American Journal of Industrial Medicine 27:611–613 (1995)

LETTER TO THE EDITOR

Paternal Occupational Exposure and Spontaneous Abortions: A Closer Look at Paternal Recall and Vinyl Chloride

Key words: paternal exposure, recall bias, spontaneous abortion, vinyl chloride

We commend Savitz et al. [1994] for their effort at summarizing the epidemiology literature regarding paternal occupational exposure and spontaneous abortion, especially as it pertains to methodological issues. They identified three major methodological issues: (1) accurate ascertainment of the occurrence of a spontaneous abortion, (2) validity of the father's exposure assignment, and (3) potential confounding by parental lifestyle factors that may be correlated with paternal occupation. Concerning the first issue, it should be noted that an article was recently published by Fikree et al. [1993] that assessed the recall agreement of pregnancy outcomes among 857 couples. Using the wives' reports as the standard, Fikree et al. [1993] found 71.2% sensitivity and 98.8% specificity for husbands' recall of spontaneous abortions. We have also observed differences in recall of spontaneous abortions by male employees. These observations showed that 20 spontaneous abortions were recalled among 96 (20.8%) lifetime pregnancy outcomes (live births, still births, and spontaneous abortions) by male employees who had their spouses/partners assist with a reproductive health survey. There were only six spontaneous abortions among 114 (5.3%) lifetime pregnancy outcomes recalled by male employees who chose not to involve a spouse/partner. These data support the opinion of Savitz et al. [1994] that paternal occupational exposure studies "should routinely seek reproductive outcome information from the woman, whenever possible."

Based on the Infante et al. [1976a] data collected from male employees only, Savitz et al. [1994] suggested that further epidemiologic research be initiated on paternal occupational exposure to vinyl chloride and spontaneous abortion. Infante et al. [1976a] reported an age-adjusted fetal death loss of 15.8%, as recalled by male workers (N = 95) who had potential exposure to vinyl chloride, compared to 8.8% recalled by rubber and polyvinyl chloride fabrication male workers (N = 158). When the analysis was restricted to men under age 30, they reported 20.0% fetal death loss for the vinyl chloride group compared to 5.3% for the nonexposed group.

Although they alluded to the fact that the risks reported by Infante et al. [1976a]

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Accepted for publication June 27, 1994.

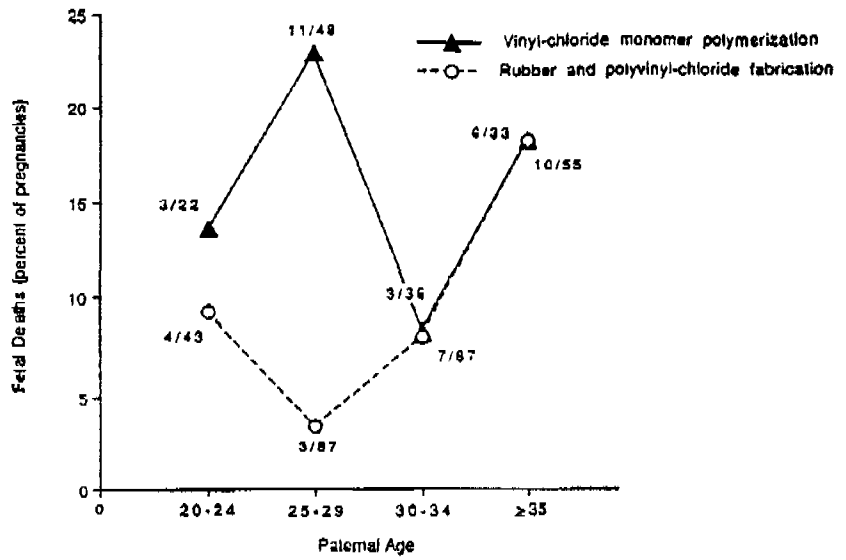

Fig. 1. Fetal deaths by paternal age and potential exposure to vinyl chloride monomer as defined by Infante et al. Note: the rubber and polyvinylchloride fabrication group was considered not exposed to vinyl chloride monomer. The ratios in the graph are the number of fetal deaths divided by pregnancies per each age group (adapted from Infante et al., 1976a,b: Stallones, 1987].

were observed primarily among the younger male employees, Savitz et al. [1994] were apparently unaware of additional paternal age-specific fetal death loss data requested by Paddle [1976] and subsequently published by Infante et al. [1976b]. These additional data demonstrated that the difference in the overall age-adjusted risks (15.8% vs. 8.8% in the original published work) was the result of divergent age-specific fetal death loss percentage in only one of the four 5-year age strata (Fig. 1).

The late Reuel Stallones, in a commentary on the use and abuse of subgroup analyses in epidemiology [1987], asked the following questions concerning the Infante et al. [1976a] data: "Why was the harm limited to the 25- to 29-year age group? Why was the rate higher in the exposed 25–29-year age group than in either of the two older exposed age groups? Why was the rate lower in the nonexposed 25–29-year age group than in the younger, nonexposed age group?" Stallones' conclusion was "No answers to these questions are evident; a sensible conclusion is that something went wrong in the study, resulting in aberrant findings, and that the study therefore should be discarded. If published at all, the data should appear in a textbook of epidemiology as a most pertinent example of the value of a subgroup analysis in discovering a problem, internal to the research, which renders invalid the results obtained for the total group and which might have been accepted had the subgroup analysis not been done." Hatch et al. [1981] have also raised other concerns about the analyses in Infante et al. [1976a].

Savitz et al. [1994] suggested that the dominant lethal test may be the animal study most relevant to human spontaneous abortion. In this regard we note that Short et al. [1977] reported a negative result for vinyl chloride in the dominant lethal assay

in male rats exposed to vinyl chloride levels as high as 1,000 ppm for 6 hours daily over an 11-week period. Anderson et al. [1976] found no response to vinyl chloride in the dominant lethal assay in male mice exposed briefly to levels as high as 30,000 ppm.

In summary, we again commend Savitz et al. [1994] for their ambitious and comprehensive review of the literature concerning paternal occupational exposures and spontaneous abortion. However, we concur with Stallones' [1987] conclusions. We believe there is no justification for continuing to use the data of Infante et al. [1976a] to support the suggestion in the epidemiology literature of a positive association between paternal occupational exposure to vinyl chloride and spontaneous abortion. If other epidemiology reviewers do find the conclusions of Infante et al. to be credible, then we believe they should at least offer the reader their answers to Stallones' three questions.

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American Journal of Industrial Medicine 27:615–616 (1995)

LETTER TO THE EDITOR

Reply to Olsen, Ramlow, and Hearn

Key words: occupational exposure, vinyl chloride, spontaneous abortion, paternal risks

Dr. Olsen and colleagues [1994] share our concerns with the quality of paternal reports of reproductive events, particularly spontaneous abortion, and cite evidence for their fallibility. Reliance on paternal reports constitutes one of the deficiencies in the study by Infante et al. [1976a], although Olsen et al.'s main concern is with the pattern of results and their interpretation.

The constellation of results presented by Infante et al. [1976a,b] yield evidence of a positive association between paternal exposure to vinyl chloride and spontaneous abortion in their wives that should be viewed as tentative for a number of reasons. In favor of a causal interpretation is the pattern of similar risk between exposed and unexposed populations prior to employment. A sizable increase in risk was seen only among the wives of exposed men subsequent to employment. A notable reduction in excess risk among exposed men when restricted to couples that experienced fewer than three spontaneous abortions [Infante et al., 1976b; Hatch et al., 1981] diminishes the support for that association, presuming that repeat spontaneous abortions are more likely to be due to intrinsic maternal factors than to a persistent adverse effect of paternal vinyl chloride exposure. In the case of vinyl chloride, animal data such as the dominant lethal results cited by Olsen et al. [1994] are of limited value in ruling out human effects [Hatch et al., 1981].

The pattern of age-specific results appears to be most troubling to Olsen et al. [1994]. Infante et al. [1976a] reported an overall increase in risk which appeared to be concentrated in younger workers, as we noted in our review [Savitz et al., 1994]. In spite of the apparent heterogeneity in risk as a function of paternal age, a summary measure for the total population remains a useful description of the average effect of vinyl chloride [Pearce, 1989]. The principal strength of that summary is that it is less vulnerable to fluctuations due to small numbers, in contrast to the age-specific results. The pattern presented by Stallones [1987] taken from Infante et al. [1976b] is clearly quite erratic since it is based on such small numbers.

