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Research Protocol

**A Matched Case-Control Study of Soft Tissue Sarcoma**

Agent Orange Projects Office  
Department of Medicine and Surgery  
Veterans Administration

and

Department of Soft Tissue Pathology  
Armed Forces Institute of Pathology

March 1984

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## I. Introduction

There is much concern in the United States that many veterans report health problems that possibly stem from their military service in Vietnam. Their complaints include a wide variety of medical problems such as psychological, dermatological and physiological illnesses, reproductive disorders and even cancer. Agent Orange was the herbicide most commonly applied in Vietnam by the United States Air Force between 1965 and 1971. It was a mixture of the two commercial herbicides, 2,4-D (2,4-dichlorophenoxyacetic acid) and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid). The 2,4,5-T contained minute amounts of an extremely toxic chemical, dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin or TCDD), which contaminated the herbicide during the manufacturing process. TCDD is teratogenic and carcinogenic in experimental animals (Poland and Knutson, 1982; Kociba et al., 1978; NCI, 1980).

The possibility that exposure to the herbicide may induce rare forms of cancer in humans such as soft tissue sarcoma (STS) has been suggested from recent studies in Sweden (Hardell and Sandstrom, 1979; Hardell, 1981). The Swedish studies have shown that persons reporting exposure to phenoxy herbicides have a 5 to 6 fold higher risk of developing STS compared to persons without such exposure. A similar risk was reported by one of the Swedish investigators for malignant lymphoma (Hardell et al., 1981).

These significant observations have not yet been replicated by other research teams and studies by Finnish (Riihimaki, 1982) and New Zealand investigators (Smith et al., 1982) failed to show an association of STS with exposure to phenoxy herbicides. However, several confirmed cases of STS have been reported among workers involved in the manufacturing or use of phenoxy herbicides (Cook, 1981; Honchar and Halperin, 1981; Moses and Selikoff, 1981). These industrial workers, in contrast to the herbicide applicators, are believed to be exposed to relatively high levels of the TCDD contaminant.

Soft tissue sarcomas are a complex and diverse group of malignant neoplasms that originate in nonepithelial extraskeletal supporting structures of the body, excluding the hematopoietic-lymphatic system, the glia and supporting tissues of specific organs and tissues (Enzinger, et al., 1969). Soft tissue sarcomas account for about 1% of all malignant neoplasms and for about 2% of all cancer deaths. The average annual age-adjusted incidence rate is 3.89 per 100,000 and it is estimated that about 8,000 patients are diagnosed with STS each year in the United States (Cutler and Young, 1975). The most common histologic types are malignant fibrous histiocytoma, leiomyosarcoma, sarcoma not otherwise specified, liposarcoma and fibrosarcoma in that order.

Little is known about the etiology of STS. The epidemiologic study of STS has been especially difficult because of uncertainties in the morphologic classification of this diverse group of neoplasms. In addition, the International Classification of Disease (ICD), being site-oriented, does not distinguish between the heterogeneous types of sarcoma.

A small proportion of cases are probably related to Mendelian syndromes and the familial multiple-cancer syndrome (Tucker and Fraumeni, 1981; Blattner et al., 1979). An excess of STS has also been reported in patients receiving therapeutic immunosuppression for renal transplantation and other conditions (Hoover and Fraumeni, 1973; Kinlen et al., 1979). Some cases are associated with genetically determined immunodeficiency syndromes (Spector et al., 1978). Patients with chronic lymphocytic leukemia are also prone to STS (Greene et al., 1978).

There is very limited information on environmental risk factors for STS. A small fraction of STS is induced by heavy external radiation therapy for various benign disorders and malignant tumors. Nearly all cell types of STS have been described following radiation, the most common being fibrosarcoma (Kim et al., 1978; Czesnin and Wronkowski, 1978). Some radioactive materials used for diagnostic or therapeutic purposes may induce sarcomas at or near sites of deposition (Falk et al., 1979a; McKillop et al., 1978). The best known examples of associations between specific chemicals and STS of specific cell types is angiosarcoma of the liver and exposure to vinyl chloride or inorganic arsenical compounds. Among 168 deaths from hepatic angiosarcoma during 1964-1974 in the United States, 37 deaths were associated with vinyl chloride, thorotrast, or

inorganic arsenic (Falk et al., 1979b). The increased risk of developing STS among Swedish workers exposed to phenoxy herbicides or chlorophenols was described earlier.

In view of the concern raised by many veterans that their contact with Agent Orange during Vietnam service may increase the risk of developing STS and conflicting research findings in the scientific literature regarding association between exposure to phenoxy herbicides and STS, we have decided to conduct an independent epidemiologic study.

## II. Research Questions

### A. Phase I: Study based on the existing records

1. Does military service in Vietnam increase or decrease the risk of developing STS among veterans?
2. Is there a trend in the odds of developing STS with increasing probability of exposure to Agent Orange?
3. Does the histopathology and anatomic site of STS among Vietnam veterans differ from those of non-Vietnam veterans and non-veterans (i.e., individuals who never served in the military)?

### B. Phase II: Study based on the existing records and information obtained from interviews

4. What are the other host or environmental risk factors for the development of STS? Factors to be considered are:
  - (a) Occupational and non-occupational exposure to phenoxyacetic acids herbicides and other chlorophenols;
  - (b) Exposure to phenoxyacetic acid containing drugs such as clofibrate;
  - (c) Other factors such as genetic syndromes, immunologic deficiency, lymphedema, trauma and exposure to ionizing radiation, asbestos, arsenic, vinyl chloride and steroids.

