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Assessed occupational exposure to chlorinated, aromatic and Stoddard solvents during pregnancy and risk of fetal growth restriction

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Abstract

Objectives—Previous experimental and epidemiological research suggests that maternal exposure to some organic solvents during pregnancy may increase the risk of fetal growth restriction (FGR). We evaluated the association between expert-assessed occupational solvent exposure and risk of small for gestational age (SGA) infants in a population-based sample of women in the National Birth Defects Prevention Study.

Methods—We analysed data from 2886 mothers and their infants born between 1997 and 2002. Job histories were self-reported. Probability of exposure to six chlorinated, three aromatic and one petroleum solvent was assessed by industrial hygienists. SGA was defined as birthweight<10th centile of birthweight-by-gestational age in a national reference. Logistic regression was used to estimate ORs and 95% CIs to assess the association between SGA and exposure to any solvent(s) or specific solvent classes, adjusting for maternal age and education.

Results—Approximately 8% of infants were SGA. Exposure prevalence to any solvent was 10% and 8% among mothers of SGA and non-SGA infants, respectively. Among women with ≥50% probability of exposure, we observed elevated but imprecise associations between SGA and

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exposure to any solvent(s) (1.71; 0.86 to 3.40), chlorinated solvents (1.70; 0.69 to 4.01) and aromatic solvents (1.87; 0.78 to 4.50).

Conclusions—This is the first population-based study in the USA to investigate the potential association between FGR and assessed maternal occupational exposure to distinct classes of organic solvents during pregnancy. The potential associations observed between SGA and exposure to chlorinated and aromatic solvents are based on small numbers and merit further investigation.

Introduction

Organic solvents are one of the most ubiquitous exposures in the workplace due to their extensive applications across varied industries. This group of volatile, carbon-based chemicals are frequently used to dissolve or disperse other chemicals into mixtures, and can be found in numerous occupational, household and personal use products such as paints, fuels, adhesives, inks, cosmetics, pharmaceuticals, cleaning solutions and pesticides.[1]

As the number of women of reproductive age in the workforce continues to grow in the USA and elsewhere, understanding the potential reproductive and perinatal effects of solvent exposure is important. Experimental research in animal models has demonstrated that many organic solvents cross the placental barrier and can be embryotoxic, genotoxic and teratogenic; some have been classified as probable reproductive hazards.[2] A number of recently published systematic reviews of environmental and occupational risk factors for reproductive outcomes indicate that in epidemiological studies, maternal solvent exposure during pregnancy has been inconsistently associated with various adverse outcomes among offspring, including fetal loss, reduced birthweight and birth defects.[3–7]

Fetal growth restriction (FGR), also called intrauterine growth restriction, is a condition in which a fetus does not achieve his or her genetically-determined growth potential in utero due to complicating factors such as placental pathology, maternal conditions during pregnancy, exogenous environmental insults or a combination thereof. Since FGR is often challenging to assess, surrogate measures of FGR at birth are frequently employed such as low birthweight (typically defined as birthweight <2500 g regardless of gestational age), term birthweight (≥37 weeks gestation) and small for gestational age (SGA), with SGA accounting for the expected distribution of weight for a given gestational week.[8] Despite differences in assessment, compromised fetal growth is a useful predictor of perinatal morbidity and mortality, as well as a potential risk factor for adverse health conditions later in life.[9]

Several epidemiological studies of varied designs have investigated the association between maternal solvent exposure during pregnancy and FGR in offspring; many, but not all, have reported modest associations for exposure to ‘any solvent’ or individually assessed solvents. Study populations have ranged from occupational cohorts, such as petrochemical[10,11] and laboratory[12,13] workers, to geographically localised communities impacted by soil and drinking water contamination.[14,15] Though five population-based studies of occupational solvent exposure and FGR have been conducted to date, [6–20] only one was conducted in the USA.[20] Owing to differences in industry practices and safety standards as well as local

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government regulations, occupational exposure profiles may differ significantly between populations with regard to prevalence of exposure to individual solvents as well as relevant parameters such as frequency and dose. Such differences in exposure profiles may explain, at least in part, what are often interpreted as 'inconsistent' results across studies of maternal solvent exposure and adverse perinatal outcomes. Synthesis of results across studies is further impeded by critical differences in exposure assessment strategies, ranging from exclusive reliance on self-reported use of solvents and solvent-containing products, to expert review and application of complex job-exposure matrices.

