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SRI International

A CASE-CONTROL STUDY OF THE RELATIONSHIP BETWEEN EXPOSURE TO 2, 4-D AND SPONTANEOUS ABORTIONS IN HUMANS

Final Report

August 14, 1981

Prepared for:

National Forest Products Association
and U.S. Department of Agriculture — Forest Service

File

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EXECUTIVE SUMMARY

A Case-Control Study of the Relationship Between Exposure to 2,4-D and Spontaneous Abortions in Humans

In May 1980, a study of the possible association of the phenoxy herbicide 2,4-D with human spontaneous abortions (miscarriages) was undertaken by SRI International. The study was sponsored jointly by the National Forest Products Association and the U.S. Department of Agriculture, Forest Service. Because 2,4-D is used extensively in the forests and farmlands of the Pacific Northwest, the states of Washington and Oregon were selected as the study's locale.

The study investigation identified two groups of people, "cases" and "controls," and then looked backward in time to see how their experiences with regard to 2,4-D exposure might have differed. The cases were women who had experienced a miscarriage in the previous 2 years. The comparison group (controls) were women of similar age and socioeconomic circumstance who had experienced a full-term delivery within this period.

The study population was identified from the ranks of grain farmers, forest workers, and herbicide applicators in the two Northwest states. Potential members of the population were first contacted by a postal questionnaire. In the second stage of data collection, all those reporting miscarriages and a random sample of those reporting live births in the postal questionnaires were interviewed extensively by telephone. Questions in the telephone interviews, which were addressed to husbands and wives separately, concerned work and home exposure, particularly during the 2-month time period around conception. Additional questions sought information on possible confounding variables such as cigarette smoking,

major illnesses, and the use of legal and illegal drugs. The telephone survey provided the primary data for the test of the hypothesis that spontaneous abortions might be associated with phenoxy herbicide exposures.

Considerable effort was expended in validating both occurrence of spontaneous abortions and occupational exposure. In examining the validated data, we noticed that the fact of occurrence (abortion or occupational phenoxy exposure) was more accurately recalled than the date of occurrence.

In conducting the analysis, data on farm and forest/commercial workers were treated separately. Occupational exposure, because of its frequency and dose implications, was emphasized over home and casual environmental exposures for two reasons: reporting of nonoccupational exposures is likely to be highly subjective and difficult to validate, and the exposures that did occur would probably be low. Therefore, the only type of exposure validated was occupational exposure.

The data on 134 miscarriages and 311 live births did not indicate a positive association between phenoxy herbicide exposure in males and subsequent spontaneous abortions in their wives. Stratifying the data for farm workers and forest/commercial workers also did not show an association. Although the overall comparisons did not support an association between paternal exposures and reproductive problems, in an isolated subgroup of wives of young forest/commercial workers (21 cases and 54 controls) there was a suggestive association with overall 2,4-D exposure, statistically significant at a low confidence level. No association was observed for the same age group in farmers.

Further investigation would be necessary to determine whether this latter finding is due to:

- A chance cluster, not unusual when multiple comparisons of variously grouped data are made.
- Undetected bias in the selection of the cases and controls of that subgroup.

- Association with a confounding variable that was inadequately controlled.
- A real association detected because of high fertility and high exposure in this subgroup.
- Some other cause.

In summary, the results of the study do not indicate any evident relationship between the use of 2,4-D and spontaneous abortion. The finding in young forest/commercial workers deserves further study, but does not in itself argue for restrictions on 2,4-D use pending such study.

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I INTRODUCTION AND OVERVIEW OF STUDY DESIGN AND PROCEDURES

In March 1980, the National Forest Products Association (NFPA) requested SRI International to examine the feasibility of conducting an epidemiologic study on the possible reproductive health effects of phenoxy herbicides (see Appendix A). One of the studies SRI proposed as a suitable way to address this issue was a retrospective case-control study of the possible association between exposure to 2,4-dichlorophenoxyacetic acid (2,4-D) and human spontaneous abortions. This is the report on the conduct and findings of that study, which was begun by SRI in May 1980. The U.S. Department of Agriculture--Forest Service subsequently joined NFPA in the sponsorship of the study.

It was clear that a prospective cohort study design was both inefficient and too lengthy a process for the client's needs. An alternative conventional case-control approach using cases ascertained from hospital or medical records creates two problems. The first problem is the extreme difficulty of access to records to identify potential cases as well as the problem of obtaining the patient's consent to participate. The second problem is that for cases identified in this manner the proportion of cases exposed to phenoxy herbicides would be very low, thus necessitating an enormous sample size to adequately test the exposure hypothesis. To overcome the above problems, a base population consisting of males who were occupationally exposed and those who were unexposed was identified. Wives were able to identify themselves as having had a recent spontaneous abortion or a live birth through their response to a postal questionnaire that was sent to the base population. Cases (spontaneous abortions) and controls (live births) were therefore selected without reference to their husband's exposure status from a cohort that was known to be at high risk of occupational exposure.

Since it is most likely that the rate of spontaneous abortions is an indication of male exposure to damaging factors affecting spermatogenesis, male occupational exposure was the primary focus of the study. The exposure received occupationally is presumably of greater intensity and longer duration than exposure received in any other manner. If there is a cause and effect relationship, it would become apparent in an occupationally exposed group.

Because 2,4-D is used extensively in the forest and farmlands of the Pacific Northwest, the base population was selected from the states of Oregon and Washington. The feasibility study had created a network of cooperation between SRI and the governments, industries, and agricultural associations of the two states. Public interest in and concern over the 2,4-D issue was high, and these groups were willing to participate in the study in an attempt to help answer the questions that were being raised. This cooperation made it possible to create the base population, consisting of employees of major users of 2,4-D such as government forest services and private forest industries; members of farm and ranch associations with a high rate of 2,4-D use; private, commercial, and governmental applicators licensed by each state; and others occupationally exposed to 2,4-D. The economic bases, industries, and farming as well as 2,4-D use practices are very similar within the two states.

The postal questionnaire was the first stage of data collection. It included general questions regarding recent pregnancies and demographic characteristics such as age, education, health status, and residence history. Its sole purpose, however, was to identify potential cases and controls from within the base population. The few vague questions concerning exposure were not used in any subsequent analysis of the association hypothesis.

In the second stage of data collection, all women reporting miscarriages and a random sample of those reporting live births in the postal questionnaires were interviewed extensively by telephone. Questions in the telephone interview were addressed to husbands and wives separately

and concerned work and home exposure, particularly during the 2-month time period around conception. Also included were additional questions on possible confounding variables such as cigarette smoking, major illnesses, and the use of legal and illegal drugs.

The sample size for the telephone interviews was chosen to be able to detect with 80% certainty a doubling of the relative risk for spontaneous abortion due to exposure to 2,4-D, assuming that 50% of the study population is exposed. The study population was selected so that approximately 50% of the participants would be occupationally exposed to 2,4-D. Since analysis of other types of 2,4-D exposure (e.g., exposure at home, maternal exposures, etc.) could involve exposure rates significantly different from 50%, a resultant reduction in statistical power for these analyses would be expected.

Considerable effort was expended in trying to validate both occurrence of spontaneous abortions and occupational exposure. Neither of these tasks is easy; in fact, for either variable, complete validation is impossible. Validation of male occupational exposure during the 2-month time period around conception was conducted by contacting the husbands' employers or co-workers, or obtaining records of herbicide spraying or spray practices. Validation of reproductive outcomes was carried out for all cases (miscarriages) through the wives' physicians or hospital records; confirmation of the date of conception was sought, as well as confirmation that a spontaneous abortion did in fact occur.

Throughout the study, appropriate precautions were taken to ensure confidentiality, including file security and the removal of identifiers before data processing.

II STUDY DESIGN AND PROCEDURES

Identification of Study Population

From information gathered during the feasibility study (see Appendix A), several occupational groups known to use 2,4-D were identified and, along with an occupationally unexposed group, were selected to comprise the potential study population. The objective was to select a population in which approximately 50% of the male participants were occupationally exposed to 2,4-D. The seven groups of employers and associations listed below were chosen with this objective in mind and yielded a list of 14,747 names of potential study participants (after apparent duplicates were identified and removed).

- Farm Groups

  Oregon: Cattlemen's Association, Seed Council, Wheat Growers League, and Dairymen's Association.

  Washington: Cattlemen's Association, Association of Wheat Growers, and State Dairymen's Federation.

  These groups include members of agricultural associations representing the three largest farm industries in the two states: livestock, wheat/seed, and dairy. These farm industries are known to be heavy users of 2,4-D. Most farms and ranches in Oregon and Washington are family owned and operated, without a large migrant population of farm workers. This fact made it easier to identify and keep track of the farm population.

- Forest Industry

  All private companies owning more than 50,000 acres of timber in either Oregon or Washington (over 20 companies) were asked to supply lists of employees who, in the course of their work, may have been exposed to 2,4-D sometime since January 1, 1978. It was specified that the lists should include not only licensed applicators of 2,4-D but also men who may have been exposed by working with licensed applicators or by working in recently sprayed areas or within a half mile of these areas.

The same forest industry companies were asked to provide lists of mill workers to be included in the study population to ensure adequate representation of occupationally unexposed study participants. Both exposed and unexposed forest industry groups are blue-collar workers with similar lifestyles and residence locations. Mill workers involved with paper, bark, and particleboard were excluded since they are subject to a number of possibly confounding chemical exposures. (It was not possible, however, to screen out so-called "green chain" workers, who may be exposed to chlorophenol.)

- Forest Service

  Oregon State Forest Service, Washington State Department of Natural Resources, United States Forest Service, Bureau of Land Management.

  These forest service agencies were asked to identify those employees currently holding jobs involving a high probability of either direct or indirect exposure to 2,4-D.

- Licensed Applicators

  Licensed applicator lists from both the Oregon and Washington State Departments of Agriculture included private, governmental, commercial, consultant, and trainee applicators.

  A 25% random sample from these lists provided a large enough number of licensed applicators for them to be well represented in the base population. Most of the private applicators were farmers, including some of the members of the farming associations listed above. Government applicators included the licensed applicators who were on the forest service exposed employee lists.

- Transportation

  Oregon State Highway Department, Washington State Highway Department, Washington County Road Administration.

  These employers submitted lists of employees currently holding jobs involving a high probability of either direct or indirect exposure to 2,4-D.

- Utilities

  Bonneville Power Administration, Oregon; Puget Sound Power and Light, Washington; Portland General Electric, Oregon; Oregon and Washington Irrigation Districts.

  These employers in the utilities industry submitted lists of employees with a high probability of being occupationally exposed to 2,4-D.

- Formulators and Manufacturers

  Rhone-Poulenc, Incorporated, Portland, Oregon; Charles H. Lilly Company, Portland, Oregon.

  Employers from these two companies that formulate or manufacture 2,4-D provided lists of employees who were potentially occupationally exposed to this herbicide.

These employers and associations were asked to provide names and home addresses for married men, age 35 or younger, living in either Oregon or Washington. It was not always possible, however, for these sources to furnish such highly selective employee or member lists; the lists of licensed applicators, for example, could not be screened for age or marital status. The decision to include only married men age 35 or younger was made to increase the probability that wives of these men would have experienced a pregnancy sometime since January 1, 1978. The study period was chosen to be as recent as possible to maximize female recall of reproductive events and male recall of exposure.

Data Collection

Stage I: Postal Questionnaire

A short postal questionnaire (see Appendixes B and C) with a cover letter was sent to the 14,747 people identified in the base population. The postal questionnaire was designed to screen this potential study population for ultimate selection of cases (miscarriages) and controls (live births) and to obtain basic information about certain demographic variables. These demographic variables included residence history, age, education, and health status. In addition, questions about exposure to herbicides in general, as well as phenoxy herbicides in particular, were included in order to obtain preliminary estimates of exposure.

An unusually high number of calls were received from early questionnaire recipients who demanded more specific information about the study. Their questions concerned who funded the study, what was SRI, how

did SRI get their names, what exactly was the study trying to prove, etc. The callers were usually very satisfied with the answers they received and responded that they would now send in their completed questionnaires. In an attempt to maximize the response rate, a second copy of the questionnaire was sent out to all nonrespondents, with a rewritten cover letter providing more detailed information regarding the study (see Appendix D).

During the course of the mail survey a record was kept of the dates on which the first and second copies of the questionnaire were mailed, and it was possible to identify the separate contribution of each version to the responses received. Seventy-two percent of all respondents responded to the first questionnaire. Moreover, among eligible respondents this contribution was an even higher 81%. A larger percentage of ineligible responses was received in response to the second copy of the questionnaire.

As completed questionnaires were received, a running tally was kept that categorized the eligible responses by reproductive outcome. In the series of tallies there was no observed change in the distribution of outcomes. The proportion of women reporting miscarriages compared with those reporting live births did not change as a result of the second cover letter that stated the hypothesis of the study in more detail.

Of the 14,747 families contacted, 8,287 (56.2%) ultimately responded to the postal questionnaire.* Figure 1 illustrates this stage, and subsequent stages, of developing the study population.

Because of the relatively high nonresponse rate, a limited sample of 48 of the nonrespondents were contacted by telephone. The majority of these 48 nonrespondents (56%) admitted that they did not fill out the questionnaire because of its apparent lack of importance or relevance to them. Four of the nonrespondents were male-only households; 22 of the 44 women had not

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* If the 802 nondeliverable questionnaires are discounted, the response rate is 59.4%.

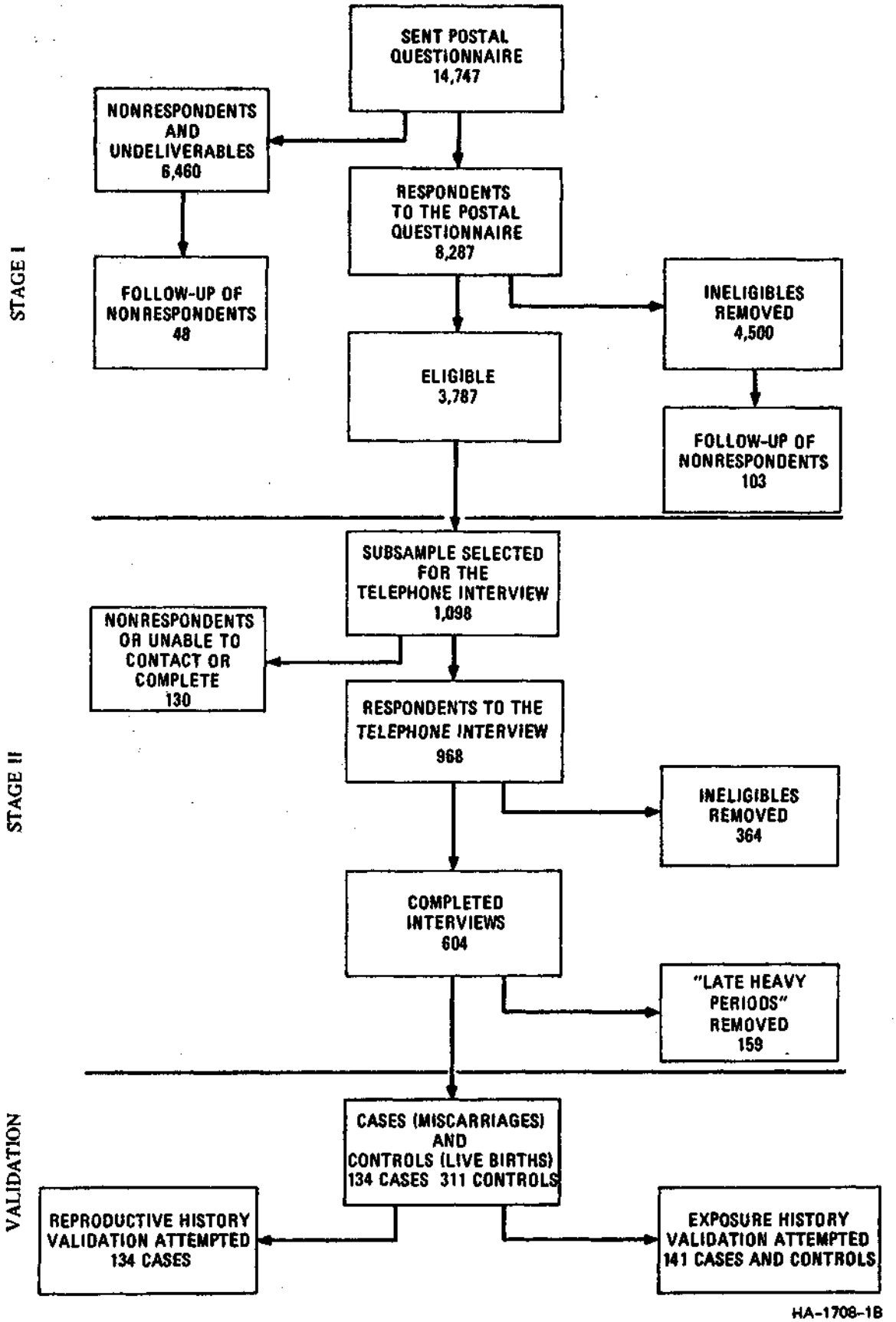

FIGURE 1 FLOW CHART OF DATA COLLECTION

been pregnant since January 1, 1978 (the beginning of the study period); and 22 had been pregnant at least once. Of those pregnancies that occurred since January 1, 1978, no miscarriages were reported.

Of the 8,287 completed questionnaires received, 3,787 respondents were identified as being eligible for further follow-up as possible study participants. The criteria for eligibility were that both husband and wife must have responded to the questionnaire, and both must have been 35 years of age or younger.

A random sample of the questionnaire respondents who did not report a pregnancy or an unusually late and heavy period after January 1, 1978, were followed up by telephone and re-asked those questions. Of these 103 ineligible respondents, 101 verified their original response to the questionnaire, and 2 noted that they had experienced a live birth in 1978 but that the conception had occurred before January 1, 1978.

Stage II: Telephone Interviews

Of the 3,787 tentatively eligible respondents, a subsample of 1,098 reporting a pregnancy or late heavy period sometime in the past 2 years were selected for an extensive telephone interview conducted by a separate survey research organization. This subset of the total eligibles comprised a random sample of couples reporting live births during the study period, a random sample of those reporting an unusually late and heavy period, and all those reporting a miscarriage.

The telephone interview was designed to elicit detailed information about the reproductive history of the female and the occupational and home exposure histories for the female and the male. In addition to this information, questions were asked concerning infant health, infant sex, residence history, work history, birth control and infertility history, smoking history, marijuana use, the use of prescription drugs, and exposure to herbicides other than 2,4-D (see Appendix H).

At the conclusion of each telephone interview, an extensive field edit was carried out to check for interview completeness, consistency, and legibility. Any inconsistencies were rectified by recontacting the respondent. Interviews were successfully completed for more than 88% (968) of the telephone interview population; 7% (76) of the interviews could not be successfully completed because of inability to contact the family by phone, refusal to cooperate with the interview, etc.; and 5% (54) of the interviews the survey research organization did not have enough time to initiate.

Of the 968 completed interviews, 364 (see Appendix E) were excluded from the final study population for a variety of reasons, such as not living with the current partner during the time of conception, living outside of Oregon or Washington during the time of conception, and reporting a pregnancy on the postal questionnaire for which the conception date occurred prior to January 1, 1978. In addition, women who reported having had a miscarriage but who also had experienced more than one therapeutic abortion in their lifetime also were deleted from the study. (It was felt that multiple therapeutic abortions might act as a possible confounding factor.) Only one woman became ineligible because of this criterion. At this point, the number of eligible couples was 604.

As noted previously, completed interviews included as potential cases those women who reported having had a late and heavy period. Because of the difficulties in validating this event and since there were enough reported miscarriages in the data base at this point to guarantee sufficient cases for a meaningful statistical analysis, the 159 couples reporting only a late and heavy period were removed from the study population. The final study population comprised 445 eligible couples.

Definitions and Validation of Reproductive Outcome

Since 129 of the 445 eligible couples (30%) reported more than one pregnancy during the study period, it was decided to use only the most

recent pregnancy in the hope of maximizing the accuracy of the pregnancy and exposure history recall. For the 55 instances in which both a live birth and miscarriage were reported during the study period, only the miscarriage information was used. (However, a special matched-pairs analysis was also conducted separately for this subset of cases.) In this manner, 134 cases (miscarriages) and 311 controls (live births) were included in the final study population (see formal definition of cases and controls, Appendix F).

Attempts were made to validate all reported cases to confirm (via physician or hospital records) that a miscarriage had, in fact, occurred and that the identification of the two months surrounding conception (the month of the last reported menstrual period plus the month of the first missed period) was also correct. The controls were not validated since it appeared unlikely that a woman would fabricate the birth of a child or forget its birth date.

Validation was attempted for all 134 of the cases and successfully completed for 75 (56%) of them. Miscarriages could not be verified if the woman did not see a doctor about her miscarriage, if her doctor could not be located, or if either the woman or her doctor refused to cooperate with the validation process. Of the 75 successful validations, 69 (92%) were confirmed miscarriages. In five of the six unconfirmed cases, the doctors felt that there was insufficient proof of pregnancy for them to diagnose a miscarriage; the other case was a hydatid mole pregnancy.

The conception date (as defined by the date of the last menstrual period) was confirmed for 29 of the 75 validated cases. Of the remaining 46 cases reporting an inaccurate date, approximately 37% erred by more than 1 month in recalling their last menstrual period.

Definitions and Validation of Exposure History

Male exposure to 2,4-D, which could potentially affect spermatogenesis, was considered the most likely mechanism linking 2,4-D exposure to

spontaneous abortions. Since human sperm have a life span of only 3 to 8 weeks and since 2,4-D is rapidly eliminated from the human body,* the critical 2,4-D exposure period for this investigation was determined to be the time immediately surrounding the date of conception. The 2-month conception period (defined by the month of the last menstrual period plus the month of the first missed period) used in this study allowed for a margin of error in identifying the exact date of conception and also made it possible to study the potential for an abortive effect due to maternal exposure very early in the pregnancy.

Occupational exposure was assumed to be generally a more concentrated exposure and to involve more days per year than home exposure. Those who were exposed occupationally would therefore be more likely to be at higher risk than those who were unexposed occupationally. Home exposure was not considered to be a negligible exposure, however; and the respondents were queried regarding home exposure, both during the 2-month time period around conception and since January 1, 1978. The questions regarding these four categories of exposure (occupational and at home, for the 2-month time period and since January 1, 1978) were also directed toward women. Eight composite exposure variables were constructed from individual questions within the telephone interview (see Appendix G).

Through review of the literature and interviews with experts knowledgeable about herbicide use in Oregon and Washington, it was learned that the most common methods of application are backpack spraying (mist blower and hand pump), injection, ground application (truck and tractor), and aerial application (airplane and helicopter). Those who apply 2,4-D are very likely to be exposed as a result of inhalation of spray or mist, ingestion via splashes, eating or smoking when hands are wet with 2,4-D, and/or dermal contact from splashes, spray, mist, wet foliage, or

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* 2,4-D has a half-life in the body of less than 2 days, and nearly complete elimination takes place within 4 to 6 days. (Hazard Alert Systems, Epidemiological Studies Laboratory, State of California, Department of Health Services, Department of Industrial Relations, June 16, 1980.)

application equipment. Protective clothing (rubber boots, gloves, coveralls, masks, etc.), when worn, very rarely prevent exposure entirely.

