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Paternal Exposure to Carbon Disulfide and Spouse's Pregnancy Experience

Sherry G. Selevan
Richard Hornung
John Fajen
Charlotte Cottrill

Department of Health and Human Services
Centers for Disease Control
National Institute for Occupational Safety and Health
Division of Surveillance, Hazard Evaluations and Field Studies
Cincinnati, Ohio

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ABSTRACT

The relationship between paternal exposures to carbon disulfide (CS_2) and pregnancy experience was studied in a population of 540 workers and their wives (236 exposed and 304 unexposed). Patterns of fetal loss and births and of time between live births were examined by comparing pregnancies conceived after paternal exposure to CS_2 to pregnancies occurring in an unexposed population. Exposure was analysed in several ways: (1) preliminary comparisons considered the presense or absense of exposure, (2) CS_2 exposure was considered as a continuous variable to examine possible dose-response relationships, and (3) exposure levels were categorized without a ranking of exposure and allowed comparison of outcomes in each exposure category directly with the outcomes in the unexposed group. Odds ratios (OR) for the effect of exposure on fetal loss calculated from logistic regression analyses were significantly less than one for all exposure models (ORs ranging from 0.06 to 0.70 for the three models). These analyses, however, had odds ratios statistically significantly greater than one (ranging from 1.14 to 1.18) for length of exposure to CS_2 (as estimated by time since first employment). The frequency of births, in three categories for exposure at conception (none, $\leq$ 5 ppm or > 5 ppm) were

compared to those expected based on person-years accumulated in each category (Standardized Fertility Ratio analysis - SFR). Although there were fewer births per person-years for the exposed populations, these deficits were not significantly different then those observed in the unexposed population. The spacing of live births (or birth interval) was examined with a Cox proportional hazards regression method for incomplete survival data. Differences in exposed and unexposed intervals were minor and non-significant. Overall, the combination of these analyses do not suggest an effect of CS_2 on these outcomes at the level of exposures found in this study (mean CS_2 exposure: 8.1 ppm; current OSHA standard: 20 ppm; recommended standards: NIOSH = 1 ppm, ACGIH = 10 ppm).

INTRODUCTION

Reports from the United States, the Soviet Union, Rumania, and Italy, suggest that carbon disulfide (CS_2) has toxic effects on reproductive function in exposed men. Early reports, by Ranelletti in 1931 (as reported by Hamilton, 1940), and by the Department of Labor and Industry in Pennsylvania (Braceland, 1938) reported sexual dysfunction, loss of libido and impotence. Later, clinical observations of male workers with carbon disulfide intoxication in Italy mention that 17 of these 100 workers volunteered information on sexual dysfunction, the severity of which coincided with the severity of patient's overall symptoms (Vigliani, 1956). No comparison data for unexposed workers were presented.

Rumanian researchers (Lancranjan et al., 1969) analyzed semen of 31 men with chronic CS_2 poisoning and of an equal number of unexposed men. The length of exposure in those with CS_2 poisoning ranged from 7 to 42 months with average exposures of 40-80 mg/m^3 CS_2 (13-26 ppm) with peak exposures up to 780 mg/m^3 CS_2 (252 ppm). Twenty-five percent of the exposed workers had some form of "spermatogenesis troubles": asthenospermia (reduced motility - 18 exposed versus 3 unexposed), oligospermia (decreased count - 11 versus 3), and teratospermia (abnormal morphology - 25 versus 4). All of these differences were statistically significant ($p < 0.001$). Later research by Lancranjan (1972) had similar findings. Both human and animal data suggest that these kinds of changes in sperm are associated with reduced fertility (Amelar, 1966; Freund and Peterson, 1976) and early fetal loss (Joel, 1966).

In the research by Lancranjan et al., 78 exposed workers also reported changes in sexual function: impairments of libido (66 percent), erection (51 percent), ejaculation (24 percent), and orgasm (15 percent).

Recent research by Hemminki and Niemi (1982) found an excess in spontaneous abortions in the spouses of male viscoes rayon workers when compared to wives of all male industrial workers (a rate of 14.9 versus 8.8, $p < 0.1$) in the community of Valkeakoski, Finland. The excess increased when the data were restricted to those with one spontaneous abortion in the four year study period, to 14.9 for the wives of viscose rayon workers versus 7.6 for the wives of all industrial workers ($p < 0.05$).

On the basis of the above information, CS_2 was chosen for further examination with a reproductive history study of spouses of male workers. CS_2 has many industrial uses: to xanthate cellulose in the production of viscose rayon and cellophane; as a solvent for rubber, waxes, gums and resins; and as an insecticide (Hamilton and Hardy, 1974). However, for many of these uses, a large number of concommitant, potentially toxic, exposures are found. The viscose rayon industry was selected for study because of the limited number of substances used in the processes, and the absence of other known/potential workplace hazards to reproduction.

MATERIALS AND METHODS

Plant Description

This Tennessee company started production of rayon filament in 1948 and rayon staple in 1956 (the rayon filament production terminated in 1974). Other products, nylon and polyester, are also made at this facility. The nylon filament plant began operations in 1963, the polyester filament in 1966, and the nylon polyester staple plant in 1967.

