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WEST 1433

AR 226-1381 * Put together package on Confidentiality
Protection *

: Study 3 teratogens instead of 1 [C-8, DMF
? F22? HFA]

STUDY OF PREGNANCY OUTCOME IN WASHINGTON WORKS EMPLOYEES:

RESEARCH PROPOSAL

- Company Wide

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Why not define ^{exposure by} Blood Levels

1. Don't know blood levels during pregnancy
2. Don't know what signif. of OF level is in relation to pregnancy.

As blood data became available, we will include in analyses.

William E. Fayerweather
Employee Relations Department
Medical Division
Epidemiology Section
April 13, 1981

Why not add Circleville?
Ans: "is lower exposure
therefore might
dilute effect"

- Wasted disposal question: potential C-8 exposure
- M.D. meets with nurses; handle study
- Keep I.O. information separate from questions on pregnancy outcome

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I. Objectives

The study's objectives are to determine whether

- a. Pregnancy outcome among female Washington Works employees is causally related to their occupational exposure to C-8.
- b. Pregnancy outcome among wives of Washington Works employees is causally related to their husbands' exposure to C-8.

II. Background and Rationale

There have been five toxicologic experiments in which C-8 was administered repeatedly to experimental animals and in which the male reproductive system was examined. In none of the studies were treatment-related testicular changes observed.

Recently 3M conducted an oral rangefinder study of C-8. The purpose of this study was to determine the upper dose level of C-8 for a subsequent oral teratology study in rats. Suspensions of C-8 and corn oil were given by oral intubation to 5 groups of time-mated female rats (Charles River Sprague-Dawley derived). The doses received were 150, 100, 75, 50, or 25 mg/kg/day of C-8. These doses were given on days 6 through 15 of gestation (i.e., the period of organogenesis). There was one control group that received only corn oil by intubation on these same days. Each dosed and control group consisted of 6 time-mated female rats.

At day 20 of gestation the rats from the 3M study were sacrificed. Four fetuses were examined from each of four dams in the 150 and 25 mg/kg/day dose groups. All of the readable fetuses

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sectioned had eye lens abnormalities. The authors noted that two previous teratology studies with chemically related compounds resulted in fetuses with similar abnormal changes in the lens of the eye.

At Washington Works significant occupational exposure to C-8 is limited to the Teflon area. C-8 is a dispersing agent that is used in nearly all Teflon polymer and copolymer processes. The monomers do not contain C-8. Based on previous analyses of blood organic fluoride levels of workers, the greatest potential for C-8 exposure occurs in four jobs: TFE process operator, FEP process operator, TFE service operator, and FEP service operator.

In the proposed study of pregnancy outcome, exposed female employees and wives of exposed male employees will be studied. Female workers are studied because they may have been exposed to C-8 during or immediately prior to their pregnancies. Wives of male workers are studied because the husbands may somehow bring C-8 home with them and expose their wives at home. There is no evidence at present to suggest that C-8 exposure affects the husband's reproductive system.

III. Specific Aims

Histories of pregnancy outcome and of potential exposure to C-8 will be ascertained for

- a. Washington Works active female employees, and
- b. Wives of Washington Works active male employees.

Potential exposure to C-8 will be determined from personal records, medical records, and employee interviews. Pregnancy outcome will be determined via self-administered questionnaires given to female employees and wives of male employees.

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If an association is observed between pregnancy outcome and having had potential exposure to C-8, the association will be assessed as to whether it is causal or whether it is due to other confounding factors.

IV. Methods

A. Study Groups

1. Workers with potential C-8 exposure

a. Definition of exposure: Teflon area

All Teflon area jobs will be defined as having potential exposure to C-8. These jobs will be further categorized as having either high or low potential for exposure.

Table I shows the exposure categorization scheme used in the previous liver function study of C-8 workers. Notice that several job titles appear in both the high and low exposure potential columns. This happens because exposure potentials for most Teflon area jobs depend on the particular time period and task considered. Within the high potential category, current TFE/FEP service and process operators have the highest potential for exposure based on blood organic fluoride levels.

Some mechanics, non-semiworks laboratorians, and chemists/engineers occasionally come in contact with C-8. However, the natures of their jobs and of the personnel record keeping system make it very difficult to determine these workers' exposure to

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C-8 or to other chemicals. For this reason, mechanics, non-semiworks laboratorians, and chemists/engineers will be defined as having unknown exposure potential.

b. Selection of exposed workers

All active male and female workers who have ever worked in a C-8 exposure job (as defined above) will be identified. Brief questionnaires will be given to these workers to determine who has ever been married. All ever married workers will be included and all never married will be excluded from the study.