With this information in mind, specific questions regarding exposure were formulated, and three categories of work exposure were established. A "high" exposure level classification was assigned to those who were directly exposed in the manufacture, formulation, mixing, or application of 2,4-D (see Appendix I, questions 7b and 8), a "medium" exposure to those who were indirectly exposed by having been in an area that was being sprayed or who came in contact with 2,4-D after it was applied (see Appendix I, questions 9 and 10), and a "low" exposure classification to those who were not exposed at work (see Appendix I, question 6). Further confirmation of exposure was established by asking whether the respondents actually inhaled, ingested, or came into physical contact with 2,4-D as a result of the specified work activities (see Appendix I, questions 12 and 14). The possible mitigating effects of protective clothing were incorporated into question 15 (see Appendix I). The same format was followed in determining the exposure of women at work (see Appendix H, questions 103b and 104, 105 and 106, 102, 108 and 110, 111).

Similarly, the most common forms of home and leisure exposure to 2,4-D were defined. This type of contact included walking through foliage recently sprayed with 2,4-D, washing or handling work clothes that had been wet with 2,4-D, home garden use of broad-leaf-weed herbicides containing 2,4-D (trade names of the most popular home herbicides containing 2,4-D were read to the respondents), and living within 1 or 2 miles of an area where aerial spraying of 2,4-D had taken place. No attempt at a graded classification was made in the definition of home exposure status levels. Only a simple "yes" or "no" defined exposure status (see Appendix I, questions 23-26; Appendix H, questions 119 and 122).

For the final analysis, combinations of responses to the above specific questions in the telephone interview were used to construct the eight exposure variables. In all these definitions, a multiple ascertainment scheme was used to lessen the distortion resulting from error on individual

questions (see Appendixes H and I.) Early in the analysis, the "high" and "medium" (direct and indirect) levels of exposure were combined and classified as "exposed" and the "low" as "not exposed" since the number of responses within each single level was too small to analyze separately. Therefore, no interpretation of a dose effect from these responses was possible.

Since an individual's responses to occupational exposure questions were dependent on the recall of events covering a 2-1/2-year period, validation of this critical exposure for the 2-month period around conception was considered essential. Accordingly, an attempt was made to validate the work exposure for all men reporting "high" or "medium" exposure during the reported conception period of their spouses and for a sample of those men who were reportedly unexposed during the 2 months around conception but reportedly exposed at some time during the study period. The validator was not aware of the case/control status of the wife.

While the strength of validation varied according to the source of verification (e.g., written records of exposure dates, signed statements from co-workers or supervisors, etc.), any exposure for which a validation attempt failed to provide more information than was contained in the respondent's original telephone interview was not considered a verifiable exposure.

In all, work exposure validation was attempted for 141 male respondents and successfully completed for 108. Of these 108 successful exposure validations, 80 original responses were confirmed and 28 were found to be somewhat inconsistent with the original interview responses. Many more "high" exposures became "low" exposures after validation than the other way around. This 74% confirmation of seven responses concerned with male work exposure seemed to indicate a reasonable awareness by husbands of their occupational exposures to 2,4-D.

III RESULTS

Postal Questionnaire

Table 1 shows the various list sources by response category. Approximately 33% of the names to whom the 14,747 postal questionnaires were sent were taken from lists of private applicators. Of this group, 61% responded, 8% were undeliverable, and 31% did not respond. The other major source of names was the lists of mill workers, which contributed 30% of the total persons to whom questionnaires were sent. The response rate for this group was the lowest, 48.4%. Commercial applicators (3.3% of total solicitated) responded more than any other group (73%).

In Table 2, the distribution by list source of eligible respondents to the mail questionnaire is compared with the final subsample of 445 cases and controls. Overall, the distribution by list source is similar for the two groups. Notice, however, that compared with their proportion among eligible respondents, government applicators are underrepresented and commercial applicators are overrepresented in the case-control subsample. Also, compared with their fraction of the total number of questionnaires mailed out (see Table 1), a smaller fraction of private applicators (19% compared with 33%) and a larger percentage of mill workers (41% compared with 30%) are represented in the subsample of cases and controls. The apparent underrepresentation of the private applicators was due primarily to the fact that a large number of subjects in this group were over age 35.

As noted previously, the employer and association list sources were selected for the study with the hope that about 50% of the males would be exposed occupationally to phenoxy herbicides. The responses on the mail questionnaires (see Table 3) indicated that 54% of the eligible male respondents had been exposed to these herbicides at some time. In addition,

Table 1

DISTRIBUTION OF POSTAL QUESTIONNAIRE RESPONSE CATEGORIES AND RATES BY LIST SOURCE

List Source	Respondents		Undeliverable		No Response		Total Solicited	
	Number	Row Percent	Number	Row Percent	Number	Row Percent	Number	Percent of Total
Farm groups	1,292	56.2	54	2.3	954	41.5	2,300	15.6
Private applicators	2,958	61.0	388	8.0	1,503	31.0	4,849	32.9
Total farm	4,250	59.4	442	6.2	2,457	34.4	7,149	48.5
Forest industry	225	69.9	10	3.1	87	27.0	322	2.2
Forest service	409	60.9	50	7.4	213	31.7	672	4.6
Transportation	224	51.6	10	2.3	200	46.1	434	2.9
Utilities	102	51.3	1	0.5	96	48.2	199	1.3
Government applicators	589	54.1	114	10.5	385	35.4	1,088	7.4
Commercial applicators	356	73.0	13	2.7	119	24.3	488	3.3
Formulators	22	59.5	2	5.4	13	35.1	37	0.3
Mill workers	2,110	48.4	160	3.7	2,088	47.9	4,358	29.5
Total forest/commercial	4,037	53.1	360	4.7	3,201	42.1	7,958	51.5
Total	8,287		802		5,658		14,747	100.0

36.4% of eligible female respondents also reported exposure to phenoxy herbicides. The fact that only 20% of 3,787 eligible respondents were not sure about exposures to phenoxy herbicides is remarkable and indicates a considerable awareness among the population as to the types of herbicides being used.

Table 2

DISTRIBUTION OF ELIGIBLE RESPONDENTS TO POSTAL QUESTIONNAIRE AND CASES/CONTROLS BY LIST SOURCE

List Source	Eligible Respondents		Cases/Controls	
	Number	Percent of Total	Number	Percent of Total
Farm groups	580	15.3	77	17.3
Private applicators	645	17.0	84	18.9
Total farm	1,225	32.3	161	36.2
Forest industry	178	4.7	26	5.8
Forest service	299	7.9	29	6.5
Transportation	179	4.7	15	3.4
Utilities	34	0.9	1	0.2
Government applicators	154	4.1	9	2.0
Commercial applicators	121	3.2	21	4.7
Formulators	21	0.6	2	0.5
Mill workers	1,576	41.6	181	40.7
Total forest/commercial	2,562	67.3	284	63.8
Total	3,787	100.0	445	100.0

Out of the 3,787 eligible respondents, 1,714 (46%) reported being pregnant within the past 2 years, 574 (33%) of these coming from the farm group and 1,140 (67%) from the forest/commercial group. Of the 1,714 pregnancies, 187 women (11%) reported having a miscarriage during this period, and 60 women (3.5%) had a therapeutic abortion; 12 women (0.7%) reported a stillbirth.

Table 3

DISTRIBUTION OF REPORTED EXPOSURE TO HERBICIDES AND PHENOXY HERBICIDES IN THE LAST TWO YEARS

Eligible Respondents to the Postal Questionnaire

	Eligible Respondents			
	Male		Female	
	Number	Percent	Number	Percent
Exposure to herbicides in general				
Never	780	20.6	1,447	38.4
Once or twice	725	19.1	1,012	26.9
Three or more times	2,274	60.3	1,307	34.7
Missing	8		21	
Total	3,787		3,787	
Exposure to phenoxy herbicide				
No herbicide exposure	767	20.6	1420	38.2
Herbicide exposure but not phenoxy	231	6.2	268	7.2
Herbicide exposure some phenoxy	840	22.5	664	17.9
Herbicide exposure most phenoxy	1,175	31.5	687	18.5
Not sure	716	19.2	677	18.2
Missing	58		71	
Total	3,787		3,787	

To examine how well the ultimate case-control sample reflected the base population of eligible respondents, we compared both groups with respect to the distribution of several key characteristics: reported exposure, exposure to phenoxy herbicide, age distribution, educational level, and health status (see Tables 3 and 4). We found no significant difference in the distribution of any of the above characteristics except for age. Since the study design employed selects for women reporting a pregnancy during the

Table 4

AGE, EDUCATION, AND HEALTH STATUS OF
ELIGIBLE RESPONDENTS AND CASES/CONTROLS

	Eligible Respondents				Cases/Controls			
	Male		Female		Male		Female	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Age (years)								
18-21	88	2.3	295	7.8	5	1.1	38	8.5
22-25	602	15.9	1,001	26.4	93	20.9	164	36.9
26-30	1,586	41.9	1,582	41.8	223	50.1	187	42.0
31-35	1,510	39.9	909	24.0	124	27.9	56	12.6
Missing	1							
Total	3,787		3,787		445		445	
Education (grades completed)								
Grade 8 or below	21	0.6	14	0.3	2	0.4	2	0.4
Some high school	231	6.1	307	8.1	19	4.3	32	7.3
High school graduate	1,105	29.2	1,340	35.4	119	26.7	150	33.7
Vocational, technical school	364	9.6	375	9.9	43	9.7	37	8.5
Some college	1,121	29.7	1,098	29.1	150	33.7	139	31.2
College degree(s)	936	24.8	649	17.2	112	25.2	85	19.1
Missing	9		4					
Total	3,787		3,787		445		445	
Health status (self-assessment)								
Poor	10	0.3	12	0.3	--	--	1	0.2
Fair	106	2.8	145	3.8	13	2.9	23	5.2
Good	1,213	32.2	1,376	36.6	132	29.9	149	33.8
Excellent	2,440	64.7	2,229	59.3	297	67.2	268	60.8
Missing	18		25		3		4	
Total	3,787		3,787		445		445	

last 2 years, cases and controls would tend to represent those eligible respondents actively trying to have children. Thus, the observed bias toward the inclusion of younger couples is expected.

From the responses to the postal questionnaire, we soon observed that the respondents from two combined list sources--farm groups and private applicators (who are primarily farmers)--were quite different in many ways from the other respondents. This "farm group," as we called it, tended to be older and better educated than the other groups, which we collectively called "forest/commercial" (see Table E-1 in Appendix E). Since age, education, and other suggested differences in demographic characteristics and lifestyles between these two groups could have an effect on reproductive outcome, the two groups were separated in the final analysis of cases and controls.

The Case-Control Sample

The case-control sample selected for analysis comprised 311 live births (controls) and 134 miscarriages (cases). Among the 134 women meeting the definition of a "case," 55 reported both a miscarriage and a live birth during the study period. For the majority of these 55 women (42, or 76% of them) the miscarriage event preceded the live birth, and for 13 (24%) the miscarriage occurred after the live birth. This finding is not at all surprising since a miscarriage preceding a live birth is a common pattern among women actively trying to have children.

For testing the overall association hypothesis, we classified all 55 cases reporting both a live birth and a miscarriage during the study period as cases. In addition, we separated this group for a special matched-pairs analysis with each woman serving as her own control.

Tables E-2 through E-4 in Appendix E describe the distribution of age, education, the various exposure variables, health status, smoking, and drug use in the total case-control sample.

Consistent with the results for eligible respondents on the postal questionnaire, we observed that husbands and wives were younger in the forest/commercial group than in the farm group and that both husbands and wives in the farm group had a higher education level than their counterparts in the forest/commercial group (e.g., 39% of the males in the farm group were college graduates, compared with 17.3% in the forest/commercial group). We found no significant difference between farm and forest/commercial groups with respect to the distribution of month of conception over the whole study period (see Figure E-1).

The two groups differed with respect to their responses to almost all herbicide exposure questions (see Table E-3). Among both men and women, exposure to 2,4-D at work and at home was consistently reported more often in the farm group than in the forest/commercial group. This higher percentage of subjects exposed in the farm group could be expected because more 2,4-D is used in agriculture than in forestry. However, a higher percentage of people exposed does not necessarily imply a difference in dose per individual.

As shown in Table E-4, the reported health status of the farm group was slightly better than that for the forest/commercial group. With respect to cigarette and marijuana smoking as well as prescription drug use, both men and women in the farm group appear less likely to be exposed to these secondary risk factors than the men and women in the forest/commercial group.

Analysis Procedures

In case-control studies, two groups of people are identified--one with disease and one free from disease--and their histories are examined to see how their previous exposure experiences differ. In this study the "disease" group, composed of women who experienced a spontaneous abortion, is compared with a similar group of women who experienced a live birth during the study period, and differences in history of exposure to 2,4-D are compared. To

perform these comparisons, conventional epidemiological methods of analysis have been used. Some definitions employed in the analysis follow.

In comparing the relative frequency of exposure to 2,4-D between the two groups, the risk to an unexposed individual is, by convention, defined as 1. This "odds ratio" (or "relative risk") is then a measure of the association between exposure to 2,4-D and spontaneous abortion. A statistical test in which a "p-value" is calculated to determine whether an increased odds ratio is statistically significant is usually a part of the formal analysis. However, most epidemiologists view this test of association (or "hypothesis testing") as an issue of secondary interest, less important than "confidence limits" on the estimate, that might reveal something about the magnitude of an effect (see Reference 2, Appendix J). In the following analysis, odds ratios are presented with their corresponding 90% confidence limits. If the lower 90% confidence limit of an odds ratio exceeds 1, the finding is considered to be significant at a p-value of 5%.* Accuracy of the limits depends on the sample size: the larger the sample size, the more accurate the limits become.

A major concern in analyses of possible associations is the control of confounding. A "confounding variable" is one that is associated with both the presumed cause (exposure) and its presumed effect (spontaneous abortion). Age may be a confounder in this study since it may affect both reproductive outcome and the frequency of exposure. For example, it is certainly plausible that the husband's age, as a correlate to wife's age, relates to fecundity and also affects the frequency and/or amount of exposure. For example, entry-level jobs of younger workers may require more frequent handling of the herbicide. To control for confounding variables, the "Mantel-Haenszel" procedure is employed through "stratification" of the data. When data are stratified by age, for example, the association is examined at different age levels.

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* That is, the probability is less than 5% that the observed association is due to chance alone.

Finally, "power" calculations are included as part of the analysis. These values provide a measure of how likely it is that a real association between exposure and spontaneous abortion will be missed. A real association is defined as an odds ratio greater than 1 (where an odds ratio of 2, for example, means a doubling of the risk). For each of a set of hypothesized odds ratios (e.g., 2, 2.5, 3), the corresponding power measures the likelihood that the study did not miss identifying a ratio that is actually that high.

In the analysis, the variable farm versus forest/commercial was treated as a possible confounder. There is evidence from Table E-3 that it is related to exposure, since the farm and forest groups differ in prevalence of exposure. Also, the total number of pregnancies was higher in the forest/commercial group: 66% compared with 33% in farmers. In fact, the ratio of cases to controls is 1:2.6 in farmers and 1:2.1 in forest/commercials--i.e., there are relatively more cases (women reporting miscarriages) in the forest/commercial group than in the farm group (see Table E-7).

Examining the distribution of age and education of husbands and wives separately in cases and controls (Tables E-5 and E-6), we noticed that for cases the husbands are older, the wives are more likely to be at both extremes of age, the wives are less educated, and the husbands have fewer college graduates than their counterparts, the controls. Also, a difference in the patterns of conception date was apparent which can best be summarized as a deficit of conceptions among controls after December of 1979 (see Figure E-2). This is not surprising since women conceiving during these months were at risk of becoming cases but were unlikely to become controls by August 1980, the time of the interviews.

In order to eliminate confounding effects, the variables group (farm versus forest/commercial), age, education, and month of conception were used to stratify the data.

Association Between Spontaneous Abortions and Exposure Variables

Husband's Work Exposure to 2,4-D

Each exposure variable was divided into nonexposed and exposed categories. The exposed category comprised moderate and high exposure responses to the telephone survey questions. The crude results for reported husband's occupational exposure to 2,4-D, overall and during the conception period, are given in Tables 5 and 6.

The results indicate no statistically significant increase in the odds ratio for either type of exposure (overall or during conception period). Further statistical testing indicates that the group-specific estimates of the odds ratio, 1.58 in forest/commercial and .97 in farmers (see Table 6) are not significantly different.

The crude results after validation as presented in Table 7 did not change the overall conclusions of no association between husband's work exposure during conception and spontaneous abortions.

Table 5

HUSBAND'S REPORTED OVERALL WORK EXPOSURE
IN CASES AND CONTROLS BY GROUP

	Farm Exposure		Forest/Commercial Exposure		Total Sample Exposure	
	Yes	No	Yes	No	Yes	No
Cases	32	11	31	60	63	71
Controls	94	24	69	124	163	148
Exposure odds ratio	.743		.929		.807	
90% confidence	[.373-1.48]		[.598-1.44]		[.574-1.13]	
Power Θ=2.0*	.38		.76		.95	
Θ=2.5	.53		.86		.99	
Θ=3.0	.64		.90		1.00	

* The parameter Θ signifies a hypothesized odds ratio.

Table 6

HUSBAND'S REPORTED WORK EXPOSURE DURING CONCEPTION PERIOD IN CASES AND CONTROLS BY GROUP

	Farm Exposure		Forest/Commercial Exposure		Total Sample Exposure	
	Yes	No	Yes	No	Yes	No
Cases	15	28	16	75	31	103
Controls	42	76	23	170	65	246
Exposure odds ratio	.969		1.58		1.15	
90% confidence	[.524-1.79]		[.883-1.82]		[.764-1.72]	
Power Θ=2.0	.47		.69		.85	
Θ=2.5	.52		.91		.95	
Θ=3.0	.92		.98		.98	

Table 7

HUSBAND'S WORK EXPOSURE DURING CONCEPTION PERIOD AFTER VALIDATION OF CASES AND WORK EXPOSURES, IN CASES AND CONTROLS BY GROUP

	Farm Exposure		Forest/Commercial Exposure		Total Sample Exposure	
	Yes	No	Yes	No	Yes	No
Cases	12	29	11	76	22	105
Controls	35	83	19	174	54	256
Exposure odds ratio	.981		1.33		1.00	
90% confidence	[.547-1.96]		[.613-3.14]		[.584-1.72]	
Power Θ=2.0	.44		.63		.87	
Θ=2.5	.79		.85		.98	
Θ=3.0	.90		.95		.99	

The association between husbands' work exposures to 2,4-D and miscarriages in their wives was further evaluated by examining the effect at different levels of education, age, and the month of conception. The stratification of the total sample of cases and controls to adjust for possible confounding effects of these factors indicated no significant elevated risks. A summary of the analysis is presented in Table E-9.

However, when stratifying the forest/commercial group by husband's age, we observed a statistically significant difference between age groups for an association with overall work exposure. In the 18 to 25 age stratum, the observed odds ratio was 3.07 with 90% confidence limits of 1.21-7.84. In Table 8 the age-specific data are given for three age categories in the farm and forest/commercial groups.

Table 8

CASES AND CONTROLS BY AGE AND BY HUSBAND'S REPORTED OVERALL EXPOSURE AT WORK IN FARM AND FOREST/COMMERCIAL GROUPS

	Farm			Forest/Commercial		
	Exposure			Exposure		
	Yes	No	Odds Ratio	Yes	No	Odds Ratio
Ages 18-25			.55			3.07
Cases	3	3		8	13	
Controls	11	6		9	45	
Ages 26-30			.86			.70
Cases	16	3		15	31	
Controls	56	9		38	55	
Ages 31-35			.87			.55
Cases	13	5		8	16	
Controls	25	9		24	22	

Tables 9 and 10 present the data for the above three age categories using husband's reported and validated exposure during the conception period.

In Tables 8, 9, and 10, no consistent trend in risk of spontaneous abortion by age is indicated in either the farm or forest/commercial group, for exposure to 2,4-D either overall or during the conception period. The elevated risk in the 18 to 25 age group of forest/commercial subjects could

Table 9

CASES AND CONTROLS BY AGE AND BY HUSBAND'S REPORTED EXPOSURE AT WORK DURING CONCEPTION PERIOD IN FARM AND FOREST/COMMERCIAL GROUPS

	Farm			Forest/Commercial		
	Exposure			Exposure		
	Yes	No	Odds Ratio	Yes	No	Odds Ratio
Ages 18-25			.65			4.33
Cases	1	5		3	18	
Controls	4	13		2	52	
Ages 26-30			.37			1.57
Cases	4	15		8	38	
Controls	27	38		11	82	
Ages 31-35			2.90			.95
Cases	10	8		5	19	
Controls	11	25		10	36	

Table 10

CASES AND CONTROLS BY AGE AND BY HUSBAND'S VALIDATED EXPOSURE DURING CONCEPTION PERIOD IN FARM AND FOREST/COMMERCIAL GROUPS

	Farm			Forest/Commercial		
	Exposure			Exposure		
	Yes	No	Odds Ratio	Yes	No	Odds Ratio
Ages 18-25			--			5.60
Cases	0	6		2	19	
Controls	4	13		1	53	
Ages 26-30			.60			.87
Cases	4	13		4	38	
Controls	22	43		10	83	
Ages 31-35			2.40			1.25
Cases	8	10		5	19	
Controls	9	27		8	38	

have resulted from an association with another confounding variable that was inadequately controlled in this group, such as occupational exposure to chlorophenol in green chain workers or any other chronic exposure. Also, the numbers in these tables are relatively small, so that from a statistical point of view, chance alone may be the best possible explanation for the significant isolated elevated risk.

A special matched-pair analysis of the association between spontaneous abortion and husband's work exposure around the conception date was conducted using the 42 women who experienced a miscarriage preceding a live birth during the study period (see Table 11). The matched-pair odds ratio of 2 has a large standard error (S.E. = 1.41) and is not statistically significant. After validation of husband's exposure around the conception date, the odds ratio rose to 3. The resultant small sample size for validated exposure and outcome variable is such that few conclusions can be drawn on the effects of herbicide exposure for this subsample.

Table 11

SPECIAL MATCHED-PAIR ANALYSIS OF 42 WOMEN
REPORTING A MISCARRIAGE PRECEDING A LIVE BIRTH
(Exposure Is Husband's Work Exposure During Conception Period)

Reported Work Exposure

Exposure for Miscarriage	Exposure for Live Birth: Yes	No	Total		
Yes	4	6	10	Odds ratio	= 2
No	3	29	32	S.E. (0)	= 1.41
Total	7	35	42		

Validated Work Exposure

Exposure for Miscarriage	Exposure for Live Birth: Yes	No	Total		
Yes	4	6	10	Odds ratio	= 3
No	2	30	32	S.E. (0)	= 2.45
Total	6	36	42		

Home Exposure to 2,4-D

The results for husbands' and wives' overall home exposure to 2,4-D are presented in Table 12.

Table 12

OVERALL HOME EXPOSURE IN CASES AND CONTROLS BY GROUP AND SEX

	Farm				Forest/Commercial			
	Husband's Exposure		Wife's Exposure		Husband's Exposure		Wife's Exposure	
	Yes	No	Yes	No	Yes	No	Yes	No
Cases	34	9	29	14	55	36	50	41
Controls	99	19	84	34	117	76	84	109
Exposure odds ratio	.73		.84		.99		1.58	
90% confidence	[.35-1.52]		[.45-1.58]		[.65-1.52]		[1.04-2.41]	

The results do not indicate a statistically significant increase in the odds ratio for the farm group, in either husbands' or wives' home exposure. Some difference in the ratio is apparent in the forest/commercial group.

When the wife's overall home exposure to 2,4-D was tested as the risk factor, we observed an odds ratio of 1.58, significant at the 5% level. The Mantel-Haenszel analyses of this crude rate--when stratified by age, education of wife, and the two types of husbands' work and home exposure--did not alter this conclusion (see Table E-10 in Appendix E). It is also interesting that when wife's exposure during the period around conception was the main exposure variable, no significant association with spontaneous abortion was evident.

