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Reduced Fertility Among Female Wood Workers Exposed to Formaldehyde

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Background *The aim of the study was to investigate whether exposure to formaldehyde, organic solvents or other chemicals in the wood-processing industry affects the fertility of women.*

Methods *For this purpose, a retrospective study on time to pregnancy was conducted among female wood workers who had given birth during 1985–1995. Data on pregnancy history, time to pregnancy, occupational exposures, and potential confounders were collected by a questionnaire; 64% (699/1,094) participated. The exposure assessment was conducted by an occupational hygienist. The data on time to pregnancy were analyzed with the discrete proportional hazards regression.*

Results *Exposure to formaldehyde was significantly associated with delayed conception: adjusted fecundability density ratio, FDR, was 0.64 (95% CI 0.43–0.92). At high exposure if no gloves were used, the FDR was 0.51 (% CI 0.28–0.92). Exposure to phenols, dusts, wood dusts, or organic solvents was not related to the time to pregnancy. Additionally, an association was observed between exposure to formaldehyde and an increased risk of spontaneous abortion (concerning previous spontaneous abortions, reported by the women). Associations between exposure to formaldehyde or to organic solvents and endometriosis, and between exposure to organic solvents or to dusts and salpingo-oophoritis were also suggested.*

Conclusions *The study suggests that a woman's occupational exposure to formaldehyde has an adverse effect on fertility.* Am. J. Ind. Med. 36:206–212, 1999. © *1999 Wiley-Liss, Inc.*

KEY WORDS: time to pregnancy; fertility; formaldehyde; organic solvents; phenols; dusts; wood dusts; spontaneous abortions; endometriosis; menstrual disorders

INTRODUCTION

In the wood processing industry, such as plywood, fibreboard, carpentry, furniture industry and some other branches, there may be exposure to formaldehyde, organic solvents, phenols, and wood preservatives. Earlier data on the effects of formaldehyde to reproductive health in humans are limited and contradictory. Menstrual disorders, dysmenorrhoea, genital infections and secondary infertility associated with them, spontaneous abortions and low birth weight of the offspring were found in excess among women exposed to formaldehyde [Shumilina, 1975]. Increased risk of spontaneous abortion has been reported among laboratory workers exposed to formaline, xylene, and toluene, mostly at pathology or histology laboratories [Taskinen et al., 1994], and among cosmetologists using formaldehyde [John et al., 1994]. Heidam [1984] did not find an increased risk for spontaneous abortions among workers in a pathology laboratory. Children of women exposed to formaldehyde in the clothing industry had significantly higher risk for stillbirth, pre-term birth, and congenital malformation than

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the referents, but the risk of spontaneous abortion was not increased [Seitz and Baron, 1990].

The major routes of occupational exposure to formaldehyde are by inhalation and through the skin. It has been shown, also, that formaldehyde crosses the placental barrier in mice [Katakura et al., 1993]. The mechanism explaining the possible reproductive effects of formaldehyde is not known.

Phenol is fetotoxic but not teratogenic in animal tests [Jones-Price et al., 1983]. Occupational exposure to phenol and other disinfectants did not cause birth defects [Hernberg et al., 1983]. Phenol has been genotoxic in several short-term tests and induced sister chromatid exchanges in human cells [Morimoto and Wolff, 1980].

Some organic solvents have been teratogenic in animal tests (e.g., chloroform and 2-ethoxyethanol), and caused retarded growth of the offspring (e.g., tetrachloroethylene, toluene, trichloroethylene, xylene, and methyl ethyl ketone) [Nordic Criteria, 1992]. In humans, occupational exposure to organic solvents has been related to menstrual disorders, reduced fertility, spontaneous abortion, stillbirth, perinatal death, and congenital malformation as well as leukemia and brain tumors in children [Lindbohm, 1995; O'Leary et al., 1991; Sallmén et al., 1995; Laumon et al., 1996].

The aim of this study is to investigate whether exposure to formaldehyde, organic solvents, or other chemicals in the wood-processing industry decreases fertility when measured as time to pregnancy (TTP).

