

Association of Spontaneous Abortion and Other Reproductive Effects With Work in the Semiconductor Industry

Marc B. Schenker, MD, Ellen B. Gold, PhD, James J. Beaumont, PhD, Brenda Eskenazi, PhD, S. Katharine Hammond, PhD, Bill L. Lasley, PhD, Stephen A. McCurdy, MD, Steven J. Samuels, PhD, Cathy L. Saiki, MS, and Shanna H. Swan, PhD

This study tested the hypothesis that fabrication room (fab) work in the silicon-based semiconductor industry is associated with an increased risk of spontaneous abortion (SAB). The study was conducted nationwide at 14 companies representing a spectrum of large to small manufacturers. A small increase in risk of SAB was observed among fab workers compared with nonfabrication room (nonfab) workers in two cohorts, historical (adjusted RR = 1.43, 95% confidence interval [CI] 0.95-2.09) and prospective (adjusted RR = 1.25, 95% CI = 0.63-1.76). Analysis of specific fab exposures in the historical cohort showed a consistent, dose-response association of SAB with photoresist and developer solvents, whose major component was ethylene-based glycol ethers. The consistency of our findings and the toxicological data for these agents suggest that this is a causal association. Independent associations of SAB with self-reported stress and with etching fluorides were observed and require further research. No significant decrease in fertility was observed among men or women working in fabs, but reduced fecundability was suggested for some women fab workers.

© 1995 Wiley-Liss, Inc.

Key words: reproduction, spontaneous abortion, miscarriage, glycol ether, semiconductor manufacturing, occupational exposures

Division of Occupational/Environmental Medicine and Epidemiology, Department of Internal Medicine, School of Medicine, and Institute of Toxicology and Environmental Health, University of California, Davis (M.B.S., E.B.G., J.J.B., S.A.M., S.J.S., C.L.S.).

Maternal and Child Health and Epidemiology Programs, School of Public Health, University of California, Berkeley (B.E.).

Environmental Health Division, Department of Family and Community Medicine, University of Massachusetts Medical Center, Worcester (S.K.H.).

Division of Reproductive Biology, Department of Obstetrics and Gynecology, School of Medicine, and Institute of Toxicology and Environmental Health, University of California, Davis (B.L.L.).

Department of Epidemiology, School of Public Health, University of California, Berkeley (S.H.S.).

Address reprint requests to Marc B. Schenker, MD, MPH, Department of Community and International Health, TB 168, University of California, Davis, CA 95616-8638.

Accepted for publication May 1, 1995.

TABLE I. Epidemiologic Components of the Semiconductor Health Study

Component	Population	Subjects	Years
Historical	Current and former full-time female employees at 1 site in seven states from each of 14 companies	One pregnancy from each of 904 women, aged 18–44, selected from 6,088 women screened	1986–1989
Prospective	Current full-time female employees at 7 sites in 2 states from 5 companies	402 women, aged 18–44, followed prospectively from 2,639 women screened	1989–1991
Cross-sectional	Current full-time male and female employees at 8 sites in 5 states from 8 companies	1,637 women and 1,538 men, aged 18–72	1989–1990

INTRODUCTION

This study was undertaken to test the hypothesis raised by Pastides et al. [1988], who found increased spontaneous abortion (SAB) rates among women working in the fabrication of silicon wafers in the semiconductor industry. If increased risk of SAB was observed, investigators would then attempt to ascertain if the risk was associated with specific jobs, exposures, or work environments. The greatest limitation of the earlier study was its small sample size of women working at only one semiconductor fabrication facility (fab). The Pastides et al. [1988] study considered only 34 pregnancies in the production facility, with little comparability between pregnancy histories of women in production and nonproduction jobs. Finally, characterization of workplace exposures, verification of pregnancy outcomes, and potential recall bias were concerns in that study.

The present investigation was designed primarily to address the potential association of SAB with work in semiconductor fabs (Table I). The first component was a large historical cohort investigation of pregnancy outcomes among current and former women employees of childbearing age [Beaumont et al., 1995; Swan et al., 1995]. The second was a prospective cohort investigation of SAB rates and menstrual cycle outcomes among current women employees [Eskenazi et al., 1995a,b; Gold et al., 1995a,b; Lasley et al., 1995]. The third component was a cross-sectional investigation of nonreproductive health outcomes among male and female semiconductor workers [McCurdy et al., 1995; Pocekay et al., 1995] and of infertility among male workers [Samuels et al., 1995].

Integral to these three epidemiologic components was a unique industrial hygiene exposure-assessment component [Hallock et al., 1995; Hammond et al., 1995; Woskie et al., 1995]. Exposure-assessment investigators were responsible for characterizing current and past exposures in participating companies and for classifying individual subjects' exposures in the three epidemiologic components. Because of the complex environment and multiple agents handled in semiconductor wafer fabs and the absence of a single specific agent hypothesized to cause SAB, a unique system of exposure assessment and characterization was developed for this study [Hammond et al., 1995].

This overview summarizes the design and interrelationships of the epidemiologic components and synthesizes the results addressing reproductive outcomes and

their relationships to fab work. Findings are considered in the light of internal consistency, available toxicological information, statistical considerations (study power, biologic plausibility, alternate explanations), and other studies in the literature. Subsequent articles in this issue provide details for each study component's methods, results, and component-specific discussions.

METHODS

Study Populations

When this study began in 1989, the available sampling frame for study subjects from participating companies was approximately 50,000 male and female workers, or 20% of all U.S. semiconductor workers, representing the spectrum of semiconductor manufacturers, from large to small, that were members of the Semiconductor Industry Association (SIA).

Historical Component

The historical cohort encompassed female semiconductor employees aged 18–44 who became pregnant while working fulltime in a participating company from 1986 to 1989 (Table I). This component was designed to provide an adequate sample size to test the study hypothesis, a representative sample of participating companies, a short recall period to improve accuracy and response rate among former workers and to reduce potential recall biases, and validation of reported SABs.

One site was selected from each of the 14 participating companies, based on an algorithm to maximize the number of female fab workers [Beaumont et al., 1995]. A sample of 7,269 women was selected, and 84% ($n = 6,088$) completed a screening questionnaire by telephone about their work and reproductive histories (Table II). During the study period, 953 women had eligible pregnancies and 904 (95%) of these completed a more detailed telephone interview on their work during that pregnancy, reproductive history, and personal habits. If a woman had more than one eligible pregnancy during the study period, one pregnancy was selected at random for the detailed work and pregnancy history. Spontaneous abortions reported to interviewers were validated or confirmed by medical records.

Prospective Component

The prospective cohort applied laboratory methods to determine pregnancy and pregnancy loss among women currently employed in the semiconductor industry [Lasley et al., 1995]. All women screened ($n = 2,639$) completed a questionnaire to identify those meeting eligibility criteria (risk of becoming pregnant) for follow-up ($n = 739$). Assays of daily urine samples collected by the 403 women who participated in the follow-up for at least 1 month identified all conceptions, whether clinically apparent or not, and provided the means to detect subclinical pregnancy loss. Daily diaries provided information on menstrual periods, so menstrual characteristics (e.g., cycle length and variability) could be related to work activities [Gold et al., 1995a]. Reproductive outcomes were determined from diaries and urinary hormones, without knowledge of work exposure [Eskenazi et al., 1995a,b; Gold et al., 1995b]. In turn, exposure assessment was carried out without knowledge of pregnancy or menstrual outcomes.

These methods provided an objective determination of reproductive outcomes,

TABLE II. Comparison of Demographics in Three Study Populations^a

Variable	Historical cohort		Prospective cohort		Cross-sectional cohort	
	Fab	Nonfab	Fab	Nonfab	Fab	Nonfab
Screened (n)	6,088		2,639		NA	
Interviewed (n)	904		481		3,175	
Work site (%)	50	50	45	55	47	53
Ethnicity (%)						
White	57	62	49	42	60	68
Asian	23	22	27	31	22	19
Filipino	17	13	20	17	ND	ND
Other	6	9	7	14	ND	ND
Hispanic	13	10	12	14	8	5
Black	3	3	3	6	4	3
Other	3	3	8	8	6	6
Education (%)						
≤ 12 years	48	33	47	23	82	59
Smoking ^b (%)	13	12	22	12	25	21
Income (%)						
≤ \$40,000	69	35	56	32	55	42
Pregnancies ^c	447	444	19	34	NA	NA

^aND, no data; NA, not applicable.

