

Maternal Occupational Pesticide Exposure and Risk of Congenital Heart Defects in the National Birth Defects Prevention Study

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BACKGROUND: Congenital heart defects (CHDs) are common birth defects, affecting approximately 1% of live births. Pesticide exposure has been suggested as an etiologic factor for CHDs, but previous results were inconsistent.

METHODS: We examined maternal occupational exposure to fungicides, insecticides, and herbicides for 3328 infants with CHDs and 2988 unaffected control infants of employed mothers using data for 1997 through 2002 births from the National Birth Defects Prevention Study, a population-based multisite case-control study. Potential pesticide exposure from 1 month before conception through the first trimester of pregnancy was assigned by an expert-guided task-exposure matrix and job history details self-reported by mothers. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariable logistic regression. **RESULTS:** Maternal occupational exposure to pesticides was not associated with CHDs overall. In examining specific CHD subtypes compared with controls, some novel associations were observed with higher estimated pesticide exposure: insecticides only and secundum atrial septal

defect (OR = 1.8; 95% CI, 1.3–2.7, 40 exposed cases); both insecticides and herbicides and hypoplastic left heart syndrome (OR = 5.1; 95% CI, 1.7–15.3, 4 exposed cases), as well as pulmonary valve stenosis (OR = 3.6; 95% CI, 1.3–10.1, 5 exposed cases); and insecticides, herbicides, and fungicides and tetralogy of Fallot (TOF) (OR = 2.2; 95% CI, 1.2–4.0, 13 exposed cases).

CONCLUSION: Broad pesticide exposure categories were not associated with CHDs overall, but examining specific CHD subtypes revealed some increased odds ratios. These results highlight the importance of examining specific CHDs separately. Because of multiple comparisons, additional work is needed to verify these associations.

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Introduction

Congenital heart defects (CHDs) are among the most common birth defects, affecting approximately 1% of all live births, though estimates vary because not all CHDs are identified soon after birth (Loffredo et al., 2001; Hoffman and Kaplan, 2002; Reller et al., 2008; Bernier et al., 2010). Data from the Baltimore-Washington Infant Study suggest that approximately 20% of these defects can be attributed to chromosomal or single gene disorders (Ferencz and Boughman, 1993). The remainder might be due to environmental exposures or a combination of genetic and environmental factors. Identifying risk factors for CHDs is complicated by the different specific CHD subtypes (e.g., total anomalous pulmonary return, transposition of the great arteries), which differ in their underlying morphogenesis and possibly risk factors.

Several observational studies have suggested that occupational pesticides might play a role in the etiology of some CHDs. A small study by Roan et al. (1984) compared children of male agricultural pilots occupationally exposed to pesticides to the children of the pilots' nonexposed siblings, and found that CHDs were reported solely among the children of the exposed agricultural pilots. A population-based study in Singapore (Chia et al., 2004) found an increased risk of CHDs among children whose mothers were involved in agricultural and fisheries work,

with a more modest risk among the children of fathers in these industries. Using data from the Baltimore-Washington Infant Study, Correa-Villasenor and colleagues (Correa-Villasenor et al., 1991) reported a nearly threefold increased risk of maternal pesticide exposure—from occupation, lifestyle, and hobbies—and total anomalous pulmonary return, despite little or no overall risk in total CHDs. A later analysis of Baltimore-Washington Infant Study data (Loffredo et al., 2001) showed a significant increase in risk of transposition of the great arteries when maternal pesticide exposure occurred in the critical period of fetal risk, and this risk was particularly increased for exposure to herbicides or rodenticides. Other studies, however, have not observed increased risks with either all CHDs or selected types of CHD with either parent's exposure to pesticides (Garcia et al., 1999; Snijder et al., 2012), or maternal exposure to pesticides (Tikkanen and Heinonen, 1992a,b; Shaw et al., 1999).

Conflicting results regarding parental pesticide exposure and CHDs may reflect several methodological challenges in the study of CHDs and occupational exposures. Because of small sample sizes, some previous studies have analyzed all CHDs as a group, even though the specific subtypes comprising the aggregate might be etiologically distinct disorders (Botto et al., 2007). Differences in exposure assessment methods and exposure misclassification inherent to some of the methods used (e.g., job title alone) might also be partially responsible for the inconsistent findings of studies of occupational pesticide exposure (Daniels et al., 2001). Population-based studies with improved exposure assessments are needed to further our understanding of the relationship between pesticide exposure and CHDs.

