

Laboratory Work and Pregnancy Outcome

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Spontaneous abortions among women working in laboratories, and congenital malformations and birth weights of the children were examined in a retrospective case-referent study. In the spontaneous abortion study there were 535 women (206 cases and 329 referents), and in the malformation study 141 women (36 cases and 105 referents). The analysis of the birth weights concerned 500 women (referents). Significant associations with spontaneous abortion were found for exposure to toluene (odds ratio [OR], 4.7, 95% confidence interval [CI], 1.4 to 15.9), xylene (OR 3.1, CI 1.3 to 7.5) and formalin (OR 3.5, CI 1.1 to 11.2) ≥ 3 days a week, adjusted for the covariates. Most of the women exposed to formalin and xylene were working in pathology or histology laboratories. No association with congenital malformation was found.

In a laboratory environment workers may be exposed to toxic chemical, physical, or biological agents. An increased occurrence of spontaneous abortions has been suggested for women working in hospital laboratories,^{1,2} in chemical laboratories in the pharmaceutical industry,³ and for women working as laboratory assistants.⁴ An increased risk of malformation in the offspring of laboratory workers has also been reported.^{3,5-8} In some studies, however, the risk of spontaneous abortion^{9,10} or congenital malformation has not been increased among laboratory assistants.^{11,12}

The aims of this study were to elucidate further the possible reproductive risks in laboratory work and to try to identify individual chemical or physical agents potentially harmful to pregnancy.

Materials and Methods

The Study Population

The study subjects were sampled from three sources: the payroll of the state-employed laboratory personnel in Finland (laboratories of the universities, research centers, etc), the Finnish Union of Laboratory Assistants, and the register of Employees Occupationally Exposed to Carcinogens.

Job titles beginning with "laboratory" and occupations termed "assistant" were used in the computer search from the state's employee payroll from the years 1970 and 1975 to 1986. The search yielded 5908 female employees. In 1987 the members of the Finnish Union of Laboratory Assistants, including also the resigned members from previous years, totalled 2426 persons. In the register of the employees exposed to carcinogens, 2734 female laboratory employees

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were registered in 1979 to 1986. These three sources overlapped partially (17%); the total number of women in the study base was 9186.

The information on the pregnancy outcome of the women in the study base was obtained from the Hospital Discharge Register supplemented by the data base on the spontaneous abortions that were treated at the outpatient clinics of the hospitals. The contents and reliability of the data base have been described elsewhere.¹³ During the years 1973 to 1986 the women in the study base had 7316 pregnancies including 5663 births (77%), 687 (9%) spontaneous abortions, and 966 (13%) induced abortions.

The study was conducted using a case-referent design. The women who had been treated for spontaneous abortion at the hospital or at the outpatient clinic were defined as cases in the spontaneous abortion part of the study. The women with only one registered spontaneous abortion during the study period were selected. For each case two referents were selected from among the women who had given birth to a baby, but did not have any registered spontaneous abortion. Women whose child was registered in the Finnish Register of Congenital Malformations were not eligible as referents. Only one pregnancy per woman was included. The study population was restricted to women in the age range of 20 to 34 years at the beginning of the study pregnancy. The referents were individually matched with the cases for age (within 24 months) at the time of conception, and with the year of the end of the pregnancy.

In the malformation part of the study, the women with a child registered in the Finnish Register of Congenital Malformations were defined as cases. Four referents for each case were selected as described above.

The possible effects of occupational exposure on the birth weight of the children were examined among the 500 referents who responded.

The information on occupational exposure, health status, medication, used contraception, smoking, and alcohol consumption during the first

trimester of the pregnancy were collected by mailed questionnaires from the study persons. The questionnaire inquired the pregnancy history and the birth weight and sex of the born child. The study pregnancy was classified as "confirmed" if the woman reported the same pregnancy that was found in the Hospital Discharge Register or in the supplementary data base on the spontaneous abortions.

In the spontaneous abortion study, 1000 questionnaires were mailed and 824 (82.4%) women responded. Fifty questionnaires were returned empty by women who had been selected from the state employees' payroll under the occupational title "assistant." According to their enclosed comments, they were university assistants from other than chemical faculties, eg, teachers or lawyers, who did not wish to participate in the study. The material for the matched analysis consisted

of 206 cases and 329 referents. The details of the formation of material are presented in Table 1.

