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ORIGINAL ARTICLE

Association between maternal occupational exposure to organic solvents and congenital heart defects, National Birth Defects Prevention Study, 1997–2002

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ABSTRACT

Objective To examine the relation between congenital heart defects (CHDs) in offspring and estimated maternal occupational exposure to chlorinated solvents, aromatic solvents and Stoddard solvent during the period from 1 month before conception through the first trimester.

Methods The study population included mothers of infants with simple isolated CHDs and mothers of control infants who delivered from 1997 through 2002 and participated in the National Birth Defects Prevention Study. Two methods to assess occupational solvent exposure were employed: an expert consensus-based approach and a literature-based approach. Multiple logistic regression was used to calculate adjusted ORs and 95% CIs for the association between solvent classes and CHDs.

Results 2951 control mothers and 2047 CHD case mothers were included. Using the consensus-based approach, associations were observed for exposure to any solvent and any chlorinated solvent with perimembranous ventricular septal defects (OR 1.6, 95% CI 1.0 to 2.6 and OR 1.7, 95% CI 1.0 to 2.8, respectively). Using the literature-based approach, associations were observed for: any solvent exposure with aortic stenosis (OR 2.1, 95% CI 1.1 to 4.1) and Stoddard solvent exposure with d-transposition of the great arteries (OR 2.0, 95% CI 1.0 to 4.2), right ventricular outflow tract obstruction defects (OR 1.9, 95% CI 1.1 to 3.3) and pulmonary valve stenosis (OR 2.1, 95% CI 1.1 to 3.8).

Conclusions The authors found evidence of associations between occupational exposure to solvents and several types of CHDs. These results should be interpreted in light of the potential for misclassification of exposure.

What this paper adds

- Previous studies have suggested an association between several subtypes of CHDs and occupational exposure to organic solvents.
- The results from this large, population-based case–control study corroborate some earlier findings and suggest additional associations for consideration.
- Because CHDs were categorised based on detailed clinical review and exposure to aromatic and chlorinated solvents was determined by industrial hygienist review, the results reported in this study are the most specific with respect to both solvent and CHD type that are currently available in the literature.

INTRODUCTION

Organic solvents are carbon-based chemicals that are widely used in occupational settings for dissolving or dispersing substances, such as fats, oils or waxes, as well as in chemical manufacturing. Millions of workers in the USA have the potential for exposure to organic solvents used in products, such as paints, varnishes, adhesives and degreasing/cleaning agents, as well as in the production of dyes, polymers, plastics, textiles, printing inks and agricultural products.[1] Most organic solvents are highly volatile, and inhalation is the most common occupational exposure route, although exposure can also occur dermally or orally.[1] Several organic solvents have been classified as probable reproductive hazards.[2]

Congenital heart defects (CHDs), with an overall birth prevalence of approximately 1%, are among the most common types of birth defects[3 4] and are a leading cause of birth defects-associated mortality, morbidity and costs.[5–7] Reported associations between CHDs and occupational solvent exposures have been inconsistent. Studies using linked data between the Finnish Register of Congenital Malformation and the Children's Cardiac Register (1982–1984) identified occupational exposure to organic solvents as a risk factor for CHD subtypes, including ventricular septal defects (VSDs)[8 9] and conotruncal defects (with exposure to 'dyes, lacquers or paints').[10] Results from the Baltimore Washington Infant Study (BWIS; 1981–1989) indicated associations between organic solvents and all CHDs combined, as well as with left ventricular outflow tract (LVOT) obstruction defects (specifically, hypoplastic left heart syndrome and coarctation of the aorta), conotruncal defects (specifically, tetralogy of Fallot and transposition of the great arteries),[11 12] pulmonary stenosis,[11–13] total anomalous pulmonary venous return[14] and Ebstein's malformation.[15]

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Neither the Finnish registry studies nor the BWIS made use of industrial hygiene expertise to assess the potential for exposure to various solvents associated with jobs held by study participants during pregnancy and based their analyses entirely on maternally reported job titles and self-reports of occupational exposures. Other studies using similar exposure assessment methods relying exclusively on self-reported job titles and exposures have not suggested a role for maternal exposure to organic solvents in the aetiology of CHDs.[16 17]

The National Birth Defects Prevention Study (NBDPS) is an ongoing, multisite, population-based case–control study exploring both genetic and non-genetic risk factors for birth defects. As part of the study, industrial hygienists estimated maternal occupational exposures to organic solvents for study participants who delivered between 1997 and 2002. Funding for the occupational exposure assessment was limited and therefore only completed for data from the first five study years. Given these exposure data and the detailed review and refined classification of all CHD cases in the study,[18 19] the NBDPS data set provides a unique opportunity to investigate the association between maternal occupational exposure to organic solvents and CHDs. Specifically, we investigated possible associations between 15 categories of CHDs and classes of organic solvents for which exposures are likely to occur in occupational settings: chlorinated solvents, aromatic solvents and a mixture of C_{10} or higher hydrocarbons known as Stoddard solvent.

