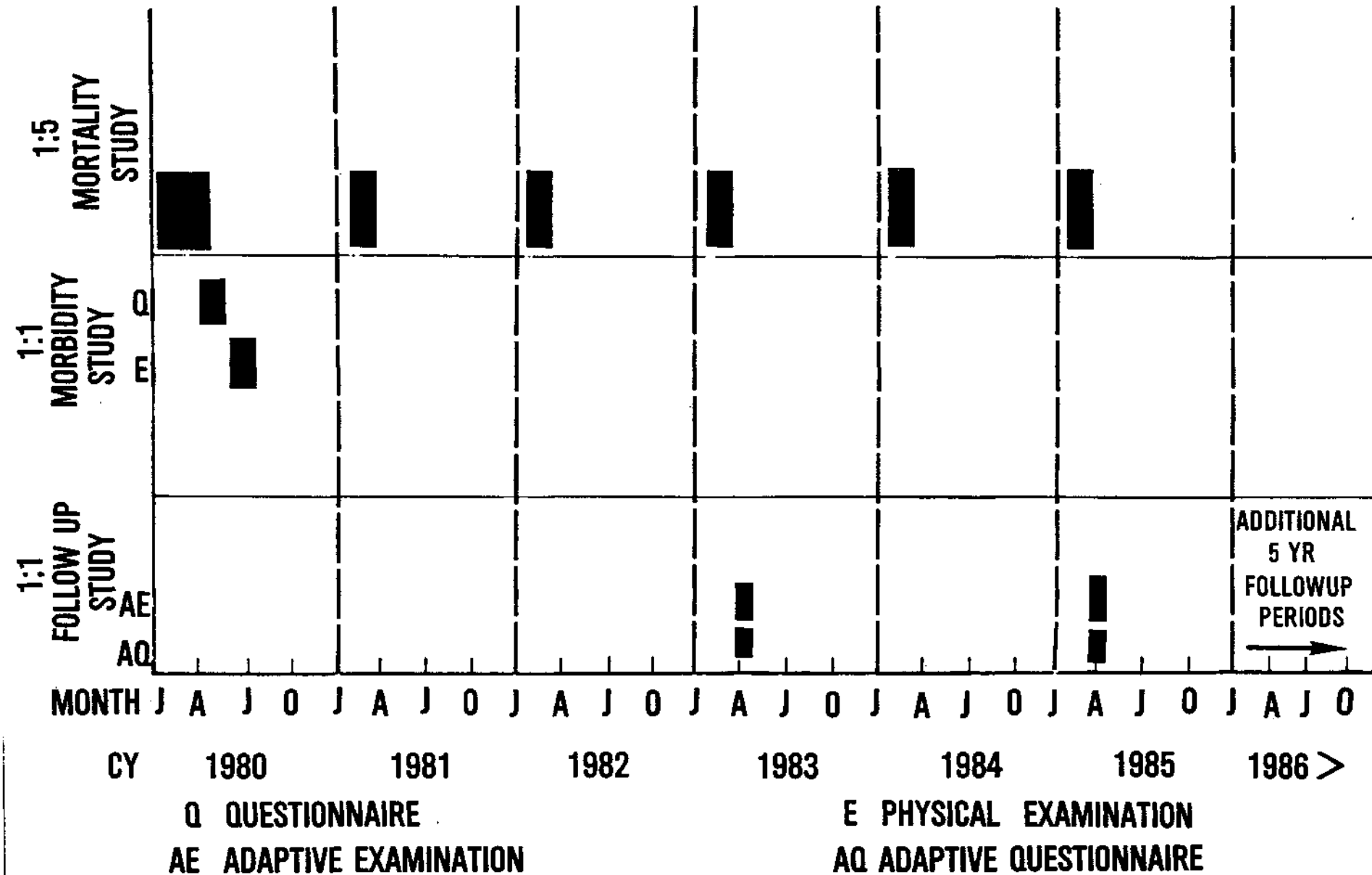
INFORMATION SOURCES

- 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

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 DISFUNCTION
• GI DISTURBANCE	• GI DISTURBANCE	• GI DISTURBANCE
• HEADACHE		
• PNEUMONITIS		
		• HYPOTHYROIDISM
		• HEARING/SMELL DISTURBANCES
• CSF PROTEIN ABNORMALITIES		
• CONVULSIONS		

