Paternal Organic Solvent Exposure and Adverse Pregnancy Outcomes: A Meta-Analysis

J. Floris S. Logman, Drs.,[1] Laurens E. de Vries, Drs.,[1] Michiel E.H. Hemels, Drs., MSc,[2,3] Sohail Khattak, MD, FRCP(C),[3,4,5] and Thomas R. Einarson, PhD[3,6]*

Background *Organic solvents are widely used, but conflicting reports exist concerning paternal exposure and adverse pregnancy outcomes. We conducted a meta-analysis to assess the risks of spontaneous abortions (SAs) and major malformations (MMs) after paternal exposure to organic solvents.*

Methods *Medline, Toxline, Reprotox, and Embase from 1966 to 2003 were searched. Two independent reviewers searched for cohort and case-control studies in any language on adult human males exposed chronically to any organic solvent. Two non-blinded independent extractors used a standardized form for data extraction; disagreements were resolved through consensus discussion.*

Results *Forty-seven studies were identified; 32 exclusions left 14 useable studies. Overall random effects odds ratios and 95% confidence intervals ($CI_{95\%}$) were 1.30 ($CI_{95\%}$: 0.81–2.11, N = 1,248) for SA, 1.47 ($CI_{95\%}$: 1.18–1.83, N = 384,762) for MMs, 1.86 ($CI_{95\%}$: 1.40–2.46, N = 180,242) for any neural tube defect, 2.18 ($CI_{95\%}$: 1.52–3.11, N = 107,761) for anencephaly, and 1.59 ($CI_{95\%}$: 0.99–2.56, N = 96,517; power = 56.3%) for spina bifida.*

Conclusions *Paternal exposure to organic solvents is associated with an increased risk for neural tube defects but not SAs.* Am. J. Ind. Med. 47:37–44, 2005. © *2004 Wiley-Liss, Inc.*

KEY WORDS: paternal exposure; organic solvent; adverse pregnancy outcome; spontaneous abortion; major malformations; meta-analysis

INTRODUCTION

Organic solvents are volatile liquids that belong to a structurally diverse group of chemicals having a low molecular weight and dissolve other organic substances such as lipids and high molecular weight compounds. Presently, they are being widely used in both the work and home environment. Usually, incidental exposure can take place around the house, while extensive exposure mostly occurs in the workplace. The use of organic solvents is widespread; they are utilized in a variety of occupations such as painting, dry-cleaning, printing, and various jobs within the chemical industry. Thus, many employees are exposed extensively to organic solvents.

Substantial research has been done into the relationship between maternal exposure to organic solvents and spontaneous abortion (SA) or other adverse pregnancy outcomes such as major malformations (MMs). These compounds have been shown to increase the risk of MMs significantly (ORs = 1.64, $CI_{95\%}$: 1.16–2.30, N = 7,036) [McMartin et al., 1998].

Several studies have indicated that paternal exposure to organic solvents may be associated with an increased risk of

[1]Faculty of Pharmaceutical Sciences, University of Utrecht, Utrecht, The Netherlands
[2]Faculty of Pharmacology, University of Toronto, Ontario, Canada
[3]Hospital for Sick Children, Toronto, Ontario, Canada
[4]Faculty of Medicine, University of Toronto, Ontario, Canada
[5]The Kids Clinic, Whitby, Ontario, Canada
[6]Faculty of Pharmacy, University of Toronto, Ontario, Canada
Contract grant sponsor: The Kids Clinic, Whitby, ON, Canada.
*Correspondence to: Thomas R. Einarson, Faculty of Pharmacy, University of Toronto, 19 Russell Street, Toronto, ON M5S 2S2, Canada. E-mail: t.einarson@utoronto.ca

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SA or MMs [Taskinen et al., 1989; Brender and Suarez, 1990; Blatter and Roeleveld, 1996; Blatter et al., 1997; Irgens et al., 2000]. Results of individual studies differ considerably [Daniell and Vaughan, 1988; Taskinen et al., 1989; Lindbohm et al., 1991] and the actual risk remains uncertain.

