OCCUPATIONAL HAZARDS

to

PREGNANT WOMEN

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ABSTRACT

The Collaborative Perinatal Project (CPP) provides data on a well described population of women numbering 55,908. Exposure to one or more hazardous work conditions was reported by 4,575 women of the 23,961 women we used for this study. The statistical analysis involved log-linear model analysis of cross classified categorical data. The influence of demographic variables was identified by testing for three factor interaction with occupational exposure categories and pregnancy outcome variables. Women with a work experience of pesticide exposure had the most adverse reproductive history, observed as more fetal deaths and stillbirths, premature low weight babies with low 5 minute Apgar scores, suspected neurological abnormalities at one year and low I.Q. at 4 years. No statistically significant interaction with demographic variables was found, indicating that all socio-economic and racial groups within that exposure group were affected comparably. In addition, occupational exposure to chemicals, heat and heavy lifting was associated with adverse pregnancy and pregnancy outcome experience. Occupational exposure to ionizing radiation and animals did not show comparable effects.

The occupational experience reported in this study was not coterminous with the pregnancies studied but reflected the integrated workforce participation and exposure to hazardous conditions for each mother up to and in some cases during the pregnancy studied.

Our aim was to explore the CPP data base to establish its usefulness for examination of the reproductive effects of exposure to occupational hazards. We have used only 43% of the core population and can recommend further analysis of data from the remaining population. The sample sizes in all exposure groups would be increased making possible more sensitive statistical analysis.

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INTRODUCTION

The specific aim of the study was:

1. To identify those in the total study of the Collaborative Perinatal Project who reported exposure to occupational hazards and to establish appropriate classifications for analysis of variables pertaining to pregnancy history, placental characteristics and the growth and development of the children who were born.
2. To examine the occupational exposure patterns of women with a work history.
3. To examine in more detail occupational conditions which appear to show associations with adverse pregnancy outcome.

Description of Total Collaborative Perinatal Population

In 1955 the protocol for a perinatal collaborative study was drawn up by the National Institute of Neurological Diseases and Blindness (NINDB) with the following objectives:

"1) to make a more precise determination of fetal, environmental and medical factors leading to the various forms of cerebal palsy;

2) to link the symptoms of this group of disorders to the causative brain damage."

The inadequacy of hospital records was recognized early in the planning of the collaborative clinical-pathological study of pregnancy and its outcome. To offset the retrospective information gathered about pregnancy and perinatal events from parents of children with defects, the prospective approach was chosen for the Collaborative Perinatal Project (CPP). Data were collected on pregnancy and perinatal events as they occurred to eliminate biases of known pregnancy outcome. The aim of the study was to examine a very large number of cases in minute detail so that the effects of perinatal factors on the health of the individual child could be evaluated. Twelve hospitals throughout the United States met the study's objective of enrolling a total of 50,000 to 60,000 pregnant women in less than a decade. The final enrollment total was 59,391. The study was continued up to the 7th birthday in 73% of the study children to permit the evaluation, not just of the immediate pregnancy outcome of perinatal death or survival, but also of any disorders or abnormalities that might only become manifest in later childhood.

In 1958 there was a pretest period when considerable time and effort were spent recruiting and training staff for the collaborating centers and the NINDB. To assure uniform data collection, great detail was given to the writing of procedures for the selection of patients, the development of forms and manuals for data recording, workshops, meetings and pretests. The creation, printing and pretesting were extremely time consuming and the revisions of forms continued through 1959. The development of forms and manuals for the later examinations of study children continued for several additional years.

Protocols were developed for obtaining neuropathological specimens from stillbirths and neonatal deaths and for follow-up examinations of survivors beyond the newborn period. The limitations of newborn appraisals in identifying congenital malformations were demonstrated by McIntosh et al. (1954) who in a follow-up of 5739 children from birth to one year of age, found over twice as many malformations at one year as were identified at birth.

In 1959 it was realized that the ability of the twelve centers to follow their study of children would greatly determine the success of the total study and each hospital had unique difficulties in its ability to follow study children. By the very nature of their populations, some hospitals were more successful than others. Four collaborating hospitals dropped out of the study for various administrative reasons. Children's Hospital in San Francisco withdrew after the pretest phase in 1959. Yale dropped out of active participation in 1961, after registering 900 pregnancies. In 1963, Columbia-Presbyterian Hospital halted its CPP obstetrical intake, but continued to follow the children through eight years of age. New York Medical College, having completed the examination of children at age four, terminated in 1970 because of insurmountable difficulties in achieving an adequate retention rate for children at age 7. While the other study institutions had a return rate of over 70%, the rate at New York Medical College was only 45-55% with little hope of improvement. This was attributed to the mobility of the Puerto Rican population that comprised a large portion of the sample.

Early development evaluation was performed at critical time periods of the study child's life. A general pediatric exam was scheduled at 4 months, an assessment of mental and motor development at 8 months, a neurological examination at 1 year, and a psychological evaluation at 4 years. A final evaluation, including neurological and psychological appraisal, was made around 7 years of age.

The registration continued for 7 years, beginning January 1, 1959 and ending December 1965.

Selection of Participants

In all of the hospitals, certain constraints were imposed upon the participants selected from the general obstetric patient population. Common disqualifications were a woman's intentions to move from the area; certain geographic areas of residence; and so called "walk-in" cases - delivery on the same day as first registration to the study.

In two of the hospitals, all presenting gravidas in the sampling frame were entered into the study. In nine hospitals systematic selection was based upon the last digit of the patient number, or the woman's day of birth or some similar device. In one hospital random sampling was used. In each of the participating institutions, the sample enrolled in the study did not differ with regard to age, ethnic group, marital status, or weeks of gestation at admission, as compared with the total group of women who initially formed the sampling frame. A woman could be represented in the CPP more than once if she had a subsequent pregnancy which was registered in a collaborating clinic (Table 1).

Data Collection

On entry to the study, during visits to the collaborating perinatal clinic, the mother provided specially trained interviewers with her medical history, socioeconomic and genetic information about herself and her family, the baby's father and his family. A medication history covering the time from the last menstrual period was also obtained. Detailed, structured forms were used and the data collection procedure was guided by the use of extensive manuals. Prenatal clinic visits were scheduled every month during the first seven months of pregnancy, every two weeks during the eighth month, and every week thereafter. Obstetricians recorded the results of physical examinations, histories, and laboratory tests. The assembled material was sent to a central facility where it was processed into computer files. Specific computer procedures were routinely employed to identify and correct mistakes in the original computer files.

When the mother was admitted for delivery her physical status was reevaluated. Her labor and delivery were recorded by a trained observer. The attending obstetrician completed a summary of the labor and delivery. Pathologists specially trained as CPP staff pathologists examined the placenta and conducted post mortem examination of stillbirths and neonatal deaths.

The neonate was first observed in the delivery room and administered Apgar tests at 5, 10, 15, and 20 minute intervals. A pediatrician then examined the child at 24 hour intervals in the newborn nursery. At two

Table 1. Percentage of Repeat Pregnancies in CPP

1st pregnancy in Study	48694	82.0%
2nd " " "	8440	14.2%
3rd " " "	1850	3.1%
4th " " "	341	0.6%
5th " " "	59	0.1%
6th " " "	7	-
Total number of pregnancies	59,391	100.0%

days of age a neurological exam was performed. Other information from the nursery period was collected from laboratory tests and nurses' observations.

After the neonatal stage, an "interval history" was taken of both the mother and child with different physical and psychological emphases at each examination from 2 to 4 years and from 5 to 8 years. Family and social history was updated by the mother at the 7-year exams. Diagnostic summaries were prepared by physicians at 1 and 7 years.

Demographic Characteristics

The pregnancies in the CPP were classified into categories of the ethnic group of the gravida: Negro, White, Puerto Rican, Oriental* and "Other." A socioeconomic index score based on the methods used by the U.S. Bureau of the Census (1963) and described in detail by Myrianthopoulos et al. (1968), was prescribed for each study woman. The CPP index, like that of the Census Bureau, combined scores for education, family income, and occupation into a single score. Occupation and educational achievement were determined for the heads of households and each of the 3 scores was ranked as a percentile. The socioeconomic index is the mean of the three scores and has a range of 0 to 95.

Using the USBC scores for the first 36,110 cases of the study and 1960 census records, Myrianthopoulos and French (1968) showed that the distribution of the socioeconomic index scores in the study population was displaced toward the low end of the scale relative to the U.S. population. The median SEI scores were 42 and 57 respectively. However most of the CPP scores fell between 20 and 49, and a few scored 60 or above.

* Racial designations used in the CPP

The median SEI score for Negro registrants was 37, higher than for the Negro population in the United States - 33. Most of the U.S. Negro population had scores under 20, while the CPP population had scores between 20 and 59. When the Whites in the study were compared with the U.S. White population, the SEI scores overlapped more. The CPP White population median SEI score was 51, while the SEI score for the U.S. population was 59. The CPP White population was a closer representation of the SEI scores in the general population.

Buffalo, the only institution in the study to register all private patients had the CPP population with the highest mean SEI score, 78. Boston and Minnesota followed with 61 and 60 respectively. These three hospitals contributed 33% of the study population; 68% of the Whites, and 5% of the Negroes, 1% of the Puerto Ricans and 64%of the "Other" ethnic groups. Charity Hospital at New Orleans, the University of Tennessee College of Medicine and the Medical College of Virginia comprised the study populations with the lowest mean SEI scores, 30, 32 and 33 respectively. Together these institutions contributed 18% of the total population, 34% of the Negroes and 3% of the Whites.

The median maternal age was 23.6. More than one third of the women were between 15 and 19 years, and one fifth between 25 and 29 years. Negro registrants median age was 23, while that of the White registrants was 24 years.

Women Lost to the Study

A case was termed "lost to the study" if the gravida refused to participate after registering, or if she moved away without a trace. These "lost to study" cases were women who dropped out of the study before completion of their pregnancy. They comprised 4.1% of the study registrants.

In order to evaluate any possible bias to the study resulting in the women "lost to study," certain characteristics of these women were examined for comparisons with those who were followed. The more highly educated mothers of both racial groups were more frequently lost to the study than those of the lower educational group. Also, fewer of the very young women, White or Negro, dropped out than expected. Neither of the above two observations were consistent by collaborating center. Nor was there consistency among the collaborating centers concerning the marital status of the two groups of gravida.

A continuous effort was made to prevent attrition of the study population during the entire study. A small number of infants had to be delivered at hospitals other than the intended collaborating clinic and so were not present for the study nursery exam. In all, 85% of the study children were successfully followed to receive the one year neurologic examination within the prescribed brief time period. Although the rate was not consistent by institution, there was a 73% rate of successful follow-up providing clinical evaluation up to the seventh year of the study child's age. (Niswander et al., 1972).

Limitations of Study of Exposure to Occupational Hazards

Access to the voluminous data base of the CPP is not a straightforward process. The accumulation and coding of data over the period from first registrations to the present by the National Institute for Neurological and Communicative Disorders and Stroke (NINCDS) has progressed through a series of stages as particular emphases developed for detailed study. The series of questions dealing with work experience and exposure to hazardous conditions was not part of earlier studies, nor is it clear what the original design was for a study of women who worked. It was only during the latter part of the enrollment period 1962 to 1965 (inclusive), that the recorded answers concerning occupation were coded. The magnitude of the effort to carry out coding from the earlier original records (approximately 35,000 registrations from 1960 to 1963) for this particular set of questions was far beyond the original intent of the project being reported here. We did not know at the time our original proposal was developed that such coding had not taken place but we decided that the available population of 23,961 was adequate for a productive exploration of the data base.

Several critical data points are difficult or impossible to retrieve. There was no linkage question to establish when exposure to a hazardous condition occurred in relation to the pregnancy under study. The question was phrased "Have you ever worked with . . . " followed by "Describe work situation" and "Approximately how long? (in months)". It was impossible therefore to establish from the coded data whether exposure had occurred many years before and terminated or over the period of time reported up to and including the current pregnancy. Detailed examination of the original records in some cases could provide direct or indirect evidence about the time of the woman's exposure. We found the reliability of the conclusions which could be reached indirectly was far from uniform as we examined individual original records for this particular item of information. We decided that only one basic assumption could be made, namely that exposure to hazardous work conditions had occurred before the date of interview. It was also assumed to be unlikely that many such exposures were related only to the few prenatal months, without exposure pre-conception. Some women could have experienced an occupational exposure to hazardous conditions only during the post conception period but we judged these to be very few and virtually unidentifiable from the responses recorded. This observation led us to the realisation that occupational exposure to hazardous conditions for the population being examined was most likely to have been a pre-conception experience. We were therefore looking at the work/reproduction relationship in a far broader context than the limited view of the immediate experience of a pregnant woman. The categories of occupational exposure must then be viewed in terms of an overall potential influence on the reproductive system. It is scarcely appropriate to view pesticide intake and resulting residue accumulation in the human body as a single event or a short term influence on a particular pregnancy. The exposure experience reported by virtually all the respondents who were identified as having worked with tobacco or cotton quite clearly reflected a long term environmental and occupational exposure. Exposure to chemicals with accumulation of a body burden for a particular chemical or its metabolites could be viewed similarly.

In contrast, effects of exposure to heat and external ionizing radiation pre-conception, although little explored in the former and only partially understood in the latter could not be expected to result in a body burden with continuous influence. However physiologic or pathologic changes in reproductive function affected by these physical agents need to be examined.

A working environment which involved lifting weights presents a physiologic environment for some women which allows them to improve their physical conditioning. For others the same conditions may be a physical stress. It is difficult therefore to know whether the self-reporting of lifting weights represents more women for whom heavy lifting was stressful, with the likely exclusion of physically stronger women who did not consider the same level of lifting as "heavy" work. The heavy lifting category in this study is the most difficult to define in terms of hazardous exposure and may be more of a descriptor of the population than a measure of stress imposed than is the case for the other exposure categories.

An estimation of "dose" can be made only indirectly from the response given to the question "Approximately how long?" describing the exposure to an occupational hazard. We coded the response into 1 to 6 months, 7 to 18 months and more than 18 months. The results, however have been presented in terms of exposure or no exposure, with the expectation that future more detailed analyses can be done in terms of dose response.

Gestation at registration in the CPP varied markedly, further complicating any estimate of post conception occupational exposure to a hazardous condition. It was therefore included as a demographic variable in the analysis.

Information obtained at the first interview concerning employment, occupational exposure to hazardous work conditions was recorded but not often coded in the early years of the CPP. Our study was confined to the 23,961 first pregnancies to the study for which answers to the questions concerning exposure to hazardous work conditions were recorded and coded. Less than 1% of the pregnancies we examined were registered from 1958 to 1961 (inclusive), so that almost all of the pregnancies with coded information on occupational hazards occurred in the latter half of the CPP enrollment period.

Subsequent pregnancies and progeny were excluded from our study. The first recorded twin in a first pregnancy to the study was considered to be the first child for which occupational information of the mother was available. There were 50 such infants.

Occupational Exposure to Hazards

Table 2 shows the format of the Socio-economic Questionnaire which provided the basic occupational exposure information we used. These questions were usually asked at the first interview at registration and for 4,575 of the 23,961 pregnancies, women reported that they had been exposed to X-rays or fluoroscope equipment, radioactive elements or isotopes, tobacco dust or leaf, steam or very high heat, chemicals and their dusts, gases or fumes, animals or birds and had lifted weights at some time in the past.

There was considerable variability among different hospitals with Tennessee and New York Medical showing the lowest percentage of pregnancies with reported occupational exposures (10.7% and 5.8% respectively) and Minnesota and Providence with the highest (34.2% and 33.2% respectively) (Table 3). The proportion of pregnancies with reported exposures remained quite consistent through the major enrollment period from 1962 to 1965 ranging from 25.7% to 28.2% for Whites, 18.0% to 24.6% for Negroes and from 5.5% to 8.3% for other races (Table 4). Comparison by race showed a higher proportion of Negroes in the exposed group than in the unexposed group and a lower proportion of Whites in the exposed group when compared with the unexposed group (Table 5). The distribution of socioeconomic status was more consistent with 60.2% in the mid-socioecnomic category (socio economic score 40 to 59) for the unexposed group and 58.0% in the exposed group. The maternal age distribution was weighted more heavily to the younger 10-19 year age group in the unexposed (26.3%) when compared with the exposed group (13.3%), with fewer in the 30-39 year age group in the unexposed group (15.4%) when compared with the

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SOCIO-ECONOMIC INTERVIEW

25. PATIENT IDENTIFICATION

SECTION D

GRAVIDA'S WORK HISTORY

Now I'd like to talk to you about the kinds of jobs you've had.

REPEAT PREGNANCY – ABRIDGED FORM

R-3. HAVE YOU CHANGED JOBS OR STARTED TO WORK SINCE ________

DATE FROM ITEM 9A

☐ NO *(skip to item 31)* ☐ YES *(do Section D)*

26. DO YOU HAVE A JOB NOW? ☐ YES *(complete 26, omit 27)* ☐ NO *(omit rest of 26, ask 27)* ☐

A. HOW MANY HOURS PER WEEK DO YOU WORK? ☐☐ HRS/WK

B. HOW LONG HAVE YOU HAD THIS JOB? ☐☐ YRS ☐☐ MOS ☐ WKS ☐☐

C. WHAT KIND OF WORK DO YOU DO ON THIS JOB? ________

27. HAVE YOU EVER HAD A JOB? ☐ YES *(complete rest of 27)* ☐ NO *(skip to 31)*

A. HOW MANY HOURS PER WEEK DID YOU WORK ON YOUR LAST JOB? ☐☐ HRS/WK

B. HOW LONG DID YOU HAVE THIS JOB? ☐☐ YRS ☐☐ MOS ☐ WKS ☐☐

C. WHAT KIND OF WORK DID YOU DO ON THIS JOB? ________

D. WHEN DID YOU STOP WORKING? ☐☐ MO. ☐☐ YEAR

28. HOW MANY OTHER KINDS OF WORK HAVE YOU DONE?

☐ ONE OR MORE *(specify number in box. Omit A.)* ☐ NONE *(ask A.)* ☐

A. HOW MANY JOBS HAVE YOU HAD? ☐ ONE *(ask item 30)* ☐ SEVERAL *(ask item 29 B)*

29. A. WHAT KIND OF WORK DID YOU DO FOR THE LONGEST PERIOD OF TIME? ________ ☐☐

B. FOR HOW LONG DID YOU DO THIS KIND OF WORK? ☐☐ YRS ☐☐ MOS ☐ WKS

30. *OCCUPATIONAL HAZARDS*

QUESTION	NO 0	YES 1	DESCRIBE WORK SITUATION	APPROXIMATELY HOW LONG? *(In Months)*
A. HAVE YOU EVER WORKED WITH X-RAY OR FLUOROSCOPE EQUIPMENT OR BEEN EXPOSED TO X-RAYS IN YOUR WORK?				
B. HAVE YOU EVER WORKED WITH OTHER RADIATION SUCH AS RADIOACTIVE ELEMENTS OR ISOTOPES?				
C. HAVE YOU EVER WORKED WITH TOBACCO DUST OR LEAF OR HANDLED TOBACCO?				
D. HAVE YOU EVER WORKED WITH STEAM OR VERY HIGH HEAT WHERE SPECIAL CARE HAD TO BE TAKEN?				
E. HAVE YOU EVER WORKED WITH CHEMICALS, THEIR DUSTS, GASES OR FUMES IN A JOB SITUATION?				
F. HAVE YOU EVER HAD TO LIFT HEAVY WEIGHTS ON ANY OF YOUR JOBS?				
G. HAVE YOU EVER HAD TO HANDLE ANY LIVE OR DEAD ANIMALS OR BIRDS ON ANY OF YOUR JOBS?				

