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Maternal occupational exposure to selected organic and chlorinated solvents and delivery of small-for-gestational age or preterm infants

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Abstract

Background: Potential reproductive effects of organic solvent exposure during pregnancy remain unclear. We investigated the association between maternal occupational exposure during pregnancy to six chlorinated solvents, three aromatic solvents, and Stoddard solvent and delivery of preterm infants or those born small-for-gestational age (SGA).

Methods: In this case-control study of SGA and preterm birth (PTB) nested within the National Birth Defects Prevention Study (NBDPS) from 1997–2011, we analyzed data from 7,504 singleton

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Institution and Ethics approval and informed consent: All interviewed study participants provided informed consent. The study protocols were approved by the Human Subjects Review Board for The Centers for Disease Control and Prevention (protocol #2087) and the Institutional Review Board for each participating site.

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live births without major birth defects and their mothers. Self-reported information on jobs held in the periconceptional period were assessed for solvent exposure. Unconditional logistic regression was used to estimate the association between maternal occupational exposure (any, none) during early pregnancy to organic solvents and PTB and SGA. Linear regression was used to examine change in mean birthweight among infants potentially associated with maternal occupational solvent exposure.

Results: Maternal occupational exposure to any organic solvents overall was not associated with an increased odds of PTB (aOR=0.94; 95% CI 0.67, 1.33) or SGA (aOR=0.93; 95% CI 0.65, 1.34). Point estimates increased modestly for higher estimated exposure versus lower, but confidence intervals were wide and not statistically significant. Maternal exposure to solvents was not associated with a statistically significant change in term birthweight among infants.

Conclusions: Occupational exposure to organic solvents at the frequency and intensity levels found in a population-based sample of pregnant workers was not associated with PTB or SGA; however, we cannot rule out any effect(s) among pregnant workers with uncommonly high exposure to organic solvents.

Keywords

PREGNANCY; OCCUPATION; ORGANIC SOLVENTS; PRETERM BIRTH; SGA; WORKER; REPRODUCTIVE HEALTH; BIRTH WEIGHT

Introduction

Organic solvents are carbon-based, lipophilic compounds commonly used in a wide range of occupations and industries. Each year, millions of workers are potentially exposed to organic solvents or solvent mixtures through contact with paints, varnishes, lacquers, adhesives, glues, degreasing, and cleaning agents.[1] The potential health hazards associated with occupational organic solvent exposure vary widely and are influenced heavily by dose, duration, and bioavailability of the chemical compound. Evidence from animal models—as well as occupational epidemiologic studies—have demonstrated that some, but not all, organic solvents are carcinogens, neurotoxins, and/or reproductive toxicants.[2,3] Although many acute and chronic adverse health effects associated with occupational exposure to organic solvents have been previously described in working adults[4], the potential for negative effects on fetal development from organic solvent exposure among pregnant workers remains unclear.

Fat-soluble organic solvents can cross the placenta during pregnancy, potentially causing oxidative damage to critical cell structures and disrupting normal fetal development.[5,6] Animal models have for decades established the teratogenic effects of select organic solvents, such as toluene.[2,7,8] Findings from early epidemiological studies among potentially high exposure populations (*e.g.,* laboratory workers, dry cleaner workers, etc.)[9], as well as several population-based studies[10–13], have been suggestive of an association between organic solvent exposure and adverse birth outcomes, including small-for-gestational age (SGA) and preterm birth (PTB). However, small sample size has contributed to imprecise (*i.e.,* low statistical power) findings in some studies[14,15], while others have reported negative

or null associations.[16–18] Challenges including small sample size, limited job history information, and the inability to discern individual solvents from solvent mixtures or other co-exposures in the workplace have all contributed to the difficulty in accurately quantifying the effects of organic solvent exposure on pregnant workers. Despite these challenges, identification of potential risk factors, specifically reproductive toxicants, is necessary to mitigate and prevent adverse health outcomes for working mothers and their infants.

In this study, we focus on PTB and SGA, which are two relatively prevalent pregnancy outcomes associated with increased infant mortality and morbidity.[19,20] Preterm birth, defined as birth prior to 37 weeks' gestation, affects approximately one out of every ten infants born in the United States, while fetuses characterized as SGA—referring to a newborn with a birth weight less than the 10th percentile for gestational age by infant sex—affect approximately 11.1% of all live births in the United States.[21,22] Infants characterized by either condition are at increased risk of intellectual and neurodevelopmental delays in childhood, as well as select chronic diseases in adulthood.[23–30] We also conducted a sensitivity analysis examining the potential effects of maternal occupational exposure to organic solvents on mean change in infant birthweight at term (*i.e.,* ≥37 weeks' gestation), as birthweight is a critical component of several birth outcome measurements that can be indicative of intrauterine growth restriction (IUGR), including SGA.

To better understand the potential effects of organic solvent exposure in the workplace on pregnancy outcomes, Desrosiers and colleagues first conducted an analysis using National Birth Defects Prevention Study (NBDPS) data from 1997–2002 that evaluated the association between expert-assessed occupational solvent exposure and risk of SGA among infants in a population-based sample of women; elevated but imprecise associations were observed between SGA and exposure to any solvent(s), chlorinated solvents, and aromatic solvents among women with ≥50% probability of exposure.[10] Since these analyses, an additional nine years of data (2003–2011) were collected and PTB was included as an additional pregnancy outcome of interest. The current study expands the work conducted by Desrosiers and colleagues (2015) by utilizing the full NBDPS analytic dataset (1997–2011) to examine associations between maternal occupational exposure during pregnancy to six chlorinated solvents (carbon tetrachloride, chloroform, methylene chloride, perchloroethylene, trichloroethylene, 1,1,1-trichloroethane), three aromatic solvents (benzene, toluene, xylene), and a petroleum mixture referred to as Stoddard solvent with delivery of non-malformed liveborn infants characterized as preterm or SGA in a population-based sample of women.