The objective of this study was to investigate the association between FGR and expert-rated occupational exposure to chlorinated, petroleum, and aromatic solvents in a population-based sample of women from eight US states.

Methods

Between 1997 and 2013, the US Centres for Disease Control and Prevention's National Centre for Birth Defects and Developmental Disabilities conducted the National Birth Defects Prevention Study (NBDPS), a large population-based case-control study exploring potential behavioural, clinical, environmental and genetic risk factors for major congenital malformations. Cases (live births, stillbirths and electively terminated fetuses with an eligible birth defect) and unmatched controls (non-malformed, live-born infants) were ascertained from the same geographical and temporal base population using standard study protocols across participating study centres.[21] Since NBDPS control participants are generally representative of their base population,[22] this group of mothers of non-malformed infants has been used to investigate the prevalence of exposures to a variety of risk factors for adverse pregnancy outcomes other than congenital anomalies.[23–25]

Study population

The study population for this analysis included mothers of NBDPS control infants with estimated dates of delivery ('due dates') between October 1997 and December 2002, and who resided in the study area in one of the following eight states: Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York and Texas. During this study period, three study centres randomly selected controls from hospital records by month and birth hospital, weighted by the number of births per hospital per year (CA, NY and TX); three centres randomly selected controls from electronic birth certificates by month weighted by the number of births per month per year (IA, MA and NJ); and two centres (AR and GA) switched from hospital to birth certificate selection beginning with January 2001 births. Following standardised procedures for recruitment and consent between 6 weeks and 24 months after delivery, mothers were asked to participate in an hour-long computer-assisted telephone interview. The structured interview collected information about a variety of demographic, behavioural, nutritional, clinical and environmental factors before and during pregnancy. Average time-to-interview after delivery among mothers of control infants during this study period was 8 months. At the time of the interview, potential participants were excluded if the mother did not speak English or Spanish, if she had previously

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participated in the NBDPS, if deceased, if incarcerated, if otherwise unable to answer the questions, if a donor or surrogate parent or if the infant was adopted or in foster care.

In this analysis, we included mothers of NBDPS control infants who participated in the telephone interview (68% of eligible women participated in the interview) and reported having at least one job anytime during pregnancy or the month before conception (73% of interviewed women reported employment). We excluded mothers with pregestational diabetes (n=20) as well as non-singleton pregnancies (n=97). Remaining were 2886 eligible mother–infant pairs. The NBDPS and this analysis were approved by the institutional review boards of the Centres for Disease Control and Prevention and all participating study centres.

Exposure characterisation

During the telephone interview, mothers were asked about employment during pregnancy and before conception. Employment was defined as compensated, volunteer or military service, including part-time work and work performed at home, for a duration of at least one consecutive month. Details of each reported job were recorded, including the employer, job title, primary tasks and duties, chemicals and machines handled on the job, dates of employment and hours and days worked per week. Jobs were then coded by occupation and industry according to the Standard Occupational Classification Manual (2000) and North American Industry Classification System (1997). Led by the National Institute for Occupational Safety and Health, a team of industrial hygienists (IH) and occupational epidemiologists developed era-specific (1997–1999; 2000–2002) and solvent-specific job-exposure databases to assess probability of occupational exposure to 10 organic solvents, including three aromatic solvents (benzene, xylene, toluene), six chlorinated solvents (carbon tetrachloride; chloroform; methylene chloride; perchloroethylene; trichloroethylene; 1,1,1-trichloroethane) and the petroleum-based mixture Stoddard solvent (also known as mineral spirits or white spirits). These highly detailed job-exposure databases were informed by an extensively reviewed collection of published reports that included direct measurements and determinants of exposure for various occupations and industries.[26–28]

Using the job-exposure databases as a reference, an IH then reviewed each job code and associated self-reported occupational information from the interview to determine an exposure classification for each solvent based on expected probability of exposure, defined as the likelihood that a specific job within an industry within the corresponding era had any exposure to the solvent of interest. For this analysis, we considered a mother-to-be *exposed* to a particular solvent if any of her jobs during pregnancy or the month before conception were classified as exposed (ie, exposure probability >0); she was considered *unexposed* to a particular solvent if all her jobs during this time were classified as unexposed to that solvent (ie, exposure probability=0).