31. HAVE YOU EVER CARED FOR, HANDLED, PLAYED WITH OR WORKED AROUND FARM ANIMALS, SUCH AS CHICKENS, DUCKS, GEESE, COWS, PIGS, HORSES, DONKEYS, MULES, SHEEP OR GOATS, ETC.? *(circle which)*

A. ☐ YES ☐ NO *(omit B and C)*
00000

B. HOW OFTEN? ☐ INCIDENTALLY ☐ FREQUENTLY ☐ OTHER

C. WHEN WAS THE LAST TIME THAT YOU DID THIS? ☐☐ MO ☐☐ YR

TABLE 3

EXPOSURE EXPERIENCE BY HOSPITAL OF REGISTRATION

Hospital	% Exposed
Boston Lying-In	22.6%
Buffalo Children's	31.5%
Charity, New Orleans	15.8%
Columbia-Presbyterian, New York	19.2%
Johns Hopkins, Baltimore	30.3%
Medical College, Richmond, VA	30.5%
University of Minnesota Hospitals, Minneapolis	34.2%
Metropolitan Hospital, N.Y. Medical	5.8%
University of Oregon, Portland	21.2%
Pennsylvania Hospital & Chidren's, Philadelphia	19.1%
Providence, RI	33.2%
Gailor Hospital, Memphis Tennessee	10.7%
TOTAL	22.6%

TABLE 4

ENROLLMENT IN CPP (1962-1965)-OCCUPATIONAL EXPOSURE

Year	White % Exposed	Black % Exposed	Other % Exposed
1962	28.2%	24.6%	8.3%
1963	26.7%	22.1%	5.5%
1964	26.4%	20.1%	6.9%
1965	25.7%	18.0%	6.7%
TOTAL	26.5%	21.5%	6.4%

TABLE 5

DEMOGRAPHIC DESCRIPTION
OCCUPATIONAL EXPOSURE TO HAZARDOUS CONDITIONS

Race	Unexposed	Exposed
White	47.2%	43.0%
Black	44.8%	55.1%
Other	8.0%	1.9%
Socio Economic Status		
SES 1	8.7%	5.0%
SES 2	60.2%	58.0%
SES 3	31.1%	37.0%
Maternal Age		
10-19 Years	26.3%	13.3%
20-29 Years	56.8%	63.5%
30-39 Years	15.4%	21.0%
40+	1.4%	3.3%
Prior Pregnancies		
-	30.1%	25.0%
1 - 3	47.3%	46.6%
4 - 6	16.5%	19.8%
> 6	6.1%	8.6%
Education		
7 yrs. or less	10.2%	7.6%
8 - 11 years	47.4%	43.9%
12 years	30.3%	29.5%
> 12	12.1%	18.9%

exposed (21.0%). The number of prior pregnancies was more comparable particularly for those with one to three prior pregnancies (47.3% unexposed, 46.6% exposed), with no prior pregnancies being more prevalent in the unexposed (30.1%) than the exposed group (25.0%). The level of education was comparable for high school graduation, 30.3% for unexposed versus 29.5% for exposed. Among the unexposed were more with less than 7 years education and fewer with more than 12 years education (10.2% and 12.1% respectively) when compared with the exposed (7.6% and 18.9% respectively).

Choice of variables and statistical design

Progress from one stage to the next during the period of this project was influenced by the time necessary to prepare computer tapes from the master files of the CPP, and transcription from the original records of exposure information for subsequent recoding and preparation of tapes. Exploration of the data base with staff of the CPP led us to decisions concerning the usefulness of particular variables in terms of the time and effort necessary to retrieve reliable information. For example, a question was asked at each prenatal examination concerning work outside the home. The master tape response for this question had been reduced to Yes or No for work outside the home at any time during pregnancy. The individual responses at each prenatal visit which could have provided some indication of the period of work during pregnancy were located on a data deck separate from the master file. We did not obtain these data until close to the end of our study period, when it was not possible to easily merge the tapes for further evaluation of this variable.

The statistical design in part affected the choice of variables. The use of contingency tables, including two-factor and three-factor analysis encourages a judicious choice of variables to constrain computer costs and print-out examination. The final choice of 44 variables developed from considerations of possible associations with hazardous work conditions and included those which described previous reproductive experience, outcome of pregnancy under study, prenatal symptoms, placental characteristics, newborn status, 8 month, 1 year, 4 year, and 7 year growth and development, and demographic characteristics (Table 6). Earlier studies of CPP data were also useful in making judgements on choice of variables (Broman et al 1975, Heinonen et al 1977).

TABLE 6

DEMOGRAPHIC AND PREGNANCY OUTCOME VARIABLES

Demographic	
Race	White, Negro, Other
Socio-Economic Index	0-39, 40-59, 60-95
Age of Gravida	<20, 20-29, 30-39, 40+ years
Gestation at Registration	<20, 20-29, 30+ weeks
Smoking during Pregnancy	Yes, No
Abdominal X-ray during Pregnancy	Yes, No
Pregnancy Experience	
Prior Premature Births	None, 1, 2, 3 or more
Prior Fetal Deaths	None, 1-2, 3 or more
Prior Stillbirths	None, 1-3, 4 or more
Current Pregnancy	Liveborn, still living Fetal Death Neonatal Death Death at less than one year Death after one year - yes, no
During Pregnancy	
Uterine Bleeding	1st, 2nd, and/or 3rd Trimester
Anemia	Yes, No
Convulsive Disorder	Yes, No
Kidney, urinary bladder infection	Yes, No
Hydramnios	Yes, No
Placental Characteristics	
Weight	0-300, 301-500, 501-2000 grams
Infarcts	None, all less than 3 cms, at least one greater than 3 cms.
Abruptio placenta	No, partial, complete

TABLE 6 (Continued)

Placental Characteristics (Cont'd.)

Placenta previs	None, total or marginal, marginal or low implantation
Single umbilical artery	No, Yes

Neonatal Characteristics

Gestation at Delivery	Less than 20 weeks, 21-34 weeks, 35-39 weeks, 40 or more weeks
Birthweight	0-1500, 1501-2500, 2501-4100, 4101+ grams
5 Minute Apgar Score	0-3, 4-6, 7-10
Hematocrit (neonatal)	0-49, 50-69, 70+

Growth and Development

8 month Mental Score		Abnormal, Suspect, Normal
8 month Motor Score		Abnormal, Suspect, Normal
1-Year	Ataxia	Yes, No
	Delayed Motor Development	Yes, No
	Seizure States	Yes, No
	Failure to Thrive	Yes, No
	Cleft Palate	Yes, No
	Neurological Abnormality	None, suspicious, abnormal
4-Year	I.Q.	25-79, 80-109, 110-175
7-Year	Neurologic Abnormality	None, Suspicious, Definite

Head Circumference

Neonatal	<30, 31-34, 35-36, 37-38, 39+ cms
4 months	≤ 36, 37-40, 41-44, 45+ cms
8 months	≤ 40, 41-43, 44-46, 47+ cms
4 years	≤ 44, 45-47, 48-50, 51-52, 53+ cms
7 years	≤ 48, 49-51, 52-53, 54-56, 57+ cms

Two-factor analysis was run for exposure to each of the hazards - ionizing radiation, animals, heat, heavy lifting, chemicals and pesticides with each of the 44 variables. Then three factor analysis was run for exposure to each of the hazards with every possible pair from the 44 variables.

We did not retain those with a confidence value of $p > 0.05$, and interpretation of three factor interactions was dependent on finding a two factor interaction between exposure to a hazard and one of the pair of variables in the three factor analysis.

The statistical approach involved log-linear model analysis of cross-classified categorical data.

When data are recorded in categories instead of on a continuous scale, they are usually cross-classified into tables of counts, referred to as contingency tables. For example, in this study the relationship (if any) between amount of radiation exposure (none, low, medium, high) socio-economic status (low, medium, high) and uterine bleeding (present or not) was examined. A frequency count of women falling in the various categories results in a 3-way contingency table (Table 7). Here, for example, X_{111} denotes the number of women with uterine bleeding who had no radiation exposure and who were in the "low" socioeconomic status level; n_{11} denotes the total number of women with no radiation exposure in the "low" socioeconomic level.

In this example, we treat amount of radiation exposure (A) and socioeconomic status (B) as factors, and presence or not of uterine bleeding (C) as a response variable. For each category of A and B we can calculate the observed proportion of women having uterine bleeding, to obtain the following table of observed probabilities (Table 8).

Table 7

		B: Socioeconomic Status								
		Low			Medium			High		
C: Uterine Bleeding		Yes	No	Total	Yes	No	Total	Yes	No	Total
A: Amount of Radiation Exposure	None	X_{111}	X_{112}	n_{11}	X_{111}	X_{112}	n_{12}	X_{131}	X_{132}	n_{13}
	Low	X_{211}	X_{212}	n_{21}	X_{221}	X_{222}	n_{22}	X_{231}	X_{232}	n_{23}
	Med.	X_{311}	X_{312}	n_{31}	X_{321}	X_{322}	n_{32}	X_{331}	X_{332}	n_{33}
	High	X_{411}	X_{412}	n_{41}	X_{421}	X_{422}	n_{42}	X_{431}	X_{432}	n_{43}
		$X_{.11}$	$X_{.12}$	$n_{.1}$	$X_{.21}$	$X_{.22}$	$n_{.2}$	$X_{.31}$	$X_{.32}$	$n_{.3}$

Table 8

		Socioeconomic Status		
		Low	Medium	High
Amount of Radiation Exposure	None	p_{11}	p_{12}	p_{13}
	Low	p_{21}	p_{22}	p_{23}
	Med.	p_{31}	p_{32}	p_{33}
	High	p_{41}	p_{42}	p_{43}

Table 9 a

		S.E. Status			
		Low	Medium	High	
Amount of Radiation Exposure	None	n_{11}	n_{12}	n_{13}	$n_{1.}$
	Low	n_{21}	n_{22}	n_{23}	$n_{2.}$
	Med.	n_{31}	n_{32}	n_{33}	$n_{3.}$
	High	n_{41}	n_{42}	n_{43}	$n_{4.}$
		$n_{.1}$	$n_{.2}$	$n_{.3}$	n

Here, $p_{ij} = X_{ij1}/n_{ij} = X_{ij1}/(X_{ij1} + X_{ij2})$.

From Table 8, we can also form three 2-way (marginal) tables:

Table 9a describes the sampled population of women by amount of exposure to radiation and socio-economic status, while Tables 9 b and 9c reflect the incidence of uterine bleeding in women according to socio-economic status (9b) and by amount of radiation exposure (9c).

In analyzing the effect of the two factors (A and B) on incidence of uterine bleeding (c), we might initially examine the effects of A and B separately. Taking this approach, we would begin by analyzing Tables 9b and 9c. In Table 9b, we would test the hypothesis that the proportions of women having uterine bleeding is the same for each socioeconomic level while in Table 9 c, the hypothesis to be tested is that the proportion of women having uterine bleeding is the same irrespective of the amount of radiation exposure. These hypotheses are tested using the usual χ^2 statistic

$$\chi^2 = \Sigma\ (\text{observed} - \text{expected})^2/\text{expected}.$$

For Table 9b, if the population proportions are the same then we would estimate the common proportion by $\hat{p}_{..1} = X_{..1}/n$ and calculate the expected frequencies by multiplying $\hat{p}_{..1}$ by $n_{.1}$, $n_{.2}$ and $n_{.3}$, respectively. Thus, the table of expected frequencies is as follows: (Table 10)

Table 9b

		C: Uterine Bleeding		
		Yes	No	
S.E. Status	Low	$X_{.11}$	$X_{.12}$	$n_{.1}$
	Med.	$X_{.21}$	$X_{.22}$	$n_{.2}$
	High	$X_{.31}$	$X_{.32}$	$n_{.3}$
		$X_{..1}$	$X_{..2}$	$n-n_{..}$

Table 9c

		C: Uterine Bleeding		
		Yes	No	
A: Amount of Radiation Exposure	None	$X_{1.1}$	$X_{1.2}$	$n_{1.}$
	Low	$X_{2.1}$	$X_{2.2}$	$n_{2.}$
	Med.	$X_{3.1}$	$X_{3.2}$	$n_{3.}$
	High	$X_{4.1}$	$X_{4.2}$	$n_{4.}$
		$X_{..1}$	$X_{..2}$	n

Table 10

Socio-economic Status		Uterine Bleeding: Yes	No	Total
	Low	$n_{.1} X_{..1}/n$	$n_{.1} X_{..2}/n$	$n_{.1}$
	Medium	$n_{.2} X_{..1}/n$	$n_{.2} X_{..2}/n$	$n_{.2}$
	High	$n_{.3} X_{..1}/n$	$n_{.3} X_{..2}/n$	$n_{.3}$
		$X_{..1}$	$X_{..2}$	n

and $\chi^2 = \sum_{j=1}^{3} \sum_{k=1}^{2} (X_{.jk} - n_{.j}X_{..k}/n)^2/(n_{.j}X_{..,}/n)$. We reject the hypothesis of equal proportions if χ^2 exceeds the upper $\alpha\%$ point of χ^2 with 2 degrees of freedom.

If we take the natural logarithm of the estimated expected cell frequencies, denoted by $\hat{m}_{jk}$, we get

$$\ell n\ \hat{m}_{jk} = \ell n(n_{.j}X_{..k}/n) = \ell n\ n_{.j} + \ell nX_{..k} - \ell n\ n\ .$$

This model can be expressed in a form similar to analysis of variance notation:

$$\hat{\ell}_{jk} = \ell n\ \hat{m}_{jk} = \hat{u} + \hat{u}_{1(j)} + \hat{u}_{2(k)}\ .$$

The model contains a grand mean (u) and terms $u_{2(k)}$ for the response variable and $u_{1(j)}$ for the socioeconomic variable. If the proportions are not equal, the model would also have an <u>interaction</u> term $u_{12(jk)}$. In general, the <u>log-linear model</u> for the expected cell frequencies is specified by

$$\ell_{ij} = \ell n\ m_{jk} = u + u_{1(j)} + u_{2(k)} + u_{12(jk)}$$

The model parameters have the following interpretations:

(a) if $u_{12(jk)} = 0$, the proportions are equal.

(b) if $u_{2(k)} = u_{12(jk)} = 0$, the overall proportion of women with uterine bleeding is 0.5.

(c) if $u_{1(j)} = u_{12(jk)} = 0$, the proportion of women in each socioeconomic status is the same, namely, 1/3.

Methods for analyzing contingency tables with more than two dimensions have, until recently, been limited. The log-linear model approach provides a general method that can be used for any number of dimensions. In particular, for a three-dimensional table, the full (saturated) log-linear model is given by

$$\ell_{ijk} = u + u_{1(i)} = u_{2(j)} = u_{3(k)} + u_{12(ij)} + u_{13(ik)} + u_{23(jk)}$$
$$+ u_{123(ijk)} \cdot$$

By setting various terms in this model equal to zero, we obtain sub-models which are directly interpretable. For example, if we set $u_{123(ijk)} = 0$, we get the zero three way interaction model. It is most easily interpreted in terms of cross-product ratios which measure <u>association</u> between categories. For the three-way table involving A: amount of radiation exposure; B: socioeconomic status; and C: incidence of uterine bleeding, the zero three-way interaction model says that the odds ratios

$$p_{11}/p_{21},\ p_{12}/p_{22} \text{ and } p_{13}/p_{23}$$

are equal, i.e., they do not <u>depend</u> on socioeconomic status. Similarly, the ratios

$$p_{11}/p_{12},\ p_{21}/p_{22},\ p_{31}/p_{32}, \text{ and } p_{41}/p_{42}$$

are equal, i.e., they do not depend on the amount of radiation exposure. Thus, we can interpret the zero three-way interaction model by saying that radiation exposure may <u>affect</u> incidence of uterine bleeding, but if it does so, it affects it independently of socioeconomic status. Alternatively, one could have an association between socioeconomic status and uterine bleeding, but this association does not depend on the amount of radiation exposure.

When there is a response variable C at two levels (as is the case with uterine bleeding) and factors A and B (as in the example used here), it is convenient to write a linear logistic model for the response variable. This model is given by

$$\lambda_{ij} = \ell n\ p_{ij}/1 - p_{ij} = \ell_{ij1} - \ell_{ij2} = W + W_{1(i)} = W_{2(j)} + W_{12(ij)}.$$

Here, $W_{12(ij)} = u_{123(ij1)} - u_{123(ij2)}$, $W_{1(i)} = u_{13(i1)} - u_{13(i2)}$, $(a)_{2(j)} = u_{23(j1)} - u_{231,2}$ and $W = u_{3(1)} - u_{3(2)}$. Hence, if $u_{123(ijk)} = 0$ then $W_{12(ij)} = 0$. In this case, the logistic model asserts that factors A and B may affect the ratio $p_{ij}/1 - p_{ij}$, but if they do, they do so <u>independently</u>. If $W_{1(i)} \neq 0$ (or $u_{1e(ik)} \neq 0$), then factor A (amount of radiation exposure) affects uterine blleding, while if $W_{2(j)} \neq 0$ (or $u_{23(jk)} \neq 0$), we would conclude that socioeconomic status <u>affects</u> uterine bleeding (or that the odds of incidence of uterine bleeding differ in the various socioeconomic strata).

Missing Values

The choice of variables carried with it the likelihood that the number of missing values would differ from one to the other. The quality of recording and coding was high in the CPP with repeated checks throughout the entire period of enrollment and subsequent coding to establish accurate entry into the data base. The recall of patients for subsequent examination could not be as closely controlled. Therefore there are few missing values relating to pregnancy variables when compared with those for the children at later examinations. There were only minor differences in the percentages of missing values between the exposure groups for those variables associated with each child examination at 4 month, 8 month, 1 year, 4 years and 7 years. Otherwise missing values were usually only 2 to 3%, with a few at 5%. There was no marked difference in the proportion of missing values between exposed and unexposed groups.

Heavy Lifting

The question asked was "Have you ever had to lift heavy weights on any of your jobs?" The interviewer was expected to ask "Tell me about this job." "Under what circumstances?". "Where was this?". If gravida says "Yes", accept it. Consider as a heavy weight what is heavy to the woman. This question elicited the most subjective response of all the questions concerning occupational hazards. The chance for self-selection into this category was therefore high. The woman with good physical conditioning would be less likely to consider heavy lifting worth mentioning, in contrast to the woman without a history of physical conditioning. However the number of women in the period of enrollment in the CPP with formal physical conditioning experience would have been quite small. We have very few criteria available to us in this study or in the clinical setting to-day to establish the level of physical activity and weight lifting capacity a woman develops during her pre child-bearing years.

Background Discussion

The general clinical view has been that physical activity to which a woman has been accustomed is not likely to be stressful during pregnancy. Chaffin (1976) believes that transfer to a less physically demanding job may provide more stress than expected only because of the unfamiliarity and muscle fatigue resulting from new forms of activity.

Snook et al (1974) examined the maximum weights and work loads acceptable to female workers. Thirty-one women, including 16 housewives and 15 who were second shift workers from a local industry (not identified in terms of chemical exposure conditions), were tested for six basic manual handling tasks, lifting, lowering, pushing, pulling, carrying and walking. The authors point out that the manual handling of materials is the principal source (23% in 1973) of compensable work injuries. The associated accidents also contribute to aggravation of existing disorders. Such statistics are an indicator of the mis-match between the strength and endurance the worker brings to the job and the demands of manual handling tasks.

Statistically significant performance differences were observed for housewives and industrial women and the authors speculate on "whether industrial women handle more weight than housewives because they can handle more weight." We can speculate similarly for our sample of women. The mean age of the housewives was 35.6 years and for industrial women 38.5 years in the Snook study, considerably older than CPP participants, and therefore the former were likely to be a more self-selected group. However we can at least infer that in one parameter, acceptable work load, the female industrial work force differs from housewives, a difference that may well be associated with other physiologic parameters not analysed by us in the CPP data.

The relationship between physical activity and physical conditioning to subsequent reproduction has seldom been examined in the United States, although the European literature shows some studies of athletes (Noack, 1974). Interest in Europe has traditionally been more directed to physical conditioning than in the U.S., e.g. ". . . pregnancy far from being an illness should be considered an intensive, day and night, nine-month period of physical conditioning because of the increased demands upon metabolism and the entire cardiovascular system" (Klaus et al 1961).

In relation to pregnancy itself, Dahlstrom et al (1960) have dealt extensively with the physical work capacity of pregnant women and disagree with earlier reports claiming that the capacity for physical work diminished during pregnancy. Indeed, Irhlman (1960) of that team suggests that the circulatory adjustment during pregnancy resembles in some respects the changes during physical training, with increases in the total amount of hemoglobin, the total blood volume and the heart volume. For many years (before 1960) in other countries, particularly Scandinavia and Australia moderate physical training during pregnancy had been recommended and Ihrman's study attempted to evaluate this recommendation in physiologic terms. He concluded that "pregnancy is characterized by a circulatory adjustment which is not influenced in any important way by a rather heavy physical training during the 20th to 30th week of pregnancy." However there is conflicting information on the potential effect of exercise on the induction of labor itself (Haufrect, 1956), and we have little guidance for evaluation of our data for this parameter.

Pomerance et al (1974) used Darling's definition of physical fitness - "Physical fitness consists of the ability of the organism to maintain the various internal equilibria as closely as possible to the resting state during strenuous exertion and to restore promptly after exercise any (equilibria) which have been disturbed." They examined physical fitness in the pregnant woman in terms of the well-being of the fetus. The variables they examined in the babies of 41 women were length of gestation, length of labor, birth weight, length and head circumferences and one minute Apgar scores. The only statistically significant association was between physical fitness score and length of labor in multiparas. The study pointed out several difficulties, particularly in estimating maximum oxygen uptake from heart rate response to submaximal work loads. The Astrand method calculations, used by Pomerance, are based on non-pregnant women and with a standard error of as much as 15% their use for evaluation of physical fitness in pregnant women is far from satisfactory.

