

Effects of Occupational Solvent Exposure on Reproductive Hormone Concentrations and Fecundability in Men

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Background Little is known about the effects of organic solvents on male reproductive health. To assess fertility and reproductive endocrine function in solvent-exposed men, we investigated time-to-pregnancy using a retrospective cohort design and cross-sectionally measured reproductive hormone concentrations in painters and millwrights compared to a reference group of carpenters.

Methods Detailed occupational, exposure, medical, and time-to-pregnancy histories were obtained by telephone interview. Plasma luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone concentrations were determined by immunoassay. Exposure indices, which summarized working life exposure to total solvents, chlorinated solvents, aromatic solvents, and thinners, degreasers, varnishes, and adhesives as a category were calculated from exposure histories.

Results FSH concentrations increased significantly with increasing exposure indices for all solvents and for chlorinated solvents. There were no significant associations of solvent exposure indices with LH or testosterone levels. LH, FSH, and testosterone concentrations also did not differ by job title. Using Cox regression, time-to-pregnancy was non-significantly longer in the painters and millwrights than the carpenters. There was no significant association between time-to-pregnancy and any of the solvent exposure indices; however, it should be noted that some of the pregnancies occurred more than 20 years previously, potentially reducing the reliability of the retrospectively collected pregnancy and exposure data.

Conclusions The significant associations between FSH levels and solvent exposure indices suggest the potential for adverse effects of solvent exposures on reproductive function in men. *Am. J. Ind. Med.* 46:614–626, 2004. © 2004 Wiley-Liss, Inc.

KEY WORDS: solvents; gonadotropins; follicle stimulating hormone; luteinizing hormone; testosterone; fertility; fecundability; time-to-pregnancy

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INTRODUCTION

Several epidemiologic studies have suggested that solvents adversely affect male and female reproductive function. Elevated odds ratios for spontaneous abortion have been reported in women with occupational solvent exposure [Pastides et al., 1988; Taskinen et al., 1989; Lindbohm et al., 1990; Windham et al., 1991], and one study found increased spontaneous abortion rates in wives of men exposed occupationally to solvents [Taskinen et al., 1989]. There is inconclusive evidence for relations between exposure to solvents and male fertility based on findings from studies of painting occupations and diagnosed infertility [IARC, 1989]. Fecundability or time-to-pregnancy, an indicator of the overall fertility of a couple, has been recognized as a more sensitive measure of effects of exposures on fertility than rates of diagnosis of infertility [Baird et al., 1986]. In women, longer time-to-pregnancy was associated with exposure to organic solvents [Sallmén et al., 1995]. Time-to-pregnancy was also lengthened in primigravida wives of men occupationally exposed to solvents, but was not lengthened in multigravida wives [Sallmén et al., 1998] or in the wives of printing workers exposed to toluene [Plenge-Bönig and Karmaus, 1998].

Physiologic indicators of male reproductive function have been investigated in relation to solvent exposure in several studies. Exposure to aromatic solvents, glycol ethers, styrene, and 2-bromopropane has been associated with reduced semen quality [Welch et al., 1988; Ratcliffe et al., 1989; Kim et al., 1996; Kolstad et al., 1999; Tielemans et al., 1999; De Celis et al., 2000]. Altered plasma levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and/or testosterone have been reported in men occupationally exposed to toluene [Mørck et al., 1988; Svensson et al., 1992a,b], 2-bromopropane [Kim et al., 1996], and trichloroethylene [Chia et al., 1997; Goh et al., 1998].

The goals of the current study were to test the hypothesis that occupational exposure to solvents in the painting profession alters gonadotropin secretion and to test the hypothesis that this exposure also reduces fertility, which may be a consequence of altered gonadotropin secretion.

MATERIALS AND METHODS

Subjects

Study subjects were recruited from among all active members of locals of the International Brotherhood of Painters and Allied Trades (two locals) and the United Brotherhood of Carpenters and Joiners (three locals), most of whom were employees at a large Department of Energy facility in eastern Washington, the Hanford Reservation.

Union locals sent study information packets and return-addressed postcards directly to their membership. The number of letters sent out by the unions is unknown, but the approximate number of active members of the five locals at the time of the study was 624. In addition to using recruitment letters, we used direct recruiting methods by attending union meetings and conducting information sessions to describe the study and providing sign-up sheets. A total of 263 potential participants returned the recruitment letters and/or signed up at the information sessions, or told their safety officers that they were interested.

Participation Rates

Of the 263 names obtained during recruitment, 37 indicated on the return letter that they were not interested in participating. The study coordinator called the remaining 226 to describe the study, answer any questions regarding the study, determine interest in participation, and to conduct the eligibility survey (see below for detailed description of eligibility survey). Eight people refused to participate once reached by phone. The refusal rate as indicated by letter and phone was 17.1%. Nine telephone numbers were disconnected and no further information was available either from directory assistance or from the unions. The remaining telephone numbers were correct; however, 29 people were unreachable over the 1 year calling period, despite the coordinator's calling at least once every 2 weeks, leaving messages, and talking to family members. This left 180 people contacted by phone and willing to participate in the study, 68.4% of the initial name pool and approximately 29% of the active members of the locals.

Eligibility

Males and females 21–75 years of age with at least 5 years of employment as a painter or millwright (there was no employment time requirement for carpenters), were eligible. Participants needed to be actively working and to have no confounding alcohol-related, viral, or metabolic risk factors for chronic hepatic injury. Because the parent study was monitoring changes in hepatic function, the occupational and medical history questionnaire was designed specifically to assess hepatic injury risk factors or exposures, such as alcohol use. Those people with a current or former ethanol consumption >75 g/day or history of alcohol abuse on the CAGE [Cutler et al., 1988] questionnaire were excluded, primarily to avoid potential confounding from changes in the liver not associated with occupational exposures. Those with a weight of greater than 150% ideal body weight were excluded for the same reason [Anonymous, 1995; Harrison et al., 2002]. Subjects were also excluded for conditions associated with reduced fertility thought to be unrelated to solvent exposure (mumps orchitis,

varicocele, endometriosis, pelvic inflammatory disease, polycystic ovarian disease).

Of the 180 potential participants, 9 (5%) did not meet the age criteria, 7 (3.9%) were retired, 10 (5.5%) no longer lived in the study area, 23 (12.8%) had unfavorable alcohol histories, 18 (10%) had unfavorable medical histories, and 11 (6.1%) were enrolled into the study, but failed to complete it. Of those with unfavorable medical histories, none was excluded for having greater than 150% ideal body weight. This resulted in a total of 102 participants or 56.7% of the potential participants, 38.8% of the contact names obtained during recruitment, and about 16% of the active members of the locals. Of these, only four eligible women were recruited. Therefore, the analyses of reproductive function were limited to the 98 men who participated in the study. Of these, 32 were painters, 25 were millwrights, and 41 were carpenters. Of the 41 carpenters, 1 did not complete an interview, resulting in a final study population of 97 (32 painters, 25 millwrights, 40 carpenters).