Outcome classification

The primary approach taken in this study to assess FGR was to classify infants using the common surrogate measure for FGR, that is, SGA. We defined SGA as birthweight below the 10th centile for a given gestational age at delivery in weeks, using national standardised sex-specific and parity-specific birthweight curves for non-Hispanic black infants, non-

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Hispanic white infants, as well as infants of Hispanic ethnicity.[2930] Both maternal parity (defined as the number of previous live births) and race/ethnicity were self-reported during the NBDPS interview. Infant sex and gestational age were obtained from birth certificates or medical records. Infants less than 20 weeks or greater than 44 weeks (n=8) were excluded from further analyses, as these gestational ages are considered out of range of the reference birthweight curves. Also excluded from further analyses were participants missing values for infant sex (n=2), parity (n=1) or birthweight (n=15).

To capture a shift in the mean of the predominant distribution of birthweight that could be potentially associated with solvent exposure, we also examined birthweight as a continuous outcome (in grams). Analyses of birthweight were conducted among term infants only (≥37 weeks gestation) as an attempt to isolate growth-restricted infants from those born preterm for underlying causes other than FGR.

Statistical analysis

We first examined the distribution by SGA classification of the following maternal and infant characteristics of a priori interest based on known/suspected risk factors for FGR: maternal age at delivery, race/ethnicity, education, prepregnancy body mass index (BMI), tobacco and alcohol use, multivitamin intake, pregnancy intention, number of previous live births, gestational diabetes, infant sex and maternal residence at delivery (study centre).

We then examined the prevalence and patterns of estimated occupational exposure. Among women classified as exposed to any of the 10 assessed solvents, approximately 85% were assessed as exposed to more than one solvent. Previous exploration of within-person correlation in assigned exposure status among exposed mothers in this study population revealed that exposure status was highly correlated between individual solvents within solvent class.[31] For example, among women considered to have exposure to any of the six assessed chlorinated solvents, 98% of those exposed to methylene chloride were also considered exposed to 1,1,1-trichloroethane. Since the independent effect of exposure to an isolated solvent could not be evaluated, we estimated effects of maternal exposure(s) grouped by solvent class (chlorinated; petroleum (Stoddard solvent); aromatic) and reported the distribution of exposure classifications for each of the 10 assessed solvents.

We used unconditional logistic regression to estimate the association between SGA and maternal exposure to solvent classes anytime during the month before conception through the end of pregnancy. In these analyses, we present both unadjusted ORs with 95% CIs as well as ORs adjusted by maternal age (referent category 26–35 years) and education (referent category >12 years), which were the only two factors associated with both solvent exposure and SGA in our data (χ^2 p value<0.05). Linear regression was used to estimate the mean difference in term birthweight among infants of exposed mothers compared to infants of unexposed mothers. In all models, the unexposed group consisted of women who were considered unexposed to *all* solvents.

To assess the potential impact of exposure misclassification on our primary effect measure estimates (ie, ORs for the association between solvent exposure and SGA), we conducted a sensitivity analysis in which we restricted the study sample to include only women with a

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probability of exposure of at least 50%, as determined by the IH during the exposure assessment process.

Statistical analyses were performed using SAS V.9.3 (2014, SAS Institute Inc, Cary, North Carolina, USA) and were independently replicated (see Acknowledgments).

Results

After accounting for the aforementioned exclusion criteria, the final analysis set consisted of 2861 mother–infant pairs. Of these, 230 infants (80%) were classified as SGA. Table 1 summarises the distributions of maternal and infant factors by SGA classification: mothers of SGA infants were significantly different than mothers of non-SGA infants with regard to age at delivery, education, prepregnancy BMI and smoking during pregnancy. Distributions of maternal race/ethnicity and number of previous live births also varied.