Guzman et al (1970) showed in a study of eight pregnant women that "the rate of increase in ventilation and cardiac output with increasing work loads are the same throughout pregnancy as in the non-pregnant state, implying that the physiologic response to mild and moderate exercise is the same in both states." They believe that the pregnant woman undoubtedly reaches her maximum work capacity at a lower level of work than in the non-pregnant state.

During pregnancy the effect of maternal physical activity on the fetus has been examined by Pernoll et al (1976). They examined fetal cardiac response to maternal exercise and note that during exercise there is a reduction in the high resistance to blood flow found in resting voluntary muscle. A relatively low resistance shunt in parallel with the placenta results when large muscle masses are exercised which could be expected to decrease effective uteroplacental blood flow.

The heart rate of the fetus is readily measurable and Stembera et al (1967) have shown that exercise test differences can be found in the phonocardiogram of healthy fetuses and of potentially distressed ones. When the study population was divided into four groups:

"1. healthy fetuses after a physiological course of pregnancy
2. fetuses whose mothers showed pathologic conditions, but in whom no signs of hypoxia appeared during or after birth,

3. fetuses with clinical symptoms of hypoxia during delivery, but in whom all signs of sustained intrauterine hypoxia receded up to one minute after birth,

4. hypoxic newborns."

the prenatal records of fetal heart rates showed differences that indicated a greater incidence of extreme variations in those with the higher potential fetal distress, more towards tachycardia than bradycardia. The exercise load of the mother was associated with far more pronounced differences in the variability of fetal heart rates in healthy fetuses when compared with those with potential hypoxia. In Group 1 (healthy fetuses) there was very little change in variations in heart rates. In Group 2 there was a marked shift towards tachycardia, Group 3 showed a shift both towards tachycardia and bradycardia and Group 4 showed a marked shift towards bradycardia. It is interesting to note that the average rate evaluated for the whole time interval of 10 minutes after maternal exercise load does not show any marked differences and varies as before the exercise load in all groups in the range of 140 to 148 beats/minute. But for the fetus in hypoxic distress bradycardia appears immediately after the exercise load of the mother, though it may only last for a very short time. These observations suggest that the higher vulnerability of some fetuses may be identifiable by their response to maternal exercise, though we cannot conclude that there is causal relationship.

Pernoll et al (1976) more recently have looked closely at the stage of gestation when carrying out exercise studies of normal pregnant women. Before 36 weeks gestation the fetal heart rate generally declined after maternal exercise but increased following maternal exercise after 36 weeks. In their view placental "respiratory reserve" may decrease in relation to fetal requirements particularly when pregnancy is close to termination and a greater stress on the fetus about to be born could result from any diversion of uterine blood flow.

Results

Exposure only to heavy lifting was recorded for 65.8% of the 2617 women in this group, with 26.8% exposed to one additional hazard, 6.4% exposed to two additional hazards and 1.0% exposed to more than two additional hazards (Table 11a). The additional hazardous exposures for the group reporting heavy lifting were to ionizing radiation (6.3%), pesticides (6.0%), chemicals (17.2%), heat (6.2%) and animals (6.0%) (Table 11b).

Except for the pesticides group those reporting heavy lifting show the least interference from additional exposure categories. Associated characteristics which were considered not to be adverse to the mother and/or the child were higher socio-economic status, more Whites than expected and early gestation at registration in the CPP when compared with all others in the study who were designated as not exposed to heavy lifting in their occupation (Table 12).

There was less anemia during pregnancy observed than expected, less kidney, urinary bladder infections during pregnancy and there were more whose gestation at delivery was recorded as more than 40 weeks.

The associated characteristics which may be considered adverse to the mother and/or the child were more mothers 30 years of age and over, more abdominal X-ray during pregnancy and more cigarette smoking during pregnancy observed than expected.

TABLE 11a

	Radiation n=394	Pesticides n=652	Chemicals n=1500	Heat n=769	Heavy Lifting n=2617	Animals n=515
One Exposure Category	35.5%	69.2%	43.6%	46.1%	65.8%	34.5%
Two Exposure Categories	39.4%	26.0%	42.8%	40.9%	26.8%	40.2%
Three Exposure Categories	21.0%	4.8%	10.9%	12.1%	6.4%	21.6%
More than Three Exposure Categories	4.0%	-	2.6%	1.0%	1.0%	3.7%

TABLE 11b

	Radiation n=394	Pesticides n=652	Chemicals n=1500	Heat n=769	Heavy Lifting n=2617	Animals n=515
Radiation	-	<1.0%	9.0%	<1.0%	6.3%	14.2%
Pesticides	1.0%	-	-	5.6%	6.0%	7.4%
Chemicals	33.0%	-	-	35.8%	17.2%	33.9%
Heat	1.0%	6.5%	18.5%	-	6.2%	5.6%
Heavy Lifting	40.0%	23.0%	29.7%	20.5%	-	32.9%
Animals	17.6%	5.6%	11.5%	4.2%	6.0%	-

Percentage of population in each exposure category exposed to an additional hazard (e.g. 1.0% of the 394 exposed to ionizing radiation were also exposed to pesticides, 33.0% also to chemicals, etc.). Primary exposure category shown underlined (horizontally), secondary exposure categories listed vertically.

TABLE 12

Occupational Exposure to Heavy Lifting

Number Exposed 2,617

Two Factor Interaction with Demographic Variables

	Observed	Expected	Significance P-Value
Race (White)	1270	1145	<0.001
Socio Economic Status (High)	896	799	<0.001
Age of Gravida (30 years)	353	199	<0.001
Gestation at Registration (<20 weeks)	1353	1214	<0.001
Abdominal X-ray During Pregnancy	858	649	<0.001
Cigarette Smoking During Pregnancy	1270	1145	<0.001

Two Factor Interaction with Pregnancy Outcome Variables

	Observed	Expected	Significance P-Value
Prior Stillbirths	304	253	0.002
Prior Fetal Deaths	177	146	0.016
Prior Prematures (18+ months exposure)*	219	187	0.031
Fetal Death (Current Pregnancy)	117	83	0.002
1st Trimester Bleeding **	475	363	<0.001
2nd Trimester Bleeding *	290	214	<0.001
3rd Trimester Bleeding **	452	356	<0.001
Anemia During Pregnancy	429	538	<0.001
Kidney Urinary Bladder Infection During Pregnancy	385	426	0.002
Gestation at Delivery (40+ weeks)*	1332	1235	0.001
5 Minute Apgar (<4)*	247	210	0.040
Neurological Abnormalities, 1 Year	139	118	0.047
4 Year I.Q. 109+	460	371	<0.001
Head Circumference 4 months > 41 cm**	532	486	0.001
4 Years > 51 cm*	79	58	<0.001
7 Years > 54 cm	136	107	<0.001
Neonatal Deaths (current pregnancy)	56	44	N.S.

In these two factor interactions, the observed/expected numbers reported here do not provide all the contingency table information which was used for Chi-Square analysis and significance probability. Where the particular stratum of interest is indicated only data relating to it is shown.

N.S. Not statistically significant

* No statistically significant three way interaction observed between
i) exposure to occupational hazard
ii) any demographic variable tested in this study
iii) any other pregnancy outcome variable tested in this study

**No statistically significant three way interaction between
i) exposure to occupational hazard
ii) any demographic variable tested in this study

The combination of advantageous demographic and pregnancy characteristics for the group exposed to heavy lifting does not lead us to expect the consistent pattern of adverse progress of prior pregnancies, observed as more stillbirths, fetal deaths and premature deliveries. For the pregnancy under study there were more fetal deaths and though not statistically significant more neonatal deaths. More uterine bleeding was reported during all three trimesters of pregnancy, seen only to a comparable extent in the group exposed to chemicals. Five minute Apgar scores less than 4 were more frequently observed. More neurological abnormalities were suspected or definite at the one year examination of the child, although more children with high I.Q. at four years (110 +) were observed than expected.

Three Factor Interaction

The larger sample size of the heavy lifting group of the occupationally exposed women provides the opportunity for more detailed examination of the three-factor interactions of all the variables examined (Tables 13a,13b). Although the number of statistically significant two-factor interactions was not many more than any of the other exposure groups, more three factor interactions became evident statistically, and direct examination of the three-factor contingency tables was more fruitful because of the larger cell numbers. Those statistically significant three factor interactions which showed a clear pattern in the contingency tables are useful in developing a better description of the characteristics of the population exposed to heavy lifting than is possible with the other exposure groups. An interpretation of a statistically significant three factor interaction can be that there is a differential association of exposure to the occupational

TABLE 13a

Occupational Exposure to Heavy Lifting

Number Exposed 2,617

Three Factor Interaction with Demographic Variables

		Significance P-Value
Race	Socio Economic Status	<0.001
	Gestation at Registration	0.001
	Abdominal X-ray during Pregnancy	0.022
	Age of gravida	<0.001
	Hydramnios	0.013
Socio Economic Status	Abdominal X-ray during Pregnancy	0.002
	Age of Gravida	<0.001
	Prior Stillbirths	0.034
	Hydramnios	0.042
	Head Circumference at 7 years	0.006
Gestation at Registration	Kidney, Urinary Bladder Infection	0.003
	4-year I.Q.	0.024
Cigarette Smoking during Pregnancy	Anemia during Pregnancy	0.048
	Kidney, urinary bladder infection during pregnancy	0.033
	Neurological Abnormalities (7 years)	0.035
Age of Gravida	8 month Mental Score	0.014
	8 month Motor Score	0.004
	Delayed Motor Development (1 year)	0.010
	4 Year I.Q.	0.010

TABLE 13b

Occupational Exposure to Heavy Lifting

Number Exposed 2,617

Three Factor Interaction with Pregnancy Outcome Variables

		Significance P-Value
Prior Stillbirths	Socio Economic Status	0.034
First Trimester Bleeding	Placental Infarcts	0.027
	4 Year I.Q.	0.018
Third Trimester Bleeding	Kidney, Urinary Bladder Infection during Pregnancy	0.013
Anemia during Pregnancy	Failure to Thrive	0.017
	Cigarette Smoking during Pregnancy	0.048
Kidney, Urinary Bladder Infection during Pregnancy	Gestation at Registration	0.003
	Cigarette Smoking during Pregnancy	0.033
	Third Trimester Bleeding	0.013
	Neurologica Abnormality (1 yr)	0.041
	Head Circumference (7 yr)	0.037
Bacterial Infection during Pregnancy	Placental Infarcts	0.022
	Placental Weight	0.018
5 minute Apgar	Head Circumference (8 months)	0.007
4 Year I.Q.	Birthweight	0.013
	Maternal Age	0.010
	Gestation at Registration	0.024
Neurologic Abnormality (7 yr)	Cigarette Smoking during Pregnancy	0.035

hazard with the combinations of categories for the other two variables, e.g. abdominal X-ray during pregnancy was experienced by more women of low socioeconomic status who reported heavy lifting than was the case for those who did not so report and who were of middle and upper socio economic status (significance p-value < 0.001). Interpretation of the contribution of the individual cells to the Chi-square in the three factor interaction does not infer statistically significant differences for the individual variables being examined in those cells. However a qualitative description of interacting variables can be made.

The excess number of fetal deaths in the pregnancy under study of the women exposed to heavy lifting was not differentially associated with any other third variable examined in this study. That is fetal deaths among women exposed to heavy lifting appear to be similarly associated with all three racial categories, all three socio-economic levels, all maternal age groups, those with or without first trimester bleeding etc.

A low Apgar score at five minutes was also similarly associated with all categories within each variable and overall (i.e. the two factor interaction) was more frequently observed among the newborn of women exposed to heavy lifting when compared with all those who were not.

More neurological abnormalities (suspected or definite) at one year were also found without apparent interaction with any other demographic or pregnancy outcome variable.

In contrast more children with suspected neurological abnormalities at 7 years were observed among children of unexposed women who smoked than expected and fewer than expected were observed among children of unexposed women who did not smoke. Yet more children with suspected neurological abnormalities at 7 years were observed than expected whose mothers were nonsmokers but who were in the heavy lifting group, so that any firm interpretation of the three factor interaction for exposure to heavy lifting, cigarette smoking during pregnancy and neurological abnormalities at 7 years becomes difficult. However, the significance p-value was only 0.035.

The prior reproductive experience of the women exposed to heavy lifting shows a consistent pattern of excess stillbirths, fetal deaths and premature births. Prior stillbirths were observed more in those of low socio-economic status exposed to heavy lifting than expected but no three way interactions were found for prior fetal deaths and premature births indicating that the experience of heavy lifting and prior pregnancy outcome was not associated differentially with any other demographic or pregnancy outcome variable. That is, black women did not experience any more reproductive loss than did white women.

Uterine bleeding throughout pregnancy was also observed more in those exposed to heavy lifting, with no three factor interaction with any demographic variable. In that both first trimester uterine bleeding and placental infarcts are evidence of placental instability their interaction with exposure to heavy lifting may well be a reflection of the vulnerability of the pregnancies observed for this group. More third trimester uterine bleeding was observed than expected among those exposed to heavy lifting who had kidney, urinary bladder infection. Overall the pattern of a poor pregnancy experience for those whose work involved heavy lifting is consistent without apparent interference from any confounding variables examined in our analysis, other than a low socio economic status with prior stillbirths in exposed women.

More children with high I.Q. at 4 years (110+) were observed than expected for mothers exposed to heavy lifting. There was a three factor interaction between exposure to heavy lifting, 4 year I.Q., and first trimester uterine bleeding with fewer children being observed with high 4 year I.Q. (110+) than expected where the exposed mother experienced first trimester uterine bleeding. More high 4 year I.Q. children were observed than expected among the exposed mothers who had not experienced first trimester uterine bleeding, and in children of exposed mothers under twenty years of age. More low 4 year I.Q. (25-79) was observed than expected in children of exposed mothers aged 20 to 29. Older age of gravida (35+) was not associated with lower I.Q. or delayed motor development. Therefore it cannot be concluded that older mothers in this group contributed a higher risk component to the exposed population, even though there were more of them when compared with the unexposed population.

An examination of the three factor interactions between exposure to heavy lifting, cigarette smoking and other variables showed only slightly more exposed women who smoked than expected with kidney urinary bladder infection and anemia during pregnancy. Although possible, smoking during pregnancy does not appear to be a seriously confounding factor in the association of adverse pregnancy experience and exposure to heavy lifting.

Abdominal X-ray during pregnancy was associated with exposed women who were black and exposed women of low socioeconomic status. There was no other statistically significant three factor interaction between exposure, abdominal X-ray during pregnancy and any other variable examined. It does not appear likely that abdominal X-ray during pregnancy was a seriously confounding factor affecting the associations between heavy lifting and pregnancy outcome.

In summary the reported experience of occupational heavy lifting at some time during a woman's work life is associated with adverse pregnancy outcome including uterine bleeding throughout pregnancy. It is difficult to identify any specific etiology to link these factors. It can be noted that reporting the experience of heavy lifting is far more subjective than any of the other exposure categories except possibly heat exposure. However in the case of heavy lifting a confounding factor impossible to examine is the likelihood that those reporting heavy lifting are the women whose physical conditioning and physiologic capabilities make lifting particularly onerous for them and would also be more likely to influence their pregnancies adversely. The women who were pregnant in the early sixties had spent their adolescence and early adulthood in a society which placed no value on physical conditioning for women. Occupational exposure to heavy lifting could for these women have been an overly demanding stress in addition to pregnancy.

The affirmative response to the question on heavy lifting must be an indicator for other far less obvious maternal characteristics. It is also possible that these women experienced less physical stress in the form of heavy lifting during the pregnancy under study, in view of their perception of stress.

Beyond noting the association between exposure to heavy lifting and adverse pregnancy outcome we can only conjecture on the possible etiological relationship.

IONIZING RADIATION

The following instructions were given to the interviewer concerning the question on exposure to ionizing radiation:

When the answer is YES to "Have you ever worked with X-ray or fluoroscope equipment or been exposed to X-rays in your work?" - ask "Tell me what you did and where you did it. For about how long?". Record this in months where possible, if less than a month, record in weeks or days as needed. Be sure to include time unit where less than a month.

Possible Answer: Used machine to check fit of children's shoes in shoe store.

"Have you ever worked with other radiation such as radioactive elements or isotopes?" Either handling them or cleaning up areas where they were used? In probing this question emphasize that it is about radioactive elements or substances that you are asking. If the gravida does not know what you are talking about, just tell her "you would know if you had been working with such things."

As a result of this mode of questioning the radiation exposure information recorded for each woman on registration was sufficiently specific in virtually all cases to allow a sorting into ten categories:

1. Exposure as X-ray technician, use of shoe fluoroscopy as salesperson.
2. Reported holding patients being X-rayed.
3. Escorted patients to radiology department or next room to X-ray equipment.
4. Industrial exposure, e.g. reported X-ray use for candy inspection (verified by health physicist in Boston).

5. Use of radioisotopes.
6. Cobalt-60 exposure.
7. Ultra-violet radiation.
8. Nursing care for patients with radium inserts and other sealed radioactive sources.
9. Problematic exposure.
10. In radioisotope area - visits only.

Excluded were those in categories 3,7,9 and 10, i.e. those who escorted patients to the radiology department but did not clearly indicate presence during irradiation of patient, ultra violet radiation, problematic exposure, (comment reported indicated that the woman did not understand what ionizing radiation was, e.g., "I had a radioactive bar put into my typewriter"), visiting the radioisotope area. When length of time at the job was less than one month she was excluded. In none of these cases did it seem likely that a significant radiation dose could have been experienced and the decision to exclude was additionally based on the latter criterion. A total of 120 women were judged to be unexposed on the basis of insufficient evidence to establish occupational exposure to ionizing radiation. Escorting of patients to the radiology department was the largest single group transferred to the unexposed category.

The distribution of exposure categories was:

X-ray technician, shoe fluoroscopy	112
Holding patients during irradiation	117
Industrial expcsure	9
Use of radioisotopes	72
Cobalt 60 exposure	5
Radium inserts, sealed sources	79
Total	394

Unfortunately there is now no means of establishing the radiation dose which these women experienced. Film badges were not in general use in hospitals in the late fifties and early sixties and badging of workers using radioisotopes was in its infancy. However it is possible to describe a range of radiation doses which individuals working in these settings experienced in that period, information derived from published reports and state surveys.

Background Discussion

A recent publication of the National Council on Radiological Protection and Measurements deals with radiation protection for medical and allied personnel (NCRP, 1976) and provides current estimates of exposure rates from secondary radiation to persons manually restraining patients during radiographic procedures. The exposure at eye level, dependent on X-ray machine specifications and operation can range from 15 to 75 milliroentgen. These ranges represent ideal conditions with leakage radiation less than 1% of the useful beam. Fifteen to twenty years ago lead aprons were seldom used and collimation of the X-ray beam was unreliable.

Probably the most serious deficiency in the entire area of X-ray diagnosis up to the present is the inadequate training of X-ray technicians. Today only New York, New Jersey, California, Kentucky and Puerto Rico have legal requirements for licensing X-ray technicians. Professional radiology associations have voluntary standards, but most states do not enforce them. Recent Senate Committee hearings received testimony from the Director of the Bureau of Radiological Health "In most states individuals can walk in off the street" and be hired to X-ray patients for physicians (Villeforth, 1977). Many of the women in the radiation exposed category of the CPP population worked for private physicians and could be described in that manner.

The NCRP has also developed exposure rates surrounding the bed of a patient containing 100 mg of radium or 200 mCi of gold (^{198}Au) or 300 mCi of iodine (^{131}I) (Figure 1). The precautions currently expected in the nursing of patients with radioactive inserts are quite rigorous in comparison with the past. Film badges are now worn, there is minimum patient contact compatible with adequate nursing care, rotation of nursing personnel, and strict isolation of the patient with controlled disposal of all excreta. These procedures are in marked contrast with the attitude of inevitable acceptance of risk which prevailed up to about 1970.

A survey of medical radium installations in Wisconsin was made from 1968 to 1970. The conclusion was that the majority of registrants, (that is medical radium installations) were unable to demonstrate that personnel exposure aspects of radium use met acceptable standards "simply because personnel monitoring was not performed on all or even most of the individuals exposed to radiation from the use of radium" (Tapert et al., 1975).

"Survey findings show that personnel monitoring was provided to at least one individual during radium use at about 50 percent of the installations. At these installations the individual monitored was usually the radiologist who wore a film badge as a matter of routine. Other exposed individuals (anesthesiologists, gynecologists, surgery room nurses or technicians, floor nurses or aides) were very infrequently monitored. At the remaining installations personnel monitoring was not provided for any individual during radium treatments . . ."

