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Time to pregnancy among male workers of the reinforced plastics industry in Denmark, Italy and The Netherlands

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Objectives The relationship between occupational styrene exposure and male fecundity was examined.
Methods Among 1560 Danish, Italian, and Dutch reinforced plastics workers, 220 styrene-exposed workers and 382 unexposed referents who had fathered a child were identified. A total of 768 historical styrene measurements conducted in 1970—1996 in the study companies formed the basis for semiquantitative exposure assessment in combination with measurements of urinary styrene metabolite levels. All the subjects were interviewed about work conditions and other factors potentially related to reduced fecundity. Fecundity was measured as the reported time to pregnancy (number of months a couple needed to conceive their youngest child).
Results A statistically nonsignificantly reduced fecundity was observed for the styrene-exposed workers [fecundity ratio 0.79, 95% confidence interval (95% CI) 0.59—1.05]. But no consistent pattern of a detrimental effect on fecundity was found when time to pregnancy was related to worktasks indicating higher styrene exposure levels or semiquantitative or quantitative measures of styrene exposure. The workers with high exposure showed a fecundity ratio of 1.09 (95% CI 0.69—1.72).
Conclusions It is unlikely that styrene exposure has a strong effect on male fecundity.

Key terms fecundity, fertility, male, occupation, solvents, styrene exposure.

High-level styrene exposure is encountered in the reinforced plastics industry (1). The metabolism of styrene is well documented, and valid biomarkers of internal exposure are available (2). The compound is neurotoxic, and the styrene metabolite styrene oxide is mutagenic (3). Recently we suggested, based on a longitudinal study of workers of the reinforced plastics industry, that styrene exposure may reduce sperm count (4). An increased proportion of sperm with abnormal morphology has also been reported for the workers in this industry (5). Other organic solvents have been suggested to deteriorate human spermiogenesis (6—10).

Thus styrene was chosen as an obvious candidate for assessing the suggested hazardous effects of organic solvents on male reproduction. Fecundity can be measured by the time to pregnancy (11), even for men (12, 13).

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Table 1. Workers included in the study from 3 Danish, 9 Italian, and 14 Dutch reinforced plastics companies, all employed between 1981 and 1997.

Status	Denmark		Italy		The Netherlands		Total	
	N	%	N	%	N	%	N	%
All production workers	1116	100.0	280	100.0	164	100.0	1560	100.0
Unmarried	115	10.3	82	29.2	16	9.8	213	13.7
Nonrespondents	227	20.3	1	0.3	68	41.5	296	19.0
Refusing to participate	101	9.0	2	0.7	19	11.6	122	7.8
Married with no children	160	14.3	35	12.5	14	8.5	209	13.4
Last pregnancy due to contraceptive failure	21	1.8	24	8.5	4	2.4	49	3.1
Time to pregnancy not reported	36	3.2	2	0.7	5	3.0	43	2.8
Observation period <13 months	14	1.3	11	3.9	1	0.6	26	1.7
Included in analysis	442	39.5	123	43.9	37	22.6	602	38.5

Table 2. Characteristics of 602 workers from the Italian, Dutch, and Danish reinforced plastics industry according to exposure status 12 months prior to the birth of the youngest child.

Characteristic	Exposure status			
	Exposed		Unexposed	
	N	%	N	%
Father's age[a]				
<30 years	86	39.1	179	46.9
30—34 years	86	39.1	144	37.7
≥35 years	45	20.5	55	14.4
Mother's age[b]				
<25 years	42	19.1	114	29.8
25—29 years	104	47.3	145	38.0
≥30 years	71	32.3	103	27.0
Mother primipara	85	38.6	119	31.2
Oral contraception prior to pregnancy	102	46.4	175	45.8
Genital disorder of father	6	2.7	10	2.6
Genital disorder of mother	8	3.6	33	8.6
Smoking father	118	53.6	275	72.0
Smoking mother	87	40.0	212	55.0
Country				
Denmark	110	50.0	332	86.9
Italy	85	38.6	38	10.0
The Netherlands	25	11.4	12	3.1
Length of employment in reinforced plastics industry				
< 1 year	8	3.6	154	40.3
1—4 years	29	13.2	107	28.0
≥5 years	183	83.2	121	31.7

[a] Three exposed and 4 unexposed men did not report their age.
[b] For 3 exposed and 20 unexposed wives their husbands did not report age.