METHODS

Study population

NBDPS cases were identified from eight birth defects surveillance systems throughout the USA (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York and Texas).[20] Cases in the study had at least one of over 30 eligible birth defects and were live born, stillborn or electively terminated. Control infants (live born infants without major birth defects) were randomly selected from birth certificates or birth hospital records from the same geographic populations that gave rise to the cases. The NBDPS annually enrolled all eligible cases and approximately 150 controls per study centre. Mothers of cases and controls were interviewed by telephone in either English or Spanish using a computer-based questionnaire 6 weeks to 24 months after the estimated date of delivery. Interviewers obtained information on maternal demographic characteristics, exposures (eg, nutritional, behavioural, occupational) and medication use both before and during pregnancy. The participation rate for mothers of control infants was 67% and for mothers of CHD cases was 69%. The NBDPS was approved by the institutional review boards of Centers for Disease Control and Prevention and the participating study centres.

Clinical review and classification of CHDs

The systematic review of all NBDPS cases by clinical geneticists resulted in the exclusion of those with recognised or strongly suspected single-gene conditions or chromosome abnormalities. All CHD cases were confirmed by echocardiography, cardiac catheterisation, surgery or autopsy,[18 19] and their diagnostic information was reviewed by a team of clinicians with expertise in paediatric cardiology and clinical genetics for classification on two axes. The first axis of classification focused on the heart itself. 'Simple' cardiac defects were anatomically discrete or a well-recognised single entity (eg, hypoplastic left heart syndrome or tetralogy of Fallot). 'Associations' were common uncomplicated combinations of (typically two) cardiac defects (eg, VSD and pulmonary valve stenosis). CHDs that included three or more distinct defects were considered 'complex'.[18] The second axis of classification considered whether the infant had defects outside the heart. Infants with no major extracardiac defects were classified as isolated CHD cases, while those with extracardiac defects were classified as multiple CHD cases.[18 19] Clinical reviewers also determined the specific CHD phenotypes of every case according to rigorous guidelines.[18]

Inclusion criteria

Mothers of CHD case or control infants delivered on or after 1 October 1997 who had an estimated date of delivery on or before 31 December 2002 composed the initial study population (N=8733). Those who worked in paid, volunteer or military service, including part-time and full-time jobs, jobs at home, jobs on a farm or jobs outside the home that lasted 1 month or more between the period of 3 months before conception through the end of the index pregnancy were eligible for these analyses (N=6333 (N=2997 control mothers; N=3344 case mothers)). We excluded those with a first-degree family history of CHD (N=31 control mothers; N=121 CHD case mothers) and mothers with pregestational diabetes (N=15 control mothers; N=102 CHD case mothers), as these are strong risk factors for CHDs. Additionally, mothers of CHD cases with extracardiac defects (N=520) or cases with associated or complex CHDs (N=554) were excluded. The final study population included 2951 mothers of controls and 2047 mothers of simple isolated CHD cases. We analysed CHD cases in the aggregate ('any CHD') and by specific subtype with at least 50 cases. The total group of 'any CHD' includes all subtypes that are reported individually, as well as subtypes with fewer than 50 simple isolated cases representing diagnostic groups that were too sparse to be analysed individually.

During the study period, there were a few changes in the eligibility of specific CHDs as well as changes in state protocols for ascertainment. Simple isolated muscular VSDs were only included in the NBDPS during the first year of data collection.[21] In addition, California began ascertaining cases with pulmonary valve stenosis according to the NBDPS criteria for births on or after 1 January 2002. Control samples for these specific CHDs were accordingly restricted by ascertainment dates and study centre.

Exposure assessment

Each mother was asked to report whether she worked in a full-time or part-time job for at least 1 month in duration, from 3 months before conception through the end of pregnancy. If she did report working, she was asked a series of questions about each job she held, including the job title, main tasks and duties, and any chemicals or substances to which she thought she was exposed or machines she used while working. Beginning and ending dates for each job were collected, as well as the hours per day and days per week worked (online appendix 1). Each job was coded for occupation and industry using the Standard Occupational Classification System and the North American Industry Classification System.[22 23] Two independent exposure assessment strategies were then conducted by a team of industrial hygienists and occupational epidemiologists: an expert consensus-based approach[24–26] and a literature-based approach.[27–29]

The expert consensus-based approach involved the independent classification of exposure by two industrial hygienists, blinded to case status.[25 26] After reviewing all self-reported

information from the questionnaire, the hygienists rated each maternal job as potentially exposed to any of six chlorinated solvent (defined as carbon tetrachloride, chloroform, methylene chloride, perchloroethylene, 1,1,1-trichloroethane or tricholoroethylene) and/or Stoddard solvent; exposure to aromatic solvents was not estimated using this approach. Discrepancies in exposure assignment between the two hygienists were resolved by majority consensus among the original two hygienists and a third.