Materials and Methods

Study population

The National Birth Defects Prevention Study (NBDPS) was a large, population-based case-control study designed primarily to investigate risk factors for major structural birth defects.[31] The NBDPS was conducted in ten US states: Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah, although not all study sites contributed for all the study years.

Randomly selected live-born infants without a chromosomal or major structural birth defect identified from birth records and hospital delivery records were recruited as controls from the same population areas the birth defects registries covered. Because these controls have been demonstrated to be generally representative of the population of non-malformed live births in the geographic regions covered by the NBDPS[32], they have been used as essentially a birth cohort in other studies of pregnancy-related factors and outcomes.[33–35] Our study is nested within the NBDPS, and our study population consists of mothers of liveborn infants without a birth defect(s) with estimated dates of delivery between October 1, 1997, and December 31, 2011.

Specifically, data were available on 11,829 mothers of infants without birth defects who participated in the computer-assisted telephone interview (CATI) in either English or Spanish (65% of eligible mothers of infants without birth defects participated in the interview). Our eligible study population included mothers who reported employment for at least one calendar month during the periconceptional window of exposure (*i.e.*, one month prior to conception through the first trimester) (68.9% of those mothers interviewed) and provided enough job history information to assess occupational exposure to organic solvents (99.8% of mothers who reported employment) (Figure 1). Because pregestational diabetes and multiple pregnancies are strong risk factors for both birth outcomes of interest, NBDPS participant mothers with Type 1 or Type 2 diabetes prior to the index pregnancy (N=52), as well as non-singleton pregnancies (N=260), were excluded from analyses because there were too few exposed pregnancies among these mothers to allow for stratification. In addition, infants with ambiguous or unreported sex at birth (N=4) and those infants born outside the range of 22 to 44 weeks' gestation (N=3) were also excluded (Figure 1). The final study population consisted of 7,504 eligible mother-infant pairs. The NBDPS and this analysis were approved by the Institutional Review Boards of the Centers for Disease Control and Prevention and all participating study centers, and all participating mothers provided informed consent.

Exposure Assessment

Mothers self-reported occupational information during the NBDPS interview, including company name, participant's job title, what the company produced, the participant's main job activities and duties, and chemicals or equipment used. All responses were recorded as open free text. All jobs that were performed for at least one month during the periconceptional window were recorded. Jobs were then coded by occupation and industry using the Standard Occupational Classification (SOC) System and the North American Industry Classification System (NAICS).

Maternal occupational exposure assessment to chlorinated, aromatic, and Stoddard solvent(s) took place in two batches over the 15 years of the study's recruitment (first assessment period from 1997–2002 and second assessment period from 2003–2011); both used the same definitions, source materials, and methods—though staff performing exposure assessments changed between the assessments. Two industrial hygienists (IH), blinded to case status, reviewed the full job descriptions to assign probability of direct and indirect exposure, intensity of direct and indirect exposure, frequency of direct and indirect exposure,

and a subjective rating of the reviewer's confidence in the score based on the strength of data from similar occupations. Inter-rater reliability and validity of the exposure assessment strategy has been previously described.[36]

As some women had multiple jobs during the relevant window during pregnancy, job exposure measures were summarized to assign exposure estimates of probability, intensity, frequency, and duration of exposure for each organic solvent of interest for each participant. Cumulative occupational exposure, as parts per million (ppm)-hours for chlorinated and aromatic solvent classes or milligram per cubic meter (mg/m^3)-hours for Stoddard solvent, was estimated for each job using a calculation that incorporated weighted intensity, frequency, self-reported work frequency, and number of days worked in the exposure window. For participant mothers reporting more than one job during the periconceptional window of exposure, the estimate of total organic solvent exposure was the sum of the job-specific cumulative exposures in that period. For exposure-response analysis, estimated organic solvent exposure categories included no organic solvent exposure, below (low), and at or above (high), the median of the cumulative exposure of organic solvents (any and by class) among liveborn infants without SGA or PTB. For this analysis, we considered a pregnant worker to be exposed to a particular solvent if any of her self-reported job(s) held during the periconceptional period were rated by the IH as 'exposed' (*i.e.*, probability of exposure >0); she was considered unexposed to a particular solvent if her self-reported job(s) during this time were rated as 'unexposed' (*i.e.*, probability of exposure=0).

Outcome Classifications

All variables necessary to determine both primary outcome classifications, including due date, infant birth weight (grams), gestational age at delivery, and infant sex were self-reported during the CATI. Fetal growth restriction was identified based on SGA, defined as birth weight below the 10^{th} percentile for a given gestational age at delivery and infant sex. Infants born SGA were identified using a US-based birth weight for gestational age reference reported by Talge and colleagues.[37] Sex-specific, 10^{th} percentile birth weight values determined SGA and non-SGA infants within the study population from 22 through 44 weeks' gestation. Preterm birth (PTB) was classified as birth occurring prior to 37 completed weeks of gestation, following the National Center for Health Statistics (NCHS) standards.[21] The increased sample size of the current study was utilized to replicate a sensitivity analysis first conducted by Desrosiers and colleagues (2015) examining changes in mean birthweight (grams) among infants potentially associated with maternal occupational solvent exposure during early pregnancy. Infant birthweight (grams) was analyzed as a continuous outcome and analyses were conducted among 'term' infants (i.e., birth occurring ≥37 weeks' gestation) to identify meaningful inferences from the potential influence of maternal occupational solvent exposure on mean change in infant birthweight. We restricted to term infants to reduce the potential for skewed data resulting from infants who weigh less at delivery because they are premature.