2. Workers with no potential C-8 exposure

a. Definition of non-exposure

All non-Teflon area jobs, with the exception of the jobs with unknown exposure potential (e.g., mechanic), will be defined as having no potential for C-8 exposure.

b. Selection of non-exposed workers (controls)

All of the plant's non-exposed active female workers will be selected as controls for the exposed female workers.

For each C-8 exposed active male employee, one matched non-exposed male employee will be chosen as a control. Matching will be on payclass, birth date (± 3 years), and adjusted service date (± 3 years). The control for each exposed worker will

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be the first eligible employee appearing in the yearly employee roster after the exposed worker's name.

Each male and female control will be given a questionnaire to determine whether he/she has ever been married. All never married controls will be dropped from the study. For the male subjects, new controls will be chosen to replace those controls who either were never married or who refused to participate in the study.

B. Sources of Data

1. Exposure histories

Plant personnel will be responsible for:

- determining which active employees have ever had potential exposure to C-8.
- collecting detailed exposure histories on the study subjects.

These histories will be assembled from personnel records, medical records, and employee interviews. The work histories should contain:

- name
- color (white/non-white)
- birth date
- payclass
- date hired
- all jobs having C-8 exposure potential
- month and year the worker moved in and out of C-8 jobs

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- each job's exposure potential (high or low)
- blood organic fluoride level and date taken

Exposure histories will be recorded on code sheets that will be designed and supplied by Medical Division.

2. Pregnancy outcome data

All female study subjects will be asked to complete a self-administered questionnaire on pregnancy outcome.

All male subjects will be given an initial questionnaire to determine whether they have ever been married and whether they are now living with their wives. Males who have been married but who no longer live with their wives (e.g., because of divorce, separation, or death) will be asked to complete the pregnancy outcome questionnaire themselves. Males who are now living with their wives will be asked to give the questionnaire to their wives to complete. Never married workers will be dropped from the study.

C. Major Response Variables

The major measures of pregnancy outcome, which are to be ascertained via a self-administered questionnaire, include:

1. # Pregnancies
2. # Spontaneous abortions/miscarriages
3. # Stillbirths
4. # Induced abortions (for medical or personal reasons)
5. # Live-born children
6. # Live-born children with birth defects or other problems at birth

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7. Types of birth defects or problems observed at birth

8. Birth weights

D. Potentially Confounding Variables

Information on a number of potentially confounding factors will be ascertained via the pregnancy outcome questionnaire. These include:

1. Maternal age
2. Paternal age
3. Infectious diseases (e.g., rubella)
4. Family history of malformations/miscarriages/stillbirths
5. Medications/drugs
6. Ionizing radiation
7. Smoking
8. Chemical exposures outside the plant (e.g., other occupations)
9. Alcohol
10. Number of previous marriages
11. Birth control/desire for more children
12. Color/ethnicity (to be determined by plant personnel).

E. Quality Control

If the final product of this study is to fair well against peer review from outside of the Company, steps must be taken to assure, measure, and document the quality of the data collected.

1. Validation of pregnancy outcome supplied by female workers

The responses on 100% of the female workers' questionnaires should be validated. A worker's responses could be validated by checking existing Du Pont medical records and by contacting the worker's personal physician. This

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last step would only be done after having obtained the worker's informed consent to do so.

2. Validation of pregnancy outcome supplied by husbands

The responses on 10% of the questionnaires given to workers' wives should also be compared with the responses given independently by their working husbands. This comparison will help document the quality of the responses given by husbands.

3. Validation of work histories supplied by the plant

After work histories for exposed and nonexposed subjects have been sent to Medical Division, data from a 10% sample of these subjects will be auditted. For this audit the plant will be asked to supply the records from which these work histories have been assembled.

F. Pilot Study

Prior to giving questionnaires to all study subjects, a pilot study should be done. This pilot study should include about 5 male and 5 female workers who have had no potential C-8 exposure. It will allow us to pre-test the pregnancy outcome questionnaire and other study procedures.

V. Sample Size

A. Female Employees

Currently there are 32 exempt, 130 non-exempt, and 159 wage roll females actively employed at the plant. As of April 1, about 50 of these women worked in the Teflon

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area. Only about one dozen of these women were in jobs having a high potential for C-8 exposure.