Detailed employment, exposure, medical, and time-to-pregnancy histories were obtained by structured telephone interview by the study coordinator. Each subject also underwent phlebotomy at Kadlec Medical Center in Richland, WA. One aliquot of blood was centrifuged, serum was separated, and serum was stored at -20°C until reproductive hormone assays were performed. Another aliquot of whole blood was stored at -20°C until assay for lead.

The study protocol was approved by the Institutional Review Board of the University of Washington.

Subject Interviews

Time-to-pregnancy data were gathered using a modified version of a previously validated structured interview form for women [Baird et al., 1986]. Data were obtained about the dates and outcomes of all pregnancies fathered. Detailed information was also obtained on the most recent pregnancy, including number of months of uncontracepted intercourse before pregnancy, breastfeeding before that pregnancy, use of contraception before that pregnancy, and smoking of the female partner during that pregnancy.

The structured occupational history elicited information about job history, including job titles, number of years in each job, average hours per week and months per year in each job, and time spent in painting-related tasks in each job (supervision, preparation, painting indoors, painting outdoors, etc.). For each method of applying paint (spraying, brushing, rolling, other) the type, if any, of respiratory protection used was also characterized.

Additionally, data were gathered on neurological, respiratory, and mucous membrane irritation symptoms, medications, educational level achieved, marital status, age, ethnicity, tobacco use, and alcohol use.

All interviews were conducted by telephone between December 16 1998 and August 18 1999 by one of the authors

(A.B.). The interviews took approximately 45 min to complete.

Exposure Assessment

The structured exposure interview was designed for painters and was previously used to study the neurobehavioral effects of chronic occupational solvent exposure [Daniell et al., 1999]. The subjects were asked to estimate the number of years and number of times per week they worked with each of 71 substances, including various metals and solvents. These data were used to calculate solvent exposure indices for each subject, providing continuous exposure variables that were used in alternative analyses of the data. The exposure index for a given substance was calculated as the product of the number of years of use times the frequency weight. The frequency weight was 0.2 for one exposure per week, 0.4 for two per week, and so on up to 1.0 for five or greater exposures per week. A separate exposure index was calculated for each substance for the time-to-pregnancy analyses using exposure data for the calendar year in which the pregnancy of interest ended and the calendar year preceding the pregnancy. Exposure variables summarized the use of mixed solvents (thinners, degreasers, varnishes, and adhesives), chlorinated solvents (sum of exposure indices for 22 individual solvents), aromatic solvents (toluene, xylenes, and benzene), and total solvent use (aromatic solvents, chlorinated solvents, thinners, degreasers, adhesives, varnishes, plus miscellaneous other solvents). An exposure index for metals (lead, mercury, arsenic, beryllium, and copper) and individual exposure indices for each of the metals were not significantly related to job, time-to-pregnancy, or to LH, FSH, or testosterone concentrations in bivariate analyses. Therefore, these were not included in the models.

Lead Assay

Lead concentrations in whole blood were measured at the University of Washington Clinical Laboratory using graphite furnace absorption spectroscopy with Zeeman correction. The coefficients of variation were 8% at 18 $\mu\text{g}/\text{dl}$, and 5% at 34 and 50 $\mu\text{g}/\text{dl}$.

Hormone Assays

Plasma LH and FSH were measured using Wallac DELFIA time-resolved fluoroimmunoassays (Turku, Finland). These are solid-phase, two-site, sandwich fluoroimmunoassays, using two monoclonal antibodies (mouse anti-human) directed against two different antigenic determinants of the gonadotropin, one of which is labeled with europium. For LH the laboratory interassay coefficients of variation (CV) were 6.2%, 6.9%, and 14.2%, and the

intraassay CVs were 3.5%, 2.8%, and 7.2% for the high, medium, and low control samples. For FSH the interassay CVs were 3.2%, 4.1%, and 20.9%, and the intraassay CVs were 2.5%, 2.3%, and 12.9% for the high, medium, and low control samples, respectively. Plasma testosterone was measured by the Wallac DELFIA (Turku, Finland) solid phase fluoroimmunoassay that uses polyclonal anti-testosterone antibodies derived from rabbit. Intra- and inter-assay CVs were 5% and 10%, respectively. The technicians performing the assays were blinded to the exposure or job status of the subjects.

Statistical Analyses

Bivariate analyses were performed to determine which potentially confounding variables were associated at the $P < 0.2$ level with the exposure as estimated by job category. The variables identified in this way were tested in the multivariate models and were retained if they were significantly associated with the outcome of interest at the $P < 0.2$ level.

The time-to-pregnancy data were analyzed using a Cox proportional hazards model with time-to-pregnancy modeled as a continuous variable [Baird et al., 1986; Weinberg et al., 1994; Joffe, 1997] and with job category as the exposure variable. Time-to-pregnancy analyses were also performed using solvent exposure indices for the calendar year of and the calendar year preceding the pregnancy as exposure variables. To further identify additional potential confounding variables, crude fecundability ratios were first calculated from Cox proportional hazards models containing only one predictor variable. Variables associated with time-to-pregnancy at the $P < 0.2$ level in the crude analyses were also tested in the multivariable analyses and were retained if they were significantly associated with time-to-pregnancy at the $P < 0.2$ level.

Time-to-pregnancy was calculated in two ways. Some individuals were able to provide an actual number of months it took them and their partner to conceive. Others were only able to approximate TTP as "less than 3 months," "3–12 months," or "greater than 12 months." Therefore, TTP was included in the model either as a composite variable, combining data from these two groups of individuals, or as a variable containing only data from those individuals who were able to give an actual number. For the combined variable, "less than 3 months" was coded as 3 months, "3–12 months" was coded as 8 months, and "greater than 12 months" was censored at 12 months. Exact estimates of TTP were not changed for the combined variable. The results of the analyses using these two exposure variables were essentially the same. Therefore, the combined variable is presented here.

LH and FSH concentrations and the solvent exposure indices were not normally distributed; therefore, log base 10 transformations were used. Analysis of covariance

(ANCOVA) was used to compare logs of LH and FSH or untransformed testosterone concentration among the three job title groups. The General Linear Model procedure (multiple linear regression) was used to analyze the associations between log transformed LH and FSH or untransformed testosterone concentrations and the log transformations of the continuous exposure indices.

All statistical analyses were performed using SPSS Version 10.0 (SPSS, Chicago, IL) for the MacIntosh.

RESULTS

Demographic Variables

The demographic and other characteristics of the three exposure groups are shown in Table I. There was a significant difference in age among the three groups, with the painters being younger than the millwrights or carpenters. Millwrights had significantly higher whole blood lead concentrations than painters or carpenters, but the highest lead level was only 8 $\mu\text{g}/\text{dl}$. There was a tendency for fewer painters to have completed high school and for the painters to have fewer years of vocational training and fewer years of college. Table II displays variables related to the pregnancy for which time-to-pregnancy data were gathered for the 75 subjects who were able to estimate time-to-pregnancy, out of the 83 subjects who had ever had a child. The three exposure groups again differed significantly by age at the time of interview, but not in terms of age at the time of the pregnancy of interest. There were also trends towards differences among the groups in terms of use of contraceptives and wife's breastfeeding before the last pregnancy, as well as in whether the couple was actively trying to avoid pregnancy.