^bSmoking during pregnancy for historical cohort subjects.

^cHistorical cohort totals exclude 11 unconfirmed SABs. Prospective cohort totals include only first pregnancies.

but they were labor intensive and more expensive than those used in the historical cohort. The personnel and sample-handling requirements made it more feasible to conduct this component at a limited number of sites near the University of California (UC), Davis. In contrast to the historical cohort, for which interviewing could continue until a target number of women with eligible pregnancies had been identified, the size of the prospective cohort was based on actual conception rates, which could not be controlled. Ultimately, industry layoffs, finite study resources, and other limitations determined the size of the cohort. The number of pregnancies was affected not only by sample size but also by a lower pregnancy rate in working women than in the U.S. population of women as a whole [Ventura et al., 1988].

Thus, the historical and prospective components were designed with complementary strengths to address the primary study hypothesis. Objective determination of conception and clinical and subclinical SABs in the prospective cohort was balanced against the small number of conceptions. Analysis of menstrual cycle data was not limited by number of pregnancies, because all women in the cohort contributed diary data on menstrual activity. In contrast, the historical sample was adequate to examine SAB rates in relation to specific tasks and exposures.

Cross-Sectional Component

Semiconductor manufacturing involves many potentially hazardous physical, chemical, and ergonomic exposures [LaDou, 1986], but few health studies have been conducted in the industry. The cross-sectional component was largely a hypothesis-generating investigation. With limited resources and no specific hypotheses, the investigation was restricted to a questionnaire-based survey to identify health out-

comes and exposures requiring further study. To optimize resources, investigators administered questionnaires to a large representative population rather than administering examinations or physiological tests (e.g., pulmonary function, nerve conduction velocity, neuropsychological battery) to a much smaller subset of workers.

The cross-sectional component involved eight sites in eight companies (Table I). A stratified sampling scheme identified the sites at random, based on probability in proportion to size [McCurdy et al., 1995]. The final sample consisted of 3,175 subjects (78% participation), with 51% women ($n = 1,637$) and 47% fab employees ($n = 1,489$) (Table II).

In addition to evaluating nonreproductive health outcomes, the cross-sectional component assessed fertility among current male and female employees. All subjects answered a question on history of unsuccessful attempts to achieve pregnancy for at least 1 year. In addition, males responded to a detailed set of questions about their fertility history and their wives' reproductive history. These responses were analyzed in relation to workplace exposures and other potential risk factors [Samuels et al., 1995].

Industrial Hygiene Exposure Assessment

The traditional approach to exposure assessment for occupational epidemiologic studies was precluded by the many chemical, physical, and ergonomic agents used in semiconductor manufacturing, the need to estimate historical exposures, the finite study resources, and the lack of a single exposure or work process as the suspect cause of SAB among fab workers. Instead of collecting numerous time-weighted average (TWA) samples, study industrial hygienists used a unique three-tiered approach to characterize exposures. By this method, they determined whether or not an individual worked in a fab, then categorized *work groups* for individuals using similar processes or equipment, and finally characterized exposures to individual chemical, physical, and ergonomic agents.

Classification of fab-nonfab and work-group status for all study subjects was based primarily on responses to questions designed by exposure-assessment investigators and was incorporated into epidemiologic questionnaires. However, exposure determinations for each chemical and physical agent incorporated information from site visits to all operating fab rooms, notebooks on historical work practices completed by company industrial hygienists, and responses to questions about work practices reported by subjects on questionnaires [Hammond et al., 1995; Woskie et al., 1995].

RESULTS

Study Populations

The study sample for the historical component was the most representative of women working in the U.S. semiconductor industry. This was reflected in the range of sizes of companies (<100 to >6,000 employees), the response rate among subjects screened and selected for in-depth interviews (95%), and the low refusal rate (2%). To enable investigators to achieve a balance between fab and nonfab workers during sample selection, companies initially identified employees with histories of fab work during the study period. However, study industrial hygienists made the final exposure assessments.

The population for the prospective cohort came from seven sites in five companies in two states. One location was northern California, an area with approximately half of all U.S. semiconductor workers, and the other was Utah, a large regional semiconductor manufacturing area. Unlike companies in the historical cohort, which spanned the range of work-force sizes, companies in the prospective component were among the largest. Workers in the prospective cohort represented the ethnic and demographic character of the two study areas (Table II). The California sites employed an ethnically diverse population that was less than 30% white, approximately 40% Asian, and 15% Hispanic. In Utah, the population was over 80% white, less than 10% Hispanic, and less than 5% Asian.

Cross-sectional participants were representative of employees in participating companies nationwide. The addition of men and the inclusion of all age groups expanded the spectrum of participants and resulted in differences from subjects in the other components. For example, cross-sectional subjects had a lower educational level, lower mean family income, and higher prevalence of smokers than historical and prospective participants (Table II). The ethnicity of subjects in the cross-sectional component was similar to that of the historical cohort and reflected the industry nationwide.

Spontaneous Abortions and Fabrication Room Work

Based on the historical cohort investigation, the crude relative risk of SAB for fab ($n = 447$) vs. nonfab workers ($n = 444$) was 1.45 (95% CI = 1.02–2.05; Table III) [Beaumont et al., 1995]. Univariate adjustment for variables potentially associated with SAB had little effect on this relative risk, with the range of adjusted relative risks for fab vs. nonfab being 1.32–1.64. Adjustment for confounding factors in a multiple logistic regression model also resulted in little change in the relative risk of fab work in the historical cohort (RR = 1.43; 95% CI = 0.95–2.09). Noteworthy among risk factors independently associated with SAB in the multiple logistic model was age >35 years (RR = 1.81; 95% CI = 1.04–2.97), cigarette smoking during the pregnancy (RR = 1.34, 95% CI = 0.81–2.17), and prior SAB (RR = 1.64, 95% CI = 1.05–2.45). Women who reported feeling extremely stressed at work also had a significantly higher risk of SAB (RR = 2.18, 95% CI = 1.39–3.26). Asians had significantly lower risks of reported SAB than whites (RR = 0.49, 95% CI = 0.26–0.91), although this was primarily the result of pregnancies in the early study years, suggesting poor recall. The risk of SAB was higher among fab than nonfab workers during all four study years.

A similar elevated fab vs. nonfab relative risk was observed in the prospective cohort. The crude risk ratio for SAB of women in the prospective cohort (first pregnancy only per woman) was 1.39 (95% CI = 0.84–2.31) [Eskenazi et al., 1995a]. The number of conceptions was too small to yield stable risk estimates for individual covariates, so adjustment was made for potential confounding variables using the risk model derived in the historical component. This slightly decreased the relative risk estimate for fab work (RR = 1.25, 95% CI = 0.63–1.76). Considering only clinically apparent pregnancies and SABs in the prospective cohort (theoretically similar to recalled events in the historical cohort) increased the crude relative risk to 2.10, but with a wide confidence interval (95% CI = 0.51–8.62) due to the small sample size.

