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Maternal occupational exposure to organic solvents during early pregnancy and risks of neural tube defects and orofacial clefts

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Abstract

Objectives—Though toxicological experiments demonstrate the teratogenicity of organic solvents in animal models, epidemiologic studies have reported inconsistent results. Using data from the population-based National Birth Defects Prevention Study, we examined the relation between maternal occupational exposure to aromatic solvents, chlorinated solvents and Stoddard solvent during early pregnancy and neural tube defects (NTDs) and orofacial clefts (OFCs).

Methods—Cases of NTDs (anencephaly, spina bifida and encephalocele) and OFCs (cleft lip ± cleft palate and cleft palate alone) delivered between 1997 and 2002 were identified by birth defect surveillance registries in 8 states; non-malformed control infants were selected using birth certificates or hospital records. Maternal solvent exposure was estimated by industrial hygienist review of self-reported occupational histories in combination with a literature-derived exposure database. Odds ratios (OR) and 95% confidence intervals (CI) for the association between solvent class and each birth defect group and component phenotype were estimated using multivariable logistic regression, adjusting for maternal age, race/ethnicity, education, pre-pregnancy body mass index, folic acid supplement use and smoking.

Results—The prevalence of exposure to any solvent among mothers of NTD cases (n=511), OFC cases (n=1163) and controls (n=2977) was 13.1%, 9.6% and 8.2%, respectively. Exposure to chlorinated solvents was associated with increased odds of NTDs (OR=1.96; CI=1.34, 2.87), especially spina bifida (OR=2.26; CI=1.44, 3.53). No solvent class was strongly associated with OFCs in these data.

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Conclusions—Our findings suggest that maternal occupational exposure to chlorinated solvents during early pregnancy is positively associated with the prevalence of NTDs in offspring.

Keywords

congenital abnormalities; occupational exposure; solvents

Organic solvents are a group of volatile carbon-based chemicals common in occupational settings due to their wide application as cleaners, degreasers and reagents in varied industrial processes. These solvents are commercially available in thousands of industrial formulations and are used in the production of paints, adhesives, inks and dyes, dry cleaning solutions, pesticides, fuels, cosmetics and pharmaceuticals. Millions of workers in the United States are potentially exposed to organic solvents,[1] but the current prevalence of occupational exposure among pregnant women is unknown.

A number of organic solvents are recognized reproductive toxins, although the specific mechanisms by which they exert developmental toxicity and teratogenesis in particular are not well understood.[2,3] One leading hypothesis is that these compounds produce oxidative stress (OS) to which early embryonic development is strongly susceptible.[4,5] The capacity to induce embryonic OS has been demonstrated for several organic solvents including benzene, carbon tetrachloride, chloroform, methylene chloride, perchloroethylene and trichloroethylene.[6,7] Animal models of ethanol-induced OS suggest that OS causes alterations in gene expression and interferes with normal cellular activity of the neural crest cell population, ultimately leading to brain and facial abnormalities.[8-11] Neural tube defects (NTDs) and orofacial defects (OFCs) are two major groups of congenital anomalies thought to result from abnormal embryological development of neural crest cells, and thus may be particularly susceptible to oxidative stressors.

Both NTDs and OFCs are relatively common congenital anomalies that result in significant infant mortality, childhood morbidity and healthcare costs. In the U.S., the estimated national prevalence of anencephaly, spina bifida and encephalocele is approximately 2.5, 3.7 and 0.9 per 10,000 births, respectively.[12] Cleft lip ± cleft palate and cleft palate alone affect 10.5 and 6.4 infants per 10,000 births, respectively.[12] Both defect groups are thought to have a multifactorial etiology, with a significant genetic component that likely interacts with a number of shared environmental factors. The few established risk factors for NTDs and OFCs include parental age, race/ethnicity, socio-economic status, maternal body mass index (BMI), maternal diabetes, folic acid intake, smoking and alcohol use, infant sex, parity and family history of a birth defect.[13,14]

Though a number of epidemiologic studies have investigated the potential association between maternal occupational exposure to organic solvents and NTDs or OFCs, inconsistent results between studies are difficult to interpret given important limitations in study design and exposure assessment.[15-23] For example, some studies have combined major malformations that are embryologically or pathogenetically distinct into one outcome group of interest; this practice may dilute effect measure estimates by masking etiological heterogeneity between phenotypes.[24]

