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Indirect Fertility Analysis in Painters Exposed to Ethylene Glycol Ethers: Sensitivity and Specificity

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Semen analysis has proven useful in the clinical diagnosis of infertility and is the most widely used method of monitoring the effects of occupational exposure on male fertility. Collection and analysis of semen samples in a field setting, however, require a highly motivated population and excellent technical resources, limiting the widespread application of the method. Techniques of monitoring male worker fertility using questionnaires to avoid some of the difficulties of semen analysis have been developed. These methods compare the rate of observed births for wives of workers with expected birth rates derived either from U.S. fertility tables or from unexposed workers. The present study compares the sensitivity of this questionnaire method with that of semen analysis in an evaluation of reproductive function in men exposed to ethylene glycol ethers. The reproductive function of 74 married painters exposed to ethylene glycol ethers was compared with that of 51 married controls employed at a shipyard. The groups differed in sperm count, but the questionnaire method showed no effect of exposure on fertility. This analysis suggests that the questionnaire assessment of fertility is less sensitive than semen analysis as a screening tool for male reproductive function.

Key words: reproductive outcome, semen analysis, questionnaire methods, occupational exposures

INTRODUCTION

Semen analysis is of proven benefit in the diagnosis of male infertility in a clinical setting and has been used frequently in the study of human populations. Semen analysis has been used to assess effects of chemical exposure in man for at least 85 different chemicals [Wyrobek, 1983]. The analysis usually includes sperm viability, sperm count (either as total sperm/ejaculate or sperm count/ml of ejaculate), sperm motility, and sperm morphology. New methods of measuring motility and morphology have been developed, and these have improved the usefulness of semen analysis in population studies.

Each variable in semen analysis has limitations that affect its use in epidemiologic studies. Sperm count has been most widely used and is best correlated with the man's ability to effect a pregnancy, yet even with attention to all factors known to

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affect count, such as abstinence and collection methods, there is still a wide range of "normal count" in individuals and populations. This variability limits our ability to detect small differences between populations. Sperm motility is very sensitive to time and temperature after collection, and analyses should be conducted within 2 hr of ejaculation. What constitutes normal sperm morphology is not defined, and only a few abnormalities in shape have been well linked to infertility.

To overcome some of these difficulties, another method has been proposed to monitor male fertility. The number of births to the wives of male workers is determined using a standardized questionnaire and is compared with expected numbers derived from national fertility statistics or expected numbers derived from a matched control group [Wong et al., 1979; Levine et al., 1980]. This method could be used to identify groups with decreased fertility, allowing more invasive and/or expensive testing to be carried out only as needed.

For this method to be used as the first method of monitoring male fertility, with semen studies reserved for instances when the questionnaire method detects an effect of exposure on fertility, the questionnaire should be known to be at least as sensitive as semen analysis in detecting an effect of exposure. For surveillance to be effective, it needs to detect a change at as early a stage as possible, so that an intervention can be made. The ideal instrument is both sensitive and specific, allowing identification of toxicants that will affect fertility if exposure continues and determining this at the earliest possible stage of effect. The questionnaire method has been compared with semen analysis in two studies [Levine et al., 1981; Hamill et al., 1982].

Ethylene glycol ethers were chosen as the exposure of interest for this study because of their widespread use and their demonstrated effect on spermatogenesis in animals. Ethylene glycol ethers are widely used in industry in paints, varnishes, thinners, and solvents in resins, in textile printing, and in a variety of coating operations [Clapp et al., 1984]. With chronic oral or inhalation exposure, the ethylene glycol ethers cause focal testicular atrophy and disruption of the seminiferous tubules in mice, rats, and rabbits [Hardin et al., 1984; Zenick et al., 1984; Chapin and Lamb, 1984; Barbee et al., 1984; Foster et al., 1984; Nagano et al., 1979; Miller et al., 1984; Hanley et al., 1984]. Two studies of men exposed to EGME or ethylene glycol monoethyl ether (EGEE) have found a decreased sperm count [Ratcliffe et al., 1989; Welch et al., 1988], whereas one study found no effect [Cook et al., 1982].