Conclusions about any of the age-specific risk ratios are thus of limited value. The study tells us very little about the effect of vinyl chloride on reproductive risks among 25–29-year-old men or any other specific age group, including those for which no apparent elevation in risk was found. The three questions raised by Stal-

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Accepted for publication June 27, 1994.

lones [1987] concerning why the harm was limited to 25–29-year-olds, why the rate was higher in exposed 25–29-year-olds than in older exposed groups, and why the rate was lower in the nonexposed 25–29-year-olds than in younger, nonexposed groups are, of course, not answerable. The only candidate explanation is a statistical aberration due to small numbers (synonymous with "unknown"). Concluding that "something went wrong" more generally in the study ignores the myriad unexplained sources of variability in small studies, and is neither informative nor testable. In spite of the erratic pattern in relation to paternal age, neither Stallones [1987] nor Olsen et al. [1994] have proposed a methodologic bias that might have produced it.

Legitimate concerns with the deficiencies in the study by Infante et al. [1976a] render the results far from conclusive, yet we noted that there have been no attempts at replication. A study of the same topic that is free from the principal deficiencies of Infante et al. [1976a], namely reliance on paternal report and limited study size, is the only way to evaluate whether "something went wrong."

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Vinyl Chloride

American Journal of Industrial Medicine 25:361–383 (1994)

Review of Epidemiologic Studies of Paternal Occupational Exposure and Spontaneous Abortion

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The question of whether paternal exposures influence risk of spontaneous abortion is of great public interest, with the possibility supported by laboratory investigations. Thirty-nine studies of male occupational exposure and risk of spontaneous abortion were examined, with the methods and results tabulated. Many of those reports were limited by exposure data based on maternal report of the father's job title or by potentially inaccurate paternal reports of spontaneous abortion, though the quality of more recent studies is markedly enhanced. Mercury has been implicated most strongly based on recent studies that included quantitative exposure estimates; a number of studies showing associations for exposure to anesthetic gases. Suggestive associations have also been found inconsistently for exposure to lead, rubber manufacturing, selected solvents, and some pesticides. Further study is encouraged, but with more intensive effort to measure accurately both spontaneous abortion and occupational exposures.

Key words: fathers, occupational exposure, mercury, pesticides, solvents, spontaneous abortion, paternal reproduction risk

INTRODUCTION

Over the past decade, there has been a growing interest in the potential role of male occupational exposures in reproductive health. A male contribution to infertility is now well accepted, with at least one agent (dibromochloropropane) an established cause of male infertility [Whorton et al., 1977]. The phenomenon of concern in this review is the possible impact of paternal workplace exposures on the risk of spontaneous abortion. Such an association might be mediated by maternal exposure through contamination of the home environment [Knishkowy and Baker, 1986], concentration of the agent in semen [Stachel et al., 1989], and passage through sexual intercourse, or transmission of the agent directly on the sperm [Yazigi et al., 1991].

Of particular interest here is a more direct paternal effect on the fetus. Genetically damaged sperm that remain capable of fertilization might produce an impaired conceptus that is more likely to result in a pregnancy loss. Paternally mediated abnormalities in development are the presumed phenomenon underlying such concerns

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Accepted for publication February 24, 1993.

as male exposure to Agent Orange and birth defects in their offspring [Erickson et al., 1984], and ionizing radiation and childhood leukemia [Gardner et al., 1990]. Although there is not yet a well-established male exposure proven to influence post-conception reproductive events in general, or spontaneous abortion in particular, there are several lines of evidence that strongly support the possibility, including the sizable body of epidemiologic data reviewed here.

Experimental studies of male laboratory animals (mostly rodents) have clearly indicated the potential for developmental toxicity following paternal exposure to ionizing radiation and mutagenic chemicals. These studies have shown that the full spectrum of developmental endpoints appear to be responsive to paternal exposure, including gene mutations, chromosomal aberrations, lethality, congenital anomalies, tumors, neurobehavioral deficits, and growth retardation [Olshan and Faustman, 1993]. In vivo assays used to assess paternal genetic effects include the specific locus test, dominant skeletal, dominant cataract, and dominant lethal tests, and the heritable translocation test [Russell and Shelby, 1985].

The most relevant test to human spontaneous abortion is probably the dominant lethal test [Green et al., 1985]. A dominant lethal mutation is defined as a genetic defect occurring in the gamete that permits fertilization but results in embryonic death. The genetic basis for these deaths is believed to be structural or numerical chromosome abnormalities in the germ cell of the treated male, with death occurring before or after implantation. An EPA-Genetox working group summarized the published studies using this assay [Green et al., 1985] and found that, of the 140 chemicals tested, 65 (46%) were determined to be positive. Although the dominant lethal test is not a direct analog of human spontaneous abortion, it does demonstrate that the agent affects the paternal genetic material. For the sizable fraction of human spontaneous abortions that are due to chromosomal abnormalities (estimated at 40% by Kline et al. [1989]), the assay is more directly applicable. Litter size reduction in laboratory animal studies is also relevant to human spontaneous abortion. Reduced litter size has been found following male exposure to ionizing radiation and ethylnitrosurea [Russell and Hunsicker, 1988; Selby and Russell, 1985].

Occupational exposures are clearly capable of adversely influencing human semen [Wyrobek et al., 1983a,b], yet few studies have attempted to evaluate whether abnormal semen characteristics are associated with spontaneous abortion. Case-control studies from the 1960s [Furuhjelm et al., 1962; Joel, 1966] found that conceptions ending in spontaneous abortion were more likely to be the product of "abnormal" semen than pregnancies that were successful. The semen abnormalities linked to poor pregnancy outcome were reduced sperm concentration, increased proportion with abnormal morphology, elevated sperm concentration, and reduced DNA content of the sperm. Given the era in which these studies were conducted, the lack of technological sophistication in semen evaluation, as well as methodological deficiencies concerning confounding, analytic methods, and selection of control groups are expected. The question of whether agents that influence sperm grossly may adversely affect the health of the resulting conceptus remains largely unexamined.

In this review, we will summarize the epidemiologic evidence concerning associations between paternal exposures and the risk of spontaneous abortion. The methodologic strategies of the past studies will be critically examined to note the key limitations and to recommend specific improvements needed to extend knowledge on this topic. Of particular concern in this research area is the challenge in accurately

ascertaining the occurrence of spontaneous abortion, the validity of exposure assignment based on job title, and the potential for confounding by lifestyle factors of the mother or father that are correlated with paternal occupation, all discussed in more detail after the presentation of the results. Finally, given the array of studies to date, the most promising avenues for further research will be noted.

METHODS OF REVIEW

We attempted to identify all studies in which the father's occupation was examined in relation to the risk of spontaneous abortion in his partner. Literature searches, cross-checking reference lists, and consultation with experts were used to make this compilation of evidence as complete as possible. In many instances, spontaneous abortion was only one among many outcomes considered, or paternal occupational exposures were one among many potential risk factors considered, raising questions about whether our search was completely successful. Studies that contained fewer than five exposed cases in all the associations they reported [e.g., Goldsmith et al., 1984] were excluded from the review. Studies were not excluded on the basis of qualitative criteria, but we attempted to provide sufficient methodologic information for the reader to make independent evaluations of the quality of the evidence.

Information abstracted for this review is presented in nine text tables and an appendix, with the studies arranged in chronological order within the tables. Table I presents key methodological data on the studies, including the source population, sources of exposure and outcome data, number of spontaneous abortions, and response proportion, in order to provide some insight into the potential biases and limitations of the various studies. The final column in Table I reports the categories of exposure examined in each study, serving as an index to the following seven tables, which are organized to present results for a specific category of exposure.

The source population, delineated as "general population" or "occupational cohort" was noted since, in general, occupational cohorts provide the opportunity for more refined exposure assessments than studies of the general population, but may be less generalizable. The number of spontaneous abortions reported in Table I includes all observations of spontaneous abortion used in any relevant analysis within the paper, even though the number of spontaneous abortions included in any specific analysis was often smaller. The response proportion noted in Table I is that reported by the original author for the total study population, including both the exposed and unexposed. In a number of studies, the reported response proportion provides a rather favorable assessment of the representativeness of the sample population, since individuals who were excluded because of migration or incomplete records were omitted from the denominator. The response proportion typically reports only the proportion who had complete data in records or agreed to the interview, and does not take into account unusable data or missing values on specific items of interest.