SUBJECTIVE SIGNS AND SYMPTOMS

ANXIETY

DECREASED LEARNING ABILITY

DEPRESSION

PARESTHESIAS

FATIGUE

DECREASED LIBIDO

APATHY

SLEEP DISTURBANCES

LOSS OF DRIVE

ANOREXIA

EPIDEMIOLGIC 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 PROTCOL

- 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

DESIGN SCHEMATIC

EXPOSED

R' m_R' $1-m_R'$ R s_R RS f_{RS} RSF

$1-s_R$ $RS\bar{F}$

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

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

| 1:5 MORTALITY ANALYSIS | 1:1 QUESTIONNAIRE | 1:1 PHYSICAL EXAMINATION |

f_{CS} CSF

CONTROL

C'' C' m_C' $1-m_C'$ C s_C CS $CS\bar{F}$

$1-s_C$ $C\bar{S}$ $f_{C\bar{S}}$ $C\bar{S}F$

UNUSED

REPLACEMENTS $C\bar{S}\bar{F}$
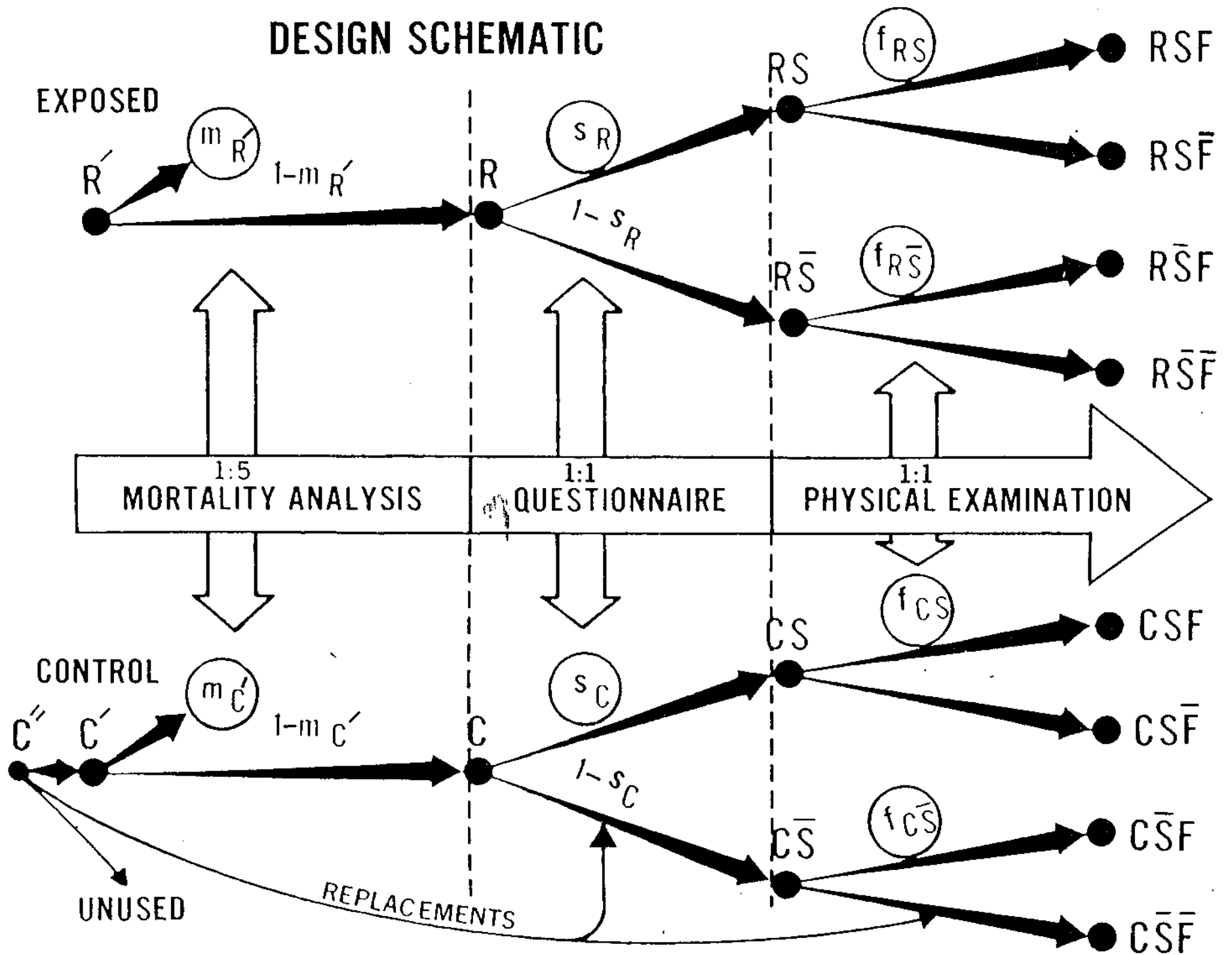
INTERPRETATION OF HORIZONTAL COMPARISONS