The prevalence of estimated occupational exposure to organic solvents during the month before conception through the end of the pregnancy was 10.1% among mothers of SGA infants and 8.4% among mothers of non-SGA infants (table 2). Exposure prevalence varied between and within solvent classes. Regardless of SGA classification, the highest prevalence of exposure was to the group of chlorinated solvents (7.9% of SGA infants; 7.2% of non-SGA infants), whereas only 3% or fewer of the women were considered exposed to Stoddard or aromatic solvents. Within the solvent class, exposure prevalence to individual solvents varied considerably. For example, among women considered exposed to chlorinated solvents, most were considered exposed to methylene chloride and/or 1,1,1-trichloroethane (6.3% each among non-SGA infants), with few considered exposed to carbon tetrachloride (<1%).

Table 3 presents results for the logistic regression analyses of SGA. Among women with any probability of exposure during the month before conception or pregnancy, exposure to any solvent(s) was not associated with SGA (adjusted OR=1.16; 95% CI 0.73 to 1.83). When examining exposure effects by solvent class, we did not observe an association with SGA for chlorinated solvents (1.03; 0.62 to 1.71) nor Stoddard solvent (0.98; 0.44 to 2.18). However, we observed a modest but imprecise increase in the odds of SGA among infants whose mothers were exposed to aromatic solvents (1.60; 0.71 to 3.58). The association with aromatic solvents was driven by assessed exposure to toluene and/or xylene: approximately 3% of mothers of SGA-infants were considered exposed to toluene and/or xylene, compared to 2% of mothers of non-SGA infants. The proportion of mothers exposed to benzene was equal between groups (approximately 0.5%).

When restricting the study sample to only women with at least 50% probability of exposure (compared to women with no exposure to any solvent), the magnitude of the observed estimated effect estimates increased. Women with higher probability of exposure at work to any solvent (n=10) were 1.7 times more likely (95% CI 0.86 to 3.40) to deliver a growth-restricted infant compared to women with no probability of exposure, after adjusting for maternal age and education (table 3). Of the seven women with assessed exposure to Stoddard solvent, none had ≥50% probability of exposure. Six women (33.3%) had a higher

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probability of exposure to both chlorinated solvents and aromatic solvents. The estimated ORs for chlorinated solvents (1.70; 0.69 to 4.01) and aromatic solvents (1.87; 0.78 to 4.50) were both elevated but imprecise.

Maternal exposure to any solvent (or any solvent class) was not associated with a meaningful change in the distribution of term birthweight (table 4). The difference in mean birthweight at term after adjustment for maternal age and education between infants of mothers exposed to any solvent and infants of unexposed mothers was 16.1 g (95% CI −46.2 to 78.4).

Discussion

In our population-based study of nearly 3000 mother–infant pairs from eight US states, we did not consistently observe strong evidence of an association between assessed maternal occupational exposure to organic solvents in general (combining any exposure to the 10 solvents included in our occupational exposure assessment) during the peripregnancy period and FGR, defined as either SGA or change in mean birthweight at term. After adjusting for maternal age and education, the OR for any potential solvent exposure and SGA was 1.16 (0.73 to 1.83; 23 exposed cases). However, when restricting the exposed group to only women with a job(s) considered to have a higher probability of exposure (≥50%), the observed association between SGA and exposure to any solvent increased in magnitude to 1.71 (0.86 to 3.40; 10 exposed cases).

When considering any probability of exposure to each specific class of solvents (chlorinated; petroleum (Stoddard); aromatic), we observed a modest but imprecise increase in the odds of having an infant classified as SGA among women exposed to aromatic solvents in particular (1.60; 0.71 to 3.58). Among women with at least 50% probability of exposure to aromatic solvents, the OR increased to 1.87 (0.78 to 4.50). Similarly, for chlorinated solvents, the estimated OR increased from 1.03 (0.62 to 1.71) among women with any probability of exposure to 1.70 (0.69 to 4.01) among women with higher probability of exposure.