MATERIALS AND METHODS

The men under study worked at a large shipbuilding facility in the northeastern United States. The site was chosen for study after a health hazard evaluation performed by NIOSH [1983] found evidence of exposure of the painters to ethylene glycol ethers. The shipyard employed 900 painters, of whom 600 were men. Men who lived within an approximate 20 mile radius of the clinical site of the study were invited to participate; this range was chosen to allow the men to deliver semen samples within 1 hr of collection. There were 94 painters who participated in the study; 73 provided semen samples. Controls were recruited from two job classifications in which the majority of jobs entailed no work aboard the ships: clerks and the marine draftsmen, of whom 55 participated in the study and 40 provided a semen sample. Details about working conditions in the shipyard, recruitment, and participation are discussed elsewhere [Welch et al., 1988; Sparer et al., 1988].

Each participant was seen at the clinical site. At this visit, the study team administered a questionnaire, performed a physical examination, described the technique for semen collection, and scheduled a time for the participant to bring back the sample. Semen analysis included sperm viability, density, motility, and morphology and pH and volume; video recording was used for sperm motility. A more detailed description of the semen analysis is presented in a previous report [Welch et al., 1988].

The questionnaire elicited information on basic demographics, medical conditions, and personal habits that have been reported to affect semen parameters. A section was developed that included the information required for the fertility analysis under study; this included the age of employee's wife, race, ages of all live-born children, date of marriage to male employee, and date of widowhood or permanent separation. The questionnaire data were analyzed using the software package designed by Richard Levine, MD, from the Chemical Industry Institute of Toxicology (CIIT). The program generates an expected number of births for the spouse of each married employee, using U.S. fertility charts. The estimate takes into account birth cohort, race, parity, and calendar year. A "standardized fertility ratio" (SFR) is computed as the ratio of observed to expected births. An SFR greater than 1 indicates a higher fertility rate in the study group than the U.S. population, and an SFR less than 1 indicates a lower fertility rate.

Participants were included in the fertility analysis if they had ever been married; no other exclusions were used. Men were included in the semen analysis portion of the study if they returned a semen sample. The two groups then differ somewhat; some men who returned a semen sample had never been married, and some men who completed a questionnaire did not return a semen sample.

Among 94 painters who filled out questionnaires, 79 were ever married; five of them were missing essential data and were not used in the analysis. There were 52 of 55 controls who were ever married; one was not included because of missing data. Due to an error in printing of the questionnaire, spouse age and date of marriage were unknown for 24 of 74 painters and for one of 51 controls. Spouse age was an average of 2.5 years lower than husband age in both painters and controls. When the wife's age was unknown, she was assigned an age 2.5 years younger than her husband. Date of marriage when unknown was assigned as 1 year before the oldest child was born or the date of hire if there were no children. A separate SFR was also calculated based only on the participants for whom complete data were available.

The reproductive experience for painters and controls was divided into preemployment (years married before hire), and exposure years, for three age categories. For each individual, "years at risk" were calculated as the number of years during which the worker was married and employed at Electric Boat, excluding any years during which he was separated, divorced, or widowed. "Preemployment" years were calculated as any married years before employment in the shipyard. Births that occurred 1 year or more from date of hire at the shipyard were considered to occur during the "at-risk" period.

Probabilities of having a birth for each year at risk for each individual were generated based on U.S. data. These were summed to derive total expected births for both painters and controls. The observed and expected births were compared as follows: Let E(c) = expected births in controls based on national fertility charts. Let O(c) = observed births among controls. O(c) is assumed to be Poisson distributed for

TABLE I. Characteristics of Exposed and Unexposed Men Included in Fertility (Questionnaire) Analysis Among Shipyard Painters and Controls*

	Exposed	Unexposed	p
No. of individuals	74	51	
Average age (years)	40.4 ± 12.2	48.8 ± 10.3	<0.01
Current smokers (%)	50	25	<0.05
Vasectomy (%)	15	25	NS

*Note that the group included in the fertility analysis and the group included in the semen analysis differ; see Materials and Methods for further explanation.

any group of individuals with a mean of aE(c) where a is an adjustment for any local factors that make the group under study different from the group from which U.S. data were derived. Similarly, let E(p) = expected births among painters and O(p) = observed births among painters. O(p) is assumed to Poisson distributed with a mean of abE(p), where b represents the exposure effect. The standardized fertility ratio (SFR) for controls = O(c)/E(c)a; the SFR for painters = O(p)/E(p)ab and b = SFR(p)/SFR(c). The null hypothesis is that b = 1 or that b > 1. If exposure affects fertility, b will be < 1.