### III. Study Design

A matched case-control study design will be used, in which individuals with STS (cases) are compared with individuals without STS (controls) with respect to Vietnam service, probable Agent Orange exposure and other possible risk factors. The case-control method is chosen primarily because it is well suited to the study of rare diseases (annual incidence of STS is 3.9/100,000), it is relatively quick and inexpensive, and it allows the study of multiple potential causes of the disease.

#### 1. Cases

Cases will be drawn from accession lists of the Armed Forces Institute of Pathology (AFIP). The AFIP offers a unique resource to contribute to this study. The AFIP routinely provides consultation services for pathologists throughout the United States, especially for conditions such as STS which present special diagnostic problems. One quarter to one third of the STS's occurring in the United States are sent to AFIP for review. Thus, the AFIP is one of the largest single registries in the world for this group of tumors. The uniformity and high quality of diagnoses at AFIP give it an added advantage as a resource for epidemiologic studies.

Selection will be restricted to males, who were diagnosed as STS patients sometime between January 1, 1975 and December 31, 1980 and were aged 20 to 40 at the time of diagnosis. These eligibility criteria are established 1) to restrict the study to persons who were potentially at risk of exposure to Agent Orange; that is, persons would have been aged 18 to 23 sometime during 1965 and 1971, the period when Agent Orange was most heavily used in Vietnam, 2) to allow a minimum of 4 years of latency period, and 3) to reduce selection bias by restricting the cases to those referred to AFIP before the recent publicity on Vietnam service (or Agent Orange exposure) and the risk of developing STS.

The subject of possible selection bias by restricting cases to those from the AFIP registry has been considered at length. It was concluded that if a decision to refer the cases to the AFIP was made without information on study factors (Vietnam service, Agent Orange exposure and other phenoxy herbicide exposure), the use of the AFIP registry for selecting cases is still valid.

In other words, unless there are differential referral patterns with respect to the presence or absence of study factors, one can make use of this unique resource for a valid epidemiologic study.

It will be almost impossible to prove that there was no selection bias. However, a limited review of AFIP registry data has shown that the proportion of "military age" (25-40 years old) cases among the total male soft tissue sarcoma cases and the total number of male cases referred to in the AFIP stay remarkably the same throughout the study period (1975-1980), which may indicate no large influx of military age cases to the AFIP. (see Attachment 1)

It is well demonstrated that misclassification of soft tissue sarcoma may present a greater problem than possible selection bias. In a recent paper Percy et al. (1981) of the NCI reported that only about 56% of the soft tissue sarcoma deaths coded on the death certificates were confirmed by hospital records. Furthermore, the National Institute for Occupational Safety and Health (Fingerhut et al., 1983) reported in a scientific meeting that two of the seven cases of soft tissue sarcoma cases previously reported in industrial workers which had generated much attention were found to be carcinomas. This determination was made by Dr. Franz Enzinger (AFIP) and his associate after reviewing all seven slides.

## 2. Controls

Controls will be selected from the patient logs of referring pathologists or their pathology department. This is to duplicate the selective factors (e.g., socioeconomic status, area of residency, etc.) which bring people to these hospitals or clinics. Excluded from consideration as controls will be diagnoses of STS, non-Hodgkin's lymphoma and Hodgkin's disease. The latter two conditions have been associated with exposure to phenoxyacetic acid herbicides, chlorophenols, or their contaminants (Hardell, 1981). A contact person in each referring pathology unit, usually a medical assistant or nurse, will be asked to select the two sequential patients who matched the case by race, sex and age: one with a malignant neoplasm, and one with a non-malignant disease in the log book following the STS case. A pilot study is needed to test the feasibility of this control selection method.



There are several reasons for choosing two controls per case: one control from other cancer patients and the other control from non-cancer patients. First, 2:1 matching will increase the statistical power of the study. This will be discussed in the following section. Second, possible recall bias and interviewer bias can be minimized by selecting other cancer patients as controls. The cancer patient may try harder to remember his exposure to well publicized chemical carcinogens and radiation. Recall bias may, therefore, occur when these patients are compared with individuals with no cancer. In addition, the interviewer may tend to probe the cancer patients or their families more intensively for histories of exposure than they might for the control subjects or their families. Third, on the other hand, it is also possible that exposure to phenoxy herbicides and chlorophenols may cause some of the cancers in the control group and this would mask an association between an exposure to these chemicals and STS. Having non-cancer patient controls would eliminate this possibility.

Recall bias or interviewer bias will not be a problem for Phase I, determining military service status, because this will be verified by records kept by the Veterans Administration\* and the National Personnel Records Center\*\*.

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\* VA BIRLS (Beneficiary Identification and Records Locator Subsystem). The Veterans Administration maintains a file of nearly 40 million computerized records known as the BIRLS file. It contains the veteran's name, date of birth and social security number and/or service numbers. Although Vietnam service is one of the information categories represented, this information is not provided on most of the records. Prior to 1972 only veterans who filed a claim for VA services were placed in the BIRLS file. Since January 1973 the names of all discharged veterans have been listed.

\*\* National Personnel Records Center (NPRC). The NPRC is the major repository for records of veterans who have been discharged from the service. This is believed to be the best records center for determining the Vietnam service status of veterans. Absence of the study subject's record in the center would indicate that he did not serve in the military or that he was still on active duty.

#### IV. Statistical Considerations

##### 1. Sample size determination

The number of people to be selected for the study depends on the specifications of four values: (1) the relative frequency of risk factor among controls in the target population,  $P_0$ , (2) a hypothesized relative risk associated with the risk factor that would have sufficient public health importance to warrant its detection,  $R$ , (3) the desired level of significance,  $\alpha$ ; that is, the probability of making an error of claiming that the risk factor under investigation is associated with disease when in fact it is not; (4) the desired study power,  $1-\beta$ ; that is, the probability of claiming that the risk factor is associated with disease when in fact it is.

