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Spontaneous Abortions Among Women Exposed to Organic Solvents

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We investigated the association between medically diagnosed spontaneous abortions and occupational exposure to organic solvents. The study population was composed of women biologically monitored for solvents. The workers were classified into exposure categories on the basis of work description and the use of solvents as reported in the questionnaires, and on biological exposure measurements. The odds ratio of spontaneous abortion for solvent exposure, adjusted for potentially confounding factors, was significantly increased (2.2, 95% confidence interval [CI] = 1.2–4.1). The increase was most consistent among workers exposed to aliphatic hydrocarbons: the odds ratio for high exposure was 3.9 (95% CI = 1.1–14.2) and for exposed graphics workers 5.2 (95% CI = 1.3–20.8). The odds ratio was increased also among toluene-exposed shoe workers (9.3, 95% CI = 1.0–84.7). The results of the study support the hypothesis of a positive association between spontaneous abortion and exposure to organic solvents during pregnancy and suggest that exposure, especially to aliphatic hydrocarbons, increases the risk of abortion.

Key words: aliphatic hydrocarbons, maternal exposure, reproductive hazards

INTRODUCTION

Organic solvents are one of the most prevalent sources of chemical exposure among working women. They are used widely in various fields of industry, the most important of which are the plastics, graphics, and metal (degreasing) industries; the manufacture and use of paints, lacquers, and adhesives; and dry cleaning. It has been estimated that in Finland about 50,000 workers (2% of the labor force) are occupationally exposed to organic solvents.

Some epidemiologic studies have suggested that organic solvents may have harmful effects on the developing embryo/fetus. An increased risk of spontaneous abortion has been observed in occupations involving exposure to solvents, such as painting [Heidam, 1984a], dry cleaning [Kyyrönen et al., 1989], and pharmaceutical factory work [Taskinen et al., 1986]. An excessive number of abortions has also been reported in women exposed to solvents in manufacturing [McDonald et al., 1988b].

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Congenital malformations have been associated with solvent exposure [Kucera, 1968; Holmberg, 1979; Holmberg and Nurminen, 1980; Holmberg et al., 1982; McDonald et al., 1987; Tikkanen and Heinonen, 1988]. In addition, an excess of abortions [Strandberg et al., 1978; Lindbohm et al., 1984; Axelsson and Rylander, 1989] and malformations [Meirik et al., 1979; Hansson et al., 1980; Blomqvist et al., 1981; Ericson et al., 1982, 1984] has been observed among laboratory workers. In these studies, exposure to organic solvents has been suggested as one of the potential etiologic factors. Some studies, however, have shown no elevated risk associated with solvents used in laboratory work [Olsen, 1983; Axelsson et al., 1984; Heidam, 1984b].

Most of the epidemiologic studies have examined the association between pregnancy outcome and occupations with solvent exposure or exposure to organic solvents in general. They have not usually analysed the effects of specific solvents in detail. Here, we examine the association between medically diagnosed spontaneous abortions and occupational exposure to different types of specific solvents. The study population is composed of women biologically monitored for at least one of six solvents, namely, styrene, toluene, xylene, tetrachloroethylene, trichloroethylene, and 1,1,1-trichloroethane. As biological measurements are usually done on heavy and well-documented exposures, we consider this work force to be particularly suitable for a study on reproductive outcomes.

MATERIAL AND METHODS

The study population was identified using three data sources: the records of women biologically monitored for solvent exposure at the Institute of Occupational Health in 1965–1983, the nationwide data base on pregnancies in Finland, and the Finnish Register of Congenital Malformations (Fig. 1). The Finnish legislation on occupational health care requires regular health examinations for workers exposed to agents hazardous to health. Therefore, workers regularly exposed to, e.g., organic solvents, are biologically monitored. Most of the biological monitoring is done as a service activity at the Institute of Occupational Health, and the laboratory adheres to repeated quality control tests. Exposure measurements included were: the mandelic acid concentration in urine for styrene; trichloroacetic acid concentration in urine for trichloroethylene; methylhippuric acid concentration in urine for xylene; and the concentration of tetrachloroethylene, toluene, and 1,1,1-trichloroethane in blood. There were 8,547 exposure measurements performed on 3,265 women.