Since exposure to 2,4-D from aerial spraying was a major component of overall home exposure, a comparison of male and female perceptions regarding this specific type of exposure was carried out. Table E-11 (Appendix E)

presents the distribution of responses in husbands and wives to the question of aerial spraying exposure to 2,4-D. As can be seen, there is an overall low concordance (28%) between the responses of husbands and their wives with respect to aerial spraying exposure. The lack of concordance demonstrates differences in perception of exposure and in response to questions regarding such exposures, but does not speak directly to the validity of such responses. The wives, who may spend more time in the home environment, may be more aware of and report such exposures more accurately. Unlike occupational exposure responses, which were validated, responses to questions regarding home exposures to 2,4-D would appear to be more suspect and difficult to validate. Consequently, one must be cautious in interpreting the findings of elevated risks related to wives' overall home exposure.

Secondary Risk Factors

The associations between spontaneous abortion and the following (secondary) risk factors were analyzed: wife taking prescription drugs, wife smoking cigarettes, and wife and husband smoking marijuana. Tables 13 and 14 display the observed relationship between the reported information on these variables taken from the telephone questionnaire in the farm and forest/commercial groups separately.

Table 13

ASSOCIATION BETWEEN SPONTANEOUS ABORTIONS AND WIFE SMOKING CIGARETTES OR TAKING PRESCRIPTION DRUGS, BY GROUP FOR CASES AND CONTROLS

	Farm				Forest/Commercial			
	Smoking Cigarettes		Prescription Drugs		Smoking Cigarettes		Prescription Drugs	
	Yes	No	Yes	No	Yes	No	Yes	No
Cases	11	31	9	34	42	48	30	61
Controls	37	81	35	34	91	102	64	129
Exposure odds ratio	.79		.65		.98		1.00	
90% confidence	[.41-1.53]		[.33-1.29]		[.65-1.49]		[.64-1.55]	

Table 14

ASSOCIATION BETWEEN SPONTANEOUS ABORTIONS AND SMOKING MARIJUANA, BY GROUP FOR CASES AND CONTROLS

	Farm				Forest/Commercial			
	Wife Smoking Marijuana		Husband Smoking Marijuana		Wife Smoking Marijuana		Husband Smoking Marijuana	
	Yes	No	Yes	No	Yes	No	Yes	No
Cases	1	42	4	39	10	79	15	74
Controls	3	115	7	111	12	180	36	151
Exposure odds ratio	1.17		1.69		1.91		.86	
90% confidence	[.23-5.96]		[.61-4.73]		[.93-3.93]		[.50-1.50]	

The results show no association of miscarriages with wife taking prescription drugs or wife smoking cigarettes. From Table 14 there is an indication of a possible increased risk with wife smoking marijuana in the forest/commercial group. When stratifying for husband's marijuana use in a Mantel-Haenszel analysis, the summary odds ratio was 2.25 with a 90% confidence limit of .97-5.23. No significant difference of the effect at the different levels (husband's smoking marijuana, yes or no) was observed. In addition, we evaluated the effect of husband's age by stratifying husband's smoking history of marijuana by age (into below 25 years and 25 or above). The resulting summary odds ratio of .91 was not different from the crude ratio of .86. Neither was a significant difference of the effect in the two age strata indicated by the corresponding statistical heterogeneity test.

IV DISCUSSION AND INTERPRETATION

In this section, we first discuss the strengths and potential weaknesses of the study design and then offer our interpretation of the results. Inevitably, the inherent limitations of the study design open some of our interpretations to debate. However, we have attempted to indicate where we hold conclusions firmly and where we believe the study results are inconclusive.

Study Design

The case-control study design, with a preselected population of subjects that are more likely than the general population to be exposed to 2,4-D, was chosen for its speed, efficiency, and economy. Nevertheless, such a design must be examined critically for potential biases introduced by the method of selecting cases and controls. If, for example, we had selected cases and controls only from women hospitalized for spontaneous abortion or parturition, these are almost invariably different from persons with the same conditions who were not hospitalized. Furthermore, the frequency and intensity of 2,4-D herbicide exposure in hospitalized women would be low since most would be urban dwellers, and major problems in obtaining permission to contact the women would be encountered.

Our design, using a population known to have a large proportion of couples with 2,4-D exposures and self-reported reproductive events, overcomes the problem of a hospital-based population but raises other questions of bias that must be investigated or at least acknowledged. In particular, our population of farm workers, licensed applicators, forest workers, mill workers, and so on, is clearly not representative of the general population. However, as more likely to be exposed to substantial doses of herbicides than the general population, they are more likely to

demonstrate an adverse effect should a real association exist. This unconventional approach, we believe, strengthens our study design.

We had hoped that cases and controls selected from a base population would not differ from each other on any demographic variable confounding the two important variables, reproductive outcome and 2,4-D exposure. Subsequent analysis proved that, indeed, they were not significantly different.

Moreover, for any bias to significantly affect the estimated risk, it must affect both the outcome and exposure variables simultaneously. If, for example, an overreporting of exposure occurred nearly equally in both cases and controls, it would require a very large error in reporting to mask a risk that does in fact exist.

In our base population from the Pacific Northwest, we expected substantial awareness of the herbicide issue because of intense publicity in the study areas about possible links between 2,4-D and spontaneous abortion. Furthermore, our follow-up cover letter was rather explicit about the association being tested and further increased awareness of the issue. The following biases could therefore be operating:

- Couples who experienced both a miscarriage and previous 2,4-D exposure might be more likely to answer the mail questionnaire than those who did not, because of their great concern and high motivation.
- Couples who experienced a normal delivery following 2,4-D exposure might be more likely to answer it in an attempt to "prove" the safety of the herbicide, for example, to protect jobs.
- Couples who received the follow-up letter stating the hypothesis of the study might be more likely to answer with one of the above two biases.

We could check only the third possibility directly. No obvious differences in pregnancy outcomes were discernible between eligible respondents from the first mailing and those from the second. Furthermore, the large majority of total eligible respondents came from the first

mailing, not the second. Thus, whatever bias may have been introduced by the second letter could not markedly influence the findings. Of the other two possibilities, we believe that the former is somewhat more likely, although the comparison of the responses from the first and second mailings suggests that publicity-based bias may be small in any case. If that belief is true, our study would tend to show more association than truly exists.

Once we selected cases and controls for telephone interviews, the potential for further bias decreased because our strategy was to select the most recent pregnancy to minimize recall error for either spontaneous abortion or 2,4-D exposure. The validation procedures also reduced this error. We did not extensively follow up the nonrespondents, and therefore cannot rule out systematic error from selective reporting of miscarriage by exposed couples. This bias would also, almost surely, tend toward showing more association than exists.

A second limitation of our study design, as finally executed, was our inability to examine dose-exposure relationships. Originally, the study was designed to use a number of work exposure categories for 2,4-D usage. During the data-gathering process, it became clear that, lacking any specific exposure quantification, workers could be categorized into only two groups: those with high or moderate exposure and those with low or no exposure. To characterize exposure somewhat more precisely, we attempted to record and validate the reported date of exposure and met this goal with moderate success. However, in interpreting the data it should be emphasized that fact of exposure was more accurately reported than date of exposure. In summary, the net effect of these problems is to reduce the validity of the data on exposure around the time of conception. However, we are highly confident of the "overall" occupational exposure category.

In conducting the analysis we elected, for reasons mentioned earlier, to treat data from the farm and forest/commercial groups separately. We also emphasized occupational exposure because of its presumed greater frequency, higher dose, or both. Our analysis pays less attention to reported home and casual environmental exposure for two reasons: such

reporting is likely to be highly subjective and difficult or impossible to validate as to dose and frequency.

Postal Questionnaire

The overall response rate to the postal questionnaire was 56.2%, sufficient to identify a population that gave us enough cases and controls for the main portion of the study. Furthermore, 54% of the males and 35.4% of the females reported some previous exposure to 2,4-D herbicides. Thus, our strategy succeeded in selecting a sufficient number of cases and controls with a high percentage reporting previous exposure. This assured considerable statistical power for subsequent analyses. The lowest response rate (38.4%) occurred among the mill workers, who were originally included in the study under the presumption that they would have relatively little 2,4-D exposure and could be used to dilute the study population to achieve an overall exposure rate of close to 50%.

Only those respondents who had reported a pregnancy or suspected pregnancy during the time of interest were selected for the telephone survey. Table 2 in Section III shows an overall similarity between the distribution (by source list) of the case-control sample and the distributions of the mail survey eligible respondents within the farm and forest/commercial groups. We also believe it unlikely that there was bias, by pregnancy experience between lists over the past 2 years. The difference in pregnancy experience in farm versus forest/commercial groups was accounted for in part by carrying out separate analyses for these groups. It is therefore highly unlikely, though not impossible, that important confounding occurs from selection of cases and controls by both exposure status and reproductive experience.

We did not test the 2,4-D/miscarriage association hypothesis on the postal questionnaire data because its whole purpose was to identify, from a number of occupation groups, cases and controls suitable for the ultimate study.

Telephone Survey

The telephone survey provided the data for the test of the hypothesis associating exposure to 2,4-D with spontaneous abortion. Eleven percent of reported pregnancies, among eligible respondents of the postal questionnaire, ended in spontaneous abortion. This figure is well within the usual range of 10% to 20% observed in other populations. The descriptive statistics of the telephone survey revealed no unusual incidence of problems associated with the delivery or early health of the infants born (see Appendix E). In the final analysis, only women reporting spontaneous abortions were selected as cases, and women reporting late, heavy periods were excluded. Although this decision undoubtedly excludes some very early spontaneous abortions, we decided that cases included in the analysis should be as clearly defined and unambiguous as possible to avoid introducing a large amount of error from respondent uncertainty. Even with the precautions taken in this study to validate almost all of the reported spontaneous abortions, there still is a possibility of overreporting among the exposed, since our interest in the association between exposure and spontaneous abortions was probably known to most of the recipients of the postal questionnaire. It is also possible that non-exposed couples were less likely to respond to the postal questionnaire. Both of these possibilities for bias would seem to favor the potential for a false positive association between 2,4-D exposure and miscarriages.

Tables 5 through 7 display the relationship between the husband's occupational exposure and the risk of spontaneous abortion. In neither the forest nor the farm group was there any significant increase in the odds ratio; the ratio for the forest workers (1.58) was slightly higher, but not significantly so, than that reported for farmers (0.97) when the definition of exposure was limited to the 2 months around conception.

Table 7 shows the results of the analysis when validated data on abortion and occupational exposure were substituted for the reported data as necessary. With the validated data, the farm group showed no great change in odds ratio, and the ratio dropped from 1.58 to 1.33 in the forest/commercial group. When we stratified the forest/commercial group by

husband's age and tested for an association with work exposure overall, we observed significant differences in odds ratios. The youngest such workers (18-25 years of age) showed a statistically significant odds ratio of 3.1, while the older two age strata showed ratios markedly below 1. This discrepancy persisted when using validated data on exposure during conception, but the numbers of exposed cases and controls in the young workers were insufficient for statistical significance. The same age stratification in the farm group did not show similar trends, and none of the odds ratios here were statistically significant. In fact, the trend in odds ratios with exposure during the conception period is in the opposite direction, with the oldest farm age group showing risks of 2.9 or 2.4 after validation, neither being statistically significant.

This inconsistency between the age trends in the two groups creates additional uncertainty about the interpretation of the statistically significant finding in the young forest/commercial group. That the association is a true one, as opposed to a chance occurrence, becomes somewhat less plausible in light of this observation. On the other hand, of all age groups, the youngest forest/commercial workers, with their high rate of fecundity and possibly higher doses encountered in entry-level jobs, would be the most likely group to show a relationship. Finally, the associations found in this particular age group could also result from a confounding variable that was inadequately controlled, for example, exposure to chlorophenol among "green chain" workers, which may influence pregnancy outcome.

Table 11 details the occupational 2,4-D exposure, during the conception period, of husbands of the 42 women who experienced a term pregnancy after a spontaneous abortion within the study time period. In principle, this situation would provide the ideal test of the hypothesis, because each woman serves as her own control. However, the only informative data are from those instances in which exposure differs for the two pregnancies. From Table 11, only nine (eight after validation) women contributed such data. Of the eight, six had a miscarriage after exposure and a live birth after no exposure; two had a miscarriage after no exposure and a live birth after exposure. Although the data weakly indicate a possible exposure-abortion

association, the numbers do not approach statistical significance. The amount of information from these eight women is too small to be convincing.

Table 12 demonstrates the lack of association between the exposures of the husband at home (any time or around conception) and spontaneous abortions. Among the forest/commercial wives (Table 12), there was a significant elevation of the odds ratio (1.58) concerning home exposure overall. Table E-11 (Appendix E) shows a marked husband-wife inconsistency about residential exposure, correspondingly reducing the validity of this finding. Furthermore, some bias may be introduced by the increased likelihood of cases to recall or report 2,4-D exposure as compared with controls, even had exposure not differed. Given that the effect was not found in farm group wives, nor in the forest/commercial wives exposed around conception, we believe that the above association probably represents recall bias.

Table 13 shows no association between spontaneous abortion and either prescription drug use or cigarette smoking, in either forest/commercial or farm groups. This lack of association with smoking is not consistent with previous studies; we have no explanation for this finding except that our smoking variable was not limited to pregnancy. For marijuana use, Table 14 indicates that some of the odds ratios with maternal use approach significance. However, we neither demonstrated an association, nor do we have sufficient statistical power to declare no association with marijuana use. The increase in relative odds created by stratifying wife's use by husband's use could suggest synergism between husband and wife use of marijuana, but the data are again too scanty to permit a firm conclusion.

The study design employed provides a reasonable test of the hypothesis that male exposure to 2,4-D herbicide is related to subsequent risk of spontaneous abortion in the wife of the worker. The results of the study do not indicate any evident relationship between the use of 2,4-D and spontaneous abortion. The finding in young forest/commercial workers deserves further study, but does not in itself argue for restrictions on 2,4-D use pending such study.

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SRI International

Appendix A

June 9, 1980

FEASIBILITY STUDY REPORT
FOREST HERBICIDES PROJECT

Prepared for:

National Forest Products Association
Washington, D.C.

Prepared by:

Nancy Bergelin
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FEASIBILITY STUDY REPORT
FOREST HERBICIDES PROJECT

Background

Dr. Thomas Milby of Environmental Health Associates, Inc. (Berkeley, Ca.) is a technical advisor to the Natural Forest Products Association (NFPA). In the first part of March of this year, NFPA requested that Dr. Milby travel to Oregon to evaluate the phenoxy herbicides situation. On March 18, 1980, Dr. Milby met with Dr. Robert Morgan at SRI International to discuss a cooperative health survey in the Oregon, Washington area. At this meeting, it was suggested by Dr. Morgan that SRI perform a feasibility study before proceeding with a survey.

On March 20, Dr. Milby presented a report of this meeting to NFPA at the Bohemian Club in San Francisco recommending that SRI perform the feasibility study. Verbal approval for the study was given on March 21 and the written feasibility proposal (No. HSC-80-73) was sent to NFPA on March 25.

In this proposal, SRI suggested visiting Oregon in order to have discussions with state agricultural and forestry representatives, industry representatives, spraying companies, and members of farm organizations. The purpose of these discussions was to estimate the number of persons potentially available for study, judge their likelihood of participation, and locate suitable control (unexposed) groups. The estimated number of persons available, their geographic location and exposure, and their demographic factors would then be used to design a more definitive study and produce realistis estimates of time and money required.

Written acceptance of the feasibility study was given to SRI by NFPA on March 31, 1980.

Project Personnel

The SRI project team was supervised by Robert W. Morgan, M.D., an epidemiologist with considerable experience in field studies. Dr. Morgan's work has included prior studies in reproductive outcomes after exposure to environmental agents.

The project leader was Cary Young, a Senior Medical Scientist. He is a board-certified physician in general preventive medicine and has had experience in diverse public health and research activities, including reviewing and advising on the scientific content and relevance of numerous projects and reports. For several years he served as epidemiologist with the National Center for Disease Control and the National Institute for Occupational Safety and Health. At SRI, Dr. Young has directed a major project for the National Cancer Institute, dealing with control and intervention strategies for environmentally-related cancers.

Nancy Bergelin, R.N., who performed much of the Oregon field work, is a nurse epidemiologist with a broad background as a consultant in nursing procedures for in-plant occupational health programs. She has coordinated health and safety workshops, managed medical surveillance programs, provided emergency care of occupational injuries and illnesses, and developed procedures for, and performed multiphasic tests. At SRI, Ms. Bergelin has supervised a program to identify health hazards and has conducted medical surveys of selected risk groups for identification and evaluation of occupationally and environmentally induced diseases. She is a certified audiometric technician, certified x-ray technician, and has been certified in Occupational Health Nursing by the American Board for Occupational Health Nurses.

Field Visits and Client Meetings

Oregon

During the period, March 24-28, Nancy Bergelin and Cary Young met with contacts recommended by NFPA - a) to establish cooperation for the project b) to determine if an appropriate study population exists, and c) to discuss the herbicide issue. The Oregon contacts included the following:

1) Oregon Agricultural Aviation Association. Jerral Harchenko, President of this association met with SRI representatives and expressed his willingness to cooperate in such a study. He explained job functions of aerial applicators, their level of exposure and what occupational job titles we might encounter.
2) Oregon State University. Faculty members from OSU included: Logan Norris, Ph.D. (Chemist), Frank Dost, Ph.D. (Toxicologist), James Witt, Ph.D. (Toxicologist), Professor Michael Newton.

During this meeting, the Alsea II study and their critique of that study was discussed. In addition, the following topics were reviewed: a) the demography of various areas of Oregon, b) phenoxy herbicides and health effects, and, c) their willingness to assist with the study, if needed.

3) Good Samaritan Hospital. Sheldon Wagner, M.D., Environmental Health Dept., Corvallis, Oregon. Dr. Wagner has been involved in reviewing cases that may be in some way associated with exposure to herbicides. He was able to input about the political issues, as he sees them, regarding the herbicide controversy.
4) State Department of Agriculture, Bill Kosesan, Director of Plant Division. Mr. Kosesan has been involved in investigating potential environmental and/or health effects of exposure to herbicides. He has, thus far, investigated approximately 17 cases, most involving phenoxy herbicides and has not found any adverse effects.

From the meeting with Mr. Kosesan, SRI was able to compile a potential source of lists of exposed persons and approximate numbers of persons in each job category. In addition, Mr. Kosesan was able to inform us of 2,4-D and give us names of others in the area we might contact.

5) State Department of Forestry. Carl Smith. By meeting with Carl Smith, SRI was able to obtain information about spraying practices in the forest areas, to learn about the Oregon Forest Practices Act and to acquire lists of forest land owners (including private, county and state owners). In addition, SRI was able to gain full support for the study.
6) Georgia-Pacific. William Moshofsky, V.P. Government Affairs. Discussed with the SRI representative various types of epidemiological studies that could be done, some of the studies that have been done, and their willingness to cooperate should SRI undertake a study.
7) Longview Fiber Co. Lee Robinson, V.P. of Timber. Lee Robinson is the chairman of the Board of the Oregon Food and Fiber Coalition. This organization is made up of associations which would have members who use and apply phenoxy herbicides, for example, Southern Oregon Resources, Teamsters, Organization of Nurserymen, Grass Seed Association, Feed and Seed Supply, Agricultural Chemical Association,

National Grain Association, Farm Bureau, Wheat Growers Association and Applicators Association. This coalition is composed of private associations only and does not contain state agencies.

Mr. Robinson was anxious to have the study conducted in Oregon and was willing to cooperate. He requested more details about the study design.

After the SRI field team returned from Oregon, several more organizations were contacted. These contacts included:

Jim Corlett, Oregon Forest Protection Association; David Nelson, Oregon Seed Council; Ivan Packard and Wes Grilley, Oregon Wheat Growers League; Dick Kosesan, Oregon Farm Bureau; Donals Ostensoe, Oregon Cattleman's Association; Cleve Dumdi, Oregon Sheep Grower's Association and W.C. Harris, Oregon State Grange Association. All these contacts were able to furnish technical information as to the uses of the herbicides and all made suggestions about potential sources for lists of names of exposed individuals.

In addition to the Oregon Associations, several organizations in California were contacted in the event that the study might include persons in the Northern California area. Information was gathered concerning local use practices and state licensing rules so that a comparison could be made with those of Oregon. It was learned that the applicator licenses are basically the same, however, some differences do exist in the state rules. The organizations contacted included: The California Forest Protection Association, The California State Department of Forestry, and The California State Department of Food and Agriculture.

Washington, D.C.

On April 2, 1980, Dr. Robert Morgan (SRI) and Dr. Thomas Milby (Environmental Health Associates) met at the Washington, D.C. office of the NFPA with various representatives of government agencies and national associations to discuss the progress of the feasibility study (Oregon data) and to establish liaison with these groups. The following individuals were present at this meeting: Neal Davis and John Niesses (USDA), William McCredie, Robert Kirschner, John Hall and Robert Holcomb (NFPA), John Festa and Blaine Fielding (API), Buck Waters (BLM) and Harold Collins (NAAA).

The agenda for this meeting included a general discussion on SRI International and its ability to carry out the study. Also, a summary was given of the information gathered by Cary Young and Nancy Bergelin in their Oregon visit. In addition, similar studies such as the NAAA questionnaire survey and the NCI Study were discussed. Finally, a case control study approach was proposed and two future studies were suggested. One study would concern herbicide exposure and birth defects, the other would involve herbicide exposure and spontaneous abortions.

Following this meeting, Dr. Morgan and William McCredie spoke with representatives of two government agencies, the VA and the EPA, regarding the Herbicide Study.

Washington

Dr. Robert Morgan followed his visit to Washington, D.C. with a trip to the state of Washington. On April 14, he met with interested parties to discuss the status of the feasibility study and to seek cooperation should the 2,4-D Study begin. The following people met with Dr. Morgan: Robert Mathews, Washington State Pest Management Alliance; Jim Ely, A-1 Spray Service and Bud Johnson, Washington Tree Service, (respresenting the Washington State Chapter of the International Pesticide Applicators Association); Stuart Bledsoe, Washington Forest Products Association; Boyd Peterson and Monty Shaffer, Washington State Wheat Growers Association.

Formulation of Proposals

Information From Meetings

From the meetings in Oregon, Washington, D.C. and Washington, it seemed apparent that

1) the associations whose memberships are involved with using herbicides 2,4-D would be cooperative with SRI should a study be undertaken;
2) the population involved can be documented and is large enough to study;
3) and there is concern about the issue of herbicide use and its effects on health.

SRI Staff were also able to learn some of the technical aspects concerning the use of the herbicides.

Literature Review

Herbicides have been studied for their effects upon health in many areas. These papers include studies looking for associations between herbicides and tumors, herbicides and birth defects and herbicides and spontaneous abortions. Most of these studies have not been definitive or have been criticized because of design flaws. Perhaps the most controversial of these reports was issued in February, 1979 by the EPA, "Report of Assessment of a Field Investigation of Six-Year Spontaneous Abortion Rates in Three Oregon Areas in Relation to Forest 2,4,5-T Spray Practices". The study concluded that there existed a significantly higher abortion rate index in the study area which correlated to spray patterns. This report was subsequently criticized for design faults, perhaps the most thorough criticism being published by Oregon State University, "A Scientific Critique of the EPA Alsea II Study and Report" in October, 1979.

After reviewing the current literature in the area, it became apparent that well designed and well executed studies were needed in two, possible three, areas: herbicides and spontaneous abortions, herbicides and birth defects, herbicides and tumor incidence. Please see attached bibliography for other references reviewed.

Study Design

Prospective or Retrospective Study?