A χ^2 test was done for significant differences between painters and controls in their observed to expected birth ratio. The mean sperm count and density for painters and controls were compared using analysis of variance, after a cube root transformation to convert sperm density and count per ejaculate to a normal curve [Welch et al., 1988; Mortimer and Lenton, 1983]. Fisher's exact test was used to test the difference in the proportions of men in each group with oligospermia.

RESULTS

Characteristics of the Groups

Cumulative data on number of individuals, age, rate of smoking and rate of vasectomy are presented in Table I. The painters and controls differed significantly in average age, years of employment in the shipyard, percent of current smokers, and some measures of alcohol consumption. They did not differ in alcohol consumption of at least one drink per day, rate of vasectomy, the presence of varicocele on physical examination, testicular size, and medications (no use was noted of any medications associated with fertility in either group).

Semen Analysis

Mean sperm count and count per ejaculate were lower in the painters than in the controls after controlling for age, smoking, and abstinence in the model (p = 0.10 for density and p = 0.11 for count per ejaculate). The proportion of men with a sperm count <20 million was higher in the exposed group, 13.5% vs. 5% in the controls (p = 0.12) (see Table II). Three of these painters were azoospermic, and one was essentially azoospermic with a count of 0.2 million. Neither of the two affected controls was azoospermic.

There was a difference in sperm count between smokers and nonsmokers in the exposed group. Since the groups differed in the rates of smoking, the rate of oli-

TABLE II. Fischer's Exact Test for Sperm Density and Total Sperm Count Among Shipyard Painters and Controls*

	Exp	Unexp	Total	p
Count per cc				
≤20 million	10	2	12	
>20 million	63	38	101	0.13
Total	73	40	113	
Count per ejaculate				
≤100 million	24	8	32	
>100 million	49	32	81	0.2
Total	73	40	113	
Count per ejaculate, nonsmokers only				
≤100 million	12	5	17	
>100 million	21	27	48	0.05
Total	33	32	65	
Count per ejaculate, smokers only				
≤100 million	12	3	15	
>100 million	28	5	33	0.49
Total	40	8	48	

*Note that the group included in the fertility analysis and the group included in the semen analysis differ; see Materials and Methods for further explanation. Oligospermia defined as a count/cc of ≤20 million, and as a count/ejaculate of ≤100 million.

gospermia was analyzed separately for smokers and nonsmokers. Among the nonsmokers, the exposed group had a higher rate of oligospermia ($p = 0.05$).

Among the four azoospermic men, two were never married, and one had a child prior to exposure. Among the oligospermic controls, one had children, and the other did not. Among the oligospermic painters, four of six had children, one had never married, and one had married but had no children.

Fertility Analysis

Table III describes the years at risk, preemployment years, and number of children born in these periods. Table IV displays the SFRs for painters and controls for both preemployment and employed years.

Both painters and controls had an SFR during the exposure period of >1 and there was no significant difference in the fertility of the two groups. For the period when the subjects were married but not yet employed at the shipyard, there was no significant difference between the two groups. An SFR was calculated including only the 50 painters and 50 controls for whom age of spouse and date of marriage were known. This did not differ from the SFR generated with assumptions made for age and date of marriage as described in Materials and Methods.

When exposed painters were compared with their own preemployment history, there was no significant difference in fertility. The controls' preemployment fertility was higher compared with fertility after employment.

DISCUSSION

Although several toxicants have been shown in epidemiologic studies to affect fertility and other reproductive outcomes, the mechanism and site of action are not

TABLE III. Fertility (Questionnaire) Analysis Among Shipyard Workers

Maternal age (years)	Years married		Numbers of births	
	Exposed	Unexposed	Exposed	Unexposed
Preemployment reproductive history				
16–25	124	55	51	19
26–35	209	128	36	33
36–45	100	37	4	4
Employment reproductive history				
16–25	90	106	25	22
26–35	171	285	16	43
36–45	172	311	3	7