To identify the pregnancies among the biologically monitored workers, they have been linked by a personal identification coding system to the nationwide data base on medically diagnosed pregnancies, treated in the hospital between 1973 and 1983, and to the Finnish Register of Congenital Malformations from 1973 to 1982 (Fig. 1). The data base includes information on all births (International Classification of Diseases [ICD] codes 650–662) and spontaneous abortions (ICD codes 643, 645) retrieved from the Hospital Discharge Register and hospital polyclinic (outpatient clinic) records in Finland. The Register covered 94% of all officially recorded births in Finland, in 1973–1983, and we have estimated that about 80–90% of all recognized spontaneous abortions can be detected from the Register and polyclinic records. The proportion of spontaneous abortions from all pregnancies (spontaneous abor-

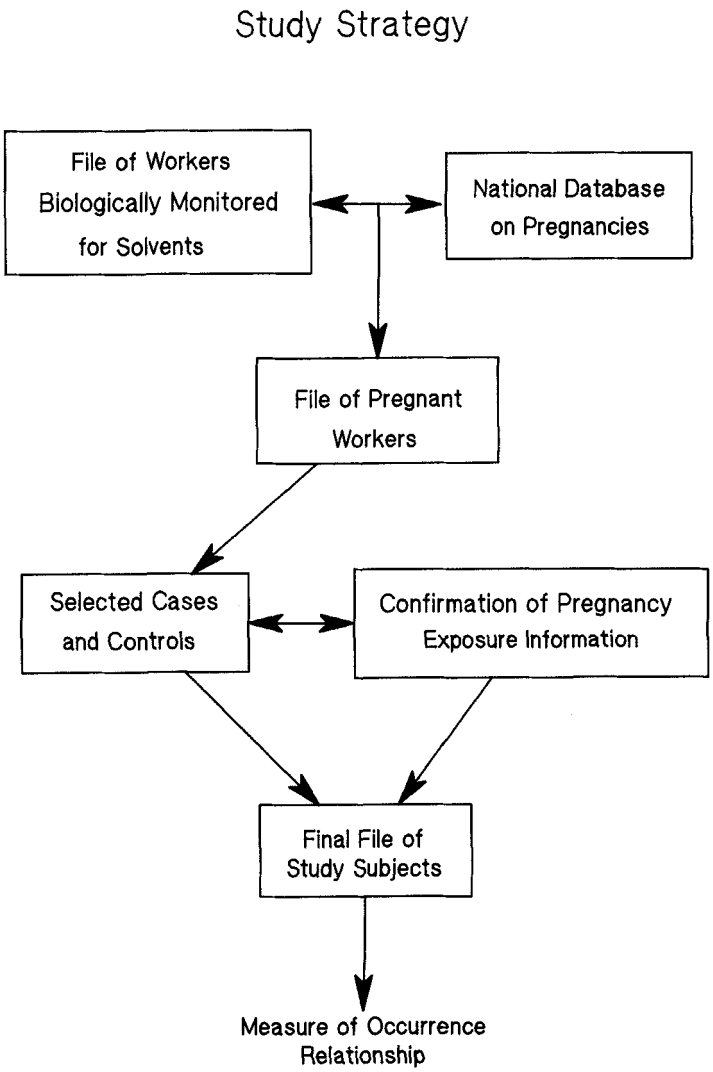

Fig. 1. Study strategy in an investigation on spontaneous abortion and exposure to organic solvents.

tions, induced abortions, and births) was, in this data base, 8.9% in 1973–1983. The content, technical quality, and validity of the data base on pregnancies has been described in detail elsewhere [Lindbohm and Hemminki, 1988].

The registering of malformations is based on compulsory notification of all malformations detected during the first year of life [Saxen, 1983]. Only eleven congenital malformations were detected from the register. The number was too small for meaningful analysis.

The study was conducted using a case-control design. The women with a spontaneous abortion were defined as cases. If the woman had had two or more

spontaneous abortions, only one was randomly selected. Three controls were selected for every case from the women who had given birth, but only one pregnancy per woman was included. Only those women who had neither a registered spontaneous abortion, nor a registered malformed child during the study period, were qualified as potential controls. The controls were matched with the case for age at the time of conception within 2.5 years, using the nearest available matching. No controls were found for two cases due to their age (44 and 43 years). Three controls were available for 104 cases, two for eight cases and only one for eight cases.