In making a decision about which study type to use, the characteristic advantages and disadvantages of each must be considered. Prospective studies have the advantage that they provide a direct estimate of risk, that is, the risk of a spontaneous abortion in a woman whose husband is exposed to herbicides, could be determined. In a retrospective study, this estimate is obtained indirectly.

Another important advantage to a prospective study is that if the criteria and procedures of the study are established in advance, the possibility of subjective bias in obtaining the necessary information is decreased. In a retrospective study, one has to depend on the individual's memory for information on the occurrence of an event, say exposure to herbicides, or on the availability of some record.

Two other advantages of prospective studies are:

1) one can obtain information on people whose status has changed with regard to the characteristic exposure, and

2) information can be obtained on the relationship of the characteristic (i.e. exposure) to other diseases (tumors, spontaneous abortion, and birth defects).

However, there are important disadvantages to prospective studies which made that design incompatible with this study. Prospective studies are usually more difficult and expensive to execute, requiring large study populations and long periods of observation for definite results*. Because of the time frame for this study, only a retrospect (case-control) approach would be appropriate. It is accepted by the scientific community that a well executed retrospective study can be as accurate and informative as a prospective study.

Biological Plausibility

For a casual association to be considered to exist, there should be some biological plausibility between development of the disease and the factor studied. From our knowledge of reproductive physiology (see attached summary of reproductive physiology), it would seem most logical to consider:

1) the association between the male's exposure and spontaneous abortion, and

2) the association between the females's exposure and birth defects. Even though these would be the main thrusts of the studies, female exposure and spontaneous abortion can be considered in analysis.

Sample Size and Statistical Analysis

From SRI's meetings with representatives of farm groups, forest industries, the U.S. Forest Service, and private applicators, it was possible to estimate a population of at least 7,000 individuals approximately 50% of which are exposed to 2,4-D, in the course of their day-to-day work. This should assure us of 100 cases and 200 controls with appropriate exposure. The table presented in the proposal on spontaneous abortion and herbicide exposure gives more detail about the power expected with various relative risks. If the population contains cases in which 57% are exposed to 2,4-D and controls in which 40% are exposed, we should be able to detect a relative risk of 2 with greater than 85% certainty.

*Ref: Lilienfeld, AM, Foundations of Epidemiology,
Oxford University Press, 1976.

For the Neural Tube Defects Study, with the same number of cases and controls, we would expect to find a tripling of risk with better than 90% certainty. (See discussion in attached Neural Tube Defects Proposal.)

The data will be analyzed after producing simple cross tabulations and other types of descriptive statistics. Relative risk estimates for exposed and unexposed can be determined. In addition, the data may lend itself to dose-response analysis. That is, if an association exists we would anticipate seeing a high relative risk associated with a high exposure and a low relative risk with a low exposure.

It is necessary to control for various confounding variables such as major underlying illnesses, previous pregnancy history, cigarettes, alcohol use, drug use, and others. Data will be collected for these factors and analyses performed after stratification. The data should then show a consistency of association or lack of association across the various strata.

After considering the above discussed background material (population, cooperation, study design, biological feasibility, statistical analysis, etc.) two proposals were written. One proposal presented a design for studying herbicides and spontaneous abortions, the other proposed studying herbicides and neural tube defects.

On April 25, at Crown Zellerbach in San Francisco, Dr. Morgan presented SRI's findings of the feasibility study and both proposals to the Technical Review Panel of NFPA. In attendance at this meeting were: Dr. Thomas Milby, EHA, Inc.; Roger Larson, and Duane Blum, Crown Zellerbach; Bill Lawrence and Orv Harrelson, Weyerhauser; and Lee Robinson, Longview Fiber Company.

Both proposals were taken under consideration by the panel.

SUMMARY OF REPRODUCTIVE PHYSIOLOGY

A brief review of reproductive physiology may be useful to understand the effect of environmental agents on reproduction. Both mutagenesis and teratogenesis will be considered.

All of the ova released during a woman's reproductive life are fully formed at the time of her birth. Thus, her genetic contribution is essentially predetermined, and not much subject to later modification by environmental factors (mutagens) acting upon her in adulthood.

Conversely, sperm are short-lived; any effects on sperm whould not last more than 3 to 4 weeks unless there is permanent testicular damage (sterility) or ongoing exposure.

As a result of the male-female differences in susceptibility to genetic damage, we should consider the possible genetic impact of adult exposure to potential mutagens. Clearly, exposure of adult females should have little or no consequence for human mutation; male exposure is more threatening. Most human mutations are not compatible with life (e.g., they are lethal). Lethal mutations are almost invariably aborted spontaneously by the mother; about 2/3 of all spontaneous abortions are lethal mutations. Thus, the rate of spontaneous abortions is an indicator of male exposure to factors damaging spermatogenesis.

Adverse environmental effects operating after conception are, naturally, mediated by maternal exposure and the ability of the agent to cross the placental barrier. Possible effects range from none through to fetal death. If the insult occurs during the first three months, organ development may be damaged (e.g., thalidomide producing limb defects). Substances causing impaired organ development are known as teratogens. Although, at least in animals, some substances can act as both mutagens and teratogens, they differ in action, time of insult, and person exposed.

One can summarize the possible action of environmental agents on reproduction by noting that spontaneous abortions likely represent male exposure

a few weeks prior to conception; birth defects represent a maternal exposure a few weeks after conception.

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Appendix B

SRI International (formerly Stanford Research Institute) is a non-profit research organization.

Dear Pacific Northwest Resident:

You have been selected as a participant in an important study concerning the effects of herbicides (weed killers) on health and pregnancy. The enclosed questionnaire represents the initial step in this study and will provide us with a broad overview of participants, so that we may select different groups for different interviews.

YOUR ANSWERS ARE VITALLY IMPORTANT TO THE ACCURACY AND VALIDITY OF THIS SURVEY, EVEN IF YOU HAVE NOT BEEN EXPOSED TO ANY WEED KILLERS OR ARE NOT MARRIED! The questionnaire should take you no more than 5 minutes to complete. Please do so as soon as possible and return it to us in the enclosed stamped envelope.

All data collected will be held in strict confidence. A five-digit identification number (in the upper right-hand corner of the questionnaire) is included only to enable us to cross your name off our follow-up list after we have received your questionnaire.

If you are not married but are living together as married, please complete the "husband" and "wife" portions of the questionnaire as though you were married. Please note that questions 8 and 9 should be completed only by women. (If you live alone, please complete only the "husband" portion if you are a man or the "wife" portion if you are a woman.)

In appreciation for your participation, we will send you, if you like, a summary of the study results. If you have any questions about the study, please feel free to call either of us collect at (415) 326-6200, extension 3936 (Dr. Morgan) or extension 4164 (Dr. Russell).

Thank you very much for your help. We look forward to receiving your questionnaire in the next few days.

Yours sincerely,

Robert W. Morgan, M.D.

Susan H. Russell, Ph.D.

SHR/mmj
Enclosures

P.S. If this is the second copy of the questionnaire you have received, please simply write "duplicate" on the first page and return it to us in the enclosed stamped envelope.

SRI International
333 Ravenswood Ave. • Menlo Park, CA 94025 • (415) 326-6200 • Cable: SRI INTL MNP • TWX: 910-373-1246

Appendix C

PRELIMINARY SURVEY OF HERBICIDE (WEED-KILLER) EXPOSURE

CONFIDENTIAL

1. How long have you lived at your present address--that is, the home you live in now?
(PLEASE CHECK ONE BOX IN EACH COLUMN)

HUSBAND	WIFE	
☐	☐	1. 6 months or less
☐	☐	2. 7 - 12 months
☐	☐	3. 13 - 18 months
☐	☐	4. 19 - 24 months
☐	☐	5. More than 24 months (more than 2 years)

2. How long have you lived in this area (within 50 miles or so of where you live now)?
(PLEASE CHECK ONE BOX IN EACH COLUMN)

HUSBAND	WIFE	
☐	☐	1. 6 months or less
☐	☐	2. 7 - 12 months
☐	☐	3. 13 - 18 months
☐	☐	4. 19 - 24 months
☐	☐	5. More than 24 months (more than 2 years)

3. What is your current age?
(PLEASE CHECK ONE BOX IN EACH COLUMN)

HUSBAND	WIFE	
☐	☐	1. Under 18 years old
☐	☐	2. 18 - 21 years old
☐	☐	3. 22 - 25 years old
☐	☐	4. 26 - 30 years old
☐	☐	5. 31 - 35 years old
☐	☐	6. 36 - 40 years old
☐	☐	7. Over 40 years old

4. What is the highest grade of school you have completed?
(PLEASE CHECK ONE BOX IN EACH COLUMN)

HUSBAND	WIFE	
☐	☐	1. Grade 8 or below
☐	☐	2. Some high school
☐	☐	3. Completed high school
☐	☐	4. Vocational or technical school
☐	☐	5. Some college
☐	☐	6. Completed 4 years of college (Bachelor's degree) or more

5. In the last two years, about how often do you think you have been exposed to herbicides (weed killers)? By exposed we mean using them yourself or being in an area while herbicide spraying was taking place. (Please do not include washing clothes that have been exposed to herbicides.)
(PLEASE GIVE YOUR BEST ESTIMATES: CHECK ONE BOX IN EACH COLUMN)

HUSBAND	WIFE	
☐	☐	1. Never, as far as I know
☐	☐	2. Once or twice
☐	☐	3. Three or more times

6. As far as you know, were any of these weed killers phenoxy herbicides? (The most common names for phenoxy herbicides are 2,4-D; 2,4,5-T; 2,4,5-TP, and Silvex.)
(PLEASE GIVE YOUR BEST ESTIMATES, CHECK ONE BOX IN EACH COLUMN)

HUSBAND	WIFE		
☐	☐	0.	Question doesn't apply to me--haven't been exposed to any herbicides (weed killers) at all in the last two years.
☐	☐	1.	None were phenoxy herbicides
☐	☐	2.	Some were phenoxy herbicides
☐	☐	3.	Most or all were phenoxy herbicides
☐	☐	9.	Not sure how many were phenoxy herbicides

7. How would you rate the general state of your health?
(PLEASE CHECK ONE BOX IN EACH COLUMN)

HUSBAND	WIFE		
☐	☐	1.	Poor
☐	☐	2.	Fair
☐	☐	3.	Good
☐	☐	4.	Excellent

8. (TO BE ANSWERED BY WOMEN ONLY): During the past two years, have you had any menstrual periods that seemed to you to be <u>unusually</u> late and heavy?

☐	1.	Not sure, don't remember
☐	2.	Yes
☐	3.	No

9. (TO BE ANSWERED BY WOMEN ONLY): Have you been pregnant at any time in the past two years? Please include any miscarriages, abortions, or stillbirths you may have had.
(PLEASE CHECK ONE OR MORE BOXES, AS APPLICABLE)

☐ 1. I am not sure whether or not I have been pregnant in the last two years.

☐ 2. Yes, I have been pregnant in the last two years and:
(PLEASE CHECK ALL THAT APPLY)

☐ (1) I had a baby

☐ (2) I had a miscarriage

☐ (3) I had a therapeutic (elective) abortion

☐ (4) I had a stillbirth

Please add here any information you feel we should know about your pregnancy:

_____

_____

_____

☐ 3. No, I have not been pregnant in the last two years.

10. Is your residence address the same as the mailing address we have used for this questionnaire?

☐ 1. Yes, residence and mailing addresses are the same.

☐ 2. No, my residence address is:

Street: _____

City: _____ State: _____ ZIP: _____

11. We may find it necessary to ask you some further questions about your answers here. It will therefore help us a great deal if you can give us your home telephone number:

Area code: _____ Number: _____

☐ Please check here if you would like a summary of the survey results.

THANK YOU VERY MUCH FOR YOUR PARTICIPATION
PLEASE RETURN THIS QUESTIONNAIRE IN THE ENCLOSED STAMPED ENVELOPE TO:

Dr. Susan Russell
Center for Community Health Studies
SRI International
Menlo Park, California 94025

Dear Pacific Northwest Resident:

Recently, we mailed you a questionnaire dealing with herbicides and pregnancy. If you have already completed and returned it, many thanks. If you have not yet had a chance to respond, we would be most grateful if you would do so now. The accuracy of our study depends on your responses. We have enclosed a second copy of the questionnaire and a stamped reply envelope for your convenience. Your answers will be held in strict confidence, of course.

Because we've had a number of inquiries about SRI and about this study, we thought you might be interested in learning a little more about us.

SRI is a non-profit research organization conducting research in a wide variety of fields, under contract to government, private, and commercial clients. We were originally associated with Stanford University, but since 1968 we have been independent. We take great pride in our independent nature, and we go to great lengths to maintain an unbiased stance in our research.

This study is being sponsored by the National Forest Products Association (NFPA) and by the U.S. Department of Agriculture. The NFPA is a Washington, D.C., based association of forest products related companies.

The study is designed to determine if women whose husbands are exposed to 2,4-D have a higher or lower incidence of miscarriages than do women whose husbands are not exposed to 2,4-D. We do not know at this time what the answer to this issue is, nor do we have any preconceived notions as to what the answer will be.

The mail survey is being used primarily to find women who have been pregnant within the past two years. A random sample of these women will then be contacted by telephone and asked detailed questions about their pregnancy and about their exposure to 2,4-D. Their husbands will also be asked detailed questions about exposure to 2,4-D. In addition, both husband and wife will be asked about various possible "confounding" variables—that is, other things that might be related to miscarriages. Some women who did not report a pregnancy in the mail survey will also be contacted by phone to confirm their answers to the questionnaire. We have imposed the two-year limit on the survey because of the difficulty of remembering details any further back than that.

The questionnaire was sent to about 15,000 families in Oregon and Washington. The names were obtained from large employers in these areas, from agriculture associations, from herbicide application license lists, and so on. Most of the persons on our lists are in occupations that have a high likelihood of exposure to herbicides. However, about a fourth of the group are mill workers, who were selected as a control group unlikely to be exposed to herbicides in their jobs.

PLEASE COMPLETE AND RETURN THE QUESTIONNAIRE WHETHER OR NOT YOU HAVE BEEN PREGNANT OR EXPOSED TO HERBICIDES, OR ARE MARRIED! THE STATISTICAL VALIDITY OF THE STUDY DEPENDS ON OUR RECEIVING RESPONSES FROM A VERY HIGH PERCENTAGE OF PERSONS TO WHOM WE HAVE SENT QUESTIONNAIRES.

We hope this answers any questions you may have had about this study. Please help us make this important study a success. If you would like a summary of the results, simply check the appropriate box on the last question.

Sincerely,

Susan H. Russell, Ph.D.
Manager, Survey Research Program

Robert W. Morgan, M.D.
Director, Center for Community Health Studies

SRI International
333 Ravenswood Ave. • Menlo Park, CA 94025 • (415) 326-6200 • Cable: SRI INTL MNP • TWX: 910-373-1246

Appendix E

DESCRIPTIVE STATISTICS AND TABLES

Ineligibles Removed After or During Telephone Interviews

• Potential cases with more than one therapeutic abortion in lifetime	1
• Interview disqualified due to inconsistencies among responses	4
• Conception occurred outside Oregon and Washington	10
• Participants were over age 35 at the time they responded to the postal questionnaire	13
• Participant couldn't give exact (month-year) date that reproductive event occurred	15
• Participant was not living with current partner at time of conception	22
• Participant was still pregnant	25
• Participant was not pregnant and did not have a late heavy period since January 1, 1978	246
• Other - Conception occurred prior to 1-1-78, participant filled out postal questionnaire that was addressed to neighbor or relative, etc.	28
Total	364

Descriptive Statistics of Eligible Respondents on the Telephone Interview*

Of the total live births, 150 (48.1%) were girls and 161 (51.9%) were boys. Most women (59.2%) reported that the live birth was delivered on time, while some (25.8%) reported late delivery and a few (15%) reported an early delivery. Very few (7.4%) reported any health problems with the infant.

Of the cases defined, 121 (89.6%) saw a doctor about the miscarriage, and of these, 113 reported that the physician confirmed their miscarriage. The most frequent symptoms reported by these women were swollen or tender breasts (68.2%), nausea (45.5%), overwhelming fatigue (40.9%), more frequent than usual urination (36.4%), and excessive or unusual hunger (13.6%).

The respondents reported using birth control devices in the 6 months prior to conception 42.2% of the time. Of these, 10.2% used an intrauterine device (IUD) only, 29.1% used birth control pills and 2.9% used both. 6% percent of the cases and 6.1% of the controls used an IUD. Users of birth control pills were 16.6% of the cases and 15.1% of the controls.

Eighty-eight individuals reported difficulty getting pregnant, of which 55 saw a physician about this problem. Of the 18 men who were tested for an abnormal sperm count by the physician, only five had an abnormal test result.

Over 60% of the women reported working outside the home since January 1, 1978. Of these, 27.1% reported doing farm work, and 17.7% reported exposure to herbicides. Three percent worked with herbicides other than 2,4-D, and 2.7% worked with 2,4-D. Of those working with 2,4-D, 1.9% worked around open containers of 2,4-D; 1.6% mixed 2,4-D with water or other compounds; 0.8% had done backpack spraying with 2,4-D; 0.4% had done injection spraying of 2,4-D; 0.2% applied 2,4-D from a plane or helicopter; 0.8% applied 2,4-D from a tractor or truck; and 1.6% cleaned equipment that was used to apply 2,4-D.

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* The statistics refer to a total sample of 513 individuals before the exclusion of LHP (late heavy period).

A slightly higher percentage reported indirect exposure to 2,4-D: 6.8% worked within 2 miles of 2,4-D use; 4.7% worked near an area where 2,4-D was applied from the air; 4.1% worked near 2,4-D was applied from the ground; and 3.7% came in contact with foliage sprayed with 2,4-D.

Of the men interviewed, 58.4% were exposed to herbicides at work since January 1, 1978. Forty percent reported work exposure to 2,4-D, and 45.6% reported exposure to other herbicides. Thirty-eight percent worked around open containers of 2,4-D, 36.6% mixed 2,4-D with water or other substances; 14% had done backpack spraying; 6% had performed injection spraying; 4.9% applied 2,4-D from the air; 28.5% applied 2,4-D from a tractor or truck; and 34.9% remembered cleaning equipment used for applying 2,4-D.

The men also reported the following frequency of indirect exposure: 48.6% worked within 2 miles of 2,4-D application; 65.5% worked near where 2,4-D was applied from the air; 56.4% worked near an area where 2,4-D was applied from the ground; and 60% had contact with foliage sprayed with 2,4-D.

Table E-1

AGE AND EDUCATION OF HUSBANDS AND WIVES BY GROUP
IN ELIGIBLE RESPONDENTS TO POSTAL QUESTIONNAIRE

HUSBAND, AGE

FREQUENCY / PERCENT / ROW PCT / COL PCT	MISSING	18-21 YEARS	22-25 YEARS	26-30 YEARS	31-35 YEARS	TOTAL
FARM	0	23	150	505	547	1225
	.	0.61	3.96	13.34	14.45	32.36
	.	1.88	12.24	41.22	44.65	
	.	26.14	24.92	31.84	36.23	
FOREST	1	65	452	1081	963	2561
	.	1.72	11.94	28.55	25.44	67.64
	.	2.54	17.65	42.21	37.60	
	.	73.86	75.08	68.16	63.77	
TOTAL	.	88	602	1586	1510	3786
	.	2.32	15.90	41.89	39.88	100.00

WIFE, AGE

FREQUENCY / PERCENT / ROW PCT / COL PCT	UNDER 18 YEARS	18-21 YEARS	22-25 YEARS	26-30 YEARS	31-35 YEARS	TOTAL
FARM	1	67	288	501	368	1225
	0.03	1.77	7.60	13.23	9.72	32.35
	0.08	5.47	23.51	40.90	30.04	
	20.00	23.10	28.77	31.67	40.48	
FOREST	4	223	713	1081	541	2562
	0.11	5.89	18.83	28.55	14.29	67.65
	0.16	8.70	27.83	42.19	21.12	
	80.00	76.90	71.23	68.33	59.52	
TOTAL	5	290	1001	1582	909	3787
	0.13	7.66	26.43	41.77	24.00	100.00

HUSBAND, EDUCATION LEVEL

FREQUENCY / PERCENT / ROW PCT / COL PCT	GRADE 8 OR BELOW	SOME HIGH SCHOOL	GRAD HIGH SCHOOL	VOC, TEC SCHOOL	SOME COLLEGE	COLL.DEG(S)	TOTAL
FARM	8	28	213	119	402	453	1223
	0.21	0.74	5.64	3.15	10.64	11.99	32.37
	0.65	2.29	17.42	9.73	32.87	37.04	
	38.10	12.12	19.28	32.69	35.86	48.40	
FOREST	13	203	892	245	719	483	2555
	0.34	5.37	23.61	6.48	19.03	12.78	67.63
	0.51	7.95	34.91	9.59	28.14	18.90	
	61.90	87.88	80.72	67.31	64.14	51.60	
TOTAL	21	231	1105	364	1121	936	3778
	0.56	6.11	29.25	9.63	29.67	24.78	100.00

WIFE, EDUCATION LEVEL

FREQUENCY / PERCENT / ROW PCT / COL PCT	GRADE 8 OR BELOW	SOME HIGH SCHOOL	GRAD HIGH SCHOOL	VOC, TEC SCHOOL	SOME COLLEGE	COLL.DEG(S)	TOTAL
FARM	4	40	324	131	389	336	1224
	0.11	1.06	8.56	3.46	10.28	8.88	32.36
	0.33	3.27	26.47	10.70	31.78	27.45	
	28.57	13.03	24.18	34.93	35.43	51.77	
FOREST	10	267	1016	244	709	313	2559
	0.26	7.06	26.86	6.45	18.74	8.27	67.64
	0.39	10.43	39.70	9.53	27.71	12.23	
	71.43	86.97	75.82	65.07	64.57	48.23	
TOTAL	14	307	1340	375	1098	649	3783
	0.37	8.12	35.42	9.91	29.02	17.16	100.00

Table E-2

AGE, EDUCATION LEVEL DISTRIBUTIONS IN
FARMER AND FOREST/COMMERCIAL GROUPS
(Case/Control Subsample)

Variables	Farm Group				Forest/Commercial Group			
	Male Number	Male Percent	Female Number	Female Percent	Male Number	Male Percent	Female Number	Female Percent
Age (years)								
18-21	0	0.0	9	5.6	5	1.8	29	10.2
22-25	23	14.3	40	24.8	70	24.6	124	43.7
26-30	84	52.2	83	51.6	139	48.9	104	36.6
31-35	54	33.5	29	18.0	70	24.7	27	9.5
Total	161		161		284		284	
Education								
Grade 8 or below	1	0.6	0	0.0	1	0.4	2	0.7
Some high school	0	0.0	2	1.2	19	6.7	30	10.6
Grad high school	24	14.9	34	21.1	95	33.4	116	40.8
Voc tech school	17	10.6	18	11.2	26	9.1	19	6.7
Some college	56	34.8	58	36.0	94	33.1	81	28.5
Grad college	63	39.1	49	30.5	49	17.3	36	12.7
Total	161		161		284		284	