Another limitation common to retrospective studies is exclusive use of job title (e.g., “nurse”) as a surrogate for exposure; this strategy is less able to discriminate exposure profiles within groups of occupation and industry than more detailed assessments incorporating expert review of occupational histories.[25] The resulting bias is of special concern in studies where the overall prevalence of exposure is low, since misclassification

of even a few unexposed individuals as exposed can lead to substantial attenuation of observed effect estimates.[26]

Given the prevalent use of organic solvents in the workplace and their suspected capacity to exert developmental toxicity in humans, potential teratogenic effects in offspring among women exposed during pregnancy warrant further investigation in studies designed to minimize both exposure and outcome misclassification. We investigated the association between maternal occupational exposure to organic solvents during early pregnancy and the prevalence of NTDs and OFCs in a large, population-based sample of women for whom exposure was assigned using a comprehensive job-exposure database and expert review of self-reported occupational histories.

METHODS

The National Birth Defects Prevention Study (NBDPS) is an ongoing, multi-site, population-based case-control study designed to investigate a range of risk factors for major congenital anomalies.[27] Participating birth defect surveillance programs identified cases of NTDs and OFCs among live births; additionally, cases among fetal deaths greater than 20 weeks gestation and prenatally diagnosed elective terminations were also ascertained by the majority of study sites. Non-malformed live birth controls were randomly selected using either birth certificates or hospital records from the same base population as cases in each state. Mothers of cases and controls were interviewed by telephone in either English or Spanish up to 24 months after the date of delivery. Using pregnancy calendars to aid recall, interviewers elicited information about demographic, environmental, nutritional, behavioral and clinical factors before and during pregnancy. The NBDPS is approved by the institutional review boards of the Centers for Disease Control and Prevention and all participating sites.

Our study population included employed mothers of cases of NTDs (n=521), OFCs (n=1249) and non-malformed controls (n=2997) delivered between 01 October 1997 and 31 December 2002. These mothers had participated in the NBDPS interview (71% of cases participated; 68% of controls), reported having at least one job during the time between the 3 months before the estimated date of conception (EDC) through delivery (67% of participating cases were employed; 72% of controls), and were from the following NBDPS sites: Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York and Texas. The average infant age at interview was 10 months for NTD cases, 10 months for OFC cases, and 8 months for controls.

We excluded women with pregestational diabetes (7 NTD cases; 17 OFC cases; 20 controls). For analyses of NTDs, we further excluded 3 cases and 5 controls with a first degree family history of NTDs; for analyses of OFCs, we excluded 69 cases and 8 controls with a positive family history.

Outcome classification

Clinical geneticists at each site performed a standardized review of abstracted medical records to confirm eligibility of cases for the NBDPS.[28] Eligible cases were then further classified by NBDPS clinicians as having one isolated major congenital anomaly, multiple major anomalies, or a pattern of anomalies representing a complex developmental syndrome. Cases with anomalies of known etiology (e.g., single-gene disorders and chromosomal abnormalities) were excluded from the NBDPS. Neural tube defects were further classified by major component phenotype: anencephaly and craniorachischisis (BPA modification of ICD-9 [29] 740.0; 740.1), spina bifida (741.0; 741.9) and encephalocele (742.0). Orofacial defects were further classified into two component phenotypes: cleft

palate alone (749.0 except 749.08) and cleft lip with or without cleft palate (749.1 except 749.19; 749.2).

Exposure characterization

The occupational history section of the maternal interview identified mothers who were employed for at least one month duration from three months preceding the EDC through the end of pregnancy. Employment was defined as compensated, volunteer or military service, including part-time work and work performed at home. For each reported job, mothers were asked about 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; up to 6 jobs could be recorded. Jobs were then coded by occupation and industry according to the Standard Occupational Classification Manual (2000) and North American Industry Classification System (1997), and assessed for exposure to 10 organic solvents including 3 aromatic solvents (benzene, xylene, toluene), 6 chlorinated solvents (carbon tetrachloride, chloroform, methylene chloride, perchloroethylene, trichloroethylene, 1,1,1-trichloroethane), and the petroleum-based mixture Stoddard solvent (also known as mineral or white spirits). Comprehensive era-specific (1997-1999; 2000-2002) and solvent-specific job-exposure databases were developed for NBDPS by a team of occupational epidemiologists and industrial hygienists (IH). These job-exposure databases, based on extensive literature reviews of published papers reporting direct measurements and determinants of exposure for various occupations and industries, were then used in combination with IH review of self-reported job information to estimate the probability of exposure for each reported job. Probability was defined as the likelihood that a specific job within an industry within a given era had any exposure to the solvent; each job was assigned one of the following categories for exposure probability: 0 (unexposed), <10%, 10-49%, 50-89% and ≥90%.