A questionnaire was mailed to the study subjects to obtain data on their employment, occupation, workplace, and occupational exposure during the first trimester of pregnancy. The women were asked to describe their work tasks in detail and to report whether their work included painting, lacquering, glueing, printing, rubber work, plastics work, degreasing, lamination, or dry cleaning. They were also asked if they had handled any of the solvents monitored (styrene, toluene, xylene, tetrachloroethylene, trichloroethylene, and 1,1,1-trichloroethane) and to report other solvents they had handled (e.g., white spirit, lacquer, petrol, stoddard solvents, thinner) and their frequency (daily, 1–4 days a week, less than once a week). Furthermore, data on the women's pregnancy and work histories, chronic and acute diseases, as well as smoking and use of alcohol during the first trimester of pregnancy were also sought.

Information regarding heavy lifting at work or at home also was requested [Taskinen et al., 1986; McDonald et al., 1986]. A score variable was formed to analyze the effects of daily lifting at work or at home. The lifts were scored as follows: 5–9 kg = 1 point, 10–19 kg = 3 points, and ≥20 kg = 5 points per lift. The points were summed and the score variable was used in the analysis in three categories: no lifts (<5 points), light lifts (5–29 points), and heavy lifts (≥30 points).

Two members of the study group classified the women by likelihood of exposure and by level of exposure without knowing who was a case or a control. The classification was based on the occupation, work description, and use of solvents as reported by the study subjects, and on biological exposure measurement data when available. In many cases it was also possible to confirm the reported data on employment from the independent laboratory log books. The data agreed with each other nearly without exception. The likelihood of exposure was categorized based on consideration of individual cases as follows: *not exposed,* if the work tasks did not involve handling of solvents, no exposure was reported by the worker and no exposure measurement had been made; *potentially exposed,* if the work tasks might have involved the use of solvents (e.g., glueing), but no solvent exposure or an undefined solvent exposure was reported by the worker and no exposure measurement had been made; *exposed,* if exposure measurement had been made when holding the same job and the work tasks implied solvent exposure, or if solvent exposure was reported. In the final analysis, workers potentially exposed to a specific solvent were combined with the "no exposure" category of the specific solvent variable. This did not affect the results.

Three exposure levels were distinguished: high, low, and none. The level of exposure was assessed on the basis of the reported frequency of the use of solvents and the available information on typical levels of exposure in that particular job, as based on industrial hygienic knowledge. The feasibility of biological monitoring data

TABLE I. Response Rate of the Cases and the Controls and the Final Study Population in a Study of Women Exposed to Organic Solvents in Finland in 1973–1983

	Cases	Controls	Total
Total population	120	336	456
Respondents (% of total)	102 (85.0)	288 (85.7)	390 (85.5)
Reported pregnancy of interest (% of respondents)	80 (78.4)	286 (99.3)	366 (93.8)
Final population for matched analysis	73	167	240

for classification of exposure was limited because the solvent measurements describe only short-term exposure (from 2 hours to a few days) and only 5% of the workers had been measured during the first trimester of pregnancy. Thus, exposure classification was based mainly on the work task description and reported solvent usage, and monitoring results supported the information.

Exposure was defined as *high* if the worker handled solvents daily or 1–4 days a week, and the level of exposure, according to biological exposure measurements or industrial hygiene measurements available at the Institute, was high. Exposure was defined as *low* if the worker handled solvents 1–4 days a week, and the level of exposure, according the measurements of the Institute, was low, or if the worker handled solvents less than once a week. Otherwise, the level of exposure was defined as *none*. After classification, the work tasks and the related exposures were listed by the level of exposure, which was checked by an independent, experienced industrial hygienist.

The odds ratios for exposure were estimated with the logistic regression model for individually matched data, based on the conditional likelihood function. The statistical significance for separate variables was evaluated by comparing the respective standardized regression coefficients with a normal distribution [Breslow and Day, 1980].