TABLE IV. Fertility (Questionnaire) Analysis Among Shipyard Workers

	Exposed	Unexposed	Totals
SFR for preemployment years[a]			
No. of individuals	74	51	125
Obs. births	91	56	147
Exp. births	54.71	32.87	87.58
SFR	1.66	1.70	1.68
SFR for employed years[b]			
No. of individuals	74	51	125
Obs. births	44	72	114
Exp. births	27.85	52.80	80.65
SFR	1.58	1.36	1.44

[a] $\chi^2 = 0.64$ ($p > .10$); $b = 0.88$.
[b] $\chi^2 = 0.832$ ($p > .10$); $b = 1.19$.

understood in many cases. One agent could act at several sites and cause infertility, fetal loss, and birth defects; lead, for example, has been reported to cause all three outcomes. The choice of parameter to use for a study of reproductive effects is therefore difficult, since multiple outcomes could occur from a single agent, or one outcome such as infertility could be the result of the action of an agent at several stages. Infertility could be due to sexual dysfunction, hormonal disorders, or sperm abnormalities. The questionnaire method used in this study has intrinsic appeal in that it measures the outcome of interest, the birth of children, rather than only one of the steps leading to that outcome.

This questionnaire method has other advantages over semen analysis; it is inexpensive, noninvasive, and easily administered to large numbers of employees. It can be used retrospectively to study effects from which workers have recovered. Although immediate effects of chemicals that are testicular toxicants cannot be assessed by questionnaire, because an exposure must produce a decreased number of births to be detected, it can detect a decreased number of births once the acute effects are over. In this situation, providing there is recovery of testicular function, semen analysis will no longer be as useful. In addition, this method could be particularly useful in studying populations of subfertile men that include individuals who cannot achieve an erection or ejaculation; these men would be unable to provide semen

samples for analysis but do have reduced fertility. However, the sensitivity and specificity of this method have not been tested.

Four studies using this method have been reported [Wong et al., 1979; Levine et al., 1980, 1981; Hamill et al., 1982; Lauwerys et al., 1985]. Of these studies, two included both a fertility analysis and semen analysis on the same group. In one study [Hamill et al., 1982] both methods found no effect of exposure on either outcome measurement, and in one [Levine et al., 1980] both the semen analysis and the questionnaire showed an effect of exposure.

Whorton et al. [1977] investigated reports of infertility among pesticide workers producing dibromochloropropane (DBCP) and found a profound effect, with 11 of 36 exposed male workers having sperm counts under 1 million. DBCP had also been shown to be a testicular toxicant in rats, guinea pigs, and rabbits. Levine et al. [1980, 1981] retrospectively applied this questionnaire method of fertility analysis to these same workers, using data collected at the time of the semen study. They compared births prior to employment and during employment in nonexposed areas with births during employment in exposed areas, adjusting for maternal age, parity, and birth cohort. They found a significant difference in the observed to expected birth ratio for the exposed period. An effect on fertility could have been detected years earlier than it was suspected by the workers if ongoing surveillance using the questionnaire had been instituted.

In 1982, Hamill et al. published a study of fertility of workers exposed to toluene diamine (TDA) and dinitrotoluene (DNT). The analysis included exposure assessment, medical and reproductive histories, sperm count, and serum levels of follicle-stimulating hormone (FSH). Evaluation of fertility by both semen analysis and reproductive questionnaire revealed no effects.

In the present study, using this questionnaire method, no effect on fertility was detected during exposure to ethylene glycol ethers in a group of shipyard painters. A significant difference in the rate of oligospermia between nonsmoking painters and controls, and a marginally significant difference in the sperm count between all painters and all controls was observed. This comparison suggests that semen analysis is a more sensitive method of detecting the effects of workplace exposure on the male reproductive system.

The questionnaire method has several limitations that could explain why it did not detect an effect found using semen analysis. First, the sample size requirements may have been high. Second, the expected values based on U.S. data may be imprecise and not represent a true expected number of births; this would reduce the efficiency of the comparison. Third, there could be a difference in fertility between the groups due to nonwork factors that masks an exposure effect, and the analysis cannot adequately account for this.

The fertility analysis on the basis of births can require several years of exposure to detect a difference; sensitivity increases with increasing numbers of birth studied. Levine et al. generated power curves to determine needed sample size to detect various levels of difference in birth rates. For this sample, power to detect a difference in b at significance level $p < 0.10$, can be estimated from sample curves [Levine et al., 1980]. For this study, the probability (power) of detecting a 20% decrease in fertility ($b = 0.8$) is close to 60%, and that of detecting a 40% decrease ($b = 0.6$) is close to 100%. Based on these numbers, this sample was of adequate size to detect an effect.

