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## Time to pregnancy for men occupationally exposed to styrene in several European reinforced plastics companies

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Occupational exposure to organic solvents has been suggested to exert a detrimental effect on human spermogenesis and male fecundity (1—3). An increased occurrence of spontaneous abortions has also been attributed to the husband's exposure to organic solvents (4). Styrene is an organic solvent used for the production of plastics. Styrene is neurotoxic and the styrene metabolite styrene oxide is mutagenic. An increased proportion of sperm with abnormal morphology has been reported for workers exposed to high levels of styrene (5). Styrene is found in high concentrations in workroom air of the reinforced plastics industry, while other exposures suspected to be hazardous for male fecundity are absent (6). Time to pregnancy has been suggested as a valid measure with which to evaluate environmental effects on fecundity (7). In the present study we examined the possible hazardous effect of styrene on male fecundity by relating quantitative estimates of occupational styrene exposure with time to pregnancy.

### Subjects and methods

Three Danish, 4 Italian, and 14 Dutch companies, producing containers, wind mill rotor blades, sailing yachts, artificial marble or military vessels of reinforced unsaturated polyester by hand lamination or spray lamination were recruited for the present study. A total of 116 recently employed Danish male workers, 164 currently employed Dutch workers, and 199 currently employed Italian workers were identified from company personnel rosters between 1995 and 1997. Out of these 1479 men, 1009 (68%) went through a personal interview or answered a postal questionnaire. The 643 men who were living as married and had fathered a child were candidates for the study. Men who reported a contraceptive failure (N=42) or who did not recall the time to pregnancy (N=35) were excluded. This was also the case for the 25 men who fathered a pregnancy less than 13 months before the date of data collection to ensure a similar observation period for all study subjects because we

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<sup>5</sup> The Asclepios project on occupational hazards to male reproductive capability is a biomedical research project of the European Union that was carried out in 14 European centers in 1993—1998. The project was coordinated by The Steno Institute of Public Health, University of Aarhus Denmark, and it included the following researchers: Belgium, Gent (P Kiss, A Mahmoud, M Vanhoorne, H Verstraeten); Denmark, Aarhus (A Abell, JP Bonde, SB Larsen, G Danscher, E Ernst, H Kolstad), Copenhagen (A Giwercman); England, London (A Dale, M Joffe, N Shah); Finland, Helsinki (M-L Lindbohm, H Taskinen, M Sallmen), Turku (J Lähdetie); France, Paris (P Jouannet, P Thonneau), Strasbourg (A Clavert); Germany, Erlangen (KH Schaller, W Zschiesche); Italy, Brescia (P Apostoli, S Porru), Milano (L Bisanti), Pietrasanta (L Lastrucci), Rome (M Spanò); The Netherlands, Nijmegen (N Roeleveld, H Thuis, GA Zielhuis), Zeist (W de Kort); Poland, Lodz (K Sitarek).

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censured all participants after 13 months of waiting time to pregnancy. Thus 541 men were included in the analysis, in which we only focused on the time to pregnancy for the youngest child.

Company exposure levels of styrene were documented by 720 measurements of workroom air conducted in the 3 Danish (N=699) and 5 of the Dutch companies (N=21) between 1960 and 1995. No Italian data were available. All but 24 samples were collected by charcoal absorption tubes. The dependency of styrene level on calendar year (categorized into 7 periods), sampling method (personal, stationary), duration of sampling (<2 hours, ≥2 hours), dimension of product (<10 m<sup>2</sup>, ≥10 m<sup>2</sup>), production method (hand or spray lamination, other) and country (Denmark, The Netherlands) was assessed in a linear regression model with the general linear modeling procedure of SAS (statistical analysis system) after log-transformation of the styrene levels to take account of the skewed distribution. Thirty percent of the variability of the styrene levels was explained by calendar year. The styrene levels declined significantly from about 150 ppm (parts per million) during the early 1970s to about 25 ppm during the late 1990s. Sampling method, duration of sampling, country, dimension of product, and production method did not contribute significantly to the variability of the styrene levels.

From 28 workers who were employed in the 3 Danish companies and who were enrolled for a parallel study of semen quality (8), 187 measurements of mandelic acid (the principal styrene metabolite) in postshift urinary samples were obtained to assess the internal exposure following styrene exposure. Frequency of laminating or molding reinforced plastics goods (days/week) and the use of protective devices showed the strongest prediction of mandelic acid level. A relative measure of the internal exposure was calculated for these 2 factors using the workers' laminating daily without any protective devices as reference (the workers with the highest mandelic acid level).

From the year preceding the reported year of pregnancy each of the 541 workers was assigned a workroom air styrene level, and, according to the reported lamination frequency and use of protective devices, they were

assigned a relative measure of the internal exposure. An exposure index incorporating the expected external exposure level and the modifying effect of work conditions was calculated by multiplying these 2 measures. The index was classified into 4 categories (unexposed, low, medium, high). All the pregnancies occurring before employment in a reinforced plastics company were classified as unexposed.

Fecundability ratios were estimated by the discrete analogue of the Cox regression with the SAS PHREG procedure. All waiting times to pregnancy were censored after 13 months to exclude the possible effects of medical intervention for infertility. In addition to exposure variables, the models included time-to-pregnancy starting date (the date of the beginning of the waiting time to pregnancy classified in 2-year intervals), study center (3 Danish, 1 Italian, 1 Dutch), maternal age, maternal and paternal smoking habits, oral contraceptive use, and parity. These were decided upon a priori and included as dummy variables in all the analyses.