For the literature-based approach, agent- and era-specific (1997–1999, 2000–2002) job-exposure matrices were developed after a comprehensive review of the published literature, including measurement data abstracted from industry technical reports and industrial hygiene contextual information. Additional details have been described in the literature.[27–30] The job-exposure matrices were used in combination with an expert industrial hygiene review of the self-reported job information from the questionnaire to classify each maternal job as exposed or unexposed to each of three aromatic solvents (benzene, toluene and xylene), six chlorinated solvents (carbon tetrachloride, chloroform, methylene chloride, perchloroethylene, 1,1,1-trichloroethane and trichloroethylene) and Stoddard solvent. Each maternal job's probability of exposure to each solvent was rated as 0, 1%–9%, 10%–49%, 50%–89% and ≥90% by the industrial hygienists.

In both approaches, exposure was defined as that which occurred for any duration from 1 month before conception through the end of the first trimester—a time period that includes the most relevant windows for cardiac development.[31] For each exposure assessment method, for each class of solvent or Stoddard solvent, a mother was considered exposed if she reported having one or more jobs at any point during this time period that were rated as exposed by that method. She was considered unexposed if all her jobs during this time period were rated as unexposed to all the evaluated solvents by that method or if she was employed exclusively outside the periconceptional time period (eg, employed only in the third trimester).

Exposure and covariate definitions

Using exposure data from the expert consensus-based approach, we analysed exposure to (1) any solvent (ie, any chlorinated solvent or Stoddard solvent), (2) any chlorinated solvent and (3) Stoddard solvent. Although exposure data for individual solvents were available from the literature-based approach, we ultimately analysed exposure to (1) any solvent (ie, any chlorinated or aromatic solvent or Stoddard solvent), (2) any aromatic solvent, (3) any chlorinated solvent and (4) Stoddard solvent to facilitate comparison of results across approaches and because of methodological issues discussed below, including exposure correlation within solvent class. Because we had no a priori reason to favour the results from one exposure assessment approach over another, we present results based on both approaches.

Three maternal demographic characteristics that have been associated with CHDs as a group and/or with specific CHD lesions and are likely to be associated with occupational exposures were identified a priori as potential confounders: maternal age (<20, 20–24, 25–29, 30–34 and ≥35 years), maternal race and ethnicity (non-Hispanic white, non-Hispanic black or African American, Hispanic and other race), and maternal education (less than high school, completion of high school and more than high school). Two additional potential confounders were considered: maternal smoking, associated with increased risk for some CHD phenotypes,[32 33] and folic acid supplement intake, associated with a decreased risk for some CHD phenotypes.[34] Both were categorised dichotomously (any/none) based on use during the month before pregnancy or any time during the first trimester.

Statistical analysis

Exploratory data analysis included the calculation of frequency distributions of the selected covariates and solvent exposures among mothers of CHD cases and controls. χ^2 Tests of association were used to assess the statistical significance of differences in these frequency distributions. We also assessed the overlap in exposures within each exposure assessment method. Solvent-class-specific multiple logistic regression models, including the five a priori covariates noted above, were used to estimate adjusted ORs and 95% CIs for CHD subtypes with more than one exposed case. Finally, we conducted a sensitivity analysis of the literature-based approach using the estimates of probability of exposure for each solvent. For each solvent class, we assessed the impact of restricting the exposure to mothers with jobs in which the probability of exposure was ≥50%.

RESULTS

Exploratory analyses

Considering mothers of all CHD cases combined compared with mothers of controls, there were no significant differences with respect to the prevalence of exposure or the socio-demographic and behavioural characteristics considered (table 1). However, the two exposure assignment approaches yielded different prevalences of exposure. Using the expert consensus-based approach, approximately 4% of controls and 5% of cases were exposed to any solvent during the periconceptional period; using the literature-based approach, approximately 8% of controls and 10% of cases were exposed to any solvent.

