Solvent use and time to pregnancy among female personnel in biomedical laboratories in Sweden

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Abstract

Objectives—To elucidate possible effects on fecundability from chemical, biological, and physical agents in laboratories, a retrospective study based on a questionnaire was conducted among female personnel who worked in Swedish biomedical research laboratories. Female personnel in non-laboratory departments were used as a reference group. The maximum number of women included in the analyses was 560. This corresponded to 2519 menstrual cycles. These women had given birth at least once during the period 1990–4.

Methods—Time to pregnancy was used to estimate the fecundability—that is, probability of conception of a clinically detectable pregnancy per cycle. The fecundability ratio (FR) between exposed and unexposed cycles was calculated with a discrete time analogue of the Cox's proportional-hazards model. The FR estimates below unity indicate subfecundity.

Results—Work with organic solvents in general in laboratory work, gave a decreased adjusted fecundability ratio (FR) of 0.79 (95% confidence interval (95% CI) 0.68 to 0.93). Moreover, work with acetone and use of viruses also showed decreased FRs, 0.72 (0.53 to 0.97) and 0.66 (0.49 to 0.90), respectively.

Conclusions—The results of the present study give some indications of reduced fecundability for work with specific agents in laboratories, and support previously reported findings of a negative influence of organic solvents on fecundity among female laboratory personnel.

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Keywords: laboratory work; organic solvents; time to pregnancy

Laboratory work and the use of organic solvents have been connected with several adverse pregnancy outcomes in previous epidemiological reports—for example, spontaneous abortions, malformations, decreased birth weight, infants large for their gestational age (LGA), and reduced fertility—most of which studied reproduction in women.^{1–7}

The studies about spontaneous abortions are generally concentrated on clinically recognised miscarriages because of the technical complexity of detecting very early spontaneous abortions—for example, by measuring concentrations of human chorionic gonadotropin.⁸ To study fecundability including estimation of the

early pregnancy loss, the time to pregnancy (the number of menstrual cycles required to conceive) can be calculated from data collected by self administered questionnaires.⁹ This type of investigation has been validated in previous studies to show that the method is feasible.^{10–11}

Animal studies in mammals on teratogenicity of organic solvents resulting in malformations as well as effects on embryonal growth have been conducted with specific solvents separately.^{12–13} There are studies that describe neurobehavioural effects in the rat from 1,1,1-trichloroethane¹⁴ and cardiac teratogenicity from trichloroethylene metabolites.¹⁵ Such teratogenicity could conceivably result in more severe malformations and thus early spontaneous abortions. Epidemiological studies also indicate a connection between organic solvents and spontaneous abortions as well as malformations.^{16–17}

The possible role of organic solvents in decreased fecundability among female workers has previously been investigated in the epidemiological literature.^{7–18} Daily low exposure to toluene was associated with subfecundity.¹⁸ When exposure to organic solvents was based on information from a questionnaire and biological exposure measurements, the results supported the hypothesis that daily or high exposure to solvents was associated with reduced fertility.⁷

The present study was conducted on the same study base as a separately reported investigation of pregnancy outcome of female personnel in Swedish biomedical research laboratories⁶ and aimed to identify potential hazardous factors in the laboratory environment which may be associated with reduced fecundability.

Materials and methods

COHORT INFORMATION

All the women born in 1945 or later who had worked for at least 1 year, 50% or more of full time, between 1 January 1990 and 31 December 1994 in biomedical or certain non-laboratory departments (included as an internal reference group) at the Karolinska Institute or at the Universities of Gothenburg, Linköping, Lund, Stockholm, Umeå, or Uppsala, were identified from the records of the Swedish Employee Salaries and Pension Board. The present cohort was defined after linkage to the Swedish medical birth registry by including those women who had given birth to at least one child during this period (n=1052).

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Flow chart describing the restriction procedure for defining the time to pregnancy study base. X and Y represent unknown numbers.