RESULTS

The response rate in the spontaneous abortion study, after four mailings, was 85.5%, and it was similar among the cases and the controls (Table I.) The pregnancy of interest was reported by 78% of the cases of spontaneous abortion and by 99% of the controls (births). The final population for the analysis was restricted to the matched case-control sets, who confirmed their pregnancy and reported in detail their occupational exposures during early pregnancy (73 cases and 167 controls). The decrease in the number of controls was due mainly to the matching procedures; i.e., only units formed by a case and her individually matched controls were accepted. If a case did not respond or confirm pregnancy, all controls of this set were also excluded. Additionally, eight controls and five cases with their controls, who were classified as potentially exposed to solvents in general, were excluded from the final analysis. One case with a uterus anomaly and one case with an IUD in situ during pregnancy were also excluded. Any control with a reported spontaneous abortion or a malformed child, which was not found in our data base, was left out (N = 5).

The study subjects had been biologically monitored at least once for exposure to styrene, toluene, xylene, tetrachloroethylene, trichloroethylene, or 1,1,1-trichlo-

TABLE II. Distribution of Cases of Spontaneous Abortion and Their Controls by Occupation, Finland, 1973–1983, %

Occupation	Cases	Controls
Employed	82	76
Laboratory work	5	7
Clerical work	4	7
Sales work	3	4
Iron and metalware work	4	5
Shoe and leather work	8	2
Painting and lacquering	5	5
Graphics work	10	2
Plastics product work	4	8
Cleaning work	10	5
Laundry and dry cleaning	5	6
Other work	21	24
Unknown	3	1
Not employed	18	24
Total	100	100
(N)	(73)	(167)

roethane at the Institute of Occupational Health. The measurements for styrene were relatively highest; 38% of the results exceeded the Finnish reference value of the exposed workers (Finnish Threshold Limit Value) (Appendix A). Almost all of the results for the women monitored for tetrachloroethylene indicated exposure, and the reference value of the exposed was reached in 15% of the measurements. The levels of xylene and 1,1,1-trichloroethane exposure were low; none of the results exceeded the reference value of the exposed.

Seventy-eight percent of the study subjects were employed during the first trimester of pregnancy of interest (Table II). Most often they were employed in the production of plastic goods, cleaning work, laboratory work, or clerical work. Table III presents the distribution of the cases and controls in the final study population by the pregnancy-related variables studied.

Exposure to organic solvents in general was more common among the cases (42 of 73 cases, 58%) than among the controls (70 of 167 controls, 42%). The odds ratio of spontaneous abortion for solvent exposure, adjusted for previous spontaneous abortions, parity, smoking, and use of alcohol was significantly increased: 2.2 (95% confidence interval [CI] 1.2–4.1) (Table IV). Fever diseases and lifting were excluded from the analysis; their odds ratios were not significantly different from unity, and their inclusion in the model had no essential effect on the odds ratio for solvents.

Table V shows the odds ratios for specific solvents, adjusted for the potentially confounding factors given above and for all other solvents. The odds ratio was higher than unity for all the main groups of solvents. For aliphatic hydrocarbons (mainly white spirit type of mixtures of aliphatic hydrocarbons with 0–15% aromatic compounds), the odds ratio was 2.1 (95% CI = 0.9–5.1). The odds ratios of four of six specific solvents were increased, but not statistically significant. The increase was highest for 1,1,1-trichloroethane. However, four of seven 1,1,1-trichloroethane exposed workers (3 cases, 1 control) also had handled white spirits. The odds ratio for

TABLE III. Spontaneous Abortion Cases and Their Controls (Births) by Pregnancy History, Diseases, Personal Habits, and Lifting at Work or at Home, During the First Trimester of Pregnancy, Finland, 1973–1983

	Cases		Controls	
Variable	N	%	N	%
Parity				
0	21	29.6	74	44.3
1	32	45.1	59	35.3
≥ 2	18	25.4	34	20.4
Previous spontaneous abortions[a]	8	11.3	9	5.5
Fever diseases	5	7.4	25	15.4
Smoking	26	36.1	53	31.9
Use of alcohol				
< Once a week	33	46.5	52	31.3
≥ Once a week	2	2.8	6	3.6
Lifting at home (score)				
Light (5–29 points)	10	14.7	23	14.5
Heavy(≥ 30 points)	7	10.3	13	8.2
Lifting at work (score)				
Light (5–29 points)	13	18.8	28	17.3
Heavy (≥ 30 points)	14	20.3	33	20.4
Total number	73		167	

[a]Includes all previous abortions of the cases and previous abortions of the controls before the study period 1973–1983.