Because nonfab nonoffice workers are potentially exposed to chemical or phys-

TABLE III. Spontaneous Abortions (SAB) in the Semiconductor Health Study^a

Outcome	Historical cohort relative risk (95% confidence interval)	Prospective cohort relative risk (95% confidence interval)
Fab vs. nonfab workers		
Crude		RR = 1.39 (0.82–2.20)
Clinical SAB	RR = 1.45 (1.02–2.05)	RR = 1.79 (0.40–8.01) ^b
Adjusted	RR = 1.43 (0.95–2.09)	RR = 1.25 (0.63–1.76)
Work group		
Crude		
MASK	RR = 1.69 (1.17–2.44)	RR = 1.47 (0.85–2.54)
DOPEFILM	RR = 1.28 (0.81–2.03)	RR = 1.57 (0.86–2.86)
SUPV/ENGR	RR = 1.21 (0.54–2.70)	RR = 1.47 (0.61–3.55)
Adjusted		
MASK	RR = 1.78 (1.17–2.62)	RR = 1.30 (0.59–1.84)
DOPEFILM	RR = 1.17 (0.68–1.93)	RR = 1.39 (0.51–1.96)

^afab, fabrication; nonfab, nonfabrication; MASK, masking supergroup; DOPEFILM, dopants and thin film supergroup; SUPV/ENGR, supervisors and engineers.

^bRR = 1.79 if all pregnancies are included in denominator of rate; RR = 2.10 if only clinical pregnancies are included in both numerator and denominator.

ical hazards, the risk of SAB among fab workers was compared with that for office workers. This analysis produced negligible changes in the relative risk of SAB among fab workers in the historical and prospective cohorts.

Spontaneous Abortions and Work Groups

The industrial hygiene analysis indicated that employee process groups were stable entities located in particular areas of the fab and associated with similar processes and materials [Hammond et al., 1995]. Therefore, the second-tier analysis of SAB in relation to exposure was based on classification into a work group or pair of work groups, called a *supergroup*, classification. In the historical component, the unadjusted relative risk of SAB among women during the first trimester of pregnancy was higher in fab supergroups involved in masking (MASK) (RR = 1.69, 95% CI = 1.17–2.44) or dopants and thin film (DOPEFILM) (RR = 1.28) than among nonfab women (Table III) [Beaumont et al., 1995]. Within the MASK supergroup, the etching (ETCH) work group (RR = 2.15, 95% CI = 1.40–3.29) was at higher risk than the photolithography (PHOTO) workgroup (RR = 1.53, 95% CI = 1.02–2.30). Adjusted relative risks and analyses by participation in only one work group during the first trimester of pregnancy showed similar patterns: higher risk in MASK than in DOPEFILM and, within the MASK supergroup, higher risk in ETCH than in PHOTO.

Similarly, analysis of the prospective component by supergroup showed higher SAB risk among MASK and DOPEFILM workers than among nonfab workers. However, the small number of pregnancies resulted in wide but comparable confidence intervals for the two supergroups. In the adjusted model, relative risks were 1.30 (95% CI = 0.59–1.84) for MASK and 1.39 (95% CI = 0.51–1.96) for DOPEFILM (Table III). The small number of pregnancies in the prospective cohort only allowed analysis of SAB in the two supergroups but not in the four work groups.

Spontaneous Abortions and Specific Agent Exposures

For the historical cohort, SAB risk by specific agents was analyzed in detail [Swan et al., 1995]. This analysis utilized the 14 agents selected by study industrial hygienists, based on toxicological evidence and exposure prevalence. Some agents were grouped by common uses or functional groupings (photoresists, fluoride, cleaning solvents, dopant gases). Using an algorithm incorporating questionnaire responses and site-visit data, we classified four levels of exposure (0–3) for the 14 target agents, recognizing that the limited measurements of air concentrations of each agent were well below occupational standards [Woskie et al., 1995]. The use of questionnaire responses and workplace assessments to categorize individual exposures meant that exposure was not based solely on subject's recall. Eight of the 14 target agents showed no significant independent association with SAB in univariate analyses in the historical component [Swan et al., 1995]. These included the dopant gases (antimony, arsenic, boron, phosphorus) and the physical agents (extremely low-frequency magnetic fields and radiofrequency radiation). Further analyses of these agents failed to show a consistent pattern suggesting any clinically significant association with SAB.

The most consistent finding in the agent-specific analyses was an association of SAB with photoresist chemicals (ethylene-based glycol ethers [EGE], propylene glycol ethers [PGE], n-butyl acetate, xylene) and with fluoride exposure among subjects in the ETCH work group. Cluster analysis confirmed that exposure to photoresist chemicals tended to occur together among subjects in the historical cohort [Hines et al., 1995]. Women exposed to any photoresist chemical had an adjusted relative risk for SAB of 1.35 (95% CI = 0.89–2.01); this risk increased to 2.18 (95% CI = 1.30–3.40) for women in higher exposure categories and was even greater for women working only in the MASK supergroup. Analyses of individual photoresist chemicals showed similar relative risks and dose responses for EGE, n-butyl acetate, and xylene but not for PGE. The SAB rate for women with the highest exposures to EGE, n-butyl acetate, and/or xylene was 30% (10 out of 33).

Fluoride also showed a strong association with SAB (adjusted RR = 1.79, 95% CI = 1.22–2.54). The higher risk among women exposed to fluoride was highly significant for women in the MASK supergroup, for whom fluoride is part of buffered-oxide etching mixture (RR = 2.24), but only slightly elevated among women exposed to fluoride outside the ETCH work group (RR = 1.23). Analysis of SAB rates among women exposed to photoresist chemicals, buffered-oxide etch, or both showed that each agent was independently associated with SAB, the highest risk being among women exposed to the highest levels of both photoresist chemicals and buffered-oxide etch. Conversely, fab women with no exposure to photoresist chemicals or buffered-oxide etch (n = 196) had no higher risk for SAB than nonfab workers (adjusted RR = 0.98).

Self-reported stress was strongly associated with SAB in the historical cohort (adjusted RR = 2.18) but only among fab workers, for whom a dose-response with the amount of stress was observed [Swan et al., 1995]. The "stress variable" was based on a single question: "Considering the activities you were required to perform, the time pressures operating, and the general environment and supervision, in general how stressful was your work during the first three months of your pregnancy (or before you changed your job activities)?" Analysis of individual stress-related questions concerning workplace conditions showed that this single stress question was

equally predictive of SAB in the full regression models. Women who reported high stress levels and worked in high-risk work groups or in the presence of agents associated with increased risk of SAB had higher relative risks of SAB than women who did not report increased stress or who were not exposed to these agents. The magnitude of SAB risk for MASK supergroup workers was relatively unchanged when stress was added to the models, and stress had little effect on associations between SAB and exposure to photoresist chemicals or buffered-oxide etch, yet stress was a strong independent risk factor for SAB.

In the prospective component, the small number of pregnancies resulted in only those agents associated with increased SAB risk in the historical cohort being analyzed. Although not statistically significant, this limited analysis tended to confirm an association between EGE and SAB but not between fluoride and SAB. Evaluation of stress in this cohort was similarly limited by the small sample size. However, the baseline question found higher stress among fab than among nonfab women.

Other Reproductive Outcomes

Many other reproductive outcomes were analyzed in the three study components (Tables III and IV). In the cross-sectional population, the standard infertility question of "ever trying unsuccessfully for one year or more to get pregnant" was weakly and insignificantly associated with fab work in men and women. Among the 2,639 women screened for the prospective component, infertility was not significantly associated with fab work. In the cross-sectional sample, a more sensitive fertility analysis of men who had ever been married showed no evidence of decreased fertility in fab workers (aFR [adjusted fertility ratio] = 0.98, 95% CI = 0.80–1.19) [Samuels et al., 1995].

In the prospective component, the crude conception rate was slightly, but not significantly, lower among fab than among nonfab women (RR = 0.91, 95% CI = 0.54–1.53). However, logistic regression models of the probability of conception in each cycle ("fecundability"), controlling for multiple covariates, including opportunity for intercourse and type of contraception, resulted in lower fecundability ratios (FR), although no model achieved statistical significance (FR = 0.56–0.68) [Eskenzi et al., 1995b]. When fecundability was analyzed by supergroup, results suggested some reduction among DOPEFILM women (FR = 0.64, 95% CI = 0.28–1.46) but little decrease among MASK women (FR = 0.94, 95% CI = 0.47–1.85).