This study compares the time to pregnancy of 220 styrene-exposed and 382 unexposed male workers of the reinforced plastics industry. Preliminary results have previously been presented (14).

Subjects and methods

Study population

All 1560 currently or recently employed workers identified from personnel files of 3 Danish, 9 Italian, and 14 Dutch reinforced plastics companies using hand or spray lamination techniques were invited to participate in the study between February 1995 and August 1997 (table 1). Two hundred and thirteen men reported being unmarried and were not eligible for the study. Of the remaining men, 122 refused to participate, while 296 did not respond to our invitation.

In all 929 men filled out a questionnaire (N=375) and went through a face-to-face interview (N=161) or a telephone interview (N=393). Accordingly the response rate was higher than 69%. Identical questionnaires developed in cooperation between the 3 centers were used regardless of the method of data collection (15).

For the 720 men who reported that they had fathered at least 1 child, we focused on the youngest child. The 49 who reported a contraceptive failure and the 43 who did not recall time to pregnancy were excluded. This was also the case for the 26 who fathered the child within 13 months prior to data collection to ensure comparable data, because we censored time to pregnancy at 13 months. Accordingly 602 men were then included in the analysis (table 2).

Of these men, 220 conceived their child when employed in the reinforced plastics industry (between 1969 and 1996). For 382 men this point in time occurred before or after employment in the reinforced plastics industry (between 1959 and 1995); they were considered unexposed and served as internal referents.

Time to pregnancy

Time to pregnancy was assessed by the number of months a couple needed to conceive their youngest child. The men answered the question "How many months did it

take your wife to get pregnant?" They also reported whether or not the pregnancy resulted from a birth control failure, the last contraceptive method used (if any), parity, and life-style factors during the year before the birth of the child.

Exposure assessment

Workroom air levels of styrene and questionnaire data on individual work conditions formed the basis for a semiquantitative exposure classification. Individual biological markers of internal styrene dose were available for a subset of the workers.

Workroom air levels of styrene were monitored by 9 of the participating companies independently of this study. They provided 768 measurements from 3 Danish (N=698), 1 Italian (N=49), and 5 Dutch companies (N=21), all collected by charcoal tube or passive diffusion and analyzed by gas chromatography between 1970 and 1996. The number of samples by 5-year calendar periods varied between 30 (1980—1984) and 350 (1990—1994). Altogether 689 (90%) were personal samples, and 542 (71%) were short-term samples (<2 hours). Prior to 1990, measurements were only available from Denmark.

From a multiple regression model including country (Denmark, Italy, and The Netherlands), calendar year (6 periods), sampling method (personal, stationary), and sampling duration (<2 hours, ≥2 hours), styrene levels in workroom air were estimated for the 3×6 cells defined by country and calendar-year period. The exposure levels declined from 500 mg/m^3 in 1970—1974 to <80 mg/m^3 in 1995—1996. Twofold exposure levels were indicated for Italy and The Netherlands when compared with Denmark.

The questionnaire focused on work in the reinforced plastics industry 12 months before the birth of the youngest child. This fixed point in time accounted for the duration of pregnancy and spermatogenesis and was furthermore selected to improve the feasibility of the data collection.

The questionnaire was comparable to the one used in a previous study of styrene-exposed reinforced plastics workers (4). In that study, urinary measurements of mandelic acid (a styrene metabolite) were paired with detailed information on work conditions during the sampling period. The frequency of hand and spray lamination and the use of a respirator showed the strongest prediction of mandelic acid level, and the following weights could be calculated from the relative distribution of the median urinary mandelic acid levels: (i) full-time lamination and no respirator 1.00 (reference), (ii) full-time lamination and respirator 0.64, (iii) part-time lamination and no respirator 0.43, (iv) part-time lamination and respirator 0.24, (v) no lamination and no respirator 0.08, and (vi) no lamination and respirator 0.01. In our study, these weights were used to classify the workers according to expected relative levels of internal exposure according to the reported frequency of hand and spray lamination and respirator use. Workers fathering the child outside employment in the industry were assigned a weight of 0.00

A semiquantitative exposure index that also accounted for differences in workroom air levels was then calculated by multiplying these weights by the workroom air styrene levels estimated for the time-to-pregnancy starting year (the year starting to obtain a pregnancy) and country. The index was finally categorized into 4 groups with a comparable number of exposed subjects.