Tables II–VIII present the results from the studies that were reviewed, divided into seven broad categories of exposure: metals, solvents, anesthetic gases, pesticides, physical agents, hydrocarbons and automobile exhaust, and miscellaneous industries, occupations, and agents. The heterogeneity within some of these categories should be noted, with solvents including a variety of exposures in the plastics and rubber industry, and pesticides broadened to include sterilizing agents and wood preservatives. The results tables include the exposed group used in each analysis and

TABLE I. Reports on Paternal Occupational Exposure and Spontaneous Abortion: Study Designs and Methods

Reference	Source population	Source of exposure data	Source of outcome data	Number of spontaneous abortions	Response proportion (%)	Exposures Studied[a]
Cohen et al. [1974]	Occupational cohort	Paternal report	Paternal report	853	94	A
Bous et al. [1975]	General population	Maternal report	Karyotype	546[b]	58	Pa
Cohen et al. [1975]	Occupational cohort	Paternal report	Paternal report	281	48	A
Knill-Jones et al. [1975]	Occupational cohort	Paternal report	Paternal report	1,452	70	A
Infante et al. [1976]	Occupational cohort	Company records	Paternal report	73	62–77	S
Sanoukii [1976]	Occupational cohort	Workplace monitoring	Paternal report	NA[c]	NA	S
Rosenberg and Vantinen [1978]	Occupational cohort	Paternal report	Paternal report	62	69	A
Temin [1979]	Occupational cohort	Paternal report	Paternal report	54	92	A
Cohen et al. [1980]	Occupational cohort	Paternal report	Paternal report	680	74	A
Khattar et al. [1980]	Occupational cohort	Paternal report	Paternal report Hospital records	29	61	P
Carmelli et al. [1981]	Occupational cohort	Paternal report	Maternal report	134	56	P
Lauwerys et al. [1981]	Occupational cohort	Paternal report	Paternal report	93	47	A
Beckman & Nordstrom [1982]	Occupational cohort	Paternal report	Paternal report Hospital records	134	89	M
Hamill et al. [1982]	Occupational cohort	Workplace monitoring Paternal report	Paternal report	48	83	S
Kline et al. [1982]	General population	Maternal report	Karyotype of fetus Prenatal clinic records	992	79	M Pa H Ms
Smith et al. [1982]	Occupational cohort	Paternal report Employer records	Maternal report Medical records	92	86	P
Townsend et al. [1982]	Occupational cohort	Company records	Maternal report	298	62	P
Can et al. [1983][d]	General population	NA	Maternal report	9,419	NA	P
Hemminki et al. [1983]	General population	Census records	Hospital registry	210	83	M Ms
Nordstrom et al. [1983]	Occupational cohort	Company records Paternal report	Hospital records Paternal report	68	89	Pa
Lindbohm et al. [1984]	General population	Census records	Hospital registry	3,599	91	M S H Ms
Morgan et al. [1984]	Occupational cohort	Company records Paternal report	Maternal report Paternal report Hospital records	22	63	Ms
Roan et al. [1984]	Occupational cohort	Paternal report	Maternal report	103	28	P
Savitz et al. [1984]	Occupational cohort	Union records Paternal report	Maternal/paternal reports	220	35	S
Suskind & Hertzberg [1984]	Occupational cohort	Work location Company records	Paternal report	120	53[e]	P
Brodsky et al. [1985]	Occupational cohort	Paternal report	Paternal report	672	73	M
Daniell & Vaughan [1985]	General population	Birth certificate	Birth certificate	NA	91	S
Stellman et al. [1988]	Occupational cohort	Paternal report Military records	Paternal report	427	NA	P
CDC [1989]	Occupational cohort	Paternal report	Paternal report	2,756	84–87	P
Alexer et al. [1989]	Occupational cohort	Company records Biological monitoring	Paternal report	170	81	M
Aschengrau & Monson [1989]	General population	Medical records Military records	Hospital records	201	94	P
McDonald et al. [1989]	General population	Maternal report	Hospital records Maternal report	10,893	NA	M S P Pa H Ms
Taskinen et al. [1989]	Occupational cohort	Solvent registry Biological monitoring Paternal report	Hospital registry Outpatient records	120	75	S Ms
Gargnis et al. [1990]	Occupational cohort	Employer information	Paternal report	488	81	A
Restrepo et al. [1990]	Occupational cohort	Paternal report Workplace monitoring	Paternal report	81	95	P
Cordier et al. [1991]	Occupational cohort	Company records Biological monitoring	Maternal report	70	77	M
Lindbohm et al. [1991a]	General population	Census records	Hospital registry	8,731	NA	M S P Pa H Ms
Lindbohm et al. [1991b]	Occupational cohort	Paternal report Biological monitoring	Hospital registry Clinic records	213	74	M S Pa H
Rupa et al. [1991]	Occupational cohort	NA	NA	1,555	NA	P

[a]M = metals, S = solvents; A = anesthetic gases; P = pesticides; Pa = physical agents; H = hydrocarbons and automobile exhaust; Ms = miscellaneous industries, occupations, and agents.
[b]Karyotypically abnormal case-control.
[c]NA = not available.
[d]Cited in Sterling and Arundel (1986).
[e]Excludes losses because of mortality.

an estimate of the risk ratio with 95% confidence interval (CI) contrasting exposed to unexposed men. The desired 95% CIs were often not provided and had to be derived from the data using test-based methods [Rothman, 1986] for risk ratios or odds ratios as required [Alcser et al., 1989; Beckman and Nordstrom, 1982; Boue et al., 1975; Brodsky et al., 1985; Cohen et al., 1974, 1975; Hamill et al., 1982; Hemminki et al., 1983; Infante et al., 1976; Kharrazi et al., 1980; Knill-Jones et al., 1975; Lauwerys et al., 1981; Morgan et al., 1984; Nordstrom et al., 1983; Rosenberg and Vanttinen, 1978; Roan et al., 1984; Rupa et al., 1991; Savitz et al., 1984; Smith et al., 1982; Sterling and Arundel, 1986; Suskind and Hertzberg, 1984].

Exposure classification was often based on a combination of job title or employment setting and an inference regarding the specific agents of interest. The author's terminology and intentions were retained in describing the exposures. When a broad array of exposures were analyzed, only exposures for which there were five or more exposed cases were tabulated. Papers frequently included multiple analyses of closely related groups. To restrict the size of the tables and to retain clarity, it was necessary to present these results selectively. When multiple unexposed groups were analyzed and all comparisons produced similar results, results were presented for the largest unexposed group or the one thought least likely to introduce bias. When multiple unexposed groups produced different results and none was clearly superior to the others, all analyses were tabulated. Adjusted results were provided when confounding was present and the adjusted results were available. Indications of effect modification by age or other factors were not routinely included in the results tables but are discussed in the text where relevant.

The Appendix table presents additional information on study location, study type, confounders addressed, definition of cases, and baseline risk of spontaneous abortion. The potential confounders listed for a given study include all confounders addressed in any exposure examined within that study but not all results provided statistical adjustments for the entire list of factors. Footnotes are used in the results tables to indicate potentially important discrepancies between the confounders listed for a given study and the confounders addressed for a given exposure. Included among the confounders addressed are those risk factors which the authors claimed to have accounted for, sometimes based on inappropriate methods such as statistical testing of differences between study groups or relying only on an impression that the groups were not notably different. The baseline risk of spontaneous abortion was computed for the unexposed when possible, but in some studies only the overall rate of spontaneous abortion among exposed plus unexposed was available.

RESULTS OF REVIEW

As summarized in Table I, 39 studies published over the last 18 years have provided data to evaluate the potential link between paternal occupation and spontaneous abortion. Only 8 appeared in the 1970s, with notable growth to the present and 4 appearing in 1991 alone. The attributes of those studies vary markedly and are noted as relevant in discussing the agents which they address. Most studies have relied on maternal or paternal self-report for both exposure and pregnancy outcome data. Study sizes vary markedly, from around 20 to nearly 10,000 spontaneous abortions. Response proportions range from under 50% to around 90%, with an obvious potential for influencing the study's validity.

TABLE II. Results of Studies of Paternal Exposures to Heavy Metals and Spontaneous Abortion

Reference	Agent, industry, or occupation	RR	95% CI
Beckman & Nordstrom [1982]	Copper smelter (lead, arsenic, mercury, cadmium)	1.5	0.9–2.3
Kline et al. [1982]	Metals	0.5[a]	0.2–1.1
		1.0[b]	0.4–2.2
Hemminki et al. [1983]	Metallurgical industry (zinc, cobalt)	1.1	0.8–1.5
	Metal industry	0.7	0.4–1.5
Lindbohm et al. [1984]	Metals manufacturing	0.9	0.8–1.0
	Metal-plate and construction steel	1.4	1.0–1.9
Brodsky et al. [1985]	Dentistry (mercury)	0.9	0.7–1.1
Alcser et al. [1989]	Urinary mercury levels 2,000–3,999 μg/l	1.1	0.8–1.6
	Urinary mercury levels 4,000–9,000 μg/l	1.7	1.1–2.5
McDonald et al. [1989]	Ore, metal, stone processing	1.2	0.9–1.5
	Metal machining	1.0	0.9–1.2
	Metal fabricating	0.9	0.7–1.2
Cordier et al. [1991]	Urinary mercury levels 1–19 μg/l	1.3	1.0–1.7
	Urinary mercury levels 20–49 μg/l	1.7	1.0–3.0
	Urinary mercury levels >49 μg/l	2.3	1.0–5.2
Lindbohm et al. [1991a]	Lead	0.9	0.8–1.0
	Nickel and nickel oxides	1.0	0.9–1.1
	Chromium/chromium compounds	1.0	0.9–1.1
	Metals	1.0	0.8–1.1
	Wire & pipe drawers	1.2	0.5–3.1
Lindbohm et al. [1991b]	Blood lead levels 1.0–1.4 μmol/l	1.0	0.6–1.7
	Blood lead levels 1.5–1.8 μmol/l	1.3	0.5–3.4
	Blood lead levels >1.8 μmol/l	1.6	0.6–4.0
	Blood lead levels 1.0–1.4 μmol/l during spermatogenesis	0.7	0.3–1.9
	Blood lead levels >1.4 μmol/l during spermatogenesis	3.8	1.2–12.0
	Cadmium	1.4	0.6–3.4
	Chromium	0.9	0.5–1.6
	Nickel	1.1	0.6–1.9
	Zinc	2.2	0.8–5.5
	Copper	2.8	1.1–7.0

[a]Public clinic patients, normal karyotype.
[b]Public clinic patients, abnormal karyotype.