Sample size for the study was determined under the following conditions:

- (1)  $\alpha = 0.05$
- (2)  $\beta = 0.2$  or  $1-\beta = 0.8$
- (3)  $R = 2$
- (4)  $P_0 = 0.05$
- (5) two sided test
- (6) two matched controls per case

Under these conditions we will need a total of 400 cases and 800 controls. Please see attachment 2 for detailed calculation. Assuming about an 80% success rate for obtaining appropriate records and information for other conditions, we will start with 500 cases of STS from the AFIP file.

## 2. Analyses of Data

The data will be analyzed using conventional epidemiologic and biostatistical methods including the following:

- a. When a single univariate binary risk factor is considered, the following matched analysis with two controls per case is used:

$$X^2 = \left[ \frac{P_2 - P_1}{\text{s.e.}(P_2 - P_1)} \right]^2 = \frac{[(m-1) B - mA]^2}{mB - \sum_{i=1}^N n_i^2}$$

$$P_1 = \frac{A}{N(m-1)}, \text{ The proportion of controls having risk factor}$$

$$P_2 = \frac{B - A}{N}, \text{ The proportion of cases having the risk factor}$$

where, A = the total number of controls with the risk factor

B = the total number of either cases or controls having the risk factor

N = the total number of matched triples

m = 3 (1 case + 2 controls)

$n_i$  = number of either case or controls having the risk factor within a given triple

$x_i$  = number of controls with the risk factor within a given triple

The odds ratio is calculated as follows:

$$O = \frac{(m-1) (B-A) - \sum_{i=1}^N x_i (n_i - x_i)}{A - \sum_{i=1}^N x_i (n_i - x_i)}$$

b. An attempt to explore the individual and joint effects of a number of variables will be made using multivariate statistical analysis based on the linear logistic model. This technique enables one to investigate the effect of several variables simultaneously in the analysis while allowing for the matched design (Holford et al., 1978; Breslow et al., 1978).

## V. Proposed Study Strategies

### A. Phase I: A study based on the existing records

#### 1. Case selection

- a. Tabulate all male STS cases referred to AFIP during January 1, 1975 and December 31, 1980 by specific diagnosis and by age.
- b. Identify from the AFIP records the males aged 20-40 at the time of diagnosis.
- c. Randomly select a total of 600 cases among all eligible cases.
- d. Obtain necessary information from AFIP records (name, age, name of pathologist and his location, etc.) for each case.

#### 2. Control selection

- a. Secure the consent of the pathologist whose patients will be approached to participate in the study.
- b. Select controls from pathology log books with the cooperation of referring pathologists or their assistants. Controls will be matched to case by sex, race (white, black, other), age\*. The first two eligible patients (one with cancer excluding STS, non-Hodgkin's lymphoma, and Hodgkin's disease and one with non-malignant disease) filed immediately after the case will be selected for controls.

#### 3. Determination of military service status

- a. Provide the National Personnel Records Center (NPRC) in St. Louis a listing or computer tape containing full names of both cases and controls, social security number and other identifying information obtained from the AFIP, referring pathologists and VA BIRLS.

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#### \* Age Criteria for Controls

<u>AFIP Accession Year of STS cases</u>	<u>Age Range for Controls</u>
1975	22 - 33
1976	23 - 34
1977	24 - 35
1978	25 - 36
1979	26 - 37
1980	27 - 38

- b. The NPRC will search and pull military personnel records for on-site review by VA contractor employees.
  - c. The contractor will review and extract necessary information from the file.
  - d. Cases or controls from non-military hospitals whose records are not kept in the NPRC could be either non-veterans (never served in the military), or still on active duty. However, if one assumes that active duty servicemen use military hospitals especially for the treatment of illness that requires referral to pathologists and since these cases and controls are from non-military hospitals it would be almost certain that they did not serve in the military or that they are on reserve duty.
  - e. The cases and controls from military hospitals will be referred to the military personnel records centers of each branch of service for ascertaining active duty status and obtaining appropriate military records.
  - f. The names and social security number (SSN) of cases and controls will be cross checked with the VA BIRLS file. The BIRLS file contains a record for each VA beneficiary and as of January 1973, BIRLS began including records for all veterans at separation from military service.
  - g. In collaboration with the Army Agent Orange Task Force, the VA will develop an Agent Orange exposure ranking scheme based on military unit and other information extracted from military records.
4. Initial analysis of data obtained from the available records.

The first three research questions listed on page 5 can be addressed with information obtained from the records.

B. Phase II

1. Locate cases and controls with help from pathologists, the surgeon's office and/or primary physicians. Since cases and controls medical records go back only a maximum of 9 years, it may not be insurmountable to locate them.

However, this effort will be complemented by the following tracing mechanisms:

- a. IRS-NIOSH-SSN
- b. Telephone directory
- c. Post Office
- d. State motor vehicle department
- e. Credit bureau

2. Develop a questionnaire and obtain OMB clearance.

3. Prepare introductory and informed consent letters and obtain consent of cases and controls, or their next-of-kin prior to conducting interviews, in accordance with existing regulations.