Covariates—Potential confounders were identified through a directed acyclic graph (DAG)[38] analysis (supplemental Figure 1)[39, 40] based on previous literature of factors known to influence maternal occupational exposure to organic solvents, SGA, and PTB, which

included: maternal residence at delivery (NBDPS study location), maternal age at delivery (≤20 years, 21–25 years, 26–34 years, ≥35 years), maternal race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Other Non-Hispanic, maternal nativity (U.S.-born, foreign-born), maternal education (≤12 years, >12 years), maternal pre-pregnancy body mass index (BMI) (underweight range, <18.5 kg/m^2; healthy weight range, 18.5 to <24 kg/m^2; overweight range, 25 to <30 kg/m^2; or obesity range, >30 kg/m^2), maternal smoking status (any use during periconceptional period, none), maternal alcohol use (any use during periconceptional period, none), and maternal secondhand smoke exposure (any exposure from home and/or work during periconceptional period, none). The final models were adjusted for maternal education (referent =>12 years) and maternal residence at delivery, which were the minimally sufficient set of confounders resulting from the DAG (supplemental Figure 1).

Statistical Analysis

Select demographic and behavioral factors of mother/infant pairs were described. Frequencies and percentages were calculated, as well as chi-square tests (excluding missing values) to assess differences between mothers of SGA, non-SGA, PTB and non-PTB infants. The prevalence of maternal occupational exposure (any vs. no exposure) during the periconceptional window was estimated for any solvent exposure and solvent classes (aromatic, chlorinated, Stoddard), stratified by SGA and PTB. To describe occupational exposure to solvents among our study population, prevalence of exposure (any vs. no exposure) by job was estimated and presented by SOC major group.

Unconditional logistic regression was used to estimate unadjusted crude (cOR) and adjusted odds ratios (aOR) and 95% confidence intervals (CI) for the associations between periconceptional maternal exposure to organic solvents (any and by class), and SGA and PTB. To assess cumulative occupational exposure to solvents, exposure-response analyses were conducted in three categorical groups (none, low, high) determined by median cumulative exposure levels among mothers of infants not born prematurely or not characterized as SGA. Linear regression was used to estimate the mean difference in birthweight (grams) among term infants of exposed mothers compared to term infants of unexposed mothers. We also conducted a sensitivity analysis to account for potential exposure misclassification by restricting the study sample to include only women with an exposure probability of at least 50%, as determined by the expert IHs during exposure assessment. Because this was a continuation of a prior analyses by Desrosiers and colleagues (2015), we also stratified the main analysis by both exposure assessment periods (*i.e.*, 1997–2002 vs. 2003–2011) to identify any notable differences. In all models, women considered ‘unexposed’ are those participant mothers with no assigned exposure to *any* organic solvent during the periconceptional window exclusively. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) and independently replicated by a second analyst.

Results

After eligibility and exclusion criteria were met, a total of 7,504 infant/mother pairs were analyzed (Figure 1). Approximately 6.9% (517/7,504) of study infants were classified as SGA; 7.7% (577/7,504) were born premature. Table 1 displays frequency distributions and chi-square tests of select mother/infant pair demographic and behavioral characteristics described by birth outcome of interest. Overall, study participant mothers were most commonly non-Hispanic White, did not smoke, had greater than a High School education, and were aged between 26 and 34 years of age at delivery. Self-reported jobs that were most frequently rated as incurring some exposure to organic solvents (vs. no exposure) were in the SOC major groups of production (n=134 exposed jobs; 23.8%), personal care and service (n=83 exposed jobs; 14.8%), healthcare practitioners and technical (n=80 exposed jobs; 14.2%) and building and grounds cleaning and maintenance (n=58 exposed jobs; 10.3%) (supplemental Table 1).

Maternal occupational organic solvent exposure among our study population is described in Table 2. Among all study participant mothers, approximately 5.8% were determined to have exposure to chlorinated solvents, while only 1.9% were exposed to aromatic solvents and 1.8% to Stoddard solvent. Exposure variability was observed within the aromatic and chlorinated solvent classes. For example, among mothers occupationally exposed to chlorinated solvents, approximately 4.7% were exposed to 1,1,1-trichloroethane compared to less than 0.5% to carbon tetrachloride. Co-exposures were also common. Over one-third (33%; n=166) of participant mothers were determined to have exposure to more than one solvent class, while over 80% of participant mothers were determined to have co-exposures within solvent classes (93.7% within the aromatic solvents; 81.5% within the chlorinated solvents) (data not shown). The distribution of occupational exposure to any organic solvent, as well as solvent class, did not differ meaningfully across outcomes of interest; however, maternal occupational exposure to both aromatic and Stoddard solvent was higher among mothers of SGA and PTB infants, compared to mothers of non-SGA/non-PTB infants (2.3–2.5% vs. 1.8–1.9% for SGA; 2.3–2.4% vs. 1.8–1.9% for PTB, respectively). Exposure to chlorinated solvents was slightly lower among SGA infants compared to non-SGA infants (5.4% vs. 5.8%, respectively), while exposure to chlorinated solvents was similar between both preterm and non-preterm infants (5.9% vs. 5.8%, respectively).