TABLE IV. Odds Ratio of Spontaneous Abortion for Organic Solvents, Logistic Regression Model

Variable	Odds ratio	95% Confidence interval	p Value
Solvents	2.2	1.2–4.1	0.01
Previous spontaneous abortion	2.3	0.8–6.9	0.15
Parity ≥1	2.2	1.0–4.7	0.04
Smoking	1.2	0.6–2.2	0.64
Use of alcohol	1.5	0.9–2.7	0.16

styrene was low, 0.3, and the difference from unity was of borderline significance (95% CI = 0.1–1.0).

The three most common solvents with an increased odds ratio were analyzed by the level of exposure. The odds ratios for tetrachloroethylene and aliphatic hydrocarbons, adjusted for potentially confounding factors, increased with the level of exposure; for toluene, the reverse was the case (Table VI). High exposure to aliphatic hydrocarbons was associated significantly with an excess of spontaneous abortions (odds ratio 3.9, 95% CI = 1.1–14.2).

The association of tetrachloroethylene, toluene, and aliphatic hydrocarbons with spontaneous abortions was also examined by detailed occupational task (Table VII). The odds ratio of spontaneous abortion for aliphatic hydrocarbons was increased among graphics workers (5.2, 95% CI = 1.3–20.8) and painters (2.4, 95% CI =

TABLE V. Odds Ratio of Spontaneous Abortion for Specific Organic Solvents, Logistic Regression Models*

Variable	Number of exposed cases/controls	Odds ratio	95% Confidence interval	p Value
Aromatic hydrocarbons	21/31	1.6	0.8–3.3	0.21
Styrene	3/17	0.3	0.1–1.0	0.05
Toluene	15/20	1.6	0.7–3.8	0.25
Xylene	5/7	1.3	0.4–4.5	0.67
Halogenated hydrocarbons	14/28	1.4	0.6–3.2	0.38
Tetrachloroethylene	8/15	1.4	0.5–4.2	0.51
Trichloroethylene	3/13	0.6	0.2–2.3	0.45
1,1,1-trichloroethane	4/3	3.4	0.7–16.9	0.14
Aliphatic hydrocarbons	13/13	2.1	0.9–5.1	0.10

*The models include the following variables: previous spontaneous abortions, parity, smoking, use of alcohol, and exposure to other solvents.

TABLE VI. Odds Ratio of Spontaneous Abortion for Selected Organic Solvents, Logistic Regression Models*

Variable	Number of exposed cases/controls	Odds ratio	95% Confidence interval	p Value
Toluene				
Low exposure	10/11	1.8	0.7–4.7	0.23
High exposure	5/8	1.4	0.4–4.9	0.64
Tetrachloroethylene				
Low exposure	2/9	0.5	0.1–2.9	0.45
High exposure	5/6	2.5	0.6–10.5	0.22
Aliphatic hydrocarbons				
Low exposure	5/8	1.1	0.3–3.9	0.90
High exposure	8/5	3.9	1.1–14.2	0.04

*The models include the following variables: previous spontaneous abortions, parity, smoking, use of alcohol, and exposure to other solvents.

0.5–13.0), but not among other workers. However, in the latter group, the proportion of highly exposed was only 30%, whereas in the two former groups it was 69%. The odds ratio was increased also among toluene-exposed shoe workers (odds ratio 9.3, 95% CI = 1.0–84.7) and dry cleaners exposed to tetrachloroethylene (odds ratio 2.7, 95% CI = 0.7–11.2).

Aliphatic hydrocarbons were not biologically monitored, but industrial hygienic measurements have been performed by the Institute of Occupational Health in two printing houses, which contributed subjects to this study (Appendix B). In two of four measurements, the concentrations of white spirit in air exceeded, during the cleaning of the printing machine, the Finnish Threshold Limit Value (150 ppm). All the printers included in this study reported that their work included cleaning of the machine.