4. Develop an interview schedule. Conduct a pretest and make necessary revisions.

5. Conduct telephone interviews of the cases and controls, or their next-of-kin.

6. Review, edit and code all completed interviews.

7. Analyze data.

8. Final Report.



## VI. Confidentiality

Confidentiality of all records pertaining to individuals in the study will be carefully protected. Names of individuals will be used solely to locate persons for the purpose of determining their military service status and of interviewing. Personal identifiers will not be retained on any data record used for analysis, nor will they be included in any publication or other presentation of study results. Records with personal identifiers will be under the control of VA and AFIP investigators or their agents and will not be accessible to other individuals or groups.

## Acknowledgements

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## DISTRIBUTION OF POTENTIAL CASES BY CALENDAR YEAR

Calendar Year	Age	Potential Cases	AFIP Total
1975	22-33	81 (10%)	806
1976	23-34	70 (8.9%)	789
1977	24-35	75 (9.2%)	819
1978	25-36	69 (8.2%)	843
1979	26-37	74 (8.2%)	905
1980	27-38	71 (8.3%)	853

## Attachment 1B

MALE SOFT TISSUE SARCOMAS DIAGNOSED BY THE AFIP BY 5-YEAR AGE  
CATEGORY AND CALENDAR YEAR

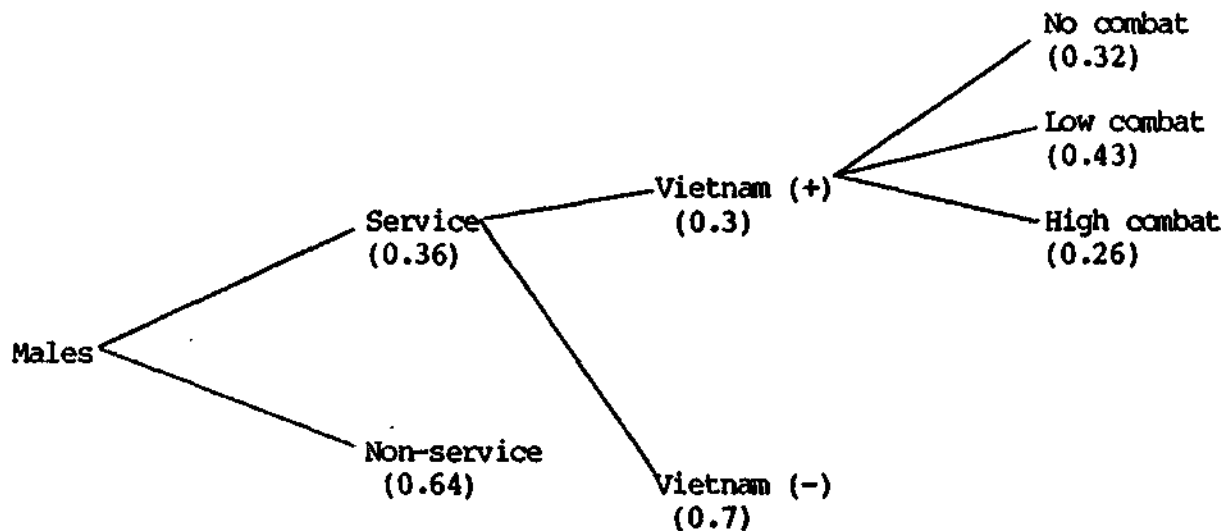
Calendar Year	Age Category				Total (0-75+)
	26-30	31-35	36-40	26-40	
1975	66	37	54	157 (19.5%)	806
1976	47	37	42	126 (16%)	789
1977	68	37	55	160 (19.5%)	819
1978	42	34	32	108 (12.8%)	843
1979	51	45	39	135 (14.9%)	905
1980	54	36	56	146 (17.1%)	853
	328	226	278	832	5,015

DISTRIBUTION OF POTENTIAL CASES BY  
TYPE OF MEDICAL INSTITUTE

<u>Hospital</u>	<u>Number</u>	<u>Percentage</u>
Civilian Hospital	354	80.5
Military Hospital	50	11.3
Army	(22)	
Navy	(11)	
Air Force	(17)	
Veterans Hospital	35	8.0
Public Health Service	1	0.2
	440	100.0

Attachment 2A

a. The relative frequency of the risk factor among controls in the target population,  $P_0$



(1) risk factor = Vietnam service/high combat duty

Assuming the servicemen in the Vietnam/High combat category were most likely exposed to Agent Orange, the  $P_0$  was calculated as follows:

$$P_0 = 0.36 \times 0.3 \times 0.26 = 0.029$$

(2) risk factor = Vietnam service

$$P_0 = 0.36 \times 0.3 = 0.11$$

(3) risk factor = Vietnam service/combat (high + low)

$$P_0 = 0.36 \times 0.3 \times (0.43 + 0.26) = 0.07$$

(4) risk factor = Occupational and non-occupational herbicide exposure NCI assumes  $P_0 = 0.1$



Attachment 2B

Sample Size and Power with Multiple Controls per Case (Ref: Case Control Studies, James J. Schlesselman, Oxford University Press, 1982, P 150-151)

$$n = \frac{[Z_{\alpha} \sqrt{(1 + 1/c) \bar{p} \bar{q}} + Z_{\beta} \sqrt{P_1 Q_1 + P_0 Q_0/c}]^2}{(P_1 - P_0)^2}$$

where  $p = (P_1 + cP_0)/(1 + c)$

$c = 1$  or  $2$

$P_1 = P_0 R/[1 + P_0 (R - 1)]$

$P_0 =$  Relative frequency of risk factor among controls in the target population.