Viscose rayon is produced by soaking sheets of wood pulp (cellulose) in a sodium hydroxide solution to form alkali cellulose. Then the excess alkali solution is removed and the alkali cellulose is shredded (into "crumb") and aged in closed containers to allow the oxygen in the air to depolymerize the cellulose. After aging, the crumb is reacted with CS_2 to form a soluble sodium zanthate derivative, which is then dissolved in a sodium hydroxide solution. The viscous solution is filtered to remove impurities and undissolved cellulose. Air is removed from the viscose and it is allowed to "ripen". The viscose is extruded into a spin bath containing sulfuric acid, sodium sulfate and surfactants which coagulates the material. This is done through spinnerets, removable devices which contain 10-10,000 holes, allowing fibers of various sizes to be made. The fibers may remain as they are (termed "filament") or cut into uniform length ("staple"). Then, the product is washed and treated to obtain the final characteristics desired. The exposures were highest in the spinning and washing areas (Fajen, 1982; Fajen et al., 1981; Jones and Selevan, 1977).

In the nylon and polyester plants, workers were potentially exposed to caprolactan, dimethylterephtalate, ethylene gylcol, methanol and Dowtherm (Fajen, 1982).

Population Description

Workers were identified by the records of all current employees supplied by the company in April, 1978. The entire plant site had a total workforce of 3397 (April, 1978); aproximately 1650 of them were production workers and most of the production employees were male. The final population consisted of exposed and unexposed male hourly employees, first employed 1950 or later, with a minimum employment of one year, and still employed at the time of the survey. Of the male production workers with at least one year's employment, 271 were in the viscose rayon staple area and were still employed there at the time of the survey. In the other production areas of the plant, 385 male workers had been employed at least one year and had never been employed in the viscose rayon plant or employed in plant-wide maintenance. Since the rayon staple plant opened before the polyester and nylon filament plants, the rayon staple plant workers were somewhat older than those in other areas.

All workers were considered married, the last qualifying criterion for inclusion in the study population, until the survey team determined otherwise. Of the population identified for study, 540 (236 exposed, 304 not exposed) were finally considered eligible for the study when it was determined that they were married. Data on pregnancies and health and demographic characteristics were obtained from the wives of workers by telephone interviews using a standardized questionnaire (NIOSH, 1979).

Exposure Data

CS_2 exposure of the father prior to each pregnancy was estimated using company employment and industrial hygiene records. The company performed area air samples for CS_2 from the opening of the rayon filament plant (from 1948 until it was closed in 1974) and the opening of the rayon staple plant (from 1957 to the present). The area samples were systematically collected in areas of perceived high exposure, using the colorimetric method of analysis. The area samples cannot be directly related to an individual's exposure. Therefore, an annual exposure index was developed by the NIOSH industrial hygienist using correction factors developed between area and personal levels measured during the 1979 NIOSH survey (Fajen, 1982). The date of conception was estimated for each pregnancy using the wife's interview data on date of the end of the pregnancy and length of gestation. The CS_2 level associated with each pregnancy was estimated using the work histories of the father for the four months prior to the estimated date of conception; this allowed time for expression of effects in sperm (Manson and Simons, 1979).

The comparison population may have had minimal exposure to CS_2 since the cafeteria used by all employees was adjacent to the building in which viscose rayon was produced. Industrail hygiene measurements in the other plants and the cafeteria estimated the levels of CS_2 at 0.2 ppm. However, for the purposes of this study, they were considered unexposed to CS_2. The exposure of the comparison group to other chemicals was minimal, with the levels always well under existing OSHA standards, and levels recommended by NIOSH and ACGIH (Table 1).

Exposure Models

Three exposure models were used in the regression models described in the next section: in preliminary analyses, the outcomes were classified as exposed or not exposed. In more detailed analyses, the exposed pregnancies were examined by estimated exposure levels and by broad exposure categories ($\leq$ 5ppm and > 5ppm). The specific, continuous exposure levels assume an increasing or decreasing dose-response relationship. This assumption may not hold due to a shift in outcomes observed with different exposure levels. For example, very high exposures might result in infertility while lower ones might result in excess fetal loss. Therefore, to examine this possibility, the broad exposure categories were also used: two dummy variables described three exposure levels so that a dose-response relationship was not imposed on the analysis. In the comparison population, pregnancies occurring both before and during employment were included due to the time lag between the opening of the different parts of the facility. Unexposed areas opened later, and relatively small numbers of pregnancies occurred during employment in those areas.

RESULTS

Response Rate

A total of 477 wives completed interviews resulting in an 88.6 percent response rate. The response rate for the exposed population was 90.7 percent, and for the comparison population, 86.5 percent. The husbands of the respondents and non-respondents within each exposure category did not differ in regard to the number of years employed at the company, but exposed respondents were younger than exposed non-respondents (Table 2).

Population Characteristics

A total of 546 pregnancies were available for analysis after restricting the population to white respondents (due to the small proportion of non-whites: 4.5 percent), to single births, to pregnancies occurring within the current marriage, and to the time period between 1950 and 1978. Tables 3 and 4 describe the characteristics of the restricted study population and the pregnancies.

Exposure-specific description of the pregnancies are found in Table 5. Most of the exposed pregnancies (94 percent) had levels of CS_2 exposure less than the current OSHA (Occupational Safety and Health Administration) standard of 20 ppm, many (73 percent) were less than the ACGIH (American Congress of Government Industrial Hygienists) level of 10 ppm; only 22 percent were less than the NIOSH recommended level of 1 ppm.

The analysis consisted of three parts: logistic regression analysis of fetal loss, calculation of standardized fertility ratios (SFR) based on live births and person-years of observation in each exposure grouping, and Cox regression/survival analysis method applied to time intervals between live births. For clarity, the description of each specific analysis and its results are reported together.