In the study on congenital malformations, the questionnaire was mailed to 248 persons; 207 (83.5%) responded. Twelve persons (assistants from other than chemical faculties, see above) returned empty questionnaires. The material for the matched analysis consisted of 36 cases and 105 referents (Table 2).

Exposure Assessment

Self Reports. The exposure to individual chemicals was assessed on the basis of the reported frequency of the use of the chemical. If the chemical was handled 1 or 2 days a week, the exposure was classified as rare. If the chemical was handled at least 3 days a week, the exposure was classified as frequent. A chemical was defined as a carcinogen if classified as a human

TABLE 1
Response Status and Final Population in the Study of Laboratory Workers and Spontaneous Abortion

	No. of Cases	No. of Referents	Total
Mailed questionnaires	335	665	1000
Returned questionnaires	268 (80.0%)	556 (83.6%)	824 (82.4%)
Returned empty	18 (5.3%)	33 (5.0%)	51 (5.1%)
Study pregnancy not confirmed*	24	4	28
No information on work		1	1
Referent child stillborn or malformed		9	9
Extrauterine pregnancy or induced abortion	5		5
Noninformative response	2	2	4
After matching:			
Case had no referent	13		13
Referent had no case		178	178
Final study population	206	329	535

* Pregnancies found in the data base, but not reported by the women.

TABLE 2
Response Status and Final Population in the Study of Laboratory Workers and Congenital Malformations

	No. of Cases (%)	No. of Referents (%)	Total (%)
Sent questionnaires	50	198	248
Returned	41 (82)	166 (86.8)	207 (83.5)
Returned empty	4	13	17
Referent's child malformed, excluded		1	1
No information on work	1		1
Referents with no case		47	47
Final study population	36	105	141

carcinogen (group 1), a probable human carcinogen (group 2A), or a potential human carcinogen (group 2B) by the International Agency for Research on Cancer.¹⁴

Occupational Hygienic Assessment of Solvent Exposure. Two occupational hygienists well acquainted with the working conditions of laboratories assessed the overall exposure to organic solvents. The hygienists did not know the pregnancy outcome of the women whose exposure they assessed. The assessment was based on the description of the work task and the use of the solvents, including estimations of the quantity, the using time and frequency and the use of a fume hood. An exposure index was calculated as follows:

Exposure index, $EI = Q \times T \times F \times FH$, where

Q = Quantity of the solvent used:
<0.5 mL at time or "very little"
= 0.1

6–100 mL = 1

>100 mL to 1 L = 3

>1 L = 5

T = Time of use

Seldom = 0.5

Otherwise the no. of hours per day = 1 to 7

F = Frequency of use

Seldom = 0.5

Otherwise the no. of days per week = 1 to 5

FH = Use of fume hood

Yes = 1

Sometimes = 3

No = 6

The scale 1 to 6 for FH was selected because the use of a fume hood decreases the exposure to one-sixth of that without a fume hood.¹⁵

Statistical Analyses. The odds ratios of the variables in the spontaneous abortion and malformation study were estimated with the logistic regression for individually matched data, based on conditional likelihood.¹⁶ The 95% confidence intervals (CI) were calculated by means of the standard errors of the parameters, assuming the normal distribution.

The covariate was considered as a potential confounder, and included in

the multivariate models, if the odds ratio of the covariate exceeded 1.5 or if it was significant ($P < .05$). Smoking, alcohol consumption, and employment status were considered as potential confounders on a prior decision.

The birth weight was analyzed with the standard linear regression. The confidence intervals are based on the standard errors of the parameters.

Results

Spontaneous Abortions

Among women gainfully employed the odds ratio (OR) of spontaneous abortion was not increased (OR 0.9, CI 0.5 to 1.7); among women employed in a laboratory, a slight but not statistically significant increase was found (OR 1.4, CI 0.9 to 2.2). In the analysis, employment, alcohol consumption, parity, previous miscarriages, febrile diseases during pregnancy, and used contraception at the beginning of the pregnancy were controlled for.

In the matched analysis the odds ratios of spontaneous abortion were increased among the women who were frequently (at least 3 days a week) exposed during the first trimester of pregnancy to toluene (OR 4.7, CI 1.4 to 15.9), xylene (OR 3.1, CI 1.3 to 7.5), or formalin (OR 3.5, CI 1.1 to 11.2) (Table 3).