Using self-reported job dates, we restricted the exposure period of interest to the periconceptional period, defined as one month preceding the EDC through the end of the first trimester. The periconceptional period corresponds to the critical window in embryologic development during which NTDs and OFCs are thought to occur.[30] Thus, for each solvent, a mother was considered *exposed* if any of her jobs during the periconceptional period were rated as exposed (i.e., probability of exposure > 0 for any job). She was considered *unexposed* if she did not have a job during the perioconceptional period or if all her jobs during that time were rated as unexposed (i.e., exposure probability = 0 for all jobs).

Statistical analysis

Using the dichotomous exposure variable previously described (exposed/unexposed), we examined the prevalence of estimated exposure to each solvent and solvent class (aromatic; chlorinated; Stoddard solvent) among mothers by case-control status. We then explored correlation in assigned exposure status within and between solvent classes among all exposed mothers of controls to determine the best modeling strategy. Exposure status was strongly correlated between individual solvents within solvent class. For example, 98% of women exposed to methylene chloride were also exposed to trichloroethane. Exposure correlation within solvent classes was substantially higher than between classes. Given strong exposure correlation among individual solvents within solvent class, we aggregated exposure(s) by solvent class for multivariable modeling.

Three sets of models were conducted for each composite defect group (e.g., NTDs) using unconditional logistic regression, and for each series of component phenotypes (e.g., anencephaly, spina bifida, encephalocele) using polytomous logistic regression (PLR).

Within each PLR model, we also evaluated heterogeneity in the estimated exposure effects across component phenotypes using likelihood ratio tests (*alpha*-level = 0.20).[31] In the first set of models, we estimated unadjusted odds ratios (OR) and 95% confidence intervals (CI) to examine the association between exposure to each solvent class and each composite or component outcome. In the second set of models, we estimated the *independent* effects of each solvent class by simultaneously including terms for each class in the models. The final set of models included terms for each solvent class as well as for the following maternal characteristics reported during the maternal interview: age at delivery, race/ethnicity, education, pre-pregnancy BMI, folic acid supplement use, and smoking. This set of established or strongly suspected risk factors for NTDs and OFCs was ultimately selected from a larger pool of available covariates (including alcohol use, parity and study site) as a minimally sufficient adjustment set of potential confounders using directed acyclic graph (DAG) analysis, which is a graphical tool used in epidemiologic studies to assess the theoretical potential for confounding from multiple measured as well as unmeasured factors simultaneously.[32]

To account for the varying levels of estimated exposure probability in the exposure assessment, we repeated the primary exposure-defect analyses restricting the exposed group to women with at least one job with an estimated probability of exposure greater than or equal to 10% for any individual solvent within each solvent class. This strategy was used to sharpen the exposure contrast by excluding women less likely to be exposed. We also repeated analyses restricting all cases to only those with an isolated NTD or OFC, since cases of isolated congenital anomalies may differ etiologically from those presenting with multiple defects.

RESULTS

Analyses consisted of mothers of 511 NTD cases (and 2972 corresponding controls) and 1163 OFC cases (and 2969 corresponding controls) who were employed for at least one month duration from three months preceding the EDC through the date of infant delivery. Table 1 summarizes the distribution of maternal characteristics in this sample.

Among all women rated as exposed to any solvent during the periconceptional period, approximately 85% were exposed to more than one solvent (data not shown). The prevalence of estimated occupational exposure to any organic solvent during the periconceptional period was 8.2% among mothers of controls, 13.1% among mothers of all NTD cases and 9.6% among mothers of all OFC cases (Table 2). The prevalence of any solvent exposure was higher among mothers of spina bifida (14.4%) and encephalocele (16.4%) cases than anencephaly (8.4%); exposure prevalence did not vary across OFC phenotypes.