Fetal Loss

Analysis

Many factors have been associated with increased fetal loss: maternal age, prior fetal loss, spacing of pregnancies, pregnancy order, cigarette smoking, alcohol consumption, socio-economic status, maternal health conditions, and medications (Leridon, 1977; Kline et al., 1977; Kline et al., 1980; Stein et al., 1980). The breakdown for these factors in this population is given in Table 4. Logistic regression (Bishop et al., 1975) allowed simultaneous control of several potential risk factors, effect modifiers and confounders. Evaluation of these factors followed procedures described by Kleinbaum et al. (1982). The initial stage of model building in multiple logistic regression, fitted by maximum likelihood estimation (Proc Logist, SAS, 1980) included CS_2 exposure and the explanatory variables described in Table 4. Exposure, maternal age, and the calendar year of the pregnancy were included in each model. The potential for chronic effects of CS_2 was estimated by a variable measuring the length of time from first occupational exposure to CS_2 to the time of the outcome. The year of the pregnancy allows examination of secular trends or, perhaps, differences in recall over time, and in the presence of maternal age, also incorporates maternal birth-cohort. Completion of high school was included as a surrogate for socio-economic status. Paternal age was also included in this phase of model building. After the interactions between these explanatory variables and the individual contribution of the variables were tested for inclusion in the model ($p \leq 0.1$), other factors (including maternal health conditions, illness and injury during pregnancy, and maternal employment during pregnancy) were considered for inclusion in the model. This two-step sequence was used because of the large number of variables to consider in a relatively small population. Odds ratios (OR) and 95 percent confidence intervals (CI) were calculated using the coefficients and their standard errors; all of these were obtained from the logistic regression analysis, which compared each CS_2 level group to the comparison populations' experience (Kleinbaum et al., 1982). Goodness-of-fit was tested using the test described by Hosmer and Lemeshow (1980).

The probability of fetal loss is greater for those women with prior fetal loss (Warburton and Frazer, 1964); this means that pregnancies within a family cannot be considered independent events. Therefore, inclusion of individual pregnancies from the same family in the analysis as independent observations violates the assumptions of many statistical tests (Kissling, 1981). The use of non-independent events artifically inflates the true size of the sample since each event contributes less information than does an independent event. The non-independent events may, to varying degrees depending on the individual study populations, artificially inflate the significance level. Therefore, the fetal loss data were examined in different ways in an attempt to generate a range of the risk associated with exposure. The analyses of fetal loss were initially done on all 546 pregnancies. Subsequent analyses excluded all pregnancies to those women meeting the definition of "habitual aborters" (three or more consecutive fetal losses - Pritchard, 1976). Three women and 13 pregnancies fell into this category. This probably did not eliminate the problems associated with non-independent events, but should have reduced the problem. An analysis using only one pregnancy from each woman would deal with the problem of non-independent events; unfortunately then numbers then become rather small (102 exposed pregnancies and 188 unexposed pregnancies).

Results

Results for the three methods of examining exposure are found in Tables 6-8. All three analyses had odds ratios (ORs) for exposure at the time of conception significantly less than one (ORs from 0.06 to 0.70). However, all three had odds ratios for length of employment with exposure to CS_2 (as estimated by time since first employment) significantly greater than one (ORs from 1.14 to 1.18). Analyses excluding those women considered "habitual aborters" had similar patterns, as did analyses using only one, randomly selected pregnancy from each woman.

Power calculations, based on stratified analyses, found that this population had 97∆ power to detect a doubling in fetal loss.

Standardized Fertility Ratios (SFR's)

The standardized fertility ratio (SFR) is the ratio of the number of live births observed in each CS_2 group to those expected if these groups experienced the same fertility patterns as the total U.S. population of white women.

$$SFR = \frac{\text{observed births}}{\text{expected births}} \times 100$$

Confidence intervals for the ratio of the true mean of the observed number of births to the number expected from the standard rates (SFR) were calculated using formulae for confidence intervals for standardized mortality ratios (Rothman and Boice, 1979).

The unexposed group could not be used as the standard for this comparison because the relatively small numbers observed in that group resulted in unstable estimates of the age- and calendar-specific birth rates. The analysis was similar to those suggested by others (Wong et al., 1979; Levine et al., 1980, 1981) and to standardized mortality ratio analyses (SMR's) which are frequently used in studies of occupational populations. In general, birth rates change with marital status, age, race, parity, and calendar time. United States rates are only available for marital status, age, race, and calendar time or for age, race, calendar time, and parity; no rates are available which cover all five factors. For this analysis, two sets of comparison rates were used: 1. five year calendar- and five year age-specific rates for married white women, and 2.

parity, five year calendar- and five year age-specific probabilities for all white women (NCHS, 1978). The period of observation for each couple began after the year of marriage and the beginning of the study period (1950), and ended at the end of reproductive capacity (surgical or natural menopause), at age 45 or the end of the study period (1978), whichever occurred first (Figure 1). All live births were examined in the first analysis. In the second analysis, where the comparison data are parity specific rates for all women, the first live birth and the time before it were excluded. Since a larger proportion of nulliparous women are unmarried than are those for higher parities, the exclusion of the first live birth would tend to increase the comparability of the United States parity-specific data for all women to those in this population in terms of marital status.

Length of observation (person-years) for each exposure category was determined by assigning each 3-month period an exposure level based on the husband's work history and departmental CS_2 levels. These five-year age- and calendar-specific person-years were tallied, and the expected number of births was calculated by multiplying the person-years with the appropriate United States rates.

Results

The results from the two analyses, restricted to whites, adjusted for age, calendar time, and marital status (Table 9) or parity (Table 10) showed statistically significant decreases in the number of live births for all groups when compared to U.S. rates. Parity-specific data for married women were not available to consolidate these two analyses into one. The X^2_{trend} which evaluates the data for a dose-response relationship for the total SFRs were not statistically significant.

The power for the total SFRs was approximately 90Δ or greater to detect a twenty-five percent deficit. The power for the each stratum was much lower, depending on the number of birth expected.