DATA COLLECTION AND ASSESSMENT OF EXPOSURE

A self administered questionnaire was sent to all 1052 women. The response rate was 72.5% after two reminders. For each pregnancy, the woman was asked whether it was planned, neither planned nor unplanned, or unplanned.¹⁹ All the pregnancies where the woman had answered in either of the first two categories in this question, was employed during time to pregnancy, and had stated the number of menstrual cycles up to the conception (number of pregnancies being 803), were initially included in the study base of the time to pregnancy investigation. These pregnancies corresponded to 587 women. A data file based on menstrual cycles was created, giving 2708 cycles in total. However, the pregnancies where women with employment were not actually working during the time to pregnancy, were excluded from the analysis and a total of 735 pregnancies and 2519 menstrual cycles for 560 working women were included (figure). Thus, the initiation was related to the time when the woman's work started and not to the calendar time. The more detailed description of data collection has been reported elsewhere.⁶

Briefly, the questionnaire included two different parts; one with questions about demographic and socioeconomic data, the woman's general health, reproductive history, and health, including questions such as cycle duration, induced abortions, and fertility problems in any of the partners, and another part

with specific questions about time to pregnancy during the years 1990-4.⁶

The second part inquired, separately for each pregnancy, how many cycles it took before the pregnancy was achieved, and if they were quite sure about this, relatively sure, or unsure, as well as the use of contraceptives and other methods of birth control.

Frequency of intercourse and whether the time of ovulation was taken into account while trying to become pregnant were asked about separately for each menstrual cycle. Furthermore, for the pregnancies which started from January 1990 and ended up to December 1994, this part of the questionnaire asked about the woman's work in any laboratory, the working period, and exposure to various agents including use of chemicals, radioactive isotopes, cell techniques, viruses, and bacteria during the time up to conception. Additional information about the woman's concurrent work place in a laboratory or non-laboratory department was derived from the answers to questions about her education and profession.

Specifically for the solvents, the periods of use were asked for, with a precision of 1 month. Use of solvents were classified as "in general" if the woman had worked with solvents any time during her employment before the conception, but use of specific solvents studied in the previous literature—for example, benzene, styrene, toluene, trichloroethylene, and xylene—were asked about separately for each unique pregnancy. The woman was also asked about work

with other solvents and was asked to name the substances she had used during each separate pregnancy. Acetone, benzene, chloroform, diethylether, and phenol were the most commonly used solvents in this group. Furthermore, a question was posed about the frequency of work with solvents separately for every menstrual cycle during each time to pregnancy period. A distinct question was asked about whether the woman was working during the time up to conception and if the work was connected to a laboratory department, and also if the woman was working directly with laboratory tasks or not.

The chemicals used in laboratories and reported by the woman were classified as organic solvents or others by an occupational hygienist without any knowledge about the outcome in the study. The total number of different chemicals reported was 76. The number of solvents included after evaluation was 45; of all chemicals, nine chemical names could not be recognised due to handwriting or spelling problems, one chemical was a known teratogenic substance but not a solvent, and 21 were other chemicals; however, these were in most cases mentioned only by one woman. In the next question, the women were asked to write down other chemicals they worked with (and work period) or chemicals they were unsure about whether they were organic solvents or not. The occupational hygienist also evaluated these answers and selected organic solvents as separate variables. Later on these chemicals were added in a list of organic solvents. The number of solvents from this group was nine, all already included in answers to the previous question.

The classification of developmental toxicants according to the system elaborated by the California Environmental Protection Agency was used to classify chemicals used in the study.²⁰

POTENTIAL CONFOUNDERS

To ascertain potential confounders, questions were also asked about work stress, physical activity, smoking, heavy lifting, the presence of small children at home, and consumption of coffee, tea, cola, soft drinks, and alcohol, as well as the father's age and work in a laboratory during the time to each pregnancy.

LEVEL OF INFORMATION

The collected exposure data, reproductive health characteristics, and potential confounders, were classified according to three different levels of information: woman specific, pregnancy specific, and cycle specific, and the analyses were performed for these levels (table 1).