Exposure Indices

The calculated exposure indices substantiated that painters had significantly greater exposure to solvents in general, to aromatic solvents, and to thinners, degreasers, varnishes, and adhesives than millwrights and carpenters and that millwrights had intermediate exposures (Table I). Only 20 of the subjects had any exposure to chlorinated solvents. The millwrights had significantly higher chlorinated solvent exposure indices than either the carpenters or the painters (Table I).

Effect of Solvent Exposure on Reproductive Hormone Concentrations

Table III shows the linear regression models for FSH, LH, and testosterone modeled as functions of the four exposure indices (total solvents, chlorinated solvents, aromatic solvents, and thinners, degreasers, adhesives, and varnishes as a category). Bivariate analyses revealed that only age,

TABLE I. Demographic and Other Variables by Job Category in Men With Minimal Exposure to Solvents (Carpenters) and Solvent-Exposed Men (Millwrights and Painters), Washington State

Variable	Carpenter (n = 40)	Millwright (n = 25)	Painter (n = 32)	P-value
		Mean ± SD		
Age (years)	46.8 ± 8.3	49.9 ± 9.2	42.7 ± 7.8	0.006
Height (m)	1.8 ± 0.06	1.8 ± 0.06	1.8 ± 0.05	0.911
Weight (kg)	91.2 ± 12.2	93.8 ± 13.3	88.6 ± 14.1	0.330
BMI ^a (kg/m ²)	28.8 ± 4.3	29.5 ± 4.2	28.0 ± 4.0	0.406
Years in job	22.8 ± 7.5	22.2 ± 9.0	19.5 ± 8.5	0.233
Years of college	0.82 ± 1.43	0.64 ± 1.08	0.31 ± 0.82	0.191
Years of vocational training	0.75 ± 1.48	0.78 ± 1.32	0.16 ± 0.57	0.073
Thinners, degreasers, varnishes, adhesives EI ^c	6.8 ± 10.3	12.0 ± 14.5	21.9 ± 17.1	<0.001
Aromatic solvent EI	1.4 ± 4.3	0.7 ± 1.8	8.1 ± 9.1	<0.001
Chlorinated solvent EI	1.0 ± 4.3	4.9 ± 8.3	2.2 ± 6.2	0.049
Total solvent EI	10.3 ± 13.5	21.1 ± 22.9	42.0 ± 32.2	<0.001
Blood lead (µg/dl)	1.1 ± 1.5	2.3 ± 1.8	1.7 ± 1.2	0.017
		Percent		
Ethnicity				0.312 ^b
Caucasian	92.5	100.0	90.6	
Hispanic	0	0	6.3	
Black	0	0	3.1	
Other	7.5	0	0	
Education (completed high school or more)	95.0	87.5	78.1	0.099
Current alcohol use				0.891
≤30 g/week	45.0	24.0	40.6	
>30 g/week to <30 g/day	17.5	36.0	25.0	
≥30 g/day	15.0	20.0	18.8	
Maximum past EtOH per day				0.517
≤30 g/week	17.5	12.0	25.0	
>30 g/week to <30 g/day	37.5	24.0	31.3	
≥30 g/day	40.0	52.0	43.8	
Marital status				0.281
Single	12.5	4.0	18.8	
Married	80.0	88.0	81.2	
Other	7.5	8.0	0	
Have had a child	80.0	88.0	93.8	0.228

Percentages may not total to 100 due to missing values and rounding. Significant differences among groups were determined by one-way analysis of variance for the continuous variables and by Pearson's Chi-square test for the categorical variables.

^aBody mass index.

^bComparison of Caucasian versus other.

^cEI, exposure index.

body mass index, and total number of years of education were associated with at least one of the hormone concentrations at a significance level of 0.2 or lower. Because all of these were associated at a significance level of 0.2 or lower with at least one of the hormone concentrations in the multivariate models, these three covariates were included in the final models. The log of FSH increased significantly with the log of chlorinated solvent exposure and with the log of total solvent exposure, and the increase in the log of FSH with

exposure to thinners, degreasers, adhesives, and varnishes as a category approached significance (Table III). Thus, FSH tended to increase by 1.3-fold for every 10-fold increase in the chlorinated solvent exposure index and by 1.2-fold for every 10-fold increase in total solvents or in thinners, degreasers, varnishes, and adhesives. There was a tendency for LH to decrease with increasing aromatic solvent exposure (Table III). There were no apparent associations between LH and any of the other solvent exposure indices. Likewise,

TABLE II. Time-to-Pregnancy Variables by Job Category in Men With Minimal Exposure to Solvents (Carpenters) and Solvent-Exposed Men (Millwrights and Painters), Washington State

Variable	Carpenter (n = 25)	Millwright (n = 21)	Painter (n = 29)	P-value
		Mean ± SD		
Age at interview (years)	49.2 ± 6.8	50.6 ± 9.1	43.0 ± 7.3	0.001
Age at study pregnancy	29.8 ± 6.3	28.4 ± 4.2	28.9 ± 4.9	0.656
		Percent of exposure group		
Contraception ^a				0.343
Not using contraception	52.0	52.4	44.8	
Irregular contraception	24.0	42.9	31.0	
Regular and consistent	24.0	4.8	24.1	
OCs last method used ^a	24.0	23.8	31.0	0.755
Wife breastfeeding ^a	52.0	52.3	58.6	0.149
Trying to become pregnant ^a	32.0	33.3	34.5	0.223
Unconcerned	60.0	33.3	48.3	
Trying to avoid pregnancy	8.0	33.3	17.2	
Partner smoked during pregnancy	24.0	30.0	48.3	0.150

^aThese variables refer to the time period before the pregnancy for which time-to-pregnancy was determined (most recent pregnancy). Significant differences among groups were determined by one-way analysis of variance for the continuous variables and by Pearson's Chi-square test for the categorical variables. OC, oral contraceptives.

there were no significant relations between testosterone concentrations and any of the exposure indices (Table III).

Table IV depicts the reproductive hormone concentrations by job category. In the final model, which included age, body mass index, and total years of education, there was no significant effect of job category on LH, FSH, or testosterone concentration. The log of LH concentration decreased

significantly with increasing body mass index and increasing total years of education ($P = 0.05$ and $P = 0.04$, respectively), and testosterone concentration also significantly decreased with increasing body mass index ($P = 0.007$). Log FSH also tended to decrease with increasing body mass index ($P = 0.52$). Both LH and FSH tended to increase with increasing age ($P = 0.19$, $P = 0.09$).