Table E-3

DISTRIBUTION OF VARIOUS EXPOSURE TYPES FOR TOTAL SAMPLE OF CASES AND CONTROLS AND FOR FARM AND FOREST/COMMERCIAL GROUPS

Exposure Types	Total Sample--Cases/Controls				Farm Group				Forest/Commercial Group			
	Male Number	Male Percent	Female Number	Female Percent	Male Number	Male Percent	Female Number	Female Percent	Male Number	Male Percent	Female Number	Female Percent
Exp. at work-conception												
Low	349	78.4	430	96.5	104	64.6	151	93.8	245	86.3	279	98.2
Moderate	22	4.9	11	2.5	10	6.2	6	3.7	12	4.2	5	1.8
High	74	16.7	4	1.0	47	29.2	4	2.5	27	9.5	0	0.0
Total	445		445		161		161		284		284	
Exp. at work-overall												
Low	219	49.2	402	90.3	35	21.7	128	79.5	184	64.8	274	96.5
Moderate	40	9.0	30	6.7	18	11.2	21	13.0	22	7.7	9	3.2
High	186	41.8	13	3.0	108	67.1	12	7.5	78	27.5	1	0.3
Total	445		445		161		161		284		284	
Exp. at home-conception												
No	340	76.4	361	81.1	110	68.3	118	73.3	230	81.0	243	85.6
Yes	105	23.6	84	18.9	51	31.7	43	26.7	54	19.0	41	14.4
Total	445		445		161		161		284		284	
Exp. at home-overall												
No	140	31.5	198	44.5	28	17.4	48	29.8	112	39.4	150	52.8
Yes	305	68.5	247	55.5	133	82.6	113	70.2	172	60.6	134	47.2
Total	445		445		161		161		284		284	

Table E-4

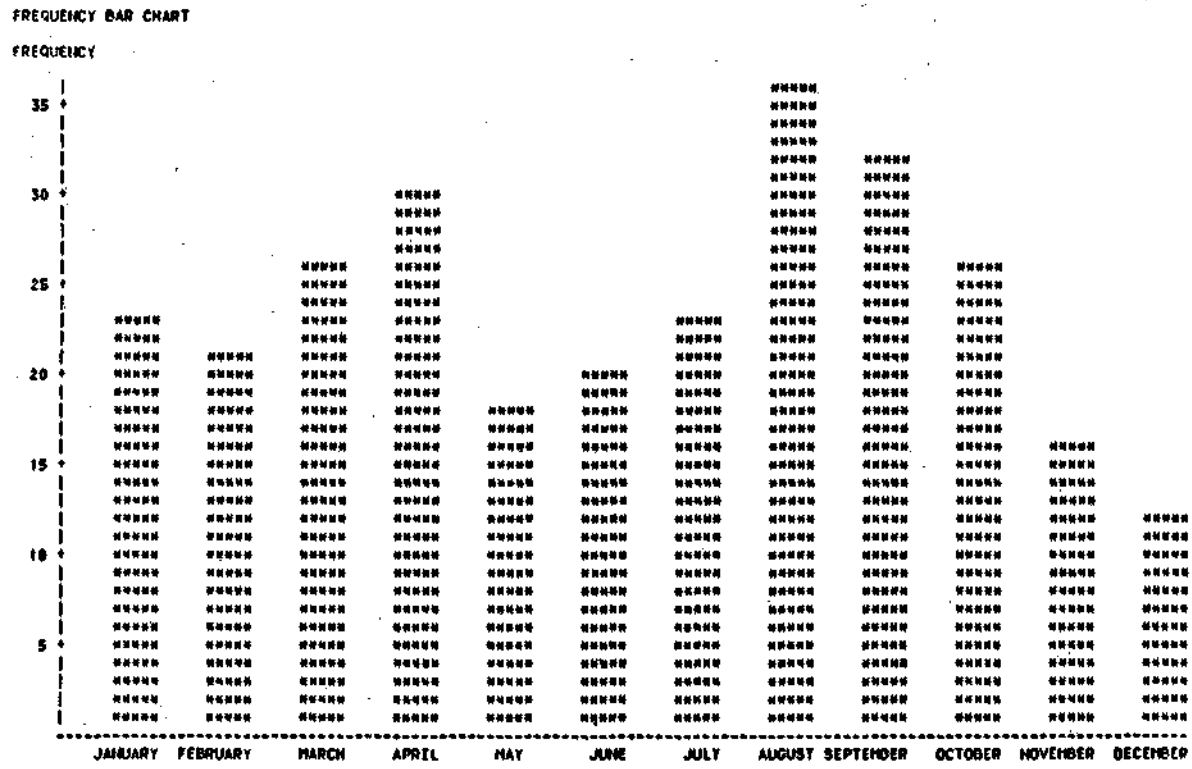
HEALTH STATUS, SMOKING, DRUG USE DISTRIBUTIONS FOR
TOTAL SAMPLE, FARMERS, AND FOREST/COMMERCIAL GROUPS

Variables	Total Sample				Farm Group				Forest/Commercial Group			
	Male Number	Male Percent	Female Number	Female Percent	Male Number	Male Percent	Female Number	Female Percent	Male Number	Male Percent	Female Number	Female Percent
Health status												
Poor	0	0.0	1	0.2	0	0.0	0	0.0	0	0.0	1	0.4
Fair	13	2.9	23	5.2	1	0.6	3	4.2	12	4.2	20	7.1
Good	132	29.9	149	33.8	35	22.0	40	25.2	97	34.3	109	38.6
Excellent	297	67.2	268	60.8	123	77.4	116	72.9	174	61.5	152	53.9
Total	442		441		159		159		283		282	
Smoking cigarettes												
No	321	72.5	262	59.1	131	81.9	112	70.0	190	67.1	150	53.0
Yes	122	27.5	181	40.9	29	18.1	48	30.0	93	32.9	133	47.0
Total	443		443		160		160		283		283	
Smoking marijuana												
No	375	85.8	416	94.1	150	93.2	157	97.5	125	81.6	259	92.2
Yes	62	14.2	26	5.9	11	6.8	4	2.5	51	18.4	22	7.8
Total	437		442		161		161		276		281	
Prescription drugs												
No	363	86.6	304	68.8	143	92.5	114	72.7	220	84.5	190	66.9
Yes	56	13.4	138	31.2	12	7.5	44	27.3	44	15.5	94	33.1
Total	419		442		155		158		264		284	

Figure E-1

Frequency Distribution of Conception Month By Group

Forest/Commercial



Farm

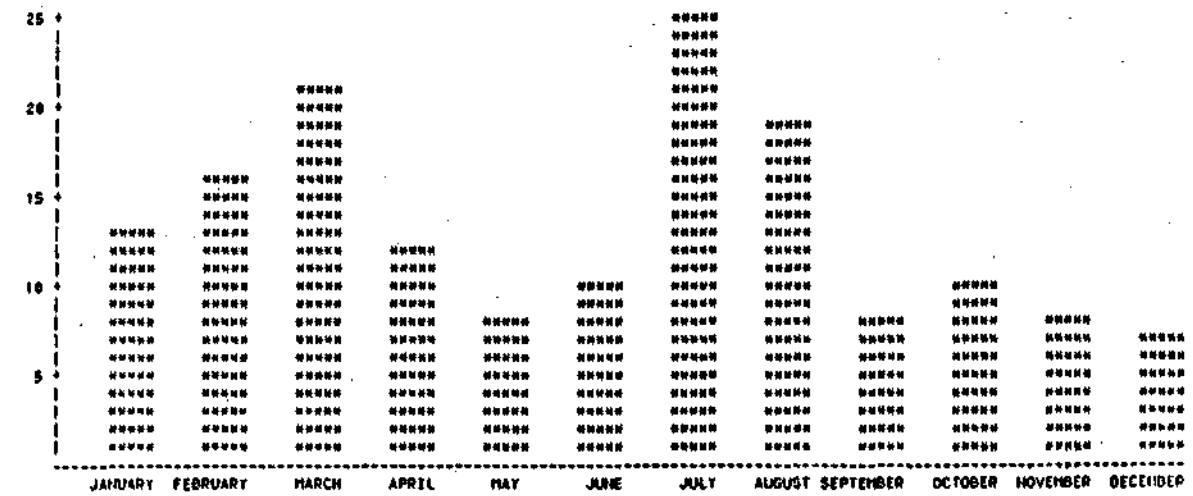


Table E-5

COMPARISON OF CASES AND CONTROLS BY HUSBAND, WIFE AGE

Farm

FREQUENCY / PERCENT / ROW PCT / COL PCT	Husband Age: 22-25 YEARS	26-30 YEARS	31-35 YEARS	TOTAL
CONTROL	17	65	36	118
	10.56	40.37	22.36	73.29
	14.41	55.08	30.51	
	73.91	77.38	66.67	
CASE	6	19	18	43
	3.73	11.80	11.18	26.71
	13.95	44.19	41.86	
	26.09	22.62	33.33	
TOTAL	23	84	54	161
	14.29	52.17	33.54	100.00

Likelihood ratio chi-square = 1.903,
DF = 1, Prob = 0.3861

FREQUENCY / PERCENT / ROW PCT / COL PCT	Wife Age: 18-21 YEARS	22-25 YEARS	26-30 YEARS	31-35 YEARS	TOTAL
CONTROL	6	29	65	18	118
	3.73	18.01	40.37	11.18	73.29
	5.08	24.58	55.08	15.25	
	66.67	72.50	78.31	62.07	
CASE	3	11	18	11	43
	1.86	6.83	11.18	6.83	26.71
	6.98	25.58	41.86	25.58	
	33.33	27.50	21.69	37.93	
TOTAL	9	40	83	29	161
	5.59	24.84	51.55	18.01	100.00

Likelihood ratio chi-square = 3.057,
DF = 3, PROB = 0.3830

Forest/Commercial

FREQUENCY / PERCENT / ROW PCT / COL PCT	Husband Age: 18-21 YEARS	22-25 YEARS	26-30 YEARS	31-35 YEARS	TOTAL
CONTROL	4	50	93	46	193
	1.41	17.61	32.75	16.20	67.96
	2.07	25.91	48.19	23.83	
	80.00	71.43	66.91	65.71	
CASE	1	20	46	24	91
	0.35	7.04	16.20	8.45	32.04
	1.10	21.98	50.55	26.37	
	20.00	28.57	33.09	34.29	
TOTAL	5	70	139	70	284
	1.76	24.65	48.94	24.65	100.00

Likelihood ratio chi-square = 0.988
DF = 3, PROB = 0.8042

FREQUENCY / PERCENT / ROW PCT / COL PCT	Wife Age: 18-21 YEARS	22-25 YEARS	26-30 YEARS	31-35 YEARS	TOTAL
CONTROL	19	84	73	17	193
	6.69	29.58	25.70	5.99	67.96
	9.84	43.52	37.82	8.81	
	65.52	67.74	70.19	62.96	
CASE	10	40	31	10	91
	3.52	14.08	10.92	3.52	32.04
	10.99	43.96	34.07	10.99	
	34.48	32.26	29.81	37.04	
TOTAL	29	124	104	27	284
	10.21	43.66	36.62	9.51	100.00

Likelihood ratio chi-square = 0.624.
DF = 3, PROB = 0.8909

Table E-6

COMPARISON OF CASES AND CONTROLS BY HUSBAND, WIFE EDUCATION LEVEL

Farm

Husband Education

FREQUENCY / PERCENT / ROW PCT / COL PCT	GRADE 8 OR BELOW	SOME HIGH SCHOOL	GRAD HIGH SCHOOL	VOC,TECH SCHOOL	SOME COLLEGE	GRAD COLLEGE	TOTAL
CONTROL	1	18	13	37	49		118
	0.62	11.18	8.07	22.98	30.43		73.29
	0.85	15.25	11.02	31.36	41.53		
	100.00	75.00	76.47	66.07	77.78		
CASE	0	6	4	19	14		43
	0.00	3.73	2.48	11.80	8.70		26.71
	0.00	13.95	9.30	44.19	32.56		
	0.00	25.00	23.53	33.93	22.22		
TOTAL	1	24	17	56	63		161
	0.62	14.91	10.56	34.78	39.13		100.00

Likelihood ratio chi-square = 2.839,
DF = 4, PROB = 0.5851

Wife Education

FREQUENCY / PERCENT / ROW PCT / COL PCT	SOME HIGH SCHOOL	GRAD HIGH SCHOOL	VOC,TECH SCHOOL	SOME COLLEGE	GRAD COLLEGE	TOTAL
CONTROL	1	23	12	44	38	118
	0.62	14.29	7.45	27.33	23.60	73.29
	0.85	19.49	10.17	37.29	32.20	
	50.00	67.65	66.67	75.86	77.55	
CASE	1	11	6	14	11	43
	0.62	6.83	3.73	8.70	6.83	26.71
	2.33	25.58	13.95	32.56	25.58	
	50.00	32.35	33.33	24.14	22.45	
TOTAL	2	34	18	58	49	161
	1.24	21.12	11.18	36.02	30.43	100.00

Likelihood ratio chi-square = 2.077,
DF = 4, PROB = 0.7216

Forest/Commercial

Husband Education

FREQUENCY / PERCENT / ROW PCT / COL PCT	GRADE 8 OR BELOW	SOME HIGH SCHOOL	GRAD HIGH SCHOOL	VOC,TECH SCHOOL	SOME COLLEGE	GRAD COLLEGE	TOTAL
CONTROL	1	10	66	16	63	37	193
	0.35	3.52	23.24	5.63	22.18	13.03	67.96
	0.52	5.18	34.20	8.29	32.64	19.17	
	100.00	52.63	69.47	61.54	67.02	75.51	
CASE	0	9	29	10	31	12	91
	0.00	3.17	10.21	3.52	10.92	4.23	32.04
	0.00	9.89	31.87	10.99	34.07	13.19	
	0.00	47.37	30.53	38.46	32.98	24.49	
TOTAL	1	19	95	26	94	49	284
	0.35	6.69	33.45	9.15	33.10	17.25	100.00

Likelihood ratio chi-square = 4.660,
DF = 5, PROB = 0.4587

Wife Education

FREQUENCY / PERCENT / ROW PCT / COL PCT	GRADE 8 OR BELOW	SOME HIGH SCHOOL	GRAD HIGH SCHOOL	VOC,TECH SCHOOL	SOME COLLEGE	GRAD COLLEGE	TOTAL
CONTROL	2	21	71	14	60	25	193
	0.70	7.39	25.00	4.93	21.13	8.80	67.96
	1.04	10.88	36.79	7.25	31.09	12.95	
	100.00	70.00	61.21	73.68	74.07	69.44	
CASE	0	9	45	5	21	11	91
	0.00	3.17	15.85	1.76	7.39	3.87	32.04
	0.00	9.89	49.45	5.49	23.08	12.09	
	0.00	30.00	38.79	26.32	25.93	30.56	
TOTAL	2	30	116	19	81	36	284
	0.70	10.56	40.85	6.69	28.52	12.68	100.00

Likelihood ratio chi-square = 5.732,
DF = 5, PROB = 0.3332

Table E-7

COMPARISON OF CASES AND CONTROLS BY MONTH, YEAR OF CONCEPTION (TOTAL SAMPLE)

Month of Conception

FREQUENCY / PERCENT / ROW PCT / COL PCT	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	TOTAL
CONTROL	22	29	32	27	15	20	38	42	30	26	18	12	311
	4.97	6.55	7.22	6.09	3.39	4.51	8.58	9.48	6.77	5.87	4.06	2.71	70.20
	7.07	9.32	10.29	8.68	4.82	6.43	12.22	13.50	9.65	8.36	5.79	3.86	
	61.11	78.38	68.09	64.29	57.69	66.67	79.17	76.36	73.17	70.27	75.00	60.00	
CASE	14	8	15	15	11	10	10	13	11	11	6	8	132
	3.16	1.81	3.39	3.39	2.48	2.26	2.26	2.93	2.48	2.48	1.35	1.81	29.80
	10.61	6.06	11.36	11.36	8.33	7.58	7.58	9.85	8.33	8.33	4.55	6.06	
	38.89	21.62	31.91	35.71	42.31	33.33	20.83	23.64	26.83	29.73	25.00	40.00	
TOTAL	36	37	47	42	26	30	48	55	41	37	24	20	443
	8.13	8.35	10.61	9.48	5.87	6.77	10.84	12.42	9.26	8.35	5.42	4.51	100.00

LIKELIHOOD RATIO CHISQUARE 9.801 DF= 11 PROB=0.5484

Year of Conception

FREQUENCY / PERCENT / ROW PCT / COL PCT	78	79	80	TOTAL
CONTROL	148	161	2	311
	33.41	36.34	0.45	70.20
	47.59	51.77	0.64	
	78.31	71.24	7.14	
CASE	41	65	26	132
	9.26	14.67	5.87	29.80
	31.06	49.24	19.70	
	21.69	28.76	92.86	
TOTAL	189	226	28	443
	42.66	51.02	6.32	100.00

STATISTICS FOR 2-WAY TABLES

CHI-SQUARE	59.278	DF= 2	PROB=0.0001
PHI	0.366		
CONTINGENCY COEFFICIENT	0.344		
CRAMER'S V	0.366		
LIKELIHOOD RATIO CHISQUARE	56.390	DF= 2	PROB=0.0001

Figure E-2

Frequency Distribution in Cases, Controls by Conception Month Within Year (Total Sample)

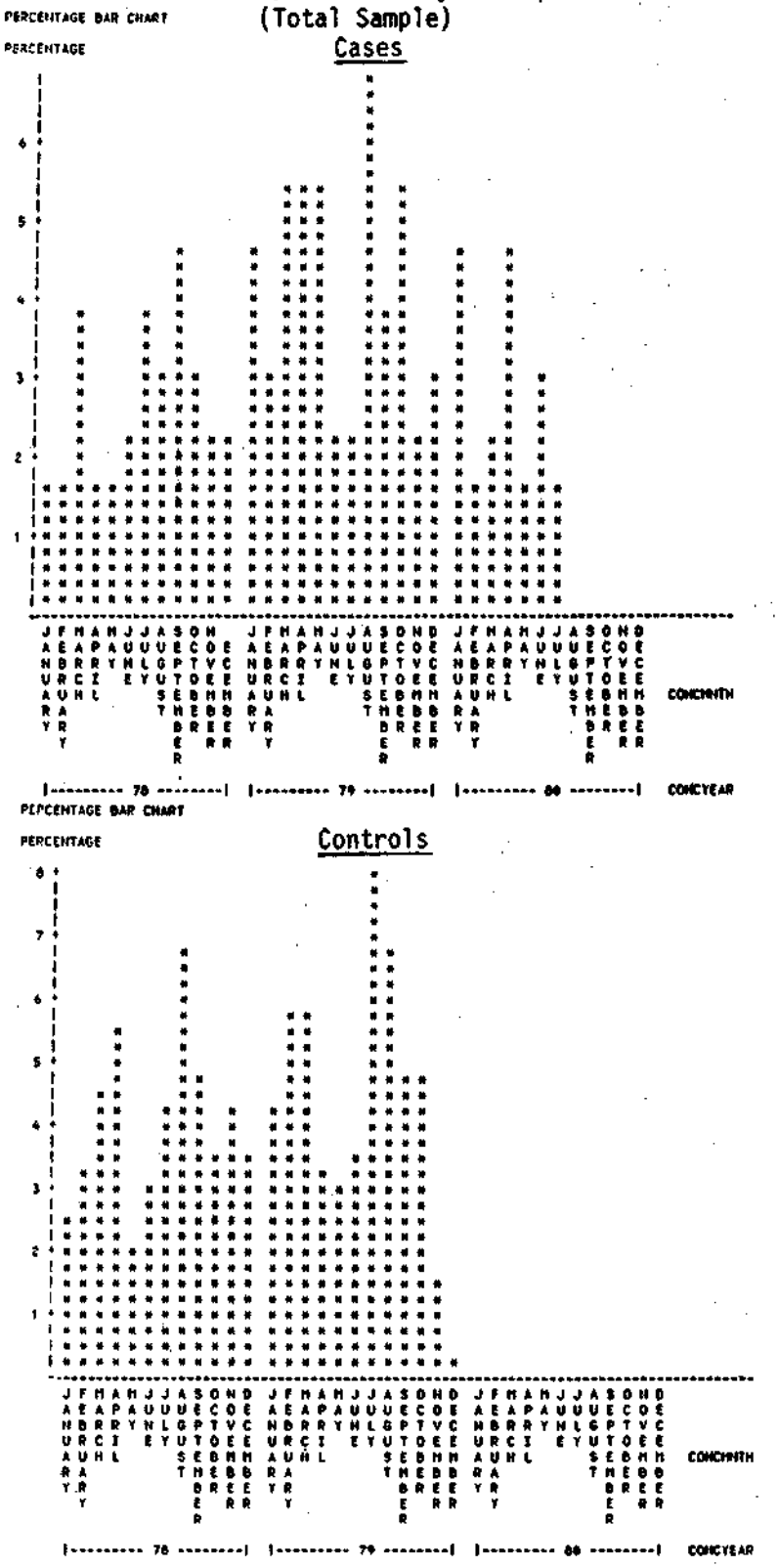


Table E-8

COMPARISON OF CASES AND CONTROLS BY LIST SOURCE
AND BY FARM AND FOREST/COMMERCIAL GROUPS

Frequency Percent ROW PCT COL PCT	List Source Farm Groups	Private Applicators	Forest Industry	Forest Service	Transportation	Government Applicators	Commercial Applicators	Utilities & Formulators	Mill Workers	Total
Control	59 13.26 18.97 76.62	59 13.26 18.97 70.24	22 4.94 7.07 84.62	20 4.49 6.43 68.97	11 2.47 3.54 73.33	5 1.12 1.61 55.56	13 2.92 4.18 61.90	3 .67 .96 100.0	119 26.74 38.26 65.75	311 69.89
Cases	18 4.04 13.43 23.38	25 5.62 18.66 29.76	4 0.90 2.99 15.38	9 2.02 6.72 31.03	4 0.90 2.99 26.67	4 0.90 2.99 44.44	8 1.80 5.97 38.10	0 0.0 0.0 0.0	62 13.93 46.27 34.25	134 30.11
	77 17.30	84 18.88	26 5.84	29 6.52	15 3.37	9 2.02	21 4.72	3 .67	181 40.67	445 100.0

Farm vs. Forest/Commercial

Frequency	Farmers	Forest	Total
Control	118	193	311
Case	43	91	134
Total	161	284	445

CHI-SQUARE = 1.39, PROB = .27

Table E-9

MANTEL-HAENSZEL ANALYSIS OF ASSOCIATION BETWEEN SPONTANEOUS ABORTIONS AND HUSBAND WORK EXPOSURE OVERALL AND DURING CONCEPTION PERIOD

	Husband Work Exposure Overall		Husband Work Exposure During Conception	
	Odds Ratio	90% Confidence	Odds Ratio	90% Confidence
Total Sample	.807	[.574-1.133]	1.15 (1.00)*	[.764-1.72]
Stratified by Group	.871	[.599-1.265] $X^2_{HOM}(1)=.196$ PROB=.66	1.25 (1.08)	[.816-1.91] $X^2_{HOM}(1)=.88$ PROB=.35
Forest/ Commercials	.929	[.598-1.442]	1.58 (1.33)	[.883-2.82]
Within Forest Commercial				
Stratified by Husband Age	.891	[.569-1.394] $X^2_{HOM}(2)=5.94$ PROB=.051	1.52 (1.26)	[.844-2.75] $X^2_{HOM}(2)=2.12$ PROB=.35
	RR in 18-25 age class was 3.08 with 90% confidence [1.21-7.84]			
Stratified by Husband Education	1.909	[.672-1.778] $X^2_{HOM}(3)=3.07$ PROB=.38	1.65 (1.38)	[.915-2.98] $X^2_{HOM}(3)=1.80$ PROB=.62

* Cases based upon validated miscarriages; exposure based upon reported and validated exposure

Table E-10

MANTEL-HAENSZEL ANALYSIS OF ASSOCIATION BETWEEN SPONTANEOUS ABORTIONS AND WIFE HOME EXPOSURE OVERALL AND DURING CONCEPTION PERIOD