Among control mothers rated as exposed using the expert consensus-based approach (N=110), 66% were considered exposed to only chlorinated solvents, 8% to only Stoddard solvent and 26% to both chlorinated solvents and Stoddard solvent (table 2). Among control mothers rated as exposed using the literature-based approach (N=240), 50% were considered exposed to only chlorinated solvents, 9% to only aromatic solvents and 6% to only Stoddard solvent. The remaining 85 mothers (35%) were rated as exposed to at least two classes of solvents. There was also substantial overlap of exposure to specific solvents *within* solvent classes in the literature-based approach (ie, among the 61 controls exposed to aromatic solvents, only 3% were exposed to only one solvent, and among the 203 controls exposed to chlorinated solvents, only 13% were exposed to only one solvent).

Expert consensus-based approach

Two borderline statistically significant associations between occupational exposure to classes of organic solvents and simple isolated CHDs were observed when using the expert consensus-based approach: any solvent and chlorinated solvents were associated with perimembranous VSDs (any solvent: OR 1.6, 95% CI 1.0 to 2.6; chlorinated solvents: OR 1.7, 95% CI 1.0 to 2.8) (table 3).

Literature-based approach

Several borderline and statistically significant associations between occupational exposure to classes of organic solvents and simple isolated CHDs were observed when using the literature-based approach: any solvent with aortic stenosis (OR 2.1, 95% CI 1.1 to 4.1) and Stoddard solvent with d-transposition of the

Table 1 Selected demographic, lifestyle and occupational exposure characteristics of mothers of infants with simple isolated congenital heart defects and control infants, National Birth Defects Prevention Study, 1997–2002

	Congenital heart defect cases (n=2047) N (%)	Controls (n=2951) N (%)	p Value*
Maternal age at delivery (years)			
<20	150 (7.3)	241 (8.2)	0.25
20–24	446 (21.8)	637 (21.6)	
25–29	543 (26.5)	787 (26.7)	
30–34	570 (27.8)	848 (28.7)	
≥35	338 (16.5)	438 (14.8)	
Maternal education			
Less than high school	219 (10.7)	295 (10.0)	0.08
High school	549 (26.8)	730 (24.7)	
More than high school	1276 (62.3)	1921 (65.1)	
Missing	3 (0.1)	5 (0.2)	
Maternal race–ethnicity			
Non-Hispanic white	1341 (65.5)	1910 (64.7)	0.48
Non-Hispanic black	278 (13.6)	374 (12.7)	
Hispanic	330 (16.1)	520 (17.6)	
Other	97 (4.7)	140 (4.7)	
Missing	1 (0.0)	7 (0.2)	
Maternal smoking during periconceptional† period			
Yes	458 (22.4)	606 (20.5)	0.12
No	1589 (77.6)	2345 (79.5)	
Missing	0 (0.0)	0 (0.0)	
Maternal folic acid intake during periconceptional† period			
Yes	1792 (87.5)	2587 (87.7)	0.63
No	205 (10.0)	310 (10.5)	
Missing	50 (2.4)	54 (1.8)	
Periconceptional† occupational exposure from expert consensus-based approach			
Any solvent	96 (4.7)	110 (3.7)	0.09
Chlorinated solvents	88 (4.3)	101 (3.4)	0.11
Stoddard solvent	31 (1.5)	37 (1.3)	0.44
Periconceptional† occupational exposure from literature-based approach			
Any solvent	194 (9.5)	240 (8.1)	0.10
Aromatic solvents	50 (2.4)	61 (2.1)	0.35
Benzene	16 (0.8)	16 (0.5)	0.28
Toluene	45 (2.2)	59 (2.0)	0.59
Xylene	47 (2.3)	60 (2.0)	0.50
Chlorinated solvents	156 (7.6)	203 (6.9)	0.30
Carbon tetrachloride	5 (0.2)	8 (0.3)	0.87
Chloroform	58 (2.8)	83 (2.8)	0.91
Methylene chloride	137 (6.7)	177 (6.0)	0.30
Perchloroethylene	82 (4.0)	108 (3.7)	0.49
Trichloroethane	138 (6.7)	175 (5.9)	0.23
Trichloroethylene	69 (3.4)	94 (3.2)	0.67
Stoddard solvent	67 (3.3)	79 (2.7)	0.21

*p Value for χ^2 test of association.
†Periconceptional defined as 1 month before conception through the end of the first trimester.