The mean level of blood toluene measurements made among the shoe workers was slightly higher (0.51 μmol/liter, 13 morning samples) than the mean among the other toluene-exposed workers (0.38 μmol/liter, 10 morning samples). The shoe workers also reported use of toluene more frequently than the other toluene-exposed workers. Industrial hygienic measurements have been performed in three of the five

TABLE VII. Odds Ratio of Spontaneous Abortion for Specific Solvents by Occupation, Logistic Regression Models*

Solvent/occupation	Number of exposed cases/controls	Odds ratio	95% Confidence interval	p Value
Tetrachloroethylene				
Dry cleaning	4/5	2.7	0.7–11.2	0.16
Other work in dry cleaners	1/6	0.6	0.1–5.5	0.68
Other work	3/4	1.3	0.3–6.6	0.72
Toluene				
Shoe work	5/2	9.3	1.0–84.7	0.05
Laboratory work	2/4	0.9	0.2–5.5	0.95
Other work	8/14	1.2	0.5–3.3	0.69
Aliphatic hydrocarbons				
Graphic work	7/3	5.2	1.3–20.8	0.02
Painting and lacquering	3/3	2.4	0.5–13.0	0.30
Other work	3/7	0.9	0.2–3.6	0.84

*The models include exposure to other solvents.

work places of the shoe workers (Appendix C). The concentration of toluene in air varied from 1 ppm to 33 ppm. Other solvents detected were acetone and hexane; the hexane levels varied between 33 and 56 ppm.

The mean level of blood tetrachloroethylene measurements, taken nearest to the pregnancy, was higher among dry cleaning workers than among other workers monitored for tetrachloroethylene exposure (2.11 μmol/liter, 6 samples vs. 0.43 μmol/liter, 7 samples).

Twenty-two cases did not confirm the spontaneous abortion registered in the hospital records. They were mailed an additional questionnaire requesting data on their occupation, solvent exposure, and living habits during the registered year of pregnancy. Eleven responded and were included with their controls in the study population. The odds ratio for solvents, adjusted for previous abortions, parity, use of alcohol and smoking, was 2.4 (95% confidence interval 1.3–4.5, $p = 0.004$) in this population. The result does not differ essentially from that observed in the original study population.

DISCUSSION

Organic solvents are volatile liquids that dissolve lipids and high-molecular-weight compounds. In view of their lipid solubility, it is likely that most organic solvents traverse the placenta into the fetus. The passage of trichloroethylene through the placenta has been shown in a study of maternal and fetal blood levels taken at delivery under trichloroethylene anesthesia [Laham, 1970]. Placental transfer of xylene has been demonstrated in the mouse [Nawrot et al., 1980]. In animal tests on mammals, organic solvents have induced malformations (chloroform, carbon disulfide, tetrachloroethane), retarded growth (benzene, tetrachloroethylene, methylene chloride, trichloroethylene, toluene, xylene), and embryolethal effects (styrene) [Barlow and Sullivan, 1982; Hemminki, 1980].

The results on spontaneous abortion and organic solvent exposure in previous

epidemiologic studies have been inconsistent. Laboratory workers have been investigated most often. A Swedish study [Axelsson et al., 1984] revealed a slight (statistically insignificant) increase in the spontaneous abortion rate among laboratory workers exposed to solvents. No increase was found in a Danish study in laboratory workers exposed to organic solvents in general [Heidam, 1984b].

In a study among pharmaceutical factory workers, frequent use of solvents, methylene chloride in particular, was related to spontaneous abortion [Taskinen et al., 1986]. Another study showed an increased risk of self-reported spontaneous abortions for painters, but not for other factory workers (mainly rubber, plastics, machines, and tin industries) or dental assistants, with alleged exposure to organic solvents [Heidam, 1984a]. Differences in the composition of the study populations, in the types of solvents used, and in the intensity of exposure may partly explain the inconsistent results. It is also unclear how well the studies were able to reconstruct the actual exposure during the first trimester.

The present investigation showed a positive association between spontaneous abortion and exposure to organic solvents in general. A detailed examination of specific solvents showed that the association was most consistent among the workers exposed to aliphatic hydrocarbons. The risk increased with the level of exposure, adding credibility to the finding. A previous study of pharmaceutical factory workers also pointed to an increased (not significant) risk of abortion associated with exposure to these solvents [Taskinen et al., 1986].

The highest risk for aliphatic hydrocarbons was found among graphic workers who were employed as offset printing workers or printing trade workers. They used the solvents for cleaning the printing machines and as diluent for printing ink. In cleaning the machines, exposure may reach a high level for a short period as indicated by industrial hygienic measurements. Aliphatic hydrocarbons include here mainly mixtures of nonaromatic mineral oil distillates with 0–15% aromatic compounds. Usually they were not used alone. The workers were also exposed, among other things, to toluene, 1,1,1-trichloroethane, thinner, and xylene. Although our data suggest that the findings are due to aliphatic hydrocarbons, we cannot exclude any combined solvent effects because of the multiple exposures to different solvents.