Exposure to Heavy Metals

Occupational agents as potential causes of spontaneous abortion have been examined in a number of mostly recent studies (Table I). Ten studies contain information that address paternal exposure to lead, mercury, and other metals in relation to spontaneous abortion (Table I and II). Many are community-based surveys, with exposure defined by inferences based on employment sector or job title rather than direct measurement. However, four studies focused directly on cohorts exposed to the metals of interest, namely, lead [Lindbohm et al., 1991b] and mercury [Brodsky et al., 1985; Alcser et al., 1989; Cordier et al., 1991]. With these exceptions, the

magnitude of metal exposure is not known and may not even be present for some of the "exposed" groups (e.g., work in the "metal industry"). Also, many of these exposure sources (e.g., copper smelter) contain a range of potentially hazardous agents, in addition to metals.

A number of studies provide evidence of positive associations, including smelter workers (RR = 1.5) [Beckman and Nordstrom, 1982], metal-plate and steel industry workers (RR = 1.4) [Lindbohm et al., 1984], men with elevated estimated lead exposure (RRs = 1.0, 1.3, and 1.6 for low, moderate, and high levels, respectively), zinc exposure (RR = 2.2), and copper exposure (RR = 2.8) [Lindbohm et al., 1991b]. Most notable is the association for high measured mercury exposure (RR = 1.7) [Alcser et al., 1989] and estimated mercury exposure (RRs = 1.3, 1.7, and 2.3 for low, moderate, and high levels, respectively) [Cordier et al., 1991] (Table II). Unique among the studies was Lindbohm et al.'s [1991b] evaluation of lead exposures around the time of spermatogenesis, which yielded a markedly elevated but imprecise risk ratio.

Contradictory null results or even inverse associations are also present in Table II, including the absence of an increased risk for dentists preparing mercury amalgams [Brodsky et al., 1985] and workers with job titles thought to indicate exposure to lead [Lindbohm et al., 1991a]. However, the most methodologically sophisticated in terms of exposure assessment [Alcser et al., 1989; Lindbohm et al., 1991b; Cordier et al., 1991] provide strong suggestions of a link between exposure to heavy metals, especially mercury, and spontaneous abortion.

Exposure to Rubber, Plastics, and Solvents

The array of agents under this rubric is quite broad, with a number of studies related to rubber, plastics, and related industries, as well as specific solvents and other agents often encountered in those work settings (Table III). In addition to the community studies that contribute results on a wide range of exposures [Lindbohm et al., 1984; McDonald et al., 1989; Lindbohm et al., 1991a], a number of studies have targeted particular exposures in this category, most notably vinyl chloride [Infante et al., 1976], toluene diamine and dinitrotoluene [Hamill et al., 1982], several specific solvents such as toluene and trichloroethylene [Taskinen et al., 1989], and perchloroethylene [Eskenazi et al., 1991]. Regardless of the results, the effort to design studies capable of implicating or exonerating specific agents is commendable.

The initial study of Infante et al. [1976] provided the first suggested link between males' occupational chemical exposures and reproductive outcome. An overall elevation in risk of spontaneous abortion was found among spouses of men working with vinyl chloride (RR = 1.8), pronounced among younger (but not older) fathers (RR = 3.7) (Table III). Maternal age was not ascertained so that it could be examined only indirectly through the closely correlated father's age.

Sanotskii [1976] reported a strong association of spontaneous abortion with chloroprene exposure, but insufficient methodological details are available to critically evaluate that observation. Risk ratios of 1.5 or greater were reported for organic solvents in general (RR = 2.3), toluene (RR = 1.5), and xylene (RR = 1.8) by Taskinen et al. [1989], in a study with unusual precision in exposure classification to specific solvents in specific industrial settings. Lindbohm et al.'s [1991a] survey found sizable associations with gasoline or benzene exposure in petroleum refineries (RR = 2.2), trichloroethane and methylene chloride (RR = 1.9) in rubber manu-

TABLE III. Results in Studies of Paternal Exposure to Rubber, Plastics, or Solvents and Spontaneous Abortion

Reference	Agent, industry, or occupation	RR	95% CI
Infante et al. [1976]	Vinyl chloride, polyvinyl chloride	1.8[a]	1.0–3.1
Sanotskii [1976]	Chloroprene and manufacturing	>3.0	NA[b]
Hamill et al. [1982]	Toluene diamine, dinitrotoluene	1.0	0.6–1.8
Lindbohm et al. [1984]	Solvents	0.9	0.7–1.1
Savitz et al. [1984]	Halogenated hydrocarbons	1.2	0.8–1.8
Daniell & Vaughan [1988]	Autobody workers	1.0	0.8–1.2
	Painters in maintenance, construction	0.9	0.8–1.1
	Fiberglass, bathtub, boat, plastics workers	0.9	0.7–1.2
	Printers, pressmen, lithographers	1.1	0.8–1.3
McDonald et al. [1989]	Laundry/dry cleaning	0.9	0.6–1.5
	Rubber, plastic fabricating	1.0	0.8–1 5
	Printing operations	0.9	0.8–1.2
Taskinen et al. [1989]	Organic solvents	2.3	1.1–5.0
	Aromatic hydrocarbons	1.6	1.0–2.4
	Styrene	1.3	0.8–2.1
	Toluene	1.5	0.9–2.5
	Xylene	1.8	1.1–3.2
	Halogenated hydrocarbons	1.1	0.6–1.8
	Trichloroethylene	1.0	0.6–2.0
	1,1,1-Trichloroethane	0.9	0.3–2.3
	Aliphatic hydrocarbons	1.5	0.9–2.5
	Acetone	1.0	0.6–1.7
	Miscellaneous solvents	1.7	1.1–2.6
Lindbohm et al. [1991a]	Petroleum refinery solvents (gasoline, benzene)	2.2	1.3–3.8
	Benzene	1.0	0.7–1 3
	Trichloroethylene	0.9	0.3–2.1
	Rubber manufacturing solvents (trichloroethylene, methylene chloride)	1.9	1.2–2.8
	Rubber chemicals	1.5	1.1–2.2
	Styrene	0.9	0.5–1.8
	Plastic manufacturing solvents (styrene)	1.0	0.7–1.5
	Plastic monomers	0.8	0.4–1.4
	Rubber product workers	1.5	1.1–2.2
Lindbohm et al. [1991b]	Organic solvent exposure	1.1	0 7–1.5

[a]Postemployment risk for exposed vs. unexposed.
[b]Not available.

facturing, and trichloroethane in general (RR = 1.5). It is difficult to juxtapose results given the diversity of agents of interest, but there are replicated positive associations present for rubber workers, and to a lesser extent for petroleum refinery products and individual solvents. No attempts to replicate the observations for vinyl chloride [Infante et al., 1976], chloroprene [Sanotskii, 1976], and specific solvents implicated by Taskinen et al. [1989] have been reported.