Are the expected values sufficiently precise? If the expected value derived from national tables differs from the "true" fertility rate of either the exposed or unexposed group, the method will lose precision and be less likely to detect an effect. The factor a should account for some of the differences between the local study group and the U.S. data. Levine et al. point out that, if a is large, it might obscure an effect on infertility as indicated by b.

Previous applications of this method have often found an SFR > 1 in the unexposed groups, as we did in this study. In the study of DBCP-exposed men, all SFRs exceeded 1 in the absence of exposure. The SFR for work in nonexposed areas in the mid-1977 period was 2.16, and for the period 1969–1977 in nonexposed areas the SFR ranged from 1.45 to 2.28. This shows us that the expected values are not very precise, and we rely a great deal on adjustments such as a to make the method usable. In some studies, a is quite large, exceeding the value we would like to detect for b.

There is one major factor in the derivation of the expected numbers that can explain why the SFRs of the groups studied are consistently higher than that predicted for them. On the questionnaire, births are reported by the male workers. The analysis assumes that it is reliable to obtain information only from married men about births to their wives; unmarried men may not report, or even know, the number of pregnancies, and married men would not report out-of-wedlock children. Birth probabilities in national data are generated from the population of all women, regardless of marital status. Inclusion of single women in the U.S. data makes the expected birth rates lower than they would be if only married women were included. Dobbins [1987] estimates that the difference in marital status between U.S. data and study groups could underestimate expected births by 20%, so the SFR in the absence of exposure could be 120.

This effect is strongest in the younger birth cohorts studied, since a higher proportion of a younger population would be single. This difference in population characteristics could account for differences in SFR seen between preemployment and exposure years in the same individuals; the preemployment years necessarily occur at a younger age.

We did find higher SFRs for both employment and preemployment years in this study; a = 1.6 for the painters and 1.9 for the controls. SFR preemployment was 1.66 for the painters and 1.70 for the controls; SFR during employment was 1.58 for the painters and 1.36 for the unexposed groups (see Table IV). It is notable that both painters and controls had SFRs >1 for the years prior to employment in the shipyard, showing higher fertility than the national cohort with which they were compared. The preemployment SFR was greater than the employment SFR for both groups but was significantly different in the controls only. As discussed above, this difference may be attributable to the fact that the controls were older at the time of employment, so their comparative U.S. populations would contain fewer single women. Had this change occurred in an exposed population, we might have attributed the difference to exposure.

Starr and Levine [1983] suggest that examining only women at parity one or greater, or only looking at men over the age of 26 years, would correct the disparity between the study groups and the U.S. reference groups based on marital status. The U.S. data would then be based mainly on ever-married women at that age or parity level, and, thus, the two groups would be comparable. In addition, if we use parity of one, the women would all be of proven fertility. However, either adjustment would

reduce the population for study and might exclude the most affected couples, those who had never had children due to occupational infertility.

Does a account for differences between the study groups and the U.S. data? Several factors other than male semen quality or reproductive function are known to affect the number of children born to a couple; this method can directly account for some of them in the derivation of the rates, and the remainder are to be accounted for indirectly with a. The calendar year and a woman's birth cohort are important, since yearly birth probabilities have changed; there was a steady increase in the probability of a woman's giving birth until 1957 and a subsequent decline. A woman's age clearly affects her probability of giving birth; probabilities are highest for women aged 20–24 years. Finally, parity level changes birth probabilities; a parity level of one is associated with highest probabilities of a subsequent birth. These two factors are considered in the derivation of expected numbers for the fertility analysis as described by Levine et al.

The analysis does not account for socioeconomic status, individual psychological factors, religious beliefs, contraceptive use or sterilization, or spouse employment status, all of which can affect birth rate. The Levine et al. method calculates a, to account for factors affecting fertility that cannot be controlled in the analysis.

Is a a reliable factor? According to Levine et al. [1980], the local factors such as contraception use, religion, socioeconomic status, and other influences on family size are assumed to vary independently of parity, age, birth cohort, and calendar year. In the calculation of an SFR for an exposed group, SFR = O(p)/E(p) = ab. The effect of exposure, b = SFR/a. If a is not constant with time, then b may be found to be higher than its true value. This is because a is derived from preexposure birth rates and is applied to postexposure rates. If a decreased over time, then the value assigned to b will increase. Such a decrease could occur if employment patterns change in an area, if social attitudes toward birth control change, or other such factors.