A small group of toluene-exposed shoe workers had an increased risk of abortion, whereas the relative risk of other workers with toluene exposure was close to unity. The shoe workers used toluene more frequently than the other toluene-exposed workers, and their blood toluene measurements indicated a slightly higher level of exposure compared to the others. Two previous studies have suggested an association between toluene exposure and adverse reproductive outcome. McDonald et al. [1987] have reported an excess of urinary tract defects, which was related to toluene exposure. An increased risk of abortion (not significant) was observed in toluene-exposed workers in the pharmaceutical industry [Taskinen et al., 1986].

Interestingly, in two of three shoe factories from which industrial hygienic measurements were available, relatively high levels of hexane (33–56 ppm) were measured. Hexane, being an aliphatic compound, may contribute to the excess of spontaneous abortions.

A suggestive increase (statistically insignificant) in the risk of abortion was found among tetrachloroethylene-exposed workers in dry cleaning. The finding is

congruent with the result of a study conducted among laundry workers in Finland [Kyyrönen et al., 1989].

The association between styrene exposure and spontaneous abortion was negative. Similar results were obtained in two earlier studies [Härkönen and Holmberg, 1982; Hemminki et al., 1984; Lindbohm et al., 1985], although our first study [Hemminki et al., 1980] and a Canadian study [McDonald et al., 1988a] suggested a positive association.

It has been suggested that an unexpected result in one reproductive outcome may be a sign of pathology in an earlier phase of the chain of reproductive events [Selevan and Lemasters, 1987]. For example, a very high exposure could result in very early, "subclinical" fetal loss, and the proportion of clinical fetal loss might therefore be less than expected. Recently, serum levels of prolactin were found to relate significantly to the urinary excretion of styrene metabolites among exposed women [Mutti et al., 1984]. Excess production of prolactin is expressed as oligomenorrhea or amenorrhoea and infertility in women. Thus, styrene might be able to interfere with reproductive events in an earlier phase causing, e.g., very early subclinical spontaneous abortions.

Differential misclassification arising from selective recall of exposure may distort the results of a study using interview data on exposure. To reduce the potential recall bias, we defined the study subjects' exposure, not only on the basis of self-reported use of solvents, but also based on information about the woman's occupation, detailed work description, answers to questions on typical tasks involving solvent exposure and on biological exposure measurements when available. Blind exposure assessment also reduces the possibility of selective misclassification.

To assess the effects of recall bias, the results of the exposure measurements, performed within 24 months before pregnancy or during its first trimester, were compared with the workers' own reports on exposure to specific solvents. The proportion of the study subjects who did not report exposure to a specific solvent, contrary to the measurements was 19% (9/47). This observation suggests some underreporting or unawareness of exposure. The finding indicates, once again, the importance of confirming the self-reported exposure data from other independent data sources in reproductive studies. Among the cases, the proportion was 18%, and among the controls it was 20%. The similarity of these proportions suggests a nondifferential misclassification of exposure, which tends to deflate the estimates of the true odds ratios toward unity [Kleinbaum et al., 1982].

The response rate in the study population was similar among the cases and the controls. It varied slightly according to the type of solvent. The most distinct difference between the cases and the controls was among those monitored for styrene, among whom the response rate was 70% for the cases, but 86% for the controls. The level of styrene exposure was higher among the nonrespondents than among the respondents; this situation prevailed both for the cases and the controls. The difference in the response rate between the cases and the controls and in the level of exposure between the respondents and nonrespondents may have artificially reduced the odds ratio for styrene exposure.

The statistical power of the study was quite low for separate solvents due to the small size of the study population and low prevalence of exposure. The probability of

detecting a twofold relative risk varied from 15% for 1,1,1-trichloroethane to 32% for toluene using $\alpha = 0.05$ [Miettinen, 1969]. The probability of detecting a threefold relative risk varied from 44% to 85%, respectively. Furthermore, as several comparisons were made, the contribution of chance cannot be excluded, although the findings of the study appear biologically plausible, and some have been suggested previously.