	Wife Home Exposure Overall			Wife Home Exposure During Conception		
	Odds Ratio*			Odds Ratio*		
	Y_1	$VALY_1$	90% Confidence	Y_1	$VALY_1$	90% Confidence
Total Sample	1.22	(1.23)	[.866-1.72]	.741	(.758)	[.472-1.164]
Farm	.838	(.956)	[.445-1.58]	.542	(.610)	[.264-1.114]
Forest/Commercial	1.58	(1.52)	[1.039-2.409]	.982	(.943)	[.540-1.785]
Within Forest						
Stratified by education of wife	1.66		[1.082-2.55] X^2_{HOM}=2.361 df=3 prob=.50	1.04		[.568-1.910] X^2_{HOM}=.330 df=2 prob=.84
Stratified by age of wife	1.61		[1.051-2.46] X^2_{HOM}=1.432 df=2 prob=.49	.998		[.557-1.789] X^2_{HOM}=1.96 df=2 prob=.37
Stratified by husband exposure at home around conception	1.58		[1.035-2.42] X^2_{HOM}=1.194 df=1 prob=.27	.969		[.529-1.776] X^2_{HOM}=1.23 df=1 prob=.27
Stratified by husband exposure at work--overall	1.69		[1.088-2.63] X^2_{HOM}=.961 df=1 prob=.33	1.004		[.577-1.746] X^2_{HOM}.328 df=1 prob-.57
Stratified by husband exposure at work--around conception	1.52		[.988-2.33] X^2_{HOM}=.03 df=1 prob=.95	.868		[.466-1.620] X^2_{HOM}1.33 df=1 prob-.25
Validated cases stratified by--validated husband exposure	1.49		[.966-2.31] X^2_{HOM}=.06 df=1 prob=.94	.853		[.444-1.640] X^2_{HOM}=.558 df=1 prob=.45

* Y_1=Cases based upon reported miscarriages

$VALY_1$=Cases based upon validated miscarriages

Table E-11

COMPARISON OF HUSBAND AND WIFE RESPONSES TO QUESTION RELATED TO EXPOSURE TO 2,4-D FROM AERIAL SPRAY (One Type of Home Exposure)

Farm

Wife Responses \ Husband Responses	YES	NO	DONT REMEMBER	TOTAL
YES	17 6.20 50.00 35.42	11 4.01 32.35 5.98	6 2.19 17.65 14.29	34 12.41
NO	18 6.57 12.33 37.50	113 41.24 77.40 61.41	15 5.47 10.27 35.71	146 53.28
NOT AWARE 2,4-D	2 0.73 14.29 4.17	10 3.65 71.43 5.43	2 0.73 14.29 4.76	14 5.11
DONT KNOW	11 4.01 13.75 22.92	50 18.25 62.50 27.17	19 6.93 23.75 45.24	80 29.20
TOTAL	48 17.52	184 67.15	42 15.33	274 100.00

Forest/Commercial

Wife Responses \ Husband Responses	YES	NO	DONT REMEMBER	TOTAL
YES	59 37.58 88.06 65.56	8 5.10 11.94 15.38	0 0.00 0.00 0.00	67 42.68
NO	18 11.46 32.14 20.00	31 19.75 55.36 59.62	7 4.46 12.50 46.67	56 35.67
NOT AWARE 2,4-D	1 0.64 33.33 1.11	1 0.64 33.33 1.92	1 0.64 33.33 6.67	3 1.91
DONT KNOW	12 7.64 38.71 13.33	12 7.64 38.71 23.08	7 4.46 22.58 46.67	31 19.75
TOTAL	90 57.32	52 33.12	15 9.55	157 100.00

Appendix F

DEFINITION OF CASES AND CONTROLS, AND LIST OF VARIABLES

I Case--a woman who had conceived since January 1, 1978, and whose pregnancy terminated in a spontaneous abortion. Also: (1) her current partner was the father of the pregnancy, (2) she lived in either Oregon or Washington during the conception and pregnancy, (3) she had not had more than one prior therapeutic abortion, and (4) both she and her mate were 35 years of age or younger.

II Control--a woman who had conceived since January 1, 1978, and whose pregnancy outcome was a live birth. Also: (1) her current partner was the father of the pregnancy, (2) she lived in either Oregon or Washington during the conception and pregnancy, and (3) both she and her partner were 35 years of age or younger.

III Variables

A. Exposure--eight definitions of exposure to 2,4-D.

1. Exposure of the male at work during the conception period. Three categories--high, moderate and low. High exposure: direct handling or working with 2,4-D during the two months around the conception period. Moderate exposure: indirect exposure; that is, exposure but not through direct handling of the herbicide. Low exposure: all individuals without direct or indirect exposure were placed in the low exposure category.

2. Exposure of husband at work since 1/1/78. Same categories of exposure--high, moderate, and low.

3. Exposure of husband at home during the conception period. Categories were either "Yes" or "No."

4. Exposure of husband at home since 1/1/78. Categories were either "Yes" or "No."

5. Exposure of wife at work during the conception period. Categories of exposure were high, moderate, or low (as for husband--see "1" above).

6. Exposure of wife at work since 1/1/78. High, moderate, or low categories (as for husband).

7. Exposure of wife at home during the conception period. "Yes" or "No" (as for husband).

8. Exposure of wife at home since 1/1/78. "Yes" or "No" (as for husband).

B. Age--As determined from the postal questionnaire. Seven categories: (1) under 18 years, (2) 18-21 years, (3) 22-25 years, (4) 26-30 years, (5) 31-35 years, (6) 36-40 years, and (7) over 40 years.

C. Socioeconomic Status--Estimated by educational level utilizing six categories from the postal questionnaire: (1) grade 8 or below, (2) some high school, (3) completed high school, (4) vocational or technical school, (5) some college and (6) college degree(s).

D. Health Status--From the postal questionnaire: (1) poor, (2) fair, (3) good, and (4) excellent

E. Number of Pregnancies--Information was acquired to select for the most recent ones.

F. Sex of Live birth--Sex of live birth was recorded to see if any differences in sex ratios existed between cases and controls.

G. Term of Delivery--Recorded as "on time" (within one week of due date), "early," or "late."

H. Infant Health Problems or Malformations--Recorded to determine if excess health problems or malformations exist in the study population.

I. Smoking--Smoking history for both woman and man, both before and during pregnancy.

J. Marijuana--Recorded use of marijuana during pregnancy, for both the woman and man.

K. Drugs--Recorded use of prescription drugs for both male and female respondents--female's use during the first three months of pregnancy, male's use during the conception period.

L. Exposure to Other Herbicides--Male and female exposure recorded from postal questionnaire.

M. Other variables defining exposure--Several variables included to help define or support the categories of exposure (high, moderate, and low)--pertaining to such questions as method of application, inhalation of 2,4-D, indirect exposure, and total days of exposure.

Appendix G

DEFINITION OF EXPOSURE VARIABLES

Exposure of husband at work during conception period

High -	E7b plus E11	Yes to any 2-6
Mod -	E9 plus E11	Yes to any 2-6
Low -	E7b plus E9	No response

Exposure of husband at work--overall since 1/1/78

High -	E7b	Yes response
Mod -	E9	Yes response
Low -	E7b and E9	No response

Exposure of husband at home during conception period

Yes	24 or 26	Yes response (#1)
No	24 and 26	No response (#2 or #3)

Exposure of husband at home--overall

Yes	23 or 25a or 25b or 25c	Yes response
No	23 and 25a and 25b and 25c	No response

Exposure of wife at work during conception period

High -	T103b plus T107	Yes to any 2-6
Mod -	T105 plus T107	Yes to any 2-6
Low -	T103b and T105	No response

Exposure of wife at work--overall

High -	T103b	Yes response
Mod -	T105	Yes response
Low -	T103b and T105	No response

Exposure of wife at home during conception period

Yes	T120 or T122	Yes response (#1)
No	T120 and T122	No response (#2 or #3)

Exposure of wife at home--overall

Yes	T119 or T121a or T121b or T121c	Yes response
No	T119 and T121a and T121c	No response

T = Wife Telephone Interview
E = Husband Telephone Interview

Appendix H

I.D. # _ _ _ _ _ _

SCREENER

Wife Telephone Interview

Hello, this is _____, calling for SRI International. You and your husband recently completed a questionnaire for SRI on herbicides and pregnancy, and I'd like to ask you some more questions about your responses.

1. WERE ANY ITEMS LEFT BLANK ON THE MAIL QUESTIONNAIRE?

   1 Yes - (ASK QUESTIONS ATTACHED TO CONTACT RECORD)
   2 No - (Q.2)

2. According to your questionnaire, both you and your husband are under 35 years old. Is that correct?

   1 Yes - (Q.4)
   2 No, husband is 35 or older → (Q.3)
   3 No, I am 35 or older → (Q.3)

3. Did (he/you/either of you) turn 35 since you mailed in the questionnaire?

   1 Yes
   2 No (either or both were 35 or older when questionnaire was mailed). Thank you very much. That's all the information we need. (EXIT)

4. Have you been at your current address since January 1, 1978? (THIS QUESTION REFERS SPECIFICALLY TO THE RESPONDENT--NOT TO HER HUSBAND)

   1 Yes - (Q.5)
   2 No - (Q.4a)

4a. We need to know your residence history since the first of 1978. Can you tell me what month and year you moved to your present address?

_____ (Write out month & year) ☐☐, ☐☐ mo. year

4b. What was your address before that date, and when did you move there? (REPEAT FOR EACH PLACE LIVED SINCE JAN. 1, 1978.

	Address	Month, year moved there
(1)	_____	☐☐, ☐☐ mo. year
(2)	_____	☐☐, ☐☐ mo. year
(3)	_____	☐☐, ☐☐ mo. year

(IF MORE THAN 3 ADDRESSES SINCE 1/1/78, WRITE IN MARGINS OR ATTACH SEPARATE SHEETS)

SCREENER

Wife Telephone Interview

5. How long have you and Mr. _____ been living together? (Did you begin living together before January 1, 1978, or since then?)

   1 Before January 1, 1978 (More than 2 1/2 years)

   2 Since January 1, 1978 When? _____ ☐☐, ☐☐
   (Write in mo. & year) mo. year

6. (LOOK AT PRECODED SHEET "PREGNANCY INFORMATION") WHICH OF THE FOLLOWING APPLY TO THE RESPONDENT?

   (CIRCLE ALL THAT APPLY.)

   01 Not sure whether or not has been pregnant in the last two years; has had an unusually late and heavy period. (Q.66) (GREEN)

   02 Not sure whether or not has been pregnant in the last two years; has not had (or doesn't remember having) an unusually late and heavy period. (Q.67) (GREEN)

   03 Has not been pregnant in the last two years; has had an unusually late and heavy period. (Q.68) (GREEN)

   04 Has not been pregnant in the last two years; has not had (or doesn't remember having) an unusually late and heavy period. (Q.69) (GREEN)

   05 Has had a baby in the last two years.

   06 Has had a miscarriage in the last two years.

   07 Has had a therapeutic (elective) abortion in the last two years. (Q.7)

   08 Has had a stillbirth in the last two years.

   09 Is currently pregnant.

   10 Has been pregnant in the last two years; has had an unusually late and heavy period. (Q.52) (YELLOW)

(ASK QUESTION 7 IF CATEGORY 05, 06, 07, 08, OR 09 IS CIRCLED.)

7. I see from your questionnaire that you have had a (baby/miscarriage/still pregnant/abortion/stillbirth) in the last two years. Since January 1, 1978, how many times have you become pregnant? Please include here any miscarriages or abortions that you have had since then. (INCLUDE HERE ONLY PREGNANCIES THAT BEGAN ON OR AFTER 1/1/78.)

   1 Once

   2 Twice

   3 More than twice (How many times? _____)

SCREENER

Wife Telephone Interview

Ask Q.8 and Q.9 in Sequence

8. (IF MORE THAN ONE PREGNANCY, SAY: Let's start with your first pregnancy since January 1, 1978.) Can you tell me when you first became pregnant? That is, what month and year did you miss your first period? (IF DOESN'T REMEMBER, PROBE FOR DUE DATE AND WORK BACKWARD--REFER TO CALENDAR AND "PREGNANCY CHART.")

9. (ASK IF NECESSARY:) What was the outcome of that pregnancy? CIRCLE APPROPRIATE CATEGORY FOR EACH PREGNANCY LISTED IN GRID BELOW.)

	Month, Year of First Missed Period	OUTCOME OF PREGNANCY				
		Live Birth	Miscarriage	Therap. Abortion	Stillbirth	Still Pregnant
(1)	_____ Due date (if app): _____	1	2	3	4	5
(2)	_____ Due date (if app): _____	1	2	3	4	5
(3)	_____ Due date (if app): _____	1	2	3	4	5
(4)	_____ Due date (if app): _____	1	2	3	4	5
(5)	_____ Due date (if app): _____	1	2	3	4	5

10. DID RESPONDENT HAVE TWO OR MORE THERAPEUTIC ABORTIONS SINCE 1/1/78?

1 Yes Thank you very much. That's all the information we need. (EXIT)

2 No (Q.11)

11. DID RESPONDENT HAVE ANY MISCARRIAGES SINCE 1/1/78?

1 Yes (Q.12)

2 No (Q.13)

12. The next question is about therapeutic (that is, elective) abortions. Have you had two or more therapeutic abortions in your lifetime?

1 Yes Thank you very much. That's all the information we need. (EXIT)

2 No (Q.13)

13. DID ALL CONCEPTIONS OCCUR BEFORE RESPONDENT AND PARTNER BEGAN LIVING TOGETHER?

1 Yes Thank you very much. That's all the information we need. (EXIT)

2 No (RECORD ON PINK "CONCEPTION" CARD EACH CONCEPTION DATE THAT ENDED IN A LIVE BIRTH OR MISCARRIAGE AND OCCURRED SINCE RESPONDENT AND PARTNER BEGAN LIVING TOGETHER. ALSO RECORD WHETHER OR NOT CATEGORY 01, 03, OR 10 IS CIRCLED ON Q.6.)

ASK APPROPRIATE SET OF QUESTIONS FOR EACH PREGNANCY LISTED ON PINK CARD:

- ASK FIRST ABOUT LIVE BIRTHS (BLUE PAGES)
- THEN ASK ABOUT MISCARRIAGES (ORANGE PAGES)

IF NO LIVE BIRTHS OR MISCARRIAGES LISTED ON PINK CARD, SEE IF RESPONDENT HAD LATE, HEAVY PERIOD. IF YES, SKIP TO Q.52 (YELLOW PAGES); IF NOT EXIT.

MISCARRIAGE

I.D. # _ _ _ _ _

MISCARRIAGE NUMBER:
1 2 3 4 5

32. When did your miscarriage occur? (REMIND OF CONCEPTION DATE IF NECESSARY)

_____ ☐☐ ☐☐ ☐☐
month/approx. day/year mo. day year

33. What week or month of your pregnancy was this?

Week number: ☐☐ OR Month: ☐☐

34. Did you see or talk to a doctor about your miscarriage?

1 Yes (Q.35)
2 No (Q.37)

35. Did the doctor confirm that you had a miscarriage?

1 Yes (Q.43)
2 No (Q.37)
9 Don't Know (ASK Q.36)

36. What did the doctor say? (RECORD VERBATIM.)

_____

_____

_____

37. Why do you think it was a miscarriage you had?
(CIRCLE "YES" FOR EACH SYMPTOM MENTIONED)

(FOR EACH SYMPTOM NOT MENTIONED, ASK:) Did you experience (SYMPTOM)?
(CIRCLE "YES" OR "NO" AS APPROPRIATE)
(BE SURE TO ASK EACH AS A SEPARATE, DISTINCT QUESTION)

	SYMPTOM	EXPERIENCE Yes	No
A.	An unusually late and heavy period	1	2
B.	More frequent than usual urination (without any pain)	1	2
C.	Swollen or unusually tender breasts	1	2
D.	Nausea (for no apparent reason)	1	2
E.	Overwhelming fatigue	1	2
F.	Excessive or unusual hunger	1	2
G.	Any other symptom or reason you thought you were pregnant (SPECIFY)	1	2

_____

_____

_____

_____

MISCARRIAGE

(ASK Q.'S 38-42 IF RESPONDENT EXPERIENCED AN UNUSUALLY LATE AND HEAVY PERIOD Q.37)
(IF NO LATE HEAVY PERIOD, SKIP TO Q.43)

38. You said you had an unusually late and heavy period. About how late was this period? (OK TO READ CATEGORIES)

1 Less than a week (less than 7 days) late

2 A week (7 days) or more late

39. Did you miss a period that you should have had the month before you had this late, heavy period?

1 Yes

2 No

40. Would you say your periods are usually regular or irregular? (IF YOU ARE ASKED, "REGULAR" IS NO MORE THAN 1 WEEK VARIATION IN LENGTH OF CYCLE)

1 Regular (Q.42)

2 Irregular (Q.43)

3 Don't know (Q.41)

41. Does your cycle vary by more than a week?

1 Yes (Q.43)

2 No

9 Don't know (Q.42)

42. About how long is your cycle--that is, how many days from the start of one to the start of the next?

DK: "Just roughly...?"
RANGE: "Would that be closer to _____ or _____?"

01 Less than 20 days

02 20-23 days

03 24-27 days

04 28-32 days

05 33-36 days

06 37-40 days

07 More than 40 days

08 It varies

09 Have no idea

(AUTOMARK IF ASKED AT Q.21 OR Q.43)

43. Have you ever smoked cigarettes?

1 Yes (Q.44)
2 No (Q.48)

44. Did you smoke cigarettes at any time during this pregnancy?

1 Yes (Q.45)
2 No (Q.46)

45. About how many cigarettes did you smoke per day during this pregnancy? (IF NECESSARY: READ CATEGORIES)

1 Less than 1/2 pack per day (Less than 10 per day)
2 1/2 - 1 pack per day
3 More than 1 pack but less than 2 packs per day
4 Two or more packs per day
9 Don't remember (DON'T READ THIS CATEGORY)

SKIP TO Q.48

46. Did you smoke cigarettes during the month or so just before this pregnancy?

1 Yes (Q.47)
2 No (Q.48)

47. About how many cigarettes did you smoke per day during the month or so before this pregnancy? (OK TO READ CATEGORIES)

1 Less than 1/2 pack per day (Less than 10 per day)
2 1/2 - 1 pack per day
3 More than 1 pack but less than 2 packs per day
4 Two or more packs per day
9 Don't remember (DO NOT READ THIS CATEGORY)

48. During the first three months of this pregnancy, did you smoke any marijuana or hashish?

1 Yes
2 No
9 Don't remember

49. As far as you can remember, during the first three months of this pregnancy, did you take any prescription drugs, that is, any drugs that were prescribed for you by a doctor? (DO NOT INCLUDE ANY DRUGS BOUGHT WITHOUT A PRESCRIPTION)

1 Yes (Q.50)
2 No ——→ (Q.51)
3 Don't remember ↗

MISCARRIAGE

50. What prescribed drugs did you take?
(CIRCLE ALL MENTIONED--DO NOT READ LIST)

01 Anti-nausea medication (anti-emetics)--e.g., Benedectine

02 Prescription vitamins with iron (folate)

03 Prescription cold or allergy medication--e.g., Sudafed, Actifed

04 Tetracycline or Sulfa

05 Other antibiotics (usually for a urinary tract infection)--e.g., Gantrisin, Ampicillin, Macrodantin, Nitrofurantoin, Cephalin, Keflin, Kephlex

06 Medication for vaginitis--e.g., Monostat, Flagyl

07 Pain medication

08 Sleeping pills (barbiturates)

09 Amphetamines (pep pills, diet pills)

10 Tranquilizers--e.g., Miltown, Valium

11 Diuretics

12 Birth control pills

13 Medication to induce period

14 Other (SPECIFY NAME AND PURPOSE) _____

_____

_____

51. (LOOK AT PINK "CONCEPTION" CARD. PUT AN "X" IN FRONT OF THE PREGNANCY YOU HAVE JUST ASKED ABOUT.) ARE THERE ANY OTHER MISCARRIAGES LISTED?

1 Yes (REPEAT Q.'S 32-51 FOR NEXT MISCARRIAGE)

2 No (LOOK AT PINK CARD.) DID RESPONDENT REPORT LATE, HEAVY PERIOD?

a. Yes (Q.52)

b. No (Q.83)

LATE/HEAVY PERIOD

I.D. # _ _ _ _ _ _

UNUSUALLY LATE AND HEAVY PERIOD

52a. I see from your mail questionnaire that in the past two years you have had a period that seemed to you to be both unusually late and unusually heavy. Is that correct?

(NOTE: RESPONDENT MAY HAVE HAD A SERIES OF LATE AND/OR HEAVY PERIODS. THIS IS NOT WHAT WE ARE INTERESTED IN. WE ARE INTERESTED IN ONE DISTINCTIVE PERIOD--ONE THAT MIGHT HAVE BEEN A MISCARRIAGE.)

1 Yes

52b. (HAS RESPONDENT TOLD YOU ABOUT ANY LONG, HEAVY PERIODS ALREADY?)

1 Yes (Q.53)
2 No (Q.54)

2 No, not correct, no single period that was both unusually late and unusually heavy. (Q.83)

53. Is this the same period I've already asked you about?

1 Yes (Q.83)
2 No (Q.54)

54. When did this late, heavy period occur--what month and year? (OBTAIN BEST ESTIMATE)

_____ month, year

☐☐ mo. ☐☐ year

(LIST THIS DATE ON THE PINK "CONCEPTION" CARD) (IMPORTANT!)

55. About how late was this period?

1 Less than a week (less than 7 days) late
2 A week (7 days) or more late

56. Did you miss a period that you should have had the month before you had this late, heavy period?

1 Yes
2 No

(ASK Q.'S 57-79 ONLY IF YOU HAVE NOT ALREADY ASKED RESPONDENT ABOUT HER PERIOD AT Q.40-42.)

(IF YOU HAVE ASKED HER ABOUT HER PERIODS, SKIP TO Q.60)

57. Would you say your periods are usually regular or irregular?
(IF YOU ARE ASKED, "REGULAR" IS NO MORE THAN 1 WEEK VARIATION IN LENGTH OF CYCLE.)

1 Regular (Q.59)
2 Irregular (Q.60)
9 Don't Know (Q.58)

58. Does your cycle vary by more than a week?

1 Yes (Q.60)
2 No
9 Don't Know (Q.59)

LATE/HEAVY PERIOD

59. About how long is your cycle--how many days from the start of one to the start of the next?

DK: "Just roughly,...?"
RANGE: "Would that be closer to _____ or _____?"

01 Less than 20 days

02 20-23 days

03 24-27 days

04 28-32 days

05 33-36 days

06 37-40 days

07 More than 40 days

08 It varies

09 Have no idea

60. During the two months or so before this late, heavy period, did you smoke cigarettes?

1 Yes (Q.61)
2 No (Q.62)

61. During these two months or so, about how many cigarettes did you smoke per day?

1 Less than 1/2 pack per day (Less than 10 per day)
2 1/2 - 1 pack per day
3 More than 1 pack but less than 2 packs per day
4 Two or more packs per day
5 Don't remember (DON'T READ THIS CATEGORY)

62. During these two months or so, did you smoke any marijuana or hashish?

1 Yes
2 No
9 Don't remember

63. As far as you can remember, during these two months or so did you take any drugs or medication prescribed for you by a doctor?
(DO NOT INCLUDE ANY DRUGS, ETC., BOUGHT WITHOUT PRESCRIPTION.)

