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Reproductive Outcomes in Wives of Lead Exposed Workers

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16. Abstract (Limit: 200 words)

A survey of reproductive outcomes in wives of workers exposed to lead (7439921) was conducted. The cohort consisted of the current wives of 376 married male employees of a lead battery (SIC-3691) manufacturer. Pregnancy data was obtained through interviews. Work histories and blood lead concentrations were obtained from company records. Lead exposures were classified as low (25 to 40 micrograms lead per deciliter (microg/dl) of blood), medium (41 to 60microg/dl), high (60microg/dl) or unexposed (less than 25microg/dl). Odds ratios (OR) of fetal loss risk were calculated from the pattern of fetal loss. OR values (adjusted only for maternal age and prior fetal loss) were: 1.5 for the low exposure group, 1.1 for medium exposure, and 0.9 for high exposure. When separated into females who smoked or did not smoke during pregnancy, the OR values were: low exposure nonsmokers, 0.64 and smokers, 6.82; medium exposure nonsmokers, 0.75 and smokers, 1.92; and high exposure nonsmokers, 0.46 and smokers, 2.29. The authors conclude that elevated OR values for fetal loss with paternal lead exposure are observed in females who smoke during pregnancy. The observed inverse dose response pattern could reflect a shift in outcome with increasing lead exposure.

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ABSTRACT

REPRODUCTIVE OUTCOMES IN WIVES OF LEAD EXPOSED WORKERS: Selevan, SG, Hornung, R, Kissling, GE, Cottrill, C, Leffingwell, SG.

To evaluate the effect of male occupational lead exposure on reproductive functions, relationships between paternal blood lead levels and pregnancy outcomes were studied in 376 male lead battery plant workers and their wives. Pregnancy data were obtained through interviews of workers' wives; work history and blood lead data were obtained from company records. Lead exposures were classified as "low" (25 - 40 µg lead/dl blood), "medium" (41 - 60 µg lead/dl blood), "high" (> 60 µg lead/dl blood), and "unexposed" (before employment or blood lead values < 25 µg lead/dl blood). The analysis consisted of examination (1) of patterns of fetal loss, and (2) of fertility and length of time between live births.

In the analysis of fetal loss, odds ratios adjusted only for maternal age and prior fetal loss were 1.5 for the low exposure group, 1.1 for medium exposure, and 0.9 for high exposure; none of these values were significantly different from 1.0. Further analysis, using logistic regression, found no significant differences in the odds ratios (OR) for lead exposure and fetal loss for non-smoking mothers. However, the ORs were elevated for paternal lead exposure in pregnancies in the cigarette smoking mothers; these ORs were largest

in the low exposure group, the only group with statistically significant findings (OR = 6.82, $p < 0.01$).

Two indirect analyses examined the possibility of decreased fertility: (1) Observed and expected frequencies of live births in the study groups were compared to frequencies expected for U.S. white women based upon calendar year, age and parity specific birth rates. In the exposed groups, the age-specific SFRs were almost always less than 100; the total SFRs for each exposure category were significantly less than expected from the U.S. population and less than for the pre-employment group ($p < 0.05$). (2) The examination, using Cox regression, of interval between births found small, non-signifi- cant differences in the three exposure groups.

INTRODUCTION

High rates of fetal and infant death have been reported with human paternal lead exposure by several observers in the early part of this century (as summarized in Hamilton, 1925; Oliver, 1914; and Weller 1915). Comparison or baseline data were usually not present, but reports of fetal loss after only paternal exposure to lead ranged from 25.6 percent to over 80 percent, and reports of infant death ranged from 25.2 percent to 40.0 percent. In 1905, Deuenbourg (cf Bell and Thomas, 1980) reported that wives of lead workers experienced greater rates of fetal loss than wives of unexposed workers. In animal studies of paternal lead exposure, decreased numbers of weaned pups and decreased birth weights were noted in guinea pigs (Weller, 1915) and rats (Stowe and Goyer, 1971).

Both human and animal data suggest that changes in sperm from any cause, such as reduced number or motility, and increases in the proportion of malformed sperm, are associated with reduced fertility (Amelar, 1966; Freund and Peterson, 1976) and increased fetal loss (Joel, 1966). Sperm changes in both humans and animals have been noted after exposure to lead. As early as 1850, the spermicidal effects of lead were reported by de Quatrefages (cf Mann, 1964). Lancranjan et al. (1975) found reduced viability and number of sperm, and increased proportions of malformed sperm in 89 lead-exposed men compared to 50

unexposed men. The changes were observed with increasing blood lead levels in the workers. Statistically significant differences were noted in workers with concurrent blood lead levels as low as 41 $\pm$ 12 µg lead/dl blood. Reduced motility, sperm count and infertility (Hilderbrand et al., 1973; Puhac et al., 1963) have been observed with paternal exposure in rats; increased proportions of abnormal sperm forms (Eyden et al., 1978; Maisin et al., 1975) and lower pregnancy rates (Varma et al., 1974) have been found with paternal lead exposure in mice.

Reports from both the turn of the century and current studies suggest an association between paternal lead exposure and sperm changes, decreased fertility, and increases in fetal and infant death. Our report examines the association of lead absorption, as measured by blood lead levels of male workers, with fetal loss and live birth patterns of their wives.

MATERIALS AND METHODS

The study group consisted of the current wives of all married male hourly employees of a lead battery manufacturer. The company under study supplied a list of all 710 hourly workers employed in March, 1977. These workers were considered married until determined otherwise. The comparison group was internal, consisting of pregnancies occurring in current wives of male workers with blood lead levels <25 µg lead/dl blood or prior to their employment at the plant. Data on pregnancies, health and demographic characteristics were obtained from the women by face-to-face interviews using a standardized questionnaire (NIOSH, 1977). Data on the workers' job histories and blood lead levels were obtained from company records.