Birth Interval Analysis

Analysis

Analysis of spacing of live births (survival analysis of the time period between live births) has been suggested for studies of occupational exposure and pregnancy outcome (Dobbins, et al., 1978). Parity-specific examinations are more appropriate because the births within a family are non-independent events and because the spacing between births increases with parity (up to a final family size of eight) (Leridon, 1977). This analysis was stratified by parity, and 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 higher parities. The stratification by parity means that this variable does not appear in the model, and also prevents problems with lack of independence between observations, since only one observation for each mother could appear in each stratum. The analysis used a Cox proportional hazards regression method for incomplete survival data

(BMDP2L, BMDP, 1981) which allowed the observation period to end for reasons other than the outcome of interest, which allows incomplete (or censored) survival data. In this study, the observation period covered the 60 months following the index (current) birth since most second and higher order births to white women (80 percent in 1970; NCHS, 1975) occur within 60 months of the preceeding birth. The observation period ended if, during the 60 month period, the woman had surgical menopause, or the end of the study occurred. This particular type of regression allowed explanatory variables to change over time; in this population, the CS_2 exposure category was allowed to change during the period of observation. Three analyses were done, using one of the following methods to classify exposure: 1) the entire time period classified as "exposed" or "not exposed"; 2) the natural log-transformed exposure levels determined for each of the sixty months; and 3) the category of exposure (none, $\leq$ 5ppm, > 5ppm) for each of the sixty months. As described before, the exposure was lagged by four months to allow for the effects of the exposure to be express in the semen. Maternal age, prior fetal loss, high school education, contraception and maternal employment outside the home were considered for use in the model. The interview data included contraceptive histories for the twelve months preceding conception; this surrogate measure was assumed to represent contraceptive use since lifetime contraceptive histories had not been obtained. If no subsequent birth was reported, the response concerning birth control for the birth under study was used.

Results

The final Cox regression model of the spacing of the live births (survival of the time period between live births) was stratified by parity and included maternal age, year of the index birth, employment of the mother during the time interval, contraception patterns, and the exposure variables (exposure at the time of the index birth and length of time since first exposure). The time since first exposure and data on contraceptive use did not improve the model and were therefore removed. Negative coefficients. which result in risk ratios less than 1, for an explanatory variable suggested that an increase in its value was associated with a greater time period between live births. The risk ratio describes the relative risk of experiencing a live birth within the five year follow-up period. The results, presented in Tables 11-13, demonstrate a non-significant increase in the time period between births, with the single exception occurring in the low exposure group in the categoric exposure analysis (Table 13).

DISCUSSION

Reproductive events in the wives of workers exposed to CS_2 were compared to reproductive events in wives of unexposed workers. These analyses demonstrated a deficit of fetal loss with increasing exposure immediately preceeding conceptions, but an increase with increasing time since first employment in the exposed areas (Tables 6-8). Only minimal, non-significant differences were found between the two groups for the interval between live births (Tables 11-13). A slight decreasing trend ($p = 0.09$) was observed for standardized fertility ratios in the first analysis including all live births and using rates for ever married women (Table 9). This trend disappeared when a parity specific analysis (using comparison rates for all women) was done (Table 10).

A major factor in the examination of these results is the accuracy of the assignment of exposure status. The measurement and assignment of exposure levels is a possible source of error resulting in misclassification of events studied. Using the consistently collected exposure data available was useful since the relative levels of CS_2 are approximated; however, the colorimetric method is not as accurate as the newer method using charcoal tubes. There are errors inherent in the measurements and in the assumptions made, especially those relating area samples to individual's exposures. All these factors affected the accuracy of the level assigned to the outcome studied; but the consistency of method suggests that relative differences are representative of the true differences.

Fetal loss

The most puzzling findings occur in the examination of fetal loss: there is a deficit in fetal loss with increasing exposure at the time of conception, but an excess in fetal loss with increasing time since first exposure. These findings could be interpreted in several ways: One unlikely interpretation of these results could be that the immediate exposure actually has a benefical effect, but chronic exposure could be hazardous. It is more likely, however, that there are inherent differences in these populations which may partially account for the statistical results observed. First, crude fetal loss rates and rates directly adjusted for gravidity and maternal age were calculated for both the exposed and unexposed groups, before and after employment, to allow a rough examination of fetal loss. The crude rates before and after first employment at the company and within each group, the exposed and the comparison groups, were almost identical (Table 14). Only small increases in the adjusted fetal loss rates were observed in both groups after employment. These data do suggest an inherent difference in the populations, either an actual biologic one, or one in recall. Birth certificate data were used to examine the recall of pregnancies. Birth certificates were obtained for all births to a randomly selected sample of 100 women in the exposed group and 100 women in the comparison group. Data recorded on the last birth certificate on the number of live births and fetal losses were compared to the women's reports up to that time. In the comparison of the data available, only minor and very infrequent differences were observed. Unfortunately, three of the five versions of the birth certificate covered in this study, used during the

1950-1967 time period, did not obtain information on early fetal losses (less than 20 weeks gestation). Early fetal loses are the majority of the total fetal losses under examination.

A comparison of both the crude and adjusted rates for high and low carbon disulfide levels in the exposed population, shows a lower rate of fetal loss in the more highly exposed pregnancies (Table 14). This is consistent with the findings in the logistic regression analysis. It is possible that the timing of the occurrence of fetal loss is changing with exposure. Increasing exposure could be associated with a greater effect (in this case, on the sperm) and might result in fetal loss occurring earlier in gestation (Wilson, 1973) and, potentially, unrecognized or forgotten if a long time period occurred between the event and interview (Yerushalmy et al., 1956).