Across all case and control mothers, exposure prevalence was highest for the chlorinated solvent class (e.g., 6.9% among controls) and lowest for the aromatic solvent class (e.g., 2.0% among controls). The distribution of probability of exposure also varied between solvent classes (data not shown). For Stoddard solvent and aromatic solvents, over 90% of exposed mothers worked in at least one job with an estimated exposure probability of at least 10%. However, for chlorinated solvents, the corresponding proportion was only 30%. Within solvent class, exposure prevalence to individual solvents varied considerably. For example, within the chlorinated solvent class, exposure prevalence among controls ranged from 0.3% for carbon tetrachloride to approximately 6.0% for both methylene chloride and trichloroethane.

In analyses of neural tube defects (Table 3), we observed a positive association with maternal exposure to chlorinated solvents (adjusted OR=1.96 [95%CI = 1.34, 2.87]) but not with aromatic solvents (0.75 [0.36, 1.55]) or Stoddard solvent (0.63 [0.33, 1.23]) after adjusting for solvent class and potential confounders. The magnitude of the effect measure was stronger for spina bifida (2.26 [1.44, 3.53]) and encephalocele (2.22 [0.84, 5.82]) than for anencephaly (1.25 [0.58, 2.71]). However, these observed differences in effect across NTD phenotypes were not statistically significant (p=0.36). Results were nearly identical when restricting cases to only those with an isolated NTD (n=448; 88%). In the secondary unadjusted analysis restricting the exposed group to women with an estimated exposure probability ≥10%, results were similar to the observed effect measure estimates for all exposed women for both Stoddard (1.31 [0.77, 2.24]; 17 exposed cases) and aromatic solvents (0.99 [0.50, 1.95]; 10). For chlorinated solvents, the unadjusted OR was closer to the null and considerably less precise (1.32 [0.77, 2.29]; 16).

In analyses of orofacial clefts (Table 4), we did not observe a strong association with maternal exposure to any solvent class. Effect measure point estimates for Stoddard solvent were slightly elevated in general, but the associated confidence intervals were wide. Restriction to isolated cases of OFCs (n=997; 86%) as well as to women with an estimated exposure probability ≥10% yielded similar results.

DISCUSSION

We observed an increased prevalence of neural tube defects among offspring of women exposed to chlorinated solvents during the periconceptional period. The observed association remained after restriction to only isolated cases of NTDs, and after adjusting for several potential confounding factors. Though effect measure estimates were stronger in magnitude for encephalocele and spina bifida than for anencephaly, formal homogeneity testing did not indicate statistically significant differences in the exposure effect across component phenotypes.

Previous studies with comparable exposure assessment and outcome classification have not consistently reported an association between occupational solvent exposure and NTDs. In a California study of occupational risk factors for NTDs, Shaw *et al.* (1999) found no association between organic solvent exposure during the periconceptional period and all NTDs combined (0.97 [0.71, 1.3]).[16] However, a study of maternal occupation among Mexican-American women in Texas found evidence that women with exposure to glycol ethers and other solvents were more likely to have an NTD-affected pregnancy.[19] To our knowledge, our study is the first to investigate maternal occupational exposure to specific classes of organic solvents and NTD phenotypes.

We did not observe a positive association between maternal occupational exposure to organic solvents and orofacial defects. This finding is not consistent with a number of recent studies, all of which have reported large effect estimates for OFC phenotypes and various solvent classes including aromatic, chlorinated and petroleum solvents.[17,21,22,33,34] Given that all but one of these studies were conducted in France, it is possible that the exposure profiles between study populations differed with respect to other parameters (intensity, solvent formulation, etc.) not assessed in this study that are relevant to the potential etiologic relationship between solvent exposure and OFC risk.

We caution against the interpretation of null findings as evidence of no association between solvent exposure and OFCs or NTDs, since various sources of bias, such as exposure misclassification, could lead to the masking of effects in our study.[35] Lengthy time-to-interview may have reduced accuracy in maternal recall of occupational histories during

pregnancy. However, the median length of time between the infant's delivery and the maternal interview (9 months for cases of NTD and OFCs; 7 months for controls) was relatively short and unlikely to be a significant source of error in recalling job title and tasks. Perhaps a more important source of exposure misclassification is that inthe absence of direct quantitative exposure measurements for each woman from workplace or biologic monitoring, our retrospective exposure assessment was limited to indirect estimation of exposure status based on published measurements from similar occupations within the same industry and era. Our estimation of exposure therefore was unlikely to capture relevant within-job variability related to exposure status as well as other potentially critical factors, such as timing and intensity. Though our exposure assessment team estimated exposure intensity, lack of sufficient variation in intensity and lack of confidence in the assigned levels among the relatively small number of exposed mothers precluded further dose-response analyses which may have been informative.