In this report, we examine the associations between subtypes of CHDs and maternal occupational exposure to insecticides, herbicides, and fungicides at the time of conception and in early pregnancy. For this purpose, we leverage unique features of the National Birth Defects Prevention Study (NBDPS), including a large overall sample size, detailed self-reported occupational histories, and industrial hygienist-assessed potential exposure to pesticides.

Methods

STUDY POPULATION

We used data from the NBDPS, a population-based case-control study of birth defects based on 8 surveillance systems (Arkansas, California, Iowa, Georgia, Massachusetts, New Jersey, New York, and Texas); details of the study design and methods have been described elsewhere (Yoon et al., 2001). Briefly, cases were ascertained through active birth defects surveillance programs in each state. Controls were a random sample of live births without major birth defects in the same geographic areas. Controls were identi-

fied from hospital delivery logs (Arkansas, California, Georgia [1997–2000], New York, Texas) or birth certificate files (Georgia [2001–2002], Iowa, Massachusetts, and New Jersey).

Computer-assisted telephone interviews were administered in English or Spanish no sooner than 6 weeks and no later than 24 months after the estimated date of delivery (EDD, also referred to as “due date”). The interview collected data on demographics, pregnancy characteristics, family history, medical and prenatal care, diet and lifestyle, and occupational history. The overall participation rate was 69.1% for control mothers and 71.6% for case mothers.

CASE CLASSIFICATION AND CLINICIAN REVIEW

Using medical record review, clinical geneticists excluded cases with known syndromes or suspected chromosomal abnormalities. Clinicians with expertise in pediatric cardiology classified CHDs by phenotype as well as classifying each case on two complexity axes: the first axis focused on the heart itself, and the second on the case as a whole (Rasmussen et al., 2003; Botto et al., 2007). On the first axis, cardiac defects that were anatomically discrete or a well-recognized single entity were classified as “simple” (e.g., tetralogy of Fallot or transposition of the great arteries); hearts with common uncomplicated combinations were considered “associated” (e.g., ventricular septal defect and atrial septal defect); and hearts with three or more distinct defects were considered “complex” (e.g., single ventricle complex). On the second axis, cases without major extracardiac defects were considered to have an “isolated” phenotype; cases with major extracardiac defects were considered to have a “multiple” phenotype.

Because pesticide exposure was infrequent, we made an a priori decision to collapse rare phenotypes (<100 cases) into larger case groups according to the NBDPS classification strategy (Botto et al., 2007). In the main analysis, we restricted to cases with isolated complexity and simple CHDs. We also included isolated cases of single ventricle (complex CHD) and isolated cases of ventricular septal defects with atrial septal defects (associated CHD).

EXPOSURE ASSESSMENT

Analysis was restricted to mothers who held at least one job (defined as paid, volunteer, or military service; including both full and part-time jobs; and jobs worked from home, on a farm, or outside of the home) for at least 1 month at any time during the 3 months before conception through the end of their pregnancies. Job descriptions provided during the maternal interview included the name of the employer, a job title, descriptions of what the employer produced or the service it provided, main job activities or duties, chemicals or substances handled or machines used on the job, usual number of days worked per week and hours worked per day, and the month and

year the job was started and (if applicable) ended (Yoon et al., 2001).

A retrospective exposure assessment was performed on the job descriptions provided by mothers with an EDD between October 1, 1997 and December 31, 2002 (the most recent data available at the time the exposure assessment began). Each reported job was given a North American Industry Classification System 2007 and 2000 Standard Occupational Classification code. Probable exposure to herbicides, insecticides, and fungicides was assigned for each job. A literature-based Job-Exposure Matrix (Samanic et al., 2008) was initially used to assign “typical” pesticide exposures ratings to each job based on its Standard Occupational Classification and North American Industry Classification System codes; these ratings were then reviewed by an industrial hygienist, using a job-specific task-exposure matrix and/or expert opinion, who determined whether ratings should be modified based on the specific information the mother provided about the job. Jobs considered possibly exposed to any type of pesticide were assigned a score for probable exposure intensity (<1, 1–9, 10–99, or 100+ mg/hr) and frequency in a typical work week (<2, 2–9, 10–19, and 20+ hr per week) for that pesticide type.

Though mothers reported jobs held in the 3 months before pregnancy and throughout the entire pregnancy, the critical period of exposure for CHDs is believed to be the 1 month before conception through the end of the first trimester (or termination of the pregnancy, if the pregnancy ended in less than 90 days from the date of conception) (Garcia, 1998; Shi and Chia, 2001). Estimated cumulative work exposure per job during this period incorporated estimated exposure intensity, hours worked, and number of days worked and was calculated as: (estimated exposure intensity in mg/hr) * (exposure frequency in hr/week)/[40 hr/week] * [(hours worked per week)/[7 days per week]] * (number of days worked in the exposure window). The resulting exposure dose estimate is job-specific rather than mother-specific; to obtain mother-specific dose estimates we summed exposure across all jobs held in the critical period. Mothers with no pesticide exposure in any job in the critical period were classified as unexposed (including mothers potentially exposed to pesticides in jobs held outside the critical period).