The excess risk for fetal loss with increasing length of exposure was examined further by comparing the two types of exposure measure. In some occupations, the heaviest exposures occur to those workers with the least seniority. Within the 170 exposed pregnancies, the model dependent correlation of the number years since first employment and the log of the exposure level at conception is $r = -0.215$; for all pregnancies, it is higher ($r = -0.774$). This suggests that there are generally higher exposure levels associated with pregnancies occurring earlier in employment.

Other research has found an association of smoking and alcohol consumption to the occurrence of fetal loss. These exposures were not found to be statistically significant factors in explaining the patterns of fetal loss. This lack of consistency with other research generates some concern that the population may not be representative or that some recall problems may be occurring.

Fertility Analyses

The examination of data on live births only in the SFR and birth interval analyses help avoid the problem of biased recall of the events and the dates they occurred, as validation of interview data in another occupational study it was found, not surprisingly, that recall was better for live births (Selevan, 1980).

Standardized Fertility Ratio Analysis

The standardized fertility ratio (SFR) was examined in two ways (Tables 9 and 10): The first analysis examined all pregnancies as compared to the U.S. rates for married women in specific age, race and calendar time periods. Parity specific rates are not available for married women, so the second analysis also adjusted for parity in all women following their first live birth. This restriction reduced the number of observations, and consequently the power of the analysis. Nulliparous women are less likely than those of at least parity one to have ever been married. Thus their exclusion results in a better comparison group for the married women in this study. Unfortunately, the parity-specific SFR analysis could be misleading in this particular population. The exclusion of nulliparous women made the

U.S. data and the study data more comparable, but also excluded those couples who were never able to conceive. Thus potentially underestimating the any deficit.

The first analysis, for married women showed a moderate, but non-significant trend (X^2_{trend} = 2.847, P = 0.09) for a decreasing SFR with increasing exposure (Table 9). This analysis was repeated, using the pre-employment experience of the exposed workers for comparison. In that case, the pre-employment SFR was 108 (162 observed versus 149.6 expected) with a X^2_{trend} of 19.49 (P < 0.01). The second, parity-adjusted analysis (Table 10) did not have a statistically significant trend; when the pre-employment exposed population was examined, the SFR was 86 (76 observed versus 88.5 expected) with a X^2_{trend} of 3.97 (P = 0.05). If the two populations, the exposed group and the comparison group, are inherently different as suggested by the fetal loss rates, then the second comparison, using the pre-employment SFR data for the exposed group, would be more appropriate. It is possible that, for various social or demographic reasons, different reproductive patterns may occur before employment as compared to those during employment. To examine this, the comparison population was split into pre- and during employment groupings and the SFRs compared (Table 15). The summary all-women parity-specific SFR for the pre-employment group was 89, and 59 for the group during employment. The pre- and during employment patterns for the exposed populations were quite similar. While these results suggest that there is no effect on the SFR with exposure, they do raise concerns about the suitability of using pre-employment comparison populations. The observed differences, pre- and during employment may be due to a younger age at marriage for the study population, and consequently a younger age at which the family is completed, than for the U.S. from which rates are obtained. The distribution of age at marriage was examined for the study population and compared to Tennessee and U.S. figures (Table 16) for 1967, the median year of marriage of the study population. The breakdown for Tennessee was available only for all women, but a comparison of U.S. figures for all women and for white women suggest that the breakdown would be similar to the total for Tennessee white women. The Tennessee women married younger than did the U.S. women, and the women in the study population married younger than either. These data support the conjecture that some of the differences in the SFR may be a result of different age distributions of the person-years among groups, and the younger age at marriage (and probably the younger age at which the family was complete) for the study population than for the U.S. population to which it was compared.

Birth Interval Analysis

The birth interval analysis, while identifying such key factors as maternal age, employment, etc., found only very minor, non-significant changes with exposure (Tables 11-13).

Conclusions

The combination of these analysis do not suggest an effect of carbon disulfide at these levels on these outcomes. The majority of the exposures

(73 percent) were under the ACGIH recommended standard of 10 ppm CS_2 and almost all (94 percent) under the current OSHA standard of 20 ppm; only 22 percent were under the NIOSH recommended standard of 1 ppm.

Meyer (1981) studied the semen of the same population covered in this study and found no difference between the exposed and comparison populations. His study was limited by a relatvely low response rate (51 percent), by the small number in each exposure category, and examined current, and fairly low, exposure levels.

The findings for the analysis of fetal loss are interesting, and a prospective epidemiological study, with decreased probability of recall problems, or one of an appropriate animal species might resolve some of the questions raised. An SFR analysis, potentially with these data, which also examines age at marriage, might resolve the questions raised concerning the SFR results.

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Table 1

Exposure of the Comparison Population, 1979, and Standards Relating to Each

	Range ppm	Number of Samples	OSHA Standard ppm	NIOSH Recommended Standard ppm	ACGIH Recommended Standard ppm
Caprolactam (vapor)	< 0.14 - 3.93*	12	none	none	5
Ethylene glycol (vapor)	0.32 - 10.10 median = 1.22	8	none	none	50
Methanol	< 0.9 - < 0.9	5	200	200 800 ppm ceiling	200
Dowtherm (Phenyl-ether-biphenyl mixture)	< 0.01 - < 0.01	7	1	none	1
Dimethylterephthalate (DMT)	< 0.015 - < 0.015	11	none	none	none

*Only one sample was above "< 0.014"

Table 2

Age and Time Since First Employment for
Exposed and Comparison Groups by Response Status