MATERIALS AND METHODS

The study base consisted of the members of the Wood and Allied Workers' Union (WAWU), wherein 5,860 female members were identified. In addition, female workers were sought by a mailed inquiry from 536 enterprises employing at least five workers. Of the enterprises, 334 (62%) responded and listed 5,171 previous or current female workers. The population sources were partly overlapping; after the restrictions and linkage of the registry information, 5,187 women were available. Linkage with the Population Register, using the personal identification codes, yielded 3,772 women who had children.

The study population was defined by using the following eligibility criteria:

1. the woman was born in 1946–1975;
2. the woman had delivered a child during 1985–1995, and the child was alive;
3. the woman's age at the beginning of the pregnancy was between 20 and 40 years;
4. the woman had worked in the wood-processing industry for at least one month;
5. the first employment in wood-related work had started at least six months before the pregnancy;
6. at the analysis stage, the data were restricted to those 602 subjects whose time to pregnancy (TTP) started after the woman's entry into the wood-related employment.

TABLE I. Response Rate, Causes of Rejections, and the Final Group of Women Wood Workers in Finland

Participation and Causes of Rejection	N (%)
Participated	699/1,094 (63.9)
Exclusions by criteria	
Contraceptive failure	38
Medical cause of infertility	8
Information reported on other pregnancy	3
TTP-time unknown	14
Job/work tasks unknown	6
TTP started before the first job in the branch	28
Final material	602

The first pregnancy that fulfilled the criteria was selected as the study pregnancy of each woman. The number of women complying with these criteria was 1,098; for four of them an address was not found. The questionnaire was mailed to 1,094 women. After two mailings 559 women (51.1 %) responded. A telephone reminder yielded 140 (12.8 %) additional responses; altogether 699 women (64 %) returned a filled-in questionnaire. The response rate for women whose pregnancies had ended in the years 1985–1990 was 57.5% (539 respondents); the response rate on pregnancies ending in the years 1991–1995 was 70.1 (555 respondents). The final group for analysis consisted of 602 women. The reasons for exclusions are listed in Table I.

Data on pregnancy history, time to pregnancy, occupational exposure, and previous gynecological diseases were collected by questionnaires. For the time to pregnancy information they were asked: ''Did you become pregnant during the first menstrual cycle when not using contraception? During the second?'' If the pregnancy started later, the women were asked to report how many months (and years) it took for the woman to become pregnant. Questions were put also on the occupational exposure of the fathers, and smoking and alcohol consumption of both parents.

Exposure Assessment

The exposure assessment was based on a detailed questionnaire. The women were asked to give the name of their workplace, occupation (professional title), and to describe their various tasks during the time-to-pregnancy period. The questionnaire included a detailed list of typical tasks and work phases in the various types of factories/enterprises in the wood-processing industry. The women were asked to fill in how many hours weekly they were exposed to formaldehyde, organic solvents, wood preserva-

TABLE II. Availability of Occupational Hygienic Measurements for Exposure Assessment of Women Wood Workers in Finland

	Women with formaldehyde measurement from own workplace, compared to all exposed women		Women with formaldehyde measurement from comparable workplaces, compared to all exposed women	
Exposure level	No. of women	%	No. of women	%
Low	32/119	26.9	55/119	46.2
Moderate	29/77	37.7	47/77	61.0
High	27/39	69.2	12/39	30.8

tives, glues or wood protecting chemicals during the time-to-pregnancy period. There were also questions on exposure to welding fumes, exhaust gases, pesticides and tobacco smoke, and on the use of personal protective equipment. An experienced occupational hygienist (T.L.) assessed the exposure of women. She was not aware of the time to pregnancy in questions or the pregnancy history.

An estimation of mean daily exposure during the time-to-pregnancy period was calculated for every person. The calculation was based on industrial hygienic measurements from the factory. If measurements were not done at the factory in question, measurements from work places of the same industrial activity were used as the basis of estimation (Table II).