Results from the exposure-response analyses are presented in Table 3. After adjusting for maternal residence at delivery and educational attainment, point estimates were elevated for the high exposure groups compared to the low exposure group for both SGA and PTB [aOR for ‘low’ exposure to any solvent=0.90 95% CI 0.57, 1.40; aOR for ‘high’ exposure to any solvent=1.52 95% CI 0.80, 2.87; aOR for ‘low’ exposure to any solvent=0.97 95% CI 0.64, 1.47; aOR for ‘high’ exposure to any solvent=1.20 95% CI 0.62, 2.33]; however confidence intervals were wide and we cannot rule out that this finding was spurious. A similarly suggestive—but not conclusive—dose-response pattern was observed between maternal occupational exposure to chlorinated solvents and PTB [aOR for ‘low exposure to chlorinated solvents=1.07 95% CI 0.69, 1.66; aOR for ‘high’ exposure to chlorinated solvents=1.23 95% CI 0.63, 2.39]. Crude analysis demonstrated an association between ‘high’ maternal occupational exposure to Stoddard solvent and SGA [cOR for

'high' exposure to Stoddard solvent=2.24 95% CI 1.10, 4.56]; however, the association was attenuated after adjustment for maternal education and residence [aOR for 'high' exposure to Stoddard solvent=1.85 95% CI 0.90, 3.81].

Table 4 shows the crude and adjusted associations between estimated maternal occupational exposure to organic solvents and SGA and PTB. After adjusting for maternal education and residence at delivery, no associations were observed between maternal exposure to any organic solvent and SGA [aOR=0.93; 95% CI 0.65, 1.34] or PTB [aOR=0.94; 95% CI 0.67, 1.33]. Similarly, no associations were observed by solvent class and SGA or PTB or when restricting to mothers where the probability of workplace exposure to organic solvents was highest (≥50%).

Maternal exposure to any solvent, as well as exposure by solvent class, was not associated with a difference in term birthweight (Table 5). After adjusting for maternal education and residence at delivery, the difference in mean birthweight at term between infants of mothers exposed to any organic solvent and infants of unexposed mothers was 47.3 grams, but the 95% confidence interval included the null value of 0 [95% CI −31.5, 126.0].

Stratifying by exposure assessment periods demonstrated an elevated, but imprecise adjusted OR for any occupational maternal solvent exposure and SGA [aOR=1.11; 95% CI 0.66, 1.89] in the first exposure assessment period (1997–2002) (supplemental Table 2). Among women in the second exposure assessment period (2003–2011), we observed a possible inverse association between occupational maternal exposure to any solvent and SGA [aOR=0.83; 95% CI 0.50, 1.37] (supplemental Table 2).

Discussion

In the current study, we did not observe any definitive associations between maternal occupational exposure to organic solvents during the periconceptional period and SGA or PTB after adjusting for maternal education and residence. This was true for general exposure (any vs. none), as well as by solvent class (chlorinated, aromatic, and Stoddard solvent). Point estimates were slightly elevated for the highest category of any solvent exposure and SGA (aOR=1.52; 95% CI 0.80, 2.87) and PTB (aOR=1.20; 95% CI 0.62, 2.33), but confidence intervals were wide. Solvent exposure was somewhat limited among our study population for both birth outcomes of interest (n=24 exposed mothers of infants born SGA; n=38 exposed mothers of preterm infants); however, overall, our analyses do not suggest any substantial association between low-dose, infrequent periconceptional solvent exposure among expectant workers and SGA or PTB.

Our findings are consistent with other studies of maternal occupational exposure to organic solvents and adverse birth outcomes. Burdorf and colleagues (2011) observed no associations between self-reported maternal occupational exposure to industrial solvents and PTB with similar sample size (N=8,880 participant mothers) (aOR=1.02; 95% CI 0.58, 1.81).[41] In the same study, using a job exposure matrix (JEM) assessment strategy to determine exposure (n=227 exposed) or restricting the analysis to only mothers with probable occupational exposure to solvents (n=69 exposed) still resulted in no significant

associations between maternal occupational solvent exposure and PTB.[41] More recently, Shirangi and colleagues (2020) observed no association between maternal occupational exposure to organic solvents (any) and SGA or percentage of optimal birthweight (POBW) among infants in a population-based, prospective birth cohort study of 4,142 pregnant workers from 2007 to 2011 in the United Kingdom [SGA aRR=1.08; 95% CI 0.36, 3.29; POBW aRR=0.89; 95% CI 0.44, 1.80].[42] In that same study, there were similar number of infants with SGA in the study sample (n=451) compared to the NBDPS (n=517) and slightly higher study participation rates (approximately 80% vs. 65% among NBDPS controls).[42] Even studies of non-occupational exposure to solvents have demonstrated similar findings. For example, Sorenson and colleagues (2010) observed that residential exposure to paint fumes during pregnancy was not associated with reduced birth weight or PTB.[43]

The initial analysis by Desrosiers and colleagues (2015) observed elevated but imprecise associations between fetal growth restriction (measured by SGA) and occupational periconceptional exposure to organic solvents (any and by chlorinated and aromatic solvent classes) among pregnant workers with a ≥50% probability of exposure; however, study findings were limited by relatively small numbers of exposed workers.[10] The current study adds nine years of analytic data (n=4,618 mother/infant pairs from 2003 to 2011) and PTB as an additional outcome of interest. Increased sample size in the current study allowed for logistic regression analyses on the association between SGA and Stoddard solvent exposure among participant mothers with ≥50% probability of exposure, as well as dose/response analyses for all solvents (any and by class), though the classification criteria for SGA was slightly different between the two studies. Findings from stratifying the analysis by exposure assessment period (1997–2002 vs. 2003–2011) echo the comparisons between the two studies as well (supplemental Table 2). Though we also observed an elevated, but imprecise adjusted OR for any solvent exposure and SGA among women in the first exposure assessment period (1997–2002), we observed a non-statistically significant inverse association between maternal occupational exposure to any solvent and SGA among women in the second exposure assessment period (2003–2011). It is possible that decreases in both occupational uses of organic solvents, as well as workplace substitutions of solvents with known and suspected health hazards, may have contributed to overall decreases in exposure among our study population and reduced our study's statistical power. Uncontrolled confounding by factors related to employment quality (*e.g.*, stable contract, predictable scheduling, paid leave) cannot be ruled out as contributing to this finding, particularly if the jobs with higher solvent exposure also tended to have other more favorable workplace conditions associated with reduced PTB or SGA risk. Despite predominantly null findings from the entire study period (1997–2011), we did observe elevated, non-significant ORs for estimated solvent exposure above the median versus below for both outcomes of interest in the current study. However, maternal exposure—particularly to Stoddard solvent—was still limited despite the increase in sample size and our findings may warrant further research. Most women in this population-based sample (even in the higher exposure group) were still exposed to these solvents infrequently and in small quantities, so these results should not be extrapolated to workplaces where very substantial and frequent exposure to these solvents occurs. Overall, though, these results are generally reassuring that infrequent and small-dose