	Exposed	Not Exposed
RESPONDENTS		
Number of Workers	214	263
Mean Time Since First Employment in Any Work Area (S.D.)	13.7 (7.5)	9.6 (4.0)
Mean of Workers Age (S.D.)	38.5 (10.0)	34.8 (8.6)
NON-RESPONDENTS		
Number of Workers	22	41
Mean Time Since First Employment in Any Work Area (S.D.)	12.0 (8.0)	12.2 (1.8)
Mean of Workers Age (S.D.)	43.8 (8.7)	34.8 (8.0)

Table 3

Characteristics of Final Study Population*

	Proportion with Characteristic	Mean	S.D.	Range
Mother's age** (March, 1979)		34.0	9.5	18-65
Father's age (March, 1979)		36.4	9.4	19-62
Mother's education (years completed)		11.0	2.0	1-19
Completed High School	59.8%			
Mother's Marital History				
Married once	84.8%			
Married two or more times	15.2%			
Median year of current Marriage		1967		1937-79
Number of Pregnancies (all marriages)		2.0	1.5	0-12
Proportion with no Pregnancies (all marriages)	13.5%			
Number of Pregnancies (current marriage)		1.8	1.5	0-12
Proportion with no Pregnancies (current marriage)	20.4%			

*446 respondent wives of white men employed 1950 and after.
**Mother's age calculated from interview data; father's age calculated from company personnel records.

Table 4

Proportion of Fetal Loss by Potential Risk Factors

Potential Risk Factor	Fetal Loss Number	Fetal Loss Percent	Live Birth Number	Live Birth Percent	Total
Mother's age category					
< 30	46	9.6	431	90.4	477
≥ 30	13	18.8	56	81.2	69
Father's age category					
< 30	42	9.9	382	90.1	424
≥ 30	17	13.9	105	86.1	122
Prior fetal loss					
one or more	12	16.2	62	83.8	74
none	47	10.0	425	90.0	472
Calendar time category					
before 1970	22	8.6	234	91.4	256
1970 and after	37	12.8	253	87.2	290
Gravidity					
1	25	12.0	184	88.0	209
2	12	7.1	156	92.9	168
3	9	9.8	83	90.2	92
≥ 4	13	16.9	64	83.1	77
High School Graduate					
yes	34	11.4	263	88.6	297
no	25	10.0	224	90.0	249
Smoked Cigarettes					
yes	32	11.3	251	88.7	283
no	27	10.3	236	89.7	263
Drank Alcohol					
yes	5	8.6	53	91.4	58
no	54	11.1	434	88.9	488
Time between Pregnancies					
< 6 months	10	18.9	43	81.1	53
> 6 months	49	9.9	444	90.1	293
CS_2 Exposure					
yes	11	6.5	159	93.5	170
no	48	12.8	328	87.2	376

Table 5

Characteristics of Pregnancies by Exposure

	Total	Comparison	Exposed	Breakdown for Exposed Group Low	High
Number of Livebirths	487	328	159	77	82
Number of Miscarriages	56	46	10	7	3
Number of Stillbirths	3	2	1	1	0
Total Pregnancies	546	376	170	85	85
Mean Exposure Level	-	-	8.1 ppm	1.9	14.3
Range	-	-	0.2-83.2	0.2-5.0	5.1-83.2
Mean Log of Exposure			1.356	0.259	2.453
Mean Age at Conception Mother (S.D.)	23.8 (5.0)	23.3 (4.8)	24.8 (5.3)	24.2 (4.7)	25.5 (5.7)
Father (S.D.)	26.3 (2.1)	25.8 (5.3)	27.4 (5.5)	26.4 (4.8)	28.5 (2.6)
Mean Parity of Mother (S.D.)	2.1 (1.4)	1.9 (1.2)	2.4 (1.6)	2.2 (1.2)	2.6 (1.9)
Timing of Pregnancies Percent Before 1970	46.9	48.1	44.1	49.4	38.8

Table 6

Logistic Regression for Fetal Loss
Exposure: Dichotomous (Any, None)

Variables in Model	Coefficient	Standard Error	P-Value	Odds Ratio	95 Percent Confidence Interval
Intercept	-5.013	1.620	< 0.01		
MAIN EFFECTS:					
Exposure to CS_2	-1.677	0.589	< 0.01	0.19	(0.06-0.59)
Years since first exposure to CS_2	0.134	0.066	0.04	1.14	(1.01-1.30)
Maternal age	0.323	0.302	0.28	1.38	(0.76-2.50)
Year of pregnancy	0.322	0.215	0.13	1.38	(0.91-2.10)
Time between pregnancies*	0.884	0.395	0.03	2.42	(1.12-5.25)
Goodness of fit: X^2_{8df} = 2.333		p = 0.969			

*$\leq$ 6 months, > 6 months

Table 7

Logistic Regression for Fetal Loss
Exposure: Log Transformation of Actual Level

Variables in Model	Coefficient	Standard Error	P-Value	Odds Ratio	95 Percent Confidence Interval
Intercept	-6.460	1.644	<< 0.01		
MAIN EFFECTS:					
Exposure to CS_2	-0.313	0.099	< 0.01	0.73	(0.60-0.89)
Years since first exposure to CS_2	0.162	0.067	0.02	1.18	(1.03-1.34)
Maternal age	0.311	0.303	0.30	1.37	(0.75-2.47)
Year of pregnancy	0.298	0.215	0.17	1.35	(0.88-2.05)
Time between pregnancies*	0.859	0.396	0.03	2.36	(1.09-5.13)
Goodness of fit: X^2_{8df} = 3.420		p = 0.905			

*$\leq$ 6 months, > 6 months

Table 8

Logistic Regression for Fetal Loss
Exposure: Categories of CS_2 - None, Low and High