STATISTICAL ANALYSIS

Because there was substantial overlap between insecticide use and use of herbicides and/or fungicides, we classified mothers according to their pesticide exposure pattern (unexposed to any pesticides (reference)/ exposed to insecticides only/ exposed to both insecticides and herbicides/ exposed to all three pesticide types). No mothers were exposed to fungicides only, and we excluded subjects exposed to herbicides only ($n = 7$) or exposed to both insecticides and fungicides ($n = 14$), due to the small num-

ber of exposed cases. We calculated crude odds ratios (ORs) and 95% confidence intervals to examine the relationship between CHD subtypes and exposure to any pesticide (yes/no) or pesticide exposure patterns. For comparison to other studies, we also examined any pesticide exposure (to any type of pesticide) as both a dichotomous and categorical dose variable.

We assessed several covariates for potential confounding: mother’s age, race/ethnicity, birth outside the United States, education, income, prepregnancy body mass index, folic acid intake, smoking, alcohol use, parity, and prepregnancy diabetes; father’s race/ethnicity, birth outside the United States, and education; household income; and the NBDPS site, first-degree family history of CHD, multiple pregnancy, and gestational diabetes in the index pregnancy. Potential confounders were selected based on prior studies and directed acyclic graphs (Greenland et al., 1999; VanderWeele and Robins, 2007). To be considered for inclusion in the model as a potential confounder, variables also had to be associated with both the outcome and exposure (among controls only) based on chi-square tests ($p < 0.20$). To remain in the model, a variable’s removal had to cause >10% change in the OR for the main effects. We created models separately for each CHD subtype and compared results using a common set of adjustment factors. Because there was little difference in the results between these two approaches, we present data with the common adjustment set. Most variables had few missing observations; however, household income had >5% missing data. As such, we used a missing indicator in the main analysis and restricted to complete data in a subanalysis; because there was little difference between those results, we did not impute missing data. We also conducted a subanalysis without any restrictions on the heart or child-defect axes (i.e., no restriction to simple, isolated cases).

The estimated exposure doses are based on mapped intensity and frequency scores rather than actual measurement data; therefore, they lack precision. The estimated exposure doses are better suited to classifying individuals as having relatively higher or lower estimated exposure doses than being used as continuous variables, because we expect their relative accuracy to be better than their absolute accuracy. We constructed categorical variables for each of the three pesticide exposure patterns (insecticides only, both insecticides and herbicides, and joint exposure to all three pesticide classes) with levels defined as no pesticide exposure of any type, less than or equal to the case median for the pesticide pattern (low), and above the case median for that pesticide pattern (high).

All analysis was performed in SAS 9.3 (copyright © 2014, SAS Institute Inc., Cary, NC) and independently replicated by a second analyst (C.M.R. and S.J.B., respectively). Data are not shown when there were three or fewer exposed cases.

TABLE 1. *Characteristics of CHD Case and Control Families of Employed Mothers, NBDPS 1997 to 2002*

Characteristic	CHD cases (N = 3318)		Controls (N = 2979)		Chi-square p-value
	N	%	N	%	
Mother					
Age at conception					0.18
<20 years old	232	(7.0%)	239	(8.0%)	
20–24 years old	738	(22.2%)	640	(21.5%)	
25–29 years old	887	(26.7%)	797	(26.8%)	
30–34 years old	907	(27.3%)	854	(28.7%)	
≥35 years old	554	(16.7%)	449	(15.1%)	
Race and ethnicity					0.92
White, non-Hispanic	2141	(64.5%)	1940	(65.1%)	
Black, non-Hispanic	437	(13.2%)	380	(12.8%)	
Hispanic	592	(17.8%)	521	(17.5%)	
Other	148	(4.5%)	138	(4.6%)	
Born in the United States					0.91 ¹
Yes	2843	(85.7%)	2556	(85.8%)	
No	471	(14.2%)	420	(14.1%)	
Missing / unknown	4	(0.1%)	3	(0.1%)	
Education					<0.01 ¹
Did not complete high school	378	(11.4%)	291	(9.8%)	
Completed high school	1877	(56.6%)	1634	(54.9%)	
Completed college or higher degree	1059	(31.9%)	1049	(35.2%)	
Missing / unknown	4	(0.1%)	5	(0.2%)	
Language of interview					0.04
English	3189	(96.1%)	2891	(97.0%)	
Spanish	129	(3.9%)	88	(3.0%)	
NBDPS site					<0.01
Arkansas	496	(14.9%)	367	(12.3%)	
California	263	(7.9%)	355	(11.9%)	
Georgia	465	(14.0%)	351	(11.8%)	
Iowa	372	(11.2%)	412	(13.8%)	
Massachusetts	513	(15.5%)	424	(14.2%)	
New Jersey	405	(12.2%)	415	(13.9%)	
New York	326	(9.8%)	342	(11.5%)	
Texas	478	(14.4%)	313	(10.5%)	
Household income					0.04 ¹
Less than \$10,000 annually	411	(12.4%)	359	(12.1%)	
10,000–29,999 annually	887	(26.7%)	694	(23.3%)	
30,000–49,999 annually	622	(18.7%)	529	(17.8%)	
50,000 or more annually	1120	(33.8%)	1059	(35.5%)	
Missing / unknown	278	(8.4%)	338	(11.3%)	