In their survey of twenty hospitals film badges were distributed for whole body monitoring and the results are shown in Table 14. These values included five high doses received by three physicians and two nurses with

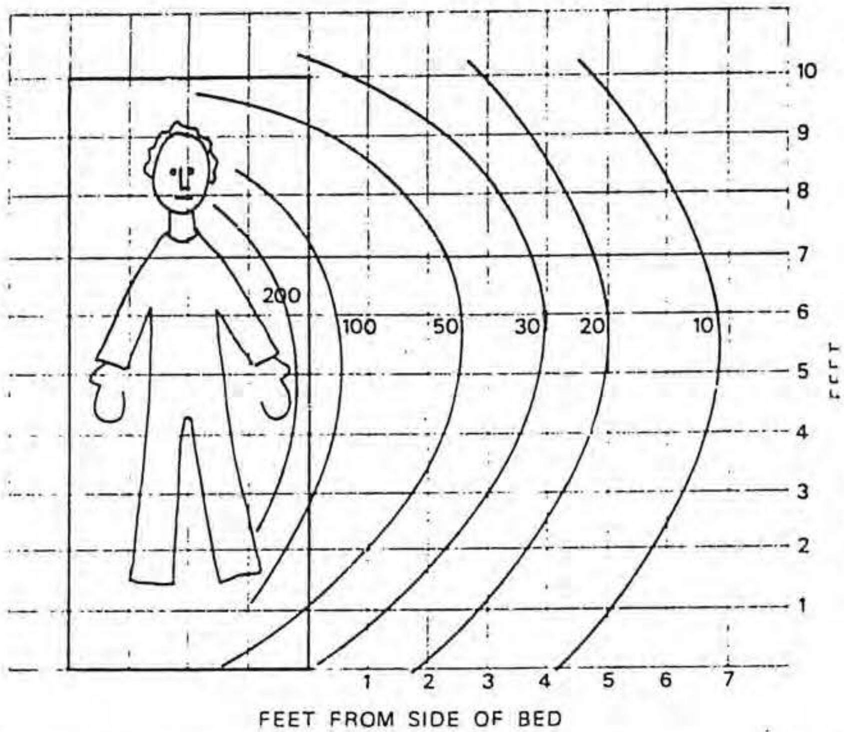

Figure 1: Description: Approximate exposure rates (mR/h) in region around the bed of a patient containing 100 mg of radium or 300 mCi of gold (^{198}Au) or 300 mCi of iodine (^{131}I). Note that although only one side is shown, the exposure pattern completely surrounds the body. Furthermore, if the patient's bed is near a wall of beaverboard or other light material, the radiation penetrates the wall with little reduction, and the exposure pattern continues beyond the wall. Adapted from Nurnberger (1960).

Table 14 Radiation dose by job category (per person)

Job Category	Number of Persons	Percent	Total dose accumulated (mrems)	Aver. dose/ person (mrems)	Range of person doses/quarter* (mrems)
Physician	30	14	5,150	172	20-1360
Aide	27	13	2,480	92	10-320
Nurse	78	38	6,560	84	10-1220
Unspecified Female	69	27	3,450	50	10-190
Unspecified Male	5	2.5	200	40	10-120
Other	5	2.5	150	30	10-40
Technician	7	3	180	26	20-50
Total	221	100	18,170		
Overall				82	10-1360

* A calendar quarter was the maximum interval. Some individuals were monitored for one month or one treatment, then rotated to a different department of the hospital (Tapert, 1975).

individual doses of 600, 1130, 1220, 1240, and 1360 mrem/individual/quarter respectively, making aides the most highly exposed group on the average. These doses would result from the frequent and extended care given the patient directly at the bedside.

Nurnberger (1960) graphically described conditions in Memphis, Tennessee in the treatment of patients with radium and other radioactive isotopes. The radiation dose absorbed by those entering the patient's room could not be determined because it was found inadvisable to use film badges or pocket dosimeters. "Our experience has demonstrated that many nurses and members of the public too, become needlessly fearful, almost bordering on panic, when they are made to wear badges or pocket dosimeters. On the other hand, simple instructions on occupancy of the room are accepted and obeyed without emotional upset."

In 1960 the permissible dose which could be received by an occupationally exposed person was 300 mrem per week. Under that restriction Nurnberger recommended that "nurses, aides and ward personnel may attend radium patients at the bedside for a total of three hours per week regardless of the number of days of treatment." In the United States the weekly maximum permissible standard for occupational exposure has been reduced to 5 rems/year or 100 mrem/week, so that the 3 hour recommendation than becomes a 1 hour recommendation for bedside care of radium patients (Tapert et al., 1975). Tapert's extrapolation from the survey results in Wisconsin shown in Table 14 , was that the 92 mrem average exposure to aides represented about one hour of bedside care.

There have been a few scattered studies of occupational exposures to radioisotopes. Blum et al (1967) have made measurements of thyroid ^{131}iodine in medical and paramedical personnel exposed to radioactive iodine in both diagnostic and therapeutic settings. Table 15 shows the range of values observed. In the extreme case among the technicians (if 18, 131 pCi was the constant burden - a rather unlikely occurrence) the annual dose could be as high as 3,840 mrads. The maximum permissible value for annual occupational exposure to radioactive iodine as recommended by the Federal Radiation Council in 1960 was 30,000 mrads. This level was established as a limit with little if any consideration given at that time to the possibility that technicians could be pregnant. Lombardi et al (1972) substantiate the view of Blum et al that there is wide variation in laboratory practices from one technician to another. In reviewing the use of technetium - 99m, which provides the highest hand dose received by nuclear medicine technologists, they concluded that with the relatively large quantities of radioactive isotopes being used routinely in hospitals, standardization of routine scanning procedures is urgently needed to minimize patient and personnel exposures.

Costa et al (1965) have shown that fetuses 6 and 7.8 cm (presumably 70-77 days old) did not absorb the radioiodine administered to the mother but the 9.5 cm fetus (presumably 80 days old) and those older exhibited radioiodine uptake and the presence of stable iodine in the thyroid gland. At about the third month of gestation, the total stable iodine content of the fetal thyroid is 0.2 - 2 ug; it increases twenty-fold between the third and sixth month, and tenfold between the sixth month and birth. The iodine content of the thyroid increases at a faster rate than its weight, so that the iodine content per gram of gland increases as pregnancy progresses.

TABLE 15

Thyroid ^{131}I Burdens

	No. of Subjects	Thyroid Burden pCi *		Range pCi	Inferred Average Annual Dose (mrads)
Unexposed Controls	62	12.3	± 20.4	0 - 58	2.7
Clinical Laboratory Supervisory Physicians and Physicisits	11	92.1	± 89.1	22 - 343	20
Clinical Laboratory Technicians	25	2,373.8	± 4,432	35 - 18,131	503
Physicians Administering Therapy	4			74 - 1,827	14 mrad/patient
Nurses - 24 hr. after therapy	6	262	± 153	98 - 441	7 mrad/patient

* Mean ± ISD

From Blum et al (1967).

"Hormonogenesis" is complete in the 3½ month (16 cm) fetus and radioiodine accumulation in the fetal thyroid can be as much as ten times that in the maternal thyroid, weight for weight.

There have been a number of published case studies showing radioiodine damage to the fetal thyroid gland from millicurie therapeutic doses, in addition to studies reporting no untoward effects. These cases are reviewed by Pfannensteil et al (1965) and they report induced congenital hypothyroidism which apparently occurred during the tenth week of embryonic life.

A comparison of average annual doses for individuals in various job categories involving medical irradiation has been compiled from a number of surveys in the United States and foreign countries. Table 16 is taken from the Bureau of Radiological Health report (Tapert et al., 1975). These mean values have been developed for the purpose of population exposure estimates so do not provide an adequate range of values suitable for our evaluation. However they do provide a relative comparison between the different treatment areas so that we could expect that in the population studied in the CPP the likelihood of increased average dose would have been highest for those involved with radium therapy and industrial radiography - five to ten fold greater than diagnostic X-ray exposure. Tapert al al. concluded from their survey and these comparisons that occupational exposure of brachytherapy health personnel has been a "long neglected facet of public health," a conclusion also reached for Pennsylvania by Gerusky et al. (1965).

We can conclude from Table 16 showing annual radiation doses which represent survey data of the mid 1960's that the women under study experienced radiation doses ranging from 165 mrem/year to at least 1,800 mrem/year.

Table 16 Some comparisons of annual radiation doses

Category	No. Individuals	Man-rems	
		Total	Individual
Diagnostic X-ray	366×10^3	60×10^3	0.165
Nuclear Medicine	$25\text{-}33 \times 10^3$	9×10^3	0.27-0.35
Ra-Rn Therapy	$20\text{-}40 \times 10^3$	35×10^3	0.9-1.8
Industrial Radiography (radioactive material)	$5\text{-}7 \times 10^3$	7×10^3	1-1.4

From Tapert et al (1975)

There were undoubtedly individuals who experienced higher doses in light of the working conditions observed and reported throughout the 1960's and into the seventies. These mean doses are well within the allowable occupational exposure standard of 5,000 mrem/year (1,250 per quarter). It is well to keep in mind also that the introduction of monitoring by the use of badges and other dosimeters in itself produces a marked improvement in general operating procedures with a secondary result of reduced exposure. The experience reported in this study was before these improvements were widespread, although Boston and Buffalo were well ahead of the rest of the country.

Results

Occupational exposure only to ionizing radiation was recorded for 35.5% of 394 individuals in this group, with 39.4% exposed to one additional hazard, 21.0% exposed to two additional hazards and 4.0% exposed to more than two additional hazards (Table 11a). The additional hazardous exposures for the radiation group were to heavy lifting (40.0%), chemicals (33.0%), animals (17.6%), pesticides (1.0%) and heat (1.0%) (Table 11b).

Together with the group exposed to animals those exposed to ionizing radiation were also exposed to more multiple hazards, particularly chemicals and heavy lifting than the rest of the exposed population.

There were more women of higher socioeconomic status, more Whites than expected, more mothers age 20 to 29, and more who registered in the study before the twentieth week of pregnancy, when compared with all those in the study population who were designated as not occupationally exposed to ionizing radiation. One associated variable which may be considered adverse to the mother and/or the child was more abdominal X-ray during pregnancy. (Table 17).

The exposed women experienced less anemia and kidney urinary bladder infection during pregnancy but considerably more first trimester bleeding and placental infarcts, most of the excess being in the category where infarcts were less than 3 cms. Hydramnios occurred in 21 mothers when 10 were expected (significance p-value 0.020).

The group had experienced fewer prior premature deliveries and for the pregnancy under study had more deliveries at more than 40 weeks. Far fewer children than expected were observed with low 8 month motor scores, delayed motor development at 1 year and low 4 year I.Q. (<80).

TABLE 17

Occupational Exposure to Ionizing Radiation

Number Exposed 394

Two Factor Interaction with Demographic Variables

	Observed	Expected	Significance P-Value
Race (White)	346	203	<0.001
Socio Economic Status (High)	333	138	<0.001
Age of Gravida (20-29)	285	229	<0.001
Gestation at Registration (<20 weeks)*	271	192	<0.001
Abdominal X-Rays During Pregnancy	140	103	0.001

Two Factor Interaction with Pregnancy Outcome Variables

	Observed	Expected	Significance P-Value
Prior Prematures*	36	68	<0.001
1st Trimester Bleeding**	93	58	<0.001
Placental Infarcts*	108	77	0.004
Kidney, Urinary Bladder Infection* During Pregnancy	45	68	0.008
Anemia During Pregnancy*	29	86	<0.001
Hydramnios	21	10	0.020
Gestation at Delivery (40+ weeks)	211	195	0.007
Delayed Motor Development (1 year)*	30	47	0.029
4 Year I.Q. (<80)*	8	34	0.001
Head Circumference 4 months (>44 cm)*	242	179	0.001
8 months (>47 cm)*	34	19	0.001
4 years (>53 cm)*	35	14	0.001
7 years (>54 cm)*	40	25	<0.001

In these two factor interactions, the observed/expected numbers reported here do not provide all the contingency table information which was used for Chi-Square analysis and significance probability reported above. Where the particular stratum of interest is indicated only data relating to it is shown.

* No statistically significant three way interaction observed between
- i) exposure to occupational hazard
- ii) any demographic variable tested in this study
- iii) any other pregnancy outcome variable tested in this study

**No statistically significant three way interaction between
- i) exposure to occupational hazard
- ii) any demographic variable tested in this study

Three Factor Interactions

The interaction between occupational exposure to ionizing radiation, diagnostic abdominal X-ray during pregnancy and gestation at delivery was seen as more mothers with no abdominal X-ray who delivered at 40 or more weeks and more mothers than expected who delivered between 35 and 39 weeks who had abdominal X-ray during pregnancy. More exposed Blacks were observed than expected who had abdominal X-ray during pregnancy. More children with high I.Q. at 4 years (110+) were found among those whose mothers were not exposed to abdominal X-rays during pregnancy. The children whose mothers did experience abdominal X-ray during pregnancy included fewer with high I.Q. at 4 years (110+) and more in the mid I.Q. category (80-109). There were more mothers than expected without hydramnios with high socio-economic status. The interaction with race was seen as more Blacks with hydramnios than expected (Table 18).

There was an excess of newborn high hematocrit (70+) among those whose mothers had first trimester uterine bleeding and occupational radiation exposure. There were more high socio-economic status women observed than expected who did no experience uterine bleeding.

In summary, the group occupationally exposed to ionizing radiation had a far better reproductive experience than those reporting exposure to other hazards, except for the increased number with hydramnios. Thirty three percent of the radiation exposed group also reported exposure to chemicals. Hydramnios was also found to be associated with that group so that it appears possible that those with double exposure experience may have contributed to that excess. Further examination of multiple exposures is needed for all exposure groups.

TABLE 18

Occupational Exposure to Ionizing Radiation

Number Exposed 394

Three Factor Interaction with Demographic Variables

		Significance P-value
Race	Hydramnios	0.009
Socio Economic Status	Race	0.001
" "	Hydramnios	0.020
" "	2nd Trimester Bleeding	0.012
" "	3rd Trimester Bleeding	0.016
Abdominal X-ray during Pregnancy	Race	0.007
" " "	Gestation at Delivery	0.001
" "	4 Year I.Q.	0.011
Age of Gravida	Hydramnios	0.047

Three Factor Interaction with Pregnancy Outcome Variables

Gestation at Delivery	Abdominal X-ray	0.001
1st Trimester Uterine Bleeding	Hematocrit (Newborn)	0.017
Hydramnios	Socio Economic Status	0.018
"	Race	0.009
"	Age of Gravida	0.047
Anemia during Pregnancy	Socio Economic Status	0.015

ANIMALS

The question on animal exposure was: "Have you ever had to handle animals or birds on any of your jobs?". The interviewer was instructed to probe "Like tending animals or eviscerating fowl or caring for animals?".

The responses were specific enough to sort this group into the following categories:

1.	Chickens, turkeys (poultry workers)	114
2.	Pet shop, animal hospitals	63
3.	Zoos, handling horses, farms	66
4.	Meat and fish processing	61
5.	Teachers, museum curators, carnivals, research students, laboratory workers	211
	Total	515

Exclusions from this group were very few on the basis of less than one month working experience.

Background Discussion

Exposure to animals carries with it the risk of infection, which has been reported in many countries (Curet et al., 1972; Field et al., 1972; Hanson et al., 1967; Luby et al., 1969; Schnurrenberger et al., 1972). However, little has been recorded concerning the relationship of the zoonoses to pregnancy outcome.

Results

Exposure only to animals was recorded for 34.5% of the 515 women in this group, with 40.2% exposed to one additional hazard, 21.6% exposed to two additional hazards and 3.7% exposed to more than two additional hazards. (Table 11a). The additional hazardous exposures for the group reporting exposure to animals were to radiation (14.2%), pesticides (7.4%), chemicals (33.9%), heat (5.6%) and heavy lifting (32.9%) (Table 11b). The group exposed to chemicals experienced more exposure to additional hazards than any other group, particularly heavy lifting and chemicals.

Associated characteristics were higher socioeconomic status, more Whites than expected and earlier gestation at registration in the CPP when compared with all those who were designated as not exposed to animals. The associated characteristics which may be considered adverse to the mother and/or the child were more abdominal X-ray during pregnancy and more older women (30 years of age and over) (Table 19).

They experienced less anemia and less kidney urinary bladder infection during pregnancy. Although there were more with first and third trimester uterine bleeding than expected the excess was slight when compared with the other exposure groups. But they were the only group to show an excess of convulsive disorders during pregnancy, 7 observed, 2.6 expected.

The group exposed to animals had experienced fewer prior premature deliveries and for the pregnancy under study had far more deliveries where the gestation was more than 40 weeks. There was a considerable excess of children in the highest 4 year I.Q. group (110+).

TABLE 19

Occupational Exposure to Animals

Number Exposed 515

Two Factor Interaction with Demographic Variables

	Observed	Expected	Significance P-Value
Race (White)	368	227	<0.001
Socio Economic Status (High)	264	156	<0.001
Age of Gravida (30+ years)	110	89	<0.001
Gestation at Registration (<20 wks.)	272	237	0.036
Abdominal X-ray During Pregnancy	172	127	<0.001

Two Factor Interaction with Pregnancy Outcome Variables

	Observed	Expected	Significance P-Value
Prior Prematures**	42	50	0.001
1st Trimester Bleeding**	90	71	0.040
3rd Trimester Bleeding	87	69	0.038
Anemia During Pregnancy	44	105	<0.001
Kidney Urinary Bladder Infection During Pregnancy**	57	84	0.007
Convulsive Disorder During Pregnancy*	7	3	0.027
Gestation at Delivery (40+ wks)	291	143	0.001
4 Year I.Q. (110+)	121	67	<0.001
Head Circumference (4 mos.) 41+cm	154	128	0.006
(8 mos.) 48+cm	157	143	0.013
(7 yrs.) 54+cm	39	28	0.029

In these two factor interactions, the observed/expected numbers reported here do not provide all the contingency table information which was used for the Chi-Square and significance probability. Where the particular stratum of interest is indicated only data relating to it is shown.

* No statistically significant three way interaction observed between
i) exposure to occupational hazard
ii) any demographic variable tested in this study
iii) any other pregnancy outcome variable tested in this study

**No statistically significant three way interaction between
i) exposure to occupational hazard
ii) any demographic variable tested in this study

Three Factor Interaction

More non-smokers exposed to animals than expected had children with high 4 year I.Q. (110+) and there were fewer such children of smokers exposed to animals. More exposed mothers who had not had abdominal X-ray had children with high I.Q. and there were fewer children with high I.Q. at 4 years whose exposed mothers had experienced abdominal X-ray during pregnancy. There were fewer children with high 4 year I.Q. whose mothers had been exposed to animals and also had third trimester bleeding, and more children with high 4 year I.Q. whose mothers had been exposed to animals but did not experience third trimester uterine bleeding (Table 20).

In summary the women reporting exposure to animals, although many of them were also exposed to chemicals and heavy lifting appear to have had the best reproductive experience of all the groups in the study, with little evidence that adverse pregnancy outcome was associated with work experience with animals.

TABLE 20

Occupational Exposure to Animals

Number Exposed 515

Three Factor Interaction with Demographic Variables

		Significance P - Value
Socio Economic Status	3rd Trimester Bleeding	0.033
Gestation at Registration	Anemia during Pregnancy	0.046
Abdominal X-ray during Pregnancy	4 year I.Q.	0.014
Cigarette Smoking during Pregnancy	4 year I.Q.	0.031

Three Factor Interaction with Pregnancy Outcome Variables

Prior Prematures	1st Trimester Bleeding	0.011
" "	Anemia During Pregnancy	0.032
3rd Trimester Bleeding	Kidney, Urindary Bladder Infection during Pregnancy	0.037
" " "	4 year I.Q.	0.018
Anemia during Pregnancy	Gestation at Registration	0.046
Head Circumference (8 months)	5 minute Apgar	0.043
4 year I.Q.	Abdominal X-ray during Preg.	0.014
" " "	Cigarette Smoking during Preg.	0.031

CHEMICALS

The question asked was "Have you ever worked with chemicals, their dusts, gases, or fumes in a job situation?" The interviewer was instructed that "detergents used by a domestic worker in the home should not be included but chemical compounds used by a charwoman who cleans offices or other commercial buildings should. Also include spotters in dry cleaning establishments, cleaners and dryers, fur finishers, etc. Probe for detail of the industry and work done. When asking this question, ask "Chemical Dusts," Chemical Gases," Chemical Fumes?"

The specificity of response sometimes provided the name of the chemical (e.g. trichlorethylene), but more often designated the type of industry or job done. It was possible to make the following categories.