Table 1 Overview of the most central topics penetrated in the questionnaire, classified according to the level of information source

Woman specific	Pregnancy specific	Cycle specific
Birth year, age	All pregnancy outcomes	Intercourse during ovulation
Education, profession	Time to pregnancy in cycles	Frequency of intercourse
Gynaecological history	Work exposures	Solvent use
General health	Planned pregnancy	Smoking
Time for solvent use	Solvent use	

DEFINITION OF TIME TO PREGNANCY

As outcome in the study, the time to pregnancy—that is, the required number of cycles to conceive (also sometimes called menstrual cycles to pregnancy)—was used to estimate fecundability.^{9 21 22} If the time to pregnancy was reported as zero cycles, the answer was interpreted as one cycle in the analysis.^{22 23} Each menstrual cycle was classified according to the exposure variables and other reproductive characteristics of the woman, pregnancy, and cycle specific level, and an indicator variable was generated for every cycle giving information on whether the cycle under this exposure resulted in a pregnancy or not. For descriptive purposes—such as calculation of average time to pregnancy—we used no censoring. However, in the statistical models censoring of time to pregnancy was introduced. If the women needed more than 12 cycles to conceive, the value was “null” for this indicator—that is, the information was right truncated and no calculations for waiting time longer than 12 months were performed. In total, among 560 women with 735 pregnancies (figure), 407 of the concurrently working women had one pregnancy, 135 had two pregnancies, 15 had three, two women four, and one woman five pregnancies. The pregnancies were both self reported and confirmed in the Medical Birth Registry.

STATISTICAL ANALYSES

As a measure of effect, the fecundability ratio (FR) between exposed and unexposed cycles was calculated, with a discrete time analogue of the Cox's proportional hazards model.²⁴ The FR was conditional on pregnancy—that is, only couples who achieved a pregnancy were included in the study.²⁵ The model was fitted with macros developed for the GLIM statistical package.^{26 27} The FR estimates below unity indicate subfertility. Confidence intervals (95% CIs) were calculated by means of standard errors of the parameters included.

In the analysis of laboratory work as exposure, the pregnancies of women both from the laboratory and non-laboratory departments were included. For analyses of solvents in general and specific laboratory exposures, the study group included only women working in laboratory departments, with those without any specific laboratory exposure as the referent group (administrative personnel, secretaries, computer personnel working inside the laboratory department). The separate analyses for each specific exposure included three different exposure categories: reference, laboratory exposure other than to the specific agent, and exposure to the specific agent. All the analyses included only observations with complete data. Hence the analyses were based on slightly different numbers of pregnancies.

If the estimate of the crude ratio differed from the adjusted ratio by more than 10%, and the SEM was not severely affected (which otherwise might indicate a seriously high correlation with the variables already included), a covariate was considered as a confounder and added in a model.

Table 2 Time to conception according to specific characteristics of the women, pregnancies and cycles