TABLE 1. *Continued*

Characteristic	CHD cases (N = 3318)		Controls (N = 2979)		Chi-square p-value
	N	%	N	%	
Pre-pregnancy BMI					<0.01 ¹
<18.5 (under weight)	187	(5.6%)	152	(5.1%)	
18.5–24.9 (normal weight)	1687	(50.8%)	1671	(56.1%)	
25.0–29.9 (over weight)	745	(22.5%)	660	(22.2%)	
≥30 (obese)	629	(19.0%)	437	(14.7%)	
Missing / out of range	70	(2.1%)	59	(2.0%)	
Smoking (1 month before to third month of pregnancy)					0.08 ¹
Yes	746	(22.5%)	616	(20.7%)	
No	2570	(77.5%)	2363	(79.3%)	
Missing / unknown	2	(0.1%)	0	(0.0%)	
Alcohol use (1 month before to third month of pregnancy)					0.01 ¹
Yes	1358	(40.9%)	1317	(44.2%)	
No	1938	(58.4%)	1650	(55.4%)	
Missing / unknown	22	(0.7%)	12	(0.4%)	
Any folic acid supplement use, 1 month before and first month of pregnancy					0.56
No	1575	(47.5%)	1392	(46.7%)	
Yes	1743	(52.5%)	1587	(53.3%)	
Parity					0.47 ¹
Primiparous	1810	(54.6%)	1653	(55.5%)	
Parous	1505	(45.4%)	1325	(44.5%)	
Missing / unknown	3	(0.1%)	1	(0.0%)	
Maternal pre-pregnancy diagnosis of diabetes (Type I or II)					<0.01 ¹
Yes	101	(3.0%)	15	(0.5%)	
No	3210	(96.7%)	2959	(99.3%)	
Missing/unknown	7	(0.2%)	5	(0.2%)	
Gestational diabetes during index pregnancy					0.01 ¹
Yes	173	(5.2%)	117	(3.9%)	
No	3138	(94.6%)	2857	(95.9%)	
Missing/unknown	7	(0.2%)	5	(0.2%)	
Father					
Race and ethnicity					0.17 ¹
White, non-Hispanic	2048	(61.7%)	1893	(63.5%)	
Black, non-Hispanic	483	(14.6%)	407	(13.7%)	
Hispanic	600	(18.1%)	504	(16.9%)	
Other	137	(4.1%)	146	(4.9%)	
Missing/unknown	50	(1.5%)	29	(1.0%)	
Born in the United States					0.73 ¹
Yes	2762	(83.2%)	2472	(83.0%)	
No	526	(15.9%)	482	(16.2%)	
Missing / unknown	30	(0.9%)	25	(0.8%)	

TABLE 1. *Continued*

Characteristic	CHD cases (N = 3318)		Controls (N = 2979)		Chi-square p-value
	N	%	N	%	
Education					<0.01
Did not complete high school	423	(12.7%)	330	(11.1%)	
Completed high school	1856	(55.9%)	1612	(54.1%)	
Completed college or higher degree	951	(28.7%)	967	(32.5%)	
Missing / unknown	88	(2.7%)	70	(2.3%)	
Infant					
Singleton					<0.01 ¹
Yes	3072	(92.6%)	2882	(96.7%)	
No	238	(7.2%)	95	(3.2%)	
Missing/unknown	8	(0.2%)	2	(0.1%)	
1st-Degree family history of CHD					<0.01
Yes	124	(3.7%)	31	(1.0%)	
No known	3194	(96.3%)	2948	(99.0%)	

Chi-Square calculated with missing/unknown data excluded.