The results of the present study support the hypothesis of a positive association between spontaneous abortion and exposure to organic solvents during early pregnancy. They suggest that exposure, especially to aliphatic hydrocarbons (e.g., in graphics work), increases the risk of spontaneous abortion. The finding of the harmful effects of toluene (or hexane) exposure in the shoe industry is based on small numbers and should be confirmed in future studies before final conclusions can be drawn.

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APPENDIXES

Appendix A. Biological Exposure Measurements of Organic Solvents Among Workers Holding the Same Job During Pregnancy and Measurement (N = 106)

Solvent	N	Median	Mean ± SE	Results> FRV of unexposed[a] (%)	Result> FRV of exposed[b] (%)	FRV of exposed
Xylene; methyl-hippuric acid in urine, mmol/liter	21	<0.1	0.7 ± 0.4	28.6	0.0	10.0
Styrene; mandelic acid in urine, mmol/liter	37	5.7	8.0 ± 1.6	73.0	37.8	7.0
Trichloroethylene; trichloroacetic acid in urine, μmol/liter	64	48.1	96.2 ± 19.2	48.4	7.8	360
Toluene in blood, μmol/liter						
Morning sample	32	0.3	0.5 ± 0.2	37.5	3.1	2.0
Afternoon sample	5	0.3	0.4 ± 0.2	40.0	0.0	(15.0)
Unknown	4	<0.1	0.05 ± 0.05	0.0	..	..
Tetrachloroethylene in blood, μmol/liter						
Morning sample	13	0.7	1.1 ± 0.3	100.0	15.4	2.5
Afternoon sample	30	0.5	1.5 ± 0.3	90.0	0.0	(12.5)
Unknown	2	0.1	0.1 ± 0.1	50.0		
1,1,1-trichloro-ethane in blood, μmol/liter						
Morning sample	3	<0.1	0.03 ± 0.03	0.0	0.0	1.2
Afternoon sample	2	0.2	0.2 ± 0.1	50.0	0.0	(12.0)
Unknown	11	0.1	0.1 ± 0.03	36.4		

[a]Finnish reference value (FRV) of unexposed is upper limit of nonoccupational exposure.
[b]Finnish reference value of exposed is national Threshold Limit Value.

Appendix B. Industrial Hygienic Measurements of Aliphatic Hydrocarbons in Two Printing Houses That Contributed Pregnancies to the Study

Pregnancies		Industrial hygienic measurements			
Observation	Discharge month/year	Month/year	Job description for measurements	Solvent	Result
Case	6/83	11/80	Washing the roller (printing machine 1)	White spirit	212–304 ppm
Control	11/79			Toluene	38–40 ppm
Control	1/79			Combined solvent content (% of TLV)	180–244%
			Washing the roller (printing machine 2)	White spirit	8–68 ppm
				Combined solvent content (% of TLV	6–45%
			Washing the roller (printing machine 3)	White spirit	4–59 ppm
				Ethanol	61 ppm
				Combined solvent content (% of TLV)	3–45%
Case	7/81	1/82	Washing the silk frame (using a respirator)	White spirit	650–1,167 ppm
			Printers	White spirit	5–7 ppm

Appendix C. Biological Toluene Exposure Measurements Among Gluers in the Shoe Industry and Industrial Hygienic Measurements in Three Shoe Factories That Contributed Pregnancies to the Study

Pregnancies		Biological measurements		Industrial hygienic measurements		
Observation	Discharge month/year	Month/year	Results (μmol/liter)	Month/year	Solvent	Result
Case	9/78	2/80–2/82	0.1–0.8	2/79	Toluene	23–33 ppm
Case	9/80	11/78–12/80	0.3–0.9		Acetone	25–43 ppm
Case	5/80	11/78–2/82	0.6–1.0		Hexane	34–46 ppm
					Combined solvent content (% of TLV)	37–51%
Control	10/75	10/80	0.1	12/73	Toluene	16 ppm
					Acetone	49–89 ppm
					Hexane	33–56 ppm
					Combined solvent content (% of TLV)	32–45 %
Control	7/80	7/81	0.2[a]	2/82	Toluene	1 ppm
					Acetone	6–11 ppm
					Ethylacetate	2 ppm
					Combined solvent content (% of TLV)	3–4%
Case	5/82	1/80–2/82	0.1–0.2			
Case	10/83	10/83	0.5[a]			

[a]Sample not taken in the morning.