TABLE III. Linear Regression Models of Serum Reproductive Hormone Concentrations With Exposure Indices as Exposure Variables in Men With Varying Levels of Solvent Exposure, Washington State

Model ^b (outcome variable, exposure variable)	β	95% CI	P-value
Log FSH, log total solvent E.I. ^a	0.07	0.005–0.14	0.035
Log FSH, log chlorinated solvent E.I.	0.11	0.01–0.21	0.029
Log FSH, log mixed solvents ^c E.I.	0.07	–0.002–0.15	0.055
Log FSH, log aromatic solvents E.I.	0.03	–0.07–0.13	0.605
Log LH, log total solvent E.I.	–0.02	–0.07–0.04	0.525
Log LH, log chlorinated solvent E.I.	0.02	–0.07–0.10	0.690
Log LH, log mixed solvents E.I.	–0.02	–0.09–0.04	0.483
Log LH, log aromatic solvents E.I.	–0.08	–0.17–0.001	0.052
Testosterone, log total solvent E.I.	–0.05	–3.41–3.31	0.977
Testosterone, log chlorinated solvent E.I.	–3.12	–8.28–2.04	0.232
Testosterone, log mixed solvents E.I.	–0.38	–4.24–3.47	0.844
Testosterone, log aromatic solvents E.I.	–1.00	–6.06–4.06	0.697

^aE.I., exposure index.

^bAll models included age, body mass index, and years of education.

^cMixed solvents included varnishes, thinners, degreasers, adhesives.

Effect of Solvent Exposure on Time-to-Pregnancy

Table V shows the crude relative risks for pregnancy related to the potential confounding variables for all pregnancies regardless of whether they resulted in a live birth. Only three of the potential confounders were associated with

TABLE IV. Mean Reproductive Hormone Concentrations by Job Category in Men With Minimal Solvent Exposure (Carpenters) and Solvent-Exposed Men (Millwrights, Painters), Washington State

Hormone	Carpenters (n = 40)	Millwrights (n = 25)	Painters (n = 32)
		Mean ± SEM	
LH (IU/L)	4.3 ± 0.3	4.3 ± 0.3	3.8 ± 0.2
FSH (IU/L)	4.0 ± 0.3	4.6 ± 0.4	4.3 ± 0.4
Testosterone (nmol/L)	23.9 ± 1.8	22.6 ± 1.9	25.7 ± 2.1

ANCOVA with age, body mass index, and number of years of education as covariates revealed no significant effects of job category on \log_{10} LH, \log_{10} FSH, or testosterone concentrations.

TABLE V. Crude Relative Probabilities of Pregnancy From Cox Proportional Hazards Models in Men With Varying Levels of Solvent Exposure, Washington State

Factor	n (%) ^a	RR ^b	95% CI
Age at interview	75 (100)	0.99	0.96–1.02
Age during time-to-pregnancy (TTP)	75 (100)	0.94*	0.89–0.99
Years since TTP	75 (100)	1.01	0.98–1.03
Breastfeeding prior to TTP pregnancy			
No	30 (40)	1.00	
Yes	41 (55)	1.29	0.77–2.16
Contraception prior to TTP pregnancy			
Using contraception	22 (29)	1.00	
No contraception	52 (69)	1.14	0.67–1.94
Oral contraceptives (OC)			
Last method before TTP	20 (27)	1.00	
Never used before TTP	23 (31)	0.97	0.50–1.88
Stopped OC, then abstained	7 (1)	2.48*	1.00–6.16
Not last method	16 (21)	1.11	0.54–2.25
Education			
Did not finish high school	11 (15)	1.00	
Finished high school	62 (83)	1.03	0.53–2.03
Total years of education	72 (96)	1.01	0.89–1.13
Current alcohol use			
<30 g/day	46 (61)	1.00	
≥30 g/day	13 (17)	0.76	0.38–1.52
Maximum past alcohol use			
<30 g/day	39 (52)	1.00	
≥30 g/day	32 (43)	0.77	0.46–1.28
Marital status			
Single	4 (5)	1.00	
Married	68 (91)	1.10	0.40–3.05
Divorced	2 (3)	1.65	0.30–9.04
Partner smoked during pregnancy			
No	47 (63)	1.00	
Yes	26 (35)	0.67**	0.40–1.14
Trying to conceive during TTP			
Trying	25 (33)	1.00	
Unconcerned	35 (47)	0.73	0.42–1.26
Trying not to	14 (19)	0.50**	0.24–1.06

^aPercentages may not total to 100 due to missing values and rounding.

^bFor continuous variables this is the relative risk per unit of the variable (e.g., per year for the age variables).

* $P < 0.05$.

** $P < 0.20$.

TTP at a significance level of less than 0.2. Older men tended to have a lower probability of pregnancy. Couples who were trying to become pregnant had higher probability of pregnancy than couples who were unconcerned one way or the other, and the latter, in turn, had a higher probability than couples who were trying not to become pregnant. Couples

who stopped using oral contraception and then abstained from intercourse or who stopped using oral contraceptives and then used a barrier method of contraception for several months before trying to conceive were more likely to become pregnant than couples who stopped using oral contraceptives and began having uncontracepted intercourse immediately, but this was based on a very small number of pregnancies. Finally, couples whose wives smoked during the pregnancy of interest had a lower probability of pregnancy than wives who did not smoke.

In all of the models, the painters and millwrights had a lower probability of pregnancy than the carpenters, but this was not statistically significant (Table VI). This can be seen in Figure 1, which depicts the survival curves for the final model that included job, man's age at the time of the pregnancy of interest, wife's smoking status during pregnancy, and whether the couple was trying to become pregnant. In most of the models tested, as shown in Table VI, the relative probability of pregnancy was non-significantly lower in the millwrights than in the painters and lower in the painters than in the carpenters. The difference in fecundability was also not statistically significant when painters and millwrights were combined into a single exposed group for comparison to carpenters. The relative risk of pregnancy for painters plus millwrights compared to carpenters was 0.78 (95% CI = 0.42–1.43). Therefore, painters and millwrights had a 22% lower probability of pregnancy per month of trying than did the carpenters. Restricting the analysis only to pregnancies that ended in a live birth or only to couples who were trying to become pregnant also did not alter the results of the analysis substantially (Table VI, Models 6 and 4). Restricting the analysis only to couples who were not using contraception further reduced the predicted probability of pregnancy in the millwrights and painters relative to the carpenters (Table VI, Model 5). There were too few first pregnancies in the data set (only 13) to restrict the analysis to first pregnancies.

Additionally, the model was run using all of the actual values for TTP or censoring them at 12 months, the time at which a couple is medically defined as infertile [Weinberg et al., 1994]. This was done to guard against "medical intervention bias," an association between the exposure of interest and the probability that an infertile couple will seek treatment for infertility [Weinberg et al., 1994]. Again, the results were essentially the same whether the data were censored or not (Table VI, Models 2 and 3).

When exposure was modeled using dichotomized exposure indices for the year preceding the pregnancy and the year of the pregnancy, there was no significant association between time-to-pregnancy and any of the solvent exposure indices (Table VI, Models 7–10). Similarly, there was no significant association between any of the continuous exposure indices for the year preceding pregnancy and the year of the pregnancy and time-to-pregnancy (data not shown).