One possible mechanism associated with adverse pregnancy outcomes due to paternal exposure to organic solvents is a direct effect on sperm DNA, producing mutations or chromosomal abnormalities. Alternately, there could be indirect effects by transmission of agents to the mother via the seminal fluid, and maternal exposure to agents brought home by the father [Olshan et al., 1991].

Organic solvents are comprised of many different chemical compounds or classes of compounds. Because exposure usually involves more than one chemical class or agent and may occur under a wide variety of circumstances, human epidemiologic studies must be interpreted with care. However, if the above results [Taskinen et al., 1989; Brender and Suarez, 1990; Schnitzer et al., 1995; Blatter and Roeleveld, 1996; Blatter et al., 1997; Irgens et al., 2000] are valid, then preventive measures should be taken to avoid exposures to organic solvents, by both males as well as females.

We present a meta-analysis to summarize the impact of paternal exposure to organic solvents with respect to several important pregnancy outcomes including SA and MMs.

METHODS

The population of interest was adult human males who had been exposed occupationally to organic solvents and who subsequently fathered children. We adopted the definition of organic solvents that was previously used by McMartin et al. [1998]. Included were aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons, aliphatic alcohols, glycols, glycol ethers, and their derivatives. The pregnancy outcomes of interest included SA, MMs in general, and specific malformations [i.e., neural tube defects (as a group, all types combined), spina bifida, and anencephaly] as described by the International Codes for Diagnosis, revision 9 (ICD 9) or equivalent. We accepted all original research articles using either a case control or cohort study design.

The inclusion criteria consisted of: adult human male population; adequate pre- or peri-conceptional paternal exposure to organic solvents; non-exposed comparison group; outcomes of interest included, but were not restricted to SA in partner or MM in child of exposed male; and cohort or case-control study design. To assure that men had adequate exposure, we included only data from men who had been ''moderately'' or ''highly'' exposed when such a distinction was made. We excluded articles if they dealt with: genetic birth defects, maternal exposures only, other known parental (both father or mother) exposures to teratogenic agents, or differences between groups in parental exposure to other risk factors (e.g., smoking).

A literature search was performed on Medline (1966–August 2004), Toxline (1960–2004), Reprotox (as of update 1, 2003), Healthstar (until July 2004), and Embase (1980–August 2004) using the key words: chemical, occupational exposure, organic solvent, paternal exposure, pregnancy outcome, MM, SA, miscarriage, adverse fetal outcome, congenital abnormality, birth defect, and teratogen. We also contacted colleagues specializing in reproductive toxicology to find any other articles on the subject. In addition, we searched all the references from the retrieved articles and reviews of the topic.

The retrieved articles were presented to two non-blinded independent reviewers for selection into the analysis using these criteria. For article selection, we calculated kappa, [Fleiss, 1981], between those judges. Discrepancies were adjudicated through consensus discussion.

From the accepted articles, a data extractor identified number of men in exposed and non-exposed groups and the number of outcomes (i.e., SA, MM) in each group. Data were extracted and entered into 2×2 tables, then verified by a second independent reviewer. Disagreements were adjudicated by a third person, whose decision was considered final.

Quality was assessed using a checklist that incorporated standard items, such as research design, subjects, analysis, confounders and bias, methods and results, previously validated by Elwood [1988], and by Lichtenstein et al. [1986]. We added questions concerning duration, quantity, time of measurement, and verification of the exposures, which were crucial for this investigation. There were 34 items for case control studies and 32 for cohort studies, with each of the items being weighted equally. To verify inter-rater reliability on application of the scale, we calculated kappa, [Fleiss, 1981], within each study and across all studies.

Cohort and case-control studies were analyzed separately as sub analyses. For cohort studies, a summary risk ratio (RRs) was calculated using a random effects model, according to the recommendations of Zhang and Yu [2002]. For each of the case-control studies, we calculated ORs along with a $CI_{95\%}$. Homogeneity among effects was tested by calculating χ^2, and publication bias was examined using a funnel plot. In the case of significant heterogeneity (i.e., $P < 0.05$), studies responsible for the heterogeneity would be identified and examined for differences. A funnel plot is a scatterplot of sample size on one axis against the corresponding outcome of the other axis. Data should be equally distributed around the average value for the outcome, with smaller studies showing a wider spread and larger studies a more narrow spread (hence, the funnel shape). Bias is detected visually by the absence of small (usually negative) studies [Egger et al., 1997].