maternal periconceptional exposure to organic solvents in the workplace do not appear to be significantly associated with PTB or infants characterized as SGA.

The NBDPS provides a unique opportunity to examine the influence of a wide range of occupational exposures on reproductive outcomes. Because our study population of singleton infant/mother pairs is generally representative of infants from the ten included US states during the study years[32], results are more generalizable compared to other types of studies (*e.g.*, hospital- or workplace-based studies). Details of the exposure assessment strategy have been previously published[36], but the use of expert IH raters (as opposed to a JEM alone)—including corresponding interrater reliability—reduces the potential for misclassification bias. In addition, because the study population was limited only to participant mothers reporting at least one job for at least one month during the periconceptional period, confounding was minimized for variables predicting employment among women (*e.g.*, select socioeconomic factors, sources of external stress, family structure characteristics, etc.) were likely not influential in the current study.[44] NBDPS participants' reported employment and job histories also highlight a study strength. Less than 1% (n=14/7,837) of participant mothers who reported employment for at least one month during the periconceptional period did not provide sufficient job history information to assess occupational exposure to organic solvents; therefore, participant reporting of employment and job histories are an unlikely source of bias in this study.

Though sample size was robust, maternal occupational exposure to organic solvents among mothers of infants characterized as SGA or preterm was still infrequent (6.6%) (exposed mothers of SGA infants, n=34; exposed mothers of preterm infants, n=38), which may have led to imprecise estimates. In addition, the exposure window for the current study was restricted to the periconceptional period and does not account for potential influences of maternal organic solvent exposure later in pregnancy on either SGA or PTB. However, approximately 93.6% of participant mothers in our study sample worked the same or similar job(s) until delivery (data not shown) indicating that participant exposure likely did not change substantially throughout pregnancy. Reliance on theoretical and retrospective occupational exposure to organic solvents—as opposed to real-time quantitative measurements—may have led to some degree of non-differential misclassification. We also cannot completely rule out selection bias—where mothers predisposed to a higher prevalence of occupational organic solvent exposure and with adverse birth outcomes may have been more inclined to take part in the study—though the participation rates of NBDPS controls (65%) are relatively high.[31] Additionally, while the most recent estimate of SGA prevalence in the U.S. general population is approximately 11.1%, we noted a lower-than-expected prevalence of SGA in our study sample (approximately 6.9%).[22] Study participant mothers reported higher proportions of protective factors for SGA, such as not smoking and higher educational attainment, which may have contributed to the lower prevalence of SGA observed in our study.

Co-exposures among occupational studies of solvents still present a challenge and warrant some caution in finding interpretations. For example, among participant mothers determined to have exposure to aromatic solvents, approximately 73.4% (n=105) had exposure to both xylene and toluene, while approximately 20.3% (n=29) of mothers had exposure to all three

aromatic solvents making it difficult to discern individual solvent effects (data not shown). Furthermore, our findings are representative of the unique exposure distributions within solvent class. For instance, among chlorinated solvents of interest, there were approximately 340 (4.5%) participant mothers with exposure to methylene chloride and only 13 (0.2%) participant mothers with exposure to carbon tetrachloride (Table 2). Because we were unable to examine associations between individual solvents and SGA and PTB, our results reflect the specific distribution of exposure within solvent classes among our study population.

A primary strength of the NBDPS is its' ability to allow the study the association between select occupational exposures and pregnancy and birth outcomes. Though exposure to organic solvents is common among many industries, exposure was low within our study population. Occupational safety and health concerns over organic solvent exposure and suspected reprotoxicity have led to industry-wide substitutions and the phasing out of several solvents that may— at least in part—explain such infrequent and low-dose exposures within the study period (1997–2011). Most participant mothers who were determined to have occupational exposure to solvents still had estimated exposure intensities and frequencies that were far below the current OSHA permissible exposure limits (PELs). For example, maternal occupational exposure to carbon tetrachloride within our study population was very infrequent (*e.g.*, only 13 out of 7,504 mothers with determined exposure) and even where exposure was estimated to occur more frequently, it was often low-dose. For example, among the 135 participant mothers determined to have been occupationally exposed to toluene, approximately 97 (71.9%) had estimated exposure levels well below the current OSHA PEL (200 ppm averaged over an 8-hour shift) (data not shown). Therefore, it is likely that non-significant increases in effect observed between maternal exposure to organic solvents and SGA or PTB may be influenced heavily by high, but still infrequent exposures.

Results from the current study contribute to a growing body of literature that suggests maternal periconceptional exposure to organic solvents in the workplace—at levels well below current PELs—do not appear to be associated with premature delivery or infants characterized as SGA. However, because of the predominant occurrence of infrequent and low-dose exposure within our study population, we cannot rule out any effect(s) among pregnant workers with unusually high exposure to organic solvents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Availability of data and materials:

The study questionnaires and process for accessing the data used in this study is described at https://www.cdc.gov/ncbddd/birthdefects/nbdps-public-access-procedures.html. The code book and analytic code may be made available upon request.