TABLE VI. Association Between Employment As a Painter or Millwright or Work With Solvents and Fecundability in Washington State; Cox Proportional Hazards Models

Model ^a	Relative probability of pregnancy	95% CI	P-value	n
1. TTP ^b censored at 12 months				
Carpenters	1.00			57
Millwrights	0.65	0.29–1.44	0.29	
Painters	0.80	0.41–1.58	0.52	
2. TTP censored at 12 months				
Carpenters	1.00			74
Millwrights	0.63	0.32–1.24	0.18	
Painters	0.78	0.43–1.40	0.40	
3. TTP not censored				
Carpenters	1.00			74
Millwrights	0.65	0.34–1.27	0.20	
Painters	0.77	0.43–1.37	0.37	
4. Pregnancies for which couples were trying to conceive				
Carpenters	1.00			25
Millwrights	0.63	0.21–1.90	0.41	
Painters	0.73	0.24–2.21	0.56	
5. Pregnancies for which couples not using contraception at all during TTP				
Carpenters	1.00			39
Millwrights	0.48	0.16–1.42	0.19	
Painters	0.70	0.30–1.66	0.42	
6. Pregnancies that ended in live births only				
Carpenters	1.00			53
Millwrights	0.62	0.26–1.48	0.28	
Painters	0.76	0.36–1.64	0.49	
7. Chlorinated solvent exposure during TTP				
No	1.00			74
Yes	0.85	0.46–1.58	0.62	
8. Aromatic solvent exposure during TTP				
No	1.00			74
Yes	1.05	0.61–1.82	0.86	
9. Varnishes, adhesives, degreasers, and thinners exposure during TTP				
No	1.00			74
Yes	1.02	0.60–1.74	0.95	
10. Total solvent exposure during TTP				
No	1.00			74
Yes	1.07	0.62–1.84	0.82	

^aAll models included age of the man at the pregnancy of interest. All models included wife's smoking during the pregnancy of interest. All models except models 4 and 5 also included a categorical variable indicating whether a couple was trying to conceive, unconcerned, or trying not to conceive. Models 1–6 used current job title as the exposure variable. Models 1, 4, 5, and 6 include only those pregnancies that occurred while the man was working in his current occupation. Models 7–10 used dichotomized exposure variables that indicated whether the man was exposed to solvents during the calendar year of and the calendar year preceding the pregnancy.

^bTTP, time-to-pregnancy, the number of months it took for the couple to conceive. TTP was censored at 12 months for all models except model 3. n indicates the number of pregnancies included in that model.

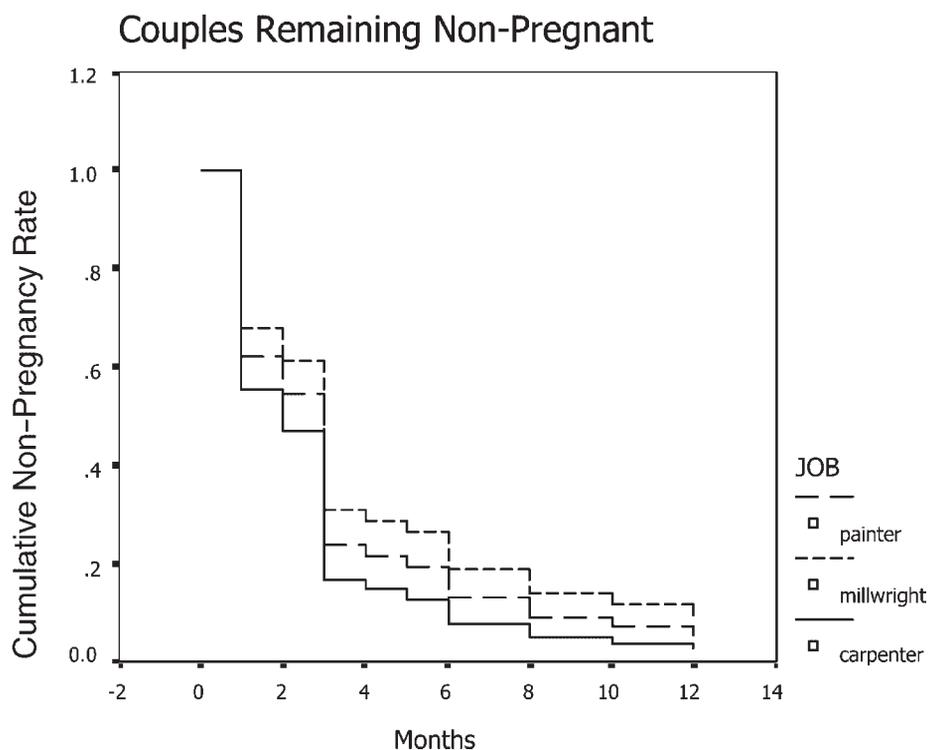


FIGURE 1. "Survival" curve from Cox proportional hazards analysis of the effect of job category on the number of months to pregnancy (censored at 12 months) adjusted for man's age at the time of the pregnancy of interest, whether the wife smoked during the pregnancy, and whether or not the couple was trying to conceive (trying, unconcerned, or trying not to). Only pregnancies that occurred while the man was working in his current occupation are included. Older age and trying not to become pregnant were significantly associated with longer times-to-pregnancy ($P = 0.002$, $P = 0.03$, respectively); working as a millwright and wife's smoking were non-significantly associated with longer times-to-pregnancy ($P = 0.29$, $P = 0.09$, respectively).

CONCLUSIONS

This study investigated reproductive hormone concentrations and fecundability in three groups of men with different levels of occupational solvent exposure. FSH increased significantly with increasing exposure to all solvents combined and to chlorinated solvents as a category, in the absence of any statistically significant relationships of exposure with LH or testosterone levels. There were also no significant differences in LH, FSH, or testosterone concentrations among the three occupational groups. Fecundability was not statistically significantly associated with solvent exposure or job category.

In the present study, two of the solvent exposure indices were positively associated with plasma FSH concentration. These exposure indices are semi-quantitative indicators of occupational lifetime exposure. Increased FSH concentrations are often observed in the setting of primary testicular damage, due to reduced negative feedback by inhibin from the Sertoli cells [Klingmüller and Haidl, 1997]. Two halogenated propanes, the nematocide dibromochloropropane and the solvent 2-bromopropane, are examples of primary testicular toxicants that cause oligospermia and azoospermia

and elevated FSH concentrations [Whorton et al., 1977; Whorton and Foliart, 1983; Kim et al., 1996]. Thus, the positive associations observed in the present study between solvent exposure and serum FSH may represent a secondary effect due to testicular damage caused by solvent exposure. Unfortunately, testicular damage could not be assessed directly in the present study because semen analyses were not performed.