Our study was limited by small sample size, driven primarily by the low prevalence of estimated solvent exposure in our study population. Though our study had larger numbers of both NTD and OFC cases than most previous investigations, the results from the multivariable logistic models adjusting for multiple potential confounders were based on small numbers and often imprecise, especially for encephalocele. However, effect measure sizes in both unadjusted and adjusted analyses were similar for all exposure-defect combinations. A further consequence of small sample size is that if the effect of exposure truly varied across NTD or OFC phenotypes, the likelihood ratio tests of homogeneity may have been underpowered to detect such heterogeneity.

The majority of exposed women in our study population were judged to be exposed to multiple solvents, and the observed exposure correlation was highest within solvent classes. Though correlation in exposure status was expected since mixtures of individual solvents are frequently used in the workplace, the observed correlation was also a function of the exposure assessment method. For example, a number of organic solvents were used for spot treatment in dry cleaning operations from 1997 to 2002, making it challenging if not impossible to identify the specific solvent(s) to which any given woman with a dry cleaning job was exposed. In such scenarios, the job would be assigned a non-zero probability of exposure to all solvent(s) potentially used in that occupation and industry. Therefore, exposure ratings in our study were likely more sensitive than specific, and the observed correlation in exposure status was thus high among solvents that were used simultaneously or were otherwise mutually prevalent in a given job. Given this exposure correlation, another limitation of our study was that we were unable to examine the potential effect of exposure to each of the 3 aromatic and 6 chlorinated solvents *individually*. Grouping solvents by major chemical class addressed some of the challenges of within-class correlation. However, the toxicity of solvents is known to vary across individual solvents within class, and analyses by solvent class in our study may be biased in an unpredictable direction if exposure effects of individual solvents are not additive but rather synergistic or antagonistic.[36,37]

In case-control studies with a low prevalence of exposure, suboptimal specificity in the exposure assessment despite good sensitivity can lead to substantial attenuation of effect estimates.[26] We attempted to refine the exposure contrasts in our study and reduce misclassification by restricting exposed women in a secondary analysis to those with at least one job with an estimated probability of exposure greater than or equal to 10% for any individual solvent within each solvent class. This strategy did not change the observed results for Stoddard solvent and aromatic solvents since the vast majority of mothers rated as exposed to these solvents had a job with an estimated exposure probability ≥10%. In contrast, only one third of mothers rated as exposed to chlorinated solvents had a job with an

estimated exposure probability ≥10%. The unadjusted OR for chlorinated solvents and NTDs in this restricted sample was closer to the null (1.32 *vs.* 1.85) but also considerably less precise given the loss in sample size. We note that the association we observed between chlorinated solvents and NTDs was therefore based on a sample of women with jobs generally estimated to have a low probability of exposure. This might imply that chlorinated solvent exposure has a strong effect on NTD risk, though a more likely explanation may be that the assigned exposure probabilities based on expected prevalence of exposure to chlorinated solvents in a given occupation and industry did not accurately reflect individual probability of exposure or another more relevant exposure measure (e.g., peak internal dose) in our study population.

We did not collect information in this study about non-occupational sources of solvent exposure, and thus cannot address the relative contribution of recreational exposure. Previous studies of NTDs considering household or hobby use of products containing solvents report inconsistent results. [18,20]

Lastly, although participation in the NBDPS was similar between cases (71%) and controls (68%) during our study period, we cannot dismiss the potential for selection bias if participation was systematically associated with high (or low) probability of occupational exposure to one or more solvents. Though the impact of such bias is unknown in the absence of explicit information about occupation among non-participants, a previous NBDPS analysis has shown that women in this study population are employed in a wide variety of occupations and industries.[38]

Despite its limitations, our study also has several notable strengths. The NBDPS is a geographically and ethnically diverse population-based study with a relatively large number of controls and carefully classified cases, including cases ascertained among stillbirths and electively terminated pregnancies. We obtained extensive data from the maternal interview about occupational history and potential confounders including maternal age at delivery, race/ethnicity, education, pre-pregnancy BMI, and periconceptional folic acid supplement use and smoking. The relatively short recall period minimized the potential for recall error in these self-reported data. Our exposure assessment process utilized comprehensive literature-based job-exposure databases to estimate probability of exposure to 10 organic solvents for every reported job held during the critical window of developmental susceptibility for NTDs and OFCs. Though resource intensive, this strategy avoids recall bias associated with exclusive use of self-reported exposure in case-control studies. Finally, by restricting eligibility to women who reported having at least one job shortly before conception and during pregnancy, we attempted to mitigate residual confounding by socio-economic status and other factors related to employment status.