Population Description

Of the total hourly population (710 male workers), 569 were known to be married; 395 wives completed interviews. Only 18 workers were not located and their marital status remains unknown (Figure 1). The husbands of the respondents and non-respondents did not differ in regard to the number of years employed at the lead battery company or on their average blood lead levels during 1976 and 1977 (Table 1), suggesting that the workers' current blood lead levels did not affect the likelihood of their wives' participation in the study.

A total of 745 pregnancies were available for analysis after restricting the population to pregnancies of white respondents (due to the small proportion of non-whites: 4.8 percent), single births, and pregnancies occurring within the current marriage and after 1952, the first year in which sufficient exposure data (blood lead levels) were available. Tables 2 and 3 describe the characteristics of the parents and of the restricted study population.

Exposure Data

Lead exposure of the father at the time of each pregnancy was estimated using company employment records and periodic blood lead values collected for each employee through the company's monitoring program. In the early days of the monitoring program, which began in 1952, the frequency of the determinations for each worker was variable; more recently, blood lead levels were determined at least once per year. The blood lead level associated with each pregnancy was estimated using the mean of all blood lead values of the father for the four months prior to and two months following the estimated date of conception. This date was estimated using the wife's interview report of length of gestation and the date the pregnancy ended. A large number of the exposed pregnancies, 393, had blood lead values for the workers during this period; 73% of these had two or more measurements. For workers with no measurements during that time period, blood lead levels were estimated using yearly departmental mean blood lead levels. If a worker was employed in more than one department during

the interval, the estimate was weighted by the length of time the worker spent in each department. A three month time delay after employment in a specific department was allowed before the worker was assigned that department's mean blood lead value, to allow time for a change in the worker's blood lead level and allow time for expression of effects in sperm (Manson and Simons, 1979).

OSHA (1978), based on research and testimony, has recommended that workers' blood lead levels not exceed 40 µg lead/dl blood "to provide necessary protection against the effects of lead exposure . . . " The OSHA air lead level was designed to "provide a dramatic reduction in the number of workers whose blood lead levels are currently greater than 40 µg/100g and will virtually eliminate all bloods lead levels above 60 µg/100g". For consistency with commonly used exposure categories, and since there is inherent variability in the procedures for measuring blood lead levels (Lerner, 1975), lead levels were grouped into broad categories for all analyses: pre-employment or unexposed (< 25 µg lead/dl blood), low (25 - 40 µg lead/dl blood), medium (41 - 60 µg lead/dl blood), and high (> 60 µg lead/dl blood). The exposure data were grouped in an attempt to gain a clearer understanding of the effects of the different exposure levels on the outcomes under study without assuming a dose-response relationship; where possible, a continuous exposure measure was also evaluated.

Two sets of analyses were done: (1) comparison of fetal loss by logistic regression analysis, and (2) an indirect examination of

fertility using both (a) standardized fertility ratios (SFR) based on live births and person-years of observation in each blood lead group, and (b) Cox regression/survival analysis applied to the time intervals between live births. Statistical findings with probabilities less than 0.05 were considered to be statistically significant.

Part I: Fetal loss

Preliminary analyses compared the rate of all fetal loss within each blood lead category to pre-employment rates (to give risk ratios). These risk ratios were stratified on maternal age (< 30, ≥ 30) and on the occurrence of any fetal loss prior to the event, and were examined using the Mantel-Haenszel procedure (Mantel and Haenszel, 1959).

Logistic regression allowed simultaneous control of several potential risk factors, effect modifiers and confounders (Bishop et al., 1975). This detailed analysis was not possible with stratified analysis due to small numbers in some of the strata. These factors were examined using maximum likelihood estimation in logistic regression (Proc Logist, SAS, 1980) following procedures described by Kleinbaum et al. (1982). The initial stage of model building in multiple logistic regression, included blood lead level in the categories described above; in addition, analyses examined the estimated blood lead levels as a continuous variable, and as a dichotomous measure (exposed or not) to see if additional information on the relationship between exposure and fetal loss could be derived. In the primary analysis of the categories of blood lead levels, dummy variables described the exposure groups with no assumption of a dose-response relationship. The additional potential risk factors of prior fetal loss (any or none), maternal age (number of years),

gravidity, alcohol and cigarette use, spacing of pregnancies, illness and injury during pregnancy, and maternal employment during pregnancy were tested for inclusion in the final model (criterion for inclusion $p \leq 0.10$). These factors have been associated with increased fetal loss in other studies (Leridon, 1977; Kline et al., 1977; Kline et al., 1980; Stein et al., 1980). The mother's completion of high school was included as a surrogate of socio-economic status, and year of the pregnancy was included to estimate secular trends and/or as a surrogate measure of recall bias. Interaction terms were tested for inclusion at $p \leq 0.05$. Odds ratios (ORs) and 95 percent confidence intervals (95% CI) were calculated for each lead exposure group compared to the pre-employment pregnancies (Kleinbaum et al., 1982). Goodness of fit of the model was tested (Hosmer and Lemeshow, 1980).