$R =$  A hypothesized relative risk

$Q_1 = 1 - P_1$

$\bar{q} = 1 - \bar{p}$

STUDY POWER WITH TWO CONTROLS PER CASE

P <sub>0</sub>	100 Triplets			200 Triplets			300 Triplets			400 Triplets		
	R			R			R			R		
	1.5	2	3	1.5	2	3	1.5	2	3	1.5	2	3
0.05	14	34	72	27	56	94	30	72	98	38	82	99
0.10	20	52	91	35	79	99	48	92	99	59	97	99
0.15	26	63	96	45	89	99	60	97	99	72	99	99

alpha = 0.05

R = relative risk

P<sub>0</sub> = relative frequency of risk factor among controls in the target population

STUDY POWER WITH ONE CONTROL PER CASE

P <sub>0</sub>	100 Pairs			200 Pairs			300 Pairs			400 Pairs		
	R			R			R			R		
	1.5	2	3	1.5	2	3	1.5	2	3	1.5	2	3
0.05	10	23	55	17	42	85	22	56	96	28	69	99
0.10	15	39	80	27	65	98	37	82	99	46	92	99
0.15	20	50	90	31	79	99	48	92	99	59	97	99

alpha = 0.05

R = relative risk

P<sub>0</sub> = relative frequency of risk factor among controls in the target population

ID No. \_\_\_\_\_

VA/AFIP Soft Tissue Sarcoma Study

Hello, my name is [interviewer's name]. I am calling on behalf of the Veterans Administration. As you know from the letter you recently received from us, you have been selected to participate in a study of environment and health, sponsored by the VA and the Armed Forces Institute of Pathology. I would like to ask you some questions about your [or (name of study subject)'s] jobs, smoking habits, medical history and so forth.

Your participation in this study is voluntary. All of the information collected will be kept completely confidential and neither names nor any other identifying information will appear in any report of the study. The interview takes about a half hour to complete. Your participation in this study is most appreciated.

Please make yourself comfortable and let us begin.

Interviewer Initials \_\_\_\_\_

Date \_\_\_\_\_

Time Started \_\_\_\_\_ am/pm

### SECTION A - BACKGROUND INFORMATION

If the respondent is not study subject, list the relationship of respondent to study subject: \_\_\_\_\_

In the first section of the interview, I will ask you some questions about your (your \_\_\_\_\_) education, religion, background.

**IF THE RESPONDENT IS THE STUDY SUBJECT, GO TO A3.**

A1. How many years did you know your \_\_\_\_\_?

\_\_\_\_\_ # of years

A2. Approximately how many days per month did you talk or visit with your \_\_\_\_\_ during most of his adult life?

\_\_\_\_\_ Days/Month

A3. What is your ( \_\_\_\_\_ )'s date of birth?

\_\_\_\_\_ Month/Day/Year

A4. What city, county and state or foreign country were you (was your \_\_\_\_\_) born?

\_\_\_\_\_ City/State/County or Foreign Country

A5. How many years of schooling did you (your \_\_\_\_\_) complete?  
(Do not read categories to respondent.)

Less than 8 years	01
8 through 11 years	02
12 years or completed high school	03
Post high school training other than college (e.g., vocational or technical training)	04
Some college	05
College graduate	06
Postgraduate	07
Other (Specify) _____	08

SECTION A - BACKGROUND INFORMATION

A6. In what religion were you (was your \_\_\_\_\_) raised?  
(Do not read categories to respondent.)

None	01
Catholic	02
Jewish	03
Latter Day Saints (Mormon)	04
Protestant	05
Other (Specify) _____	06

Most people in the United States have ancestors who came from other part of the world. Some have mixed ethnic backgrounds.

A7. What is your racial background? Are you White, Black, Hispanic, Asian or Pacific Islander or American Indian or Alaskan native (Circle all that apply).

White	1
Black	2
Hispanic	3
Asian or Pacific Islander	4
American Indian or Alaskan native	5
Other _____	6

A8. What is your (\_\_\_\_\_ 's) father's ethnic background?

A9. What is your (\_\_\_\_\_ 's) mother's ethnic background?

RECORD BELOW. IF MORE THAN ONE ETHNICITY IS GIVEN FOR THE FATHER OR MOTHER, RECORD ALL THAT APPLY
--

Father's

English, Scotch, Welsh	01
French	02
German	03
Greek	04
Irish	05
Italian	06
Spanish, Portugese	07
Other European	08
Czechoslovakian	09
Russian	10
Other Eastern European (Polish, Lithuanian, etc.)	11

## SECTION A - BACKGROUND INFORMATION

## Father's

Scandinavian (Norwegian, Danish, Finnish, Swedish)	12
American Indian	13
Central American	14
Mexican	15
Puerto Rico	16
South American	17
West Indian	18
Chinese	19
Indian, Pakistani	20
Japanese	21
Other Asian Countries or Pacific Islanders	22
African	23
Middle Eastern	24
Other (Specify) _____	25
Unknown	26

## Mother's

English, Scotch, Welsh	01
French	02
German	03
Greek	04
Irish	05
Italian	06
Spanish, Portugese	07
Other European	08
Czechoslovakian	09
Russian	10
Other Eastern European (Polish, Lithuanian, etc.)	11
Scandinavian (Norwegian, Danish, Finnish Swedish)	12
American Indian	13
Central American	14
Mexican	15
Puerto Rico	16
South American	17
West Indian	18

SECTION A - BACKGROUND INFORMATION

Mother's

Chinese	19
Indian, Pakistani	20
Japanese	21
Other Asian Countries or Pacific Islanders	22
African	23
Middle Eastern	24
Afro-American	25
Other (Specify) _____	26
Unknown	27

A10. How tall are you (was your \_\_\_\_\_)?

\_\_\_\_\_  
Feet/Inches

A11. Before 19 , what was your ( \_\_\_\_\_ 's) usual adult weight?