Abnormalities in reproductive hormone concentrations have been inconsistently associated with occupational solvent exposure in men. Reduced LH, FSH, and testosterone concentrations were associated with recent toluene exposure in the printing industry in two studies [Svensson et al., 1992a,b]. In contrast, chronic toluene exposure was associated with increased FSH and unchanged LH and testosterone concentrations in a third study [Mørck et al., 1988]. The association of recent toluene exposure with reduced LH and FSH levels in these studies suggests that toluene may act by acutely suppressing LH and FSH secretion at the pituitary or hypothalamic level. However, in a controlled exposure study with human volunteers, a 3 hr inhalational exposure to 50 ppm toluene did not appreciably alter LH or FSH mean concentrations or the frequency or amplitude of LH or FSH

peaks in men or in women compared to sham-exposed controls [Luderer et al., 1999]. There was a slight, 5% decline in mean LH concentrations in the toluene-exposed men compared to the sham-exposed men [Luderer et al., 1999]. The present study found a non-significant trend towards decreasing LH concentrations with increasing lifetime exposure to aromatic solvents. In another controlled human exposure study, repeated exposure of male volunteers to the mixed petroleum distillate white spirit for 6 hr a day for 5 days significantly suppressed serum FSH levels compared to controls [Pedersen and Cohr, 1984], but LH was not measured. White spirit contains appreciable levels of aromatic solvents [Lewander et al., 2002]; therefore, it is possible that the effects of white spirit on FSH secretion were due to the toluene component. In contrast to the finding in the present study of increased FSH with increasing exposure to chlorinated solvents as a category, increasing years of exposure to the chlorinated solvent trichloroethylene were significantly associated with decreasing serum FSH and testosterone concentrations in two studies of one occupational cohort [Chia et al., 1997; Goh et al., 1998].

Fecundability has not previously been studied in painters and millwrights, although fecundability has been studied in other solvent-exposed occupational groups. An association between occupational solvent exposure in a heterogeneous group of men from many occupations and reduced fecundability was found for primigravida wives of solvent-exposed men, but not for multigravida wives [Sallmén et al., 1998]. In the present study time-to-pregnancy tended to be longer in the primigravida wives of the painters than the carpenters, but the data set only included 13 first pregnancies (data not shown). A study of printing workers with exposure to toluene failed to find an effect on fecundability in male workers [Plenge-Bönig and Karmaus, 1998]. Fecundability was non-significantly reduced in men occupationally exposed to styrene in the reinforced plastics industry [Kolstad et al., 2000]. In the present study, time-to-pregnancy was non-significantly longer in painters and millwrights than in carpenters.

Other studies have investigated semen quality in men exposed occupationally to various solvents. Painters and other workers exposed to glycol ether solvents had abnormalities in some semen parameters compared to control workers [Welch et al., 1988; Ratcliffe et al., 1989], and certain glycol ethers are potent testicular toxicants in numerous laboratory animal species [Kalf et al., 1987]. Occupational exposure to styrene was associated with increased abnormal sperm morphology and decreased percentages of dead sperm in a study of male patients at an infertility clinic [Jelnes, 1988]. A more recent study of newly hired styrene workers found significantly reduced sperm concentrations 6 months after the onset of exposure to styrene, but no significant effects on sperm motility, morphology, or viability [Kolstad et al., 1999]. Occupational exposure to aromatic

solvents was associated with reduced semen quality in a case-control study [Tielemans et al., 1999] and in a cross-sectional study of rubber workers [De Celis et al., 2000]. The latter study found significantly decreased sperm counts, sperm motility, and percent of sperm with normal morphology in the exposed men. Solvent exposure in general was associated with reduced fertility as defined by abnormal semen parameters in a case-control study [Cherry et al., 2001]. Six of eight electronics workers who were exposed to the halogenated solvent, 2-bromopropane, had oligospermia or azoospermia [Kim et al., 1996]. Supporting the findings in humans, reduced sperm concentrations and motility and decreased germ cell numbers by histology were observed following inhalational exposure of male rats to 2-bromopropane [Ichihara et al., 1997; Yu et al., 2001].

This study has a number of strengths and limitations. A strength of this study is that we examined the effects of solvent exposure on fecundability and reproductive hormone concentrations in two occupational groups that differed in patterns of solvent use, but worked at the same large site and were similar in most other respects, with the exception of age. Information about specific occupations can be useful in beginning to identify solvents or patterns of solvent use that have the greatest effects on reproductive health. Another strength is that the analyses were performed using two different types of exposure variables, classification of exposure by job title alone and semi-quantitative, historical solvent exposure indices. Limitations of this study include the low power to detect effects on fecundability due to the smaller than planned sample size, low participation rate, long time interval between the most recent pregnancy and the study for many of the men, obtaining information on time-to-pregnancy from the male partner only, the absence of exposure measurements, the use of single measurements of hormone concentration for LH and FSH, which have significant minute-to-minute variability, and the lack of semen analyses. Regarding exposure assessment, it would have been difficult to do exposure monitoring in a representative way for a study of this kind because of the heterogeneous patterns of solvent use in the occupations we studied. Therefore, we turned to a retrospective questionnaire method, recognizing that recall of exposures in the distant past may not be accurate. Inaccurate recall of past exposures would likely have resulted in bias towards the null, unless men with fertility problems differentially reported greater or lesser exposures. This sort of differential reporting of exposures due to a known fertility problem seems unlikely because we excluded men with conditions known to be associated with infertility. The reliability of retrospective occupational exposure histories collected from the same men on two occasions 9 years apart was found to be good, with an intra-class correlation coefficient of 87% [Brower and Attfield, 1998]. Studies that have compared maternal reports of exposure to chemicals obtained during pregnancy versus

those obtained after pregnancy have had conflicting results. Till et al. [2002] found that women reported longer durations of exposure to various chemicals 3–7 years after a pregnancy than they had reported for the same substances during the pregnancy. In contrast, Farrow et al. [1996] found good agreement between women's reports of exposures to 48 substances early in pregnancy and after miscarriage. Surprisingly, they noted a small, but consistent trend towards reporting exposures less frequently after miscarriage than early in pregnancy [Farrow et al., 1996].

The time-to-pregnancy portion of our study may also be limited by the retrospective collection of pregnancy data, in some cases 20 years or more after the pregnancy, and by the collection of data from the male rather than the female member of the couple. It has been determined that accurate recall of time-to-pregnancy among women can be obtained at the group level a median of 14 years later [Joffe, 1997]. The only study of which we are aware that assessed the quality of time-to-pregnancy data obtained from men found that the time-to-pregnancy data provided by men corresponded closely with previously published distributions and estimates of time-to-pregnancy [Joffe, 1989]. Unfortunately, time-to-pregnancy data were not obtained from the men's female partners in that study. A measure of the internal consistency of the time-to-pregnancy estimate revealed that serious discrepancies occurred with nearly equal frequency in men and women and that discrepancies were more likely with increasing time since the pregnancy, especially 30 years or more [Joffe, 1989]. A study comparing pregnancy histories reported by husbands and wives found that the sensitivity of reports of live births by men (relative to their wives' reports) was 90.1% and that this did not decline appreciably with time since the birth of greater than 10 years compared to 0–5 years [Fikree et al., 1993]. Complete agreement on the date of birth was observed in 88.5% of live births reported by both husband and wife, and agreement within ± 12 months was observed in 98.8% [Fikree et al., 1993]. Another study of elderly women (median age of 75.5) and proxies, found that male proxies, about three quarters of whom were husbands, underreported on number of childbirths in 12% of cases [Robbins et al., 2000]. Thus, the available studies suggest that men may not be as reliable as their partners in providing pregnancy data; however, the studies also suggest that they may not be as unreliable as is often supposed.