Urinary levels of mandelic acid and phenylglyoxylic acid (styrene metabolite) were available from 119 of the Italian workers (769 end-of-shift samples). The sum of mandelic acid and phenylglyoxylic acid declined from a median value of 610 mg/l in 1982—1984 to a median value of 69 mg/l in 1995—1996 (regression coefficient -45 mg/year, P-value 0.0001). These data were used for a separate exposure classification.

Statistical analysis

Fecundity ratios (the ratio of the odds for pregnancy among the exposed and unexposed workers) were estimated by the discrete analogue of the Cox regression model with the SAS PHREG procedure (16). A higher value for the fecundity ratio indicates higher fecundity (shorter time to pregnancy). Time to pregnancy was censured after 13 months to take into account the possible effects of medical intervention for infertility (17). In addition to exposure variables, the models included: maternal age (<25, 25—29, 30—34, ≥35 years), maternal and paternal smoking habits (smoker, nonsmoker), last contraceptive used (oral, other), parity (mother primipara, multipara), length of employment in the reinforced plastics industry (<1, 1—4, ≥5 years), time-to-pregnancy starting year (5 periods), country (Denmark, Italy, The Netherlands), and an interaction term for oral contraceptive use and time to pregnancy. The model was decided upon a priori, and the complete model was used for all the analyses. All the explanatory variables were introduced as dummies when appropriate, except in the trend analysis, for which the continuous exposure variables were included in the full models.

Results

A statistically nonsignificantly reduced fecundity was found for the men employed in the reinforced plastics industry 12 months prior to the birth of the youngest child when this group was compared with the unexposed workers (table 3). However, work conditions indicating

Table 3. Crude and adjusted fecundity ratios (FR) by work conditions, year starting to obtain a pregnancy, and length of exposure in the reinforced plastics industry among 602 male workers from Denmark, Italy, and The Netherlands, 1970—1996. (N =number of workers, 95% CI = 95% confidence interval)

Work characteristic	N	Subjects by time to pregnancy			Crude FR	Adjusted FR[a]	95% CI
		0—5 months	6—13 months	>13 months			
Unexposed	382	270	62	50	1.00	1.00	.
Work conditions in the reinforced plastics industry							
No lamination or part-time lamination with filter mask	90	64	11	15	0.92	0.68	0.48—1.00
Part-time lamination without filter mask or full-time lamination with filter mask	89	69	12	8	1.24	0.88	0.61—1.26
Full-time lamination without filter mask	41	32	6	3	1.26	0.94	0.59—1.50
Time-to-pregnancy starting year in the reinforced plastics industry[b]							
1970—1979	20	17	0	3	1.19	0.94	0.49—1.80
1980—1984	16	11	2	3	0.80	0.62	0.30—1.27
1985—1989	54	41	5	8	1.05	0.86	0.52—1.41
1990—1997	128	94	22	12	1.11	0.76	0.52—1.11
Length of exposure in the reinforced plastics industry[c]							
< 1 year	23	16	3	4	0.93	0.81	0.46—1.44
1—4 years	76	60	11	5	1.26	0.98	0.67—1.43
≥5 years	96	80	9	7	1.49	1.08	0.73—1.60
All exposed	220	165	29	26	1.09	0.79	0.59—1.05

[a] Adjusted fecundity ratios were obtained from a proportional hazards model that included maternal age, use of oral contraceptives, maternal and paternal smoking habits, time-to-pregnancy starting year, length of employment in the reinforced plastics industry, and country.
[b] Two workers not reporting the date of birth of the child were not included.
[c] For 21 exposed workers with a time-to-pregnancy starting date prior to employment in the reinforced plastics industry and for 4 workers with missing data, the length of exposure could not be calculated. All 25 workers were not included in the analysis.