great arteries (OR 2.0, 95% CI 1.0 to 4.2), right ventricular outflow tract (RVOT) obstruction defects (OR 1.9, 95% CI 1.1 to 3.3) and pulmonary valve stenosis (a subtype of RVOT obstruction defects) (OR 2.1, 95% CI 1.1 to 3.8) (table 4). After restricting exposed mothers to those with at least one job rated as exposed with a 50% or greater probability (81/194 (42%) cases; 80/240 (33%) controls), we observed several additional associations: any solvent exposure with any CHD (OR 1.4, 95% CI 1.0 to 1.9) and septal defects (OR 1.5, 95% CI 1.0 to 2.3), and Stoddard solvent exposure with any CHD (OR 2.8, 95% CI 1.3 to 6.2), septal defects (OR 3.1, 95% CI 1.2 to 8.0), perimembranous VSD (OR 3.7, 95% CI 1.1 to 12.2) and atrial septal defects (OR 3.8, 95% CI 1.2 to 12.6). Perimembranous VSD and atrial septal defects are subtypes of septal defects. The originally observed associations of any solvent exposure with aortic stenosis and Stoddard solvent with d-transposition of the great arteries were not estimated because there was only one exposed case of each CHD. The originally observed associations of Stoddard solvent with RVOT obstruction defects and pulmonary valve stenosis strengthened, but lost precision (OR 4.6, 95% CI 1.4 to 15.3 and OR 4.2, 95% CI 1.1 to 16.2, respectively) (online appendix 2).

DISCUSSION

Overall, our results indicate that maternal occupational exposure to organic solvents during the period of 1 month before conception through the first trimester of pregnancy is a potential risk factor for some specific CHD phenotypes. The observed associations with individual CHDs may warrant further investigation, given that some of these associations have been previously reported in the literature. We observed associations with specific subtypes of LVOT obstruction defects, RVOT obstruction defects, conotruncal defects and septal defects. Associations between solvents and LVOT obstruction defects were previously observed in the BWIS—specifically, with 'degreasing agents' (which may include the solvents analysed in the current study as well as others not analysed here). BWIS data also showed an association with hypoplastic left heart syndrome, an LVOT obstruction defect subtype, for which we did not see any associations in our data. In addition, BWIS data showed an association between a high cumulative solvent level and a different LVOT obstruction defect subtype, coarctation of the aorta.[11 12] Our results for Stoddard solvent and RVOT obstruction defects, specifically pulmonary valve stenosis, are consistent with findings from the BWIS, which also reported an association between pulmonary valve stenosis and 'degreasing agents'.[11] Our results for perimembranous VSD were previously suggested by Finnish data (though their results were reported for VSDs in the aggregate, not by VSD subtype)[8] but not in data from the BWIS.

With respect to the similarity of associations across exposure assessment methods, arguably septal defects and RVOT obstruction defects were more consistently associated with solvents than LVOT obstruction defects or conotruncal defects. Given that the previous literature has reported associations across several subtypes, these results add to the literature suggesting that associations are present but do not clarify which of these associations are more likely to be causal.

The exact biological mechanism whereby exposure to organic solvents during the periconceptional period could result in CHDs is unknown. One potential mechanism of interest is oxidative stress.[35] Several chlorinated solvents are known to cause oxidative stress in animal models. Additionally, there is evidence from animal models that maternal exposure to chlorinated solvents is associated with CHDs. For instance, toxicological studies using both chick embryos and fetal rats have shown an increased risk for CHDs in animals exposed to the chlorinated solvent trichloroethylene and its metabolites. No particular CHD subtypes have predominated—septal defects as well as left-sided and right-sided obstructive defects have been reported.[36 37]

The potential for exposure misclassification in one or both exposure assessment strategies is the most important potential limitation of the current study.[38] A recent analysis of the NBDPS expert consensus data found that inter-rater reliability of exposure status (yes/no) improved substantially when discordant ratings were resolved via consensus conference.

Table 2 Prevalence of solvent exposure among control mothers by exposure assessment approach, National Birth Defects Prevention Study, 1997–2002

Literature-based approach (N=240 controls exposed)			Consensus-based approach* (N=110 controls exposed)		
Solvent classes	**N**	**% of Exposed**	**Solvent classes**	**N**	**% of Exposed**
Aromatic solvents only	21	8.8	Chlorinated solvents only	73	66.4
Chlorinated solvents only	119	49.6	Stoddard solvent only	9	8.2
Stoddard solvent only	15	6.3	Chlorinated + Stoddard	28	25.5
Aromatic + Chlorinated	21	8.8			
Aromatic + Stoddard	1	0.4			
Chlorinated + Stoddard	45	18.8			
Aromatic + Chlorinated + Stoddard	18	7.5			
Aromatic solvents (N=61 controls exposed)					
No. of individual solvents					
1	2	3.3			
2	44	72.1			
3	15	24.6			
Chlorinated solvents (N=203 controls exposed)					
No. of individual solvents					
1	27	13.3			
2	66	32.5			
3	20	9.9			
4	32	15.8			
5	50	24.6			
6	8	3.9			

*Consensus-based approach did not ascertain exposure to aromatic solvents.