Characteristic	Laboratory department				Non-laboratory department			
	Pregnancies/ cycles (n)	Cycles to conception (mean)	Pregnant in first cycle (%)	>12 Cycles to pregnancy (%)	Pregnancies/ cycles (n)	Cycles to conception (mean)	Pregnant in first cycle (%)	>12 Cycles to pregnancy (%)
Pregnancy No:								
1	152/612	5.4	38.8	8.6	116/481	6.0	32.8	8.6
2	142/415	3.0	40.8	1.4	113/361	3.4	37.2	3.5
≥3	117/336	3.5	44.4	4.3	95/314	3.8	41.1	4.2
Mother's age:								
<29	108/282	2.8	47.2	0.9	97/280	3.0	43.3	3.1
30–34	219/705	4.1	42.5	5.0	138/509	4.5	36.2	5.1
≥35	84/376	5.7	29.8	9.5	89/367	6.0	30.3	9.0
Father's age:								
<29	102/278	3.5	41.2	2.0	80/240	3.1	42.5	3.8
30–34	168/491	3.4	48.2	4.8	111/392	5.1	33.3	6.3
Father's work:								
Non-laboratory	284/997	4.4	40.8	5.3	303/1084	4.4	36.3	5.6
Laboratory	122/358	3.3	41.8	4.1	16/45	2.8	50.0	0.0
Duration of employment (y):								
1–5	26/67	2.7	57.7	3.8	113/384	4.1	44.2	6.2
≥15	90/427	6.3	24.4	12.2	45/235	9.5	11.1	13.3
Known fertility problems:								
No	375/1110	3.1	42.9	2.4	288/979	3.8	37.2	3.5
Yes	30/237	16.8	13.3	36.7	27/155	12.3	33.3	29.6
Smoking cigarettes/day:								
None	348/1150	4.0	41.4	4.6	253/885	4.2	38.3	5.1
1–9	24/89	6.0	33.3	12.5	22/74	3.7	36.4	4.5
10–19	20/50	2.3	50.0	0.0	19/106	11.4	15.8	21.1
≥20	15/50	4.3	40.0	6.7	22/37	2.1	45.5	0.0

Uncensored data are shown for female laboratory and non-laboratory personnel who worked ≥1 year at the participating Swedish universities and gave at least one birth during the period 1990–4. The number of women was 560 and the total number of pregnancies 735 (laboratory 411, non-laboratory 324). Fewer pregnancies for a specific characteristic are due to missing values for that particular characteristic.

Multiple pregnancies of one woman were included in the analysis. To analyze the dependency from several pregnancies per woman, a simulation analysis with five different selections of data sets was conducted. Each data set included the pregnancies from women with only one pregnancy during 1990–4, and one randomly chosen pregnancy per woman

among those who had several pregnancies during 1990–4.

This study has been approved by the ethics committee of the Karolinska Institute and by the Swedish Data Inspection Board.

Results

In the descriptive analyses, where 560 women were included, the number of pregnancies was 735; women working in laboratories contributed 411 and women in non-laboratory departments 324 pregnancies. In 58% of the exposed pregnancies, the mother had been working with solvents before the conception. Of women who had been exposed to solvents, 35.1% became pregnant during the first menstrual cycle, whereas the corresponding number among non-exposed employees was 49.1%.

The specific characteristics of women connected to reproductive outcome are presented in table 2. The mean numbers of cycles to conception in uncensored data at the first pregnancy for women working in laboratory and non-laboratory departments were 5.4 and 6.0, respectively, and then lower for subsequent pregnancies. The mean numbers were higher than 12 cycles for both groups in cases with known fertility problems (16.8 and 12.3). Mother's or father's age increased time to conception in both exposure groups.

Descriptive outcomes are presented specifically for pregnancies of female laboratory personnel relative to different biomedical exposure agents in the laboratory environment (table 3 (uncensored data)). The mean numbers of cycles to conception were higher than for the other exposures: developmental toxicants (5.5 cycles); cell techniques (5.3 cycles); and viruses (5.9 cycles).

The analysis of work in a laboratory department in general, with complete data, included

Table 3 Time to conception for female personnel in laboratory departments only (number of pregnancies=411), according to occupational agents specific for the biomedical research laboratory environment