1 Yes (Q.64)
2 No
3 Don't remember (Q.65)

LATE/HEAVY PERIOD

64. What prescribed drugs did you take?
(CIRCLE ALL MENTIONED--DO NOT READ LIST)

01 Anti-nausea medication (anti-emetics)--e.g., Benedectine

02 Prescription vitamins with iron (folate)

03 Prescription cold or allergy medication--e.g., Sudafed, Actifed

04 Tetracycline or Sulfa

05 Other antibiotics (usually for a urinary tract infection)--e.g., Gantrisin, Ampicillin, Macrodantin, Nitrofurantoin, Cephalin, Keflin, Kephlax

06 Medication for vaginitis--e.g., Monostat, Flagyl

07 Pain medication

08 Sleeping pills (barbiturates)

09 Amphetamines (pep pills, diet pills)

10 Tranquilizers--e.g., Miltown, Valium

11 Diuretics

12 Birth control pills

13 Medication to induce period

14 Other (SPECIFY NAME AND PURPOSE) _____

_____

_____

65. During these two months or so, did you experience (READ FIRST ITEM BELOW)? (REPEAT FOR EACH ITEM: BE SURE TO ASK EACH AS A SEPARATE, DISTINCT QUESTION.)

		EXPERIENCE? Yes	No	Don't Remember
A.	More frequent than usual urination (without any pain)	1	2	9
B.	Swollen or unusually tender breasts	1	2	9
C.	Repeated nausea	1	2	9
D.	Overwhelming fatigue that you couldn't relate to particularly hard work or long hours	1	2	9
E.	Excessive or unusual hunger	1	2	9

Go to Q.83

I.D. # _ _ _ _ _ _

NOT / NOT SURE PREGNANT

01 - NOT SURE IF PREGNANT, DID HAVE LATE, HEAVY PERIOD

66. I see from your questionnaire that you are not sure if you have been pregnant in the last two years, and you have had a period that seemed to you to be both unusually late and unusually heavy. Is that correct?

1 Yes (Q.72)

2 No, was definitely pregnant (GO BACK TO Q.7 SCREENER)

3 No, did not have late and heavy period and was definitely not pregnant (Q.70)

4 No, did not have late and heavy period, but not sure if pregnant (Q.72)

5 No, did have late and heavy period but was definitely not pregnant. (GO BACK TO Q.54 - YELLOW)

---

02 - NOT SURE IF PREGNANT, NO UNUSUAL PERIODS

67. I see from your questionnaire that you are not sure if you have been pregnant in the last two years, and you have not had or don't remember having had any periods that seemed to you to be unusually late and heavy. Is that correct?

1 Yes (Q.72)

2 No, was definitely pregnant (GO BACK TO Q.7 SCREENER)

3 No, did have late, heavy period (GO BACK TO Q.54 - YELLOW)

4 No, was definitely not pregnant (Q.70)

---

03 - NOT PREGNANT, DID HAVE HEAVY, LATE PERIOD

68. I see from your questionnaire that you have not been pregnant in the last two years, but you have had a period that seemed to you to be unusually late and heavy. Is that correct?

1 Yes (GO BACK TO Q.54)

2 No, have been pregnant in past two years (GO BACK TO Q.7 SCREENER)

3 No, have not had an unusually late and heavy period (Q.70)

---

04 - NOT PREGNANT, NO UNUSUAL PERIODS

69. I see from your questionnaire that you have not been pregnant in the last two years and you haven't had, or don't remember having had any periods that were both unusually late and unusually heavy periods. Is that correct?

1 Yes (Q.70)

2 No, have been pregnant in past two years (GO BACK TO Q.7 SCREENER)

3 No, have had an unusually late and heavy period (GO BACK TO Q.54 - YELLOW)

---

70. Have you missed any periods in the past two years that you can remember?

1 Yes (Q.71)

2 No Thank you very much. That's all the information we need (EXIT).

71. Do you have any idea why you missed?

1 Yes (Why?) _____

_____

2 No _____

_____

NOT / NOT SURE PREGNANT

72. Why do you think you might have been pregnant? (CIRCLE "YES" FOR EACH SYMPTOM MENTIONED)

(FOR EACH SYMPTOM NOT MENTIONED, ASK:) Did you experience (SYMPTOM)? (CIRCLE "YES" OR "NO" AS APPROPRIATE)

SYMPTOM	EXPERIENCE? Yes	No
A. An unusually late and heavy period	1	2
B. More frequent than usual urination (without any pain)	1	2
C. Swollen or unusually tender breasts	1	2
D. Nausea	1	2
E. Overwhelming fatigue	1	2
F. Excessive or unusual hunger	1	2
G. Any other symptom or reason you thought you were pregnant (SPECIFY)	1	2

_____

_____

_____

_____

(ASK Q.'S 73a-77 IF RESPONDENT EXPERIENCED AN UNUSUALLY LATE AND HEAVY PERIOD AT Q.72). (IF NO LATE HEAVY PERIOD, SKIP TO Q.78)

73a. When did this unusually late and heavy period occur - what month and year? (OBTAIN BEST ESTIMATE)

_____ month, year ☐☐, ☐☐ mo. year

(LIST THIS DATE ON THE PINK "CONCEPTION" CARD)

73b. About how late was this unusually late and heavy period? (IF NECESSARY: READ CATEGORIES)

1 Less than a week (Less than 7 days) late

2 A week (7 days) or more late

74. Did you miss a period you should have had the month just before you had this late, heavy period?

1 Yes

2 No

75. Would you say your periods are usually regular or irregular?

1 Regular (Q.77)

2 Irregular (Q.78)

9 Don't Know (Q.76)

NOT / NOT SURE PREGNANT

76. Does your cycle vary by more than a week?

1 Yes (Q.78)
2 No (Q.77)
3 Don't Know (Q.77)

77. About how long is your cycle--how many days from the start of one period to the next?

OK: "Just roughly,...?"
RANGE: "Would that be closer to _____ or _____?"

01 Less than 20 days
02 20-23 days
03 24-27 days
04 28-32 days
05 33-36 days
06 37-40 days
07 More than 40 days
08 It varies
09 Have no idea

78. Did you smoke cigarettes around the time you (think you might have been pregnant/had this unusually late and heavy period)?

1 Yes (Q.79)
2 No (Q.80)

79. About how many cigarettes did you smoke per day during this time? (OK TO READ CATEGORIES)

1 Less than 1/2 pack per day (Less than 10 per day)
2 1/2 - 1 pack per day
3 More than 1 pack but less than 2 packs per day
4 Two or more packs per day
9 Don't remember (DON'T READ THIS CATEGORY)

80. Did you smoke any marijuana or hashish during this time?

1 Yes
2 No

NOT / NOT SURE PREGNANT

81. As far as you can remember, during this time did you take any drugs or medication prescribed for you by a doctor?
(DO NOT INCLUDE ANY DRUGS, ETC., BOUGHT WITHOUT A PRESCRIPTION)

1 Yes (Q.82)
2 No
3 Don't remember (Q.83)

82. What prescribed drugs did you take?
(CIRCLE ALL MENTIONED--DO NOT READ LIST)

01 Anti-nausea medication (anti-emetics)--e.g., Benedectine
02 Prescription vitamins with iron (folate)
03 Prescription cold or allergy medication--e.g., Sudafed, Actifed
04 Tetracycline or Sulfa
05 Other antibiotics (usually for a urinary tract infection)--e.g., Gantrisin, Ampicillin, Macrodantin, Nitrofurantoin, Cephalin, Keflin, Kephlax
06 Medicaiton for vaginitis--e.g., Monostat, Flagyl
07 Pain medication
08 Sleeping pills (barbiturates)
09 Amphetamines (pep pills, diet pills)
10 Tranquilizers--e.g., Miltown, Valium
11 Diuretics
12 Birth control pills
13 Medication to induce period
14 Other (SPECIFY NAME AND PURPOSE) _____

_____

_____

BIRTH CONTROL

I.D. # __ __ __ __ __

83. Since January 1, 1978, have you taken any birth control pills? (PAUSE FOR ANSWER) Since January 1, 1978, have you used an IUD?

1 IUD only (Q.86)
2 The pill only (Q.84)
3 Both
4 Neither (Q.87)

84. Are you taking birth control pills now?

1 Yes (Q.86)
2 No (Q.85)

85. Within two or three months after you stopped taking the pill, were your periods regular or irregular?

1 Regular
2 Irregular
3 Hasn't been 2 or 3 months since stopped
4 Got pregnant
9 Don't know, don't remember

(ASK FOR EACH METHOD USED Q.83.)
86. During what months since January 1, 1978, have you used (the pill/an IUD).

The pill: _____

_____

IUD: _____

_____

87. Since January 1, 1978, have you tried to become pregnant and been unable to do so? (IF MORE THAN ONE ATTEMPT ASK Q.'S 88-93 ABOUT MOST RECENT ATTEMPT)

1 Yes (IF RESPONDENT HAS LIVED WITH CURRENT PARTNER SINCE 1/1/78, SKIP TO Q.89; IF NOT, ASK Q.88)
2 No (Q.94)

88. Was this <u>since</u> you began living with (PARTNER'S NAME)?

1 Yes (Q.89)
2 No (Q.94)

89. Did you see a doctor about becoming pregnant?

1 Yes (Q.90)
2 No (Q.94)

BIRTH CONTROL

90. Did the doctor do any tests on your husband?

1 Yes (Q.91)
2 No (Q.93)

91. Did the doctor do a sperm count or a semen analysis?

1 Yes (Q.92)
2 No
9 Don't Know (Q.93)

92. Was the result normal or abnormal?

1 Normal (Q.93)
2 Abnormal (Q.94)
3 Don't Know (Q.93)

93. Where you nursing (breast feeding) during the time you were trying to become pregnant?

1 Yes
2 No

94. Could you tell me your height please?
(ROUND TO NEAREST EVEN INCH.)

☐☐ feet ☐☐ inches.

95. What is your current weight?

☐☐☐ pounds

96. Do you currently have any serious medical problems? (ANYTHING THE RESPONDENT FEELS IS SERIOUS) (RECORD SURVEY RESEARCH)

1 No
2 Yes (What are they?) _____

_____

_____

_____

97a. Have you been employed outside your home any time since January 1, 1978? Please include volunteer work.

1 Yes (Q.97b)

2 No (Q.101)

97b. Are you currently employed outside your home, or not?

1 Yes (Q.98)

2 No (Q.100)

98. What is your job title in the job you have now? (WRITE IN TITLES OF ALL CURRENT JOBS)

_____

99. Have you had (this job/these jobs) since January 1, 1978?

1 Yes (Q.101)

2 No (Q.100)

100. What was your job title in the (other) jobs you have held since January 1, 1978, and when did you hold these jobs?

Job Title	Month/Year Began	Month/Year Ended
_____	☐☐ ☐☐	☐☐ ☐☐
_____	☐☐ ☐☐	☐☐ ☐☐
_____	☐☐ ☐☐	☐☐ ☐☐
_____	☐☐ ☐☐	☐☐ ☐☐
_____	☐☐ ☐☐	☐☐ ☐☐

IF JOB TITLE IS NOT-DESCRIPTIVE, ASK "What type of work is that?"

101. Since January 1, 1978, have you done any farm work?

1 Yes

2 No

(IF NO ON BOTH 97a AND 101, SKIP TO Q.119) (IF YES ON EITHER 97a OR 101, ASK Q.102)

Now I'm going to ask you a few questions about possible exposures you might have had to herbicides in your (job/work on the farm). Later we will ask you about possible exposures to herbicides around your house, but for now, please concentrate only on your (job/work on the farm).

102. Since January 1, 1978, have you been exposed to herbicides in (your job/your work on the farm), as far as you know? By "exposed", we mean working with them yourself or working in an area where they are being used.

1 Yes (Q.103)

2 No → (Q.119)

3 Have no idea → (Q.119)

EXPOSURE

103a. Since January 1, 1978, has your work (in your job/on the farm) ever directly involved manufacturing, formulating, mixing, loading or applying any herbicides other than 2,4-D? (BE SURE TO SAY EACH TYPE OF WORK SLOWLY AND CLEARLY)

1 Yes
2 No
9 Have no idea

103B. How about 2,4-D itself? (Since January 1, 1978, have you done any of these activities with 2,4-D?)

1 Yes (Q.104)
2 No (Q.105)
3 Have no idea (Q.104)
4 Not aware 2,4-D (Q.121C)

104. I'm going to read some possible ways people can be directly exposed to 2,4-D. For each, please tell me whether or not you have done this since January 1, 1978.

Have you personally (READ FIRST ITEM) any time since January 1, 1978? (REPEAT QUESTION FOR EACH ITEM LISTED)

		Yes	No	Don't Remember
A.	Worked around open containers of 2,4-D	1	2	9
B.	Mixed 2,4-D with water or other substances	1	2	9
C.	Done backpack spraying of 2,4-D	1	2	9
D.	Done injection-type spraying of 2,4-D	1	2	9
E.	Applied 2,4-D from a plane or helicopter	1	2	9
F.	Applied 2,4-D from a tractor or truck	1	2	9
G.	Cleaned equipment that has been used in applying 2,4-D. (For example, nozzles, hoses, or windshields that are coated with 2,4-D)	1	2	9
H.	Come in direct contact with 2,4-D in other ways in your (job/work on the farm) What other ways?	1	2	9

_____

_____

IF "NO" TO ALL, ASK "In what way were you exposed to 2,4-D?

IF GET "INHALING" AT H, ASK "What were you doing at that time? (Record above.)

(IF YES TO ANY OF THE ABOVE, SKIP TO Q.107)
(IF NO TO ALL OF THE ABOVE, ASK Q.105)

105. Since January 1, 1978, have you ever worked within two miles of where 2,4-D was being applied or in areas within one or two days after 2,4-D had been applied?

1 Yes (Q.106)
2 No (Q.119)
3 Don't Know (Q.106)

EXPOSURE

106. Now, I'm going to read some ways people can be indirectly exposed to 2,4-D. For each, please tell me whether or not you have done this any time since January 1, 1978. Any time since January 1, 1978 have you (READ FIRST ITEM) (REPEAT FOR EACH ITEM LISTED)

	Yes	No	Don't Remember
A. Worked near forest or farm areas when 2,4-D was being applied by airplane or helicopter.	1	2	9
B. Worked in forest, farm, roadside, railroad or other areas while 2,4-D was being applied from the ground (tractor, truck, backpack etc.)	1	2	9
C. Come into contact with foliage in forest, farm, roadside, railroad or other areas within one or two days after 2,4-D has been applied.	1	2	9
D. Come in contact with 2,4-D in other ways in your (job/work on the farm). What are those ways?	1	2	9

_____

_____

IF "NO" TO ALL, ASK "In what way were you exposed to 2, 4-D?"

IF GET "INHALING" AT D, ASK "What were you doing at that time?" (Record above.

(IF YES TO ANY OF THE ABOVE, ASK Q.107; IF NO TO ALL, SKIP TO Q.119)

EXPOSURE

Ask Q.107 and Q.108 in Sequence

107. (LOOK AT PINK "CONCEPTION" CARD. IN THE LEFT HAND COLUMN, ENTER THE MONTH BEFORE EACH CONCEPTION OR LATE, HEAVY PERIOD)

Now I'd like you to think about the kinds of work you just told me about. During the months of (READ FIRST SET OF MONTHS AND YEARON PINK CARD), about how many days, if any, did you (KINDS OF WORK FROM Q'S 104 OR 106.) (RECORD RESPONSE IN "1ST" COLUMN) (IF NECESSARY READ CATEGORIES).

CONCEPTION/PERIOD:					DAYS OF "EXPOSED" WORK
1st	2nd	3rd	4th	5th	
1	1	1	1	1	None→(Ask other conception/period; otherwise Q.109)
2	2	2	2	2	1 or 2 days
3	3	3	3	3	3-10 days (Q.108)
4	4	4	4	4	11-20 days
5	5	5	5	5	21-30 days, or
6	6	6	6	6	More than 30 days
9	9	9	9	9	Don't remember (DO NOT READ THIS CATEGORY)

108. Now think about these (NUMBER) days during (MONTHS, YEAR) when you did that kind of work. On these days, do you think you ever got 2,4-D *on your skin* or clothing, inhaled the mist or dust of 2,4-D, or ingested any 2,4-D? You might have ingested 2,4-D by splashing it on your face, eating or smoking after you had had 2,4-D on your hands, or something like that. (RECORD RESPONSE IN "1ST" COLUMN)

CONCEPTION/PERIOD:					CONTACT, INHALED OR INGESTED?
1st	2nd	3rd	4th	5th	
1	1	1	1	1	Yes
2	2	2	2	2	No
3	3	3	3	3	Don't know, don't remember

(REPEAT QUESTIONS 107-108 FOR EACH PAIR OF MONTHS LISTED ON PINK CARD, AND RECORD RESPONSES IN APPROPRIATE COLUMN.)

EXPOSURE

109. Now, think about the period between January 1, 1978 and (MOST RECENT MONTH AND YEAR LISTED). During this time how many days in total do you think you did that kind of work we've been talking about. (Read list if necessary). (IF NECESSARY: REPEAT TYPES OF WORK AT Q.104 AND Q.106).

0 None (GO TO LEAD IN BEFORE Q.119.)
1 10 days or less
2 11-20 days
3 21-40 days
4 41-60 days
5 Over 60 days
9 Have no idea (DO NOT READ THIS CATEGORY)

(AUTOMARK "YES" IF ANY "YES" AT Q.108)

110. On these (NUMBER) days, do you think you ever got 2,4-D on your skin or clothing, inhaled the mist or dust of 2,4-D, or ingested any 2,4-D?

1 Yes
2 No
9 Don't know, don't remember

111. Since January 1, 1978, have you usually worn (READ EACH ITEM LISTED BELOW) when you worked with or were around 2,4-D?

		Yes	No
A.	Rubber or plastic gloves	1	2
B.	Rubber or plastic boots	1	2
C.	Cloth coveralls	1	2
D.	Rubber or plastic coveralls	1	2
E.	Goggles	1	2
F.	A cloth mask	1	2
G.	A rubber or plastic mask	1	2
H.	A respirator	1	2
I.	Any other protective clothing (IF "OTHER", DESCRIBE)	1	2

_____

_____

112. It is important to the validity of this study for us to be able to verify all reported exposures to 2,4-D. Do you have any records you could send us that would verify the times you were working with 2,4-D?

1 Yes What kind of records and for what periods of exposure?

_____

_____

_____

_____

We will send you a postage-paid envelope for these records.

2 No Have no records

113. Do you have a supervisor we could contact to verify the times you were exposed to 2,4-D? (IF NECESSARY: It would just be a quick phone call)

1 Yes (Q.114)

2 No (Q.116)

114. What is your supervisor's full name? _____

115. And what is (his/her) phone number at work? AREA: ___ NUMBER: _____

(IF NO PHONE NUMBER AVAILABLE, ASK:) Can you tell me the company's name and address?

_____

_____

_____

116. Do you have any co-workers we could contact to verify the times you were exposed to 2,4-D?

1 Yes (Q.117)

2 No (Q.118)

117. Could you give me their names and phone numbers, please? (GET ONE OR TWO NAMES AND NUMBERS)

(1) Name: _____

Phone: AREA: _____ NUMBER: _____

Is this a work or home phone number?

1 Work

2 Home

Place of work if no phone number available

COMPANY: _____

CITY: _____ STATE: _____

(2) Name: _____

Phone: AREA: _____ NUMBER: _____

Is this a work or home phone number?

1 Work

2 Home

Place of work if no phone number available

COMPANY: _____

CITY: _____ STATE: _____

118. (ASK ONLY IF HAVE NOT OBTAINED SUPERVISOR OR RECORD VERIFICATION)

Is there any other way we might be able to verify the times you were exposed to 2,4-D?

1 Yes DESCRIBE AND OBTAIN NAMES, PHONE NUMBER, PROMISE TO SEND ETC., AS APPROPRIATE.

_____

_____

_____

_____

_____

2 No other way to verify

EXPOSURE

Now, I'm going to ask you a few questions about possible exposures you might have had to herbicides around your house. Please do not mention any exposures to herbicides you may have had in your (job/work on the farm).

119. Since January 1, 1978, have you lived within one or two miles of where 2,4-D has been applied by airplane or helicopter?

1 Yes (Q.120)

2 No

9 Don't know → (Q.121)

3 Not Aware 2, 4-D (Q.121C)

120. As far as you know, was 2,4-D spraying taking place during (READ FIRST PAIR OF MONTHS AND YEAR LISTED ON PINK "CONCEPTION" CARD)? (REPEAT QUESTION FOR EACH PAIR OF MONTHS LISTED.)

CONCEPTION/PERIOD					SPRAYING DURING MONTHS OF INTEREST?
1st	2nd	3rd	4th	5th	
1	1	1	1	1	Yes
2	2	2	2	2	No, don't know
3	3	3	3	3	Did not live at that home during those months

121. Since January 1, 1978, do you remember having done any of the following?

	Yes	No	Don't Know
A. Have you walked through foliage within one or two days after 2,4-D has been applied to it? (DO NOT INCLUDE ANY WORK-RELATED CONTACT HERE)	1	2	9
B. Have you personally washed or handled any clothes that have been in contact contact with 2,4-D?	1	2	9
C. Have you personally used broad-leaf herbicides on your lawn or garden, such as Weed'n Feed or Weed-B-Gon, Super D Weedon, Hormotox, or Lawn Weed Killer or any other broad-leaf herbicides? (RECORD ANY KINDS MENTIONED AS USED THAT ARE NOT LISTED ABOVE)	1	2	9
_____			
_____			
_____			
D. Have you had any other kind of contact with 2,4-D other than job-related contact? What was that?	1	2	9
_____			

(IF YES TO ANY OF THE ABOVE, ASK Q.122; IF NO TO ALL, SKIP TO Q.123.)

EXPOSURE

122. (LOOK AT PINK "CONCEPTION" CARD.) Do you think you had any of these kinds of home or leisure contacts with 2,4-D during the months of (READ FIRST PAIR OF MONTHS LISTED ON PINK CARD)? (REPEAT FOR EACH PAIR OF MONTHS LISTED)

CONCEPTION/PERIOD					
1st	2nd	3rd	4th	5th	HOME, LEISURE CONTACT WITH 2,4-D?
1	1	1	1	1	Yes
2	2	2	2	2	No
9	9	9	9	9	Don't know, don't remember

123. Now, we need to ask Mr. (NAME OF HUSBAND/PARTNER) some questions about his exposure to herbicides. Is he available now for ten minutes or so? (IF NO: When would be the best time for us to reach him?) (RECORDS DAYS AND TIME)

_____

_____

124. Thank you very much. That's all the information we need. Would you like to receive a summary of the study results?

1 Yes

2 No

Thank you again for your help.

Appendix I

HUSBAND

I.D. # _ _ _ _ _ _

Inv. # _ _ _ _ _ _

Inv. Name _____

Husband Telephone Interview

Hello, this is _____ calling for SRI International. As your wife may have told you, we'd like to ask you some questions as part of our survey on herbicides and pregnancy.

1. Have you been at your current address since January 1, 1978? (THIS QUESTION REFERS SPECIFICALLY TO THE RESPONDENT--NOT TO HIS WIFE.)

1 Yes

2 No 1a. We need to know your residence history since the first of 1978. Can you tell me what month and year you moved to your present address?

_____ (Write out month & year) ☐☐, ☐☐ mo. year

1b. What was your address before that date, and when did you move there? (REPEAT FOR EACH PLACE LIVED SINCE JAN. 1, 1978.)

	Address	Month, year moved there
(1)	_____	☐☐, ☐☐ mo. year
(2)	_____	☐☐, ☐☐ mo. year
(3)	_____	☐☐, ☐☐ mo. year

(IF MORE THAN 3 ADDRESSES SINCE 1/1/78, WRITE IN MARGINS OR ATTACH SEPARATE SHEETS)

2a. Are you currently employed, or not?