κ Coefficients increased from 0.59 to 0.81 for chlorinated solvents, and from 0.55 to 0.92 for Stoddard solvent when comparing estimates developed before the conference with a set of estimates developed after the conference on different jobs.[24] Exposure misclassification was therefore reduced to some degree by using the consensus assessments as the final estimated exposure status; however, some inaccuracy in true exposure assignment likely remains, resulting in the potential for residual exposure misclassification.

Both the consensus-based and the literature-based approach were subject to exposure misclassification due to the correlation of exposures within a solvent class. There was generally insufficient detail available from the maternal questionnaire responses for the industrial hygienists to identify specific chlorinated solvents, singly or in combination, to which the mother was exposed during her job, especially because several chlorinated solvents may be used interchangeably in some tasks and jobs, such as degreasing. This overlap would have made the interpretation of associations with individual solvents challenging, and therefore, the decision was made to conduct an analysis based on solvent classes instead. Although this decision mitigated the problem of interpreting individual solvent results, it may have resulted in a dilution of any true associations with individual solvents, as was likely the situation in the expert

Table 3 Adjusted* associations between exposure to classes of solvents estimated from expert consensus-based approach and selected simple isolated congenital heart defects, National Birth Defects Prevention Study, 1997–2002

		Any solvent		Chlorinated solvents		Stoddard solvent	
	N†	**N‡**	**OR (95% CI)**	**N‡**	**OR (95% CI)**	**N‡**	**OR (95% CI)**
Any congenital heart defect	2047	96	1.2 (0.9 to 1.6)	88	1.2 (0.9 to 1.6)	31	1.2 (0.7 to 1.9)
Conotruncal defects	470	24	1.3 (0.8 to 2.0)	22	1.2 (0.8 to 2.0)	7	1.1 (0.5 to 2.5)
Tetralogy of Fallot	245	12	1.1 (0.6 to 2.2)	11	1.1 (0.5 to 2.2)	2	0.6 (0.2 to 2.7)
D-Transposition of the great arteries	167	11	1.8 (0.9 to 3.4)	10	1.7 (0.9 to 3.4)	5	2.1 (0.8 to 5.5)
Anomalous pulmonary venous return	60	2	0.9 (0.2 to 3.6)	2	1.0 (0.2 to 4.1)	0	Not estimated
Left ventricular outflow tract obstruction defects	344	9	0.7 (0.4 to 1.4)	8	0.7 (0.3 to 1.4)	3	0.6 (0.2 to 2.0)
Hypoplastic left heart syndrome	147	0	Not estimated	0	Not estimated	0	Not estimated
Coarctation of the aorta	125	4	0.9 (0.3 to 2.6)	3	0.8 (0.2 to 2.4)	1	Not estimated
Aortic stenosis	69	5	2.0 (0.8 to 5.2)	5	2.2 (0.9 to 5.7)	2	1.9 (0.4 to 8.3)
Right ventricular outflow tract obstruction defects	302	19	1.6 (0.9 to 2.7)	17	1.6 (0.9 to 2.7)	6	1.6 (0.7 to 3.8)
Pulmonary valve stenosis	235	14	1.5 (0.9 to 2.7)	12	1.4 (0.8 to 2.7)	5	1.6 (0.6 to 4.2)
Septal defects	793	42	1.3 (0.9 to 1.9)	39	1.3 (0.9 to 2.0)	15	1.5 (0.8 to 2.7)
Ventricular septal defect—perimembranous	351	21	1.6 (1.0 to 2.6)	20	1.7 (1.0 to 2.8)	7	1.6 (0.7 to 3.7)
Ventricular septal defect—muscular	108	6	1.3 (0.5 to 3.2)	6	1.4 (0.5 to 3.5)	1	Not estimated
Atrial septal defect—secundum or not otherwise specified	316	15	1.0 (0.6 to 1.9)	13	1.0 (0.5 to 1.8)	7	1.7 (0.7 to 3.8)

*Multivariable logistic regression models adjusted for maternal age, race–ethnicity, education, periconceptional smoking and periconceptional intake of folic acid supplements.
†Total number of cases.
‡Number of cases exposed to solvent.