List of abbreviations:

NAICS	North American Industry Classification System
SOC	Standard Occupational Classification
PTB	Preterm Birth
SGA	Small-for-Gestational Age
NBDPS	National Birth Defects Prevention Study
DAG	Directed Acyclic Graph
CATI	Computer-assisted telephone interview
IH	Industrial Hygienist

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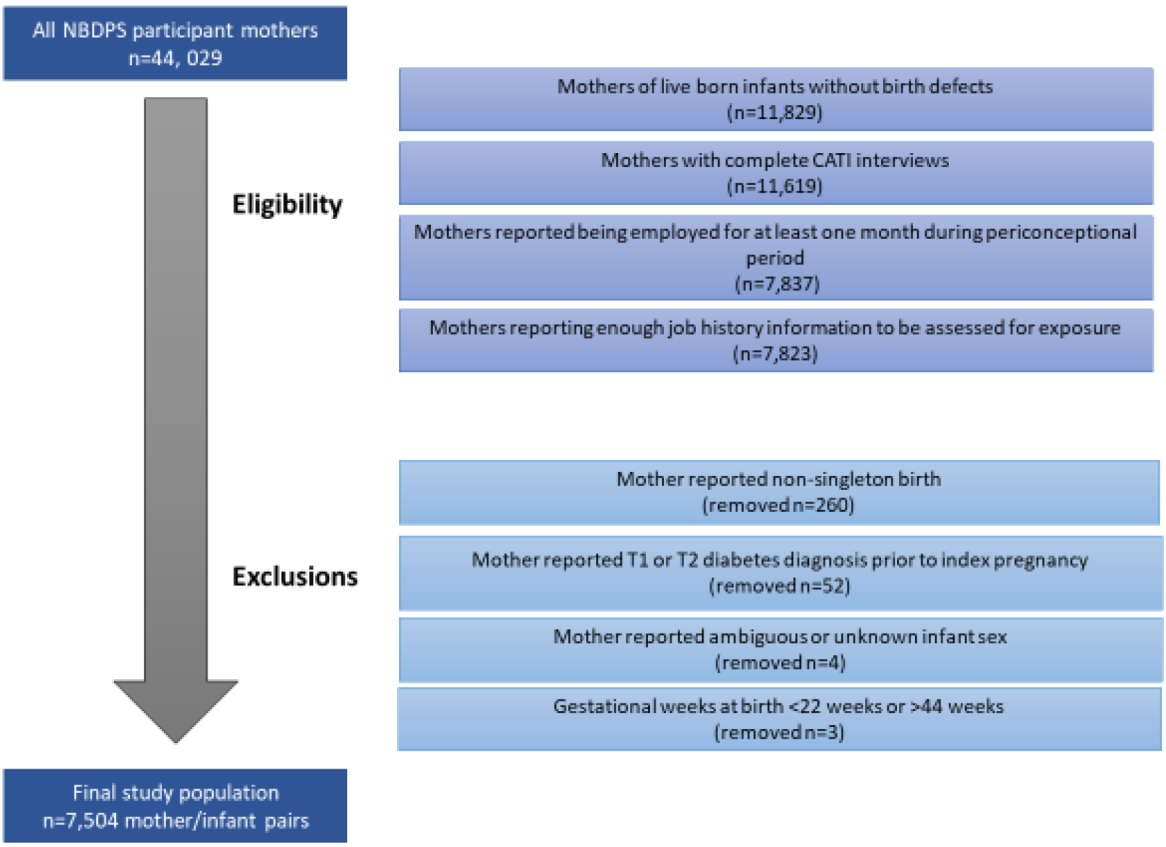

Figure 1.

Study population eligibility and exclusion criteria, National Birth Defects Prevention Study, USA, 1997–2011.

Table 1.

Distribution of maternal and infant characteristics by classification of small-for-gestational age (SGA) and preterm birth (PTB) among infants without birth defects, National Birth Defects Prevention Study, USA, 1997–2011.

	SGA (n=517)		non-SGA (n=6,987)			PTB (n=577)		non-PTB (n=6,927)		
Maternal Characteristics	**n**	**(%)**	**n**	**(%)**	***X*² p-value**	**n**	**(%)**	**n**	**(%)**	***X*² p-value**
Occupational exposure to any organic solvents during the periconceptional period					*NS*					*NS*
Exposed[a]	34	6.6	467	6.7		38	6.6	463	6.7	
Unexposed	483	93.4	6,520	93.3		539	93.4	6,464	93.3	
Maternal residence at delivery					*<0.01*					*<0.01*
Arkansas	83	16.1	881	12.6		100	17.3	864	12.5	
California	35	6.8	642	9.2		45	7.8	632	9.1	
Georgia	74	14.3	763	10.9		71	12.3	766	11.1	
Iowa	54	10.4	936	13.4		86	14.9	904	13.1	
Massachusetts	61	11.8	941	13.5		70	12.1	932	13.5	
New Jersey	29	5.6	338	4.8		22	3.8	345	5.0	
New York	47	9.1	619	8.9		33	5.7	633	9.1	
North Carolina	41	7.9	606	8.7		47	8.2	600	8.7	
Texas	58	11.2	617	8.8		70	12.1	605	8.7	
Utah	35	6.8	644	9.2		33	5.7	646	9.3	
Maternal age at delivery					*<0.01*					*NS*
≤20 years	83	16.1	691	9.9		70	12.1	704	10.2	
21–25 years	154	29.8	1,663	23.8		141	24.4	1,676	24.2	
26–34 years	201	38.9	3,615	51.7		270	46.8	3,546	51.2	
≥35 years	79	15.3	1,018	14.6		96	16.6	1,001	14.5	
Maternal race/ethnicity					*<0.01*					*<0.01*
Non-Hispanic White	266	51.5	4,529	64.8		332	57.5	4,463	64.4	
Non-Hispanic Black	98	19.0	760	10.9		97	16.8	761	11.0	
Hispanic	109	21.1	1,277	18.3		112	19.4	1,274	18.4	
Other Non-Hispanic	44	8.5	421	6.0		36	6.2	429	6.2	
Maternal nativity					*<0.05*					*NS*
U.S.-born	415	80.3	5,885	84.2		491	85.1	5,809	83.9	
Foreign-born	102	19.7	1,094	15.7		86	14.9	1,110	16.0	
Missing	0	0.0	8	0.1		0	0.0	8	0.1	
Maternal education					*<0.01*					*<0.05*
<12 years	69	13.4	642	9.2		67	11.6	644	9.3	
High school diploma or equivalent	146	28.2	1,563	22.4		152	26.3	1,557	22.5	
>12 years	302	58.4	4,769	68.3		358	62.1	4,713	68.0	
Missing	0	0.0	13	0.2		0	0.0	13	0.2	