Menstrual cycle data from diaries of fab and nonfab women showed that fab women had small but generally not statistically significant increases in mean cycle length, variability in cycle lengths, percentages of long or short cycles, and mean days of menstrual bleeding (Table V) [Gold et al., 1995b]. Menstrual cycle analysis by work group showed that fab women in the thin film and ion implantation (TFII) work group tended to have longer adjusted mean cycle length (34.8 days) than nonfab women (32.5 days, $p = 0.07$). When analyses were restricted to women assigned to only one work group, this difference became statistically significant (36.1 vs. 32.0 days, $p = 0.02$), as did the mean variability in cycle length (6.7 vs. 4.1 days, $p = 0.01$).

DISCUSSION

This study provides evidence for higher SAB rates among women working in silicon-wafer fabs than among women working in nonfab locations in the semicon-

TABLE IV. Other Reproductive Outcomes Among Fabrication-Room (Fab) and Non-Fabrication-Room (Nonfab) Employees in the Semiconductor Health Study*

Outcome	Prospective cohort	Cross-sectional cohort
Menstrual cycle		
Length (days)	$\Delta = 0.03$ day, $p = 0.97$	ND
Variability (mean ln SD)	$\Delta = 0.6$ day, $p = 0.12$	ND
Long cycles (% ≥ 35 days)	RR = 1.00 (95% CI = 0.64–1.45)	ND
Short cycles (% < 24 days)	RR = 1.41 (95% CI = 0.85–2.12)	ND
Mean days of bleeding	$\Delta = 0.13$ day, $p = 0.45$	ND
Conception rate (pregnancies/100 women)	RR = 0.91 (0.54–1.53)	ND
Crude		
Fecundability (pregnancies/cycle)		
All women	FR = 0.51 (0.27–0.95)	ND
MASK	FR = 0.75 (0.37–1.55)	ND
DOPEFILM	FR = 0.32 (0.11–0.90)	ND
Infertility (≥ 1 year)		
Men	ND	OR = 1.17 (95% CI = 0.79–1.74)
Women	OR = 1.11 (95% CI = 0.71–1.71)	OR = 1.09 (95% CI = 0.72–1.46)
Fertility, male	ND	FR = 0.98 (0.80–1.19)

*ND, no data; RR, relative risk; CI, confidence interval; FR, fecundability ratio; MASK, masking supergroup; DOPEFILM, dopants and thin film supergroup; OR, odds ratio.

TABLE V. Rates of Spontaneous Abortion (SAB) and Relative Risks in Studies of Semiconductor Fabrication (Fab) vs. Nonfabrication (Nonfab) Workers

	SAB rate (%)		Adjusted	
	Fab	Nonfab	Relative risk	95% CI ^a
Historical studies				
DEC ^b	35.3	17.8	1.98	1.19–5.30
SIA	14.1	10.4	1.43	0.95–3.09
IBM	16.7	15.1	1.40	0.90–1.90
Prospective studies				
SIA	63.2	45.5	1.25	0.63–1.74
IBM	57.0	44.0	1.30	0.90–2.00

^aCI, confidence interval; DEC, Digital Equipment Corporation; SIA, Semiconductor Industry Association.

^bIncludes photolithography and diffusion workers only.

ductor industry. Consistent findings from the historical and prospective components provide the greatest support for that conclusion. These two components, which involved different populations and used different methods, arrived at similar SAB risk ratios in comparisons of fab and nonfab women. Adjusted SAB risk ratios of 1.43 and 1.21, respectively, were noted. This small difference may reflect statistical variability, although differences in outcomes measured (clinical vs. clinical and subclinical pregnancies), in populations investigated, and in study time frames may also have contributed to the observed difference.

In view of the positive association between fab work and SAB, we attempted to identify fab-specific work processes or exposures associated with the increase. The historical cohort was the primary population for this effort because of its larger size. Analysis of SAB by supergroup revealed a greater risk in the MASK than in the DOPEFILM supergroup. Within the MASK supergroup, SAB risk was greater in ETCH than in PHOTO. Although differences in risk between supergroups were not found in the prospective component, the confidence intervals for supergroups in the prospective cohort included point estimates from data analyses for the historical component.

Historical cohort data also suggested that photoresist/developer solvents and buffered-oxide etch were associated with increased SAB risk. This analysis considered the specific agent(s) to which a woman was exposed, independent of her work group(s). There was a consistency of the findings for the photoresist chemicals and fluoride used in etching in the historical cohort. Moreover, exposure to the photoresist or developer solvents (EGE, n-butyl acetate, and xylene) was highly correlated among women working in fabs, limiting the ability of investigators to analyze outcomes following exposure to any single photoresist chemical. Nevertheless, the association between exposure to photoresist or developer solvents and SAB was strongly dose related, with an adjusted SAB risk threefold higher in the highest exposed group than in women not exposed to these agents [Swan et al., 1995]. EGE were the predominant components of photoresist and developer solvents. The relationship between these chemicals and SAB risk was further supported by the lack of evidence for increased SAB risk among fab women not exposed to photoresist chemicals or fluoride.

Another important finding was the absence of an independent association of SAB with dopant gases (arsenic, phosphorus, boron, antimony), cleaning solvents (acetone, isopropyl alcohol, methanol), or radiation from electromagnetic fields or radiofrequency sources. However, the association of self-reported stress with SAB in the historical cohort is noteworthy. Although the presence of stress was based on self-report, consistency and strength of the association suggest that further work is needed to understand this risk factor. The greater prevalence of reported stress among fab than nonfab women in the prospective component supports the conclusion that the self-reported stress in the historical component was not due only to recall bias. Furthermore, the association of greater reported stress with exposure to a greater number of chemical agents suggests that responses to the stress question may reflect greater workplace exposures or greater numbers of assigned tasks. Specific workplace exposures and stress could both contribute to increased risk of SAB, particularly since modeling suggested that they posed independent risks.

A fundamental question is raised by these findings: Is there a generalized "fabrication-room effect" on SAB, or is the association restricted to specific jobs or agents? Our study cannot completely resolve this question. Because the highest risk of SAB was consistently seen among women in the MASK supergroup and women who handled photoresist or developer solvents or buffered-oxide etch, it appears that exposures within the fab—and not the room environment per se—are responsible for the increased risk.

These findings must be considered in light of their biological plausibility, strength and consistency of association, and other possible explanations, including chance and bias or confounding. Finally, they must be considered in the context of

other studies of workplace hazards to reproduction and of semiconductor workers in particular.

Biological Plausibility

Analyses of SAB in the prospective component suggested a greater relative risk of clinical than occult SAB among women working in fabs. The crude fab-nonfab risk ratio for clinical and occult SAB was 1.24. Considering only clinical pregnancy outcomes in the prospective component (comparable with outcomes studied in the historical cohort) gave a crude RR of 2.10. This possible difference in risk of clinical and occult SAB among fab workers may relate to reduced fecundability among fab women in the prospective cohort. There is a possible biological association between low fecundability and decreased early SAB: Occult SAB may indicate reproductive health, since most women who experience occult SABs go on to have normal pregnancies [Wilcox et al., 1988].

Similarly, increased menstrual cycle length and variability among women in the TFII work group [Gold et al., 1995b] may relate to the increase in SABs or to the decrease in fecundability in the DOPEFILM supergroup [Eskenazi et al., 1995b]. However, the prospective cohort was selected, in part, to exclude menstrual abnormalities. In addition, these measures of cycle length and variability are crude indices of abnormal ovarian function. Thus, our menstrual cycle results require confirmation and better assessment of ovarian function. Although some epidemiologic studies have found associations of abnormal cycle lengths with reproductive risk factors (e.g., smoking) or with abnormal ovulation, the data are sparse. More accurate assessment of hormonal function requires daily measurement of luteinizing hormone, progesterone, and estrogen or their metabolites.

The lack of a reported history of infertility among men and women in the cross-sectional component and among women in the screened prospective component suggests no fab-related reduction in fertility. However, results of this crude measure of infertility may be biased by a reverse "healthy worker effect" or other selection factors among working populations. The more sensitive fertility analysis among men in the cross-sectional population found no evidence of reduced fertility among male fab workers [Samuels et al., 1995].