\_\_\_\_\_  
Lbs.

A12. In 19 , were you (was your \_\_\_\_\_) married, widowed, divorced, separated or never married?

Married	1
Widowed	2
Divorced	3
Separated	4
Never married	5
Not sure	6



SECTION B - MILITARY HISTORY

Now I am interested in whether you (your \_\_\_\_\_) ever served in the U.S. military.

B1. Did you (your \_\_\_\_\_) serve in the U.S. military like the Army, Navy, or Air Force?

Yes	1
No	2
Not Sure	3

**IF NO OR NOT SURE GO TO B10.**

B2. In what years did you (your \_\_\_\_\_) serve in the military?

From \_\_\_\_\_ To \_\_\_\_\_

B3. Which branch did you (your \_\_\_\_\_) serve in?

(Read)	Army	1	Marines	4	Reserves	7
	Navy	2	Coast Guard	5	Not Sure	8
	Air Force	3	National Guard	6		

B4. Did you (your \_\_\_\_\_) serve in Vietnam?

Yes	1
No	2
Not Sure	3

**IF YES, CONTINUE, IF NO OR NOT SURE SKIP TO B8.**

B5. Could you tell me the names of places or areas in Vietnam where you (he) served?

\_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 Not Sure

B6. Do you think you were (he was) exposed to Agent Orange?

Yes	1
No	2
Not Sure	3

B7. How were you (was he) exposed?

Describe \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 Not Sure

SECTION B - MILITARY HISTORY

B8. When you (he) first entered the military were you (was he) drafted or did you volunteer?

Volunteer	1
Draft	2
Not Sure	3

B9. There is no requirement that you provide us your social security number or any other information for that matter. But we could get more information about your (his) troop movements from the military if we had your (his) serial number or social security number. Would you mind giving us them?

SSN	_____
Serial Number	_____
Not Sure	_____

B10. Were you in Vietnam for some reason other than military service?

Yes	1
No	2
Not Sure	3

**IF YES, CONTINUE; IF NO OR NOT SURE SKIP TO SECTION C.**

B11. could you tell me the names of places or areas in Vietnam where you (he) worked?

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
Not Sure

B12. Do you think you were (he was) exposed to Agent Orange?

Yes	1
No	2
Not Sure	3

B13. How were you (was he) exposed?

Describe \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
Not Sure

SECTION C - OCCUPATIONAL HISTORY

Now, I am interested in your (his) occupational history.

C1. First, what was your ( \_\_\_\_\_ 's) usual occupation during most of your (his) adult life, that is, the job you (he) held the longest?

\_\_\_\_\_  
Usual Occupation

**IF STUDY SUBJECT NEVER WORKED, CHECK HERE AND GO TO C24.**

C2. In what year did you (your \_\_\_\_\_) start working as a (usual occupation)?

\_\_\_\_\_  
Year

C3. In what year did you (your \_\_\_\_\_) stop working as a (usual occupation)?

\_\_\_\_\_  
Year

C4. What were your (his) activities or duties?

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
Activities/Duties

C5. For what kind of company did you (he) work, that is, what did they make or do?

\_\_\_\_\_  
Type of Company

C6. What is the name and location of this company?

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
Name and Location

SECTION C - OCCUPATIONAL HISTORY

Q. C7-C20. IF RESPONDENT ANSWERS YES TO PART A, ASK B-D, I.E., GO ACROSS ROWS BEFORE GOING DOWN THE COLUMNS

	a. Did you (your _____) ever work...	b. What is the name and location of the company or employer you (your _____) worked for?	c. In what year did you (your _____) first work...	d. In what year did you (your _____) last work...
C7...mixing or formulating pesticides	Yes 1 No 2		_____ Year	_____ Year
C8...treating seeds with fungicides	Yes 1 No 2		_____ Year	_____ Year
C9...on a highway, railroad, utility, or right-of-way maintenance crew?	Yes 1 No 2		_____ Year	_____ Year
C10...as a gardener, a landscaper, florist, or some other horticultural occupation?	Yes 1 No 2		_____ Year	_____ Year
C11...at a non-farm job applying pesticides, insecticides, herbicide or fungicides?	Yes 1 No 2		_____ Year	_____ Year
C12...as a veterinarian?	Yes 1 No 2		_____ Year	_____ Year

## SECTION C - OCCUPATIONAL HISTORY

	a. Did you (your _____) ever work...	b. What is the name and location of the company or employer you (your _____) worked for?	c. In what year did you (your _____) first work...	d. In what year did you (your _____) last work...
C13..in the chemical industry, for example, manufacturing drugs, or chemicals (other than pesticides)	Yes 1 No 2		_____ Year	_____ Year
C14..in a sawmill?	Yes 1 No 2		_____ Year	_____ Year
C15..in a wood-working occupation, for example, furniture or cabinet making?	Yes 1 No 2		_____ Year	_____ Year
C16..in the construction industry, for example, as a builder, painter or carpenter?	Yes 1 No 2		_____ Year	_____ Year
C17..machining metal or refining metal?	Yes 1 No 2		_____ Year	_____ Year
C18..in a job with exposure to radiation	Yes 1 No 2		_____ Year	_____ Year
C19..at an incinerator?	Yes 1 No 2		_____ Year	_____ Year
C20..in manufacturing or repairing electrical transformers and capacitors?	Yes 1 No 2		_____ Year	_____ Year
C21..in lumbering, logging, or forestry?	Yes 1 No 2		_____ Year	_____ Year

SECTION C - OCCUPATIONAL HISTORY

C22. While working at the various jobs did you (your \_\_\_\_\_) come in contact with any of the following substances:

	Yes	No	When
Asbestos	_____	_____	_____
Arsenic compounds	_____	_____	_____
Defoliant or herbicides	_____	_____	_____
Insecticides or pesticides	_____	_____	_____
Degreasing chemicals	_____	_____	_____
Vinyl chloride	_____	_____	_____
X-ray or nuclear radiation	_____	_____	_____

C23. Have you ever been exposed for a month or more to a job or work area which you think may have been harmful to your health (excluding accidents)?