In summary, we observed a positive association between maternal occupational exposure to chlorinated solvents during the periconceptional period and the prevalence of NTDs in offspring. Though not consistently reported in previous epidemiologic studies, this finding is biologically plausible given that NTDs may be particularly susceptible to oxidative stressors like organic solvents. Recurring weak associations observed in epidemiologic studies of suspected teratogens may reflect true underlying causal mechanisms and merit further attention.[35] To establish (or refute) causality, future studies should ideally be designed to improve upon previous limitations in exposure assessment and outcome classification in an effort to produce unbiased estimates. For example, studies with novel biomarkers, like meconium or newborn blood spots, would present a distinct opportunity to revisit this research question with an independent source of exposure assessment. Additional experimental research is also needed to advance our understanding of the possible biologic mechanisms by which organic solvents may cause congenital anomalies.

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What this paper adds

- Though organic solvents have been shown to be teratogenic in some animal models, epidemiologic studies have reported both positive and null associations.
- Limitations of previous studies include the aggregation of multiple etiologically distinct major malformations, as well as exclusive use of job title or self-reported exposure.
- This analysis is intended to examine the relation between maternal occupational exposure to aromatic solvents, chlorinated solvents and Stoddard solvent during early pregnancy, estimated using expert review and job-exposure databases, and the prevalence of neural tube defects or orofacial clefts in offspring.
- The results of this study indicate that maternal occupational exposure to chlorinated solvents during early pregnancy is positively associated with neural tube defects, particularly spina bifida.

Table 1

Distribution of select demographic and behavioral factors among employed[a] mothers of cases of neural tube defects, orofacial clefts and non-malformed controls, National Birth Defects Prevention Study, United States, 1997-2002.

Covariate	Controls[b] (n = 2977)		All NTDs (n = 511)		All OFCs (n= 1163)	
	n	(%)	n	(%)	n	(%)
Maternal age at delivery						
<20 years	240	(8.1)	47	(9.2)	109	(9.4)
20-25 years (R)	798	(26.8)	140	(27.4)	339	(29.2)
26-35 years	1600	(53.8)	259	(50.7)	578	(49.7)
≥ 36 years	339	(11.4)	65	(12.7)	137	(11.8)
Maternal race/ethnicity						
White, non-Hispanic (R)	1929	(65.0)	304	(59.5)	807	(69.5)
Black, non-Hispanic	376	(12.7)	58	(11.4)	74	(6.4)
Hispanic	525	(17.7)	123	(24.1)	214	(18.4)
Other	140	(4.7)	26	(5.1)	67	(5.8)
Missing	*7*		*0*		*1*	
Maternal education						
<12 years	294	(9.9)	72	(14.1)	152	(13.1)
12 years	736	(24.8)	153	(30.0)	306	(26.3)
>12 years (R)	1942	(65.3)	285	(55.9)	704	(60.6)
Missing	*5*		*1*		*1*	
Pre-pregnancy BMI						
Thin/normal weight (<25) (R)	1824	(62.6)	272	(55.2)	698	(61.5)
Overweight (25 ≤ BMI <30)	662	(22.7)	105	(21.3)	246	(21.7)
Obese (≥30)	430	(14.8)	116	(23.5)	191	(16.8)
Missing	*61*		*18*		*28*	
Folic acid supplement use[c]						
Little/no use (≤30 days)	638	(21.8)	123	(24.4)	251	(21.8)
Some use (>30 days, <daily)	1498	(51.1)	243	(48.2)	593	(51.6)
Daily use (R)	795	(27.1)	138	(27.4)	306	(26.6)

Covariate	Controls[b] (n = 2977)		All NTDs (n = 511)		All OFCs (n= 1163)	
	n	(%)	n	(%)	n	(%)
Missing	*46*		*7*		*13*	
Maternal smokingc						
Any	607	(20.4)	95	(18.6)	300	(25.8)
None (R)	2370	(79.6)	416	(81.4)	863	(74.2)

NTD, neural tube defect; OFC, orofacial cleft; BMI, body mass index; R, referent category

[a]Employed in at least one job for at least one month duration between three months preceding the estimated date of conception through the date of infant delivery.