Laboratory exposure	Pregnancies (n)	Cycles (n)	Cycles to conception (mean)	Pregnant in first cycle (%)	>12 Cycles to pregnancy (%)
Solvents in general:					
No	172	493	3.5	49.1	2.3
Yes	239	870	4.4	35.1	6.7
Acetone:					
No	345	1134	4.0	41.7	4.1
Yes	44	169	4.6	34.1	11.4
Benzene:					
No	391	1289	4.0	41.2	4.6
Yes	12	45	4.0	41.7	8.3
Chloroform:					
No	334	1142	4.2	40.4	5.1
Yes	69	192	3.0	44.9	2.9
Diethylether:					
No	365	1243	4.2	40.5	4.9
Yes	24	218	2.6	45.8	4.2
Phenol:					
No	337	1116	4.1	40.7	4.7
Yes	66	218	3.7	43.9	4.5
Developmental toxicants:					
No	340	1094	3.7	41.8	4.1
Yes	63	240	5.5	38.1	7.9
Cell techniques:					
No	269	820	3.4	42.0	3.3
Yes	142	543	5.3	39.4	7.7
Radioactive isotopes:					
No	216	685	4.0	40.7	4.6
Yes	195	678	4.2	41.5	5.1
Viruses:					
No	365	1157	3.8	42.5	4.9
Yes	46	206	5.9	30.4	4.3
Bacteria:					
No	283	901	3.9	41.3	4.2
Yes	128	462	4.5	40.6	6.3

Uncensored data are shown for women who worked ≥1 year at the participating Swedish universities and gave at least one birth during the period 1990–4.

Table 4 Fecundability ratio (FR) for general and specific occupational exposure to solvents, and specific laboratory exposures other than solvents

Exposures	Crude FR*	95% CI	Adjusted FR†	95% CI
Fecundability ratio for occupational exposure to solvents in general‡:				
No solvent exposure (reference)	1.00	—	1.00	—
Solvent exposure	0.80	0.68 to 0.94	0.79	0.68 to 0.93
Fecundability ratio for specific solvents§:				
No specific laboratory exposures	1.00	—	1.00	—
Other exposures than acetone	0.92	0.76 to 1.12	0.87	0.72 to 1.05
Acetone	0.78	0.58 to 1.07	0.72	0.53 to 0.97
Other exposures than benzene	0.90	0.74 to 1.09	0.85	0.71 to 1.03
Benzene	0.91	0.52 to 1.58	0.75	0.44 to 1.29
Other exposures than chloroform	0.86	0.71 to 1.05	0.82	0.68 to 0.99
Chloroform	1.07	0.84 to 1.37	0.96	0.75 to 1.22
Other exposures than diethylether	0.88	0.73 to 1.07	0.83	0.69 to 1.00
Diethylether	1.12	0.80 to 1.58	1.06	0.77 to 1.46
Other exposures than phenol	0.89	0.71 to 1.21	0.84	0.69 to 1.01
Phenol	0.93	0.71 to 1.21	0.90	0.70 to 1.16
Fecundability ratio for specific laboratory exposure others than solvents¶:				
Developmental toxicants	0.84	0.63 to 1.10	0.81	0.63 to 1.06
Other exposures than cell techniques	0.98	0.80 to 1.21	0.89	0.73 to 1.09
Cell techniques	0.81	0.65 to 1.01	0.81	0.65 to 1.00
Other exposures than isotopes	0.91	0.72 to 1.14	0.87	0.70 to 1.08
Radioactive isotopes	0.90	0.73 to 1.10	0.84	0.69 to 1.03
Other exposures than viruses	0.94	0.77 to 1.14	0.89	0.74 to 1.07
Viruses	0.74	0.54 to 1.01	0.66	0.49 to 0.90
Other exposures than bacteria	0.93	0.76 to 1.14	0.87	0.72 to 1.07
Bacteria	0.86	0.69 to 1.08	0.82	0.66 to 1.01

*Crude FR calculated with adjustment only for cycle order. TTP censored at 12 months.

†Adjusted FR calculated with adjustment for cycle order, mother's age, father's age, father's laboratory work and reported fertility problems.

‡The analysis included only women in laboratory work 291 women, 375 pregnancies, 1324 cycles.

§The analysis included only women in laboratory work 279 women, 353 pregnancies, 1296 cycles. The reference group in all analyses includes women working in laboratories with no laboratory exposure.

¶The analysis included only women in laboratory work 279 women, 353 pregnancies, 1296 cycles. The reference group in all analyses includes women working in laboratories with no laboratory exposure.