Variables in Model	Coefficient	Standard Error	P-Value	Odds Ratio	95 Percent Confidence Interval
Intercept	-4.937	1.614	< 0.01		
MAIN EFFECTS:					
Exposure to CS_2					
Low	-1.354	0.612	0.03	0.26	(0.08-0.86)
High	-2.850	0.970	< 0.01	0.06	(0.01-0.39)
Years since first exposure to CS_2	0.169	0.072	0.02	1.18	(1.03-1.36)
Maternal age	0.340	0.304	0.26	1.41	(0.77-2.55)
Year of pregnancy	0.305	0.214	0.15	1.36	(0.89-2.06)
Time between pregnancies*	0.869	0.396	0.03	2.39	(1.10-5.18)

Goodness of fit: $X^2_{8df} = 4.375$ $p = 0.822$

*$\leq$ 6 months, > 6 months

Table 9

Standardized Fertility Ratio (SFR)
Adjusted for Age, Race, Marital Status and Calendar Time

Age	Comparison Population Obs.	Exp.	SFR	Low Exposure (.2-5ppm) Obs.	Exp.	SFR	High Exposure (>5ppm) Obs.	Exp.	SFR
15-19	78	111.9	70 (55- 87)*	14	21.3	66 (36-110)	8	14.2	56 (24-111)
20-24	126	185.7	68 (57- 81)	36	44.2	81 (57-113)	26	47.5	55 (36- 80)
25-29	92	106.6	86 (70-106)	15	33.2	45 (25- 75)	36	47.4	76 (53-105)
30-44	32	37.0	87 (59-122)	12	19.1	63 (30-110)	12	24.4	49 (25- 86)
Total+	328	441.2	74 (67- 83)	77	117.8	65 (52- 82)	82	133.5	61 (49- 76)
Adjusted++	328	328	100	77	90.3	85 (67-107)	82	105.0	78 (62- 97)

*95 percent confidence intervals

+$\chi^2_{\text{trend,1 df}}$ = 2.847 p = 0.09

++Adjusted to comparison population; weights were applied to all age-specific expected values to result in SFRs for the comparison population of 100.

Table 10

Standardized Fertility Ratio (SFR)
Adjusted for Age, Race, Parity and Calendar Time

Births and Person-years Restricted to
Those Occurring After the First Live Birth

Age	Comparison Population			Low Exposure (.2-5ppm)			High Exposure (> 5ppm)		
	Obs.	Exp.	SFR	Obs.	Exp.	SFR	Obs.	Exp.	SFR
15-19	16	25.3	63 (36-103)*	8	7.6	105 (45-207)	2	3.4	59 (7-212)
20-24	69	99.3	70 (54- 88)	21	27.2	77 (48-118)	17	33.9	50 (29- 80)
25-29	60	84.2	71 (54- 92)	11	26.8	41 (20- 73)	31	41.4	75 (51-106)
30-44	27	33.7	80 (53-117)	11	17.8	62 (31-111)	11	21.0	52 (26- 94)
Total+	172	242.5	71 (61- 82)	51	79.4	64 (48- 84)	61	99.7	61 (47- 79)
Adjusted++	172	172	100	51	59.0	86 (64-114)	61	75.7	81 (62-104)

*95 percent confidence intervals

+$\chi^2_{\text{trend},1\ df} = 2.847$ p = 0.09

++Adjusted to comparison population; weights were applied to all age-specific expected values to result in SFRs for the comparison population of 100.

Table 11

Examination of Interval Between Live Births Using A Dichotomous Exposure Variable

Variables in Model	Coefficient	Standard Error	Risk Ratio*	95 Percent Confidence Interval
Exposure to CS_2 (Dichotomous: any or none)	-0.062	0.184	0.94	(0.65-1.34)
Maternal age	-0.091	0.024	0.91	(0.87-0.96)
Year of index birth	-0.034	0.013	0.97	(0.94-0.99)
Employment during interval	-0.779	0.171	0.46	(0.33-0.64)
Fetal loss during interval	-0.859	0.511	0.42	(0.15-1.15)
Stratified by Parity				

*The risk ratio is the mean relative risk of experiencing a birth within five years of the preceeding birth; negative coefficients (resulting in risk ratios less than one) are related to a longer interval between births.

Table 12

Examination of Interval Between Live Births
Exposure: Log Transformation of Actual Level

Variables in Model	Coefficient	Standard Error	Risk Ratio*	95 Percent Confidence Interval
Exposure to CS_2	-0.020	0.022	0.98	(0.94-1.02)
Maternal age	-0.089	0.024	0.91	(0.87-0.96)
Year of index birth	-0.035	0.013	0.97	(0.94-0.99)
Employment during interval	-0.780	0.171	0.46	(0.33-0.64)
Fetal loss during interval	-0.877	0.511	0.42	(0.15-1.13)
Stratified by Parity				

*The risk ratio is the mean relative risk of experiencing a birth within five years of the preceeding birth; negative coefficients (resulting in risk ratios less than one) are related to a longer interval between births.

Table 13

Examination of Interval Between Live Births
Exposure: Categories of CS_2 - None, Low and High

Variables in Model	Coefficient	Standard Error	Risk Ratio*	95 Percent Confidence Interval
Exposure to CS_2				
Low	0.151	0.231	1.16	(0.74-1.83)
High	-0.368	0.254	0.69	(0.42-1.14)
Maternal age	-0.085	0.024	0.92	(0.88-0.96)
Year of index birth	-0.036	0.013	0.96	(0.94-0.99)
Employment during interval	-0.782	0.171	0.46	(0.33-0.64)
Fetal loss during interval	-0.871	0.511	0.42	(0.15-1.14)
Stratified by Parity				

*The risk ratio is the mean relative risk of experiencing a birth within five years of the preceeding birth; negative coefficients (resulting in risk ratios less than one) are related to a longer interval between births.