The observed association with aromatic solvents in our study population was driven specifically by assessed exposure to toluene and/or xylene. Posthoc analyses revealed that among the 58 women considered exposed to either toluene or xylene, all but one woman were considered exposed to both; estimating effects for exclusive exposure to either toluene or xylene was thus impossible. Both toluene and xylene have been linked in previous experimental and epidemiological studies with an increased risk of FGR and other adverse perinatal outcomes, particularly among pregnant women exposed to higher doses via recreational solvent abuse.[1332–35]

One of the first population-based investigations of maternal occupational solvent exposure as a potential risk factor for FGR was conducted in a small community in the San Jose area of California.[20] This cross-sectional study of 1000 births (1980–1985) assigned exposure status based on self-report and job title, and reported an OR for low birth weight (LBW; defined <2500 g) of 2.86 (95% CI 0.89 to 9.12) based on only three exposed cases; no effect

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for SGA was observed (OR not reported). During a similar time period (1987–1988), German investigators applied a job exposure matrix (JEM) to assess occupational solvent exposure in a cohort of approximately 3500 births originally assembled to investigate potential effects of the Chernobyl accident.[19] Probability, intensity and frequency of exposure were accounted for, and a modest increase in the odds of SGA was reported for low (1.3; 0.6 to 2.5) and moderate (2.2; 0.8 to 6.1) exposure (no women were considered to have 'high' exposure). SGA as well as LBW (defined as <3000 g) were later examined in a Finnish case–control study (1996–1997; approximately 1500 births) in relation to self-reported exposure to any solvents at work anytime during pregnancy or the 3 months before.[18] In this study, the unadjusted ORs for SGA and LBW were 1.72 (1.08 to 2.69) and 1.39 (0.87 to 2.13), respectively. As in our study, estimated effects reduced in magnitude after adjustment (SGA 1.67 (1.02 to 2.73); LBW 1.17 (0.71 to 1.93)), though the association between solvent exposure and SGA remained statistically significant. This less conservative definition of LBW (<3000 g) was then applied in a population-based cohort study in Rotterdam (2002–2006) in which exposure to 'industrial solvents and dry cleaning agents' was assessed for approximately 6000 pregnancies using a JEM and self-reported occupational histories obtained via interview; the OR for any solvent exposure and LBW was 1.21 (0.88 to 1.66).[17] Most recently, a large population-based cohort study in a small Russian municipality (1973–2005; approximately 26 000 births) used job title to assign exposure to organic solvents (exposed jobs included only 'painters, painter-plasterers, and spoolers') and reported a significant decrease in mean birthweight (−52.7 g; −85.1 to −20.5) as well as a significant increase in the odds of LBW (1.68; 1.18 to 2.41) among mothers employed in an 'exposed' occupation during pregnancy.[16]

Minimising exposure misclassification—both differential and non-differential—is a critical concern when using indirect methods for retrospective exposure assessment to investigate occupational exposures experienced during pregnancy. A major strength of our study is that exposure to 10 specific solvents was assessed for each job that a mother reported having performed during pregnancy by a team of IH with the aid of highly detailed era-specific and solvent-specific job-exposure databases developed specifically for this study population. This exposure assessment strategy is much more comprehensive than relying on job title alone, and is also less vulnerable to the recall error and potential bias associated with exposure assignment based strictly on self-reported exposure to solvents and solvent-containing products at work. Further, ours may be the first population-based study to investigate the potential effect on fetal growth of maternal occupational exposure to solvents grouped by chemical class; this is significant because solvent classes are known to often have unique toxicity profiles and also have different applications across occupations. Despite these advantages, our exposure assessment has limitations. We did not collect information about possible *non-occupational* exposure to solvents incurred via recreational activities, personal hobbies or environmental contamination. Further, our exposure classification for this analysis does not account for additional exposure parameters beyond probability of exposure, such as frequency and intensity of exposure, which could potentially modify the observed effects. Since our exposure and outcome are dichotomous, the expected effect of this limitation would be to dilute the intended exposure contrast and bias the observed effect measure estimates toward the null. We attempted to assess the

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potential impact of such exposure misclassification on our results for our primary measure of growth restriction in infants, SGA, by restricting the sample of exposed women to only those with at least one job rated as having a higher probability of exposure (≥50%) by the IH during the exposure assessment process. This sensitivity analysis demonstrated that, despite a decrease in sample size, the magnitude of the association between solvent exposure and SGA increased for exposure to both chlorinated and aromatic solvents.