From 1965 through 1980 there were 103 leaves of absence due to pregnancy (table II). Thirteen of these leaves were among wage roll employees.

B. Male Employees

Over 300 men, or about ten percent of the plant's workforce currently work in the Teflon area. Within the Teflon area, 60 to 70 workers are in jobs that have high potential for C-8 exposure. Since each exposed male will be matched with one non-exposed male, the total number of males included in the study will be over 600. The number of active workers who no longer work in the Teflon area is unknown. The number of births to wives of male employees is also unknown.

C. Statistically Significant Excesses

The national incidence rate for craniofacial malformations is about 2 per 1000 live births, and the rate for malformations of all types is about 20 per 1000. Given these background rates, table III shows the minimum number of births with malformations that must be observed in the study group to say that there is a statistically significant excess ($p < 0.05$). For instance, 2 malformations in 10 exposed live births is a significantly higher rate than a national rate of 2 per 1000. Two malformations per 10 exposed live births is also significantly higher than a plant rate of 0 per 50 nonexposed births.

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VI. Analyses

1. Data on C-8 exposed female workers will be analyzed separately from data on wives of exposed male workers.
2. C-8 exposed female workers and wives of exposed male workers will be compared with four control groups:
 - Female W.W. workers never exposed to C-8
 - Wives of male workers at W.W. never exposed to C-8
 - Non-W.W. female employees at another Du Pont plant
 - Wives of non-W.W. employees at another Du Pont plant.
3. All of the measures of pregnancy outcome mentioned in the earlier section on major response variables will be analyzed.
4. The analyses will be adjusted for the effects of the potentially confounding variables mentioned earlier. Binary regression and Mantel-Haenszel methods will be used for these adjustments.
5. Analyses will take into account that only exposures occurring immediately prior to conception or during the first trimester of the pregnancy are likely to produce malformations.
6. Hypothesis testing will be two-tailed, and significance will be judged at the 0.05 probability level.

VII. Confidentiality and Informed Consent

Any female employees, male employees, or wives of male employees who are asked to participate in this study will be

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asked to first read, understand, and then sign an informed consent statement. This informed consent statement will clearly describe:

- The study's purpose and design.
- Potential risks and benefits to individuals who decide to participate in the study.
- How the data will be used.
- The individual's right to refuse to participate at any time in the study without prejudice to him/her.
- How the study's results will be reported back to the individual.

All completed questionnaires, data forms, and raw data will be stored under lock and key or in limited-access computer files. Only the principal investigators will have unlimited access to these data.

When the study is finished, the collected data will be stored in Du Pont's Hall of Records.

All results will be published in aggregate or group forms only. Individual workers will not be identified.

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TABLE I: EXPOSURE CATEGORIZATION SCHEME USED IN LIVER FUNCTION STUDY OF C-8 WORKERS AT WASHINGTON WORKS

<u>HIGH EXPOSURE POTENTIAL</u>		<u>LOW EXPOSURE POTENTIAL</u>	
<u>NO.</u>		<u>NO.</u>	
4-1	TFE Service Operator	4-2	TFE Service Operator
6-2	TFE Process Operator	6-4	TFE Process Operator
4-5	FEP Service Operator	4-6	FEP Service Operator
6-7	FEP Process Operator	6-8	FEP Process Operator
6-9	Semiworks Laboratorian	6-10	Semiworks Laboratorian
8-11	Mechanic (good possible)	6-12	TEFZEL-TELOMER A Operator
8-13	Mechanic (possible)	7-14	MONOMER Operator
6-15	Laboratorian (Tech Assistant)	8-16	Mechanic (unlikely)
WS-17	Engineer or Chemist	WS-18	TFE Production Foreman
		6-20	Laboratorian
		WS-20	Chemist or engineer

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TABLE II: NUMBER OF PREGNANCIES BY YEAR (OF LEAVE OF ABSENCE) AND BY PAYCLASS:
WASHINGTON WORKS FEMALE EMPLOYEES 1965 - 1980

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	Year of leave of absence																65 - 80
	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	
WAGE	0	0	0	0	0	1	0	0	0	1	1	2	1	2	3	2	13
SALARY	6	7	7	4	7	10	12	8	7	4	4	3	2	3	3	3	90
TOTAL	6	7	7	4	7	11	12	8	7	5	5	5	3	5	6	5	103