Toluene exposure was common in various types of laboratories, for example in university, industrial, pharmaceutical, and biochemical laboratories. Pathology/histology laboratories employed a greater proportion of the cases (8/10) than of the referents (4/7) exposed to formaline. Majority of the cases (8/10) and referents (5/7) exposed to formalin were also exposed to xylene. About half of the women exposed to xylene worked in pathology/histology laboratories (9/16 cases, 5/12 referents). Simultaneous exposure to other solvents was common, too; one referent was exposed to formalin only, and two cases and referents to xylene only.

The odds ratios were above unity also for frequent exposure (at least 3 days a week) exposure to isopropanol

(OR 2.7), methylene chloride (OR 1.5) and trichloroethylene (OR 1.6) (Table 3), but the 95% confidence intervals included one.

An analysis of the chemical groups showed that the odds ratio of spontaneous abortion was significantly increased for frequent (at least 3 days a week) exposure to aromatic hydrocarbons (OR 2.7, CI 1.3 to 5.6) (Table 4). Odds ratios below unity were found for infrequent exposure to aliphatic (OR 0.4, CI 0.2 to 0.9) and halogenated hydrocarbons (OR 0.6, CI 0.4 to 1.1). Among carcinogens the odds ratios were increased for cytostatic drugs and the radioactive isotopes (4.0 and 1.8, respectively), but neither reached statistical significance (Table 5).

To estimate the effect of overall solvent exposure (formaline excluded) on pregnancy outcome, the solvent score was used. The odds ratio of spontaneous abortion was significantly increased (OR 2.3, CI 1.1 to 4.3) for high exposure (score >50) (Table 4).

Congenital Malformations

The odds ratios of congenital malformations for occupational exposure were not increased (Table 6). The odds ratio for malformations of the women who were employed during the pregnancy was significantly below unity. For smoking (OR 1.7, CI 0.5 to 5.6) and febrile disease (OR 2.4, CI 0.8 to 7.6), the odds ratios were elevated but the increases were not statistically significant. The malformations were of several types. Reported medication during pregnancy did not show any association with malformations.

Birth Weights

The mother's employment in a laboratory was associated with lower birth weight of the child (decrease, 133 g; CI -246 to -20 g), but gainful employment in general had no influence on the birth weight. Exposure at the most 2 days a week to xylene associated significantly with increased birth weight. Exposure at least 3 days a week to ethyl acetate and metal compounds showed a tendency for a

TABLE 3
Odds Ratios of Spontaneous Abortion for Exposure to Organic Solvents:
Multivariate Logistic Regression Models

Exposure*	Odds Ratio	95% Confidence Interval	No. of Cases/Referents
Acetone			
1	1.2	0.7-1.8	41/71
2	1.3	0.7-2.4	27/30
Acetonitrile	1.4	0.4-4.7	7/7
Benzene	0.8	0.4-1.7	11/25
Carbon tetrachloride	1.0	0.5-2.2	13/22
Chloroform			
1	0.7	0.4-1.3	20/40
2	1.3	0.5-3.2	10/14
Cyclohexane	1.4	0.6-3.3	10/14
Ethanol			
1	1.0	0.6-1.7	44/71
2	1.2	0.7-2.0	37/57
Ether			
1	1.0	0.6-1.7	31/50
2	0.5	0.3-1.5	11/25
Ethyl acetate			
1	0.8	0.3-1.9	10/22
2	0.7	0.2-2.3	5/8
Formalin			
1	0.7	0.3-1.4	12/28
2	3.5	1.1-11.2†	11/8
Heptane	1.3	0.5-3.1	13/18
Isopropanol			
1	0.9	0.5-1.7	18/35
2	2.7	0.9-8.1	11/6
Methanol			
1	0.8	0.4-1.3	24/48
2	1.2	0.6-2.2	22/28
Methylene chloride			
1	1.2	0.5-3.0	11/14
2	1.7	0.6-5.0	7/8
Petroleum benzine	1.0	0.3-3.4	5/8
Toluene			
1	0.8	0.4-1.6	17/32
2	4.7	1.4-15.9†	10/6
1,1,1-trichloroethane	1.0	0.3-3.1	6/9
Trichloroethylene	1.6	0.5-4.8	7/9
"White spirit"	1.0	0.4-2.7	8/11
Xylene			
1	1.3	0.7-2.5	19/27
2	3.1	1.3-7.5†	16/12

* Each solvent is included separately in the multivariate model. Class 1 = exposed 1 or 2 days a week; 2 = exposed 3 to 5 days a week. Values are adjusted for employment, smoking, alcohol consumption, parity, previous miscarriages, failed birth control, and febrile disease during pregnancy.