The probability of fetal loss can be greater for women with prior fetal loss (Warburton and Frazer, 1964). Factors, such as prior fetal loss, may be related in pregnancies within the same family; for this reason, inclusion of several pregnancies from the same family in the analysis, with each considered an independent observation, violates the assumptions of many statistical tests (Kissling, 1981). The use of non-independent events tends to overestimate the true size of the population since some observations contribute overlapping information. The effect of this overestimation of population size may, to varying degrees depending on the individual study populations, artificially inflate the significance level. Each woman could potentially contribute several pregnancies to the study, in addition, each of these

could be in different exposure groups; forty percent of the families contribute to only one exposure group. The fetal loss data were examined in several ways in an attempt to asses the risk associated with exposure. The analyses of fetal loss were initially done on all 745 pregnancies; however 5 women had experienced three or more consecutive early fetal losses, a generally accepted description of 'habitual aborters' (Pritchard and MacDonald, 1976). The analyses were repeated, excluding all 30 pregnancies for these 5 women. In another analysis, one pregnancy per woman was randomly selected; this considerably reduced the statistical power of the analysis but avoided the problem of non-independent events.

RESULTS

The crude risk ratio comparing fetal loss in each blood lead group to pre-employment experience was 1.73 for the low blood lead group, 0.83 for the medium blood lead group, and 1.08 for the high blood lead group (Table 5). Comparisons for each blood lead category, after control for maternal age and prior fetal loss, generally resulted in risk ratios closer to 1.00 than the crude estimates; none of these risk ratios were significantly different from 1.0 (Table 5).

Odds ratios (OR) for the three exposed groups were calculated from the logistic regressions (Table 6). The analysis of all pregnancies showed statistically significant interaction of low versus no exposure with cigarette smoking. The OR patterns for the two higher blood lead

level groups were similar to those for the low exposure group, but they were not significantly different from one. When all pregnancies for those women reporting 3 or more consecutive early fetal losses were excluded (Table 7), the results were similar to those of the total population; however, all the odds ratios were somewhat higher. The ORs for non-smoking women became greater than one. The analysis of the pregnancies randomly selected from each woman yielded similar results, but the confidence intervals were wider due to the smaller numbers. The other two logistic analysies looked at the exposure measure in different forms: 1. The odds ratios using lead as a continuous variable was 0.99 per unit of exposure (not significant - NS) and 2. the odds ratios when the exposure was defined dichotomously were 0.69 (NS) for pregnancies for non-smokers and 4.35 (NS) for pregnaices for smokers.

The interaction observed between cigarette smoking and blood lead level suggested that an additional analysis, separating the population in smokers and non-smokers was appropriate (Table 8). The patterns observed in the earlier analysis are repeated: Low lead level had odds ratios of 0.64 (NS) and 6.82 ($p < 0.01$) for pregnancies of non-smokers and smokers, respectively; those in the medium lead level groups had odds ratios of 0.75 (NS) and 1.92 (NS); and those in the high lead level groups had odds ratios of 0.46 (NS) and 2.29 (NS).

Part II: Fertility Analyses

METHODS

Standardized Fertility Ratios (SFRs)

The standardized fertility ratio (SFR) is the ratio of the number of live births observed in each blood lead group to those expected if these groups had experienced the same patterns as U.S. white women of similar demographic characteristics. This measure has been described by others for studies of fertility in occupational settings (Wong et al., 1979; Levine et al., 1980) and is similar to standardized mortality ratios (SMRs), a frequently used measure in studies of occupational populations. Birth rates change with marital status, age, parity, and calendar time. For this analysis, five year parity-, calendar- and age-specific rates for white women were obtained (NCHS, 1978). First births, and the time preceding them, were excluded from this analysis to make the U.S. data for all women more comparable to the study group of married women. U.S. parity-specific rates restricted to married women are not available. The period of follow-up for each couple began after the first live birth and the beginning of the study period (1952), and ended at the end of reproductive capacity (surgical or natural menopause), at age 45 or the end of the study period (September, 1977), whichever occurred first. An additional analysis also included the time between surgical or natural menopause and age 45, since the data for the U.S. rates include these

person-years. The husband's exposure category for each three month period of follow-up was determined from his blood lead levels; departmental levels were used when the husband's values were not available. These five-year age- and calendar-specific person-years were summed, and the expected number of births were calculated by multiplying the person-years with the appropriate United States rates. Different mean ages and parities of the women, and timing of the pregnancies within the study period were observed for the different blood lead groups (Table 3) when compared to the pre-employment group. To reduce the lack of comparability among the exposure groups, age-specific results were compared in addition to total SFRs. The SFR is the ratio of the observed live births to the expected live births multiplied by 100. Confidence intervals were calculated using formulae for confidence intervals for standardized mortality ratios (Rothman and Boice, 1979).

Birth Interval Analysis

Analysis of the time period between live births using survival analysis techniques has been suggested as an indirect meausre of fertility for studies of occupational exposure and pregnancy outcome (Dobbins, et al., 1978). Parity-specific comparisions are more appropriate because the temporal spacing between births increases with parity (Leridon, 1977) and because the births within a family may be non-independent events. The outcome of one pregnancy may affect the timing of a subsequent birth due to social or health factors. This

analysis of live birth spacing was restricted to the time periods between parities one and two, parities two and three, and parities three and four, due to the small numbers of pregnancies at high parities. The Cox regression method for time-dependent covariates with incomplete survival data was used (BMDP2L, BMDP, 1981). This allowed the use of incomplete (or censored) data, that is, data collected for a period of time which ended in other than the outcome of interest. This analysis program allows stratification on specific variables (in this case, parity) and then combines the stratum-specific estimates. In this study, the observation period covered the 10 years following the specific (or index) birth. This time period could be less if, during the 10 year period, the woman had surgical menopause or the study period ended. This particular type of regression allows potential risk factors to change over time; in this population, the blood lead category was allowed to change during the study period. Maternal age, fetal loss during the interval, year of the birth, high school education, smoking and drinking patterns, contraception and maternal employment outside the home were evaluated for use in the model. Contraception data were available for the twelve months preceeding conception of the specific pregnancy; these data were used as the surrogate information for the entire time period.