NBDPS, National Birth Defects Prevention Study; CHD, congenital heart defect.

Results

We evaluated 7505 jobs held by 6353 mothers of eligible CHD case and control infants. Of these, we excluded 33 mothers with missing/insufficient job descriptions that could affect the overall classification of their exposure. We also excluded 23 mothers who could not complete the interview in English or Spanish without translation assistance. This left 3318 infants with CHDs and 2979 nonmalformed infants eligible for analysis.

Characteristics of case and control families are listed in Table 1. Maternal age, maternal education, language of interview, NBDPS site, household income, prepregnancy body mass index, maternal alcohol use in the month before conception or the first 3 months of pregnancy (B1–P3), maternal prepregnancy diagnosis of diabetes, paternal race/ethnicity, and paternal education were associated with both case or control status and any pesticide exposure among control mothers at $p < 0.20$ and were considered possible confounders.

Overall, 31.5% of case mothers and 30.7% of control mothers were considered potentially occupationally exposed to pesticides. Most of these mothers were either exposed to insecticides only (67.9% of pesticide-exposed mothers); had joint exposure to insecticides, fungicides, and herbicides (24.7% of pesticide-exposed mothers); or had joint exposure to insecticides and herbicides (6.3% of pesticide-exposed mothers) (Table 2). Among jobs considered exposed to insecticides only, school teachers (20.2%), servers in full-service restaurants (10.2%), and sales

workers/cashiers in limited-service eating places (7.0%) were most common in this population. These jobs were typically rated as having low-intensity and low-frequency exposures. The most common jobs rated as exposed to both insecticides and herbicides were hotel and building cleaners (25.9 and 25.2%, respectively) and landlords providing services to buildings and dwellings (14.3%). Jobs exposed to all three pesticide classes were more diverse, with retail sales workers in grocery stores (12.6%), gas stations (7.3%), and agricultural workers in fruit and tree nut farming (6.6%) being the most common (data not shown).

Included CHDs, as a group, were not associated with maternal exposure to insecticides only, both herbicides and insecticides, or all three pesticide classes. This group represents only CHDs eligible for inclusion in NBDPS, rather than any CHD, so care should be exercised in comparing this group to other studies. In analyzing specific CHD subtypes, we observed a crude association only for hypoplastic left heart syndrome with or without ventricular septal defect or anomalous pulmonary venous return (HLHS ± VSD, APVR) and exposure to both herbicides and insecticides (OR = 2.52; 95% CI, 1.12–5.68); refining the case definition to include only HLHS without VSD or APVR increased the estimate (OR = 3.15; 95% CI, 1.39–7.12) (Supplementary Table S1, which is available online). Results were similar, although less precise, after adjusting for maternal education, NBDPS site, income, prepregnancy maternal body mass index, maternal alcohol consumption,

TABLE 2. Patterns of Assessed Occupational Pesticide Exposure, during 1 Month prior through First Trimester of Pregnancy, among Employed CHD Case and Control Mothers, NBDPS 1997 to 2002

Pesticide exposure pattern	CHD cases (n = 3318)		Controls (n = 2979)	
	N	%	N	%
No pesticide exposure	2273	(68.5%)	2063	(69.3%)
Exposed to herbicides only	3	(0.1%)	3	(0.1%)
Exposed to insecticides only	702	(21.2%)	630	(21.1%)
Exposed to fungicides only	0	(0.0%)	0	(0.0%)
Exposed to both herbicides and insecticides	70	(2.1%)	54	(1.8%)
Exposed to both herbicides and fungicides	0	(0.0%)	0	(0.0%)
Exposed to both insecticides and fungicides	8	(0.2%)	6	(0.2%)
Exposed to all three pesticide classes (insecticides, fungicides, and herbicides)	262	(7.9%)	223	(7.5%)

Groups are mutually exclusive.

NBDPS, National Birth Defects Prevention Study; CHD, congenital heart defect.

language of interview, and paternal education (for HLHS \pm VSD, APVR: OR = 2.43; 95% CI, 0.99–5.96; for HLHS without VSD/APVR: OR = 3.15; 95% CI, 1.27–7.82) After adjustment, an association was also observed for secundum atrial septal defect (ASD2, OR = 1.66; 95% CI, 1.04–2.66) and exposure to insecticides, herbicides, and fungicides (Table 3).