1. Jewelry industry	242
2. Beauticians	145
3. Glues, paints, lacquers working with shoes, furniture, art.	139
4. Chemicals used in photography, duplicating and printing	140
5. Farm produce - pesticide exposure.	Separate Category
6. Electronic industry	123
7. Laboratory workers - biology	130
8. Other laboratory workers - inorganic and organic chemicals.	123
9. Laboratory technicians in hospitals.	94
10. Rubber industry	46
11. Organic solvents - cleaning metals, clothes, etc.	158
12. Plastic industry (Toy manufacture, meat wrappers)	89
13. Teachers - chemicals in art and science instruction	21
14. Lint and dust (undefined)	Excluded
15. Stenographers and others not directly exposed	Excluded
16. Anesthetists	50
Total	1500

Category 5, indicating pesticide exposure was excluded and examined separately under that designation. Categories 14 and 15 were excluded, exposure to lint and dust (undefined) and stenographers not directly exposed and placed in the unexposed group.

Work experience of less than one month was a criterion for exclusion, a very small percentage. Some exposure designations were made on the basis of job description, even though chemical exposure was not specified by the respondent (e.g. jewelry worker).

Background Discussion

Laboratories

Until only the most recent years, laboratory manuals have failed to stress the toxicity and health hazards posed by substances used daily in chemistry laboratories. The brief sections on laboratory safety in chemistry books and manuals discuss the mechanical safety hazards such as fire, explosion, corrosive agents, proper glassware storage and set-up, and the correct fittings for corks and stoppers for reagent bottles. The description of hazards in the chemical laboratory listed in the opening chapters of standard laboratory manuals has changed very little from the early thirties to the seventies (Fieser, 1963, Streitwieser et al, 1976). All are concerned with the issues of safety while presenting only the most cursory descriptions of health hazards. In contrast with radiation laboratory workers, chemists have not adopted the smallest possible dose as their criterion for establishing acceptable exposures. Considering these last two points, the laboratories using organic compounds particularly have usually been unhealthy places of employment. Chemistry laboratories are also notoriously poorly ventilated. The hood space is rarely adequate and the hoods are often improperly designed or installed. This is true today as well as in the fifties and sixties.

A technician in a hospital, biology or chemistry laboratory devotes considerable time to processes involving organic compounds. Basic methods in frequent use are distillation, crystallization, extraction, and chromatography. During the fifties and early sixties, extractions were performed with ethyl and diethyl ether, although their use was limited industrially because of the great fire hazard potential. Common water-immiscible solvents were: petroleum ether, benzene, carbon tetrachloride, chloroform, ethylene dichloride, butanol and ligroin.

In crystallization, a highly effective means of purifying a solid substance, the most common solvents used were the following:

> water, ligroin, methanol, benzene, ethanol (95%), chloroform, acetic acid, carbon tetrachloride, acetone, carbon disulfide, ether, toluene, petroleum ether, aniline

Two miscible solvents of different solvent power constitute a useful solvent pair. Thus organic solvents are often mixed in the laboratory. Commonly used solvent pairs are:

> methanol - water, ethanol - water, acetic acid - water, acetone - water, ether - methanol, ether - acetone, ether - petroleum ether, benzene - ligroin

A good evaluation of a pesticide analytical laboratory was reported in 1968 by Applegate, and could represent for us the possible extreme conditions experienced by laboratory workers in the CPP.

In a pesticide analytical laboratory large quantities of volatile solvents are used to extract pesticides from various types of biological samples. In the air-conditioned laboratory examined all evaporations and concentrations of volatile solvents approached but did not reach the maximum levels allowable in 1968. Organic solvents used in the daily processing of samples allowed a build-up of vapors in the laboratory to the extent that a background reading for hydrocarbons was 340 to 380 ppm each morning before analytic procedures began.

Tables 21, 22, and 23 provide data for an evaluation of atmospheric concentrations in the laboratory where commonly used hydrocarbons were in routine use.

Table 21 - Chemicals Used in a Five-Day Period (ml)

	July 31	Aug 1	Aug 2	Aug 3	Aug 4	Total
Chloroform	2,600	0	0	0	0	2,600
Hexane	650	860	370	805	370	3,005
Ethyl acetate	4,775	2,000	500	275	190	7,740
Petroleum benzin	4,820	9,320	8,740	5,235	6,260	34,575
Acetonitrile	200	3,260	1,500	2,600	3,600	11,160
N, N-Dimethyl-formamide	0	4,500	0	0	0	4,500

Applegate (1968)

Table 22 - Atmospheric Hydrocarbon
Concentrations (ppm)

Time (hr)	July 31	Aug 1	Aug 2	Aug 3	Aug 4
800	350	380	350	340	380
900	510	570	450	370	380
1,000	610	720	560	500	1.080
1,100	810	840	620	620	1,050
1,200	1,050	840	800	780	1,150
1,300	1,260	840	1,000	960	1,290
1,400	1,440	960	1,210	1,490	1,320
1,500	1,560	1,350	1,400	1,170	1,140
1,600	1,260	1,080	1,450	680	780
1,800	800	840	720	560	660
2,000	640	780	700	440	520

Threshold Limit Values of Selected Hydrocarbons

Name	TLV (ppm)
Chloroform	50
Hexane	500
Ethyl acetate	400
Petroleum distillate (naptha)	500
Acetonitrile	20
N, N-Dimethylformamide	10

Applegate (1968)

Very little research has been carried out to test the teratogenicity of the substances used regularly in organic chemistry procedures. The absence of an agent from Shepard's catalog (1973) in no way indicates that it is not teratogenic. It has most likely never been tested and for those chemicals that have been determined to be teratogenic, the concentration of the teratogen that the embryo or fetus can tolerate before damage occurs is not known.

Jewelry Industry

Most of the women who reported work experience in the jewelry industry registered at the Providence, Rhode Island hospital. Today one half of the country's jewelry industry is located in Rhode Island and 30.6% of the manufacturing plants in the state are involved in the jewelry industry employing 24,600 people. The industry is of long standing and has traditionally employed a high proportion of women. Fortuitously a 1976 project organized by Brown University students has resulted in a very detailed evaluation of processes and hazardous conditions in the industry and the following information comes from their observations and booklet (in press).*

Working conditions today are far from being in compliance with OSHA standards and it can be assumed that in the early sixties they were no better. Small factories in stables, lofts, basements, and houses, invariably of 19th century vintage are characteristic of the unorganized Rhode Island jewelry industry which is dependent on an unstable fashion market and labor intensive high volume piece work.

Trade secrets, non-standardized processes and sweat shop conditions all contribute to a particularly complex and hazardous chemical environment.

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* Courtesy Margaret M. Quinn.

Several major processes are involved in the jewelry industry - metal casting, stamping and pressing, grinding, polishing, buffing, metal cleaning, electroplating, soldering, spray painting, lacquering, enameling, and gluing. About the framework of these main procedures are a variety of preparation and finishing jobs such as set up and charge, stringing, racking, dipping, carding, and packaging. Women perform all of these operations to a varying degree, although they usually have the jobs that prepare and finish a "major" operation and transfer production pieces from one process to another. Most processes in jewelry manufacturing are usually carried out in the same shop, so that harmful working conditions can affect all those in the general vicinity of the hazard as well as those working with it directly. High heat in summer and poor ventilation in winter are the rule rather than the exception.

Metal Casting

The most popular casting process for costume jewelry is rubber mold casting. White metal, an alloy usually composed of 32% tin, is cast into rubber molds at 300^{o}-400^{o}F. Higher percentages of tin comprise the better quality white metals along with varying amounts of lead, copper, zinc, arsenic, mercury, cadmium, and beryllium. The rubber molds themselves are cut with soldering irons. When the natural rubber molds combust, benzene-soluble hydrocarbons such as benzo(a) pyrene and anthracenes are released. Before the molten white metal is poured, talc is used to dust the rubber mold. Asbestos and silica-contaminated talcs are common in the Rhode Island industry. The liquid metal is transferred from open vat to mold with a ladle by the "pot tender." It is a common practice to compound the metals in the jewelry plant. Lead is stored in-house in powder form; beryllium in small ingots of 2% Be-Cu alloy composition. Each formulation is likely to be unique so that little knowledge of its constituents is ever available.

Investment or lost wax casting produces the most ornate or detailed jewelry such as fine filigreed designs or school rings that require little finishing. Copper alloys and precious metals are generally cast at approximately 3000°F, though low temperature white metal is occasionally cast by this method.

The lost wax molds are made from a pastry mixture of lime or clay base plaster (up to 30% silica) and very fine silica powder (up to 70% silica). "Shakeout" is the industry's term for the breaking of the plaster molds about the newly cast jewelry piece, and is traditionally done by hand with the sand flying into the workers' breathing area. The Rhode Island Department of Health has measured levels of silica during shakeout at 32 times the threshold limit value.

In die casting molten metal is forced into a metal mold or die. Zinc-aluminum and copper alloys are commonly used while white metal is used only occasionally. Muriatic acid (impure hydrochloric acid) is employed as an industrial cleaner for the metal dies.

Grinding, Polishing, Buffing

After a jewelry piece is cast it must be ground, polished and buffed to finish the metal surface or prepare it for plating. These operations involve mechanical abrasion of the jewelry casting to grind off the rough edges and impart smoothness and sheen to the metal surface. Much of the grinding, polishing, and buffing in the jewelry industry is done by hand. Different colored metal surfaces and the brightest lusters are obtained with very finely powdered buffing abrasives such as lime, unfused aluminum oxide, iron oxide and chromium oxide. Airborne particles and dusts are generated in the work area by the high powered wheels and in some instances, oils are added to the wheels causing mists.

Metal Cleaning Degreasing and Plating

After the cast jewelry has been ground, polished, and buffed it is usually plated with a more attractive or durable alloy, unless it was originally cast with a precious metal. Before the plating can be done the metal surface of the production piece must be free of all grease, oils, abrasives, and/or metal oxides. Three categories of cleaning materials are used for the essential pre-electroplating process: organic solvents, acids, and alkalies.

In the 1950's and 1960's, the most common degreasing solutions by far were trichloroethylene and perchloroethylene. Methyl chloroform, trichloroethane and ethylene dichloride were also used. Only very recently, with the rising suspicion of trichloroethylene and perchloroethylene as human carcinogens, have attempts been made to replace these solvents with other organic solvents thought to be less harmful.

The solvents are placed in large, tub-like degreasing machines and heated until they vaporize. Racks of jewelry are hung in the solvent vapors to be cleaned. The top layer of the degreasing tanks is supposed to be lined with cooling coils to condense the trichloroethylene vapors back in the tank. The pieces of jewelry that have been cleansed are also supposed to be moved to the cooling zone of the degreasing tank to remove the solvent on each article before it is carried to the electroplaters. Jewelry workers are often pressured to accelerate production so that metal pieces are removed from the cooling zone much too quickly. Quite frequently the tanks are poorly ventilated, the condensing coils malfunction, the amperage of the vaporizers is increased, and workers are not informed of the hazards of organic solvents. Sulfuric, hydrochloric and nitric acids are most commonly used to clean and activate metal in addition to the alkalis, sodium and potassium hydroxide. Splashing usually occurs around degreasers so that acid and alkaline mists can be generated when the tank temperature rises. Oxides of nitrogen and arsine can be formed under these conditions. "Brighteners" tend to be trade secrets used during an early stage of plating, the "copper strike" and may include metallic cobalt, selenium, saccharin, thiourea, dextrin and molasses! Hydrogen cyanide gas can form in the vicinity of tanks used for cyanide-copper, acid-gold, cyanide-gold, rhodium and silver plating.

Other processes include soldering, annealing, glueing, lacquering, enamelling and plastic embedding so that lead, cadmium and fluorine fumes, carbon monoxide, asbestos dust, epichlorohydrin and polyamine vapor, lacquer and enamel solvent aerosols, and methyl methacrylate vapors can be in the work environment of a jewelry maker. During the 1950's and sixties benzene was still being used as a solvent and thinner. Toluene and xylene are more likely to be used now.

Women have traditionally been employed "racking up," which involved hanging the individual pieces of jewelry on to metal racks for cleaning and plating. They are likely to be seated at a long work table with piles of metal racks beside them on the floor and hundreds of pieces of jewelry before them, rapidly filling a rack with fifteen to twenty pieces of jewelry. The environment is one of intense concentration, speed, and fumes from degreasing and plating tanks which are usually in close proximity.

Most of the jewelry workers in the CPP reported "racking" or "stamping" as their occupation and on the basis of our knowledge of working conditions in the industry they were categorized as being exposed to chemicals.

Any effort to consider the biological effect of a single chemical agent would be virtually futile due to the non-specialist nature of the industry. Most shops use many processes over a period of time.

Electronics Industry

Over the one hundred years since the invention of the electric light bulb women have been in the majority in the manufacture of electronic products. Exposure to beryllium in the fluorescent lamp industry caused illness and death in the 1940's with pregnant women being particularly at risk (Hardy, 1965). Today more than 75% of the workers making semiconductors and printed wiring circuit boards are women. Organic solvents likely to be found in the workplace are: isopropyl alcohol, toluene, xylene, petroleum naptha, trichlorethylene, methylene chloride, methyl chloroform (trochloroethane), acetone, methyl ethyl ketone, ethyl acetate, cellusolve, chloroform and freons. Current inspection of plants by state and federal occupational safety and health agencies frequently show ventilation inadequacy across the country, with solvent exposures sufficient to cause dizziness, headaches and euphoria in workers (Talbot and Hricko, 1977).

Soldering and welding operations also result in the formation of toxic gases such as phosgene and as in the jewelry industry the soldering process may involve solders of diverse metal content, including cadmium and lead. Resin core solders can release formaldehyde and fluorides.

Polyesters heat cured with peroxides or epoxy resins cured with phenol cause skin and eye irritation. Toluene di-isocyanate and similar compounds are used to form polyurethane. Polychlorinated biphenyls and chloronapthalenes are used to protect parts from corrosion. Electroplating involves use of nickel and chromium solutions with resulting acid mists. Cyanide baths are used in zinc, cadmium and gold plating.

Health hazard evaluations by NIOSH in the mid 1970's have repeatedly recommended installation of better ventilation systems, particularly in soldering, plating, degreasing operations, spraying and washing of circuit boards. Today many electronics companies have installed closed systems and "clean rooms." By comparison we can assume that conditions of chemical contamination in the period 1961-1965 were no better than those being reported today. The economic history of the industry has been considerably more progressive than in the jewelry industry and we can fairly confidently rate the hazards of the electronic industry as the less severe, an opinion based in part on the relative size and age of buildings used in the two industries. Twenty years ago some electronics companies were as small as jewelry companies but jewelry manufacture has never reached the level of environmental control found today in some electronic operations.

Results

Exposure only to chemicals was recorded for 43.6% of the 1500 women in this group, with 42.8% exposed to one additional hazard, 10.9% exposed to two additional hazards and 2.6% exposed to three or more additional hazards (Table 11a). The additional hazardous exposures for the chemical group were from radiation (9.0%), heat (18.5%), heavy lifting (29.7%), and animals (11.5%) (Table 11b).

Associated characteristics were higher socioeconomic status, more Whites than Blacks and more early registrations (<20 weeks gestation) in the CPP, when compared with all those in the study population who were designated as not exposed to chemicals. There were more with abdominal X-ray during pregnancy and more women over 30 years of age among those exposed to chemicals (Table 23).

During pregnancy they experienced less anemia and kidney urinary bladder infection, more delivered at 40 or more weeks gestation and there were fewer with low placental weights (<500 gms). They experienced more bleeding in all three trimesters, had more placental infarcts and more hydramnios than expected. More prior stillbirths and fetal deaths were reported by mothers exposed to chemicals. More newborn infants were observed with high hematocrit (>70) than expected and at 4 years there were more children with high I.Q. (110+).

Three Factor Interaction

The strong interaction between exposure to chemicals, race and socioeconomic status was seen in contingency tables as an excess of Whites of high socioeconomic status and Blacks of low socioeconomic status.

TABLE 23

Occupational Exposure to Chemicals

Number Exposed 1500

Two Factor Interaction with Demographic Variables

	Observed	Expected	Significance P-Value
Socio Economic Status (High)	656	462	<0.001
Race (white)	1004	670	<0.001
Age of Gravida (30 + years)	353	199	<0.001
Gestation at Registration (<20 wks.)	377	315	<0.001
Abdominal X-ray During Pregnancy	513	371	<0.001
Cigarette Smoking During Pregnancy	743	661	<0.001

Two Factor Interaction with Pregnancy Outcome Variables

	Observed	Expected	Significance P-Value
Prior Stillbirths*	174	146	0.043
Prior Fetal Deaths*	105	84	0.014
1st Trimester Bleeding**	278	210	<0.001
2nd Trimester Bleeding	153	124	0.019
3rd Trimester Bleeding**	268	206	<0.001
Placental Infarcts	271	233	0.031
Placental Weight (<300 gms)**	318	268	0.003
Kidney Urinary Bladder Infection*	175	247	0.001
Anemia During Pregnancy	219	311	<0.001
Hydramnios	31	25	0.024
Gestation at Delivery (40+ wks)	789	714	0.002
Hematocrit (child) (high 70+)	103	83	0.028
4 Year I.Q. (high) (110 +)	303	128	<0.001
Fetal Death (current pregnancy)	59	48	NS

In these two factor interactions, the observed/expected numbers reported here do not provide all the contingency table information which was used for Chi-Square analysis and significance probability. Where the particular stratum of interest is indicated only data relating to it is shown.

N.S. Not statistically significant

* No statistically significant three way interaction observed between
- i) exposure to occupational hazard
- ii) any demographic variable tested in this study
- iii) any other pregnancy outcome variable tested in this study

**No statistically significant three way interaction between
- i) exposure to occupational hazard
- ii) any demographic variable tested in this study

Although there were fewer women in the exposed group with anemia during pregnancy there were more observed than expected among smokers exposed to chemicals. More exposed mothers with anemia had abdominal X-rays during pregnancy and fewer than expected had no anemia during pregnancy and no abdominal X-ray. There were more exposed Whites than expected with anemia during pregnancy and more Blacks with anemia during pregnancy who had not been exposed to chemicals (Table 24a and b).

In the exposed group hydramnios was observed more among those with first and third trimester uterine bleeding, those who did not smoke and among Blacks.

Considerably more placental infarcts were observed in exposed Blacks and considerably fewer in unexposed Blacks than expected.

High hematocrit in the newborn (70 +) was observed more in the babies of exposed mothers who smoked.

An excess of suspected and definite neurological abnormalities at one year was observed for the high hematocrit group whose mothers were exposed to chemicals.

Excess prior prematures were observed only in races other than Blacks and Whites. There were more exposed Blacks whose children had 5 minute Apgar scores less than 6 and fewer exposed Blacks whose children had high 5 minute Apgar scores.

More children of exposed Blacks were observed than expected with suspected and definite neurological abnormalities at 7 years.

These observations on placental infarcts, hydramnios, 5 minute Apgar scores and neurological abnormalities at 1 year could indicate a differential effect of chemical exposure by race. More placental infarcts and

TABLE 24a

Occupational Exposure to Chemicals

Number Exposed 1500

Three Factor Interaction with Demographic Variables

		Significance P - Value
Time of Gestation at Registration	Smoking	0.002
	Abdominal X-ray during Pregnancy	0.002
Socio Economic Status	Prior Prematures	0.018
	Race	<0.001
	4 Year I.Q.	0.002
	Age of Gravida	<0.001
	Abdominal X-ray during Pregnancy	0.001
	2nd Trimester Bleeding	0.014
Abdominal X-rays During Pregnancy	Race	0.003
	Prior Prematures	0.001
	Head Circumf. (4 months)	0.036
	4 yr. I.Q.	0.013
Race	Socio Economic Status	<0.001
	Gestation at Registration	0.030
	Abdominal X-ray during Pregnancy	0.003
	Age of gravida	0.030
	Anemia during Pregnancy	0.034
	Hydramnios	0.009
	Placental Infarcts	<0.001
	5 minute Apgar Score	0.020
	Prior prematures	0.001
	4 year I.Q.	0.007
	Neurological Abnormalities 7 Years	0.002
Age of Gravida	Gestation at Delivery	0.005
	Prior Prematures	0.002
	Socio Economic Status	<0.001
	4 yr. I.Q.	0.013
Cigarette Smoking during Pregnancy	Anemia During Pregnancy	0.010
	Hydramnios	0.010
	Hematocrit	0.016

TABLE 24b

Occupational Exposure to Chemicals

Number Exposed 1500

Three Factor Interaction with Pregnancy Outcome Variables

		Significance P - Value
Prior Prematures	Race	0.001
1st Trimester Bleeding	5 Minute Apgar	0.015
	Neurological Abnormalities (1 year)	0.036
	Hydramnios	0.017
2nd Trimester Bleeding	Socio Economic Status	0.014
3rd Trimester Bleeding	8 Month Mental Score	0.020
	8 Month Motor Score	0.032
	Hydramnios	0.037
Placental Infarcts	Race	<0.001
Placental Weight	Head Circumf. (4 Yr.)	0.026
Anemia During Pregnancy	Abdominal X-rays During Pregnancy	<0.001
	Race	0.034
	Cigarette Smoking During Pregnancy	0.010
Hydramnios	Race	0.009
Hematocrit	5 Minute Apgar	0.010
	Neurologic Abnormalities (1 year)	0.040
	Cigarette Smoking During Pregnancy	0.016
4 Year I.Q.	Socio Economic Status	0.002
	Race	0.007
	Abdominal X-rays During Pregnancy	0.048
	Placental Infarcts	0.002
	Age of Gravida	0.013

hydramnios were observed than expected for the total chemically exposed group, despite the excess of Whites in this exposure group.