Table 4. Crude and adjusted fecundity ratios (FR) by workroom styrene exposure level for 600[a] male workers of the reinforced plastics industry of Denmark, Italy, and The Netherlands, 1970—1996. (N = number of workers, 95% CI 95% confidence interval)

Styrene exposure	Denmark				Italy				The Netherlands				All countries			
	N	Crude FR	Adjusted FR[b]	95% CI	N	Crude FR	Adjusted FR[b]	95% CI	N	Crude FR	Adjusted FR[b]	95% CI	N	Crude FR	Adjusted FR[b]	95% CI
None	332	1.00	1.00	.	38	1.00	1.00	.	12	1.00	1.00	.	382	1.00	1.00	.
Low	76	1.01	0.84	0.61-1.16	17	0.89	0.66	0.30—1.56	3	0.42	0.24	0.03—2.36	96	0.97	0.68	0.48—0.97
Medium	26	0.95	0.73	0.46—1.16	29	1.12	0.92	0.47—1.81	14	0.54	0.28	0.04—1.72	69	1.02	0.70	0.47—1.04
High	7	0.94	0.77	0.34—1.78	39	1.22	0.99	0.54—1.82	7	0.89	0.48	0.13—.1.79	53	1.32	1.09	0.69—1.72
Test for trend (P-value)	441		0.59		123		0.38		36		0.72		600		0.19	

[a] Two workers not reporting the date of birth of the child were not included.
[b] Adjusted fecundity ratios were obtained from a proportional hazard model that included maternal age, use of oral contraceptives, maternal and paternal smoking habits, time-to-pregnancy starting year, length of employment in the reinforced plastics industry, and country.

higher styrene exposure levels were unrelated with fecundity. Calendar year was suggested as a significant determinant of styrene exposure level, but starting to obtain a pregnancy during early years of employment was not associated with reduced fecundity. Long-term exposure is expected to relate to lower fecundity if the causal mechanism relies on a cumulative effect; however, the workers exposed long-term were more fecund than the workers exposed short-term.

The semiquantitative styrene exposure index, which incorporated estimated styrene levels in the workroom air, worktasks, and use of protective devices, showed reduced fecundity among the exposed Danish and Dutch workers, but not among the Italians (table 4). Tests for trend by increasing styrene exposure level were not statistically significant either for the national subsets or for the total data set. A cumulative exposure index that included duration of exposure through to the time-to-pregnancy starting date showed increasing fecundity as exposure increased (data not shown).

Thirty-four of the biologically monitored Italian workers had a time-to-pregnancy starting date within 1 year of a urinary sampling date. Increasing fecundity with increasing styrene exposure was indicated for these

workers when they were compared with the 38 unexposed Italian workers (data not shown).

Discussion

A statistically nonsignificantly reduced fecundity was observed for the styrene-exposed workers. But no consistent pattern of a detrimental effect was seen when fecundity was related to qualitative, semiquantitative, or quantitative measures of styrene exposure level. Our recent report (4) suggesting a reduced sperm count in styrene-exposed workers was thus not corroborated. These findings are, however, not necessarily in conflict because a pronounced decline in sperm count is needed to affect fecundity (18, 19). The results are, on the other hand, in line with those of a recent study of biologically monitored men. This study showed no relationship between markers of styrene exposure and time to pregnancy (9).

A total of 296 men did not respond to our invitation to participate in the study, while 122 refused to participate. The 122 refusers were slightly older (average age 38 years) than the 1142 subjects willing to participate (average age 35 years), and the proportions who had fathered a child were comparable between these 2 groups (58% versus 57%). No data were available with which to assess whether or not participation was conditional on fecundity and exposure, and selection bias cannot be ruled out. We have no reason to believe that the 118 men (8%) who experienced a contraceptive failure, did not recall time to pregnancy, or were observed for less than 13 months differed with respect to styrene exposure and that excluding them affected the validity of the study.

Even if 220 exposed workers had been studied, we would have preferred a higher statistical power, especially for the high exposure category, and our negative findings may be due to chance.

Time to pregnancy is a convenient way to obtain self-reported retrospective data on fecundity, even after long periods of time (20). It is, however, expected that men report less valid data than women and nondifferential reporting may have biased our results towards the null hypothesis.