RESULTS

Standardized Fertility Ratios

Not surprisingly, the pre-employment group differed from the lead-exposed group in mean age, parity and year of pregnancy (Table 3); the SFRs were adjusted for these differences. The blood lead groups generally exhibited deficits of live births compared to those expected with the person-years observed (Table 9). With one exception, these SFRs were always less than those observed in the pre-employment group. The total SFRs for the exposed groups were significantly less than 100. While consistently decreasing SFRs were not observed with increasing exposure category, the X^2_{trend} (Breslow et al, 1983) was suggestive of a trend for the age group 20-24 and for the total population (p for both are approximately 0.1). The analysis which included all person-years prior to age 45 resulted in numbers nearly identical to those presented in Table 9. More direct comparison of SFRs for the exposed pregnancies to the pre-employment experience would help correct for socio-economic status (SES) patterns in the population under consideration. The expected number of births for all exposure groups was divided by age- and calendar time-specific SFRs in the pre-employment group, to allow direct comparison of pre-employment experience to each exposure group. This adjustment resulted in an SFR of 100 for the pre-employment group (Table 10).

Birth Interval Analysis

The final Cox regression model of the spacing of the live births (time period between live births) was stratified by parity and included maternal age and year of the birth because of the differences in pregnancy patterns over the time of the study for United States women, employment of the mother during the time interval, and blood lead levels for each three month period for the 10 years of observation. Negative coefficients and risk ratios less than one for an explanatory variable suggested that an increase in its value was associated with a greater time period between live births; the results in Table 11 show statisictically significant increases in birth intervals for older women, for births occurring later in the study period, and for working women; the data suggest an increase in the interval with contraception. The risk ratios for the blood lead levels suggested increasing intervals with greater exposures from a risk ratio of 1.08 to 1.03 to 0.82, but these results are not statistically significant. The birth intervals for the low and medium blood lead groups were actually shorter than for the unexposed group. Analysis of these data, using a continuous blood lead measure, resulted in a risk ratio of 1.00.

DISCUSSION

Exposure Data

Few occupational health studies have sufficient biological or industrial hygiene data on the study members to examine actual, rather than hypothesized or extrapolated, exposure data. However, historic blood lead measurements were available for this population from the early 1950s through the end of the study period. As a result, exposure values for 393 pregnancies occurring during employment were based on the individual workers own blood lead levels around the estimated time of conception. This did not, however, mean that the exposure classification of the pregnancies were without error. First, the actual measurement of the amount of lead in blood is subject to considerable inter- and intra-laboratory variation (Lerner, 1975). The use of historic data, going back to the early 1950's, does not allow standardization or quantification of the measurement error. There is no reason to believe that biased misclassification of exposure is occurring; therefore errors in exposure measurements should generally bias risk extimates toward the null. Misclassification is also a potential problem for those workers with no measurements during the six month period around the estimated data of conception and for whom the exposure was estimated from yearly departmental mean levels.

Lead dust may be carried home on the clothing and hair of workers, potentially exposing family members; such exposures have been documented in children (Baker et al., 1977; Giguere et al., 1977).

This raises the question of whether any observed effects could have been the result of maternal exposure only or both maternal and paternal exposures. To attempt to estimate this potential, a sample of husband-wife pairs were asked to give blood samples for analysis. The median values for the husbands was 38 µg lead/dl blood and 13 µg lead/dl blood for their wives. The blood lead mean values for the wives increased a small amount with larger increases in their husbands blood lead values (Table 12). Therefore, it is possible, although unlikely, given the slight differences in the wives' blood lead levels compared to the much greater differences in their husbands' blood lead levels, that any effects observed were due to maternal lead exposure rather than paternal lead exposure.

Fetal Loss

Analyses of the current study found an interaction of blood lead group and smoking, with increasing odds ratios with more smoking but generally decreasing ORs with increasing level of blood lead. In the total population (Table 6), the ORs for the non-smokers are all less than 1.0 (NS). The only significantly elevated ORs were for smoking women whose husbands were in the low blood lead group. The ORs in the medium and high lead groups were lower, but greater than 1.0 (NS). Exclusion of pregnancies from "habitual aborters" (Table 7) increased the ORs; then the ORs for non-smokers were greater than 1.0 (NS). The interaction between paternal lead level and maternal smoking is hard to interpret. Perhaps the paterani lead exposure resulted in a more

"sensitive" pregnancy, one with more subtle adverse effects; then the extra insult of smoking could have shifted the endpoint from one not examined in this study to fetal loss. The patterns demonstrated by the ORs do not fit the pattern of a traditional dose-response relationship.