The daily mean exposure was calculated as the following: Daily exposure index = concentration of the chemical (in ppm for formaldehyde and phenol, and in mg/m^3 for dusts) x the proportion of the exposed work time during a work-day x 100 (100 = whole day). For organic solvents, the ratio (%) of the measured concentration and the occupational exposure limit (OEL) of the specific solvent were used. The exposure assessment was most often based on measurements made at the same work place in the high exposure level. The use of measurements from corresponding work places was most common in the moderate level of exposure (Table II). Three exposure classes were formed so that the numbers of women in the low, medium, and high exposure groups had the ratio 3:2:1. The distribution of the women in different plants, and the proportion of women with high exposure to formaldehyde, are shown in Table III.. The exposure levels at class borders are shown in Table IV.

Time-to-pregnancy data were analyzed with the discrete proportional hazards regression [Kalbfleisch and Prentice, 1980]. The outcome parameter, the fecundability density ratio (FDR), estimates a ratio of average incidence densities of pregnancies for exposed women compared to the employed, unexposed women. An FDR significantly under unity means delayed conception, an indicator of reduced fertility. The significance was tested by the likelihood ratio test. The odds ratios (OR) for other outcomes were calculated by unconditional logistic regression; adjustments were done for age, employment, smoking and alcohol consumption.

TABLE III. Numbers of Women, and Exposure to Formaldehyde in Different Plants of the Wood-Processing Industry (Percentage of women in each branch), Finland

Plant	N of women in the plants (% of all)	Exposed women (% of the exposed)	High exposure category (% of highly exposed)
Plywood	96 (18)	68 (29)	15 (38)
Laminated veneer lumber (LVL)	10 (2)	9 (4)	2 (5)
Parquet flooring	18 (3)	11 (5)	3 (8)
Chipboard	12 (2)	10 (4)	1 (3)
Fibreboard	8 (2)	4 (2)	0 (0)
Furniture	139 (27)	37 (16)	5 (13)
Fixture	19 (4)	13 (6)	1 (3)
Building joinery	47 (9)	27 (11)	8 (21)
Wooden house manufacture	14 (3)	6 (3)	0 (0)
Other wood-processing branch	77 (15)	40 (17)	4 (10)
Other branch or unknown	83 (16)	10 (4)	0 (0)

RESULTS

Time to Pregnancy

The distribution of the TTP among women with various levels of exposure to formaldehyde is shown in Table V. Exposure to formaldehyde was significantly associated with delayed conception: the adjusted fecundability density ratio (FDR) was 0.64 with the 95% confidence interval (CI) 0.43–0.92 for high exposure index category (Table VI). The FDR was lower (0.51; CI 0.28–0.92) if the exposure was high, and the women (n = 17) did not use gloves. For those at high exposure level who used gloves (n = 22), the FDR was slightly decreased, 0.79 (CI 0.47–1.23). The most common personal protection of women exposed to formaldehyde was gloves; 100/251 (40%) women used gloves always, 47/251 (19%) women occasionally. There were 10/251 (4%) of women who reported the regular use of proper (other than paper) respirator/mask; 14/251 (6%) reported occasional use.

From the potential confounders maternal smoking, irregular menstrual cycles, and previous spontaneous abortions were associated with decreased fertility, whereas parity of 2+ was associated with increased fertility (Table VII). Variables for recent contraceptive use (pill or intrauterine device) were not included in the final model because

TABLE IV. Daily Exposure Indexes for Various Chemicals, and the Range of the Measured Concentrations in the Classes*