Statistical Strength of the Results

Similarities between estimated risk in two different populations using entirely different methods argue strongly against the likelihood that chance alone explains the association of fab work with SAB. Although fab-nonfab results in the historical cohort were of borderline statistical significance, the fab-nonfab results are statistically strengthened by the consistency between the historical and prospective analyses. Furthermore, agent-specific analyses showed statistically significant results; for example, photoresist and developer solvent exposures correlated positively with SAB.

Bias or Confounding

Reporting bias has been suggested as a possible explanation for findings from several retrospective studies of SAB [Neutra et al., 1992; Swan et al., 1992]. The strongest evidence against bias as an explanation of these results is, again, the consistency of the prospective findings with the historical results and with other studies. The objective measure of outcome in the prospective component, determined inde-

pendently of exposure assessment, excludes reporting bias as a possible explanation of the prospective findings and supports the absence of bias in the historical component results.

It is more difficult to exclude any contribution of selection bias or confounding to the observed association of fab work and SAB. Careful attention was given to measuring and controlling for potential confounding factors, including both established and suspect risk factors for SAB, in both the historical and prospective components. Adjustment for these variables individually and together had little effect on the risk of fab work observed in multiple logistic models [Beaumont et al., 1995; Eskenazi et al., 1995a]. Nevertheless, fab and nonfab workers differed in measurable ways, including younger age (except in the prospective cohort that frequency-matched on age), less education, and lower family income. Although some unmeasured risk factor associated with these characteristics could affect SAB, strong evidence against such a possibility is the absence of a marked effect on the risk of fab work by adjustment for age and other known risk factors. Another possibility is that more health-conscious women preferentially avoid entering fab work because of its chemical-intensive nature or publicity about possible health hazards. However, an adjustment for degree of concern about adverse health effects of semiconductor work did not change the observed association of fab work and SAB in the historical component, providing additional evidence against a reporting bias or an unmeasured confounder. Finally, the high response rate in the historical component and the consistency of the association in current and former workers provides additional evidence against a selection bias. We cannot exclude the possibility of some selection bias, but, for the reasons noted earlier, we do not think it greatly affected our findings.

Consistency

The findings of this study are consistent with those of the original investigation of SAB and fab work [Pastides et al., 1988]. Although their crude relative risk of 1.98 for any fab work was slightly higher than the risk we observed, findings in the two studies show a marked similarity. The most elevated risk of SAB in the Pastides study (RR = 2.18) was among "diffusion" workers, a group that would include part of the MASK and part of the DOPEFILM supergroups in our study. Pastides and coworkers observed a lower risk for photolithographic workers (RR = 1.75), similar to the lower risk for the PHOTO work group of the MASK supergroup in our historical component. However, the Pastides study suggested that metals and acids were more strongly associated with high SAB risk among fab workers than were solvents, an agent-specific risk we did not confirm.

A more recent study suggested that microelectronics assembly workers had increased risk of SAB [Huel et al., 1990]. This investigation did not look at semiconductor workers and is not directly comparable to the present study. It also had serious methodological problems, including selection and possible response biases, appropriateness of the control population, and unvalidated health outcomes.

Many studies have investigated the association of solvent or other chemical exposures with SAB. A recent community-based study of California women found an association of first-trimester solvent exposure and SAB [Lipscomb et al., 1991]. Solvent exposure assessment was based on job classification or self-report and did not distinguish between electronics and semiconductor work. A Finnish study found

increased SAB in association with tetrachloroethylene exposure among dry-cleaning workers [Kyyronen et al., 1989]. Another community-based, case-control study found no increase in SAB related to solvent exposure [Windham et al., 1991]. A recent case-control study of SAB among women living in Santa Clara County (Silicon Valley) found no increase associated with any electronics work, but the study was limited by small numbers of cases and controls in semiconductor manufacturing ($n = 52$) [Shusterman et al., 1993]. Several studies of mixed chemical solvent exposures and SAB in occupations such as laboratory work have yielded varied results [Ahlborg et al., 1989; Axelsson et al., 1984; Hansson et al., 1980; Hemminki et al., 1980].

These studies provide little basis for comparison to our investigation of semiconductor workers. Exposure assessment was indirect (usually by self-report or job classification). The nature and magnitude of exposures was distinctly different, as were many of the industries studied (chemical manufacturing, dry cleaning, pharmaceuticals). These solvents were often halogenated hydrocarbons, frequently used at high exposures. In the semiconductor industry, solvent exposures as estimated by air concentrations are generally low (usually less than 10–15% of threshold limit values) and commonly involve EGE (nonhalogenated compounds) [Hallock et al., 1995]. Finally, none of these studies assessed pregnancy outcome prospectively, and possible reporting biases may explain some inconsistencies [Joffe, 1985; Neutra et al., 1992].

More relevant to the present investigation are two recent investigations of SAB among semiconductor workers. The first, a study of female employees at a single semiconductor manufacturer in Florida, found no increase in SAB risk among fab women. However, this cross-sectional investigation in an industry with high turnover did not include former employees, may have had biased results, and was thus not directly comparable with ours [Lemasters and Pinney, 1990]. The other study, a historical and prospective assessment of pregnancies and related reproductive outcomes, was conducted among employees of two IBM semiconductor manufacturing facilities in the northeastern United States [Gray et al., 1993]. Exposure assessment was based on processes, chemicals, and engineering controls used in clean rooms and on subjects' responses to questionnaires. These yielded "zones of exposure" or "exposure groups." Measured exposures to specific agents were not used in the epidemiological analysis, nor were results reported for potential exposures to agents other than EGE-based photoresist chemicals and solvents.

The IBM retrospective investigation included current and former employees who worked at IBM for at least 6 months and had not undergone surgical sterilization before 1980. The 1,963 women interviewed had experienced 1,174 pregnancies during their IBM employment since 1980 (up to 10 years of recall). The response rate was lower among former (25%) than among current (67%) employees. Female subjects were predominantly white (90%). Data analysis included all eligible pregnancies with adjustment for multiple pregnancies, whereas our historical cohort used one random eligible pregnancy per woman.

Despite differences in location, demographics, period of recall, inclusion of multiple pregnancies per woman, and exposure assessment methods, the IBM historical cohort results were remarkably similar to those in the SIA study (Table V). The adjusted odds ratio for SAB among women working in clean rooms was 1.4 (95% CI 0.9–1.9) compared with women working in non-clean-room areas. Also similar to SIA historical results was the IBM finding of significantly increased SAB rates

among women potentially exposed to EGE-based solvents, with an observed dose-response. Comparing women with "high" and "less intensive" potential exposure to EGE-photoresist and solvent, unadjusted relative risks for SAB were 2.3 and 1.3, respectively. These results are the same as the observed SIA relative risks for the two highest photoresist- or developer-solvent exposure categories [Swan et al., 1995]. The IBM investigation did not evaluate potential effects of "stress" on SAB, but the EGE analysis did compare clean-room women exposed and unexposed to EGE to control for clean-room effects such as stress.

The IBM prospective cohort included fewer women than the SIA prospective cohort ($n = 148$ vs. 402 , respectively), but more conceptions ($n = 92$ vs. 53 , respectively) during the follow-up. IBM prospective findings were also close to SIA prospective results. The IBM adjusted odds ratio for clinical and subclinical SABs for clean-room vs. non-clean-room women was 1.3 (95% CI 0.9–2.0), compared with the adjusted RR of 1.2 in the SIA study (95% CI 0.60–1.74). The IBM exposure-specific analysis, although limited by small numbers, suggested an increase in SABs during cycles with potential EGE exposure ($n = 6$, adjusted odds ratio = 2.5, 95% CI 0.9–8.5). Three pregnancies occurred in the SIA prospective cohort while the woman was working with EGE (RR = 2.0, 95% CI 1.5–2.8), and all three resulted in SABs [Eskenazi et al., 1995a].