Another advantageous feature of this study is its multistate population-based design. Since the NBDPS reference population (ie, participants enrolled as 'controls') has been previously shown to be generally representative of its base population,[22] and since the women enrolled in the study represent a wide range of occupations,[36] we expect our results to have greater generalisability to the population of women in the USA who work during pregnancy than a study conducted within a focused geographic location or industry. This is important because heterogeneity in results across previous studies may be partly attributable to substantial differences in occupational exposure profiles. Owing to differences in industry practices and safety standards as well as local government regulations, one would expect the prevalence of exposure to individual solvents as well as associated parameters, such as concentrations in the workplace environment, to differ across geographic populations and occupational cohorts, both domestically and internationally. Of the previous population-based studies of occupational solvent exposure and FGR, only one has been conducted in the USA, in a small community within San Jose, California, USA;[20] our study population is nearly three times larger and includes births from eight states across the country. Despite the relative size and representativeness of our study population, our results are, nevertheless, based on small numbers of exposed women—a limitation which is reflected in the imprecision of our effect measure estimates. For example, the potential association we observed in our data between SGA and exposure to toluene and xylene was based on only seven exposed mothers of SGA infants, six of whom were assigned a probability of exposure that was at least 50%. In the future, we hope to extend the occupational exposure assessment to mothers in the NBDPS through 2011, thereby substantially increasing our study size.

A further source of heterogeneity across previous studies is that the selected surrogate measure of FGR varies. Some studies have evaluated SGA,[18–20] while others have considered LBW with a threshold of either 2500[1620] or 3000[1718] grams. In our study, we examined two measures of FGR: SGA and change in the distribution of term birthweight. To construct a measure of SGA in our study, we used national references that accounted for infant sex, maternal parity and race/ethnicity.[2930] SGA can detect shifts in the residual distribution of birthweight that cause a higher (or lower) proportion of infants, regardless of gestational age, to fall into a high-risk group often defined by the 10th centile. Though the 10% weight-for-gestational-age cut-point for SGA is standard for many clinical and research applications, estimating the association between maternal solvent exposure during pregnancy and SGA defined using other cut-points or reference populations (including internal standardisation) may produce different results.[3738] A further limitation is that, as a measure of fetal growth, SGA does not distinguish between pathogenically growth-restricted fetuses and those who are simply born constitutionally smaller than the population average. Stratifying as we did by infant sex, maternal parity and race/ethnicity may help to mitigate this limitation to some degree, but other important factors (eg, maternal prepregnancy BMI)

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were unaccounted. To examine shifts in the whole distribution of birthweight that perhaps may not be reflected in the residual age-adjusted distribution (as measured by SGA), we assessed the impact of solvent exposure on change in mean birthweight among infants born at term (≥37 weeks). Less than 5% of preterm births are clinically indicated for significant FGR,[39] and singleton pregnancies with uncomplicated FGR are typically allowed to progress to early term or term (38–39 weeks).[40] Thus, by restricting analyses of birthweight to term births only, we attempted to assess whether solvent exposure might impact birthweight via mechanisms that are independent from those leading to spontaneous or iatrogenic preterm birth. While other studies have examined LBW (defined as either <2500 or <3000 g at any gestational age) to assess FGR,[16–1820] this dichotomy is less informative since one cannot distinguish whether observed associations with LBW are due to differences in preterm delivery, differences in fetal size or both.[41]

In conclusion, we found that women in our study population assessed to have a higher probability of workplace exposure to chlorinated and aromatic solvents had a small increased risk for delivering a growth-restricted infant, though our effect estimates were based on small numbers of exposed women and thus imprecise. Despite the growing body of experimental and epidemiological studies on the developmental toxicity of organic solvents, it remains unclear whether levels encountered by pregnant women in the workplace in the USA increase the risk of FGR among offspring. The common limiting factor of previous population-based epidemiological studies of the association between maternal occupational exposure to solvents and FGR, including our study, is exposure misclassification inherent in indirect, retrospective exposure assessment. In the future, studies with improved exposure assessment, such as studies that could directly assess exposure using biomarkers in prospectively collected biological samples during pregnancy,[42] should add a unique contribution to our understanding of the potential effects of solvent exposure during pregnancy.