Yes	1
No	2
Not sure	3

If yes,

Job/Occupation \_\_\_\_\_  
 When and for how many months? \_\_\_\_\_  
 Industry \_\_\_\_\_  
 What do you think the  
 harmful substance was? \_\_\_\_\_

C24. Did you (your \_\_\_\_\_) ever work or live on farmland?

Yes	1
No	2
Not sure	3

**IF NO OR NOT SURE GO TO C30.**

SECTION C - OCCUPATIONAL HISTORY

C25. When did you (he) work or live on farmland?

From \_\_\_\_\_ To \_\_\_\_\_

C26. Were herbicides, that is, weed killers or defoliants, ever used?

Yes	1
No	2
Not Sure	3

**IF NO OR NOT SURE, SKIP TO C30.**

C27. What are the names of the herbicides that were used?

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

C28. About how many days per year were you (was your \_\_\_\_\_) usually exposed to herbicides and how many years were you (was your \_\_\_\_\_) exposed to herbicides.

\_\_\_\_\_  
Days/Year

\_\_\_\_\_  
Total Year

C29. Did you (your \_\_\_\_\_) use any protective equipment when mixing or applying the herbicides, such as rubber gloves, masks, etc.?

Yes	1
No	2
Not Sure	3

C30. Before 19\_\_\_\_, did you (your \_\_\_\_\_) ever use herbicides, that is, weed killers or defoliants, at home, in yard work, for gardening, or for other purposes not previously discussed?

Yes	1
No	2
Not Sure	3

**IF NO OR NOT SURE, GO TO SECTION D.**

SECTION C - OCCUPATIONAL HISTORY

C31. What were the names of the herbicides or weed killers you (your \_\_\_\_\_) used?

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
Herbicides  
Not Sure

C32. For how many years did you (your \_\_\_\_\_) apply herbicides?

\_\_\_\_\_  
Years

C33. Have you (has he) been engaged in hobbies that involve the use of chemicals?

Yes	1
No	2
Not Sure	3

C34. What was (were) the hobby (hobbies)?

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

C35. What chemicals did you (he) use?

\_\_\_\_\_  
Chemical Name

C36. When did you first engage in that hobby?

\_\_\_\_\_  
Month/Year

C37. For how many years did you have that hobby?

\_\_\_\_\_  
Years



SECTION D - MEDICAL HISTORY

Now I would like to ask you some questions about your ( \_\_\_\_\_ )'s medical history.

D1. I am interested in medications and other medical treatments that you (your \_\_\_\_\_) may have taken. Before 19 \_\_\_\_\_, did you (your \_\_\_\_\_) ever:

	Yes	No	Not Sure	Year
a. Have your (his) tonsils removed?	1	2	3	_____
b. Receive radiation (for example, cobalt treatment, radioisotopes) as part of a medical treatment? (Emphasize "Before 19 ____".)	1	2	3	_____
i. To what part of the body did you (your _____) receive radiation treatment?	1	2	3	_____
	Part(s) of Body			
c. Take any cholesterol-lowering drugs, for example, clofibrate?	1	2	3	_____
d. Take any medications for seizures or epilepsy? Was it:	1	2	3	_____
Dilantin	1	2	3	_____
Phenobartital	1	2	3	_____
Mesantoin	1	2	3	_____
Hydantoin	1	2	3	_____
e. Take the drug chloramphenicol?	1	2	3	_____
f. Receive blood transfusion?	1	2	3	_____
g. Receive iron dextran, shots for anemia	1	2	3	_____
i. How many times?	_____			
ii. In which part of the body were the shots usually given?	_____			
h. Receive immunosuppressive therapy?	1	2	3	_____
i. Receive a drug to prevent from getting malaria? Was it:	1	2	3	_____
Dapsone	1	2	3	_____
Chloroquine	1	2	3	_____
Other (Specify color)	_____			
j. Apply a tar ointment to your (his) skin.	1	2	3	_____

D2. Before 19 \_\_\_\_\_, did a doctor ever tell you (your \_\_\_\_\_) that you (he) had (Disease)?

a. Chicken Pox	1	2	3	_____
b. Diabetes or sugar in your urine	1	2	3	_____

SECTION D - MEDICAL HISTORY

	Yes	No	Not Sure	Year
c. Allergies	1	2	3	_____
d. Infectious mononucleosis ("mono")	1	2	3	_____
e. Eczema	1	2	3	_____
f. Chloracne (a skin eruption resulting from a chemical exposure, not teenage acne)	1	2	3	_____
g. Heart disease	1	2	3	_____
h. Hypertension, high blood pressure	1	2	3	_____
i. Cancer (Specify Type/Site)	1	2	3	_____
j. Hepatitis, Jaundice, cirrhosis, or other liver disease	1	2	3	_____
k. Kidney stones or other urinary problems	1	2	3	_____
l. Systemic lupus erythematosus, SLE	1	2	3	_____
m. Celiac disease, nontropical sprue	1	2	3	_____
n. Neurofibromatosis, "Elephant man" disease	1	2	3	_____
o. Gardner's syndrome, familial polyps in colon	1	2	3	_____
p. Hemophilia	1	2	3	_____
q. Rheumatoid arthritis	1	2	3	_____
r. Other (1) _____				_____
(2) _____				_____
(3) _____				_____

D3. Before 19 \_\_\_\_, did you (your \_\_\_\_\_) ever have any serious injuries from accidents?      1      2      3

IF NO OR NOT SURE GO TO D7.