The factor a is derived from a comparison of the control group to U.S. data, and the expected numbers are corrected using this factor. This will not correct differences between the groups, but only differences between both groups and the U.S. data. The control group is assumed to have the same factor a as the study group, and this variable drops out in calculating b, the effect of exposure. A comparison of preemployment SFR is a measure of comparability of the groups, and it suggests that our groups are comparable. However, they may be comparable in the preemployment years but not later in time; we have no way to measure this change.

Is it appropriate to use a? Levine et al. point out that, if a is large, it might obscure an effect on fertility as indicated by b. In this study, a is relatively large, being 1.9 for the exposed group.

Wong et al. [1985] suggest that the method of comparing two indirectly adjusted ratios, using a, can lead to statistical problems and that, if an internal comparison is to be made, it should be a direct comparison between the exposed and control groups rather than a ratio constructed after comparison of each group to the national reference group. If the group is not large and its fertility rates cannot be assumed to be stable, they suggest using a Mantel-Haenszel procedure to compare the groups. The groups should be compared both preemployment and during employment and the preemployment comparison used to determine if the groups are similar. Applying this approach to our data, we find that these groups are similar in preemployment SFR and

that they do not differ during employment. This adjustment to the method still did not allow detection of the effects on male reproduction that were found using semen analysis.

By estimating spouse age and year of marriage on 25 of the painters, some bias may have been introduced. However, the SFR calculated both with and without the estimated data was not significantly different.

Wong et al. [1985] described the advantages and limitations of the method and suggest that it be used primarily for surveillance rather than as the sole method for investigation of a specific hazard. To increase the sensitivity, they suggest using an α level of 0.1 or greater and conducting in-depth follow up studies if an effect is found through this surveillance. Our comparison of SFR gave a χ^2 with a $p > 0.10$. Since the SFR for the painters was greater than that for the controls, changing the α level here would not have detected the effect seen with semen analysis.

Starr et al. [1986] suggest using logistic regression instead of indirect standardization to compare exposed and unexposed groups. In one application of logistic regression, they used a data bank of fertility studies to generate expected birth rates and included only couples with a parity of one or more. They found that factors other than age, parity, and birth cohort were significant and, in particular, found that the time between pregnancies helped predict the number of pregnancies. The use of logistic regression agreed with prior results using indirect standardization in two analyses, and not in a third. The effect of the "lag" variable was not consistent. The addition of logistic regression did not add appreciably to the applicability of this questionnaire to detection of occupational effects on male reproductive function.

The effect found using semen analysis in the present study is a subtle one, with a significant difference found only among the nonsmokers. This should be considered a preliminary result, and it is given weight by the strong animal data showing that ethylene glycol ethers cause decreased spermatogenesis and another semen analysis study in male foundry workers exposed to 2-ethoxyethanol [Ratcliffe et al., 1989]. The questionnaire method was not as sensitive to differences in reproductive parameters between the groups. As discussed above, this may be because the derivation of the SFR has too much "noise" and is not able to detect small differences between the groups. Finally, measurement of births may be intrinsically a less sensitive measure than sperm count, for sperm count can be reduced without decreasing the number of children born to a couple; it might only increase the time to pregnancy [Bostofte et al., 1982]. If our goal is to have a screening tool that will detect early changes in reproductive function, semen analysis appears to be a better method.

CONCLUSIONS

In this study, the semen analysis revealed a significant difference in the rate of oligospermia between nonsmoking control and exposed groups, whereas the fertility questionnaire did not find a difference during exposure. In a prior comparison of semen analysis and questionnaire methods, the dibromochloropropane study, the effect on semen was large (33% of the workers were rendered virtually azoospermic), and both techniques of studying the population detected an effect of DBCP on fertility. In this study, the differences in sperm count were not as great and the sensitivity of the fertility questionnaire proved lower than that of semen analysis among this population of shipyard workers. This may be due to factors that cannot be controlled

for in the questionnaire as currently designed and to differences between the study groups and the U.S. data that cannot be measured.

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