In the analysis by dose categories, high (but not low) exposure to insecticides only was associated with a slightly increased risk of any septal defect (OR = 1.30; 95% CI, = 1.02–1.66), and in particular with ASD2 (OR = 1.85; 95% CI, 1.28–2.67), compared with no pesticide exposure. High exposure to herbicides and insecticides was associated with any simple, isolated CHD (OR = 1.90; 95% CI, 1.05–3.44); any right ventricular outflow tract obstructions (OR = 3.40; 95% CI, 1.41–8.16), particularly with pulmonary valve stenosis (OR = 3.64; 95% CI, 1.31–10.15); and HLHS \pm VSD or APVR (OR = 4.10; 95% CI, 1.37–12.26), particularly HLHS without VSD or APVR (OR = 5.11; 95% CI, 1.70–15.35). However, these findings are based on small numbers of exposed cases. Among those with estimated exposure to all three pesticide classes, an association was observed with higher dose and tetralogy of Fallot (OR = 2.17; 95% CI, 1.18–3.97) (Table 4, Supplementary Tables S2–S4). ASD2 was associated with low, but not high, dose exposure to all three pesticides (supplement 4).

We conducted several subanalyses. For comparison with other studies, we evaluated any pesticide exposure as both a dichotomous (yes/no) and categorical (no exposure dose, dose at or below the median, dose above the median) variable (Supplementary Table S5). Because the majority of women rated as exposed to pesticides were rated as exposed to insecticides only, the results tended to

be similar for the analysis of any pesticide exposure and insecticide-only exposure. Creating optimal adjusted models for each CHD subtype separately, compared with using a common set of covariables, yielded similar results to those generated using the common adjustment set. Results were also similar when restricting to complete data for income, instead of using a missing indicator. When we included complex (multiple heart defects) and nonisolated (cases with extracardiac defects) CHDs in analysis, results were generally similar although point estimates were slightly attenuated and less precise for some subtypes (as predicted a priori based on increased heterogeneity of outcomes). Because there has been debate on the appropriateness of grouping Ebstein's anomaly with other right ventricular outflow tract obstruction defects, we excluded these cases from the right ventricular outflow tract obstruction group in the main analysis but conducted a subanalysis including them; results were similar in both groups.

Discussion

Using NBDPS data, we observed a few associations between potential maternal occupational exposure to pesticides in the month before conception and/or the first trimester of pregnancy and CHDs. Small sample sizes prevented us from evaluating dose-response relationships thoroughly, although we observed possible dose-response relationships for exposure to: insecticides only and septal defects, specifically ASD2; insecticides and herbicides and HLHS (both HLHS \pm VSD, APVR, and the more homogenous group of HLHS with intact ventricular septum); insecticides and herbicides and right ventricular outflow tract obstruction defects, particularly pulmonary valve stenosis;

TABLE 3. Maternal Pesticide Exposure Pattern during 1 Month prior through First Trimester of Pregnancy and Simple, Isolated CHDs among Offspring, NBDPS 1997 to 2002: Adjusted Odds Ratios and 95% Confidence Intervals

Outcome	Insecticides only			Herbicides and insecticides			Insecticides, herbicides, and fungicides		
	Exposed (n)	OR	(95% CI)	Exposed (n)	OR	(95% CI)	Exposed (n)	OR	(95% CI)
Non-malformed controls	609			48			200		
Any simple, isolated CHD	422	0.96	(0.83-1.11)	39	1.08	(0.70-1.68)	146	1.03	(0.82-1.30)
Conotruncal defects	111	1.13	(0.89-1.44)	7	0.89	(0.39-2.02)	36	1.05	(0.71-1.55)
d-Transposition of the great arteries	41	1.28	(0.87-1.87)	≤3		(NC)	15	1.30	(0.72-2.34)
d-TGA with intact ventricular septum	26	1.19	(0.75-1.89)	≤3		(NC)	9	1.26	(0.60-2.64)
Tetralogy of Fallot (TOF) and TOF variants ^a	53	1.04	(0.75-1.44)	≤3		(NC)	20	1.11	(0.66-1.86)
Tetralogy of Fallot	35	0.99	(0.66-1.47)	≤3		(NC)	16	1.31	(0.73-2.34)
Atrioventricular septal defects	9	0.75	(0.36-1.59)	≤3		(NC)	4	1.08	(0.37-3.17)
Left ventricular outflow tract obstruction	71	0.95	(0.72-1.27)	8	1.44	(0.66-3.12)	18	0.73	(0.44-1.23)
HLHS +/- VSD, APVR	31	1.00	(0.66-1.53)	6	2.43	(0.99-5.96)	11	1.00	(0.52-1.95)
HLHS	27	1.10	(0.70-1.73)	6	3.15	(1.27-7.82)	10	1.20	(0.59-2.42)
Coarctation of the aorta	27	0.95	(0.60-1.48)	≤3		(NC)	5	0.64	(0.25-1.63)
Right ventricular outflow tract obstruction ^b	52	0.78	(0.56-1.07)	5	0.94	(0.36-2.44)	17	0.91	(0.53-1.54)
Pulmonary valve stenosis (PVS) ^c	45	0.87	(0.61-1.24)	4	0.96	(0.33-2.77)	13	0.93	(0.51-1.71)
Septal defects	156	0.90	(0.73-1.11)	16	1.06	(0.59-1.93)	65	1.18	(0.86-1.61)
Perimembranous VSD	64	0.81	(0.60-1.09)	6	0.83	(0.34-2.00)	25	0.97	(0.62-1.53)
Muscular VSD ^d	24	1.61	(0.92-2.81)	≤3		(NC)	9	1.16	(0.51-2.65)
Secundum atrial septal defect	51	1.04	(0.73-1.47)	5	1.13	(0.42-3.02)	27	1.66	(1.04-2.66)
Isolated VSD plus atrial septal defect	33	1.18	(0.77-1.79)	4	1.81	(0.61-5.36)	12	1.50	(0.78-2.89)
Single ventricle complex	13	0.77	(0.41-1.44)	≤3		(NC)	7	1.40	(0.60-3.24)