Maternal Characteristics	SGA (n=517) n	(%)	non-SGA (n=6,987) n	(%)	X^2 p-value	PTB (n=577) n	(%)	non-PTB (n=6,927) n	(%)	X^2 p-value
Maternal BMI					*<0.01*					*NS*
Underweight range (BMI<18.5)	39	7.5	301	4.3		32	5.6	308	4.5	
Healthy weight range (18.5<=BMI<25	293	56.7	3,691	52.8		289	50.1	3,695	53.3	
Overweight range (25<=BMI<30)	95	18.4	1,604	23.0		130	22.5	1,569	22.7	
Obesity range (BMI>=30)	75	14.5	1,255	18.0		118	20.5	1,212	17.5	
Missing	15	2.9	136	1.9		8	1.4	143	2.1	
Maternal smoking					*<0.05*					*NS*
Yes[b]	121	23.4	1,271	18.2		118	20.5	1,274	18.4	
No	396	76.6	5,714	81.8		459	79.6	5,651	81.6	
Missing	0	0.0	2	0.0		0	0.0	2	0.0	
Maternal alcohol use					*NS*					*<0.01*
Yes[b]	219	42.4	2,981	42.7		212	36.7	2,988	43.1	
No	295	57.1	3,986	57.1		361	62.6	3,920	56.6	
Missing	3	0.6	20	0.3		4	0.7	19	0.3	
Secondhand smoke exposure					*<0.05*					*<0.05*
Any[b]	154	29.8	1,685	24.1		168	29.1	1,671	24.1	
None	362	70.2	5,284	75.6		407	70.5	5,239	75.6	
Missing	1	0.2	18	0.3		2	0.3	17	0.2	
Infant Characteristics										
Infant birthweight					*<0.01*					*<0.01*
Low (<2,500 grams)	146	28.2	212	3.0		242	41.9	116	1.7	
Normal (2,500–4,000 grams)	363	70.2	5,892	84.3		318	55.1	5,937	85.7	
Macrosomic (>4,000 grams)	0	0.0	795	11.4		8	1.4	787	11.4	
Missing	8	1.5	88	1.3		9	1.6	87	1.3	
Infant sex					*NS*					*NS*
Female	233	45.1	3,434	49.2		276	47.8	3,391	49.0	
Male	284	54.9	3,553	50.9		301	52.2	3,536	51.1	

[a] Exposed to *any* solvent

[b] Any use/exposure during the periconceptional period.

Table 2.

Prevalence of assessed occupational exposure to organic solvents during the periconceptional period among working mothers, stratified by SGA and PTB among infants without birth defects, National Birth Defect Prevention Study, USA, 1997–2011.

	SGA (n=517) n (%)	Non-SGA (6,987) n (%)	PTB (n=577) n (%)	Non-PTB (n=6,927) n (%)	Total (n=7,504) n (%)
Any solvent	34 (6.6)	467 (6.7)	38 (6.6)	463 (6.7)	501 (6.7)
Chlorinated solvents	28 (5.4)	404 (5.8)	34 (5.9)	398 (5.8)	432 (5.8)
Carbon tetrachloride[a]	-	11 (0.2)	-	13 (0.2)	13 (0.2)
Chloroform	13 (2.5)	183 (2.6)	15 (2.6)	181 (2.6)	196 (2.6)
Methylene chloride	20 (3.9)	320 (4.6)	25 (4.3)	315 (4.6)	340 (4.5)
Perchloroethylene	18 (3.5)	244 (3.5)	20 (3.5)	242 (3.5)	262 (3.5)
Trichloroethylene	11 (2.1)	217 (3.1)	13 (2.3)	215 (3.1)	228 (3.0)
1,1,1-Trichloroethane	22 (4.3)	319 (4.6)	27 (4.7)	314 (4.5)	341 (4.5)
Stoddard solvent	12 (2.3)	126 (1.8)	14 (2.4)	124 (1.8)	138 (1.8)
Aromatic solvents	13 (2.5)	130 (1.9)	13 (2.3)	130 (1.9)	143 (1.9)
Benzene[a]	-	30 (0.4)	-	30 (0.4)	31 (0.4)
Toluene	13 (2.5)	122 (1.8)	13 (2.3)	122 (1.8)	135 (1.8)
Xylene	13 (2.5)	127 (1.8)	13 (2.3)	127 (1.8)	140 (1.9)

[a]Exposure among participant mothers of n ≥3 not reported.