[b]The control group for analyses of neural tube defects further excluded 5 controls with a family of history of neural tube defects; the control group for analyses of orofacial clefts further excluded 8 controls with a family history of orofacial clefts.

[c]During the periconceptional period, from one month preceding the estimated date of conception through the first three months of pregnancy.

Table 2

Prevalence of estimated occupational exposure to organic solvents during the periconceptional period[a] among employed mothers of cases of neural tube defects, orofacial clefts and non-malformed controls, National Birth Defects Prevention Study, United States, 1997-2002.

	Controls[b] (n = 2977)		All NTDs (n = 511)		Anencephaly (n = 134)		Spina bifida (n = 316)		Encephalocele (n = 61)		All OFCs (n = 1163)		Cleft palate (n = 414)		Cleft lip ± cleft palate (n = 749)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any solvent	**242**	**(8.2)**	**66**	**(13.1)**	**11**	**(8.4)**	**45**	**(14.4)**	**10**	**(16.4)**	**111**	**(9.6)**	**39**	**(9.5)**	**72**	**(9.7)**
Missing	*23*		*7*		*3*		*4*		*0*		*9*		*2*		*7*	
Chlorinated solvents	**205**	**(6.9)**	**61**	**(12.1)**	**11**	**(8.4)**	**40**	**(12.8)**	**10**	**(16.4)**	**88**	**(7.6)**	**29**	**(7.0)**	**59**	**(8.0)**
Carbon tetrachloride	8	(0.3)	0		0		0		0		3	(0.3)	2	(0.5)	1	(0.1)
Chloroform	84	(2.8)	18	(3.6)	2	(1.5)	11	(3.5)	5	(8.2)	34	(2.9)	11	(2.7)	23	(3.1)
Methylene chloride	179	(6.1)	56	(11.1)	10	(7.6)	37	(11.9)	9	(14.8)	80	(6.9)	27	(6.6)	53	(7.1)
Perchloroethylene	111	(3.8)	27	(5.4)	5	(3.8)	16	(5.1)	6	(9.8)	44	(3.8)	15	(3.6)	29	(3.9)
Trichloroethane	177	(6.0)	57	(11.3)	11	(8.4)	37	(11.9)	9	(14.8)	80	(6.9)	26	(6.3)	54	(7.3)
Trichloroethylene	97	(3.3)	23	(4.6)	3	(2.3)	15	(4.8)	5	(8.2)	39	(3.4)	12	(2.9)	27	(3.6)
Stoddard solvent	**79**	**(2.7)**	**18**	**(3.6)**	**4**	**(3.1)**	**11**	**(3.5)**	**3**	**(4.9)**	**41**	**(3.6)**	**16**	**(3.9)**	**25**	**(3.4)**
Aromatic solvents	**60**	**(2.0)**	**11**	**(2.2)**	**3**	**(2.3)**	**6**	**(1.9)**	**2**	**(3.3)**	**24**	**(2.1)**	**10**	**(2.4)**	**14**	**(1.9)**
Benzene	15	(0.5)	3	(0.6)	2	(1.5)	1	(0.3)	0		6	(0.5)	2	(0.5)	4	(0.5)
Toluene	58	(2.0)	11	(2.2)	3	(2.3)	6	(1.9)	2	(3.3)	22	(1.9)	9	(2.2)	13	(1.8)
Xylene	59	(2.0)	11	(2.2)	3	(2.3)	6	(1.9)	2	(3.3)	23	(2.0)	9	(2.2)	14	(1.9)

NTD, neural tube defect; OFC, orofacial cleft

[a] One month preceding the estimated date of conception through the end of the third month of pregnancy.

[b] The control group for analyses of neural tube defects further excluded 5 controls with a family of history of neural tube defects; the control group for analyses of orofacial clefts further excluded 8 controls with a family history of orofacial clefts.

Table 3

Association between maternal occupational exposure during the periconceptional period[a] to organic solvents and neural tube defects, National Birth Defects Prevention Study, United States, 1997-2002.