OVERT EFFECT	SUBCLINICAL	OVER-REPORTING
$M_R > M_C$	$M_R = M_C$	$M_R = M_C$
$S_R > S_C$	$S_R = S_C$	$S_R > S_C$
$F_R > F_C$	$F_R > F_C$	$F_R = F_C$
$F_{RS} > F_{CS}$	$F_{RS} > F_{CS}$	$F_{RS} < F_{CS}$
$F_{R\bar{S}} > F_{C\bar{S}}$	$F_{R\bar{S}} \geq F_{C\bar{S}}$	$F_{R\bar{S}} = F_{C\bar{S}}$
MORTALITY/SYMPTOM/ SIGN REGRESSION ON EXPOSURE	SIGN REGRESSION ON EXPOSURE	NO REGRESSION ON EXPOSURE SEEN

$$F_R = F_{RS} S_R + F_{R\bar{S}} (1 - S_R)$$

INDIVIDUAL EXPOSURE INDEX (E_j)

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

FOR THE ith MISSION:

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

c_{ij} = DIOXIN CONCENTRATION

p_{ij} = CREW POSITION

t_j = AVERAGE MISSION DURATION

h_j = 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).

	RANCH HAND			CONTROLS		
AGE GROUP	PERSON YEARS	DEATHS	DEATH RATE	PERSON YEARS	DEATHS	DEATH RATE
1	P_{11}	m_{11}	r_{11}	P_{21}	m_{21}	r_{21}
2	P_{12}	m_{12}	r_{12}	P_{22}	m_{22}	r_{22}
3 ⋮	P_{13} ⋮	m_{13} ⋮	r_{13} ⋮	P_{23} ⋮	m_{23} ⋮	r_{23} ⋮
k	P_{1k}	m_{1k}	r_{1k}	P_{2k}	m_{2k}	r_{2k}

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

$$SMR = M \times 100$$

(BRESLOW AND DAY, 1975)

- $\lambda_{ijk} = \theta_i \phi_j \psi_k$

- **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

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

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

COX SURVIVAL MODELS

$$\lambda = \lambda_0 \, e^{\underset{\sim}{\beta} \cdot \underset{\sim}{x}}$$

WEI MORTALITY METHOD

EXPOSED PERSONNEL	MATCHED CONTROL	GEHAN/WEI SCORE	SIGN TEST
56	62	-4	-1
59	60 *	0	-1
53	58	-4	-1
57 *	55	1	+1
		$-7 = W_n$	-3

AGE AT EVENT

(* = NO EVENT)

- W_n HAS KNOWN DISTRIBUTION FOR LARGE n

- TEST MORE POWERFUL THAN SIGN TEST

QUESTIONNAIRE DATA

- FOUR DATA TYPES: DICHOTOMOUS, POLYTOMOUS, 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

DISEASE CATEGORY	AGE 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}

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

RANCH HAND CATEGORY	CONTROL CATEGORY			
	1	2	3	4
1	n_{11}	n_{12}	n_{13}	n_{14}
2	n_{21}	n_{22}	n_{23}	n_{24}
3	n_{31}	n_{32}	n_{33}	n_{34}
4	n_{41}	n_{42}	n_{43}	n_{44}