RESULTS

The literature search yielded 52 studies of which, 38 were excluded for a variety of reasons. Twelve were reviews from which the references were checked [Haas and Schottenfeld, 1979; Taskinen, 1990; Lindbohm et al., 1992; Legator and Harper, 1993; Savitz, 1994; Savitz et al., 1994; Lindbohm, 1995; Friedler, 1996; Wyszynski and Beaty, 1996; Figa-Talamanca et al., 2001; Anderson, 2003; Chapin et al., 2004], 11 did not investigate an exposure of interest; four dealt with pesticides [Goldsmith et al., 1984; Savitz et al., 1997; Garcia et al., 1998; Regidor et al., 2004], two dealt with welding [Bonde et al., 1992; Hjollund et al., 1995], two dealt with maternal exposure [Windham et al., 1991; Ford et al., 1994], one dealt with a smelter, and two dealt with occupations, which did not use organic solvents [Hemminki et al., 1980; Beckman and Nordstrom, 1982; Norgard et al., 2004]. Eight did not deal with pregnancy as the outcome of interest [Sanotskii, 1976; Daniell and Vaughan, 1988; Savitz et al., 1989; Sanjose et al., 1991; Kristensen et al., 1993; Sallmen et al., 1997; GuoBing et al., 2001; McKinney et al., 2003], one had an exposed control group [Schnitzer et al., 1995], and we were unable to extract data from four [Infante et al., 1976; Olsen, 1984; McDonald et al., 1989; Olshan and Schnitzer, 1994]. Two studies [Blatter et al., 1995, 1997] were excluded as duplicates. Thus, there were 14 studies that we used in the final analysis (Table I). The unadjusted rate of agreement between the two judges on article selection was 87%. After adjustment for chance, kappa was large at 0.72 (SE = 0.15, $P < 0.001$).

In the process of scoring article quality, we first calculated kappa between the two raters. For case control studies, 34 items were assessed and there were 32 for cohort studies. Kappas for the 14 studies ranged from 0.41 to 0.82 (mean = 0.60), and all were statistically significant ($P \leq 0.017$). Across all studies for all ratings, kappa was 0.63 ($CI_{95\%}$: 0.54–0.72).

The individual quality scores after consensus are listed as a percentage of the maximum possible score (Table I). Individual scores ranged from 41% to 88% (Mean = 65%, SD = 14%, median = 63%). One article scored below 50%, and five were awarded >70%, indicating that quality was considered sufficient for our purposes. All the studies with the highest sample sizes assessed their exposures by means of occupational codes. Therefore, these studies had low quality scores.

Men working in a variety of occupations in which they were exposed on a daily basis to organic solvents were

TABLE I. Published Studies Examining the Relationship Between Paternal Organic Solvent Exposure and Adverse Pregnancy Outcomes

	Author	Country	Study type	Sample size	Exposure assessment	Quality score
SA	Correa et al., 1996	USA	Co	589	TI, PR	81%
	Eskenazi et al., 1991	USA	Co	35	TI	63%
	Hoglund et al., 1992	Sweden	CC	218	QE	56%
	Lindbohm et al., 1991[a]	Finland	CC	16,619	NC (NCO/ISCO)	56%
	Lindbohm et al., 1984[a]	Finland	Co	1,316	NC (NCO/ISCO)	63%
	Savitz et al., 1996	USA	CC	146	TI	76%
	Stucker et al., 1994[a]	France	Co	1,354	AM, QE	81%
	Taskinen et al., 1998	Finland	CC	317	QE	88%
MM	Blatter and Roeleveld, 1996	Sweden	CC	145	NC/MBR (NCO)	79%
	Blatter et al., 1997	Holland	CC	986	TI	65%
	Brender and Suarez, 1990	USA	CC	1,871	BC (BCCIIO)	59%
	Fedrick, 1976	UK	Co	37,447	BC (RG)	41%
	Irgens et al., 2000	Norway	Co	16,766	NC (NOC)	50%
	Olshan et al., 1991[a]	Canada	CC	871	BC (COCM/SICM)	56%
	Taskinen et al., 1998	Finland	CC	121	QE	88%

SA, spontaneous abortion; MM, major malformation; CC, case control; Co, cohort; TI, telephone interview; QE, questionnaire; PR, plant records; AM, atmospheric measurement; NC, national census; MBR, medical birth register; BC, birth certificate; NCO, Nordic Classification of Occupations; ISCO, International Standard Classification of Occupations; BCCIIO, Bureau of the Census Classified Index of Industries and Occupations; RG, Register General; COCM, Canadian Occupational Classification Manual; SICM, Standard Industrial Classification Manual.