## Results

Of the 541 men, 474 (87%) obtained a pregnancy within 13 months. Altogether 188 men were employed in a reinforced plastics company about 12 months prior to the birth of the youngest child; the other 353 men were classified as unexposed to styrene. The unadjusted fecundability ratio increased by increasing styrene exposure level with a borderline statistical significance (table 1). Adjustment for female and male smoking habits, use of oral contraceptives, age of the woman, parity and time-to-pregnancy starting date did not change this finding substantially. However, after adjustment by study center, no association between styrene exposure and fecundability was seen. The Italian workers reported an overall fecundability ratio which was 50% higher than that of the Danish and Dutch workers, and they constituted a high proportion of the highly exposed workers. Therefore the unexpected inverse exposure response relation was probably due to regional differences in the reported time to pregnancy because no exposure response relations were seen within each participating center (table 2).

**Table 1.** Unadjusted and adjusted fecundability ratios (FR) by styrene exposure level for 541 pregnancies of male workers of reinforced plastics industries in Denmark, Italy, and The Netherlands, 1969–1996. (95% CI=95% confidence interval)

Styrene exposure level	Workers	Number of pregnancies according to time to pregnancy			Fecundability ratio (FR)		
		0–3 months	4–13 months	>13 months	Crude FR	Adjusted FR <sup>a</sup>	95% CI
Unexposed	353	225	83	45	1	1	
Low	61	39	12	10	1.02	0.75	0.51–1.09
Medium	77	52	16	9	1.09	0.82	0.57–1.18
High	50	37	10	3	1.43	0.90	0.57–1.40

<sup>a</sup> Adjusted fecundability ratios were obtained from a proportional hazard model that included the listed exposure variables as well as maternal age, parity, use of oral contraceptives, study center, maternal and paternal smoking habits and time-to-pregnancy starting date.

**Table 2.** Adjusted fecundability ratios (FR) according to the level of styrene exposure stratified by study center.<sup>a</sup>

Styrene exposure level	Study center									
	Denmark-1		Denmark-2		Denmark-3		Italy		The Netherlands	
	N <sup>b</sup>	FR	N <sup>b</sup>	FR						
Unexposed	118	1	78	1	136	1	10	1	11	1
Low	16	0.59	18	1.03	11	1.04	13	0.35	3	0.30
Medium	12	0.90	18	1.24	16	1.28	16	0.48	15	0.32
High	2	1.01	6	0.45	9	1.10	27	1.01	6	0.50

<sup>a</sup> Adjusted fecundability ratios were obtained from a proportional hazard model that included the listed exposure variables as well as maternal age, parity, use of oral contraceptives, maternal and paternal smoking status, and time-to-pregnancy starting date.

<sup>b</sup> Number of pregnancies.

## Discussion

These preliminary results of a European multicenter study of time to pregnancy showed no detrimental effect of styrene exposure on male fecundity. The finding is in line with the results of a recent study among men biologically monitored for solvents, showing a slightly decreased fecundability for men exposed to low and high levels of unspecified solvents, but not related to styrene exposure (9). Our results also add to a recent review finding no strong indications of reproductive hazards related to styrene exposure (10). Due to the toxicokinetic diversity of organic solvents, however, one has to be careful when generalizing our findings to other organic solvents.

Contrary to most previous studies, this study was strengthened by the availability of quantitative estimates of organic solvents in workroom air for 2 of the participating regions. Quantitative exposure estimates are a prerequisite for obtaining comparable exposure levels across different regions as qualitative estimates may be difficult to pool due to regional differences in their interpretation. Historical workroom air measurements are being collected in Italy also and will be included in the final analysis of this data set. By monitoring the internal doses of styrene in a subsample of workers, the modifying effect of work tasks and the use of protective equipment was assessed.

The exposure information of this study was obtained for a period 12 months prior to the birth of the youngest child. Workers who were hired in the reinforced plastics industry during an unsuccessful waiting period to pregnancy may therefore have been classified as exposed even if they were unexposed when they discontinued contraception to achieve pregnancy. But we found no indication of such misclassification conditional on the time to pregnancy in a subsample of Danish reinforced plastics workers who also reported exposure at the time-to-pregnancy starting date.

The styrene exposure levels decreased significantly during the study period. This occurrence may have caused time trend bias towards lower fecundability ratios because longer waiting times to pregnancy are associated with an earlier time-to-pregnancy starting date and

thus with higher exposure levels independently of any causal relation.

The study population was defined as workers recently or currently employed in the reinforced plastics industry. The workers fathering a child before employment in this industry were used as referents. Thus the referents had a higher probability of longer waiting times due to longer observation periods than the exposed workers. Therefore, we excluded the 25 men with a time to pregnancy within 13 months prior to the interview date. Therefore we believe that the suggested bias has not invalidated our findings.

The study clearly showed the necessity for comparable outcome data, in addition to comparable exposure data, across the regions participating in a multicenter study. If any aspect of the exposure effect relationship studied was modified by region, the analysis would have to be stratified by region.

In conclusion, we observed no detrimental effect of styrene exposure on male fecundity in this preliminary analysis of a European multicenter study. Data collection, however, is still in progress, and the incoming data, as well as the evaluation of the effect of cumulative exposure, may change the present results.

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