The patterns of an inverse dose-response relationship observed could be the result of an artifact resulting from misclassification, as discussed above, from some unrecognized factor, or from recall bias. Recall bias could result from differences in the timing of the pregnancies, since many more of the pregnancies for the low exposure group occurred after 1960 (Yerushalmy et al., 1956). Perhaps the recall for more recent events was better. In addition, the blood lead levels in the plant decreased over time, due to improvements in control and hygiene, and could be confounded with the results observed. However, when the age-specific rates of fetal loss for the two time periods were compared, similar results were found. Only minor differences were observed for all pregnancies, and when the families with three or more consecutive fetal losses were excluded (Table 13). Year of the pregnancy was also examined as an explanatory variable in the multiple logistic regression, but was not included in the final model due to its minor contribution. In addition, data from a sample of these women were validated from medical and/or vital records (Selevan, 1980), and the data were found to be in good agreement. A major concern in any study of fetal loss is biased recall resulting from, perhaps, knowledge of the exposure of interest. In this study, almost all the women considered their husbands exposed to lead. The

specific exposure category for each pregnancy was determined, not from the respondents, but from recorded data, which decreased the potential for bias. If concern over lead exposure might promote more complete recall of more fetal loss, then a significant excess should also be found in the high blood lead level group.

These patterns could also result from competing risks: Certain reproductive outcomes can be envisioned as sequential events, with the occurrence of a specific pregnancy outcome dependent upon survival of the pregnancy to a certain stage. For example, excess malformations in live births may not be observed if the defect is so severe that survival to birth is unlikely. Wilson (1973) described a model for the different spectrum of outcomes observed at different exposure levels, based upon the observation of female laboratory animals exposed to teratogens during pregnancy. He suggested that as the dose increases, increasing proportions of the offspring will abort or be malformed. Eventually, with higher doses, all offspring will abort, and finally, some level of exposure will become toxic/lethal to the mother. Extension of this model to exposures at various stages of reproduction, including pre-conception exposure to the father, suggests that different outcomes may be observable at different exposure levels and the expectation of increasing proportions of certain adverse outcomes with increasing exposure (a dose-response relationship) may be misleading. This difference in trends in fetal loss could have resulted from a shifting of outcomes at different blood lead levels.

Because of the potential for a shifting of outcomes at different exposure levels, a dose-response relationship was not required for the analysis of fetal loss; each blood lead level was examined separately. More fetal losses might have occurred but not been recognized as such by the woman or her physician in the high exposure group due to a shift in the timing of the loss to an earlier point in the pregnancy. The results could also have reflected a decrease in the rate of conceptions. If this shifting in outcomes occurred, reduced fertility might be expected with greater lead exposure.

Problems occur with the use of non-independent events in analyses which assume independence of outcomes; the statistical significance level may be artifically inflated. A woman who has had a fetal loss is more likely to have subsequent pregnancies end in fetal loss. When 'habitual aborters' were eliminated from the analysis, to determine if these women had a major effect on the odds ratios, the results were similar to those of the entire study population.

Fertility Analyses:

In the SFR analysis, all exposed groups exhibited overall, statistically significant, deficits of births when compared to the expected based upon age, parity and calendar-time specific rates for United States white women for the number of person-years of observation in these groups (Table 9), and when compared to the SFRs for the unexposed group (Table 10). The SFRs for some of the age-specific

higher blood lead groups were larger (NS) than those for the low blood lead group. Age- and calendar-specific rates for married white women were not available by parity; therefore, the analysis was restricted to women of parity one and greater. The restriction of this analysis to births after a woman's first live birth increased the similarity of the U.S. data to this population, because a large proportion of white U.S. women with at least one birth are currently or have been married. This could result in an underestimates of the effect of exposure, as all person-years for those with no births are excluded from the analysis. The restriction of person-years to those prior to natural or surgical menopause makes the study groups slightly less similar to the U.S. population but more similar to each other. Another analysis, including the person-years after the woman's reported menopause and prior to age 45, was essentially the same as the one reported, with only minor differences in the older age groups.

Small, non-significant differences were noted in the intervals between live births for the different blood lead levels, with generally increasing time intervals with increasing blood lead levels (Table 11).

A major advantage to examination of live birth data in the SFR and birth interval analysis is the increased confidence in the accuracy of the data. While a respondent might forget a very early fetal or embryonic loss, or the date of its occurrence, such recall problems would be less likely for live births.

The standardized fertility ratio (SFR) for the exposed groups were consistently less than those of the pre-employment group (Table 9); a general trend ($p = 0.1$) for greater deficits in births were observed with increasing blood lead level for the age group 20-24 and for the total group. Because of the differences in mean maternal age and parity for the three groups, comparisons of the age-specific categories should be emphasized, especially if age were an effect modifier for the effect of exposure. This seems unlikely, since the exposure is to the husband. Animal studies of guinea pigs and rats have noted reduced numbers of weaned pups with lead exposure (Weller, 1915; Stowe and Goyer, 1971); no animal studies have examined multiple dose levels for paternal lead exposure, so no information was available to suggest the appropriate model for evaluating the effects of differing levels of exposure on SFRs. An increasing dose-response relationship might be expected or, perhaps, a threshhold model with a plateau after some critical dose. The data observed are not inconsistent with a threshhold, and the X^2_{trend} (Breslow et al, 1983) for the total group and age group 20-24 are suggestive of a dose-response relationship.

It is possible that the baseline expectation of births for pre-employment person-years was inherently greater than for the post-employment person-years, thus making comparison of pre- and post-employment experience inappropriate in any worker population. For example, in occupational mortality studies, differences in mortality patterns are observed in workers when compared to the general U.S.

population; these differences are related to a phenomenon known as the "healthy worker effect" (McMichael et al., 1975). Levine et al. (1980, 1981) have looked at three populations in a similar analysis to the one reported here. In all of the populations, pre-employment SFRs were lower than or approximately equal to SFRs after employment as opposed to the current analyses with the pre-employment SFRs being greater than after first employment. In the third population, workers exposed to DBCP, an agent known to reduce sperm count, were compared to unexposed workers at the same plant and to their pre-employment experience; the two comparison groups had similar SFRs. These reports in other populations suggest that the differences observed in the lead-exposed population are not due to some inherent differences in the pre- and post-employment populations. The comparison of the exposed groups with the unexposed group (Table 10) results in the same statistically significant effects observed before.