[a]Studies from which 2 × 2 tables could not be extracted.

examined in the 14 studies. Included were painters, spray painters, papermakers, and workers in the printing, dry-cleaning, plastic/rubber, petro-chemical, wood, and textile industries. Some studies identified precisely which chemicals they examined [Savitz et al., 1989; Taskinen et al., 1989; Lindbohm et al., 1991]. Specific compounds mentioned were aromatic hydrocarbons, toluene, styrene, xylene, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, diethylglycol, and benzene.

Spontaneous Abortion

We identified eight studies that investigated SA, and were able to extract data for 2×2 tables from five of them [Eskenazi et al., 1991; Hoglund et al., 1992; Correa et al., 1996; Savitz et al., 1996; Taskinen et al., 1998] (Table II). Three other studies [Lindbohm et al., 1984, 1991; Stucker et al., 1994] provided ORs that were adjusted for multiple factors using logistic regression. The ORs between paternal solvent exposure and SA was small and not significant, suggesting there was no relationship.

Two of these studies [Eskenazi et al., 1991; Savitz et al., 1996] had minor problems with their data. In the former, there was a somewhat unclear description of their approach to exposure assessment. In Eskenazi et al., exact numbers were not presented, therefore, we were required to perform our own calculations. We evaluated whether the absence of these two articles had any effect on the results (sensitivity analyses). When either article and when both the studies were removed, the ORs remained small and non-significant. These sensitivity analyses confirm the suggestion of no association.

The assessment of exposure in the eight articles was challenging. Three studies [Hoglund et al., 1992; Correa et al., 1996; Taskinen et al., 1998] confirmed high and moderate/high exposure to organic solvents. The risk for SA was not significantly increased in either exposure assessment.

The funnel plot (not presented) displayed no evidence of publication bias.

Fetal Malformations

We identified six studies of 384,726 patients that examined the relationship between paternal exposure to solvents and fetal malformations and from which 2×2 tables could be extracted (Table III). When combined these studies demonstrated a significant increase in risk; however, the malformations consisted of an array of very different anomalies.

The five studies (N = 180,242) that examined neural tube defects in general demonstrated an increased risk. Relationships from both cohort and case-control studies were statistically significant and quantitatively, were essentially the same (1.78 and 1.92, respectively). For spina bifida (N = 96,517) there was an increased risk, but the risk was not statistically significant. We also found a significant relationship overall between exposure and anencephaly. Both case-control and cohort studies produced significant results.

No studies provided combinable results for any other specific malformations.

TABLE II. Results of Meta-Analyses of the Relationship Between Paternal Exposure to Organic Solvents and Spontaneous Abortion (SA)

	Sample size		Outcome		Homogeneity	
Outcome	**Studies (arms)**	**Patients**	**ORs**	**$CI_{95\%}$**	**χ^2**	***P***
SA overall[a]	5 (5)	1,248	1.30	0.81–2.11	5.87	0.209
SA[b]	4 (4)	1,102	1.62	0.99–2.66	5.60	0.133
SA[c]	4 (4)	1,213	1.33	0.87–2.27	5.55	0.135
SA[d]	3 (3)	1,067	1.38	0.75–2.53	5.27	0.072
SA-Hi[e]	3 (3)	976	1.30	0.76–2.24	3.65	0.161
SA-MH[f]	3 (3)	1,012	1.48	0.88–2.49	3.55	0.170
SA CC[g]	3 (3)	738	1.29	0.54–3.06	5.34	0.069
SA Co[h]	2 (2)	513	0.88	0.51–1.52	0.05	0.829

[a]Overall results from all studies from which 2×2 tables could be extracted.
[b]Sensitivity analysis, excluding the study by Savitz et al. [1996].
[c]Sensitivity analysis, excluding the study by Eskenazi et al. [1991].
[d]Sensitivity analysis, excluding studies by Savitz et al. [1996] and Eskenazi et al. [1991].
[e]High exposure.
[f]Moderate or high exposure.
[g]All case-control studies on SA, from which 2×2 tables could be extracted.
[h]All cohort studies on SA, from which 2×2 tables could be extracted.