Table 3.

Organic solvent exposure-response analysis for all jobs held by mothers of SGA, non-SGA, PTB and non-PTB infants, National Birth Defects Prevention Study 1997–2011.

	non-SGA	SGA				non-PTB	PTB				
	Controls	Cases	cOR	(95% CI)	aOR[a]	(95% CI)	Controls	Cases	cOR	(95% CI)	aOR[a]	(95% CI)
	n	n					n	n				
Occupational Organic Solvent Exposure												
No exposure	5,493	395	1.00	-	1.00	-	5,441	447	1.00	-	1.00	-
Low exposure	321	22	0.95	(0.61, 1.49)	0.90	(0.57, 1.40)	320	26	0.99	(0.66, 1.49)	0.97	(0.64, 1.47)
High exposure	95	11	1.61	(0.86, 3.03)	1.52	(0.80, 2.87)	93	10	1.31	(0.68, 2.53)	1.20	(0.62, 2.33)
Chlorinated solvents												
No exposure	5,551	401	1.00	-	1.00	-	5,502	450	1.00	-	1.00	-
Low exposure	264	16	0.84	(0.50, 1.40)	0.79	(0.47, 1.32)	261	23	1.08	(0.70, 1.67)	1.07	(0.69, 1.66)
High exposure	94	11	1.62	(0.86, 3.05)	1.52	(0.80, 2.87)	91	10	1.34	(0.70, 2.60)	1.23	(0.63, 2.39)
Aromatic solvents												
No exposure	5,793	416	1.00	-	1.00	-	5,738	471	1.00	-	1.00	-
Low exposure	70	8	1.59	(0.76, 3.33)	1.68	(0.80, 3.53)	73	5	0.83	(0.34, 2.08)	0.83	(0.33, 2.08)
High exposure	46	4	1.21	(0.43, 3.38)	1.02	(0.36, 2.88)	43	7	1.98	(0.89, 4.43)	1.72	(0.77, 3.87)
Stoddard solvent												
No exposure	5,800	416	1.00	-	1.00	-	5,747	469	1.00	-	1.00	-
Low exposure	53	3	0.79	(0.25, 2.54)	0.65	(0.20, 2.09)	52	8	1.89	(0.89, 3.99)	1.73	(0.81, 3.69)
High exposure	56	9	2.24	(1.10, 4.56)	1.85	(0.90, 3.81)	55	6	1.34	(0.57, 3.12)	1.12	(0.47, 2.63)

[a]Model adjusted for maternal residence at delivery and maternal education (referent= >12 years).

Table 4.

Association between assessed probability of maternal occupational exposure to organic solvents during pregnancy and small-for-gestational age (SGA) and preterm birth (PTB) among infants without birth defects, National Birth Defects Prevention Study, USA, 1997–2011.

	Any probability of exposure					Probability of exposure ≥50%		
	n	**cOR**	**(95% CI)**	**aOR**	**(95% CI)**	**n**	**aOR[a]**	**(95% CI)**
SGA								
Unexposed to any solvent	483	-	-	-	-	158	-	-
Exposed to any solvent	34	0.98	(0.69, 1.41)	0.93	(0.65, 1.34)	13	1.01	(0.57, 1.81)
Chlorinated solvent(s)	28	0.93	(0.63, 1.38)	0.88	(0.59, 1.31)	11	1.06	(0.56, 1.98)
Stoddard solvent	12	1.29	(0.71, 2.36)	1.08	(0.59, 1.99)	6	1.04	(0.45, 2.43)
Aromatic solvent(s)	13	1.36	(0.77, 2.43)	1.33	(0.74, 2.37)	7	0.92	(0.42, 2.00)
PTB								
Unexposed to any solvent	539	-	-	-	-	157	-	-
Exposed to any solvent	38	0.98	(0.70, 1.39)	0.94	(0.67, 1.33)	14	0.96	(0.55, 1.68)
Chlorinated solvent(s)	34	1.03	(0.72, 1.47)	0.99	(0.69, 1.42)	14	1.23	(0.70, 2.16)
Stoddard solvent	14	1.37	(0.78, 2.39)	1.20	(0.68, 2.11)	9	1.49	(0.73, 3.03)
Aromatic solvent(s)	13	1.21	(0.68, 2.15)	1.13	(0.63, 2.02)	8	0.91	(0.44, 1.89)

[a]Model adjusted for maternal residence at delivery and maternal education (referent= >12 years).

Table 5.

Mean change in infant birthweight at term (≥37 weeks' gestation) association with any estimated maternal occupational exposure to organic solvents during pregnancy, National Birth Defects Prevention Study, USA, 1997–2011.

					Difference in birthweight (grams) Estimate (95% CI)			
	n	(%)	Mean	(SD)	crude		adjusted[a]	
Total number of infants	6,927	-	-	-	-	-	-	-
Unexposed	6,464	93.3	3,517.2	845.2	Reference	-	Reference	-
Exposed to any solvent	463	6.7	3,559.5	917.7	42.3	(−37.9, 122.4)	47.3	(−31.5, 126.0)
Any chlorinated solvent	398	5.8	3,567.3	915.1	50.1	(−35.9, 136.2)	54.5	(−30.0, 139.0)
Stoddard solvent	124	1.8	3,509.9	717.6	−10.4	(−161.4, 140.7)	36.2	(−112.5, 184.9)
Any aromatic solvent	130	1.9	3,545.7	749.1	26.2	(−121.4, 173.7)	39.5	(−105.1, 184.0)

[a]Model adjusted for maternal residence at delivery and maternal education (referent= >12 years).