Many of the negative studies are limited in their ability to exonerate any exposures given the weak methods of exposure classification combined with poor response proportions [Savitz et al., 1984] or questionably high rates of spontaneous abortion [Daniell and Vaughan, 1988]. However, some of the negative results are more credible. Hamill et al.'s [1982] study was small but included a strong effort to

TABLE IV. Results in Studies of Paternal Exposure to Anesthetic Gases and Spontaneous Abortion

Reference	Agent, industry, or occupation	RR	95% CI
Cohen et al. [1974]	Anesthesiologists	0.9	0.8–1.1
	Anesthetic nurses	1.2	0.5–2.6
	Operation room technicians	1.8	0.8–4.1
Cohen et al. [1975]	Dentists working with anesthetics >3 hr/week	1.8	1.4–2.2
Knill-Jones et al. [1975]	Physicians working in operating room	1.1[a]	0.7–1.7
Rosenberg & Vanttinen [1978]	Anesthesiologists	0.8	0.5–1.4
Tomlin [1979]	Anesthesiologists working in operating room 20 or more hours per week	1.6	0.9–3.0
Cohen et al. [1980]	Dentists working with anesthesia 1–8 hr/week	1.1	1.0–1.4
	Dentists working with anesthesia 8+ hr/week	1.5	1.3–1.8
Lauwerys et al. [1981]	Physicians, nurses working in OR	1.1	0.7–1.8
Guirguis et al. [1990]	Physicians, nurses, other staff in OR	2.3	1.7–3.1

OR = operating room.
[a]Father exposed but mother not exposed.

accurately classify workplace exposure. McDonald et al.'s [1989] study did not identify associations for laundry/dry cleaning or rubber workers, and a number of solvents, including benzene and carbon disulfide, were not associated with spontaneous abortion in Lindbohm et al.'s [1991a] study. The most promising leads to pursue would be exposures in the rubber industry and exposures to vinyl chloride and specific solvents associated with spontaneous abortion (Table III).

Exposure to Anesthetic Gases

Given the observation that maternal exposure to anesthetic gases could increase the risk of spontaneous abortion [Tannenbaum and Goldberg, 1985], a number of studies in the 1970s addressed the possibility that paternal exposure to anesthetic gases could produce a similar effect (Table IV). All but one of the eight studies of this issue were published between 1974 and 1981, and all were based on surveys of male health professionals, generally dentists or physicians. All were questionnaire surveys of self-reported exposure and pregnancy outcome, yet the reported risk of spontaneous abortion varied rather markedly from 5.1% [Guirguis et al., 1990] to 13.2% [Rosenberg and Vanttinen, 1978] in spite of the similar methods (Appendix table). Such variation may be due to true heterogeneity in the populations, selection bias due to nonresponse patterns, or erroneous reporting. Response proportions did, in fact, vary quite markedly (41–92.4%), but there was not an obvious association between response proportion and reported risk of spontaneous abortion. The comparability of exposed and unexposed groups is unusually favorable, in that subgroups of potentially exposed health professionals (physicians, dentists, or technicians) were compared to other (presumably sociologically similar) subgroups from the same profession who were not likely to be exposed.

Most of these studies have found increased risks for the partners of anesthetic-exposed men (Table IV). Risk ratios of 1.5 or greater have been reported for operating room technicians (RR = 1.8) [Cohen et al., 1974], dentists working with anesthesia over 3 hours per week (RR = 1.8) [Cohen et al., 1975], anesthesiologists working

half-time or more in the operating room (RR = 1.6) [Tomlin, 1979], dentists working with anesthetics 8 or more hours per week (RR = 1.5) [Cohen et al., 1980], and hospital workers exposed to the operating room (RR = 2.3) [Guirguis et al., 1990]. Other studies of physicians in particular, including those with briefer exposure periods, have not found increased risk [Knill-Jones et al., 1975; Rosenberg and Vanttinen, 1978]. The suggestive evidence for dentists is noteworthy, although the dominance of the literature by a single group of investigators (with a particular approach to study methods, questionnaire design, etc.) diminishes the value of the independent replications. The traditionally intensive and uncontrolled use of anesthetics, especially nitrous oxide, in dental practice [Cohen et al., 1980] warrants further examination.

Exposure to Pesticides and Related Products

Fifteen studies have provided data to assess risks of spontaneous abortion from male exposure to pesticides, antimicrobials and related products encountered in chemical manufacturing, agricultural application, and from herbicide use in the war in Vietnam (Tables I and V). The diversity of agents and exposure settings is apparent.

Nearly all studies established exposure through paternal report, sometimes supplemented by company records [Smith et al., 1982; Townsend et al., 1982; Suskind and Hertzberg, 1984] or military records [Stellman et al., 1988; Aschengrau and Monson, 1989]. Overall, substantial attention was given to specific exposures in these studies, with most studies explicitly designed to address the agent(s) of interest. However, the degree of success in pinpointing actual exposures to Agent Orange, for example, or pesticides in agricultural applications is still quite limited.

Reproductive outcomes were typically ascertained through maternal or paternal report. In reviewing the methodological details (Table I and Appendix table), notable outliers are the baseline risk of spontaneous abortion of 1.9% in Restrepo et al.'s [1990] study and the response of only 26% in the survey of Roan et al. [1984], seriously diminishing the credibility of their results. Usually, but not always, major potential confounders such as maternal age and cigarette smoking were addressed. Even without the clearly invalid result of Restrepo et al. [1990], a twofold range in spontaneous abortion risks (5.8–11.9%) was observed across studies.

Results of pesticide studies were mixed (Table V), but again it is difficult to define which results address truly analogous exposures. DBCP exposure was found to increase spontaneous abortion risk in one study (RR = 3.0) [Khattar et al., 1980]. The results for 2,4-D, 2,4,5-T, dioxin, and Agent Orange show sporadic increases in risk, for example, among forestry workers (RR = 1.6) [Carmelli et al., 1981] and men potentially exposed to herbicides in Vietnam based on self-perception [CDC, 1988] or imputed potential exposure [Stellman et al., 1988]. Other studies of related exposures, equal or superior in quality, found no increased risk [Smith et al., 1982; Townsend et al., 1982; Suskind and Hertzberg, 1984; Aschengrau and Monson, 1989].

Rupa et al. [1991] found an increased risk of spontaneous abortion in the wives of male cotton workers in India. Although the study lacked some methodological details, the agents and exposure conditions may be worthy of closer examination. The notable associations reported by Restrepo et al. [1990] are greatly tempered by the anomalous spontaneous abortion risk of 1.9%, which suggests serious error in reporting accuracy or completeness, and the report of marked elevations in risk, even for jobs thought to involve no exposure to pesticides. Similarly, Roan et al.'s [1984]

TABLE V. Results in Studies of Paternal Exposure to Pesticides, Anti-Microbials, and Related Products and Spontaneous Abortion

Reference	Agent, industry, or occupation	RR	95% CI
Kharrazi et al. [1980]	Dibromochloropropane (DBCP)	3.0	1.3–7.0
Carmelli et al. [1981]	2,4-dichlorophenoxyacetic acid (2,4-D)		
	Farming	1.0	0.5–2.0
	Forestry/commercial applicators	1.6	0.8–3.1
Smith et al. [1982]	2,4,5-trichlorophenoxyacetic acid (2,4,5-T)	0.9	0.6–1.3
Townsend et al. [1982]	2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)	1.0	0.7–1.4
	Any dioxin	1.0	0.8–1.4
Can et al. [1983]	Agent Orange	1.2	1.2–1.3
Goldsmith et al. [1984]	DBCP	1.1	0.3–4.0
Rean et al. [1984]	Agricultural pesticides	1.2	1.0–2.1
Suskind & Hertzberg [1984]	2,4,5-T and dioxins	0.9[a]	0.6–1.2
CDC [1989]	Herbicides (any perceived exposure)	1.3	1.2–1.4
	Low	1.2	1.0–1.4
	Moderate	1.4	1.2–1.6
	High	1.7	1.3–2.1
Stellman et al. [1988]	Agent Orange		
	Handled herbicides	1.6	0.8–2.9
	Low exposure	1.3	1.0–1.6
	Moderate exposure	1.5	1.1–2.0
	High exposure	1.7	1.3–2.3
Aschengrau & Monson [1989]	Service in Vietnam	0.9	0.4–1.9
McDonald et al. [1989]	Agriculture/horticulture	1.0	0.8–1.4
Restrepo et al. [1990]	Floricultural industry		
	No pesticide job	2.4	1.1–5.0
	Low pesticide job	1.6	0.7–3.7
	Moderate pesticide job	2.0	1.2–3.3
	High pesticide job	0.7	0.1–5.3
Lindbohm et al. [1991a]	Ethylene oxide	4.7	1.2–18.4
	Impregnants of wood	1.9	0.7–5.0
	Formaldehyde (low exposure)	1.1	0.9–1.4
	Formaldehyde (high exposure)	1.0	0.8–1.4
Rupa et al. [1991]	Pesticides used in cotton production	1.7	1.6–1.9

[a]Not adjusted despite differences between exposed and unexposed in age, education, and duration of smoking.

report of a 1.5-fold increased risk for agricultural pilots is diminished in its importance by the poor response proportion. Among the diverse results that were reported, the observations most deserving of attempted replication (given study quality and biologic plausibility) are the increased risk for DBCP [Kharrazi et al., 1980], the association of spontaneous abortion with cotton pesticides (RR = 1.7) [Rupa et al., 1991], and the isolated observation of an increased risk from ethylene oxide (RR = 4.7) [Lindbohm et al., 1991a].