TABLE III. Results of Meta-Analyses of the Relationship Between Paternal Exposure to Organic Solvents and Major Malformations

	Sample size		Outcome		Homogeneity	
Outcome	**Studies (arms)**	**Patients**	**ORs**	**$CI_{95\%}$**	**χ^2**	***P***
Any malformation[a]	6 (18)	384,726	1.47	1.18–1.83	18.81	0.339
Neural tube defects-all[b]	5 (10)	180,242	1.86	1.40–2.46	6.95	0.643
Neural tube defects-CC[c]	3 (6)	8,615	1.92	1.26–2.92	5.48	0.360
Neural tube defects-Co[d]	2 (4)	171,627	1.78	1.19–2.66	1.39	0.707
Spina bifida-all[e]	3 (3)	96,517	1.59	0.99–2.56	1.99	0.370
Spina bifida-CC[f]	2 (2)	1,131	1.35	0.65–2.81	1.17	0.280
Anencephaly-all[g]	3 (8)	107,761	2.18	1.52–3.11	4.44	0.728
Anencephaly-CC[h]	1 (4)	7,484	2.45	1.49–4.02	2.00	0.573
Anencephaly-Co[i]	2 (4)	100,277	1.93	1.15–3.21	2.02	0.569

[a]Overall results from all studies from which 2 × 2 tables could be extracted.
[b]Overall results from all studies on neural tube defects from which 2 × 2 tables could be extracted.
[c]All case-control studies on neural tube defects.
[d]All cohort studies on neural tube defects.
[e]Overall results from all studies on spina bifida from which 2 × 2 tables could be extracted.
[f]Overall results from all case-control studies on spina bifida from which 2 × 2 tables could be extracted.
[g]Overall results from all studies on anencephaly from which 2 × 2 tables could be extracted.
[h]Overall results from all case-control studies on anencephaly from which 2 × 2 tables could be extracted.
[i]Overall results from all cohort studies on anencephaly from which 2 × 2 tables could be extracted.

DISCUSSION

Despite the fact that we found significant relationships between paternal exposure to organic solvents and adverse pregnancy outcomes, conclusions should be interpreted with caution. *Organic solvents* is a broad term that comprises a variety of chemical substances. Consequently, all studies may not have examined the same chemical classes.

It is possible that studies, which use some form of interviewing (Table I) may have been subject to response bias and/or recall bias. Parents tend to search for an explanation to account for the adverse outcomes and are also more willing to respond to questioning [Werler et al., 2002]. Recall bias can occur because parents of children with adverse outcomes search for an explanation, while parents of healthy children have no such motivation.

Another major problem in these studies was the assessment of exposure to the organic solvents. In these types of epidemiologic studies, it is difficult to quantify the actual exposure, the duration, and timing. With these limitations, it is not always possible to ascertain that the risk is actually caused by the organic solvent exposure or is due to other (unmeasured) risk factors. It is also possible that there has been an underestimation of the risk. Fathers of healthy children may have been classified as exposed because of their occupational code, but in fact were not exposed. They would therefore have falsely increased the number in the exposed-control group, resulting in a lower OR.

The exposure assessment between the studies varied considerably. Some studies used only an occupational code, while others used questionnaires and sometimes conducted follow-up telephone interviews to confirm (Table I). Several different occupational codes, such as the Standard Industrial Classification Manual and the Nordic Occupational Classification, were used. These codes are based on common work activities and potential exposures, as determined by industrial hygienists, and not on the actual exposure status of the individual worker. Furthermore, men working in certain occupations, who are presumed to be exposed to organic solvents, could also be exposed occupationally to other possible problem-causing agents, for example, painters may be exposed to metals such as lead.