To reduce differential reporting of time to pregnancy and to obtain high comparability for competing risk factors of subfecundity, we based our study on internal comparisons. However, due to this design, the referents differed significantly from the exposed with respect to the recall time for time to pregnancy (median recall time for referents 9.8 years versus 4.3 years for the exposed workers). Because all the analyses were adjusted by the time-to-pregnancy starting year, we believe, however, that this potential bias was minimized.

Another implication of the internal comparisons was that length of employment differed significantly between the exposed and reference workers (median 11.0 versus 1.9 years). Because short-term workers of the reinforced plastics industry may have less healthy habits (21), all the analyses were adjusted by length of employment in addition to known determinants of fecundity. Thus confounding was unlikely to have biased the results substantially, even if a possibility, since only few causes are known for subfecundity.

Most of the referents started to father their youngest child prior to employment in the plastics industry (90%) and thus had a higher probability of longer time to pregnancy than the exposed workers due to their longer observation periods. Therefore, we excluded the 26 men with a time-to-pregnancy starting date within 13 months prior to the interview date. By using this exclusion criterion, we believe that the suggested bias did not invalidate our findings.

The urinary levels of the styrene metabolites took account of company and period differences in the styrene levels in the ambient air and individual differences in worktasks, use of a respirator, and the absorption and metabolism of styrene, and thus they provide the best measure of the target dose, but such levels were only available for a small subset of workers.

Because of a lack of quantitative markers of exposure, the workers were classified according to a semiquantitative exposure index that reflected the internal styrene dose estimated by the combined effect of ambient air levels, worktasks, and use of a respirator. It has, however, to be emphasized that archival workroom air measurements were not obtained during standardized conditions, and the conditions reflect a mixture of exposure situations (eg, both routine and hot spot measurements). Furthermore, exposure peaks have not been well described by these data. However, since the recorded exposure levels are expected to correlate with peak and average exposure levels, we are confident that the exposure index provided a sound basis for our evaluation of a possible exposure-effect relationship.

The styrene exposure levels decreased significantly during the study period. This change may have caused time-trend bias towards lower fecundity ratios in the group with low-level exposure because a longer time to pregnancy is associated with an earlier time-to-pregnancy starting date and thus with higher exposure levels independently of any causal relation (22). However, this possibility would imply that our findings of no effect represented the biased result of a true gainful effect of styrene exposure on male fecundity. This is not a likely result.

For reasons of feasibility, the exposure information was obtained for a period 12 months prior to delivery. Workers hired in the reinforced plastics industry during an unsuccessful time to pregnancy may therefore have been classified as exposed even if they were unexposed

when they started to obtain a pregnancy. The opposite may apply to the workers who left employment when waiting to become pregnant. We assessed this possibility in a subsample of 239 Danish workers who also reported exposure on the time-to-pregnancy starting date. Among the 54 workers who were exposed at the time-to-pregnancy starting date, the 16 subfecund workers (time to pregnancy ≥6 months) showed a more than doubled frequency of exposure reclassification (25%) by the 12 months criterion compared with the 11% of the 38 fecund workers (time to pregnancy <6 months). Among 185 workers unexposed at the time-to-pregnancy starting date, the 54 subfecund workers showed a similar relative frequency of exposure reclassification by the 12 months criterion, but only 1 (2%) of these workers changed exposure status compared with 1% of the 131 fecund workers. The exposure estimates obtained 12 months before the delivery of the child thus may have biased the fecundity ratios away from a hazardous effect. But only if the time-to-pregnancy starting date is more appropriate for exposure assessment and if reclassification is more prevalent among those exposed at the time-to-pregnancy starting date (as was the case in this sample).

Even if only 4% of the 239 subjects changed exposure status when the time focus was changed, a fecundity ratio of 0.90 [95% confidence interval (95% CI) 0.67—1.49] was obtained when based on the criterion time-to-pregnancy starting date in contrast to a fecundity ratio of 1.00 (95% CI 0.62—1.32) when based on the 12 months criterion for this subsample of 239 workers. If this finding is valid for the total study population, we have overlooked a 10% decline in fecundity for the styrene-exposed men. This possibility can, however, not explain the lack of any exposure-response relationship in the other analyses.

To conclude, no consistent pattern of reduced male fecundity was observed as a result of styrene exposure. If the suggested styrene-dependent decline of sperm count is true, it is unlikely that the effect on fecundity is strong.

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