† $P < .05$.

dose-dependent association with decreased birth weight, but none of the findings was statistically significant.

The boys weighed significantly more (+204 g, CI +106 to +302 g) than the girls. Parity also had a positive association with birth weight.

Discussion

The results of this study suggest an association between exposure to toluene, xylene, and formalin/formaldehyde during early pregnancy and an increased risk of spontaneous abor-

tion. The results concerning these individual chemicals should, however, be interpreted cautiously because the laboratory assistants were often exposed to several solvents and chemicals simultaneously. Exposure to organic solvents or to carcinogens did not increase the risk of congenital malformations, but the number of persons in the malformation study was too small for drawing final conclusions.

There are some earlier data supporting our finding on toluene and increased risk of spontaneous abortion. Toluene exposure during pregnancy was associated with increased risk of spontaneous abortion in an audio speakers manufacturing factory, where the mean airborne concentrations of toluene were 88 ppm (range, 50 to 150 ppm).¹⁷ An increased risk of spontaneous abortion was found also in the pharmaceutical industry¹⁸ and among the women monitored biologically for organic solvent exposure,¹⁹ but the findings were not statistically significant. When the occupations of the toluene-exposed workers in the latter study were examined, shoe workers had a significantly increased risk of spontaneous abortion, whereas no increase was found for laboratory assistants.

Several case reports describe fetal alcohol syndrome (microcephaly, short palpebral fissures, micrognathia etc) in babies born to mothers who have sniffed toluene during their pregnancy²⁰⁻²²; for review see ref 23. Occupational exposure to organic solvents, including toluene, has been associated with congenital defects of the central nervous system,^{24,25} and oral clefts,²⁶ but toluene could not be singled out as the causative agent. McDonald et al (27) have reported an excess of urinary tract defects related to toluene exposure.

Toluene passes the placenta, and the concentration in mouse fetal blood is about 75% of the maternal blood concentration. No evidence for teratogenic effects has been reported in animal studies, but fetotoxicity (reduction in the mean fetal weight, retarded ossification, etc) has been found in several studies. In animal

TABLE 4
Odds Ratios of Spontaneous Abortion for Exposure to Solvent Groups:
Multivariate Logistic Regression Model

Solvent Group*	Odds Ratio	95% Confidence Interval	No. of Cases/Referents
Aliphatic			
1	0.4	0.2-0.9†	14/39
2	1.0	0.4-2.5	12/16
Aromatic			
1	0.8	0.4-1.4	26/54
2	2.7	1.3-5.6‡	24/20
Halogenated			
1	0.6	0.4-1.1	24/53
2	1.8	0.9-3.7	20/20
Solvent score§			
5-50	1.0	0.6-1.7	38/57
>50	2.3	1.1-4.3†	23/21

* Each solvent is included separately in the multivariate model. Class 1 = exposed 1 or 2 days a week; 2 = exposed 3 to 5 days a week. Values are adjusted for employment, smoking, alcohol consumption, parity, previous miscarriages, failed birth control, and febrile disease during pregnancy.

† $P < .05$.

‡ $P < .01$.

§ Formalin is not included.

TABLE 5
Odds Ratio of Spontaneous Abortion for Other Chemicals: Multivariate Logistic Regression Models

Exposure*	Odds Ratio	95% Confidence Interval	No. of Cases/Referents
Carcinogens			
1	0.9	0.6-1.5	33/62
2	1.6	0.9-2.8	39/45
Radioactive chemicals	1.8	0.9-3.9	15/15
Cytostatics	4.0	0.8-19.3	5/3
Scintillation fluids	1.6	0.5-5.6	5/6
Pesticides	1.1	0.3-3.5	5/7
Metal compounds			
1	1.2	0.7-2.1	23/34
2	1.2	0.4-3.3	8/12

* Each solvent is included separately in the multivariate model. Class 1 = exposed 1 or 2 days a week; 2 = exposed 3 to 5 days a week. Values are adjusted for employment, smoking, alcohol consumption, parity, previous miscarriages, failed birth control, and febrile disease during pregnancy.

tests, the effects have been observed at exposure concentrations of 100 to 1000 ppm (for review see ref 23).