Table 4 Adjusted* associations between exposure to classes of solvents from literature-based approach and selected simple isolated congenital heart defects, National Birth Defects Prevention Study, 1997–2002

	Any solvent		Aromatic solvents		Chlorinated solvents		Stoddard solvent	
	N†	OR (95% CI)	N†	OR (95% CI)	N†	OR (95% CI)	N†	OR (95% CI)
Any congenital heart defect	194	1.1 (0.9 to 1.4)	50	1.1 (0.8 to 1.6)	156	1.1 (0.8 to 1.3)	67	1.2 (0.8 to 1.7)
Conotruncal defects	46	1.1 (0.8 to 1.6)	13	1.1 (0.6 to 2.2)	36	1.0 (0.7 to 1.5)	17	1.3 (0.8 to 2.3)
Tetralogy of Fallot	21	0.9 (0.5 to 1.5)	6	0.8 (0.3 to 2.3)	16	0.8 (0.5 to 1.4)	6	0.9 (0.4 to 2.1)
D-Transposition of the great arteries	20	1.5 (0.9 to 2.4)	6	1.7 (0.7 to 4.1)	17	1.5 (0.9 to 2.5)	9	2.0 (1.0 to 4.2)
Anomalous pulmonary venous return	4	0.8 (0.3 to 2.2)	1	Not estimated	4	0.9 (0.3 to 2.6)	0	Not estimated
Left ventricular outflow tract obstruction defects	30	1.0 (0.7 to 1.5)	9	1.1 (0.5 to 2.4)	21	0.8 (0.5 to 1.4)	8	0.8 (0.4 to 1.8)
Hypoplastic left heart syndrome	7	0.5 (0.2 to 1.1)	2	0.3 (0.0 to 2.3)	5	0.5 (0.2 to 1.1)	2	0.4 (0.1 to 1.8)
Coarctation of the aorta	12	1.1 (0.6 to 2.1)	4	1.6 (0.6 to 4.4)	8	0.8 (0.4 to 1.9)	2	0.7 (0.2 to 2.7)
Aortic stenosis	11	2.1 (1.1 to 4.1)	3	2.3 (0.7 to 7.5)	8	1.9 (0.9 to 4.0)	4	2.2 (0.8 to 6.4)
Right ventricular outflow tract obstruction defects	35	1.3 (0.9 to 1.9)	9	1.3 (0.6 to 2.7)	31	1.3 (0.9 to 2.0)	17	1.9 (1.1 to 3.3)
Pulmonary valve stenosis	27	1.4 (0.9 to 2.2)	8	1.5 (0.7 to 3.3)	23	1.4 (0.9 to 2.3)	13	2.1 (1.1 to 3.8)
Septal defects	72	1.1 (0.8 to 1.4)	18	1.1 (0.6 to 1.9)	57	1.0 (0.7 to 1.4)	25	1.1 (0.7 to 1.8)
Ventricular septal defect—perimembranous	31	1.1 (0.7 to 1.6)	6	0.9 (0.4 to 2.0)	24	1.0 (0.6 to 1.5)	12	1.3 (0.7 to 2.4)
Ventricular septal defect—muscular	9	0.7 (0.4 to 1.6)	3	0.8 (0.2 to 2.7)	7	0.7 (0.3 to 1.6)	1	Not estimated
Atrial septal defect—secundum or not otherwise specified	32	1.2 (0.8 to 1.7)	9	1.3 (0.7 to 2.7)	26	1.1 (0.7 to 1.7)	12	1.3 (0.7 to 2.4)

*Multivariable logistic regression models adjusted for maternal age, education, race–ethnicity, periconceptional smoking and periconceptional intake of folic acid supplements.
†Number of cases exposed to solvent.

consensus-based approach as well. In addition, both exposure assessment methods were indirect and retrospective and yielded estimates of exposure with unknown sensitivity and specificity compared with true exposure status. Since there was no gold standard against which the exposure assessments could be compared, nor was there a biological marker to use for validation, it was not possible to determine the accuracy of one assessment method over another.

We expected that exposure misclassification in this study would dilute the dichotomous (yes/no during the periconceptional period) exposure contrast and, assuming there is an underlying positive association between maternal exposure to organic solvent(s) and one or more CHDs, the observed effect estimates would be biased towards the null. Our sensitivity analysis of the literature-based method was intended to sharpen the exposure contrast by limiting exposed jobs to those with estimated probability of exposure ≥50%. In this secondary analysis, two of the originally observed relationships were strengthened in magnitude (ie, Stoddard solvent and RVOT obstruction defects and pulmonary valve stenosis), though the loss in sample size reduced precision. Several previously unseen associations were noted (eg, Stoddard solvent and septal defects, and atrial septal defects), which may have been unobserved in the primary analysis due to exposure misclassification.

Several additional study limitations should be noted. First, our decision to only consider a dichotomisation of exposure limited our ability to explore an exposure–response relationship, which is one criterion of causality. Although information was available on the metrics that could allow such an investigation (intensity and frequency of exposure), our limited sample size of exposed mothers within each CHD subtype restricted our ability to further classify them by these metrics. In addition, there was insufficient variation in these other metrics to adequately conduct a CHD-subtype-specific exposure–response analysis.