D4\*. What part of your (\_\_\_\_\_'s) body was injured?

- a.
- b.
- c.

D5. What type of injury did you (your \_\_\_\_\_) have?

- a.
- b.
- c.

D6. In what year were (was your \_\_\_\_\_) injured?

- a.
- b.
- c.

\*SPECIFY RIGHT OR LEFT, IF APPLICABLE

D7. Has anyone in your (\_\_\_\_\_'s) immediate family, that is, your (his) mother, father, brothers, sisters, or children, ever had cancer of any kind?      1      2      3

IF NO OR NOT SURE GO TO SECTION E.

SECTION D - MEDICAL HISTORY

D8. Please tell me who  
your (\_\_\_\_\_'s)  
relative was who had  
cancer.

D9. What was the kind  
of cancer?

D10. At what age was  
(disease) first dia-  
gnosed?

Relative  
Relative  
Relative  
Relative  
Relative  
Relative

Initial location  
Initial location  
Initial location  
Initial location  
Initial location  
Initial location

Age  
Age  
Age  
Age  
Age  
Age

SECTION E - SMOKING AND BEVERAGE HISTORY

Now, I would like to ask you some questions about your (his) smoking history.

E1. Before 19 , were you (was he) a cigarette smoker?

Yes	1
No	2
Not Sure	3

**IF NO OR NOT SURE GO TO SECTION E6.**

E2. Did you (he) usually smoke filter or non-filter cigarettes?

Filter	1
Non-filter	2
Not Sure	3

E3. How old were you (was he) when you (he) first regularly smoked cigarette?

\_\_\_\_\_ Age

E4. For how many years did you (he) smoke cigarettes?

\_\_\_\_\_ Years

E5. Before 19 , about how many cigarettes did you (he) usually smoke per day?

\_\_\_\_\_ Cigarettes/day

E6. Before 19 , did you (your \_\_\_\_\_) ever smoke cigars or a pipe for six months or longer?

Yes	1
No	2
Not Sure	3

E7. Before 19 , did you (your \_\_\_\_\_) ever chew tobacco or use snuff for six months or longer?

Yes	1
No	2
Not Sure	3

Now I would like to ask you some questions about beverages you (your \_\_\_\_\_) may have drunk.

SECTION E - SMOKING AND BEVERAGE HISTORY

E8. Before 19       , did you (your       ) regularly drink coffee?

Yes	1
No	2
Not Sure	3

**IF NO OR NOT SURE GO TO E13.**

E9. How old were you (was your       ) when you (he) first regularly drank coffee?

                      
Age

E10. How many years did you (your       ) drink coffee?

                      
Years

E11. Did you (your       ) usually drink decaffeinated coffee (i.e., Sanka, Brim, etc.) or regular coffee?

Decaffeinated	1
Regular	2
Not Sure	3

E12. Before 19       , how many cups of coffee did you (he) usually drink per day?

                      
Cups/Day

E13. Did you (he) drink alcoholic beverages sometime?

Yes	1
No	2
Not Sure	3

**IF NO OR NOT SURE GO TO SECTION F.**

E14. Before 19       , how many 4 ounce glasses of wine did you (your       ) usually drink in a week?

                      
Glasses/Week

E15. Before 19       , how many 1 1/2 ounce glasses of whiskey or hard liquor did you (your       ) usually drink in a week?

                      
Glasses/Week

E16. Before 19       , how many 12 ounces glasses or cans of beer, ale, or similar drinks did you (your       ) usually drink in a week?

                      
Glasses/Week

SECTION F - HEALTH HABITS/SOCIAL FACTORS

F1. Before 19 , did you (your \_\_\_\_\_) have a regular physician?

Yes . 1  
 No 2  
 Not sure 3

F2. Before 19 , how many hours of sleep did you (he) usually get at night?

6 hours or less 1  
 7 hours or more 2  
 Not sure 3

F3. Before 19 , did you (he) take any of these vitamins?

For how long?

Vitamins	No	Yes, every-day	Yes, some-times	For how many years	Amount	Not Sure
Multiple vitamins (One-a-day type)						
Vitamin A						
Vitamin C						
Vitamin E						
B complex						
Cod liver oil						
Nutritional yeast						
Other (Specify)						

F4. Before 19 , how many close friends did you (he) have? (People that you feel at ease with, can talk to about private matters, and can ask for help.)

None 1  
 1 or 2 2  
 3 or more 3  
 Not Sure 4

SECTION F - HEALTH HABITS/SOCIAL FACTORS

F5. Before 19 , how many relatives did you (he) have that you (he) feel close to?

None	1
1 or 2	2
3 or more	3
Not sure	4

SECTION G -CONCLUSION

That concludes the interview. Thank you very much for your participation in this study.

Time ended \_\_\_\_\_ am/pm

INTERVIEWER REMARKS

G1. Respondent's cooperation was:	Very good	1
	Good	2
	Fair	3
	Poor	4
G2. The respondent's:		
Did not know enough information regarding the topic		01
Did not want to be more specific		02
Did not understand or speak English well		03
Was bored or uninterested		04
Was upset or depressed		05
Was physically ill		06
Had poor hearing or speech		07
Was confused by frequent interruptions		08
Was emotionally unstable		09
Other (Specify)		10