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TABLE III: MINIMUM NUMBER OF MALFORMATIONS NEEDED TO SHOW STATISTICAL SIGNIFICANCE

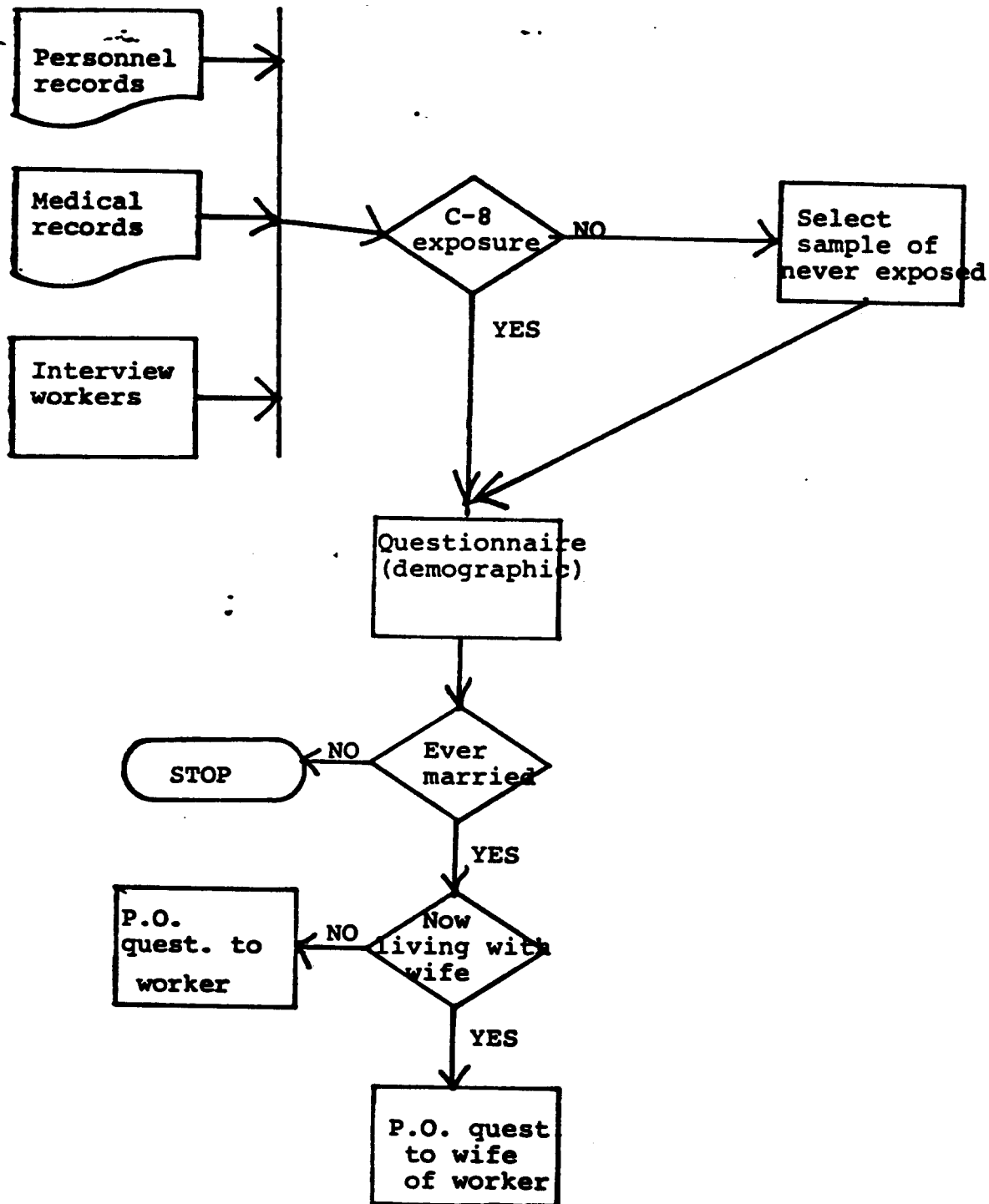
Type of malformation	Malformation incidence nation-wide	Minimum number of births with malformations that must be observed in the study group to be significantly higher than the national incidence, given a study group with N live births:			
		<u>N=5</u>	<u>N=10</u>	<u>N=50</u>	WEF000130
craniofacial	2 per 1000	1	2	2	
all malformations	20 per 1000	2	2	4	