Exposure index category	Daily exposure index, class borders			Measured concentration (ppm)		
	Lowest	Highest	Mean	Min.	Max.	Mean
Formaldehyde				**OEL 1.0 ppm**		
Low	0.1	3.9	1.8	0.01	0.30	0.07
Medium	4.0	12.9	7.6	0.05	0.40	0.14
High	13.0	63.0	21.9	0.15	1.00	0.33
Phenol				**OEL 5 ppm**		
Low	0.1	0.9	0.6	0.001	0.04	0.01
Medium	1.0	4.5	1.9	0.002	0.05	0.02
				Calculated summary concentration, % of the OEL		
Organic solvents						
Low	0.1	3.2	1.6	1.0	40.0	8.69
Medium	3.3	10.9	5.9	4.0	100.0	16.99
High	11.0	70.0	20.7	20.0	100.0	31.90
				Measured concentration (mg/m^3), OEL 5 mg/m^3		
Wood dust						
Low	0.1	29.9	14.7	0.04	3.00	0.30
Medium	30.0	69.9	44.1	0.40	3.00	0.65
High	70.0	450	109.1	0.80	5.00	1.49
Other dusts						
Low	0.1	27.9	17.4	0.02	2.00	0.56
Medium	28.0	75.9	41.2	0.40	3.00	0.76
High	72.0	490	189.1	1.00	7.40	3.82

*OEL = occupational exposure limit value.

TABLE V. Time-to Pregnancy According to the Exposure to Formaldehyde in Study of Wood Workers, Finland*

Exposure index categories	N	Time-to pregnancy in menstrual cycles, N (and %) of the women				
		1–2	3–4	5–7	8–12	13 or more
All	602	322 (51)	99 (16)	74 (12)	47 (8)	60 (10)
Formaldehyde						
Non-exposed	288	151 (52)	46 (16)	40 (14)	24 (8)	27 (9)
Low	119	69 (58)	18 (15)	13 (11)	7 (6)	12 (10)
Medium	77	41 (53)	12 (16)	11 (14)	4 (5)	9 (12)
High	39	16 (41)	3 (8)	5 (13)	7 (18)	8 (21)

*N = number of persons from where the row percentages have been calculated.

TABLE VI. Fecundability Density Ratio (FDR) for Woman's Exposure to Formaldehyde, Adjusted for Potential Confounding Factors*

Exposure to formaldehyde (index category)	No. of exposed women	FDR	95% CI	*P* value
High	39	0.64	0.43–0.92	0.02
Medium	77	0.96	0.72–1.26	0.76
Low	119	1.09	0.86–1.37	0.46
Not exposed	367	1	—	—

*Adjusted for employment (yes/no), smoking (1–14 and 15 or more cigarettes/day), alcohol consumption (1–2 drinks, 3 drinks or more/week), irregular menstrual cycles (yes/no), and number of children (one child, two or more children). CI = confidence interval.

according to the preliminary analyses these variables did not confound the results.

Exposure to organic solvents occurred mostly in painting and lacquering at the furniture factories. According to the exposure assessment, 147 women were exposed to aliphatic solvents, and 134 women to aromatic solvents. Exposure to organic solvents was not related to prolonged time to pregnancy (Table VIII). The FDRs for exposure to dusts or wood dusts did not significantly differ from unity

TABLE VII. Fecundability Density Ratio (FDR) for Potential Confounding Factors*

Factor	No. of women	FDR	95% CI	*P* value
Employment	548	0.85	0.65–1.11	0.24
Smoking				
1–14 cigarettes/day	204	0.77	0.64–0.94	0.009
≥15 cigarettes/day	73	0.67	0.50–0.88	0.004
Stopped smoking	85	1.03	0.58–1.79	0.84
Alcohol use				
1–2 doses/week	304	0.86	0.71–1.04	0.13
≥3 doses/week	84	1.11	0.82–1.48	0.37
Irregular menstruation, often or always	46	0.69	0.49–0.98	0.04
Number of previous children				
1 child	174	1.07	0.87–1.31	0.54
≥2 children	114	1.29	1.02–1.64	0.03

*CI = confidence interval.

(Table VIII). The adjusted FDR of those exposed to phenols (N = 68) was 1.56 (CI 0.93–2.53); all women exposed to phenols were also exposed to formaldehyde, but not vice versa. The FDR for formaldehyde exposure, when included in the same model, was 0.57 (CI 0.37–0.85).