Second, we were unable to account for potential exposures to solvents outside the work environment, such as through painting or cleaning/degreasing activities at home or as part of hobbies. Some solvents, such as trichloroethylene and its metabolites, are known drinking water contaminants in the USA; our study did not assess solvent exposure via drinking water.[39] The extent to which these additional sources of solvent exposure might have resulted in appreciable misclassification depends on whether such exposures occurred with comparable frequency and intensity during the period of interest. Unfortunately, we had no data to assess the extent to which non-occupational exposures contributed to the total exposure burden.

Third, biased or inaccurate recall are possibilities for at least two reasons—first, because of the time delay from delivery to interview (in our data, approximately 11 months for mothers of CHD cases and 9 months for mothers of controls), and second, because mothers of CHD cases could be more concerned than mothers of controls about their on-the-job exposures and be more likely to report exposure to substances that they perceived as hazardous. However, in our data, there were no differences in the rating of solvent exposure (using either method) by the time between delivery and interview (data not shown). In addition, because the foundation of the occupational exposure assessment was the maternal report of job title and tasks (rather than specifics of her potential on-the-job solvent exposures), we think it is relatively unlikely that these data were affected by biased recall. In theory, however, if mothers of CHD cases reported a more complete occupational history, they would have a greater probability of an accurate assignment of exposure. In our data, mothers of CHD cases and controls had a very similar distribution of the total number of jobs held (data not shown), suggesting that a differential recall of occupational history did not occur.

Fourth, selection bias could be a possibility if participation in the study was influenced by both exposure and outcome status. Participation in the NBDPS is, by design, influenced by outcome status; it is unlikely to be influenced by exposure status. As discussed above, clinical reviewers with expertise in paediatric cardiology review every CHD case to determine whether the case meets the criteria for inclusion in the study. This process of clinical review is undertaken without regard for the nature of the interview data collected (eg, completion of the questionnaire, specific responses to questions of exposure). With respect to NBDPS controls, they have been found to generally represent their base populations with respect to several maternal and paternal demographic factors.[40] As stated above, the participation rate was 69% among mothers of CHD cases and 67% among mothers of controls, and these analyses were limited to mothers who reported working for at least 1 month in duration,

at some point from 3 months before pregnancy through the end of pregnancy. Mothers who noted no employment during this time period were not assessed for occupational exposures and were therefore excluded from this analysis.

Fifth, we conducted a large number of analyses (n=105; 15 CHD categories × 7 exposure variables in the two exposure assessment approaches combined) and, given a 0.05 probability of a false-positive result, all our findings could be due to chance alone. And finally, although approximately 90% of CHDs are detected prenatally or before the infant reaches 1 year of age[41] and the NBDPS relies on high-quality birth defects surveillance systems to ascertain cases, CHDs that manifest later in childhood or in adulthood are not included in the NBDPS. Therefore, this analysis does not reflect potential associations with these late-diagnosed CHDs.

A strength of our study was that both the expert consensus-based approach and the literature-based approach were expected to provide more accurate exposure ratings than would have been available through a strategy that relied solely on maternal self-reports. The NBDPS questions asking about solvent exposure (online appendix 1, Question 12e) were relatively insensitive for ascertaining exposure; if we had relied solely on these maternal reports, our results would have been quite different. For example, as reported in the Results section, the literature-based approach identified 61 control mothers as potentially exposed to aromatic solvents. Only 10 out of these 61 mothers affirmatively answered the question about solvent exposure in the NBDPS questionnaire; 3 of the 10 responses were a specified aromatic solvent (two reported toluene and one reported xylene exposure) (data not shown).

A second strength is the large number of CHD cases available for study, all of which were carefully reviewed by clinical geneticists and clinicians with expertise in paediatric cardiology to ensure that case inclusion criteria were met and that the cases were accurately classified for analysis. The inclusion of only simple isolated CHDs ensured that we had the most homogeneous case groupings possible, and therefore, we likely substantially reduced the possibility of outcome misclassification.

Finally, this study provides results with a greater level of detail than those currently available in the literature, by reporting associations between specific solvent classes and CHD subtypes.

CONCLUSIONS

We observed associations between occupational exposure to solvents and several types of simple isolated CHDs. Some of these findings were consistent with those previously reported in the literature, and other findings were new, yet all warrant corroboration in other study populations. Despite the strengths of this analysis, the results do not allow for the drawing of definitive conclusions on specific exposure–CHD combinations. These results should be interpreted with caution in light of the potential for misclassification in both exposure assessment methods.

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Notes