	Any NTD[b]		Anencephaly[c]		Spina bifida[c]		Encephalocele[c]		
Solvent class	**OR**	**(95%CI)**	**OR**	**(95%CI)**	**OR**	**(95%CI)**	**OR**	**(95%CI)**	**p[d]**
	Unadjusted								
Chlorinated	1.85	(1.37, 2.51)	1.23	(0.66, 2.33)	1.98	(1.38, 2.84)	2.64	(1.32, 5.28)	0.23
Stoddard	1.35	(0.80, 2.28)	1.14	(0.41, 3.16)	1.34	(0.70, 2.54)	1.91	(0.59, 6.24)	0.81
Aromatic	1.07	(0.56, 2.06)	1.13	(0.35, 3.65)	0.94	(0.40, 2.20)	1.66	(0.40, 6.96)	0.80
	Adjusted for solvent class								
Chlorinated	2.02	(1.42, 2.88)	1.25	(0.59, 2.64)	2.30	(1.52, 3.48)	2.43	(1.03, 5.70)	0.29
Stoddard	0.86	(0.47, 1.55)	0.99	(0.31, 3.20)	0.79	(0.38, 1.63)	1.00	(0.26, 3.90)	0.92
Aromatic	0.72	(0.36, 1.44)	0.99	(0.28, 3.45)	0.59	(0.24, 1.45)	0.94	(0.20, 4.37)	0.76
	Adjusted for solvent class and covariates[e]								
Chlorinated	1.96	(1.34, 2.87)	1.25	(0.58, 2.71)	2.26	(1.44, 3.53)	2.22	(0.84, 5.82)	0.36
Stoddard	0.63	(0.33, 1.23)	0.66	(0.18, 2.43)	0.66	(0.31, 1.43)	0.38	(0.04, 3.21)	0.87
Aromatic	0.75	(0.36, 1.55)	1.12	(0.32, 3.94)	0.65	(0.26, 1.61)	0.67	(0.08, 5.41)	0.78

OR, odds ratio; CI, confidence interval; NTD, neural tube defect

[a] One month preceding the estimated date of conception through the end of the third month of pregnancy.

[b] Effect measure estimates for all NTDs combined estimated using unconditional logistic regression.

[c] Effect measure estimates for NTD phenotypes estimated using polytomous logistic regression.

[d] P-value for Likelihood Ratio test of homogeneity across neural tube defect phenotypes.

[e] Covariates include maternal age, race/ethnicity, education, pre-pregnancy BMI, folic acid and smoking.

Table 4

Association between maternal occupational exposure during the periconceptional period[a] to organic solvents and orofacial clefts, National Birth Defects Prevention Study, United States, 1997-2002.

	Any OFC[b]		Cleft palate[c]		Cleft lip ± cleft palate[c]		
Solvent class	**OR**	**(95%CI)**	**OR**	**(95%CI)**	**OR**	**(95%CI)**	**p[d]**
	Unadjusted						
Chlorinated	1.11	(0.86, 1.44)	1.02	(0.68, 1.52)	1.16	(0.86, 1.57)	0.57
Stoddard	1.34	(0.91, 1.96)	1.47	(0.85, 2.54)	1.26	(0.78, 1.99)	0.64
Aromatic	1.02	(0.63, 1.65)	1.20	(0.61, 2.36)	0.93	(0.51, 1.66)	0.54
	Adjusted for solvent class						
Chlorinated	1.03	(0.76, 1.40)	0.85	(0.52, 1.38)	1.14	(0.80, 1.62)	0.30
Stoddard	1.35	(0.86, 2.11)	1.63	(0.85, 3.14)	1.22	(0.72, 2.06)	0.45
Aromatic	0.92	(0.55, 1.52)	1.11	(0.54, 2.29)	0.81	(0.44, 1.51)	0.49
	Adjusted for solvent class and covariates[e]						
Chlorinated	0.96	(0.70, 1.33)	0.83	(0.50, 1.38)	1.04	(0.72, 1.51)	0.45
Stoddard	1.25	(0.78, 1.99)	1.45	(0.72, 2.87)	1.15	(0.67, 2.00)	0.59
Aromatic	0.88	(0.52, 1.49)	1.03	(0.49, 2.20)	0.80	(0.42, 1.51)	0.58

OR, odds ratio; CI, confidence interval; OFC, orofacial defect

[a] One month preceding the estimated date of conception through the end of the third month of pregnancy.

[b] Effect measure estimates for all OFCs combined estimated using unconditional logistic regression.

[c] Effect measure estimates for OFC phenotypes estimated using polytomous logistic regression.

[d] P-value for Likelihood Ratio test of homogeneity across OFC phenotypes.

[e] Covariates include maternal age, race/ethnicity, education, pre-pregnancy BMI, folic acid and smoking.