Various occupational exposures of the fathers (formaldehyde, phenols, organic solvents, metals, welding fumes, exhaust gases, pesticides, dusts, temperature over 30°C, and life style factors like smoking, alcohol consumption) as reported by the women, did not have a significant effect on the fertility of the women.

Other Outcomes

Although the time to pregnancy was the main focus in the study, risk estimations were calculated also for a few other outcomes, originally included into the questionnaire to enable to control for potential confounding. Previous spontaneous abortions were reported by 96 women, of which 52 women had the same work place during the year of spontaneous abortion as they had during the beginning of the time-to-pregnancy period. When the analysis was restricted to only these 52 pregnancies, the OR for spontaneous abortion was 3.2 (95% CI 1.2–8.3) in the high exposure, 1.8 (95% CI 0.8–4.0) in the medium exposure, and 2.4 (1.2–4.8) in the low exposure category. Exposure to formaldehyde at the high level was also associated with an increased risk (OR 4.5, 95% CI 1.0–20.0) of endometriosis. Exposure to organic solvents was associated with an increased risk of endometriosis (OR 14.7; 95% CI 3.1–70.0 for all, and 16.1; 95% CI 2.5–103 for those with same work place) and salpingo-oophoritis (OR 2.5; 95% CI 0.8–8.3). Exposure to dusts in high and medium exposure index categories was associated with an increased risk (OR 3.9; 95% CI 1.3–12.1, and 3.1; 95% CI 1.2–8.0, respectively) of salpingo-oophoritis.

TABLE VIII. Fecundability Density Ratio (FDR) for Woman's Exposure to Organic Solvents, Dusts, and Wood Dusts, Adjusted for Potential Confounding Factors,* Finland

Exposure	No. of exposed women	FDR	95% CI	*P* value
Organic solvents				
High	37	0.95	0.64–1.47	0.95
Medium	81	0.91	0.68–1.21	0.54
Low	112	0.93	0.71–1.21	0.62
Not exposed	400	1	—	—
Dusts				
High	38	1.02	0.67–1.51	0.91
Medium	76	1.13	0.85–1.48	0.40
Low	116	1.36	1.07–1.72	0.01
Not exposed	400	1	—	—
Wood dusts				
High	61	0.93	0.66–1.30	0.69
Medium	123	1.02	0.78–1.33	0.87
Low	185	1.28	0.98–1.66	0.07
Not exposed	261	1	—	—
Phenols				
Medium	24	1.56	0.93–2.53	0.09
Low	44	1.00	0.69–1.44	0.98
Not exposed	534	1	—	—

*Adjusted for employment (yes/no), formaldehyde, smoking (1–14 and 15 or more cigarettes/day), alcohol consumption (1–2 drinks, 3 drinks or more/week), irregular menstrual cycles (yes/no), and CI = confidence interval.

DISCUSSION

Time to pregnancy has not, according to our knowledge, previously been studied among women exposed to formaldehyde. Our results together with the earlier findings of adverse effects of formaldehyde to reproduction increase the evidence of reproductive toxicity of formaldehyde. Since there was no observed formaldehyde level exceeding the occupational exposure limit value (OEL 1.0 ppm in Finland), the results may indicate that even a low level of formaldehyde may have an impact on fertility. In light of the findings, the use of protective gloves seemed to prevent the adverse effect of formaldehyde exposure to the time to pregnancy.

In this study, organic solvents did not affect the TTP. In earlier studies, solvent exposure has been associated with decreased TTP in shoe industry, dry cleaning shops, and in the metals industry [Sallmén et al., 1995]. Exposure to ethylene glycol ethers and their acetates has also been related to decreased fertility [Correa et al., 1996]. Our results

may not be in real disagreement with the above-mentioned results; in different branches of the wood industry, different solvents are used, and the use of personal protection and the air concentrations of the solvents may vary. In our study, the mean concentration of organic solvents at the high exposure category was estimated to be as 32% of the occupational exposure limit value (OEL).