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Number of live births in the plant control group	# births with malformations in the control group	Minimum number of births with malformations that must be observed in the study group to be significantly higher than the control group's incidence, given a study group with N live births:			
		<u>N=5</u>	<u>N=10</u>	<u>N=50</u>	
50	0	2	2	6	
50	1	2	3	8	
50	2	3	4	10	

STUDY OF PREGNANCY OUTCOME IN WIVES OF C-8 EXPOSED WORKERS

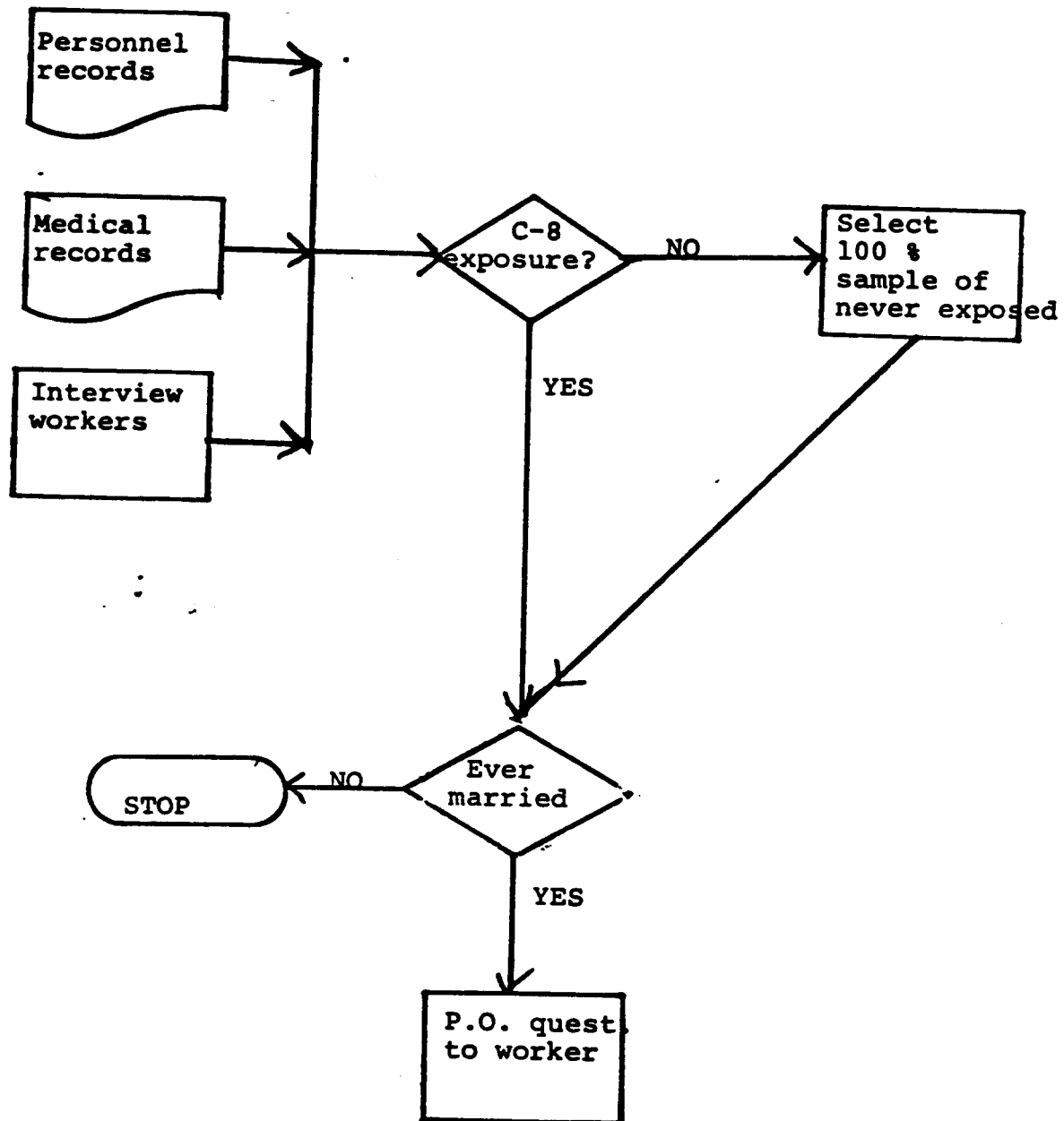


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STUDY OF PREGNANCY OUTCOME IN FEMALE WORKERS EXPOSED TO C-8



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