Although occupational exposure to xylene is common in working life, sole exposure to xylene is uncommon. Multiexposure was true also in this study because only two cases and controls were exposed to xylene alone. In epidemiological studies on reproduc-

tion, xylene is often included in the group of exposure to "organic solvents" or "aromatic solvents," on which there are reports of adverse effects on pregnancy²⁸ and the offspring (for review see ref 29). Xylene exposure in the pharmaceutical industry is associated (not significantly) with the risk of spontaneous abortion, but due to the small numbers of subjects and

the possible multiexposure, the finding is only suggestive.¹⁸ The risk of spontaneous abortion for xylene exposure was not increased in laboratory employees⁹ and women monitored biologically for organic solvent exposure.¹⁹

In Finland, occupational hygienic measurements have been conducted in only few laboratories. The concentrations of xylene in a histological laboratory were in the range of 2% to 25% of the Finnish reference value (100 ppm for 8 hours, 150 ppm for 15 minutes).

Xylene crosses the placenta in humans and rodents. In animals, xylene has caused retarded fetal weight, retarded development, and possibly resorptions, but not malformations. The lowest observed effect level in animal tests ranges from 200 to 700 ppm (for review see ref 29). These levels are not much higher than those possible in occupational environments.

Because the majority of formalin and xylene exposures seemed to occur in pathology and/or histology laboratories, the finding focuses the attention on the occupational hygiene in these laboratories. A survey of the occupational exposure to chemicals in Finland revealed that about 300 people are exposed to formaldehyde in pathology and histology laboratories. Hygienic short-term measurements have shown formaldehyde concentrations in the workroom air to range from 0.01 to 7 ppm, mean 0.45 ppm (0.01 to 9.1 mg/m³, mean 0.59 mg/m³). The exposure was highest in tasks such as the filling or emptying of sample containers and washing of dishes (1.02-7 ppm, i.e. 1.36-9.1 mg/m³), as well as in the preparation of formaldehyde solution (0.76 ppm, i.e. 1.0 mg/m³) (30). In other tasks, eg, staining, slicing, and microscopy, the concentrations varied from 0.05 to 0.29 ppm (0.07 to 0.38 mg/m³). The exposure in such laboratories, when compared to the hygienic reference value of formaldehyde for Finnish occupational environments (1 ppm = 1.3 mg/m³) may at least occasionally have been rather high.

Earlier studies on the reproductive effects of formaldehyde have given

TABLE 6
Odds Ratios of Congenital Malformation for Selected Factors: Multivariate Logistic Regression Model

Exposure*	Odds Ratio	95% Confidence Interval	No. of Cases/Referents
Employed	0.3	0.1-0.9†	27/94
Score for organic solvents (not formaline):			
5-50	1.0	0.3-3.3	9/28
>50	1.1	0.3-5.3	3/10
Aliphatic solvents	0.3	0.0-2.4	1/9
Aromatic solvents			
1	0.9	0.2-4.0	3/9
2	0.7	0.2-3.0	3/10
Halogenated solvents	0.8	0.2-2.5	5/19
Carcinogens			
1	0.6	0.2-2.1	6/22
2	0.7	0.2-3.0	3/16
Smoking	1.7	0.5-5.6	6/14
Febrile disease	2.4	0.8-7.6	7/11

* Class 1 = exposed 1 or 2 days a week; 2 = exposed 3 to 5 days a week. Values are adjusted for alcohol consumption, parity, previous miscarriages and failed birth control.

† $P < .05$.

conflicting results. Heidam (10) did not find any increased risk of spontaneous abortion among pathology laboratory workers or among workers exposed to organic solvents in laboratories. In a university laboratory 3 of 10 (30%) pregnancies of laboratory employees exposed to formaldehyde ended in spontaneous abortion, but the numbers were too small for drawing definite conclusions.⁹ Menstrual disorders, anemia during pregnancy, threatened abortion, and low birth weight have been reported in excess among factory workers exposed to formaldehyde,³¹ but because of lacking data the validity of the results cannot be evaluated (for review see ref 32).