The findings of the Cox regression/survival analysis suggested a slightly longer time period between live births with increasing lead exposure (NS), but the risk ratios for the exposed groups ranged from 1.08 to 0.82, suggesting intervals both longer and shorter than the exposed group. The actual interpretation of birth interval data is difficult; longer birth intervals were assumed to be surrogate measures of fertility and/or fetal loss. Factors such as maternal age and employment did significantly lengthen the interval between births; this suggests that the approach is a potentially useful one.

SUMMARY AND CONCLUSIONS

Most studies of reproduction and occupational exposure have examined one phase; this study has examined several. ORs for fetal loss with paternal lead exposure in pregnancies to non-smoking women were not significantly different from 1.0. Elevated odds ratios were observed for paternal blood lead for fetal loss in women who smoked cigarettes during pregnancy. Higher odds ratios were observed for the low blood lead group than for the higher blood lead groups, resulting in an inverse dose-response relationship. The dose-response pattern could potentially reflect a shift in outcome with increasing exposure, for example, from fetal loss to subfertility. The analysis of standardized fertility ratios are not inconsistent with an effect of lead on fertility; non-significant and very minor trends were found for increasing time intervals between live births with increasing exposure levels. Other, larger populations need to be examined to determine the whether trends observed suggest a health effect of lead on male reproduction.

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Figure 1

Description of the Plant Population

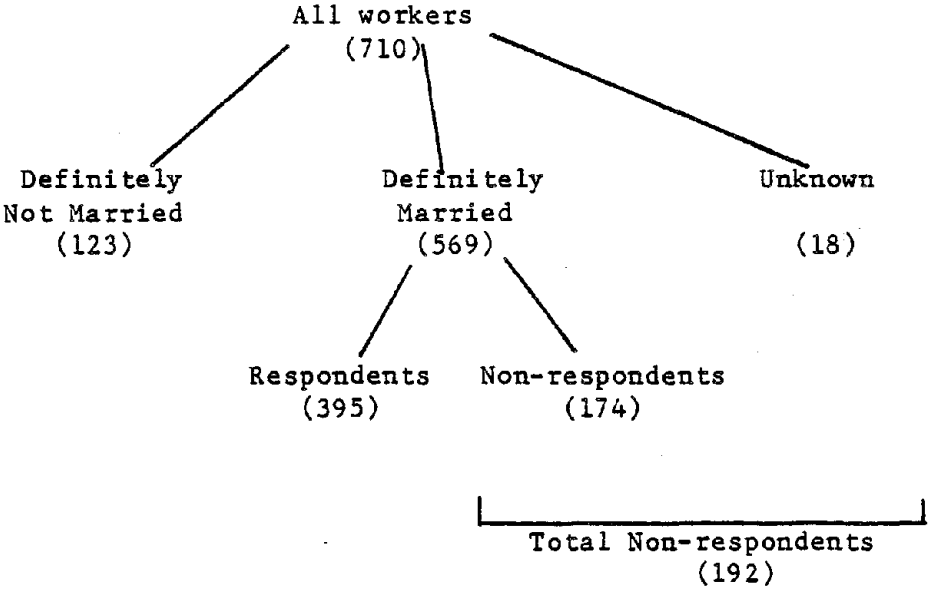

Table 1

Demographic Characteristics of Respondents and Non-Respondents at the Time of Interview

		Non-respondents	
	Respondents	Married	Unknown Marital status
Total number	395	174	18
Age at time of interview (August, 1977)	46.1 (45.3-46.9)*	48.0 (46.8-49.2)	45.8 (42.1-49.5)
Time from first date of employment	22.5 (21.8-23.1)	24.0 (23.0-24.9)	22.4 (19.7-25.0)
Husbands' average blood Lead values for 1976-1977	38.9 (37.7-40.1)	38.7 (37.3-40.1)	35.3 (31.3-39.3)

95% Percent Confidence intervals

Table 2

Characteristics of Final Study Population
(N = 395)

	Proportion with Characteristic	Mean	S.D.	Range
Fathers age, August, 1977*:		45.6	8.3	28-66
Mothers' ages, August, 1977+:		42.9	8.2	24-65
Mothers' Education (years completed):		11.3	1.9	4-17
Completed High School	63.6%			
Mothers' Marital History:				
Married Once	81.1%			
Married two or more times	18.9%			
Median Year of current marriage		1955		1934-1976
Number of Pregnancies (All marriages):		3.1	1.7	0-11
Proportion with no pregnancies:	5.9%			
Number of Pregnancies (Current marriage):		2.6	1.8	0-8

* Fathers' ages are from company records
+ The following data are from interviews

Table 3

Characteristics of Pregnancies by Exposure Category

	Pre-Employment or None	Low	Medium	High	Total
Number of Livebirths	139	112	333	62	646
Number of Early Fetal losses*	17	24	43	5	89
Number of Late Fetal losses	0	2	6	2	10
Total Pregnancies	156	138	382	69	745
All Pregnancies					
Mean age of mother at conception (S.D.)	21.6 (4.5)	24.4 (5.2)	24.3 (4.6)	24.3 (5.4)	23.8 (4.9)
Mean gravidity of mother (S.D.)	2.1 (1.4)	2.8 (1.4)	2.9 (1.7)	2.8 (1.6)	2.7 (1.6)
Year of pregnancies					
Percent before 1960	65.4%	23.9%	44.0%	79.7%	48.1%
Mean year of conception	1958	1962	1961	1958	1960
Livebirths					
Sex Ratio**	107.5	107.4	108.1	100.0	107.1

* Early fetal losses were those outcomes reported as misscarriages; last fetal losses were those reported as stillbirths.
** Sex ratio = (number of males/number of females) x 100.