542 women with 706 pregnancies which generated 2429 menstrual cycles. With work in a non-laboratory department as a reference group, an adjusted FR of 1.06, (95% CI 0.93 to 1.21) was obtained.

For work with solvents in general (only women working in biomedical research laboratories with complete data were included), with exposure to no solvents as reference (291 women, 375 pregnancies, and 1324 cycles), an FR of 0.79 adjusted for cycle order, with 95% CIs of 0.68 to 0.93, was obtained (table 4). The FRs for specific solvents, analyzed for each exposure separately, are shown in table 4 (279 women, 353 pregnancies, and 1296 cycles), where the reference category consisted of those who worked in a laboratory department without connection to any of the specific laboratory exposures. An adjusted FR of 0.72 indicating subfertility was obtained for work with

acetone (95% CI 0.53 to 0.97), and the FR for laboratory exposures other than acetone was 0.87 (95% CI 0.72 to 1.05).

Table 4 shows FRs for laboratory exposures other than solvents. A decreased adjusted FR of 0.81 was found for work with cell techniques (95% CI 0.65 to 1.00), and for viruses the FR was 0.66 (95% CI 0.49 to 0.90). The FRs in table 4 were adjusted for the cycle order, mother's age, father's age, father's laboratory work, and reported fertility problems.

The simulation study with only one of the woman's pregnancies included (chosen randomly) resulted in equal or even somewhat lower FRs in analyses of solvents in general, shown in table 5. The 95% CIs were very slightly influenced without any effect on significance.

Discussion

The results of the present study support previous findings of a negative influence on fecundability from organic solvents.⁷⁻¹⁸ Use of acetone and viruses also gave decreased FRs.

The laboratory and non-laboratory study groups were homogenous for age distribution, place of birth (Sweden, other Nordic countries, elsewhere), education, age at menarche, mean age at first pregnancy, use of contraceptives (which was low in both exposure groups), and proportion of induced abortions.⁶ These covariates can therefore not be considered as confounders in the present study.⁹ Cigarette smoking²⁸ was slightly higher in the non-laboratory group (data not shown), and use of narcotic drugs was not asked for because of the very low use expected in these occupational categories.

The study information was collected retrospectively with self administered questionnaires 5 months to 5 years after the end of the pregnancy in question. This period is reasonably short for the woman to be able to give reliable answers, diminishing the risk of recall bias.⁹⁻²⁹ The response rate of the study was relatively low (72.5%) but no analyses of non-responders were performed for ethical reasons. The proportion of people eligible for inclusion in the study among the non-responders was therefore unknown. The available data on background factors showed that the two groups were homogenous for health, diseases, and socioeconomic factors.⁶

Questionnaires were completed seriously in both exposure groups, with answers to many private and sensitive questions, which could be shown by comparing several answers from women with corresponding variables from the medical birth registry and we thus interpreted this fact to indicate that possible reporting errors were not differential. Validation studies of time to pregnancy^{10-11,30} have been conducted to estimate bias and loss of power from misclassification, showing that the misclassification tends to be non-differential and bias is towards null, thereby concluding that the use of a self administered questionnaire is feasible in epidemiological studies about fecundability.¹⁰

No measurement of exposure has been performed because of the complexity of the laboratory exposures and difficulties in tracing a

Table 5 Fecundability ratios for occupational exposure to solvents in general obtained from a simulation study with one randomly chosen pregnancy per woman

Simulation no	Women (n)	Pregnancies (n)	Cycles (n)	Adjusted FR*	95% CI
All†	291	375	1324	0.79	0.68 to 0.93
1	291	291	1041	0.76	0.64 to 0.91
2	291	291	1042	0.76	0.63 to 0.91
3	291	291	1068	0.74	0.62 to 0.84
4	291	291	1070	0.76	0.63 to 0.91
5	291	291	1045	0.77	0.65 to 0.93

*Adjusted FR calculated with adjustment for cycle order, mother's age, father's age, father's laboratory work, and reported fertility problems. TTP censored at 12 months.