Exposure to Physical Agents

Of the six studies providing data on male exposure to physical agents (ionizing and non-ionizing radiation, heat), only one [Nordstrom et al., 1983] was focused on

TABLE VI. Results in Studies of Paternal Exposure to Physical Agents and Spontaneous Abortion

Reference	Agent, industry, or occupation	RR	95% CI
Boue et al. [1975]	Ionizing radiation	1.3	1.1–1.5
Kline et al. [1982]	Electrical	1.2[a]	0.6–2.3
	Heat	2.0[a]	0.9–4.9
	Nonionizing radiation	0.7–1.8[b]	—
Nordstrom et al. [1983]	Electromagnetic fields		
	Other jobs (lowest voltage)	0.6	0.3–1.1
	Switchyard/line construction (moderate)	0.6	0.3–1.1
	Switchyard workers (high voltage)	1.0	0.5–1.7
McDonald et al. [1989]	Ionizing radiation	0.9	0.6–1.3
Lindbohm et al. [1991a]	Radon exposure	1.2	0.8–1.8
Lindbohm et al. [1991b]	X-rays	1.5	0.6–3.6

[a]Public patients, normal karyotype.
[b]Range of risk ratios across normal/abnormal karyotype, public/private clinic.

this particular topic, so that the quality of exposure assessment was generally limited (Table VI). Suggestive associations were found for ionizing radiation in two studies [Boue et al., 1975; Lindbohm et al., 1991b], with modestly elevated risk ratios of 1.3–1.5. Nonionizing radiation, a ubiquitous but poorly defined exposure, was found by Kline et al. [1982] to be associated with spontaneous abortions of both normal and abnormal karyotype but only among private patients. Nordstrom et al. [1983] did not find power-frequency electromagnetic fields to be associated with increased risk. Given clear evidence that ionizing radiation causes mutations [BEIR, 1990] and that heat can impair sperm function [Levine et al., 1990], this avenue appears to be worthy of pursuit in spite of the results currently available. The only data on heat exposure provided a suggestively positive result [Kline et al., 1982].

Exposure to Hydrocarbons and Exhaust

Several studies provided data on miscellaneous hydrocarbon and motor vehicle exhaust exposures, all as components of broader surveys (Table VII). Nonetheless, perhaps because of the literature linking such agents to childhood cancer in the offspring [Savitz and Chen, 1990], several investigators had considerable interest in these exposures [Kline et al., 1982; Lindbohm et al., 1984; Lindbohm et al., 1991a]. These studies address diverse exposures that are highly prevalent, such that a number of studies provide evidence of small but statistically precise elevations in risk [Lindbohm et al., 1984; McDonald et al., 1989].

Consideration of the magnitude of increase found across studies yields rather consistently close to the null. Only the risk ratios of 1.4 and 1.5 found for chimney sweeps and refinery workers, respectively [Lindbohm et al., 1991a], would constitute positive results worthy of replication. However, the presence of known mutagenic agents within these exposure groups provides a greater impetus for further study than can be derived from these results.

Exposure to Miscellaneous Industries, Occupations, and Agents

In addition to the results that fall into the above categories, many reported associations did not fall into any of the specific categories. For example, one prom-

TABLE VII. Results in Studies of Paternal Exposure to Exhaust and Hydrocarbons and Spontaneous Abortion

Reference	Agent, industry, or occupation	RR	95% CI
Kline et al. [1982]	Auto fumes (narrow)	1.2[a]	0.8–1.7
	Auto fumes (narrow)	1.3[b]	0.4–3.7
	Auto fumes (narrow)	1.0[c]	0.6–1.5
	Hydrocarbons (narrow)	1.2[a]	0.7–2.3
	Hydrocarbons (narrow)	1.2[c]	0.6–2.6
Lindbohm et al. [1984]	Polycyclic aromatic hydrocarbons	1.0	0.9–1.1
	Automobile exhaust and fumes	1.0	0.9–1.1
	Service station attendants	1.2	1.0–1.6
McDonald et al. [1989]	Mechanics and repairers	1.1	1.0–1.2
	Transport operations/materials handling	1.0	0.9–1.1
Lindbohm et al. [1991a]	Polycyclic aromatic hydrocarbons (moderate/high)	1.0	0.9–1.2
	Polycyclic aromatic hydrocarbons (low)	1.0	0.9–1.0
	Gasoline	0.9	0.8–1.1
	Chimney sweeps	1.5	0.9–2.4
	Refinery workers	1.4	0.8–2.5
Lindbohm et al. [1991b]	Carbon monoxide	1.1	0.8–1.7

[a]Normal karyotype, public clinic patients.
[b]Normal karyotype, private clinic patients.
[c]Abnormal karyotypes, public clinic patients.

inent study [Morgan et al., 1984] addressed wastewater treatment plant workers who are not easily classified elsewhere (Table VIII).

Notably elevated risk ratios (2.0 or greater) have been found for chemical crushers (RR = 2.2), cloth sewers (RR = 2.5), caretakers of fur-bearing animals (RR = 2.3) [Lindbohm et al., 1984], all wastewater treatment plant workers (RR = 2.1), and mechanical, instrument, and electrical workers in the wastewater treatment plant (RR = 4.9) [Morgan et al., 1984]. Associations between 1.5 and 2.0 have been reported for leather industry workers (RR = 1.8) [Hemminki et al., 1983] and for watchmakers (RR = 1.5) [Lindbohm et al., 1991a].

A number of specific agents that could plausibly be linked to spontaneous abortion (e.g., mutagens, miscellaneous industrial chemicals) were queried or imputed by investigators in a number of studies but did not yield any notably positive associations (Table VIII). None of the reported risk ratios reached 1.5, providing little basis for directing future study efforts. The explicit goal of studies such as these is to suggest agents more worthy of detailed examination, and leads from the above results are rather nonspecific in their suggestions for further study of hazardous chemicals in industry and health care.

DISCUSSION

Summary of Results

The literature providing data to evaluate possible associations between paternal occupational exposures and spontaneous abortion is large but, at least until recently, not of high quality. Most studies examining the issue did so without having focused on this particular topic, with limited effort to measure exposure or outcome or both

TABLE VIII. Results in Studies of Miscellaneous Paternal Exposures/Occupations and Spontaneous Abortion

Reference	Agent, industry, or occupation	RR	95% CI
Kline et al. [1982]	Chemicals	0.7–0.8*	—
	Food	0.7–1.2*	—
Hemminki et al. [1983]	Chemical industry	0.8	0.4–1.6
	Textile industry	0.8	0.4–1.8
	Leather industry	1.8	0.8–3.9
Lindbohm et al. [1984]	Chemical crushers	2.2	1.1–4.3
	Cloth sewers	2.5	1.3–5.0
	Caretakers of fur-bearing animals	2.4	1.3–4.4
	Textile dust	1.0	0.6–1.5
	Animal microorganisms	1.3	0.9–1.9
	Other chemicals	0.9	0.7–1.2
Morgan et al. [1984]	Waste water treatment plant workers		
	All job titles	2.1	0.9–4.5
	Process operators	0.9	0.1–6.8
	Mechanical, instrument, electrical	4.9	1.5–15.6
McDonald et al. [1989]	Physical scientists	1.2	0.9–1.6
	Physicians/dentists	1.0	0.7–1.2
	Technicians/art	1.1	0.8–1.2
	Chemical processing	0.9	0.6–1.4
	Food, beverage, wood, textiles	1.0	0.9–1.2
	Wood, stone machining	1.2	0.8–1.8
	Electrical fabricating	0.9	0.7–1.0
	Wood, textile, leather fabricating	1.0	0.8–1.1
	Construction trades	1.0	0.9–1.1
	Stationary equipment/miscellaneous manufacturing	1.1	0.9–1.4
Taskinen et al. [1989]	Carcinogens	1.3	0.9–2.1
	Dusts	1.4	0.7–2.6
Lindbohm et al. [1991a]	Watchmakers	1.5	0.8–2.7
	Textile machine setters/operators	1.2	0.8–1.9
	Textile finishers and dryers	1.3	0.8–2.4
	Mutagens (high exposure)	1.0	0.9–1.2
	Mutagens (low exposure)	1.0	0.9–1.0

*Range of risk ratios across normal/abnormal karyotype, public/private clinic.

in the detail that would be desired. Nonetheless, some suggestions emerge from the literature regarding specific agents that are worthy of further evaluation. Given the imprecision in exposure assessment which plagues most of this literature, the ability of negative studies to persuasively exonerate agents is quite limited.