The remarkable consistency among the two historical and two prospective investigations is notable: All show an increased risk of SAB among women with potential exposure to EGE-based photoresist or developer solvents. Both the SIA and IBM investigations suggest an increased risk of SAB among women working in semiconductor fabs, but the increase is of borderline significance, and these studies cannot resolve whether the increase resulted from fab-specific exposures (e.g., EGE) or from a "fabrication-room effect."

Clinical reports of acute glycol ether toxicity relate to exposures orders of magnitude higher than those in semiconductor manufacturing [Paustenbach, 1988]. One study of male employees involved in EGE-based processes failed to show adverse hematological or fertility indices, but interpretations from this study are limited by the low sampling fraction and the cross-sectional design [Cook et al., 1982]. Studies of reproductive health in males, who were often exposed to high glycol-ether concentrations, are sparse and not directly comparable to the semiconductor investigations of SAB in women [Cullen et al., 1983; NIOSH, 1983]. A recent case-control study of men found a highly significant association of infertility or subfertility and EGE metabolites in the urine [Veulemans et al., 1993].

Despite the lack of data in humans, particularly females, laboratory studies show that EGE induces dose-related embryotoxicity and other reproductive effects in several species of animals exposed by different routes of administration [NIOSH, 1991]. Oral and inhalational exposure to EGE in multiple species resulted in spermatogenic abnormalities and testicular atrophy [Creasy and Foster, 1984; Lamb et al., 1984; Miller et al., 1981; NIOSH, 1983; Rao et al., 1983]. EGE exposure was also embryotoxic and teratogenic following oral and inhalation administration in multiple animal species [Hanley et al., 1984; McGregor, 1984; Nagano et al., 1981; Nelson and Brightwell, 1984; NIOSH, 1983; Scott et al., 1989]. Exposures of pregnant animals to EGE levels below the OSHA-permissible exposure limit increased fetal death [NIOSH, 1983].

The few published toxicological studies generally have shown that PGE expo-

sure causes less reproductive toxicity than EGE exposure [NIOSH, 1991]. For example, rats, mice, and rabbits exposed to 1-methoxy-2-propanol glycol ether (PGME) showed no changes in testis weight or histology [Landry et al., 1983; Miller et al., 1981], and pregnant rats exposed to 600 ppm PGME during pregnancy had no adverse reproductive outcomes [Doe et al., 1983]. However, adverse pregnancy outcomes were observed with high (2,700 ppm) exposures of rats to the beta isomer of 2-methoxy-1-propyl acetate [Merkle et al., 1987], and teratogenic effects were observed in rabbits at lower concentrations [Merkle et al., 1987]. Overall, PGE showed less acute or chronic toxicity, including reproductive toxicity [NIOSH, 1991]. The few reproductive effects of PGE occurred at significantly higher concentrations than those caused by EGE. Metabolic products of EGE (alkoxyacetic acids) are more biologically active and exert greater toxic effects than PGE metabolites, consistent with the greater toxicity of EGE in toxicological studies [Brown et al., 1984; Miller et al., 1982; NIOSH, 1983, 1991].

The low measured air concentrations of glycol ethers in this study raise questions about the plausibility of the epidemiologic findings. However, full-shift TWA samples do not reflect actual doses because dermal exposure is more important than inhalation and TWA samples estimate inhalation [Clapp et al., 1984; Daniell et al., 1992]. Permeability of gloves to glycol ethers may be a problem [Zellers et al., 1992], and peak exposures, which are not reflected in full-shift measurements, may also be important. Glycol ethers are easily absorbed through the skin. Because our individual exposure estimates reflected both dermal and air concentrations, we cannot separate the contributions of those two potential routes of exposure. However, the known absorption of glycol ethers through the skin and the work practices associated with dermal exposure (e.g., cleaning up spills) suggest that dermal exposure may be of more clinical importance. Our findings on female reproduction and EGE exposure may also indicate an effect of EGE at levels lower than those previously recognized.

The provocative findings associating fluoride exposure and SAB require further investigation. Inhalation exposures of animals to hydrogen fluoride produce signs of severe mucous membrane and pulmonary irritation, with death occurring from repeated exposures at or above 8 mg/m³; no pathologic respiratory effects are observed at concentrations of 2.5 mg/m³ [NIOSH, 1976]. Inhalation exposures distribute abnormal amounts of fluoride to tissues, primarily bone. In a Russian study, rats inhaling hydrogen fluoride at 0.47 mg/m³ experienced substantially retarded fetal development, associated with generalized edema of subcutaneous cells and hydrocephaly [Lasley et al., 1995].

Fluoride is known to cross the placenta, and high-dose oral ingestion of fluoride affected reproduction in animal studies [Hodge and Smith, 1977; Theuer et al., 1971]. For example, embryotoxicity of rat fetuses (fetal death, abortion) occurred following 3–12 mg fluoride/kg/day [Devoto et al., 1972], and ingestion of more than 60 ppm fluoride by dairy cows interfered with reproduction [Hodge and Smith, 1977]. Other studies showed growth retardation and impaired reproduction in mice ingesting 100 and 200 ppm fluoride in drinking water [Messer et al., 1973]. In general, doses that cause reproductive toxicity in animals are substantially higher on a weight-for-weight basis than estimated occupational exposures.

Data on reproductive effects of human exposures to fluoride are practically nonexistent [Hodge and Smith, 1977]. A single Russian epidemiologic study appeared to show menstrual irregularities, but no differences in pregnancy outcomes,

among women exposed to fluoride in a superphosphate plant, where fluoride concentrations ranged from 0.3 to 2.8 mg/m³ [Kuznetsova, 1969]. Because postshift urinary fluoride correlated with postshift fluoride levels in serum [Kono et al., 1992] and in hair [Kono et al., 1990], biological markers of fluoride exposure could be used in semiconductor or other industries to evaluate possible reproductive toxicity. However, many other issues would need to be addressed in such a study, including fluoride dose from the water supply, dietary and supplementary ingestion, biological half-life of fluoride, dose to target organs, route of occupational exposure, and relative contribution of various sources of fluoride to total dose. Toxicological studies and our present findings suggest that further investigation is warranted.

Our finding of increased SAB risk with self-reported stress is consistent with other reports. For example, a large Montreal study of SAB found consistent increases in SAB risk with heavy lifting and other physical efforts [McDonald et al., 1988]. In that investigation, SAB was also associated with other correlates of stress, such as long hours and exposures to noise and to cold. Some individual correlates of stress were identified in the historical and prospective components of the present study, but further work is needed to characterize the nature of stress among fab workers, particularly those with multiple chemical exposures. The magnitude of the "stress effect," the ubiquity of this exposure in modern workplaces, and the possible interaction of stress with chemical or other workplace exposures provide additional support for research to understand the nature and mechanism of work- and non-work-related stress on reproduction.

CONCLUSIONS

The present findings are based on a sample from a population representing approximately 20% of the U.S. semiconductor manufacturing industry. The 14 participating companies covered a spectrum of large to small manufacturers nationwide, and the study sample represented the spectrum of participating companies. Our prospective and historical components found similar risks of SAB, particularly clinical SAB, associated with fab work. Among fab workers, the evidence was most consistent for a causal association of SAB with EGE exposure. This finding is greatly strengthened by consistency with findings from IBM historical and prospective investigations.

Further work is needed to evaluate specific exposures and work processes suggested as risk factors for SAB by this study. In particular, attention should be focused on women working in etching and photolithography areas, and women handling photoresist or developer solvents, including EGE. The effect of leaving fab work was not evaluated in this study and should be investigated. Although our data associated buffered-oxide etch with SAB, more study is needed on the nature and magnitude of this exposure among fab workers and on its potential reproductive toxicity. Fluoride exposure from buffered-oxide etch and other sources should be considered. Further research will require more focused assessment of individual exposures, including biological markers of exposure when possible. Many other industries handle agents identified in this industry, and they may provide a means to isolate effects of individual agents on pregnancy. Future studies of reproductive outcomes should evaluate interrelationships of SAB, fecundability, and menstrual-cycle perturbations. Studies in occupational settings should consider ongoing surveil-

lance of pregnancy outcomes, which would require careful attention to employee confidentiality. Finally, prudent public health policy would suggest that semiconductor company practices and policies be reviewed in light of these findings and appropriate changes made, particularly to reduce exposures to agents identified as likely causes of SAB.