†The analysis included all pregnancies where complete data were available (n=375) of the 291 women working in laboratory departments.

The analyses were repeated five times and included only women working in laboratory departments.

specific chemical agent. In the questionnaire, some agents were asked for by name, others were reported by the women themselves, corresponding relatively well to previously reported agents in a study of cancer incidence in laboratory environments (Wennborg *et al*, Karolinska Institute, unpublished data). Furthermore, laboratory work often entails methods which are used for long periods, sometimes for years (meaning that the agents might be used over several cycles). When asked for the dates when women had been working with organic solvents, most of them did not have any problem giving the year and the month start and end dates. In the laboratory environment, employees normally use logbooks or notebooks, which also can be useful in describing exposure. In an analysis of frequency of exposure in the present study about solvents in general (data not shown), no dose-response effect was found. This may not be surprising as solvents with varied inherent toxicity can be used with different frequencies.

The previous report about reproductive outcomes in the present study base showed increased risk estimates for spontaneous abortions with work with chloroform.⁶ However, no increase in the time to pregnancy was found for chloroform.

One of the advantages of the time to pregnancy method is its broad coverage of the reproductive process³¹ and its usefulness for estimating effects on fertility at very early stages. It can therefore be of value while studying occupational exposures, because all exposures that influence the biological processes of conception and early growth of the embryo could theoretically reduce fertility.⁹ Such processes include germ cell toxicity and mutations, ovulation, transfer, fertilisation, implantation, and embryo survival which can be influenced both by short term and long term acting environmental exposures. Sallmén *et al*,⁷ however, hypothesise that the effect of organic solvents on reproduction is short term. Furthermore, there are also studies indicating teratogenic and embryotoxic effects of certain viruses and other microorganisms, some of which are well established (cytomegalovirus, toxoplasmosis). Cell techniques could be a potential source of viruses; several types of retroviruses can be present in cultured mammalian cells.³²

In time to pregnancy studies related to the woman's exposures, potential confounding factors such as the partner's spermatogenesis and sperm function, as well as the frequency of intercourse can affect the fecundability.²¹ To attempt to control possible effects of laboratory exposures of the partner, questions about the partner's occupation were included in the questionnaire. Moreover, the frequency of intercourse and planned intercourse during ovulation were investigated.

The occurrence of self reported previous problems with fertility in either the woman or her partner was a confounding factor in the subcohort of laboratory employees (with laboratory tasks and without laboratory tasks) indicating a possible connection to exposure. The analyses of specific exposures were adjusted for

this risk factor. Heavy lifting and irregular working hours did not act as confounders in this population.

The number of women analyzed in the study is relatively low, but the 95% CIs of the present FR analysis confirmed that the generated number of pregnancies and menstrual cycles was sufficient, as shown by a power analysis according to previous suggestions.⁹ The analyses of the present study have included all the woman's pregnancies between 1990 and 1994 where she was working during the time to pregnancy. The employed group of women is considered to contain a higher proportion of subfertile women than the group of non-employed, called the "infertile worker effect".⁷ This bias can be avoided by restricting the analysis to working women only,^{33 34} which was the approach followed in the present study.

The fact that some women contributed with more than one pregnancy must be taken into consideration. Problems related to this aspect have been discussed in the epidemiological literature.^{23 35 36} Previous studies have shown that including several pregnancies per woman and performing the analysis with random effect models could result in somewhat wider 95% CIs, but the significance was in most cases not effected.³⁷ The results from our simulation analyses with inclusion of only one of the woman's pregnancies, confirmed a very slight effect on the width of the 95% CIs due to the influence on the SEMs of the parameters^{23 37} without any effect on significances.

In summary, we have found that the use of solvents in general is associated with reduced fecundability of women working in laboratory environments, which confirms previously published results. Moreover, indications were obtained of reduced fecundability in connection with work with cell techniques and viruses; exposures which are previously not widely recognised in this context.

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