Table 4

Proportion of Fetal Loss by Other Potential Risk Factors

Potential Risk Factor		Fetal Loss Number	Fetal Loss Percent	Live Births Number	Live Births Percent	Total Number
Prior Fetal Loss:	Number with None	63	(10.6%)	533	(89.4%)	596
	Any Fetal Loss	36	(24.2%)	113	(74.8%)	149
Maternal Age:	< 30	76	(11.7%)	573	(88.3%)	649
	≥ 30	23	(24.0%)	73	(76.0%)	96
Mean maternal age (S.D.)+		25.4	(5.8)	23.5	(4.7)	23.8(4.9)
Year of pregnancy:	Before 1960	39	(11.9%)	288	(88.1%)	327
	1960 and after	60	(14.4%)	358	(85.6%)	418
Mean Year (S.D.)		1961	(5.5)	1961	(5.3)	1961
Gravidity:	1	15	(8.1%)	171	(91.9%)	186
	2	24	(11.9%)	177	(88.1%)	201
	3	17	(10.2%)	150	(89.8%)	167
	4+	43	(22.5%)	148	(77.5%)	191
HS Graduate:	No	32	(12.4%)	226	(87.6%)	258
	Yes	67	(13.8%)	420	(86.2%)	487
Smoked Cigarettes:	None	60	(11.3%)	469	(88.7%)	529
	< 1 pack	16	(17.4%)	76	(82.6%)	92
	≥ 1 pack	23	(18.6%)	101	(81.4%)	124
Mean number of cigarettes per for smokers (SD)		17.6	(7.8)	17.1	(7.8)	17.2(7.8)
Drank Alcohol:	No	57	(14.0%)	351	(86.0%)	408
	Yes	42	(12.5%)	295	(87.5%)	337
Pregnancy spacing:	≤ 6 months	20	(18.0%)	91	(82.0%)	111
	> 6 months	79	(12.5%)	555	(87.5%)	634
Mean number of months (S.D.)		37.9	(47.4)	45.7	(46.1)	44.6(46.3)
Is family defined as "habitual aborters"* - - yes		21	(21.2%)	9	(1.4%)	30

+ S.D.: Standard deviation

* 3 or more consecutive fetal losses

Table 5

Crude Risk Ratios for All Fetal Loss

	Pre-Employment	Low	Medium	High
Fetal Loss	17	26	49	7
Total Pregnancies	156	138	382	69
Crude Risk ratio	1*	1.73	0.83	1.08
Adjusted risk ratio+	1*	1.5	1.1	0.9
95 percent C.I.		(0.8-3.0)	(0.6-1.9)	(0.3-2.3)
X^2_{MH}		0.54	0.03	0.10

* Reference Category
+ Adjusted for maternal age (< 30, $\geq$ 30) and prior fetal loss

Table 6

Results of Logistic Regression
for Fetal Loss

Variables in model	Coefficient	Standard Error	P-value
Exposure			
Low vs none+	-0.443	0.434	0.31
Medium vs none+	-0.335	0.342	0.33
High vs none+	-0.622	0.549	0.26
Maternal age+	0.903	0.263	<0.01
Prior fetal loss+	3.494	1.285	<0.01
Packs of Cigarettes/day+	-1.144	0.902	0.20
INTERACTIONS:			
Low Exposure*Smoking	2.962	1.039	<0.01
Medium Exposure*Smoking	1.481	0.962	0.12
High Exposure*Smoking	1.616	1.074	0.13
Maternal age*prior loss	-1.061	0.494	0.03

+Statistical significance of main effects should not be interpreted in the presence of interaction terms including those effects.

Odds Ratios Based on Logistic Regression

Cigarette Smoking:	None	0.5 packs/day	1 pack/day
Low Blood Lead Level:			
Odds Ratio	0.64	2.82	12.41
95 percent C.I.	(0.27-1.50)	(1.05-7.58)	(2.02-76.37)
Medium Blood Lead Level:			
Odds Ratio	0.71	1.50	3.15
95 percent C.I.	(0.37-1.40)	(0.60-3.78)	(0.55-17.97)
High Blood Lead Level:			
Odds Ratio	0.54	1.20	2.70
95 percent C.I.	(0.18-1.58)	(0.37-3.94)	(0.38-19.27)

Table 7

Results of Logistic Regression for Fetal Loss
Excluding all Pregnancies for Women with
3 or More Consecutive Fetal Losses

Variables in model	Coefficient	Standard Error	P-value
Exposure			
Low vs none+	0.317	0.522	0.54
Medium vs none+	0.374	0.450	0.41
High vs none+	0.114	0.619	0.85
Maternal age	0.765	0.240	<0.01
Loss	0.147	0.303	0.63
Cigarette smoking+	-0.718	1.035	0.49
INTERACTION:			
Low Exposure*Smoking	2.246	1.166	0.05
Medium Exposure*Smoking	0.860	1.100	0.43
High Exposure*Smoking	1.237	1.185	0.30

+Statistical significance of main effects should not be interpreted in the presence of interaction terms including those effects.