There were more children of exposed mothers than expected with low I.Q. (< 80) at 4 years in the middle and high socioeconomic categories, and fewer with high I.Q. (110 +) at 4 years in the high socioeconomic category of exposed mothers. The interaction between exposure, race and I.Q. at 4 years was explained by more exposed Whites observed than expected in the mid-range I.Q. (80 - 109) and more exposed blacks than expected in the high I.Q. group (110 +). Although for the chemical group as a whole there was an excess of high I.Q. at 4 years (110 +) it would appear that the children of exposed mothers of high socioeconomic status were not as evident in the high I.Q. at 4 years group as might have been expected. Similarly children of exposed White mothers did not make as large a contribution to the high 4 year I.Q. group as expected.

In summary, the group exposed to chemicals, which was predominantly White, experienced less kidney, urinary bladder infection during pregnancy and anemia during pregnancy, more full term delivery and high 4 year I.Q.in children However, first and third trimester bleeding, prior stillbirths and prior fetal deaths were all observed more often than expected among women exposed to chemicals and for these variables there was no three factor interaction observed with any demographic variable examined, indicating a comparable experience throughout the exposed group. Among exposed Blacks, placental infarcts, hydramnios, low 5 minute Apgar scores and neurological abnormalities at 7 years were observed more than expected, the first two of these showing a statistically significant excess for the whole chemical exposed group. Hydramnios was negatively associated with cigarette smoking in the exposed group. Chemical exposure and cigarette smoking together were associated with high hematocrit in the newborn. High I.Q. at 4 years in children of exposed mothers, although found more in the exposed group overall, showed an unexpected decrement for Whites and those of high socio-economic status, who were more likely to be laboratory workers and teachers.

These observations of a group who experienced a wide range of chemical exposures indicate that unstable pregnancies mav be associated with some of them.

PESTICIDES

The allocation of individuals to the pesticide exposed group was indirect. The question "Have you ever worked with tobacco dust or leaf, or handled tobacco?" was further expanded by the interviewer to elicit from the respondent if they worked "on a farm picking or stripping or shaking tobacco leaf; or in a warehouse, handling; or in the manufacture of cigars, cigarettes, or other tobacco products?". (Record "No" for selling of packaged cigarettes and cigars or tobacco). All those who responded "Yes" to farm work of this nature were designated as exposed to pesticides. Similarly those who reported cotton picking and other field work or specific pesticides in the chemical exposure question were included. Those excluded had reported less than one month contact with such work conditions, and represented less than 2% of the total.

Background Discussion

Pesticides Exposure (1960-1965)

Control of pesticide use by the small farmer in the sixties stemmed indirectly from the U.S. Department of Agriculture (USDA). A pesticide was registered for sale with the department (and also with the appropriate state department when necessary) for specific crop use, which allowed for commercial distribution to pesticide formulators or to farmers directly. Since the identification of persistent pesticides (primarily chlorinated hydrocarbons) in human tissues, food, soil and water in the early sixties the registration process has been used to reduce the use of chlorinated pesticides by replacing them with organophosphate pesticides of short half-life in the biosphere.

Cotton and tobacco were not generally considered to be in the same category as food crops although cotton seed is used in edible oil production and tobacco is inhaled with absorption into the blood of smoke constitutents, which include pesticide residues. Guthrie et al (1967) claimed on the basis of chemical analysis of smoke from tobacco grown in the early sixties that approximately equal amounts of organo chlorine insecticides would be inhaled from 1 pack of cigarettes a day when compared with daily intake of food.

In 1964 the U.S. Senate of the 88th Congress held hearings (chaired by Senator Ribicoff) on interagency co-operation in environmental hazards concerning pesticides. The testimony and discussions dealt primarily with careless use and the possible excessive use of pesticides. The recent publication of "Smoking and Health" by the Surgeon-General of the U.S. Public Health Service was reviewed in terms of the adequacy of co-operation and information sharing of pesticide information by scientists in the two departments. It was apparent that the possibility that pesticide residues in cigarettes might be implicated in the rising lung cancer rate was an important issue, not only in health terms but also in relation to world trade requirements concerning pesticide residues in food and tobacco to be exported.

The hearings mark a particular stage in pesticide use and control in the United States. Endrin (an organo chlorinated pesticide) coincidentally during the hearings was removed from the list of pesticides registered for many crop uses, including tobacco. It was the time for policy makers at the federal level to acknowledge the profligate use of organo chlorinated pesticides over the previous ten years. Since 1964 DDT and TDE have been cancelled from USDA registration and many states have also taken action on other tobacco pesticides. For example, North Carolina has cancelled registration of aldrin, dieldrin, heptachlor, chlordane and lindane, in addition to DDT and TDE for use on tobacco (Tso, 1972).

The primary pesticides used until 1948 had been inorganic compounds, e.g. lead arsenate. From 1917 to 1951 the arsenic in United States tobaccos increased from about 10 ppm to 50 ppm, but with the change-over to organo-chlorinated pesticides about 1950 there was a reduction to below 5 ppm by about 1960 (Guthrie et al 1967). Although there is now little use of organo-chlorinated pesticides the high concentrations in soil are still reflected in measurable levels in tobacco. Farm workers are instead exposed to organo phosphate pesticides which present a different spectrum of health and safety hazards.

Tso (1972) lists an array of chemicals used or being tested on tobacco but concludes that in any one growing season a relatively uniform and smaller list of pesticides is used across the 5 or 6 major growing states for seedbed preparation (which is generally confined to a smaller area with controlled application), field sterilization prior to planting (which usually involves injecting or ploughing in fumigant and other agents), weedkiller (which may be sprayed before, at or after transplanting), and application on plants in the field (which are sprayed or dusted from the air or ground level). In addition the carriers of these agents can be water or solvents such as xylene and heavier aromatic solvents (acetone, methyl ethyl ketone, methyl and ethyl alcohol) to formulate emulsifiable concentrates.

Field tobacco is harvested by priming (pulling) the ripe leaves (two to three each week for about five weeks). To control the insect complex, insecticide application may be made as frequently as weekly, depending on infestation levels and weather conditions.

Although the growing and harvesting schedule differs for cotton, insecticide applications may be more frequent (weekly intervals for eight to 12 weeks), particularly as there is little effect on the length and strength of cotton fibers and residue levels do not present the same problem in a product which is not ingested. However, residue levels in cotton seed, meal and oil are now monitored.

Description of clinical symptoms associated with insecticide exposure are useful in reconstructing working conditions in the early 1960's. A case report from North Carolina in 1962 included the conditions of contamination in a 13-year-old who experienced two episodes of severe neuropathy

(Jenkins et al, 1964). "In May, 1962 aldrin had been spread on the fields in which the boy worked. In June he began to work in the fields where, because of frequent rain, the pesticide containing mud clung to his person for hours at a time. It was his job to dust the tobacco plants by hand with dichlorodiphenyldichloroethane (DDD) and as a prank he would frequently dust himself and his friends with 10% DDD mixture, so that he was exposed to this substance both through inhalation and through his skin." Although recovery took almost a year he returned to work in the same field in May 1963 when similar symptoms developed.

These extreme exposure conditions provide some idea of the careless use of pesticides and the kind of working conditions growing adolescents could experience. Whether this individual also showed higher susceptibility than the rest of his family is not certain as others were not similarly affected. It is evident however that awareness of the dangers inherent to pesticide use for young and old workers and family members was minimal in the environment of small farms in tobacco and cotton growing areas.

The U.S. Senate Hearings of 1964 examined the pesticide exposure resulting from aerial application. One exhibit was an educational bulletin warning that problems were being encountered when workers were present in the fields. Residential areas were also a source of concern, e.g. "Avoid pesticide drift onto homes, barns, communities . . . . Fly swath runs parallel to these areas and avoid turns over them, when practicable . . . . After completing a job, do not dump pesticide remaining in the aircraft on the way back to the airstrip." Extensive testimony was recorded on aerial spraying reflecting the problems associated with control of drifting and effects of climatic conditions. Senator Ribicoff concluded ". . . there is a vacuum in existence in this Nation concerning the basic health of pilots, the basic health of people, the efficacy of the applications, and their impact not only on the crops but on people in adjoining areas to the crops."

It is evident from a review of research trends, trade journals and personal interviews with professionals involved with the tobacco industry and related public health responsibilities that 1960 to 1963 could be viewed as a peak period for exposure to organo-chlorinated pesticides for families and field workers living and working on tobacco and cotton farms.

In the period of the early sixties a cotton farmer had a choice of about 15 basic insecticides prepared in approximately 25 formulations. The choice was influenced by insecticide prices and the presence of insecticide resistance. For example boll weevil and worm resistance to the organo-chlorinated insecticides was already widespread. In the early '50's aldrin and dieldrin had been widely used but was insignificant by the '60's. Endrin was being used alone or in combination with parathion and the number of applications averaged 8 to 10 per season. Because of insect resistance organo-phosphate insecticides were being more extensively used on cotton before tobacco, where the change was influenced both by concern for environmental build-up of organo chlorinated insecticides and the international trade restrictions on residues in tobacco. (By 1973 West Germany precluded sale of tobacco or leaf products containing over 0.1 ppm DDT-TDE).

Despite the intensive evaluation of insecticide use from the agricultural viewpoint it has been difficult to identify studies of populations whose home and work environments were integrally bound to an annual cycle of pesticide use. The most extensive studies have been done in Dade County, Florida, with the demographic designations being made on the basis of race and occupational exposure, defined as direct contact as formulator or applicator. The occupationally exposed were all identified as men and sex designation was given in the general population group, so that no female group has been considered as being anything other than equivalent to the total female population. Stratification of human pesticide concentrations by age, race and sex within a population were realized from the studies of Wasserman et al (1967) in Israel and Zavon et al (1965) and Hoffman et al (1967) in the United States. Data from Davies et al (1972) from Dade County, Florida in 1965-1967 (Table 25) show the marked difference within a population for which there was no information available on occupational exposure to insecticides. The fat tissue samples were taken at necropsy from persons accidentally or violently killed in Dade County and not necessarily residents. The age dependency was interpreted as evidence for a 5 to 10 year storage equilibrium period for human populations, under conditions of exposure in the Florida environment of the early 1960's. The analyses by Wassermann et al in Israel (1967) and Brown (1967) in Canada support this estimate. The sex differences in DDT and DDE levels have also been noted in England and Israel and there is still speculation as to whether dietary, hormonal and/or occupational characteristics are the causes. No large population of women has ever been examined to provide detailed information on their pesticide exposure, despite household extermination and cleaning procedures which are part of most women's home job

TABLE 25. Concentration of DDT-derived Materials in Necropsy Adipose Tissue from 159 Persons Killed in Dade County, Florida 1965-67

Race and	Number of Persons	Residues in PPM DDT-Derived Materials	
		Mean	Range
		MALES	
White			
0-5	11	5.8	0.49-25.7
6-10	7	8.7	3.8 -16.0
11-20	13	8.7	4.7 -21.1
21-30	13	8.0	1.9 -15.3
31+	15	9.0	3.0 -16.0
Total:	63		
Nonwhite			
0-5	10	7.4	0.81-25.1
6-10	3	16.5	13.4-19.5
11-20	2	17.2	14.9-19.5
21-30	7	17.6	9.9-21.5
31+	7	22.0	13.1-32.8
Total:	29		
		FEMALES	
White			
0-5	6	5.0	2.0- 8.1
6-10	7	10.0	3.8-17.3
11-20	9	8.4	2.0-14.3
21-30	12	8.8	3.6-14.0
31+	10	6.1	2.0-11.7
Total:	44		
Nonwhite			
0-5	7	8.4	2.6-25.4
6-10	1	19.0	19.0
11-20	4	11.5	8.9-16.8
21-30	5	12.6	7.9-20.1
31+	6	15.7	8.8-28.1
Total:	23		

From Davies et al (1972).

responsibilities. Davies et al (1972) in examining the blood level in children found that by seven years of age children reached levels comparable to those found in adults. Thirteen homes of the 56 children (age one to seven) in the study were visited and the overall subjective impression was that those in dwellings in poor condition or in housing projects located near agricultural areas had higher blood levels of pesticide residues.

Keil et al (1972) confirmed earlier findings of Davies (1972) and Edmundson (1970) of two to three times higher DDT and DDE levels in Blacks when compared with Whites. The difference is evident in children 6 to 9 years of age as well as adults. No adequate explanations have yet been found for these differences although Davies (1972) has shown marked socio-economic differences in Florida, where domiciliary use of insecticides is high.

Fat storage of DDT has been widely reported in human studies. By the mid sixties total storage of DDT and its metabolites in fat in U.S. residents had been generally quantitifed at about 10 parts per million. (Dale et al 1963, Hoffman et al 1964, Zavon et al 1965, Hayes et al 1965, Davies et al 1965). In contrast, for occupationally exposed men values of 35 to over 1,000 ppm were reported (Hayes et al 1956, Quimby et al 1965, Mattson et al 1953). Edmundson (1972) discussed the limitations of fat content as a measure of DDT storage because of variations in the chemical characteristics and content of fat in different body organs. However, these studies had shown that in general an equilibrium develops between absorption of DDT, storage and excretion.

After relatively long periods fat storage levels reach a constant level which appear to be little affected by additional intake. For human beings the plateau appears to be reached in about 52 weeks. Little consideration has been given to fat distribution differences between men and women and changes occurring during the reproductive years.

The relationshop between fat storage and blood levels has been difficult to establish. Surveillance programs of highly exposed pesticide workers have lead to examination of blood transport and urinary excretion and efforts made to relate these measures to fat storage (Robinson et al 1966).

Morgan et al (1971) concluded that penetration of DDT into adipose tissue is a nonuniform process. They observed a consistent increase in adipose levels of DDT even after dosing had stopped in experimental subjects, which suggested a shifting from other storage sites into subcutaneous fat. No experimental data are available on female subjects and it is virtually impossible to extrapolate quantitatively from dosing experiments on male subjects. The distribution of fat in women is hormone-influenced and women therefore experience particularly marked alterations in anatomical, physiological, and biochemical patterns of fat distribution from puberty, through childbearing to the menopause (Skerlj et al, 1954). The most conservative condition in terms of DDT human adipose storage could be assumed to be those pertaining to the adult male as described by the ingestion experiments of Morgan et al (1971). The time course of serum and adipose saturations would be affected by these unknown redistribution effects and it is of interest to note that Morgan et al found that first-order curves fitted to the serum p,p' DDT curves during dosing suggested that 95% steady-state values would be reached in about 8½ months of dosing.

But there was no indication that steady-state concentrations in subcutaneous fat tissue were being attained over the same period. Despite these limitations the percentage of dose stored for p,p'-DDT administered daily to 2 individuals at two dose levels for 183 days was estimated to be 68% and 54% and for o,p'-DDT, 32% and 31%. Storage of p,p'-DDE (more likely to be of dietary origin in the population at large) was estimated to be 91% of the administered daily dose. It is evident that there are marked differences between storage efficiencies of the isomers and metabolites which affect our understanding of the relationship between dietary environmental/occupational intake and adipose storage. The time required for excretion of DDT and its metabolites from body stores was generally described by Morgan et al for their male subjects as being considerably slower than for monkeys, dogs and rats.

An important observation by Hayes (1965) was that excretion of chlorinated hydrocarbons proceeds much more slowly from low storage levels than from high levels and time constants for logarithmic excretion curves fall progressively with storage level.

The propensity for human adipose storage increases from p,p'-DDD $\leq$ o,p'-DDT $<$ p,p'-DDT $<$ p,p'-DDE. The stability of the adipose store probably bears a similar relationship in that concentrations of the isomers and metabolites in the general population appear to show this pattern.

The conclusions concerning human contamination with DDT are far from definitive in view of the limitations of human experimentation and the paucity of data on women but it should be evident that transportation in and out of fat deposits is an important influence on the relationship of serum and adipose tissue concentrations.

Although Morgan et al (1971) have concluded on the basis of their data on male subjects that there may be a fair correspondence between serum and lipid concentrations during periods of addition or depletion of body stores, female subjects are unlikely to show the same relationship. It is entirely possible that lability of DDT isomers and metabolites differs markedly between men and women with observable changes appearing during and after pregnancy and lactation when adipose tissue changes may be extreme. To date there are no data available to reflect the effects of these physiologic changes on pesticide storage in women.

Reproductive Effects

Placental transfer of DDT was first reported in dogs in 1949 (Finnegan et al) and subsequently confirmed in rabbits (Pillmore et al 1963a), deer (Pillmore et al 1963b) and mice (Backstron et al 1965). Deves (1962), and Wasserman et al (1967) measured DDT in body fat of human stillborns and neonates, and Rappolt et al (1968) measured DDT in human placentas and umbilical cords. Curley et al (1969) analyzed ten different organ tissues of stillborns and nonsurviving neonates and cord blood in 30 normal term babies in two Atlanta Georgia hospitals. The mothers were identified as having "had no known special exposure to pesticides." Despite such selection there was a wide range of values for a variety of chlorinated hydrocarbons in the nonsurvivors, most particularly o,p'-DDT and p,p'-DDD in adipose tissue, with extreme outlying values for which no explanation was available. Cord bloods from the normal term babies were within the range of values reported for human populations at that time. Zavon et al (1967) had also reported an unexplained wide range of values for DDE concentrations (0.08 to 8.90 ppm) in tissue samples of 52 stillborns. DDT degradation may also occur, resulting in high concentrations of its metabolites. The unanswered question remains - what were the pesticide residue levels in the adipose tissue and blood of their mothers?

A study on dairy cattle did show some of these relationships. Three treatment groups and a control group of cows each were administered DDT during pregnancy. There was one stillborn calf in each of the low, medium and high dose groups and their body fat contained 2, 97 and 210 ppm of DDT, while their dams' estimated body fat levels at calving were 6, 247, and 331 ppm respectively. No differences in behavior of the cows of the different intake groups were noted during the feeding period of the experiment and no signs of DDT poisoning were observed. The authors concluded that "no effects on health or reproduction could be attributed to the treatments" (Laben et al 1965).

Zavon et al (1969) concluded that all children born in the United States are likely to have trace quantities of chlorinated hydrocarbon insecticide in their tissues and that placental passage does occur. (Their tissue samples were taken from 68 neonates from 13 cities in the United States).

A Dade County, Florida study also included analysis of paired maternal and cord blood obtained at the time of delivery. Blood from newborns and women during late pregnancy, amniotic fluid, vernix caseosa and placenta were also obtained. O'Leary et al (1972) concluded that there was no evidence for a change in the metabolism of DDT during pregnancy on the basis of the consistency of maternal DDE levels between pregnant and non-pregnant women in Dade County. As in other studies black women had higher blood levels of DDE. Amniotic fluid and cord blood levels were considerably lower than maternal levels but as the vernix caseosa contained such high levels of DDE particularly, as well as DDT when compared with placenta it was evident that transplacental passage occurred. Although claiming that premature infants born at the fourth and seventh month and products of conception of 4 weeks gestation showed "significant levels of DDE" O'Leary et al did not report the values.

An important study from the Wasserman group in Israel (Polishuk et al 1977) of extracted lipids of fetal blood and placenta, maternal blood and uterine muscle showed a pattern of pesticide concentrations which suggested quantitative differences in the ability of these tissues to metabolize and/or store organochlorine compounds.

Teratogenic Effects

An epidemic of congenital limb deformities of swine occurred in Missouri, where nicotine in the tobacco stalks eaten by pregnant sows was implicated. However it was noted that maleic hydrazide at 115 ppm was also a contaminant on the stalks, but due to its low toxicity in rats was disregarded as a likely cause. They did mention its carcinogenic and mutagenic properties but did not consider these to be pertinent in view of the high nicotine content (Menges et al 1970).