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What this paper adds

- Previous research suggests that maternal exposure to some organic solvents during pregnancy may increase the risk of fetal growth restriction (FGR) in offspring. Limitations of previous studies include small study size and exclusive reliance on self-reported exposure.
- In a population-based sample of women from eight US states (1997–2002), we evaluated the association between expert-assessed probability of occupational exposure to 10 organic solvents using era-specific and solvent-specific exposure databases and measures of FGR at birth, including small for gestational age (SGA) and birthweight.
- Results of this study suggest that the odds of delivering an infant who is SGA may be modestly higher for women considered to have ≥50% probability of occupational exposure during pregnancy to any solvent(s) (1.71; 0.86 to 3.40), chlorinated solvents (1.70; 0.69 to 4.01) or aromatic solvents (1.87; 0.78 to 4.50) compared to women considered to have no occupational exposure to any solvent. No association was observed for women with any probability of exposure (>0%).
- We did not observe evidence of a strong association between maternal occupational organic solvent exposure during pregnancy and FGR among offspring. The potential associations observed between SGA and exposure to chlorinated and aromatic solvents among women considered by the expert raters to have a higher probability of exposure (≥50%) are based on small numbers and merit further investigation.

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Table 1

Distribution of maternal and infant factors by classification of small for gestational age* (SGA) among infants without birth defects, National Birth Defects Prevention Study, USA, 1997–2002

	SGA (n=230)		non-SGA (n=2631)		
Characteristic	**n**	**(%)**	**n**	**(%)**	**χ^2 p value**
Age at delivery (years)					
<20	13	(5.7)	223	(8.5)	≤0.01
20–25	80	(34.8)	704	(26.8)	
26–35	100	(43.5)	1425	(54.2)	
36+	37	(16.1)	279	(10.6)	
Race/ethnicity					
White non-Hispanic	143	(62.2)	1709	(65.0)	0.08
Black non-Hispanic	21	(9.1)	339	(12.9)	
Hispanic	52	(22.6)	464	(17.6)	
Other	14	(6.1)	119	(4.5)	
Maximum years of education (years)					
<12	34	(14.8)	258	(9.8)	0.03
12 (high school)	62	(27.0)	650	(24.8)	
>12	134	(58.3)	1717	(65.4)	
Missing	0		6		
Pre-pregnancy BMI					
Underweight (BMI<18.5)	18	(8.1)	130	(5.0)	≤0.01
Normal (18.5≤BMI<25)	141	(63.5)	1465	(56.8)	
Overweight (25≤BMI<30)	38	(17.1)	599	(23.2)	
Obese (BMI≥30)	25	(11.3)	386	(15.0)	
Missing	8		51		
Smoking during pregnancy†					
No	168	(73.0)	2102	(79.9)	≤0.01
Yes	62	(27.0)	529	(20.1)	
Alcohol use during pregnancy†					

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	SGA (n=230)		non-SGA (n=2631)		
Characteristic	**n**	**(%)**	**n**	**(%)**	**χ^2 p value**
No	124	(54.4)	1470	(56.0)	0.63
Yes	104	(45.6)	1153	(44.0)	
Missing	2		8		
Multivitamin/folic acid use‡					
Any	115	(50.0)	1393	(53.0)	0.39
None	115	(50.0)	1238	(47.0)	
Pregnancy intention					
Intended	111	(59.7)	1223	(59.3)	0.93
Not intended	75	(40.3)	838	(40.7)	
Missing	44		570		
Previous live births					
None	88	(38.3)	1170	(44.5)	0.07
≥1	142	(61.7)	1461	(55.5)	
Gestational diabetes					
No	222	(96.5)	2529	(96.1)	0.76
Yes	8	(3.5)	102	(3.9)	
Infant sex					
Female	107	(46.5)	1332	(50.6)	0.23
Male	123	(53.5)	1299	(49.4)	
Maternal residence at delivery					
Arkansas	33	(14.4)	331	(12.6)	0.71
California	25	(10.9)	316	(12.0)	
Georgia (Atlanta)	22	(9.6)	309	(11.7)	
Iowa	29	(12.6)	368	(14.0)	
Massachusetts	32	(13.9)	368	(14.0)	
New Jersey	35	(15.2)	358	(13.6)	
New York	23	(10.0)	306	(11.6)	
Texas	31	(13.5)	275	(10.5)	

* Defined as birthweight <10th centile for gestational age in weeks based on published sex-specific, parity-specific and race-specific standardised birthweight curves in national external reference populations.