Table 14

Proportion with Fetal Loss

	Before Employment (Percent)		After Employment (Percent)	
	Crude	Adjusted*	Crude	Adjusted
Comparison Population	12.1	11.2	13.1	14.6
Total Exposed Population	6.4	5.3	6.3	6.4
Low Exposure Group (≤ 5 ppm)	---	---	8.9	12.8
High Exposure Group (> 5 ppm)	---	---	3.5	6.4

*Direct adjustment for maternal age in five year categories, and parity (1,2,3 and 4 or greater) using the age and parity distribution of the entire group.

Table 15

Comparison of Parity-Specific SFR's in the Exposed and Comparison Populations Before and After First Employment

	Comparison Population			Exposed Population		
	Obs.	Exp.	SFR	Obs.	Exp.	SFR
Before Employment	83	92.8	89 (71-111)	76	88.5	86 (68-107)
Person-years:						
number		523.25			488.25	
mean age		26.5			26.1	
mean parity		3.35			3.24	
After Employment	89	149.8	59 (48-73)	112	179.0	63 (52-75)
Person-years:						
number		1207.25			1600.5	
mean age		28.2			30.1	
mean parity		2.86			3.27	

Table 16

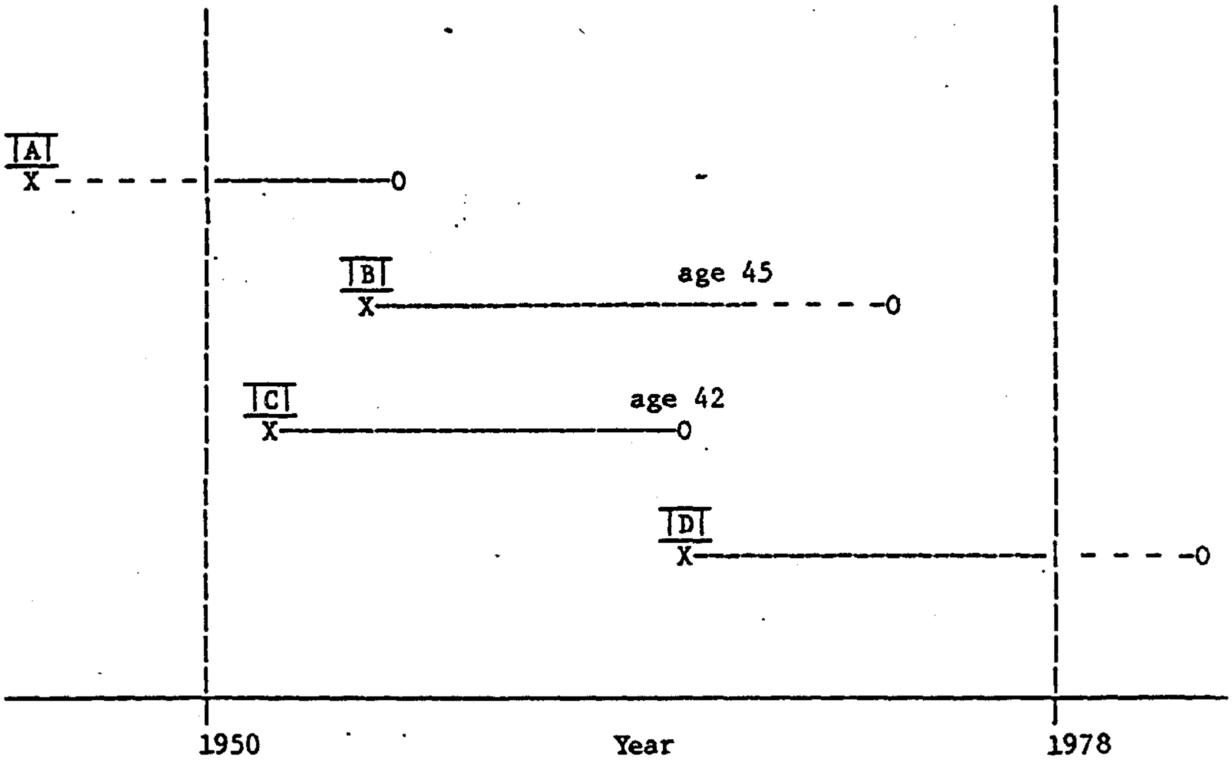
Comparison of Age at Marriage for Study Population, and State and U.S. Data*

Age of Bride	Final (white) Study Population Number	Percent	Total 1967 Tennessee Population Number	Percent	Total 1967 United States Population Number	Percent	White 1967 United States Population Number	Percent
18	90	20.0	6,680	17.7	139,197	10.3	83,126	10.9
18-19	151	33.6	10,010	26.5	346,278	25.7	203,791	26.6
20-24	143	31.8	12,540	33.2	561,378	41.7	316,720	41.5
25-29	46	10.2	3,740	9.9	140,189	10.4	72,978	9.6
30-34	10	2.2	1,920	5.1	66,370	4.9	35,093	4.6
35-44	10	2.2	2,850	7.6	94,383	7.0	51,598	6.8
Total under 45	450	100.0	37,740	100.0	1,347,795	100.0	763,306	100.0

*Data from NCHS, 1970

Figure 1

Demonstration of the
Accumulation of Person-years for
the Standardized Fertility Ratio
Analysis for Four Representative Women



X = year of marriage
O = end of reproductive capacity (as represented by natural or surgical
Menopause)
— = person years-counted

Only person-years between 1950 and 1978 were counted for A and D, all person-years were counted for B, and only those before age 45 for C.