An earlier clinical report from Kentucky had also implicated tobacco stalk ingestion during early pregnancy for the appearance of skeletal anomalies in pigs (Grove 1969). The veterinarian noted that since tobacco had been grown in central Kentucky for more than 100 years and this teratogenic problem had not been recognized before it was more likely that chemicals or their combination with the plant were a likely explanation.

All the studies cited so far assumed that the major source of insecticide exposure was food. Wasserman et al (1967) in Israel were concerned with the role of air pollution and the importance of the inhalation route and McIntosh (1955) had considered at a much earlier time the importance of particle size of insecticidal suspensions. Overall there has been minimal attention accorded the lung as the route of entry in terms of deposition and absorption, which may in part explain the ignoring of populations living in rural areas with sporadic and frequent high air levels of insecticides. In view of the widespread aerial and ground level spraying of tons of pesticides each year and the likelihood that the same populations were at risk to exposure annually in many agricultural areas, especially in cotton and tobacco growing states, it is surprising that Stockinger (1969), Campbell et al (1965) and Jager (1970) considered that air exposure was negligible, except for house spraying campaigns in other countries for control of malaria, yellow fever etc. The families of tenant farmers and small landowners of the 1950's and '60's, whose numbers were diminishing rapidly as they moved to the northern cities, were the most intensively exposed population during that period other than formulators and applicators. Our study population made up of those who grew up on those farms, although for many, their prenatal and delivery experience was in the northern cities of Boston, Philadelphia, and Baltimore.

Results

Exposure only to pesticides was recorded for 69.2% of the 652 women in this group with 26.0% exposed to one additional hazard, and 4.8% exposed to two additional hazards (Table 11a). The additional hazardous exposures for the pesticide group were to heat (5.6%), heavy lifting (23.0%) and animals (5.6%) (Table 11b). The group reporting pesticide exposure showed the least interference from all other occupational hazards, when compared with the other exposure groups.

There were more women who were black and of low socioeconomic status, and more who were thirty years of age and over. However there were more who registered with the CPP before 20 weeks gestation than expected and fewer who smoked cigarettes, when compared with those not exposed to pesticides (Table 26).

First and second trimester uterine bleeding was more frequent and there were more with low placental weights (< 300 grams). There were more cases of hydramnios, more premature deliveries and more low birthweight (< 2500 grams) babies. There were 31 fetal deaths in the pregnancies under study when 21 would have been expected, a difference which was not statistically significant. These mothers had reported a significant excess of prior stillbirths, fetal deaths and premature deliveries. For the children, there were more who had low Apgar scores at 5 minutes (< 4), more with high hematocrit (70 +), suspected or definite neurological abnormalities at one year and low I.Q. at 4 years.

Three Factor Interactions

The absence of three factor interactions for most of the adverse pregnancy outcome variables which were significantly associated with exposure to pesticides is unique with this exposure group. The two exceptions were

TABLE 26

Occupational Exposure to Pesticides

Number Exposed 652

Two Factor Interaction with Demographic Variables

	Observed	Expected	Significance P-Value
Race (Black)	543	299	<0.001
Socio Economic Status (Low)	309	240	<0.001
Age of Gravida (30+ years)	185	117	<0.001
Gestation at Registration (<20 weeks)	287	315	0.026
Cigarette Smoking	221	296	<0.001

Two Factor Interaction with Pregnancy Outcome Variables

	Observed	Expected	Significance P-Value
Prior Stillbirths*	107	65	<0.001
Prior Fetal Deaths*	61	37	0.007
Prior Prematures*	157	110	<0.001
1st Trimester Uterine Bleeding	126	93	<0.001
2nd Trimester Uterine Bleeding*	74	55	0.013
Placental Weight (<300 gms)*	50	43	0.022
Hydramnios	28	16	0.027
Gestation at Delivery (<35 weeks)*	88	65	0.003
Birthweight (<2500 gms)**	93	74	0.004
5 Minute Apgar (<4)*	85	54	0.004
Hematocrit (70+ Lowest Neonatal)*	57	35	0.004
Neurological Abnormalities, 1 Year**	63	44	0.029
4 Year I.Q. (Low)*	75	54	<0.001
Head Circumference Neonatal > 30 cms*	26	20	0.027
4 months > 41 cms*	295	267	0.006
8 months > 44 cms	169	159	0.032
7 years > 57 cms*	91	57	0.001
Fetal Deaths (current pregnancy)	31	21	NS

In these two factor interactions, the observed/expected numbers reported here do not provide all the contingency table information which was used for Chi-Square analysis and significance probability. Where the particular stratum of interest is indicated only data relating to it is shown.

N.S. Not statistically significant

* No statistically significant three way interaction observed between
i) exposure to occupational hazard
ii) any demographic variable tested in this study
iii) any other pregnancy outcome variable tested in this study

**No statistically significant three way interaction between
i) exposure to occupational hazard
ii) any demographic variable tested in this study

first trimester bleeding and hydramnios which were observed more than expected in exposed Blacks. Additionally hydramnios was observed more than expected in exposed women of low socioeconomic status (Table 27).

More exposed women age 30 to 40 were observed to be of low socioeconomic status than expected and there were more observed than expected of low socioeconomic status who registered in the CPP after 30 weeks gestation, although more Blacks than expected registered in the CPP before 20 weeks gestation. Exposed women of high socioeconomic status also tended to register late in their gestation (after 20 weeks) and more Whites than expected registered after 30 weeks gestation.

Hydramnios was associated with black women (26 of the 28 cases) of low socioeconomic status but was observed more than expected in those women who had also been exposed to pesticides.

First trimester bleeding was also observed more than expected in exposed Blacks. Third trimester bleeding was observed more than expected in women who smoked during pregnancy but were not exposed. There were also more exposed women observed than expected who experienced both 2nd and third trimester uterine bleeding.

Anemia during pregnancy was observed more than expected in the exposed women of high socioeconomic status and in younger exposed and unexposed women.

Delayed motor development at one year was observed more than expected in the children of exposed women of low socioeconomic status and suspected neurological abnormalities at one year were observed more than expected in the children of exposed mothers who had placental infarcts.

In summary, the women exposed to pesticides show a clear cut pattern of adverse pregnancy outcome, not all of which can be attributed to low socioeconomic status or race. There is an association of pesticide

TABLE 27

Occupational Exposure to Pesticides

Number Exposed 652

Three Factor Interaction with Demographic Variables

		Significance P - Value
Race	Gestation at Registration	0.037
"	1st Trimester Bleeding	0.035
"	Hydramnios	0.004
"	Socio Economic Status	<0.001
Socio Economic Status	Age of Gravida	0.001
" " "	Gestation at Registration	0.020
" " "	Delayed Motor Development (1 yr.)	0.040
" " "	Anemia during Pregnancy	0.005
" " "	Hydramnios	0.001
Age of Gravida	Anemia during Pregnancy	0.004

Three Factor Interaction with Pregnancy Outcome Variables

1st Trimester Bleeding	Race	0.035
2nd Trimester Bleeding	3rd Trimester Bleeding	0.036
Anemia During Pregnancy	Socio Economic Status	0.005
" " "	Age of Gravida	0.004
Hydramnios	Socio Economic Status	0.001
"	Race	0.004
Neurologic Abnormality (1 Yr)	Placental Infarcts	0.031

exposure with prior stillbirths, prior fetal deaths, prior prematures and low birthweight in the current pregnancy, second trimester uterine bleeding, low placental weight, low 5 minute Apgar scores, high hematocrit, more suspected neurological abnormalities at one year and low 4 year I.Q. without any third factor interaction with potentially confounding demographic factors. Those variables for which there was three factor interaction with exposure and low socioeconomic status or with race (hydramnios, and first trimester bleeding) were observed more than expected in the exposed women of each demographic category.

HEAT

The question asked concerning heat was "Have you ever worked with steam or very high heat where special care had to be taken?" The interviewer was expected to "probe for the kind of work and the work situation. Some possible situations are: in chemical processes, steam laundry, commercial cooking, metal processing, rubber processing. This would include operation of a steam mangle or ironer in a commercial laundry or hospital or a cleaning and laundry establishment, but not the use of a steam iron in a private home. If gravida thinks she did, record as "Yes".

The specificity of responses allowed separation into five categories:

1.	Autoclave and sterilizing instruments	Excluded
2.	Laundry work	422
3.	Steam guns, jets, steam press equipment	214
4.	High radiant heat	113
5.	Food table -cafeteria	Excluded
	Total	769

The exclusion of work with autoclave and sterilizing instruments was based on the view that such activities are usually very local in their effect and those reporting this form of exposure were working either for private physicians or in hospitals. Most of those reporting work with food tables and cafeterias were viewed similarly.

Background Discussion

Extensive analyses of mortality rates during episodes of extreme heat in a number of U.S. cities have established that excess mortality does occur (Ellis, 1972, Schuman, 1972). The seriousness of excessive heat as a primary or contributing cause of death has been well recognized by clinicians but appears to be little recognized by the lay public to-day, particularly with the advent of air conditioning for those who can afford it. Although Ellis' review of the national experience from 1952 to 1967 showed that for heat related deaths men outnumbered women, Schuman's more detailed comparison of mortality in St. Louis and New York during the severe heat wave of late June and mid-July of 1966 showed the largest increase in deaths among women in both cities, white females in New York - 56%, and non-white women in St. Louis - 140%. These observations indicate at least comparable physiologic vulnerability for women to adverse effects from heat exposure.

It is well to keep in mind the severe heat conditions in many factories, particularly on the first hot summer days or during subsequent heat waves, and it seems likely that some of the women in our study, e.g. in jewelry factories (invariably old buildings with little ventilation) and laundries to cite only two extreme possibilities, had repetitive experience of excessive heat as part of their work environment.

Ellis believed he noted a slight excess of maternal deaths in July and August over the years 1952 to 1967 from complications of pregnancy, childbirth and the puerperium, although the numbers were small and he derived his data from state vital statistics. Unfortunately the accuracy and analysis of vital statistics in relation to heat waves has not been particularly sophisticated in the past and it is difficult to draw firm conclusions from much of the available data. Morbidity has been even less examined but it is generally agreed that incapacitating heat disorders may have long term sequelae, particularly cardiovascular and neurologic effects. For the reproductive system we have little but folklore. The veterinary literature is considerably more scientific but species differences appear to be too varied for extrapolation to the human condition. The effects of heat on fertilization has long been observed in domestic animals - cows, sheep and rabbits. Uhlberg et al (1967) have examined embryonic death in sheep and cattle under heat stress conditions by use of embryo transfer experiments. They conclude that a slight increase in temperature even for a short period is sufficient to affect the spermatozoa before fertilization or the ovum immediately after fertilization, resulting in death of the resulting embryo. There is little substantive information on the effects of heat stress on preconception ovarian function and none that provides an evaluation of the human experience.

Anecdotal comment concerning laundry workers by early U.S. Department of Labor Studies (Women's Bureau, 1931) gives the impression that the reproductive experience was likely to be adverse. However the socioeconomic status was clearly a serious confounding factor. McDonald (1958) noted in a prospective study of 3,295 working women and their pregnancies that a higher proportion of the mothers of infants with major defects had been engaged in certain types of heavy work early in pregnancy, particularly laundry workers. Four of the 27 laundry workers had infants with major defects - anencephalus, hydrocephalus, congenital heart defect and hypospadias.

These isolated comments on laundry workers are among the most tantalizing in the reproduction literature. The hot environment has probably been the most constant feature of laundry work over the past 100 years, but we have no accumulation of anecdotal or scientific observation to assess the effects of heat on human reproduction.

Acclimatization is a critical factor in human tolerance to the adverse impact of heat so that the first days of a heat wave or initial exposure to hot working conditions could be expected to be particularly stressful. Work teams tend to help newcomers or returnees under such conditions in foundries, etc. We have more physiological studies on stress comparing women and men than for most other work environments, but the observed differences in responses are difficult to understand because of the interaction of heat tolerance and work performance.

It has been shown for resting-in-heat studies that young women maintain a higher body temperature and lower sweat production than young men for the same heat exposure and that sweating does not begin until a higher temperature is reached in women. Heat stress in women has been repeatedly observed in relation to the time delay in onset of sweating (Lofstedt B. 1966). Despite the clear physiologic evidence that women must reach a higher body and skin temperature (Hertig et al 1963) for the onset of sweating it is believed that a comparable degree of heat acclimatization for women and men occurs, probably with different regulating factors influencing each sex.

Henschel (1973) makes the summary comment that "data in general support the conclusion that there is a reduction in work-in-heat tolerance as a function of age, sex, physical fitness and acclimatization." Our data from the CPP can provide little detail on the latter two factors.

Little insight can be gained directly on the relation of the physiological changes during pregnancy and heat tolerance. Although many pregnant women have consciously noted their improved tolerance of cold in terms of comfort, detailed observations of a scientific nature are lacking. Measurements of skin temperature of the fingers have shown increases after 30 minutes at room temperature of 17°C before pregnancy to 34°C at term for fingers and from 20°C to 27°C for toes (Burt, 1949). Hytten et al (1971) believe that finger temperature in late pregnancy may be "close to the physiological maximum and is similar to the temperature reached in non-pregnant subjects when reflex vasodilation is caused by immersing the feet in hot water. In late pregnancy little or no increase occurs with such reflex heating." The basal body temperature fluctuates with the menstrual cycle with an increase of 0.3 to 0.6°C after ovulation which is maintained until about mid-pregnancy, when it declines to normal levels (Buxton et al, 194?).

The relationship of heat tolerance to the changes in the body composition, particularly increased amounts of body fat during pregnancy (Thomson et al, 1961) to my knowledge have not been investigated. Taggart et al (1967) have shown that increases in skinfold thickness (a measure of subcutaneous fat) occur up to at least 30 weeks of pregnancy and decrease a considerable amount between 38 weeks of pregnancy and the first post-partum week.

This sparse data base indicates that individual variability in several physiological parameters would make interpretation of the results of this study on heat exposure quite difficult. In addition, response to the question on heat exposure is likely to be an unreliable measure of the actual experience.

Results

Exposure only to heat was recorded for 41.6% of the 769 women in this group, with 40.9% exposed to one additional hazard, 12.1% exposed to two additional hazards and 1.0% exposed to three or more additional hazards (Table 11a). The additional hazardous exposures for those exposed to heat were from radiation (1%), pesticides (5.6%), chemicals (35.8%), heavy lifting (20.5%) and animals (4.2%) (Table 11b).

The group reporting work exposure to heat were of lower socio economic status, there were more Blacks and more women over thirty years of age. They smoked more and had more abdominal X-ray during pregnancy when compared with those not exposed to heat. However one characteristic not considered adverse to the mother and/or child was early registration (< 20 weeks gestation) in the CPP (Table 28).

The group reported far more prior stillbirths, fetal deaths and premature deliveries than expected and although the difference was not statistically significant there were 21 neonatal deaths in the pregnancies under study when 13 were expected.

These mothers experienced more first and third trimester bleeding and anemia during pregnancy. There were more children with high hematocrit (> 70), with low I.Q. (< 80) at four years and definite and suspected neurologic abnormalities at 7 years.

Three Factor Interactions

Anemia during pregnancy and hematocrit in the newborn were the only two variables significantly associated with exposure to heat that also showed interaction with a third demographic variable, age of gravida (Table 29).

TABLE 28

Occupational Exposure to Heat

Number Exposed 769

Two Factor Interaction with Demographic Variables

	Observed	Expected	Significance P-Value
Race (Black)	440	347	<0.001
Socio Economic Status (Low)	313	279	<0.001
Age of Gravida (30+ years)	162	79	<0.001
Gestation at Registration (<20 weeks)	430	381	0.028
Abdominal X-Ray During Pregnancy	259	195	<0.001
Cigarette Smoking During Pregnancy	412	345	<0.001

Two Factor Interaction with Pregnancy Outcome Variables

	Observed	Expected	Significance P-Value
Prior Stillbirths*	132	76	<0.001
Prior Fetal Deaths*	83	44	<0.001
Prior Prematures*	181	128	<0.001
1st Trimester Bleeding**	138	109	0.030
3rd Trimester Bleeding**	139	107	0.001
Anemia During Pregnancy	198	162	<0.001
Hematocrit (Child) (High)	58	43	0.029
4 Year I.Q. (Low)*	88	66	<0.001
Neurologic Abnormalities (7 yrs)*	110	74	0.001
Neonatal Deaths (current pregnancy)	21	13	NS

In these two factor interactions, the observed/expected numbers reported here do not provide all the contingency table information which was ued for Chi-Square analysis and significance probability. Where the particular stratum of interest is indicated only data relating to it is shown.

N.S. Not statistically significant

* No statistically significant three way interaction observed between
i) exposure to occupational hazard
ii) any demographic variable tested in this study
iii) any other pregnancy outcome variable tested in this study

**No statistically significant three way interaction between
i) exposure to occupational hazard
ii) any demographic variable tested in this study

TABLE 29

Occupational Exposure to Heat

Number Exposed 769

Three Factor Interaction with Demographic Variables

		Significance P - Value
Socio Economic Status	Race	<0.001
	Placental Infarcts	0.035
Race	Age of Gravida	<0.001
	Abdominal X-ray During Pregnancy	<0.001
	Kidney, Urinary Bladder Infection during Pregnancy	0.006
	5 Minute Apgar	0.038
	Neurological Abnormalities (1 yr.)	0.030
Age of Gravida	Hematocrit	0.020
	Head Circumference (Neonatal)	0.045
	Anemia during Pregnancy	0.001
Cigarette Smoking During Pregnancy	Birthweight	0.007
	Hydramnios	0.006
Gestation at Registration	Hematocrit	0.006
Abdominal X-ray during Pregnancy	Hydramnios	0.003

Three Factor Interaction with Pregnancy Outcome Variables

1st Trimester Bleeding	Head Circumference (4 yr.)	0.020
	Head Circumference (7 yr.)	0.001
3rd Trimester Bleeding	Neurologic Abnormality (7 yr.)	0.027
	Head Circumference (8 months)	0.016
Anemia During Pregnancy	Kidney, Urinary Bladder Infection	0.008
	Placental Infarcts	0.017
	Neurologic Abnormality (7 yr.)	0.015
	Age of Gravida	0.001
Hematocrit	Placental Infarcts	0.030
	Age of Gravida	0.020
	Gestation at Registration	0.006
4 Year I.Q.	Placental Infarcts	0.039
	Neurologic Abnormality (7 yr.)	0.006

High hematocrit was seen in more infants of 30 to 40 year old exposed mothers and there was more anemia during pregnancy in mothers 20 to 30 years old.

More exposed women with anemia had children with suspected or definite neurological abnormalities at seven years of age.

More exposed women with placental infarcts had children with high hematocrit at birth.

There were fewer cases of hydramnios in those exposed women who had abdominal X-ray during pregnancy than expected and more cases of hydramnios in those exposed who did not have abdominal X-ray during pregnancy, which probably reflects the pattern of diagnostic X-ray use. Similarly hydramnios was observed less than expected in exposed smokers and more in exposed non-smokers in the three factor interaction.

Placental infarcts were more associated with exposed women of low socio economic status.

The birthweight, cigarette smoking and heat exposure interaction was partially explained by more unexposed and exposed smokers who delivered infants 1500 to 2500 grams.

Five minute Apgar score, race and heat exposure interaction showed more exposed Blacks than expected with high Apgar scores.

In summary, the association of seven clearly adverse pregnancy outcome variables:

prior stillbirths

prior fetal deaths

prior premature births

1st and 3rd trimester uterine bleeding

low 4 year I.Q.

suspected or definite neurological abnormalities at 7 years with exposure to heat appears to be comparable for all demographic characteristics of the exposed group. However, the three factor interactions of other pregnancy outcome variables are more intertwined with the disadvantageous demographic characteristics of socio-economic status, race, age of gravida and cigarette smoking than the other exposure groups.

The heat and pesticide exposure groups are the most comparable in sample size and in their demographic characteristics but the heat exposed group does not present as clear cut a picture of associated adverse effects. It may be that exposure to heat was only one additional and comparable disadvantage for this group, rather than an over-riding disadvantage, which appears to be the case for pesticide exposure.

Summary Discussion

Work experience brings with it exposure to physical and chemical agents over a period of time. Each childbearing experience involves 9 months and may occur before, during and/or after these exposures. There are likely to be few opportunities allowing examination of pregnancy experience which is coterminous with an exposure which has not occurred before conception. We were unable to clearly identify women with such well defined characteristics and concluded that in almost all cases of reported exposure to hazardous conditions, at least part of the woman's exposure experience was most likely to have occurred during an undefinable period pre-conception. Therefore the expectation that we can examine a direct relationship between occupational exposure and a particular pregnancy experienced at the same time is in our view unrealistic.

Gestation at registration in the CPP varied markedly, further complicating any estimate of post conception occupational exposure to a hazardous condition. This variable was therefore included as a demographic variable in the analysis.