ACKNOWLEDGMENTS

Support for this work was provided primarily by the Semiconductor Industry Association to the Division of Occupational/Environmental Medicine and Epidemiology at the University of California, Davis. We thank the SIA and SIA Worker Task Force for their ample cooperation and support. Creation of an independent Science Advisory Panel by the SIA was an important process that could be a model for industry-funded research [Cullen et al., 1994]. For this the SIA deserves recognition and credit. The Scientific Advisory Panel provided valuable advice and assistance during this long and complex study, and we appreciate their help and direction. We greatly appreciate the cooperation, time, and support of companies participating in the study, and especially the assistance of human resources and industrial hygiene personnel. Support was also provided by a Research Career Development Award from the National Institute of Environmental Health Sciences (5-K04-ES000202) to Dr. Ellen Gold.

A large research staff, including field coordinators, interviewers, coders, and programmers, contributed much to this study. We thank the U.C. Davis administrative staff for clerical assistance. Subcontracts for research were arranged with the University of Massachusetts Medical Center; the University of California, Berkeley; the Western Consortium for Public Health; and the California Public Health Foundation. We appreciate the many people at these institutions who worked on this effort. Finally, this study would not have been possible without the cooperation of thousands of employees of the semiconductor industry. We are grateful for the time and effort they gave.

REFERENCES

- Ahlborg G Jr, Hogstedt C, Bodin L, Barany S (1989): Pregnancy outcome among working women. *Scand J Work Environ Health* 15:227-233.
- Axelsson G, Lutz C, Rylander R (1984): Exposure to solvents and outcome of pregnancy in university laboratory employees. *Br J Ind Med* 41:305-312.
- Beaumont JJ, Swan SH, Hammond SK, Samuels SJ, Green R, Hallock MF, Dominguez C, Boyd P, Schenker MB (1995): Historical cohort investigation of spontaneous abortion in the Semiconductor Health Study: Epidemiologic methods and analyses of risk in fabrication overall and in fabrication work groups. *Am J Ind Med*, 28:735-750.
- Brown NA, Holt D, Webb M (1984): The teratogenicity of methoxyacetic acid in the rat. *Toxicol Lett* 22:93-100.
- Clapp DE, Zaebst DD, Herrick RF (1984): Measuring exposures to glycol ethers. *Environ Health Perspect* 57:91-95.
- Cook R, Bodner K, Kolesar R, Uhlmann CS, VanPeenen PF, Dickson GS, Flanagan K (1982): A cross-sectional study of ethylene glycol monomethyl ether process employees. *Arch Environ Health* 37:346-351.
- Creasy DM, Foster PMD (1984): The morphological development of glycol ether-induced testicular atrophy in the rat. *Exp Mol Pathol* 40:169-176.

- Cullen MR, Rado T, Waldron JA, Sparer J, Welch LS (1983): Bone marrow injury in lithographers exposed to glycol ethers and organic solvents used in multicolor offset and ultraviolet curing printing processes. *Arch Environ Health* 38:347-354.
- Cullen MR, Schenker MB, Upton A, Buffler P, Robins T, Fine L, Wiencek R, Widess E, Chiazzini L (1994): The private funding of public research: New directions in the administration of occupational and environmental health research. *J Occup Med* 36:1348-1354.
- Daniell W, Stebbins A, Kalman D, O'Donnell JF, Horstman SW (1992): The contributions to solvent uptake by skin and inhalation exposure. *Am Ind Hyg Assoc J* 53:124-129.
- Devoto FC, Perrotto BM, Bordoni NE, Arias NH (1972): Effect of sodium fluoride on the placenta in the rat. *Arch Oral Biol* 17:371-374.
- Doe JE, Samuels DM, Tinston DJ, de Silva Wickramaratne GA (1983): Comparative aspects of the reproductive toxicology by inhalation in rats of ethylene glycol monomethyl ether and propylene glycol monomethyl ether. *Toxicol Appl Pharmacol* 69:43-47.
- Eskenazi B, Gold EB, Lasley B, Samuels SJ, Hammond SK, Wight S, Rasor MO, Hines CJ, Schenker MB (1995a): Prospective monitoring of early fetal loss and clinical spontaneous abortion among female semiconductor workers. *Am J Ind Med*, 28:833-846.
- Eskenazi B, Gold EB, Samuels SJ, Wight S, Lasley B, Hammond SK, Rasor MO, Schenker MB (1995b): Prospective assessment of fecundability of female semiconductor workers. *Am J Ind Med*, 28:817-831.
- Gold EB, Eskenazi B, Hammond SK, Lasley B, Samuels SJ, Rasor MO, Hines CJ, Overstreet J, Schenker MB (1995a): Prospectively assessed menstrual cycle characteristics in female wafer-fabrication and nonfabrication semiconductor employees. *Am J Ind Med*, 28:799-815.
- Gold EB, Eskenazi B, Lasley B, Samuels SJ, Rasor MO, Overstreet J, Schenker MB (1995b): Epidemiologic methods for prospective assessment of menstrual cycle and reproductive characteristics in female semiconductor workers. *Am J Ind Med*, 28:783-797.
- Gray RH, Corn M, Cohen R, Correa A, Hakim R, Hou W, Shah F, Zauer H (1993): "Final Report: The Johns Hopkins University Retrospective and Prospective Studies of Reproductive Health Among IBM Employees in Semiconductor Manufacturing." Baltimore, MD: The Johns Hopkins University.
- Hallock MF, Hammond SK, Hines CJ, Woskie SR, Schenker MB (1995): Patterns of chemical use and exposure control in the Semiconductor Health Study. *Am J Ind Med*, 28:681-697.
- Hammond SK, Hines CJ, Hallock MF, Woskie SR, Abdollahzadeh S, Iden CR, Anson E, Ramsey F, Schenker MB (1995): The tiered exposure assessment strategy in the Semiconductor Health Study. *Am J Ind Med*, 28:661-680.
- Hanley TR Jr, Yano BL, Nitschke KD, John JA (1984): Comparison of the teratogenic potential of inhaled ethylene glycol monomethyl ether in rats, mice, and rabbits. *Toxicol Appl Pharmacol* 75:409-422.
- Hansson EJ, Jansa J, Wande H, Kallen B, Ostlund E (1980): Pregnancy outcomes for women working in laboratories in some of the pharmaceutical industries in Sweden. *Scand J Work Environ* 6:131-134.
- Hemminki K, Franssila E, Vaino H (1980): Spontaneous abortion among chemical female workers in Finland. *Int Arch Occup Environ Health* 45:123-126.
- Hines CJ, Selvin S, Samuels SJ, Hammond SK, Woskie SR, Hallock MF, Schenker MB (1995): Hierarchical cluster analysis for exposure assessment of workers in the Semiconductor Health Study. *Am J Ind Med*, 28:713-722.
- Hodge HC, Smith FA (1977): Occupational fluoride exposure. *J Occup Med* 19:12-39.
- Huel G, Mergler D, Bowler R (1990): Evidence for adverse reproductive outcomes among women microelectronic assembly workers. *Br J Ind Med* 47:400-404.
- Joffe M (1985): Biases in research on reproduction and women's work. *Int J Epidemiol* 14:118-123.
- Kono K, Yoshida Y, Watanabe M, Watanabe H, Inoue S, Murao M, Doi K (1990): Elemental analysis of hair among hydrofluoric acid exposed workers. *Int Arch Occup Environ Health* 62:85-88.
- Kono K, Yoshida Y, Watanabe M, Tanioka Y, Orita Y, Dote T, Bessho Y, Takahashi Y, Yoshida J, Sumi Y (1992): Serum fluoride as an indicator of occupational hydrofluoric acid exposure. *Int Arch Occup Environ Health* 64:343-346.
- Kuznetsova LS (1969): The effects of the various operations in the manufacture of superphosphate on the sex organs of female workers. *Gig Tr Prof Zabol* 13:21-25.
- Kyyronen P, Taskinen H, Lindbohm ML, Hemminki K, Hienonen OP (1989): Spontaneous abortions and