The design of this study was unique: we tried to mimic prospective design by using as the study pregnancy the first pregnancy ending with the birth of a child after entering into the wood-processing industry. This type of study is less prone to so-called time trend bias, which may be prominent in retrospective studies on time to pregnancy if the prevalence of exposure under study has changed over calendar time [Weinberg et al., 1993]. The purpose was to include a sufficient number of exposed and unexposed subjects in the study population. In most cases, the time-to-pregnancy period did start either during or after the first employment in the branch. However, in 28 cases, the TTP-period had started before entering to the branch. These women were excluded. The results were essentially similar if these women were included in the study because most of these women were not employed at the time the TTP started. In addition, only a few women could not report the length of time to pregnancy, when the recall time ranged from one to eleven years. In conclusion, it is feasible to use this design when there is a priori information on the dates of pregnancies available.

We consider the quality of exposure assessment good in this study, since the results of occupational hygienic measurements, conducted about in the middle of the study period in the wood-processing enterprises in Finland, were available for the study [Liukkonen et al., 1990, 1992]. The exposure of most women could be verified from the hygienic measurement data from their work places. The occupational hygienist responsible for the measurements did the exposure assessment using the measurement data and the detailed work task descriptions from the questionnaires. However, the information on the exposure of the fathers was based only on the reports of the women. Thus, the results on the male effects to the time to pregnancy are not conclusive.

The participation in the study was not optimal despite two mailings and a telephone reminder. There is room for bias caused by selective participation, if the participation is low. Selection has, however, not influenced the results on smoking, irregular menstruation, and earlier miscarriages, which are earlier known to lengthen the time to pregnancy [Sallmén et al., 1995; Baird and Wilcox, 1985; Bolumar et al., 1996]. Also, the dose-response pattern over the level of the exposure to formaldehyde suggests that our finding is not caused by selection bias, although the presence of such a bias cannot be totally excluded. However, in the future, new ways to increase participation in this kind of research projects should be found.

The unexpected associations between the self-reported exposure to formaldehyde or organic solvents and endometriosis are interesting although the numbers of exposed women were small and the confidence intervals wide. In earlier studies, exposure to organic solvents, dusts, and video display terminal work have been associated with an increased risk for endometriosis [Smith et al., 1997]. The etiology of endometriosis is not clear, but decreased immunological response has been suspected as a possible cause [Garzetti et al., 1995; Cummings and Metcalf, 1995; Rier et al., 1993; Arnold et al., 1996]. Also, genetic predisposition has been suggested as one factor in the pathogenesis of endometriosis since significantly more women with endometriosis than healthy women lacked activity of the glutathione S-transferase M1 (GSTM1) enzyme *(an enzyme that corresponds to detoxification processes)* [Baranova et al., 1997]. According to the authors, the observed high frequency of GSTM1 gene deletion among the endometriosis patients suggests a possible contribution of environmental toxins in the pathogenesis of the disease due to lack of the enzyme activity.

Association between the exposure to organic solvents or dusts with salpingo-oophoritis was a new finding, too. Earlier, Smith et al. [1997] found an association between exposure to dust and organic solvents, and tubal infertility. Infection is a common cause for tubal infertility, and hypothetically, dusts or other external agents might modify the effects of the infectious agents in the inner genitalia. Other possible causes of the infections in the sexual organs, e.g., the number of earlier sexual partners, were not inquired into in this study. Bias due to rather low participation, or reporting bias are possible explanations for the findings, too. Chance findings are also possible, since multiple analyses were conducted.

Endometriosis and salpingo-oophoritis may also cause secondary decrease of fertility or delay of conception, e.g., due to tubal occlusion. The possible double role of these diseases as potential results of exposure and possible causes of decreased fertility need to be investigated further in other studies. However, on the basis of this study these additional findings may be taken as possible hypotheses for further studies.

CONCLUSIONS

The results suggest that a woman's occupational exposure to formaldehyde has an adverse effect on fertility. The prevention of exposure by using protective gloves when handling formaldehyde had a beneficial effect on the time to pregnancy. The possible occupational risk factors of endometriosis and salpingo-oophoritis should be explored in further studies.

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