An effort was made to retrieve information on the husband's occupation and work experience. Paternal occupation was recorded with far less accuracy than was maternal occupation and many women appeared to have little understanding of their husband's work. The reports provided by the wives were clearly unreliable, with insufficient description to provide clues for any occupational exposure to hazardous conditions.

The identification of women in the CPP exposed to hazardous work conditions can now lead to a better examination of rare events, using case controls and other statistical methods. The problem of exposure to multiple hazards within each primary exposure group needs further analysis. One approach, using the same contingency table analysis would be to include each additional hazard as another demographic variable. Parity and birth order should also be further evaluated.

An estimation of "dose" from an occupational hazard could only be made indirectly from the response given to the question "Approximately how long?", describing the exposure to an occupational hazard. We coded the response into 1 to 6 months, 7 to 18 months and more than 18 months. The results however are being presented in terms of exposure or no exposure, with the expectation that future more detailed analyses can be done in terms of a dose response relationship.

Prematurity was identified as less than 35 weeks gestation and was found to be associated with exposure to pesticides and not with any of the other exposure groups. We also included a category for gestation of 40 weeks or more and found those exposed to ionizing radiation, heavy lifting and animals were associated with longer gestation. Although we recorded this observation as a pregnancy outcome variable not usually considered to be adverse to the mother or child, more detailed examination is suggested. Ouellette et al (1977) in their study of alcohol abuse during pregnancy noted an increase in the proportion of postmature infants from 8% and 9% for abstinent and moderate drinkers to 20% for heavy drinkers, although the difference did not meet their statistical criterion of a p value less than 0.01.

An examination of outcome variables and statistical power was not possible during the period of this study. However an extrapolation from calculations made by Kline et al (1977) provides some information. They estimated the sample size and relative risk necessary to detect a change in the frequency of spontaneous abortion in cohorts of pregnant women with a power of 0.80.

	Frequency in Exposed	Frequency in Unexposed	Relative Risk	Sample size Needed for Each Exposed and Unexposed Group
Incidence of Spontaneous Abortion	0.20	0.15	1.3	901

The power to detect an effect is greater in the largest of the exposure groups in our study where the absolute frequencies were larger in some categories of pregnancy outcome variables, e.g. high 4 year I.Q. in children of those exposed to chemicals. The relative risk was greater than 2 (frequency in exposed 0.2, unexposed 0.09): Sample size for the exposed 1500 and unexposed 24,387 was more than adequate to ensure an acceptable power for the statistical tests we made. Further examination of Type 2 error does seem feasible for many of the outcome variables, particularly for the groups exposed to chemicals and heavy weights.

Animals

It is evident from the summary table of two factor interaction (Tables 30,31,32,33) that occupational exposure to animals does not appear to impose serious stress on the course and outcome of pregnancy. The excess of uterine bleeding was slight in these women who were somewhat older than the comparison group and also smoked more during pregnancy. It is possible that the advantages of a higher proportion of Whites with higher socioeconomic status and early gestation at registration when compared with those not occupationally exposed to animals have overridden any adverse impact if it exists. The

TABLE 30

All Occupational Exposures
Summary Table

Two Factor Interactions with Pregnancy Outcome Variables
(Significant Probability of Associations)

Considered Adverse for Mother and/or Child.

	Radiation	Pesticides	Chemicals	Heat	Heavy Lifting	Animals
Prior Fetal Deaths	-	0.007*	0.014*	<0.001*	0.016*	-
Prior Stillbirths	-	<0.001*	0.043*	<0.001*	0.002	-
Prior Prematures	-	<0.001*	-	<0.001*	0.031*	-
Fetal Deaths	-	-	-	0.002	-	-
Neonatal Deaths	-	-	-	-	-	-
Death at less than 1 year	-	-	-	-	-	-
Death at more than 1 year	-	-	-	-	-	-
1st Trimester Uterine Bleeding	<0.001**	<0.001*	<0.001**	<0.030**	<0.001**	<0.040*
2nd Trimester Uterine Bleeding	-	0.013**	0.019	-	<0.001*	-
3rd Trimester Uterine Bleeding	-	-	<0.001**	0.001**	<0.001**	0.038
Low Placental Weight	-	0.022*	-	-	-	-
Placental Infarcts	0.004*	-	0.031	-	-	-
Abruptio Placenta	-	-	-	-	-	-
Placenta Previa	-	-	-	-	-	-
Single Umbilical Artery	-	-	-	-	-	-
During Pregnancy -						
Anemia	-	-	-	<0.001	-	-
Convulsive Disorder	-	-	-	-	-	0.027*
Kidney, Urinary Bladder Infection	-	-	-	-	-	-
Hydramnios	0.020	0.027	0.024	-	-	-
Early Gestation at Delivery	-	0.003*	-	-	-	-
Low Birthweight	-	0.004**	-	-	-	-
Low 5 Minute Apgar	-	0.004*	-	-	0.040*	-
High Hematocrit Neonatal	-	0.004*	0.028	0.029*	-	-

* No statistically significant three way interaction observed between
i) exposure to occupational hazard
ii) any demographic variable tested in this study
iii) any other pregnancy outcome variable tested in this study

**No statistically significant three way interaction between
i) exposure to occupational hazard
ii) any demographic variable tested in this study

TABLE 31

All Occupational Exposures
Summary Table

Two Factor Interactions with Pregnancy Outcome Variables
(Significant Probability of Associations)

Considered Adverse for Mother and/or Child

	Radiation	Pesticides	Chemicals	Heat	Heavy Lifting	Animals
8 Month Mental Score	-	-	-	-	-	-
8 Month Motor Score	-	-	-	-	-	-
One Year						
Ataxia	-	-	-	-	-	-
Cleft Palate	-	-	-	-	-	-
Delayed Motor Dev.	-	-	-	-	-	-
Seizure States	-	-	-	-	-	-
Failure to Thrive	-	-	-	-	-	-
Neurological Abnorm.	-	0.029**	-	-	-	-
4 Year I.Q. (<80)	-	<0.001*	-	<0.001*	-	-
Neurological Abnorm. (7 Years)	-	-	-	0.001*	-	-
Small Head Circumference						
Neonatal	-	-	-	-	-	-
4 month	-	-	-	-	-	-
8 month	-	-	-	-	-	-
4 year	-	-	-	-	-	-
7 year	-	-	-	-	-	-

Two Factor Interaction with Demographic Variables

Considered Adverse for Mother and/or Child

	Radiation	Pesticides	Chemicals	Heat	Heavy Lifting	Animals
Socio Economic Status (Low)	-	<0.001	-	<0.001	-	-
Race (Black)	-	<0.001	-	<0.001	-	-
Age of Gravida (40+)	-	<0.001	-	<0.001	<0.001	<0.001
Gestation at Registration (Late)	-	0.026	-	-	-	-
Abdominal X-ray during Pregnancy	<0.001	-	<0.001	<0.001	<0.001	<0.001
Cigarette Smoking during Pregnancy	-	-	<0.001	<0.001	<0.001	-

* No statistically significant three way interaction observed between
i) exposure to occupational hazard
ii) any demographic variable tested in this study
iii) any other pregnancy outcome variable tested in this study.

**No statistically significant three way interaction between
i) exposure to occupational hazard
ii) any demographic variable tested in this study

Table 32

All Occupational Exposures
Summary Table

Two Factor Interactions with Pregnancy Outcome Variables
(Significant Probability of Associations)

NOT Considered Adverse for Mother and/or Child.
(experience better than expected)

	Radiation	Pesticides	Chemicals	Heat	Heavy Lifting	Animals
Fewer Prior Fetal Deaths	-	-	-	-	-	-
Prior Stillbirths	-	-	-	-	-	-
Prior Prematures (less)	<0.001	-	-	-	-	0.001**
Fewer Fetal Deaths	-	-	-	-	-	-
Neonatal Deaths	-	-	-	-	-	-
Deaths at Less than 1 year	-	-	-	-	-	-
Deaths at More than 1 year	-	-	-	-	-	-
1st Trimester Uterine Bleeding - none	-	-	-	-	-	-
2nd Trimester Uterine Bleeding - none	-	-	-	-	-	-
3rd Trimester Uterine Bleeding - none	-	-	-	-	-	-
Placental Weight (high)	-	-	0.003**	-	-	-
Placental Infarcts						
Abruptio Placenta	-	-	-	-	-	-
Placenta Previa (less)	-	-	-	-	-	-
Single Umbilical Artery (less)	-	-	-	-	-	-
During Pregnancy - Anemia (less)	<0.001	-	<0.001	-	<0.001	<0.001
Convulsive Disorder (less)	-	-	-	-	-	-
Kidney, Urinary Bladder Infection (less)	0.004*	-	<0.001*	-	0.002	0.007**
Hydramnios (less)	-	-	-	-	-	-
Late Gestation at Delivery	0.007*	-	-	-	0.001*	0.001*
Birthweight - high	-	-	-	-	-	-
5 Minute Apgar - low	-	-	-	-	-	-
Hematocrit (Neonatal)	-	-	-	-	-	-

* No statistically significant three way interaction observed between
i) exposure to occupational hazard
ii) any demographic variable tested in this study
iii) any other pregnancy outcome variable tested in this study

**No statistically significant three way interaction between exposure to hazardous work conditions and any demographic variable tested in this study.

TABLE 33

All Occupational Exposure
Summary Table

Two Factor Interactions with Pregnancy Outcome Variables
(Significant Probability of Associations)

NOT Considered Adverse for Mother and/or Child.
(Experience better than expected)

	Radiation	Pesticides	Chemicals	Heat	Heavy Lifting	Animals
8 Month Mental Score	-	-	-	-	-	-
8 Month Motor Score	-	-	-	-	-	-
One Year						
Ataxia	-	-	-	-	-	-
Cleft Palate	-	-	-	-	-	-
Motor Dev.	0.029*	-	-	-	-	-
Seizure States	-	-	-	-	-	-
Failure to Thrive	-	-	-	-	-	-
Neurological Abnorm.	-	-	-	-	-	-
4 Year I.Q. (110+)	<0.001*	-	<0.001	-	<0.001	<0.001
Neurological Abnorm. (7 Years)	-	-	-	-	-	-
Head Circumference						
Neonatal (high group)	-	0.027	-	-	0.027*	-
4 month " "	<0.001*	0.006*	<0.001	-	0.001*	0.006
8 month " "	0.001	0.032	0.040	-	-	0.013
4 year " "	<0.001*	-	-	-	<0.001*	-
7 year " "	<0.001*	0.001*	0.020	-	<0.001*	0.029*

Two Factor Interaction with Demographic Variables

NOT Considered Adverse for Mother and/or Child.

	Radiation	Pesticides	Chemicals	Heat	Heavy Lifting	Animals
Socio Economic Status (high)	<0.001	-	<0.001	-	<0.001	<0.001
Race (White)	<0.001	-	<0.001	-	<0.001	<0.001
Age of Gravida (20-29)	<0.001	-	-	-	-	-
Gestation at Registration (early)	<0.001	-	<0.001	0.028	<0.001	0.036
No Abdominal X-ray during Pregnancy	-	-	-	-	-	-
No Cigarette Smoking during Pregnancy	-	<0.001	-	-	-	-

* No statistically significant three way interaction observed between
i) exposure to occupational hazard
ii) any demographic variable tested in this study
iii) any other pregnancy outcome variable tested in this study.

**No statistically significant three way interaction between
i) exposure to occupational hazard
ii) any demographic variable tested in this study

appearance of more convulsive disorders (though few in number) during pregnancy is unique among the exposure groups studied and a case control study of this condition may be useful.

Ionizing Radiation

The group exposed to ionizing radiation had an even higher proportion of Whites of higher socio-economic status and shared the same advantage of early gestation at registration, seen in the group exposed to animals. The group was younger than those not exposed to radiation but experienced more abdominal X-ray during pregnancy. The effect of the advantages can be seen in the far better experience in prior pregnancies with many fewer prior premature births and during the pregnancy under study less anemia, less kidney urinary bladder infection and longer gestation period. The excess number of women with hydramnios, a condition of low prevalence should be further examined. More first trimester uterine bleeding and placental infarcts are clearly evident but appear not to have an impact on pregnancy outcome for this group. Although it is not feasible to reconstruct radiation dose estimates, further refinement of the total occupational plus diagnostic estimate is possible for better comparison with those not exposed to ionizing radiation.

Heat

The group occupationally exposed to heat did not share the same advantages experienced by those exposed to ionizing radiation and animals. More were Blacks and of low socioeconomic status, and of older age. They smoked more and had more abdominal X-rays during pregnancy. However they did register in the CPP earlier in gestation than those not exposed to heat. We see no advantageous pregnancy or pregnancy outcome variables associated with this group. There was a markedly poor prior pregnancy history which was not associated differentially with any demographic variables and we may conclude that Blacks and Whites and those in different socioeconomic categories contributed comparably to the excess prior fetal deaths, stillbirths and premature deaths. Uterine bleeding (first and third trimester) was also in excess for the whole group. There was an excess throughout the total group of children with low 4 year I.Q. and suspected or definite neurologic abnormalities at 7 years. The lack of interaction with demographic factors further supports the possibility that exposure to heat is associated with adverse pregnancy outcome.

Heavy Lifting

The heavy lifting group had the demographic advantages of more Whites of high socioeconomic status who registered in the CPP before 20 weeks gestation when compared with those not exposed. However there were more who smoked and who experienced abdominal X-rays during pregnancy and who were over 30 years of age than expected. They experienced less anemia and kidney, urinary bladder infection during pregnancy and more delivered after 40 weeks gestation and had children with high I.Q. at 4 years. In contrast their prior reproductive experience was poor. They experienced more uterine bleeding throughout pregnancy, had more children with low 5 minute Apgar scores and suspected or definite neurological abnormalities at one year. These adverse characteristics (except for neurological abnormalities at one year) were not associated differentially with any demographic characteristics so that it appears that the adverse pregnancy experience of the whole group reporting heavy lifting was comparable, irrespective of race and socioeconomic status. Although these relationships are clear the self-selection of individuals into the heavy lifting category presents a serious problem of interpretation. It seems likely that other unidentified characteristics are associated with women who reported heavy lifting, inferring that it was stressful to them.

Chemicals

The group exposed to chemicals also had the demographic advantages of higher socioeconomic status, more Whites and earlier gestation at registration than the unexposed with whom they were compared. The same general pattern seen for those exposed to animals, heavy lifting, chemicals and ionizing radiation, that is less anemia and urinary bladder infection during pregnancy, more full term gestation at delivery and more high 4 year I.Q. in the children was evident. Yet all other pregnancy outcome variables in our analysis were adverse, more prior stillbirths and fetal deaths, more uterine bleeding, placental infarcts, low placental weights, hydramnios and high hematocrit in the newborn. The prior reproductive loss, uterine bleeding and low placental weight were not associated with any demographic variables, which strengthens the possibility that exposure to chemicals is not compatible with optimal reproduction. It seems likely that further breakdown into smaller groups of the 1500 individuals exposed to chemicals, such as those exposed to organic solvents in the jewelry, electronic and rubber industry and cleaning jobs - a total of 569, and those in laboratories - a total of 327 may provide sample sizes large enough to examine the possible effects of similar chemicals in more detail.

Pesticides

The women exposed to pesticides had the most disadvantageous demographic characteristics of all the exposed groups. More were of low socioeconomic status, were black and of older age than those not exposed to pesticides. Fewer of them registered before 20 weeks gestation, but fewer smoked during pregnancy. The pesticide group had a considerably worse reproductive experience than any of the other exposed groups. There was a marked excess of prior stillbirths, fetal deaths and premature births. In the pregnancy under study, there was more uterine bleeding, low placental weight, premature low weight births, infants with low 5 minute Apgar scores and high hematocrit, more suspected and definite neurological abnormalities at one year and low 4 year I.Q. None of these variables was differentially associated with any demographic variable we examined. This strong pattern of adverse pregnancy outcome which may be independent of race and socioeconomic status within the exposure group is the most severe of all the groups examined. Only in the case of hydramnios was there a statistically significant association with women of low socioeconomic status who were black.

Pregnancy Outcome Variables

Hydramnios

The excess of hydramnios was statistically significant among women exposed to ionizing radiation, chemicals and pesticides and in each exposure group the condition was found more in Blacks. For those exposed to chemicals and pesticides there were more with hydramnios who were also of low socioeconomic status. Among those exposed to ionizing radiation, black women, women of low socioeconomic status and those of older age were associated more with hydramnios. The more correct term, polyhydramnios is an excessive quantity of liquor amnii. It is thought to be associated with fetal malformations of the central nervous system and gastrointestinal tract.

Hematocrit in the Newborn

High hematocrit values (70+) in the newborn (reported as the lowest measurement during the neonatal period) were associated with maternal exposure to pesticides, chemicals and heat. In the pesticide group high hematocrit values in the children were found throughout that exposed group with no statistically significant interaction with any other demographic or pregnancy outcome variable we examined. In the chemically exposed group more mothers who smoked had children with high hematocrit and more of these children had suspected or definite neurological disorders at one year. In the group exposed to high heat more mothers over 30 years of age had children with high hematocrit, more of them had registered in the CPP late in gestation and more had placental infarcts. The presence of erythrocytosis in the newborn can be considered to be a continuation of the condition in utero and to be caused by incomplete oxygen saturation of the blood. Relative polycytemia is seen in the postnatal period in association with gastroenteritis and dehydration, but otherwise is little understood. In adults polycytemia is seen in those with chronic exposure to aniline derivatives, and carbon monoxide. Acetanilid, arsenic and cobalt have also been associated with polycytemia in adults.

More detailed examination of high hematocrit values in infants and mothers exposed to heat, pesticides and chemicals seems to be worthwhile.

Measurements of head circumference at birth, 4 months, 8 months, 4 years and 7 years were included as pregnancy outcome variables. The results are difficult to interpret and we have chosen not to comment in detail. More children of women exposed to animals, ionizing radiation, heavy lifting, and pesticides had head circumferences in the highest category at three or four of the five ages when measurements were made. In contrast, children of those exposed to chemicals and heat did not show any such excess. Brandt (1976) has written extensively on the dynamics of head circumference growth before and after term and has emphasized the importance of post-natal care. There is probably some value in examining the increments in head circumference in the exposed groups in more detail on the basis of the gross differences we have found for this set of variables.

The development within the CPP population of an unexposed control sample with no evidence of adverse pregnancy characteristics is possible. The comparisons with groups of smaller sample size exposed to single hazards may then become clearer. Other refinements of the data are possible, for example testing for the reliability of a woman's response to questions on her previous pregnancy experience in consecutive pregnancies in the CPP.

SUMMARY

The Collaborative Perinatal Project provides data on a well described population of women pertaining to occupational exposure to hazardous conditions. We examined only 23,961 of the more than 59,000 women originally enrolled and recoding would be necessary to identify those among the other 35,000 who were also exposed to hazardous work conditions. It is possible then to replicate the study reported here or to expand it to a larger sample size. Exposure to one or more hazardous work conditions was reported by 4,575 women of the total 23,961 women for whom this response was coded.

The statistical analysis involved log-linear model analysis of cross classified categorical data. The influence of demographic variables was identified by testing for three factor interaction with occupational exposure categories and pregnancy outcome variables. The choice of variables pertaining to pregnancy history, placental characteristics and growth and development of the children could be extended to some behavioral characteristics, for which data will soon be available from the CPP. Several variables e.g. number of umbilical arteries, some placental characteristics, ataxia, seizure states, failure to thrive at one year explored in this study, would not need to be included in that they do not appear to be

sensitive indicators for occupational exposure effects.

Women with a work experience of pesticide exposure had the most adverse reproductive history, observed as more fetal deaths and stillbirths, premature low weight babies with low 5 minute Apgar scores, suspected neurological abnormalities at one year and low I.Q. at 4 years. No statistically significant interaction with demographic variables was found, indicating that all socio-economic and racial groups were affected comparably.

In addition, occupational exposure to chemicals, heat and heavy lifting was associated with adverse pregnancy and pregnancy outcome experience. Occupational exposure to ionizing radiation and animals did not show comparable effects.

The occupational experience reported in this study was not coterminous with the pregnancies studied but reflected the integrated workforce participation and exposure to hazardous conditions for each mother up to and in some cases during the pregnancy studied.

Recommendations

Exploration of the CPP data has identified occupational exposure to hazardous conditions for 19% of the women studied. Association of some of these exposures with adverse pregnancy outcome should now lead to more detailed evaluation of birth order, work experience during pregnancy and total period of occupational exposure to hazards. The effects of a single hazard versus multiple hazard exposures should also be examined further.

Expansion of the study population to include women enrolled in the CPP before 1962 should increase the sample size within each exposure group markedly and a new choice of pregnancy outcome variables can be made to replace those found not to be associated with exposure to hazardous work conditions.

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