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

POWER VERSUS RELATIVE RISK, 1:5 MORTALITY STUDY BY THREE DISEASE INCIDENCES
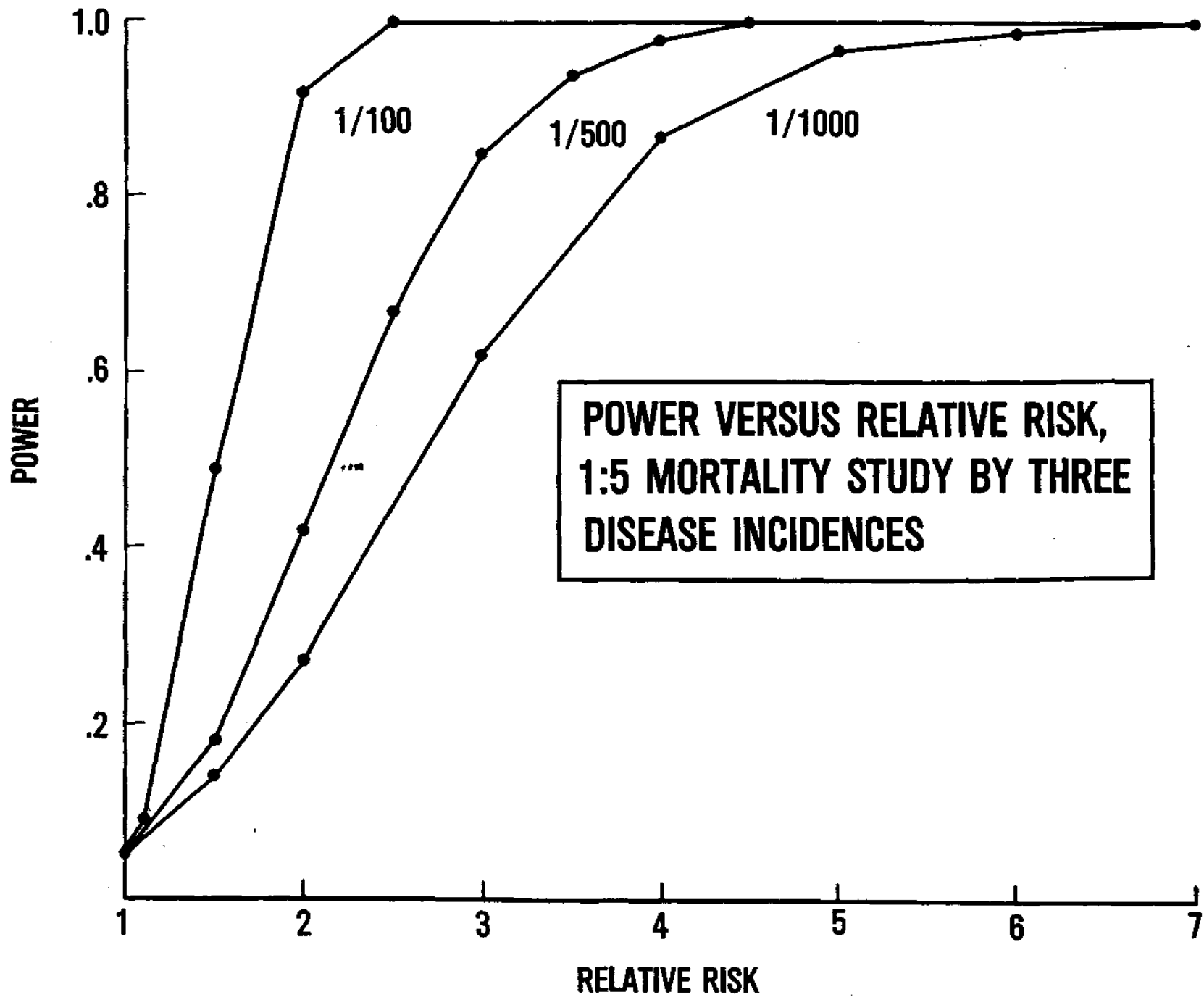
MORBIDITY STUDY
POWER — DICHOTOMOUS VARIABLES

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

$\alpha = 0.05$ (rows with r = 0)

$\alpha =$ AS INDICATED (rows with r = .1)

MORBIDITY STUDY
POWER-CONTINOUS VARIABLES

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

R	γ	POWER $= 1 - \beta$	
		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	$> .995$	$> .995$

MORTALITY-MORBIDITY STUDIES
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
250	> .99	> .995	.93	.95
300	> .99	> .995	.96	.97
350	> .99	> .995	.97	.98

$\alpha = 0.05$

REPLACEMENT CONCEPT

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

  MATANOSKI ET. AL., AMER. J. EPID., <u>101</u>, 1975

  SHEPS, MILBANK MEM. FUND., <u>44</u>, 1966

  ELVEBACK, JASA, <u>53</u>, 1958

- **ADDRESSES BIAS AND POWER CONCERNS**

  $$P(X) = \alpha \, P_c \, (X) + \beta \, P_{nc} \, (X)$$

  $$M = \alpha \, Mc + \beta \, Mnc$$

  $$BIAS = Mc - M$$

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"

H_1 = SUBJECTIVE HEALTH ASSESSMENT

H_2 = CURRENT USE OF LONG–TERM HEALTH CARE

H_3 = ABSENTEEISM

"LOGISTIC FACTORS"

L_1 = TIME FROM HOME

L_2 = TIME FROM WORK

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