1 Yes (Q.2b)

2 No (Q.4)

2b. What is your job title in the job you have now? (WRITE IN TITLES OF ALL CURRENT JOBS)

_____

_____

3. Have you had (this job/these jobs) since January 1, 1978?

1 Yes (Q.5)

2 No (Q.4)

HUSBAND

4. What was your job title in the (other) jobs you have held since January 1, 1978, and when did you hold these jobs?

Job Title	Month/Year Began	Month/Year Ended
_____	☐☐ ☐☐	☐☐ ☐☐
_____	☐☐ ☐☐	☐☐ ☐☐
_____	☐☐ ☐☐	☐☐ ☐☐
_____	☐☐ ☐☐	☐☐ ☐☐
_____	☐☐ ☐☐	☐☐ ☐☐

IF JOB TITLE IS NON-DESCRIPTIVE, ASK "What type of work is that?"

5. (SKIP TO Q.6 IF RESPONDENT IS A FARMER) Since January 1, 1978, have you done any farm work?

1 Yes
2 No

Now, I'm going to ask you a few questions about possible exposures you might have had to herbicides in your job. Later we will ask you about possible exposures to herbicides around your house, but for now, please concentrate on only your job.

6. Since January 1, 1978, have you been exposed to herbicides in your work, as far as you know? By "exposed", we mean working with them yourself or working in an area where they are being used.

1 Yes (Q.7)
2 No
3 Have no idea → (Q.23)

7a. Since January 1, 1978, has your work ever directly involved manufacturing, formulating, mixing, loading or applying any herbicides other than 2,4-D? (BE SURE TO SAY EACH TYPE OF WORK SLOWLY AND CLEARLY)

1 Yes
2 No
9 Have no idea

7b. How about 2, 4-D itself? (Since January 1, 1978; have you done any of these activities with 2, 4-D?)

1 Yes (Q.8)
2 No (Q.9)
3 Have no idea (Q.8)
4 Not Aware 2, 4-D (Q.25C)

HUSBAND

8. I'm going to read some possible ways people can be directly exposed to 2,4-D. For each, please tell me whether or not you have done this since January 1, 1978.

Have you personally (READ FIRST ITEM) any time since January 1, 1978? (REPEAT QUESTION FOR EACH ITEM LISTED)

		Yes	No	Don't Remember
A.	Worked around open containers of 2,4-D	1	2	9
B.	Mixed 2,4-D with water or other substances	1	2	9
C.	Done backpack spraying	1	2	9
D.	Done injection-type spraying	1	2	9
E.	Applied 2,4-D from a plane or helicopter	1	2	9
F.	Applied 2,4-D from a tractor or truck	1	2	9
G.	Cleaned equipment that has been used in applying 2,4-D. (For example, nozzles, hoses, or windshields that are coated with 2,4-D)	1	2	9
H.	Come in direct contact with 2,4-D in other ways in your (job/work on the farm) What other ways?	1	2	9

_____

_____

_____

IF "NO" TO ALL, ASK "In what way were you exposed to 2, 4-D?"

IF GET "INHALING" AT H, ASK "What were you doing at that time?" (Record above.)

(IF YES TO ANY OF THE ABOVE, SKIP TO Q.11)
(IF NO TO ALL OF THE ABOVE, ASK Q.9)

9. Since January 1, 1978, have you ever worked within two miles of where 2,4-D was being applied or in areas within one or two days after 2,4-D had been applied?

1 Yes (Q.10)

2 No (LEAD IN BEFORE Q.23)

3 Don't Know (Q.10)

10. Now, I'm going to read some ways people can be indirectly exposed to 2,4-D. For each, please tell me whether or not you have done this any time since January 1, 1978. Any time since January 1, 1978 have you (READ FIRST ITEM)? (REPEAT FOR EACH ITEM LISTED)

		Yes	No	Don't Remember
A.	Worked near forest or farm areas when 2,4-D was being applied by airplane or helicopter.	1	2	9
B.	Worked in forest, farm, roadside, railroad or other areas while 2,4-D was being applied from the ground (tractor, truck, backpack etc.)	1	2	9
C.	Come into contact with foliage in forest, farm, roadside, railroad or other areas within one or two days after 2,4-D has been applied.	1	2	9
D.	Come in contact with 2,4-D in other ways in your (job/work on the farm). What are those ways?	1	2	9

_____

_____

IF "NO" TO ALL, ASK "In what way were you exposed to 2, 4-D?"

IF GET "INHALING" AT D, ASK "What were you doing at that time?" (Record above.)

(IF YES TO ANY OF THE ABOVE, ASK Q.11; IF NO TO ALL, SKIP TO Q.24)

HUSBAND

Ask Q.11 and 12 in Sequence

11. (LOOK AT PINK "CONCEPTION" CARD)

Now, I'd like you to think about the kinds of work you just told me about. During the months of (READ FIRST SET OF MONTHS AND YEAR ON PINK CARD), about how many days, if any, did you...(KINDS OF WORK FROM Q'S 8 OR 10). (IF NECESSARY READ CATEGORIES)

CONCEPTION/PERIOD 1st	2nd	3rd	4th	5th	DAYS OF "EXPOSED" WORK	
1	1	1	1	1	None (ask other conception/period; otherwise Q.13.)	
2	2	2	2	2	1 or 2 days	(Q.12)
3	3	3	3	3	3-10 days	
4	4	4	4	4	11-20 days	
5	5	5	5	5	21-30 days, or	
6	6	6	6	6	More than 30 days	
9	9	9	9	9	Don't remember (DO NOT READ THIS CATEGORY)	

12. Now thinking about these (NUMBER) days during (MONTHS, YEAR) when you did that kind of work. On these days, do you think you ever got 2,4-D on your skin or clothing, inhaled the mist or dust of 2,4-D, or ingested any 2,4-D? (You might have ingested 2,4-D by splashing it on your face, eating or smoking after you had had 2,4-D on your hands, or something like that.) (RECORD RESPONSE IN "1ST" COLUMN)

CONCEPTION/PERIOD 1st	2nd	3rd	4th	5th	CONTACT, INHALED OR INGESTED?
1	1	1	1	1	Yes
2	2	2	2	2	No
3	3	3	3	3	Don't know, don't remember

(REPEAT QUESTIONS 11 AND 12 FOR EACH PAIR OF MONTHS LISTED ON PINK CARD, AND RECORD RESPONSES IN APPROPRIATE COLUMN)

---

13. Now think about the period between January 1, 1978 and (MOST RECENT MONTH AND YEAR LISTED). During this time how many days in total do you think you did that last kind of work we've been talking about. (IF NECESSARY REPEAT TYPES OF WORK FROM Q.8 AND 10. ALSO READ CATEGORIES IF NECESSARY.)

0 None (Q.23)
1 10 days or less
2 11-20 days
3 21-40 days
4 41-60 days
5 Over 60 days
9 Have no idea (DO NOT READ THIS CATEGORY)

(AUTOMARK "YES" IF ANY "YES" AT Q.12.)

14. On these (NUMBER) days, do you think you ever got 2,4-D on your skin or clothing, inhaled the mist or dust of 2,4-D, or ingested any 2,4-D?

1 Yes
2 No
9 Don't know, don't remember

15. Since January 1, 1978, have you usually worn (READ EACH ITEM LISTE BELOW) when you worked with or were around 2,4-D?

		Yes	No
A.	Rubber or plastic gloves	1	2
B.	Rubber or plastic boots	1	2
C.	Cloth coveralls	1	2
D.	Rubber or plastic coveralls	1	2
E.	Goggles	1	2
F.	A cloth mask	1	2
G.	A rubber or plastic mask	1	2
H.	A respirator	1	2
I.	Any other protective clothing (IF "OTHER", DESCRIBE)	1	2

_____

_____

16. It is important to the validity of this study for us to be able t all reported exposures to 2,4-D. Do you have any records you cou us that would verify the times you were working with 2,4-D?

1 Yes What kind of records and for what periods of exposure?

_____

_____

_____

_____

We will send you a postage-paid envelope for these records.

2 Have no records

17. Do you have a supervisor we could contact to verify the times you exposed to 2,4-D? (IF NECESSARY: It would just be a quick phone

1 Yes (Q.18)

2 No (Q.20)

18. What is your supervisor's full name? _____

19. And what is (his/her) phone number at work? AREA: _____ NUMBEF

(IF NO PHONE NUMBER AVAILABLE, ASK:) Can you tell me the company' and address?

_____

_____

_____

20. Do you have any co-workers we could contact to verify the times yc exposed to 2,4-D?

1 Yes (Q.21)

2 No (Q.22)

HUSBAND

21. Could you give me their names and phone numbers, please? (GET ONE OR TWO NAMES AND NUMBERS)

(1) Name: _____

Phone: AREA: _____ NUMBER: _____

Is this a work or home phone number?

1 Work
2 Home

Place of work if no phone number available

COMPANY: _____

CITY: _____ STATE: _____

(2) Name: _____

Phone: AREA: _____ NUMBER: _____

Is this a work or home phone number?

1 Work
2 Home

Place of work if no phone number available:

COMPANY: _____

CITY: _____ STATE: _____

22. (ASK ONLY IF HAVE NOT OBTAINED SUPERVISOR OR RECORD VERIFICATION)

Is there any other way we might be able to verify the times you were exposed to 2,4-D?

1 Yes DESCRIBE AND OBTAIN NAMES, PHONE NUMBERS, PROMISE TO SEND ETC., AS APPROPRIATE.

_____
_____
_____
_____
_____

2 No other way to verify

_____
_____

HUSBAND

Now, I'm going to ask you a few questions about possible exposures you might have had to herbicides around your house. Please do not mention any exposures to herbicides you may have had with your (job/work on the farm).

23. Since January 1, 1978, have you lived within one or two miles of where 2,4-D has been applied by airplane or helicopter?

1 Yes (Q.24)
2 No → (Q.25)
9 Don't know → (Q.25)

24. As far as you know, was 2,4-D spraying taking place during (READ FIRST PAIR OF MONTHS AND YEAR LISTED ON PINK "CONCEPTION" CARD)? (REPEAT QUESTION FOR EACH PAIR OF MONTHS LISTED.)

CONCEPTION/PERIOD					
1st	2nd	3rd	4th	5th	SPRAYING DURING MONTHS OF INTEREST?
1	1	1	1	1	Yes
2	2	2	2	2	No, don't know
3	3	3	3	3	Did not live at that home during those months

25. Since January 1, 1978, do you remember having done any of the following

	Yes	No	Don't Know
A. Have you walked through foliage within one or two days after 2,4-D has been applied to it? (DO NOT INCLUDE ANY WORK-RELATED CONTACT HERE)	1	2	9
B. Have you personally washed or handled any work clothes that have been in contact with 2,4-D?	1	2	9
C. Have you personally used broad-leaf herbicides on your lawn or garden, such as Weed 'n Feed or Weed-B-Gon, Super D Weedon, Hormotox, or Lawn Weed Killer? (RECORD ANY KINDS MENTIONED AS USED THAT ARE NOT LISTED ABOVE)	1	2	9
_____			
_____			
D. Have you had any other kind of contact with 2,4-D other than job-related contact? What was that?	1	2	9
_____			
_____			

(IF YES TO ANY OF THE ABOVE, ASK Q.26; IF NO TO ALL, SKIP TO Q.27.)

26. (LOOK AT PINK "CONCEPTION" CARD.) Do you think you had any of those kinds of home or leisure contacts with 2,4-D during the months of (READ FIRST PAIR OF MONTHS LISTED ON PINK CARD)? (REPEAT FOR EACH PAIR OF MONTHS LISTED)

CONCEPTION/PERIOD					HOME, LEISURE CONTACT WITH 2,4-D
1st	2nd	3rd	4th	5th	
1	1	1	1	1	Yes
2	2	2	2	2	No
9	9	9	9	9	Don't know, don't remember

Ask 27 and 28 in Sequence

27. (LOOK AT PINK "CONCEPTION" CARD) The last few questions are about your use of medication during the periods I've been asking you about. As far as you can remember, during (PAIR OF MONTHS AND YEAR LISTED ON PINK CARD), did you take any drugs prescribed for you by a doctor? (DO NOT INCLUDE ANY DRUGS NOT PRESCRIBED)

CONCEPTION/PERIOD					
1st	2nd	3rd	4th	5th	
1	1	1	1	1	Yes (Q.28)
2	2	2	2	2	No
9	9	9	9	9	Don't remember → (Q.29)

28. During (READ PAIR OF MONTHS LISTED ON PINK CARD) what prescription drugs did you take?

CONCEPTION/PERIOD					
1st	2nd	3rd	4th	5th	
01	01	01	01	01	Anti-nausea medication (anti-emetics)--e.g., Benedectine
02	02	02	02	02	Prescription vitamins with iron (folate
03	03	03	03	03	Prescription cold or allergy medicatior e.g., Sudafed, Actifed
04	04	04	04	04	Tetracycline or Sulfa
05	05	05	05	05	Other antibiotics (usually for a urinar tract infection--e.g., Gantrisin, Ampicillin, Macrodantin, Nitrofurantoin, Cephalin, Keflin, Kephlax
07	07	07	07	07	Pain medication
08	08	08	08	08	Sleeping pills (barbituraaes)
09	09	09	09	09	Amphetamines (pep pills, diet pills)
10	10	10	10	10	Tranquilizers--e.g., Miltown, Valium
11	11	11	11	11	Diuretics
14	14	14	14	14	
____	____	____	____	____	
____	____	____	____	____	

Repeat Q.27 and Q.28 for Each Pair of Months on Pink Card

HUSBAND

29. Since January 1, 1978, have you smoked cigarettes, or not?

1 Yes
2 No

30. As well as you can remember, during (PAIR OF MONTHS AND YEAR ON PINK CARD), did you smoke any marijuana or hashish? (REPEAT FOR EACH PAIR OF MONTHS LISTED.)

CONCEPTION/PERIOD					
1st	2nd	3rd	4th	5th	
1	1	1	1	1	Yes
2	2	2	2	2	No
9	9	9	9	9	Don't Remember

31. Thank you very much. That's all the information we need. Would you like to receive a summary of the study results?

1 Yes

2 No

Thank you again for your help.

Appendix J

DOCUMENTATION OF THE MANTEL-HAENSZEL ANALYSIS PROGRAM

The MULFF (multiple fourfold table analysis) procedure, written in IBM level H FORTRAN, produces Mantel/Haenzel and maximum likelihood statistics to measure the degree of association between a binary outcome event and a binary risk factor. The subjects to be analyzed must be tabulated in one or more mutually exclusive groups (limit 100) with each group arranged as a fourfold table:

	Exposed	Unexposed
Case	a	c
Control	b	d

In this notation, a + b are the subjects exposed to the risk factor and a + c are the subjects with the outcome being studied.

The procedure provides the odds ratio (ad/bc) and log odds for each group and calculates summary estimates using both Mantel-Haenzel and maximum likelihood methods.[1,2] The summary log odds and the associated standard error are also calculated. The significance of each table is tested using a chi-square test, and confidence intervals (90% and 95%) are provided for the odds ratio estimates. The maximum likelihood method provides smoothed estimates of the cell counts for each group. Freeman-Tukey residuals[3] are calculated to assist the analyst in identifying outliers.

The procedure has been tested with data and examples from Fleiss and Rothman; Figure J-1 shows the job setup for the examples. Figure J-2 is the corresponding output for one table. The header page identifies the procedure, lists the user comments (* in column 4), and prints a brief

dictionary of terms. Page J-5 prints each group with column and row percents. Page J-6 provides statistics for each group, summary odds, and the chi-square analysis. Page J-7 gives expected cell counts using the maximum likelihood estimates and Freeman/Tukey residuals.

Input Format

The MULFF procedure will analyze multiple sets of tables, each with from 1 to 100 groups. The input formats are:

1) Comment - '*' in column 4, Cl 5 is the FORTRAN page control character (blank = single space).

2) Table start -
   Col. 1-3 = number of groups
   Col.4 - table format code (M or C)
   Col. 5-72 = name of table or analysis

3) Group data (Format = M)
   Col. 1-12 = group name
   Col. 13-17 = exposed cases (a)
   Col. 18-22 = exposed controls (b)
   Col. 23-27 = unexposed cases (c)
   Col. 28-32 = unexposed controls (d)

4) Group data (Format = C)
   Col. 1-12 = group name
   Col. 13-17 = number exposed (a+b=N1)
   Col. 18-22 = proportion cases exposed (P1)
   Col. 23-27 = number unexposed (c+d=N2)
   Col. 28-32 = Proportion controls unexposed (P2)

```
//JOB (USER)
//*
//*FOURFOLD TABLES MANTEL/HAENSZEL METHOD
//*
//*EXEC PGM=MULFF
//*STEPLIB DD DSN=YOUR.LIBRARY, DISP=SHR
//GO.FT12F001 DD SYSOUT=A,DCB=RECFM=FBA
//GO.SYSIN  DD  *
   *      TEST RUNS OF THE FOUR FOLD TABLE PROGRAM
   *      WITH CHECK EXAMPLES FROM:
   *          'STATISTICAL METHODS FOR RATES AND PROPORTIONS',FLEISS
   *          'EPIDEMIOLOGIC ANALYSIS ...',ROTHMANN
003MEXAMPLE FROM FLEISS TABLE 10.1
1. AGE 20/34    38   67    33   72
2. AGE 20/59    56  136    61  113
3. AGE 35/59    43  102    33  112
003C
1. AGE 20/34  105 .362  105 .314
2. AGE 20/59  192 .292  174 .351
3. AGE 35/59  145 .297  145 .228

001MROTHMAN TABLE 1.1 EXAMPLE
COMBINED       688  650    21   59
002MROTHMAN TABLE 1.2 EXAMPLE
MALES          647  622     2   27
FEMALES         41   28    19   32
003MROTHMAN TABLE 2.2 EXAMPLE
STRATUM 1       15  319    64 1409
STRATUM 2        8   55    72  381
STRATUM 3       14   41    68  161
STRATUM 4       12   18    67   71
STRATUM 5       13    4    66   29
001MROTHMAN TABLE 5.2 EXAMPLE
MOTHERS          4    4   386 1250
```

FIGURE J-1 PROCEDURE MULFF RUN SETUP

```
MULTIPLE FOURFOLD  TABLE ANALYSIS

        N1  = TOTAL NUMBER EXPOSED OR AT RISK
        P1  = PROPORTION CASES EXPOSED
        N2  = TOTAL NUMBER UNEXPOSED
        P2  = PROPORTION CASES UNEXPOSED
        DM  = ADJUSTED STANDARDIZED DIFFERENCE
        WM  = WEIGHT (MANTEL-HAENSZEL)
        ODDS= ODDS RATIO
        LN ODDS= NATURAL LOG OF ODDS RATIO
        CH2L= CHI SQUARE USING LOG ODDS
        CH2M= MANTEL-HAENSZEL CHI SQ
        CHI-MH=MANTEL-HAENSZEL CHI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     SRI INTERNATIONAL
     (415)359-5272


     USER ANALYSIS COMMENTS:

TEST RUNS OF THE FOUR FOLD TABLE PROGRAM
WITH CHECK EXAMPLES FROM:
    'STATISTICAL METHODS FOR RATES AND PROPORTIONS',FLEISS
    'EPIDEMIOLOGIC ANALYSIS ...',ROTHMANN
```

FIGURE J-2 SAMPLE MULFF OUTPUT

ROTHMAN TABLE 2.2 EXAMPLE

FOUR FOLD TABLES -- RAW COUNTS

	EXPOSED	UNEXPOSED	COLUMN PERCENTS		ROW PERCENTS		COUNT
STRATUM 1							
CASE	15	64	4.5	4.3	19.0	81.0	79
CONTROL	319	1409	95.5	95.7	18.5	81.5	1728
STRATUM 2							
CASE	8	72	13.1	15.9	10.0	90.0	80
CONTROL	53	381	86.9	84.1	12.2	87.8	434
STRATUM 3							
CASE	14	68	25.5	29.7	17.1	82.9	82
CONTROL	41	161	74.5	70.3	20.3	79.7	202
STRATUM 4							
CASE	12	67	40.0	48.6	15.2	84.8	79
CONTROL	18	71	60.0	51.4	20.2	79.8	89
STRATUM 5							
CASE	13	66	76.5	69.5	16.5	83.5	79
CONTROL	4	29	23.5	30.5	12.1	87.9	33
	497	2388					2885

FIGURE J-2 (continued)

ROTHMAN TABLE 2.2 EXAMPLE

FOUR FOLD TABLES -- SUMMARY ANALYSIS

TABLE	N1	P1	N2	P2	DM	WM	ODDS	LN ODDS	CH2L	CH2M	PROB
STRATUM 1	334	0.0449	1473	0.0434	0.0349	11.3890	1.0352	0.0346	0.0139	0.0139	0.9061
STRATUM 2	61	0.1311	453	0.1589	-0.2111	7.0789	0.7987	-0.2247	0.3149	0.3154	0.5744
STRATUM 3	55	0.2545	229	0.2969	-0.2057	9.1399	0.8085	-0.2126	0.3873	0.3868	0.5340
STRATUM 4	30	0.4000	133	0.4855	-0.3412	6.1756	0.7065	-0.3475	0.7191	0.7190	0.3965
STRATUM 5	17	0.7647	95	0.6947	0.3337	3.0238	1.4280	0.3563	0.3371	0.3366	0.5618
					SUMMARY ODDS:		0.8930	0.8916	1.7723	1.7717	
					STANDARD ERROR:			0.1507			
					SHR-MEITTINEN:		0.9130				

CONFIDENCE INTERVALS FOR SUMMARY ODDS RATIO

Z	****** LOW - HIGH ******	** CHI-MH **
1.6450	.6768 1.178	-.6716
1.9600	.6418 1.242	-.6716

MANTEL-HAENSZEL ANALYSIS

TYPE	CHI SQUARED	DF	PROBABILITY
TOTAL	1.772	5.	.8797
ASSOC	.4511	1.	.5018
HOMOGEN	1.321	4.	.8579

MAXIMUM LIKLIHOOD ESTIMATOR OF RR IS 0.8930

CONFIDENCE INTERVALS FOR ML ESTIMATE OF RR

Z	***** LOW - HIGH *****	** CHI-MH **
1.6450	.6769 1.178	-.6716
1.9600	.6419 1.242	-.6716

FIGURE J-2 (continued)

ROTHMAN TABLE 2.2 EXAMPLE

FOUR FOLD TABLE -- ML ESTIMATES OF COUNTS

	EXPOSED	UNEXPOSED	FREEMAN-TUKEY DEVIATES	
STRATUM 1				
CASE	13.8555	66.1445	0.4876	-0.1722
CONTROL	321.1443	1407.8560	-0.0779	0.0505
STRATUM 2				
CASE	9.2185	71.7815	-0.1565	0.1136
CONTROL	52.7815	382.2185	0.1322	-0.0240
STRATUM 3				
CASE	15.3650	67.6350	-0.1583	0.1347
CONTROL	40.6350	162.3650	0.1730	-0.0483
STRATUM 4				
CASE	13.9143	66.0857	-0.3173	0.2030
CONTROL	17.0857	72.9144	0.3898	-0.1368
STRATUM 5				
CASE	12.1465	67.8535	0.4404	-0.1344
CONTROL	5.8535	28.1465	-0.4745	0.2964

MAXIMUM-LIKLIHOOD ANLYSIS

TYPE	CHI SQUARED	DF	PROBABILITY
HOMOGEN	1.297	4.	.8619

FIGURE J-2 (concluded)

REFERENCES

1. Joseph L. Fleiss, Statistical Methods for Rates and Proportions, Wiley, 1973. See especially Chapter 10, "Combining Evidence from Fourfold Tables."

2. Kenneth J. Rothman and John D. Boice, Jr., Epidemiologic Analysis with a Programmable Calculator, NIH Publication 79-1649, 1979. See especially Chapter 2, "Case-Control Studies."

3. Yvonne M. M. Bishop et al, Discrete Multivariate Analysis, Theory and Practice, MIT Press, 1975. See Section 4.2.3, "Other Summary Statistics" for a definition of the Freeman-Tukey residuals.