In a recent survey, female sewers exposed to formaldehyde in a garment factory were reported to have a statistically significant increase of stillbirths, premature births, and children with birth defects.³³ The miscarriage rate did not differ from that of the nationally reported average values. The formaldehyde source was the handled fabric; the measured formaldehyde concentrations ranged from 0.14 to 0.46 ppm (0.18 to 0.60 mg/m³) in personal samples and from

0.32 to 0.70 ppm (0.42 to 0.91 mg/m³) in the ambient air samples. These measured concentrations are similar to those measured in Finnish pathology/histology laboratories. An increased risk of spontaneous abortions was found among cosmetologists using formaldehyde.³⁴

Experimental studies have not revealed any other effects on reproduction (for review see ref 32) than resorptions in a study on hamsters where formaldehyde was applied topically.³⁵ Formaldehyde is, however, a potent genotoxic agent active in many short-term genetic tests in vitro and in vivo. Formaldehyde reacts with amino groups, leading to the formation of methylol adducts with nucleic acids, proteins, and amino acids.³⁶ The basis for the genetic activity of formaldehyde is suggested to be the ability to form crosslinks in DNA proteins. Formaldehyde exposure among embalmers and anatomists has been associated with increased risk of leukemia and brain and colon cancer, but not with respiratory cancers.³⁷ However, the causal role of formaldehyde is most probable for nasopharyngeal cancers among industrial workers.

In our study the odds ratio of spontaneous abortion also for frequent use of isopropanol was elevated, but not statistically significantly. Only one case and referent were exposed to isopropanol alone, the others had been exposed to several other solvents (eg, toluene, xylene, and formaldehyde). In the multiexposure situation, the suggestive finding may be due to other simultaneous exposure. Isopropanol has been found teratogenic in one animal study³⁸; for review see ref 39.

Frequent exposure to aromatic hydrocarbons was significantly associated with spontaneous abortion in this study. An association, although not statistically significant, was reported also in an earlier study (OR 1.6, CI 0.8 to 3.3).¹⁹ Odds ratios of spontaneous abortion below unity were found for infrequent (class 1) exposure to aliphatic (statistically significant) and halogenated hydrocarbons (not significant). The finding is not explainable by a known biological mechanism. It has been suggested that unexpected results in one reproductive outcome could be a sign of pathology in an earlier phase of the chain of reproductive events.⁴⁰ For example, fertility problems or increase of subclinical abortions might be underlying. The aliphatic hydrocarbon group may consist of nontoxic and toxic compounds; therefore, the result cannot be interpreted as all the compounds were harmless. The role of chance cannot be excluded either.

Because of the multiexposure we tried to analyze the effects of exposure to all types of organic solvents by using a solvent score. A high score associated significantly with increased risk of spontaneous abortion.

Exposure to carcinogens, and among them radioactive agents and cytostatics, increased the odds ratio of spontaneous abortion but with no statistical significance. Exposure to cytostatic drugs has been reported to increase the risk of spontaneous abortion.^{41,42}

In the register of employees exposed to carcinogens in Finland 7% to 8% of the notified workers are laboratory assistants.⁴³ In our material, 72 (35%) cases and 107 (32%) referents reported exposure to carcinogenic

agents during pregnancy. The most commonly reported carcinogens were chloroform, chromium (VI) compounds, benzene, carbon tetrachloride, lead and its inorganic compounds, dioxane, cadmium, arsene, and nickel and its compounds. Exposure to formaldehyde/formalin and methylene chloride was common, too. Formaldehyde and methylene chloride are not included in the list of carcinogenic agents in Finland, and are therefore not reported to the register, although they are potential carcinogens (2B) according to the IARC classification.¹⁴ The most common exposures in this study are very similar to those reported for the laboratory assistants in the Finnish register in 1986.⁴⁴

Employed women had odds ratios for malformations significantly below unity. Low socioeconomic status has been associated with malformations, and in some studies an association between malformations and maternal work in industrial occupations has been found (see review in ref 45). Odds ratios below unity for malformation have been found among children of women in technical, scientific, and administrative occupations.⁴⁶ Laboratory work belongs to such a category, and some of the women may have worked during the pregnancy in other occupations of the same category (eg, university assistants). On the other hand, sick leave or inability to work during pregnancy may involve bad health related to an adverse outcome of pregnancy. That could explain, at least partly, the low risk of malformation among the employed women. The possibility of chance cannot be excluded totally, either.