All results adjusted for: maternal education, site, income (missing indicator), pre-pregnancy maternal body mass index, maternal alcohol consumption, language of interview, paternal education.

NBDPS, National Birth Defects Prevention Study; CHD, congenital heart defect; CI, confidence interval; NC, not calculated; OR, odds ratio; HLHS, hypoplastic left heart syndrome; VSD, ventricular septal defect; APVR, anomalous pulmonary venous return.

^aIncludes TOF, TOF absent pulmonary valve, pulmonary atresia, and VSD (TOF anatomy), and double outlet right ventricle (TOF type).

^bExcludes Ebstein's anomaly.

^cPulmonary valve stenosis cases from California are limited to those occurring on or after January 1, 2002; consequently, controls from California are also restricted to those born on or after January 1, 2002 in this analysis.

^dIsolated muscular VSD cases were only enrolled between October 1, 1997, and December 31, 1999, from Arkansas and New Jersey, and between October 1, 1997, and September 30, 1998, for all other sites due to sufficient accrual of cases; consequently, controls are also restricted to the same enrollment period in this analysis.

and all three pesticides and classic TOF. While we cannot rule out that some findings are spurious, due to multiple comparisons, these results can guide future investigations.

To our knowledge, this is only the second study of CHDs and maternal occupational pesticide exposure (rather than agricultural occupation as a proxy for pesticide exposure) with sufficient sample size to evaluate multiple specific CHD subtypes. Our results did not confirm the elevated association between TGA and maternal pesticide exposure reported previously (Loffredo et al., 2001), which may be explained by differences in the exposure

assessments—this earlier study relied on self-reported exposure to pesticides, which may be vulnerable to recall bias and errors, but included both occupational and residential sources. We were able to assess occupational pesticide exposure patterns and estimated dose, though in a limited manner due to small case groups.

As research in this area continues, improved classification of exposure is critically important. Several prior studies have relied on agricultural job title to infer possible pesticide exposure; however, agricultural workers also share other potentially hazardous exposures (for

TABLE 4. Maternal Pesticide Exposure Pattern during 1 Month prior through First Trimester of Pregnancy and Congenital Heart Defects among Offspring, NBDPS 1997 to 2002: Crude Odds Ratios and 95% Confidence Intervals for High Dose Exposure Versus None