A summary of the evidence for several agents of particular interest is provided in Table IX. The recent studies suggesting positive associations of occupational exposure to metals (mercury and lead) to spontaneous abortion [Alcser et al., 1989; Lindbohm et al., 1991b; Cordier et al., 1991] are of potential importance, especially given the evidence that lead [Lancranjan et al., 1975] and mercury [Lee and Dixon, 1975] may be disruptive to spermatogenesis. Although these agents are not thought to be mutagenic, developmental alterations through other processes such as epigenetic mechanisms may be involved. Mercury, in particular, has been found to be associated with increased risk in two high-quality studies.

Solvents would be among the agents of greatest interest based on their wide-

TABLE IX. Summary of Strength of Evidence Linking Selected Paternal Exposures to Spontaneous Abortion

Agent	Elevated RR in >1 Study	RR>1.5	Evidence from high quality studies	Overall
Lead	No	Yes	Yes	Moderate
Mercury	Yes	Yes	Yes	Strong
Solvents	Yes	Yes	Mixed	Moderate
Anesthetic gases	Yes	Yes	Mixed	Strong
Pesticides	Yes	Yes	No	Weak
Phenoxy herbicides	Yes	Yes	No	Weak
Ionizing radiation	No	No	No	Very weak
Hydrocarbons	No	No	No	Very weak

spread use and potential for mutagenicity, and there are sporadic indications of increased risk associated with such exposures in the rubber and petrochemical industries. However, there has been little or no replication of the positive associations reported by Infante et al. [1976] for vinyl chloride. Sanotskii [1976] for chloroprene, or Taskinen et al. [1989] for a number of different solvents used in specific industrial settings. Known adverse effects of these agents have resulted in reductions in exposure, so that replication is not feasible.

Anesthetic gases have long been of interest as reproductive hazards given the link between exposure during pregnancy and risk of spontaneous abortion [Tannenbaum and Goldberg, 1985]. Studies of dentists and other health care workers consistently suggest an association between male exposure and spontaneous abortion, but these are all based on mail surveys and many are from the same investigators. Refinements in exposure and outcome assessment are needed in future studies, but the reduction in anesthetic gas exposures in most settings may limit the informativeness of such efforts.

Pesticides, especially Agent Orange, have been the focus of much effort but there are at most sporadic indications of positive associations. The diversity of agents and exposure circumstances that have been studied makes it particularly difficult to identify comparable studies, but there are few observations suggestive of an adverse effect of paternal pesticide exposure. Unless some means of overcoming the formidable challenges of exposure assessment can be identified (e.g, biological monitoring), additional simplistic efforts hold little promise. Exposure to Agent Orange, in particular, has been difficult to evaluate [Boyle et al., 1989; Lilienfeld and Gallo, 1989].

Ionizing radiation and hydrocarbons have produced limited support for an association with spontaneous abortion. However, the theoretical basis for interest in these highly mutagenic agents to which many people are exposed is strong enough to warrant further study, in spite of the limited epidemiologic support. Ionizing radiation, in particular, may be amenable to studies that take advantage of the unique individual monitoring programs of large numbers of workers in place at many industries.

Methodological Issues

The difficulties in conducting studies of paternal exposure and spontaneous abortion are substantial, including the challenge of isolating a paternal exposure from maternal influences, determining whether an association reflects indirect exposure to the mother rather than a direct sperm-mediated process, heterogeneity in the causes

of spontaneous abortion, and the difficulty of accurately measuring the occurrence of spontaneous abortion.

Assessment of spontaneous abortion, regardless of the exposure of interest, is challenging. Reports of clinically recognized spontaneous abortions are known to incompletely reflect the total number of conceptions that are lost [Wilcox et al., 1988]. Although valid results may still be obtained for the category of "clinically recognized spontaneous abortions," at the early gestational ages at which recognition is ambiguous the reporting may be both incomplete [Wilcox and Horney, 1984] and biased in relation to exposure status. The limited public perception of a paternal role in the etiology of spontaneous abortion makes differential reporting by exposure status somewhat less likely than for such highly publicized maternal exposures as anesthetic gases or use of video display terminals.

Males are known to be particularly unreliable informants regarding reproductive history [Selevan, 1985]. Regarding spontaneous abortions, it is not only more likely that men would forget their wife's experience but even possible that they would be unaware that an early spontaneous abortion had occurred at all. Studies should routinely seek reproductive outcome information from the woman, whenever possible, contending with the logistical difficulties that can arise in locating and interviewing spouses no longer living with the male worker of interest. Research in which both the male (for exposure information) and female (for reproductive outcome information) are interviewed is needed in spite of the additional costs.

Perhaps the most critical issue with regard to identification and classification of spontaneous abortions is the heterogeneity in the causes of spontaneous abortion. Isolation of the subset of all spontaneous abortions that are plausibly attributable to the paternal genome would markedly strengthen any true etiologic associations. One approach that has been taken in epidemiologic studies is to distinguish chromosomally normal and abnormal abortuses based on karyotyping the conceptus [Kline et al., 1989]. Some karyotypic abnormalities are attributable to the father, whereas others are clearly contributed by the mother, such that identification of the paternally derived subset of karyotypically abnormal abortuses could, in theory, be made. In practice, however, the logistical challenges of even obtaining information on the karyotype of the abortus are daunting, and the additional requirement to identify the source of the abnormality poses an additional challenge.

For karyotypically normal abortuses, a potential role for paternal factors cannot be discounted, in that there may still be genetic determinants that do not act at the chromosomal level. It may be possible to identify more simplistic indicators of spontaneous abortions most likely to be influenced by paternal exposures by stratifying cases on gestational age to determine whether early or later losses are more affected, or to restrict the analysis to mothers at low risk (young mothers, nonsmokers, etc.). Clinical and laboratory studies aimed at identifying the determining parental origin of spontaneous abortion would dramatically accelerate the development of this literature.

Until recently, exposure classification has been rather poor, often based on the wife's report of her husband's job title or the male's employment in a broad industrial category. The limitations inherent in a job title as a marker of exposure are well known [Siemiatycki, 1991], with imperfect sensitivity and specificity as an indicator of actual exposure to any particular agent. The design of these studies would generally lead to a prediction of nondifferential misclassification, i.e., the uncertainty in

going from a job title to an exposure assignment would be similar for men who had fathered conceptions resulting in spontaneous abortion as in those who had fathered conceptions resulting in live born children. Under those circumstances, the resulting risk estimates are diluted, understating the magnitude of any etiologic association [Copeland et al., 1977]. This is the principal reason that "negative" studies should not be viewed as persuasive evidence that the agents of interest do not produce increased risks. Instead, it would be safe to infer that the job categories do not have a widespread, extremely strong adverse influence on spontaneous abortion.

Confounding is always a concern, with speculation limited only by the limited knowledge of risk factors for spontaneous abortion. Paternal occupation is undoubtedly correlated with such lifestyle factors as smoking [Sterling and Weinkam, 1976; Siemiatycki et al., 1988], yet there is little evidence to suggest that paternal lifestyle factors such as smoking [Beckman and Nordstrom, 1982; Taskinen et al., 1989] or alcohol use [Halmesmaki et al., 1989; Parazzini et al., 1990] influence risk of spontaneous abortion. Confounding by other workplace agents is always possible, given that jobs with an environmental hazard rarely involve only one such agent. At present, however, with no paternal exposure that constitutes a proven etiologic agent, such concerns are highly speculative. Even among maternal factors, the only proven determinants are history of spontaneous abortion (which may reflect persistent exposure or inherent characteristics of the woman), advanced maternal age, and possibly cigarette smoking or alcohol use [Kline et al., 1989]. Since paternal occupation is a determinant of social class, and social class is closely related to maternal smoking during pregnancy [Williamson et al., 1989], maternal smoking should be considered as a potential confounding factor, yet only about half of the studies we reviewed did so (Appendix table).

A number of study design issues need to be considered in evaluating this literature and making recommendations for future research. Some studies have compared preemployment and postemployment outcomes in the same individuals [Townsend et al., 1982; Restrepo et al., 1990]. Although such a design offers the advantage of controlling for any intrinsic factors to the couple, the potential for confounding by maternal and paternal age is substantial.

Induced abortions have the potential for biasing comparisons of spontaneous abortion risks in comparisons of populations with differing induced abortion occurrence. Specifically, induced abortions remove pregnancies from being at risk of spontaneous abortion, and failure to consider them as "pregnancies at risk" artificially inflates the risk of spontaneous abortions relative to what would be found in a life table analysis [Olsen, 1984]. Alternatively, if induced abortions are counted as pregnancies at risk without noting that they ended prior to the end of the risk period for spontaneous abortion, the risk of spontaneous abortion will be artificially reduced relative to what would be found in a life table analysis [Modvig et al., 1990]. The ideal approach is to determine precise timing of all induced and spontaneous abortions and to conduct an analysis of spontaneous abortion incidence by week of gestation. However, the accuracy of reported induced abortions (especially by males) and the precision of the timing of induced and spontaneous abortions makes this strategy difficult to implement in practice.