Laboratory work during pregnancy and exposure to some laboratory chemicals showed associations with decreased birth weight of the child. The findings should be interpreted cautiously because we did not have information on the height and weight of the mother before pregnancy, although these are factors known to influence the birth weight of the child. In addition, we collected exposure information concerning the first trimester of pregnancy only; thus we do not know how the events later in the preg-

nancy may have influenced the birth weight. In earlier reports physical strain, work in a standing position, and smoking throughout the pregnancy have been associated with fetal growth retardation.⁴⁷⁻⁵⁰

The reliability of the outcome information, nonselectivity of the study population, and good exposure information are important for the validity of an epidemiological study. In this study the information on the pregnancy outcome (spontaneous abortion, normal birth, and birth of a malformed child) is reliable because it was based on the medical registers and confirmed by the study persons. Comparisons between the Hospital Discharge Register and reports of women show that only about 10% of recognized abortions are not included in the data base.¹³ The abortions not included in the data base are earlier than those treated at hospitals or at the outpatient clinics. The mean length of the pregnancies at the time of spontaneous abortion in the data base was 11.5 weeks and about the half of the abortions occurred before the 11th week of gestation. About 10% of the abortions occurred by the 6th week of gestation.¹³ Thus the data base seems to cover the clinically recognizable abortions rather well.

We could not confirm, however, the very early "subclinical" abortions, if they were not treated in a hospital or an outpatient clinic. Therefore, an agent that would cause mainly very early abortions could not have been found in this study.

There may be a selection bias in cross-sectional studies on spontaneous abortions among employed women because women who have had an abortion continue working, whereas women who deliver a child more often stop working. To avoid such a bias both the present and resigned employees and union members were enrolled in this study.

The data of this study do not indicate selective participation by the outcome of the pregnancy alone because the response rates of the cases and referents were almost identical. Selection cannot yet be totally excluded because the exposure status during pregnancy and the outcome of preg-

nancy together may, according to an earlier report, affect the participation, although the response rates are similar.⁵¹ The questionnaire information on the exposure may suffer from difficulties in recalling events. The type of laboratory and the regular work tasks are, however, likely to be remembered reasonably well, but reports of specific exposures may be defective.

Conclusions

The results of this study agree with some earlier studies in which exposure to organic solvents during pregnancy has been found to increase the risk of spontaneous abortion. Because of the multiexposure situation, the results concerning individual chemicals have to be interpreted cautiously. However, this study gives reason to check the exposure levels at least in pathology/histology laboratories, and to take occupational hygienic measures, when needed, to decrease the exposure.

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Quake Indicators

The Japanese aren't the only citizens of the world to dwell on palpitating ground. Many Californians face a similar plight with attitudes of optimism or denial.

But in Japan the constant fear of geological Armageddon has raised earthquake prediction to a national obsession—and bred its own rich lore. Does the government's fascination with clams seem dippy? Then consider the city of Tokyo's effort to predict earthquakes by observing the way catfish swim. Japanese folklore has it that the whiskered fish are uniquely sensitive to earthquakes, but that turns out to be a red herring. After 16 years of study, scientists determined that even slight vibrations from ineffectual tremors make the catfish swim strangely.

Or how about the claims of several Japanese zoo keepers, who swear that certain alligators "scream" before big jolts? At the Atagawa Tropical and Alligator Garden, on the ever-trembling Izu peninsula south of Tokyo, Satoshi Kimura keeps more than 400 alligators and crocodiles of 20 different species. The creatures—sunbathing in the mud on one recent day—rarely raise a racket. But when especially sedate species like the Siamese and Nile alligators screech together, he says, major earthquakes follow.

And what does a screaming alligator sound like? "Like humans snoring, only a lot louder," says Mr. Kimura. You can hear it 200 yards away, he says.

From "The Jittery Japanese Quake Every Time the Earth Moves," by Clay Chandler in *The Wall Street Journal*, September 1, 1993, LXXIV, pp A1, 4