Secondly, some reports [Taskinen et al., 1989; Lindbohm et al., 1991; Stucker et al., 1994; Correa et al., 1996] separated exposure into high, moderate, and low while others did not. We used only exposures that were rated as high or moderate. However, the studies that differentiated between levels of exposure usually did so based on the opinion of an industrial hygienist, and not on actual measurements such as levels in workers' blood or in air samples of the workplace. Thus, the limitations of these studies should be taken into account when interpreting the findings.

Another weakness in these studies is the different information given about the mothers and their exposures to potential teratogens. Some studies actually verified whether the mothers were unexposed; one study presumed that they

were all non-exposed since they were housewives, and others did not address the topic. Furthermore, the information gathered on the mothers was also used in some studies to adjust for confounders such as maternal age, smoking, alcohol use, family history of NTDs, etc.

In addition, the time of exposure is also of interest because the complete cycle of sperm development takes 74 days in humans [Friedler, 1996]. As a result, conception must take place within this amount of time after exposure in order to be directly influenced by the organic solvent. Most studies did not give information about the specific time of exposures relative to conception. Presumably, exposure was more or less constant over time and was expected to have occurred during the critical period. Because organic solvents are lipophilic they could be stored in the body for a long period of time. Therefore, the period of the time in which the chemical compound could cause an adverse effect, would be prolonged, depending on the kinetics of the particular solvent.

Since the exact mechanism of paternal influence on adverse pregnancy outcomes is not yet known, future studies should provide information about the time of exposure and the time of conception. A better exposure assessment, by means of measurements rather than questioning, would also be indispensable for clarification of the issue.

The results for SA, which has a reported incidence of 12%–15% [Garcia-Enguidanos et al., 2002], demonstrate that there is not a statistically significant relationship with paternal exposure to organic solvents. In addition, we also examined the results from the studies we excluded because of our inability to extract 2×2 tables. Those three studies [Lindbohm et al., 1984, 1991; Stucker et al., 1994] contained 18 arms that examined different solvents and involved 19,289 persons. Of the 18 analyses, 6 had odds ratios greater than unity, while 12 were ≤ 1. The three studies used logistic regression to correct for confounders. They all adjusted for maternal age, but differed in adjusting for other variables. When the data were combined in a random effects model (using inverse variance weighting), the summary ORs was 1.10 ($CI_{95\%}$: 0.96–1.25). This result supports our main result that there is not a statistically significant relationship with paternal exposure to organic solvents.

The relationship between exposure and spina bifida by itself, which in 2000 occurred at a rate of 20.85 per 100,000 live births in the United States [Mathews, 2002], was not statistically significant. However, the OR of 1.59 had a lower limit of 0.99 and power of 56.3%. The study by Olshan et al. [1991], which was not included in these calculations also examined spina bifida ($N = 871$). All four of the adjusted odds ratios were >1 (average 1.90), but non-significant. Therefore, the lack of statistical significance may be a result of inadequate sample size.

Nonetheless, we did find a significant increase in several other adverse pregnancy outcomes (i.e., neural tube defects in general and anencephaly associated with paternal exposure to organic solvents). In 2000, anencephaly had a reported rate of 9.40 per 100,000 live births in the United States, [Mathews, 2002]. Of interest, McMartin et al. [1998] produced similar findings (i.e., the same malformations with approximately the same odds ratios) in women exposed to organic solvents.

There has been controversy surrounding paternal exposure to organic solvents. Conflicting reports in literature have suggested increased rates of SA, central nervous system, and other malformations. This meta-analysis confirms that occupational exposure to organic solvents in fathers is associated with increased risk of central nervous system malformations, in particular neural tube defects including anencephaly. Although the incidences of spina bifida failed to reach statistical significance, it is clear that poor methodological choices and sample size may have been contributing factors. Also it is important to note that neural tube defects according to the ICD-9 does include spina bifida. Therefore, it is reasonable to conclude that based on available literature paternal exposure can cause MMs, specifically neural tube defects.

This study clearly shows that until the exact relationship is determined, not only women, but also men who wish to have children should minimize their exposure to organic solvents in the 3 months (or longer, depending on the kinetics of the particular solvent) prior to the planned conception date.

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