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† Self-reported use anytime during the first trimester and/or month before conception.

‡ Self-reported intake during the first month of pregnancy and/or month before conception.

BMI, body mass index.

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Table 2

Prevalence of assessed occupational exposure to organic solvents during pregnancy among working mothers, stratified by small for gestational age* (SGA) classification among infants without birth defects, National Birth Defects Prevention Study, USA, 1997–2002

	SGA (n=230)		non-SGA (n=2631)	
	n	(%)	n	(%)
Any solvent	23	(10.1)	219	(8.4)
Unknown exposure	3		21	
Chlorinated solvents	18	(7.9)	188	(7.2)
Carbon tetrachloride	1	(0.4)	6	(0.2)
Chloroform	6	(2.6)	77	(3.0)
Methylene chloride	15	(6.6)	165	(6.3)
Perchloroethylene	10	(4.4)	98	(3.8)
1,1,1-Trichloroethane	14	(6.2)	164	(6.3)
Trichloroethylene	7	(3.1)	87	(3.3)
Stoddard solvent	7	(3.1)	74	(2.8)
Aromatic solvents	7	(3.1)	52	(2.0)
Benzene	1	(0.4)	13	(0.5)
Toluene	7	(3.1)	50	(1.9)
Xylene	7	(3.1)	51	(2.0)

*Defined as birthweight <10th centile for gestational age in weeks based on published sex-specific, parity-specific and race-specific standardised birthweight curves in national external reference populations.

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Table 3

Association between assessed probability of maternal occupational exposure to organic solvents during pregnancy and small for gestational age* (SGA) among infants without birth defects, National Birth Defects Prevention Study, USA, 1997–2002

	Any probability of exposure					Probability of exposure >50%		
	n†	cOR	(95% CI)	aOR‡	(95% CI)	n§	aOR‡	(95% CI)
Unexposed to any solvent	204	Reference		Reference		204	Reference	
Exposed to any solvent	23	1.23	(0.78 to 1.94)	1.16	(0.73 to 1.83)	10	1.71	(0.86 to 3.40)
Chlorinated solvent(s)	18	1.12	(0.68 to 1.86)	1.03	(0.62 to 1.71)	6	1.70	(0.69 to 4.01)
Stoddard solvent	7	1.11	(0.50 to 2.44)	0.98	(0.44 to 2.18)	0	NE	
Aromatic solvent(s)	7	1.58	(0.71 to 3.52)	1.60	(0.71 to 3.58)	6	1.87	(0.78 to 4.50)

*Defined as birthweight <10th centile for gestational age in weeks based on published sex-specific, parity-specific and race-specific standardised birthweight curves in national external reference populations.

†Number of mothers of SGA-infants classified as exposed to solvents.

‡Adjusted for maternal age (referent=26–35 years) and education (referent≥12 years).

§Number of mothers of SGA-infants with ≥1 job assessed as probability of exposure ≥50%.

aOR, adjusted OR; cOR, crude OR; NE, not estimated.

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Table 4

Mean change in infant birthweight at term (≥37 weeks gestation) associated with estimated maternal occupational exposure to organic solvents during pregnancy, National Birth Defects Prevention Study, USA, 1997–2002

					Difference in birthweight (grams) Estimate (95%CI)			
	N	(%)	Mean	(SD)	Unadjusted		Adjusted*	
Total number of infants	2659							
Unknown exposure	21							
Unexposed	2416	(91.6)	3462.3	(451.9)				
Exposed to any solvent	222	(8.4)	3466.6	(476.6)	4.3	(−58.1 to 66.7)	16.1	(−46.2 to 78.4)
Any chlorinated solvent	191	(7.2)	3467.8	(470.3)	5.5	(−61.3 to 72.3)	19.9	(−46.9 to 86.6)
Stoddard solvent	76	(2.9)	3492.9	(423.8)	30.6	(−72.4 to 133.7)	56.2	(−46.7 to 159.0)
Any aromatic solvent	54	(2.0)	3545.4	(492.4)	83.1	(−39.1 to 205.3)	87.9	(−33.5 to 209.3)

*Adjusted for maternal age (referent=26–35 years) and education (referent≥12 years).