Odds Ratios Based on Logistic Regression

Cigarette Smoking:	None	0.5 packs/day	1 pack/day
Low Blood Lead Level:			
Odds Ratio	1.37	4.22	12.98
95 percent C.I.	(0.49-3.82)	(1.37-12.99)	(1.72-98.12)
Medium Blood Lead Level:			
Odds Ratio	1.45	2.23	3.43
95 percent C.I.	(0.60-3.51)	(0.77-6.49)	(0.49-24.22)
High Blood Lead Level:			
Odds Ratio	1.12	2.08	3.86
95 percent C.I.	(0.33-3.77)	(0.57-7.53)	(0.46-32.47)

Table 8

Results of Logistic Regression for Fetal Loss

Smokers versus non-smokers

Odds Ratios Based on Logistic Regression

Cigarette Smoking:	Non-smokers		Smokers	
	All Pregnancies	Without Hab. Ab.	All Pregnancies	Without Hab. Ab.
Low lead:				
Odds Ratio	0.64	1.47	6.84	6.95
95 percent C.I.	(0.26-1.55)	(0.50-4.32)	(1.75-26.74)	(1.38-34.93)
Medium lead:				
Odds Ratio	0.75	1.66	1.92	2.05
95 percent C.I.	(0.37-1.50)	(0.66-4.20)	(0.70-7.15)	(0.43-9.85)
High Lead:				
Odds Ratio	0.46	1.05	2.29	3.72
95 percent C.I.	(0.13-1.67)	(0.28-4.00)	(0.39-13.36)	(0.54-25.62)

Table 9

Standardized Fertility Ratio for
Lead Exposed Workers and their Spouses

Adjusted for Age, Parity and Calendar Time

	Pre-employment or Blood lead ≤ 25µg/dl			Blood lead levels: Low			Medium			High		
	Obs.	Exp.	SFR	Obs.	Exp.	SFR	Obs.	Exp.	SFR	Obs.	Exp.	SFR
15-19	8	9.4	85 (37-168)*	3	4.8	63 (13-183)	10	14.0	72 (34-131)	6	5.6	106 (39-233)
20-24+	34	29.2	117 (81-163)	34	34.4	99 (68-138)	111	104.5	106 (87-128)	17	28.1	61 (35-97)
25-29	19	19.7	97 (58-151)	23	38.7	59 (38-89)	101	108.4	93 (76-113)	15	26.1	57 (32-95)
30-44	10	10.5	95 (46-175)	17	27.7	61 (36-98)	38	81.3	47 (33-64)	12	13.5	89 (46-155)
Total++	71	68.8	103 (81-130)	77	105.5	73 (58-91)	260	308.2	84 (74-95)	50	73.3	68 (51-90)
Person-years			404.75			973.0			2773.75			490.75

* 95% confidence intervals

\+ $X^2_{trend,1df} = 2.628$, $p = .10$

++ $X^2_{trend,1df} = 2.552$, $p = .11$

Table 10

Standardized Fertility Ratio for
Lead Exposed Workers and their Spouses

Adjusted to Pre-employment Experience by Age and Calendar Time Period

Pre-employment or Blood lead ≤ 25 µg/dl		Blood lead levels								
		Low			Medium			High		
	SFR	Obs.	Exp.	SFR	Obs.	Exp.	SFR	Obs.	Exp.	SFR
15-19	100	3	4.0	75 (15-219)*	10	11.8	85 (41-156)	6	4.8	125 (46-272)
20-24	100	34	41.7	82 (56-114)	111	132.3	84 (69-101)	17	32.9	52 (30-83)
25-29	100	23	43.4	53 (34-80)	101	122.6	82 (67-100)	15	27.1	55 (31-91)
30-44	100	17	23.6	72 (42-115)	38	68.2	56 (39-76)	12	12.1	99 (51-173)
Total	100	77	112.8	68 (54-85)	260	334.9	78 (68-88)	50	76.9	65 (48-86)

* 95% confidence intervals

Table 11

Cox Regression--Examination of Survival

Of Time Period Between Live Births

Variable	Coefficient	Standard Error	Risk Ratio (95% Confidence Interval)
Lead exposure			
Low vs None	0.074	0.193	1.08 (0.74-1.36)
Medium vs None	0.031	0.170	1.03 (0.74-1.44)
High vs None	-0.198	0.217	0.82 (0.54-1.26)
Year of Birth+	-0.412	0.011	0.44 (0.29-0.67)
Maternal age++	-0.098	0.017	0.37 (0.27-0.53)
Employment during interval	-0.304	0.154	0.74 (0.55-1.00)
Contraception during interval	-0.084	0.154	0.92 (0.68-1.24)
Stratified by parity			

+ Risk ratio compares 1975 to 1955.

++ Risk ratio compares a mother 30 years old to one 20 years old.

Table 12

Average Blood Lead Values for Wives
by Blood Lead Category of their Husbands
at the Time of the Study

	Husband's Blood Lead Catgory*			
	≤ 25	26-40	41-60	>60
Wives' Blood Lead Value:				
Mean	11.83	13.73	15.00	16.00
95 percent CI	(10.98,12.68)	(12.53,14.94)	(13.70,16.30)	(11.36,20.64)
Number of Observations	23	49	47	6

* in µg lead/dl blood

Table 13

Age- and Time-Specific Early Fetal Loss Rates

Maternal Age	Before 1960	1960 and Later
All pregnancies in study:		
15-19	0.053	0.105
20-24	0.110	0.112
24-29	0.116	0.119
30 and above	0.152	0.234
After excluding pregnancies for women with 3 or more consecutive fetal losses:		
15-19	0.053	0.057
20-24	0.082	0.061
24-29	0.104	0.084
30 and above	0.152	0.200