The size and resulting statistical power of these studies should also be considered. Starting with a large work force, the number of informative events (pregnancies among spouses) is limited by the proportion of men who are married and have

reproductive experiences in the time period of employment, often resulting in highly imprecise risk estimates. Many of the most interesting groups, for example, workers exposed to DBCP, are too small to generate reliable risk estimates.

Accepting the inherent constraints in addressing the topic of paternal exposure and spontaneous abortion, there are a number of opportunities for advancing knowledge through improved study methods. Opportunistic studies in which paternal exposures are included in studies focused on other issues (e.g., maternal exposures) can still add valuable information. In the context of a well-designed study of spontaneous abortion (including registry-based studies), addition of a modest series of questions about the father's exposures to potentially harmful agents through habits (tobacco, alcohol, illicit drugs), at home (hobbies, home repairs), and at work (querying work activities and locations as well as specific agents) would be contributory. A more ambitious step would be the detailed ascertainment of occupational exposure histories as developed by Siemiatycki and colleagues for a community-based study of occupational carcinogens [Siemiatycki, 1991]. Their two-stage approach involves an initial interview followed by an interview with an industrial hygienist focusing in detail on activities and agents associated with the individual's work setting.

In addition to opportunistic studies, sufficient evidence has accrued to justify development of targeted studies of paternal exposures. Populations of men with potentially harmful exposures could be studied in retrospective cohort designs with attention to accurate classification of exposure presence and timing based on industry-specific job-exposure matrices. In addition to industrial exposures, men exposed to medications or men with identified sperm characteristics could be studied to assess the reproductive outcomes in their spouses. Carefully designed case-control studies in the community could obtain data on lifestyle factors as well as retrospective reports of occupational exposures.

In parallel with the evolving epidemiologic evidence, the need for additional laboratory studies should be emphasized. Insofar as the toxicologists can pinpoint exposures or suggest subsets of paternally derived spontaneous abortions, the epidemiologic literature would benefit markedly. In the absence of a clearly demonstrated example of paternally caused spontaneous abortions in humans, skepticism about the potential for this process to operate will remain. However, the absence of such clear-cut evidence is not a result of a series of carefully designed negative studies. In contrast, the present literature consists of studies of improving quality that contain a number of suggestively positive results. In combination with laboratory evidence and public concern, this research avenue deserves to be pursued to evaluate thoroughly the possibility that paternal exposures constitute an important, preventable cause of spontaneous abortions.

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APPENDIX. Paternal Occupational Exposure and Spontaneous Abortion: Study Type, Confounders, Case Definitions

Reference	Study location	Study type	Confounders addressed	Miscarriage case definition	Baseline risk of spontaneous abortion (%)
Cohen et al. [1974]	United States	Retrospective cohort	Maternal age, smoking	GA[a] <20 weeks	12.5
Bour et al. [1975]	France	Cross-sectional	None	GA <12 weeks and abnormal karyotype	NA[c]
Cohen et al. [1975]	United States	Retrospective cohort	Maternal age, smoking, pregnancy history	GA <20 weeks	9.0
Knill-Jones et al. [1975]	United Kingdom	Retrospective cohort	Maternal age, smoking, birth order; paternal age	Mean GA ± 1.1 weeks (excludes stillbirths)	10.9
Infanic et al. [1976]	United States	Retrospective cohort	Previous SAb[b], paternal age	SAbs and stillbirths	8.8
Sanotskii [1976]	Soviet Union	Retrospective cohort	NA[c]	NA	NA
Rosenberg & Vantinen [1978]	Finland	Retrospective cohort	Maternal age	Clinically recognized	13.2
Tomlin [1979]	United Kingdom	Retrospective cohort	None	NA	9.8
Cohen et al. [1980]	United States	Retrospective cohort	Maternal age, smoking, previous SAb	GA <20 weeks	6.7
Khassazi et al. [1980]	Israel	Retrospective cohort	Maternal age	NA	6.6
Caunelli et al. [1981]	United States	Nested case control	Maternal age, cigarette, marijuana smoke, paternal age, education, occupation marital status, previous SAb	Excludes stillbirths heavy, late periods	11.6[d]
Lauwerys et al. [1981]	Belgium	Retrospective cohort	Smoking, drug consumption	Excludes stillbirths	6.1
Beckman & Nordstrom [1982]	Sweden	Retrospective cohort	Maternal age, smoking, occupation, gravidity, paternal age, alcohol	Excludes stillbirths	7.2
Hamill et al. [1982]	United States	Retrospective cohort	Paternal alcohol, smoking, race, marital status	Couples with history of SAb	11.5
Kline et al. [1982]	United States	Case control	Maternal age, previous SAb, alcohol, smoking, paternal unemployment, ethnicity, public/private care	GA <28 weeks with known karyotype	NA
Smith et al. [1982]	New Zealand	Retrospective cohort	Maternal age, smoking, ethnicity	Excludes stillbirths	10.0
Townsend et al. [1982]	United States	Retrospective cohort	Maternal age, birth control method, motivation during pregnancy, smoking, alcohol	GA <20 weeks	11.9
Can et al. [1983][e]	Vietnam	Retrospective cohort	None	Excludes stillbirths	5.9
Hemminki et al. [1983]	Finland	Retrospective cohort	Season, maternal occupation	Hospitalized SAbs GA <28 weeks	9.8
Nordstrom et al. [1983]	Sweden	Retrospective cohort	Maternal age, smoking, alcohol, medications, gravidity, chemical exposures	Excludes stillbirths	9.5
Lindbohm et al. [1984]	Finland	Retrospective cohort	Maternal age, place of residence, parity, marital status	Hospitalized SAbs GA <28 weeks	7.2

Morgen et al. [1984]	United States	Retrospective cohort	Maternal race, age, education, smoking, alcohol	SAbs and stillbirths	8.3
Rhatt et al. [1984]	United States	Retrospective cohort	Maternal age, paternal age, education	SAbs and stillbirths	8.2
Savitz et al. [1984]	United States	Retrospective cohort	Maternal age, paternal age, race, marital status	SAbs and stillbirths	9.2
Susland & Hertzberg [1984]	United States	Retrospective cohort	None	Excludes stillbirths	11.9
Brudsky et al. [1985]	United States	Retrospective cohort	Maternal age, smoking	GA <20 weeks	8.3
Daniell & Vaughan [1988]	United States	Retrospective cohort	Maternal age, marital status, employment status, census tract, median income, gravidity, previous SAbs, time since last pregnancy, paternal age	Prior losses noted on birth certificate	11.6
Stellman et al. [1988]	United States	Retrospective cohort	Maternal age, smoking, paternal age, combat exposure	Excludes stillbirths	5.8
CDC [1989]	United States	Retrospective cohort	Paternal age, race, enlistment status, education, military specialty, smoking, alcohol, drug use, marital status	Excludes stillbirths	8.7
Alesci et al. [1989]	United States	Retrospective cohort	Maternal age, smoking, alcohol use, employment, previous SAb, education, paternal age	SAbs and stillbirths	9.3
Axelsengrau & Maisonet [1989]	United States	Case control	Maternal age, race, employment, smoking, parity, prior pregnancy losses, prenatal source, paternal age, race, education, birthplace	GA <28 weeks	NA
McDonald et al. [1989]	Canada	Retrospective cohort	Maternal age, gravidity, previous SAb, ethnicity, education, smoking, occupation, alcohol	GA <28 weeks	10.4[e]
Tuchmen et al. [1989]	Finland	Nested case control	Maternal age, date of conception	Clinically recognized (GA = 6–28 weeks)	8.8
Gueguis et al. [1990]	Ontario, Canada	Retrospective cohort	Maternal age, smoking, birth order, previous SAb	GA <20 weeks	5.1
Restrepo et al. [1990]	Colombia	Retrospective cohort	None	GA <20 weeks	1.9
Cordier et al. [1991]	France	Retrospective cohort	Maternal age, gravidity, smoking, alcohol, paternal age, length of recall	GA <28 weeks	9.6
Lindbohm et al. [1991a]	Finland	Retrospective cohort	Maternal age, socioeconomic status, occupational hazards	Clinically recognized	8.9
Lindbohm et al. [1991b]	Finland	Nested case control	Maternal age, smoking, febrile diseases, paternal age, smoking, previous SAb	Clinically recognized	NA
Rupa et al. [1991]	India	Retrospective cohort	Paternal alcohol, smoking, drug use, nutritional status, toxic exposures	GA <20 weeks	11.4

[a]Gestational age.
[b]Spontaneous abortion.
[c]Not available.
[d]Includes exposed population.
[e]Cited in Sterling and Arundel [1986].
[f]Cited in McDonald et al. [1987].