- congenital malformations among women exposed to tetrachloroethylene in dry cleaning. *J Epidemiol Community Health* 43:346-351.
- LaDou J (1986): The microelectronics industry. *State of the Art Reviews. Occup Med* 1:1-197.
- Lamb JC, Gulati DK, Russell VS, Hommel L, Sabharwal PS (1984): Reproductive toxicity of ethylene glycol monoethyl ether tested by continuous breeding of CD-1 mice. *Environ Health Perspect* 57:85-90.
- Landry TD, Gushow TS, Yano BL (1983): Propylene glycol monomethyl ether: A 13-week inhalation toxicity study in rats and rabbits. *Fund Appl Toxicol* 3:627-30.
- Lasley BL, Lohstroh P, Kuo A, Gold EB, Eskenazi B, Samuels SJ, Overstreet JW (1995): Laboratory methods for evaluating early pregnancy loss in an industry-based population. *Am J Ind Med*, 28:771-781.
- Lemasters G, Pinney S (1990): "Healthy Beginnings: A Report on Phase I of the Study of Reproductive Outcomes in Semiconductor Employees." Cincinnati, OH: Center for Occupational Health, University of Cincinnati.
- Lipscomb JA, Fenster L, Wrensch M, Shusterman D, Swan S (1991): Pregnancy outcomes in women potentially exposed to occupational solvents and women working in the electronics industry. *J Occup Med* 33:597-604.
- McCurdy SA, Pocekay D, Hammond SK, Woskie S, Samuels SJ, Schenker MB (1995): A cross-sectional survey of respiratory and general health outcomes among semiconductor industry workers. *Am J Ind Med*, 28:847-860.
- McDonald AD, McDonald JC, Armstrong B, Cherry NM, Cote R, Lavoie J, Nolin AD, Robert D (1988): Fetal death and work in pregnancy (abstr). *Br J Ind Med* 45:148-157.
- McGregor DB (1984): Genotoxicity of glycol ethers. *Environ Health Perspect* 57:97-103.
- Merkle J, Klimish HJ, Jäckh R (1987): Prenatal toxicity of 2-methoxypropylacetate-1 in rats and rabbits. *Fundam Appl Toxicol* 8:71-79.
- Messer HH, Armstrong WD, Singer L (1973): Influence of fluoride intake on reproduction in mice. *J Nutr* 103:1319-1326.
- Miller RR, Ayres JA, Calhoun LL, Young JT, McKenna MJ (1981): Comparative short-term inhalation toxicity of ethylene glycol monomethyl ether and propylene glycol monomethyl ether in rats and mice. *Toxicol Appl Pharmacol* 61:368-377.
- Miller RR, Carreon RE, Young JT, McKenna MJ (1982): Toxicity of methoxyacetic acid in rats. *Fund Appl Toxicol* 2:158-60.
- Nagano K, Nakayama E, Oobayashi H, Yamada T, Adachi H, Nishizawa T, Ozawa H, Nakaichi M, Okuda H, Minami K, Yamazaki K (1981): Embryotoxic effects of ethylene glycol monomethyl ether in mice. *Toxicology* 20:335-343.
- Nelson BK, Brightwell WS (1984): Behavioral teratology of ethylene glycol monomethyl and monoethyl ethers. *Environ Health Perspect* 57:43-46.
- Neutra RR, Swan SH, Hertz PI, Windham GC, Wrensch M, Shaw GM, Fenster L, Deane M (1992): Potential sources of bias and confounding in environmental epidemiologic studies of pregnancy outcomes. *Epidemiology* 3:134-142.
- NIOSH (1976): "Criteria for a Recommended Standard: Occupational Exposure to Hydrogen Fluoride." US Department of Health, Education, and Welfare. Washington, DC: U.S. Government Printing Office, HEW publication #76-143.
- NIOSH (1983): "Current Intelligence Bulletin 39: Glycol Ethers." Washington, DC: National Institute for Occupational Safety and Health, U.S. DHHS(NIOSH) publication #83-112.
- NIOSH (1991): "Criteria for a Recommended Standard: Occupational Exposure to Ethylene Glycol Monomethyl Ether, Ethylene Glycol Monoethyl Ether, and their Acetates." Washington, DC: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, U.S. DHHS(NIOSH) publication #91-119.
- Pastides H, Calabrese EJ, Hosmer DJ, Harris DJ (1988): Spontaneous abortion and general illness symptoms among semiconductor manufacturers. *J Occup Med* 30:543-551.
- Paustenbach DJ (1988): Assessment of the developmental risks resulting from occupational exposure to select glycol ethers within the semiconductor industry. *J Toxicol Environ Health* 23:29-75.
- Pocekay D, McCurdy SA, Samuels SJ, Schenker MB (1995): Musculoskeletal symptoms and ergonomic risk factors in semiconductor workers. *Am J Ind Med*, 28:861-871.
- Rao KS, Cobel-Geard SR, Young JT, Hanley Jr, TR, Hayes WC, John JA, Miller RR (1983): Ethylene

- glycol monomethyl ether II. Reproductive and dominant lethal studies in rats. *Fund Appl Toxicol* 3:80-85.
- Samuels SJ, McCurdy SA, Pocekay D, Hammond SK, Schenker MB, Missell L (1995): Fertility history of currently employed male semiconductor workers. *Am J Ind Med*, 28:873-882.
- Scott WJ, Fradkin R, Wittfoht W, Nau H (1989): Teratologic potential of 2-methoxyethanol and trans-placental distribution of its metabolite, 2-methoxy acetic acid in non-human primates. *Teratology* 39:363-373.
- Shusterman D, Windham G, Fenster L (1993): Employment in electronics manufacturing and risk of spontaneous abortion. *J Occup Med* 35:381-386.
- Swan SH, Neutra RR, Wrensch M, Hertz PI, Windham GC, Fenster L, Epstein DM, Deane M (1992): Is drinking water related to spontaneous abortion? Reviewing the evidence from the California Department of Health Services Studies. *Epidemiology* 3:134-142.
- Swan SH, Beaumont JJ, Hammond SK, VonBehren J, Green R, Hallock MF, Woskie SR, Hines CJ, Schenker MB (1995): Historical cohort study of spontaneous abortion among fabrication workers in the Semiconductor Health Study: Agent-level analysis. *Am J Ind Med*, 28:751-769.
- Theuer RC, Mahoney AW, Sarett HP (1971): Placental transfer of fluoride and tin in rats given various fluoride and tin salts. *J Nutr* 101:525-532.
- Ventura SJ, Taffel SM, Mosher WD (1988): Estimates of pregnancies and pregnancy rates for the United States, 1976-85. *Am J Public Health* 78:506-511.
- Veulemans H, Steeno O, Masschelein R, Groesenken D (1993): Exposure to ethylene glycol ethers and spermatogenic disorders in man. *Br J Ind Med* 50:71-78.
- Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC (1988): Incidence of early loss of pregnancy. *N Engl J Med* 319:189-194.
- Windham GC, Shusterman D, Swan SH, Fenster L, Eskenazi B (1991): Exposure to organic solvents and adverse pregnancy outcome. *Am J Ind Med* 20:241-259.
- Woskie SR, Hammond SK, Hines CJ, Hallock MF, Schenker MB (1995): Algorithms for estimating personal exposures to chemical agents in the Semiconductor Health Study. *Am J Ind Med*, 28:699-711.
- Zellers ET, Ke HQ, Smigiel D, Sulewski R, Patrash SJ, Han MW, Zhang GZ (1992): Glove permeation by semiconductor processing mixtures containing glycol-ether derivatives. *Am Ind Hyg Assoc J* 53:105-116.