The low participation rate in the present study might introduce bias if exposed individuals with reproductive health problems participated at a different rate than participants without such problems. This could bias towards observing an apparent effect of exposure, when in fact there was none. We had no access to information about the individuals who did not respond to the call for participants to assess whether they differed systematically from those who responded.

Regarding the limitations of the reproductive hormone measurements, the study had greater than 80% power to

detect differences in LH, FSH, and testosterone of the magnitudes previously observed with toluene exposure in the printing industry [Svensson et al., 1992a,b] even though we only obtained single measurements on these hormones, which are secreted episodically. The power to detect differences in fecundability was lower. Based on power curves generated by Baird et al. [1986], a sample size of approximately 300 exposed subjects and 300 unexposed subjects would be required for a definitive study to have 80% power at a 0.05 level of significance to detect a fecundability difference of 33%. Future studies of the effects of solvent exposure on male fertility should emphasize large sample size, as well as including semen analyses.

In addition to the effects of solvent exposure on fecundability and reproductive hormone concentrations, we also examined the effects of a number of possible confounding variables. We observed significant effects of age at the time of the pregnancy of interest and of whether or not the couple was trying to become pregnant. Neither of these is surprising. Fertility is well-known to decline with age [Vermeulen, 1993; Kidd et al., 2001], and time-to-pregnancy has been reported to increase with increasing age of the male partner in several studies [Kidd et al., 2001]. Couples who were trying to become pregnant had shorter times-to-pregnancy. This may have been because they had lower uses of contraception than couples who were not trying to become pregnant ($P < 0.001$ by Pearson's Chi square). When contraceptive use was included as a variable in the models, the parameter estimates for exposure were changed by less than 10%. Therefore, it was not included in the final models presented in Table VI. To more fully explore the potential effect of contraceptive use, we also restricted the analysis to couples who were not using contraception (Table VI, Model 5). This resulted in lower estimated relative risks of pregnancy (longer TTP) in millwrights and painters relative to carpenters, consistent with a greater prolongation of time-to-pregnancy due to contraceptive use in the carpenters than in the painters and millwrights.

In the analyses for LH and testosterone, body mass index was a significant covariate; FSH also tended to decrease with increasing body mass index. The association of increasing adiposity with decreasing LH, FSH, and testosterone concentrations has been reported previously in obese men compared to men of normal weight [Vermeulen et al., 1993; Blank et al., 1994]. Total years of education was a significant covariate for LH only. We are unaware of any published studies demonstrating a negative association between education or socioeconomic status and LH or FSH concentrations. However, low socioeconomic status has been associated with delayed puberty, and a stress-mediated suppression of the hypothalamic GnRH pulse generator has been postulated as a mechanism [Vermeulen, 1993]. LH and FSH increased non-significantly with increasing age. This increase in gonadotropin secretion with age has also been previously described [Deslypere and Vermeulen, 1984].

In conclusion, plasma FSH concentrations increased significantly with increasing exposure indices for total solvents and chlorinated solvents. Increased FSH levels in the absence of changes in LH or testosterone levels are consistent with direct testicular damage to the Sertoli cells. We also observed non-significantly lower fecundability (longer time-to-pregnancy) in solvent-exposed painters and millwrights compared to unexposed carpenters. More conclusive results will require studies of fertility in larger groups of solvent-exposed men.

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REFERENCES

- Anonymous. 1995. Metropolitan height and weight tables, 1983. In: Barker LR, Burton JR, Zieve PD, editors. Principles of ambulatory medicine. Baltimore, MD: Williams and Wilkins.
- Baird DD, Wilcox AJ, Weinberg CR. 1986. Use of time to pregnancy to study environmental exposures. *Am J Epidemiol* 124:470–480.
- Blank DM, Clark RV, Heymsfield SB, Rudman DR, Blank MS. 1994. Endogenous opioids and hypogonadism in human obesity. *Brain Res Bull* 34:571–574.
- Brower PS, Attfield MD. 1998. Reliability of reported occupational history information for US coal miners, 1969–1977. *Am J Epidemiol* 148:920–926.
- Cherry N, Labrèche F, Collins J, Tulandi T. 2001. Occupational exposure to solvents and male infertility. *Occup Environ Med* 58:635–640.
- Chia SE, Goh VH, Ong CN. 1997. Endocrine profiles of male workers with exposure to trichloroethylene. *Am J Ind Med* 32:217–222.
- Cutler SF, Wallace PG, Haines AP. 1988. Assessing alcohol consumption in general practice patients—A comparison between questionnaire and interview (findings of the Medical Research Council's General Practice Research Framework Study on Lifestyle and Health). *Alcohol* 23:441–450.
- Daniell WB, Claypoole KH, Checkoway H, Smith-Weller T, Dager SR, Townes BD, Rosenstock L. 1999. Neuropsychological function in retired workers with previous long term occupational exposure to solvents. *Occup Environ Med* 56:93–105.
- De Celis R, Fera-Velasco A, González-Unzaga M, Torres-Calleja J, Pedrón-Nuevo N. 2000. Semen quality of workers occupationally exposed to hydrocarbons. *Fertil Steril* 73:221–228.
- Deslypere JP, Vermeulen A. 1984. Leydig cell function in normal men: Effect of age, life style, residence, diet, and activity. *J Clin Endocrinol Metab* 59:955–962.
- Farrow A, Farrow SC, Little R, Golding J. 1996. The repeatability of self-reported exposure after miscarriage. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *Int J Epidemiol* 25:797–806.
- Fikree FF, Gray RH, Shah F. 1993. Can men be trusted? A comparison of pregnancy histories reported by husbands and wives. *Am J Epidemiol* 138:237–242.
- Goh VH, Chia SE, Ong CN. 1998. Effects of chronic exposure to low doses of trichloroethylene on steroid hormone and insulin levels in normal men. *Environ Health Perspect* 106:41–44.
- Harrison SA, Kadakia S, Lang KA, Schenker S. 2002. Nonalcoholic steatohepatitis: What we know in the new millennium. *Am J Gastroenterol* 97:2714–2724.
- IARC. 1989. Occupational exposures in paint manufacture and painting. IARC Monogr Eval Carcinog Risk Chem Hum Lyons: International Agency for Research on Cancer. pp 329–442.
- Ichihara G, Asaeda N, Kumazawa T, Tagawa Y, Kamijima M, Yu X, Kondo H, Nakajima T, Kitoh J, Yu JJ, Moon YH, Hisanaga N, Takeuchi Y. 1997. Testicular and hematopoietic toxicity of 2-bromopropane, a substitute for ozone layer-depleting chlorofluorocarbons. *J Occup Health* 39:57–63.
- Jelnes JE. 1988. Semen quality in workers producing reinforced plastic. *Reprod Toxicol* 2:209–212.
- Joffe M. 1989. Feasibility of studying subfertility using retrospective self reports. *J Epidemiol Commun Health* 43:268–274.
- Joffe M. 1997. Time to pregnancy: A measure of reproductive function in either sex. *Occup Environ Med* 54:289–295.
- Kalf GF, Post GB, Snyder R. 1987. Solvent toxicology: Recent advances in the toxicology of benzene, glycol ethers, and carbon tetrachloride. *Ann Rev Pharmacol Toxicol* 27:399–427.
- Kidd SA, Eskenazi B, Wyrobek AJ. 2001. Effects of male age on semen quality and fertility: A review of the literature. *Fertil Steril* 75:237–248.
- Kim Y, Jung K, Hwang T, Jung G, Kim H, Park J, Kim J, Park J, Park D, Park S, Choi K, Moon Y. 1996. Hematopoietic and reproductive hazards of Korean electronic workers exposed to solvents containing 2-bromopropane. *Scand J Work Environ Health* 22:387–391.
- Klingmüller D, Haidl G. 1997. Inhibin B in men with normal and disturbed spermatogenesis. *Hum Reprod* 12:2376–2378.
- Kolstad HA, Bonde JP, Spano M, Giwercman A, Zschiesche W, Kaae D, Larsen SB, Roeleveld N, ASCLEPIOS. 1999. Change in semen quality and sperm chromatin structure following occupational styrene exposure. *Int Arch Occup Environ Health* 72:135–141.
- Kolstad HA, Bisanti L, Roeleveld N, Baldi R, Bonde JP, Joffe M. 2000. Time to pregnancy among male workers of the reinforced plastics industry in Denmark, Italy and The Netherlands. *Scand J Work Environ Health* 26:353–358.
- Lewander WJ, Hurlbut KM, Hall AH, Dabney BJ, Wason S, Kulig K, Marcus S, Kunkle DB. 2002. Hydrocarbons. In: Toll LL, Hurlbut KM, editors. POISINDEX System Greenwood Village. CO: MICROMEDEX.
- Lindbohm M-L, Taskinen H, Sallmén M, Hemminki K. 1990. Spontaneous abortions among women exposed to organic solvents. *Am J Ind Med* 17:449–463.
- Luderer U, Morgan MS, Brodtkin CA, Kalman DA, Faustman EM. 1999. Reproductive endocrine effects of acute exposure to toluene in men and women. *Occup Environ Med* 56:657–666.

- Mørck HI, Winkel P, Gyntelberg F. 1988. Health effects of toluene exposure. *Dan Med Bull* 35:196–200.
- Pastides H, Calabrese EJ, Hosmer DW, Jr., Harris DR, Jr. 1988. Spontaneous abortion and general illness symptoms among semiconductor manufacturers. *J Occup Med* 30:543–551.
- Pedersen LM, Cohn K-H. 1984. Biochemical pattern in experimental exposure of humans to white spirit: 2. The effects of repetitive exposures. *Acta Pharmacol Toxicol* 55:325–330.
- Plenge-Bönig A, Karmaus W. 1998. Exposure to toluene in the printing industry is associated with subfertility in women but not in men. *Occup Environ Med* 56:443–448.
- Ratcliffe JM, Schrader SM, Clapp DE, Halperin WE, Turner TW, Hornung RW. 1989. Semen quality in workers exposed to 2-ethoxyethanol. *Br J Ind Med* 46:399–406.
- Robbins JM, Wolfson CM, Bergman H, Clarfield AM, Kleiman S, Bilker W, Baumgarten M. 2000. Agreement between older subjects and proxy informants on history of surgery and childbirth. *J Am Geriatr Soc* 48:975–979.
- Sallmén M, Lindbohm M-L, Kyyrönen P, Nykyri E, Anttila A, Taskinen H, Hemminki K. 1995. Reduced fertility among women exposed to organic solvents. *Am J Ind Med* 27:699–713.
- Sallmén M, Lindbohm M-L, Anttila A, Kyyrönen P, Taskinen H, Nykyri E, Hemminki K. 1998. Time to pregnancy among the wives of men exposed to organic solvents. *Occup Environ Med* 55:24–30.
- Svensson B-G, Nise G, Erfurth E-M, Nilsson A, Skerfving S. 1992a. Hormone status in occupational toluene exposure. *Am J Ind Med* 22:99–107.
- Svensson B-G, Nise G, Erfurth EM, Olsson H. 1992b. Neuroendocrine effects in printing workers exposed to toluene. *Br J Ind Med* 49:402–408.
- Taskinen H, Anttila A, Lindbohm M-L, Salimen M, Himminki K. 1989. Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. *Scand J Work Environ Health* 15:345–352.
- Tielemans E, Burdorf A, te Velde ER, Weber RFA, van Kooij RJ, Veulemans H, Heederik DJJ. 1999. Occupationally-related exposures and reduced semen quality: A case-control study. *Fertil Steril* 71:690–696.
- Till C, Koren G, Rovet JF. 2002. Agreement between prospective and retrospective reports of maternal exposure to chemicals during pregnancy. *J Occup Environ Med* 44:708–713.
- Vermeulen A. 1993. Environment, human reproduction, menopause, and andropause. *Environ Health Perspect* 101(Suppl 2):91–100.
- Vermeulen A, Kaufman JM, Deslypere JP, Thomas G. 1993. Attenuated luteinizing hormone (LH) pulse amplitude but normal LH pulse frequency, and its relation to plasma androgens in hypogonadism of obese men. *J Clin Endocrinol Metab* 76:1140–1146.
- Weinberg CR, Baird DD, Wilcox AJ. 1994. Sources of bias in studies of time to pregnancy. *Stat Med* 13:671–681.
- Welch LS, Schrader SM, Turner TW, Cullen MR. 1988. Effects of exposure to ethylene glycol ethers on shipyard painters: II. Male reproduction. *Am J Ind Med* 14:509–526.
- Whorton MD, Foliart DE. 1983. Mutagenicity, carcinogenicity, and reproductive effects of dibromochloropropane (DBCP). *Mut Res* 123:13–30.
- Whorton D, Krauss RM, Marshall S, Milby TH. 1977. Infertility in male pesticide workers. *Lancet* 2:1259–1261.
- Windham GC, Shusterman D, Swan S, Fenster L, Eskenazi B. 1991. Exposure to organic solvents and adverse pregnancy outcome. *Am J Ind Med* 20:214–259.
- Yu X, Ichihara G, Kitoh J, Xie Z, Shibata E, Kamijima M, Takeuchi Y. 2001. Neurotoxicity of 2-bromopropane and 1-bromopropane, alternative solvents for chlorofluorocarbons. *Environ Res* 85:48–52.