outcome	no pesticide (n)	high insecticide dose			high insecticide + herbicide dose			high insecticide, herbicide, and fungicide dose		
		exposed (n)	OR	(95% CI)	exposed (n)	OR	(95% CI)	exposed (n)	OR	(95% CI)
Non-malformed controls	2063	281			19			104		
Any simple, isolated CHD	1489	233	1.15	(0.95-1.38)	26	1.90	(1.05-3.44)	72	0.96	(0.71-1.31)
Conotruncal defects	332	52	1.15	(0.84-1.58)	≤3		(NC)	21	1.25	(0.77-2.03)
d-Tranposition of the great arteries	111	19	1.26	(0.76-2.08)	≤3		(NC)	5	0.89	(0.36-2.24)
d-TGA with intact ventricular septum	80	12	1.10	(0.59-2.05)	≤3		(NC)	4	0.99	(0.36-2.76)
Tetralogy of Fallot (TOF) and TOF variants ^a	175	24	1.01	(0.65-1.57)	≤3		(NC)	15	1.70	(0.97-2.99)
Tetralogy of Fallot	119	18	1.11	(0.67-1.85)	≤3		(NC)	13	2.17	(1.18-3.97)
Atrioventricular septal defects	39	5	0.94	(0.37-2.41)	≤3		(NC)	≤3		(NC)
Left ventricular outflow tract obstruction	256	32	0.92	(0.62-1.35)	5	2.12	(0.79-5.73)	8	0.62	(0.30-1.29)
HLHS +/- VSD, APVR	106	16	1.11	(0.65-1.90)	4	4.10	(1.37-12.26)	5	0.94	(0.37-2.34)
HLHS	85	11	0.95	(0.50-1.80)	4	5.11	(1.70-15.35)	5	1.17	(0.46-2.94)
Coarctation of the aorta	95	11	0.85	(0.45-1.61)	≤3		(NC)	≤3		(NC)
Right ventricular outflow tract obstruction ^b	224	31	1.02	(0.68-1.51)	7	3.40	(1.41-8.16)	5	0.44	(0.18-1.10)
Pulmonary valve stenosis(PVS) ^c	173	25	1.08	(0.70-1.68)	5	3.64	(1.31-10.15)	≤3		(NC)
Septal defects	576	102	1.30	(1.02-1.66)	9	1.70	(0.76-3.77)	33	1.14	(0.76-1.70)
Perimembranous VSD	264	38	1.06	(0.74-1.52)	≤3		(NC)	14	1.05	(0.59-1.86)
Muscular VSD ^d	69	11	1.41	(0.69-2.87)	≤3		(NC)	6	1.32	(0.52-3.34)
Secundum atrial septal defect	159	40	1.85	(1.28-2.67)	4	2.73	(0.92-8.13)	10	1.25	(0.64-2.43)
Isolated VSD plus atrial septal defect	94	17	1.33	(0.78-2.26)	≤3		(NC)	7	1.48	(0.67-3.26)
Single ventricle complex	57	6	0.77	(0.33-1.81)	≤3		(NC)	5	1.74	(0.68-4.43)

^aIncludes TOF, TOF absent pulmonary valve, pulmonary atresia and VSD (TOF anatomy), and double outlet right ventricle (TOF type).

^bExcludes Ebstein's anomaly.

^cPulmonary valve stenosis cases from California are limited to those occurring on or after January 1, 2002; consequently controls from California are also restricted to those born on or after January 1, 2002 in this analysis.

^dIsolated muscular VSD cases were only enrolled between October 1, 1997, and December 31, 1999, from Arkansas and New Jersey, and between October 1, 1997 and September 30, 1998, for all other sites due to sufficient accrual of cases; consequently, controls are also restricted to the same enrollment period in this analysis.

NBDPS, National Birth Defects Prevention Study; CHD, congenital heart defect; CI, confidence interval; NC, not calculated; OR, odds ratio; HLHS, hypoplastic left heart syndrome; VSD, ventricular septal defect; APVR, anomalous pulmonary venous return.

example, to fertilizers, zoonotic infection, animal waste products, diesel fuel), and women outside agriculture are also exposed to pesticides. We used expert assessment of job descriptions for our study, which is generally shown to have higher validity than self-reported exposure, job title, or a Job-Exposure Matrix (Teschke et al., 2002) but is more expensive and time-consuming. Even using this method, however, exposure misclassification may occur. We were also only able to assign probable exposure to pesticide classes and not specific chemicals. There are hundreds of individual chemicals classified as herbicides, insecticides, and fungicides. Our OR estimates reflect combined effects of these individual chemicals; we cannot

rule out that some individual pesticides exert different effects than the group as a whole. Additionally, “inactive” ingredients, such as solvents, used in pesticide formulations may also impact risk estimates (Gilboa et al., 2012). Due to extensive overlap between pesticide exposures in our study population, we could not fully separate effects that might be attributable to herbicides alone or fungicides alone. Patterns of pesticide exposure also reflect differences in the types of jobs individuals work; we cannot rule out that some other shared factor among pesticide-exposed jobs—or jobs with shared pesticide exposure patterns—are responsible for any effects we observed.

Another major limitation of our study is that we were unable to examine nonoccupational sources of pesticide exposures due to proximity to agricultural spraying, residential exposures, residues on food, and drinking water contaminants. For example, a recent study in an area of California with intensive agriculture noted several significant associations between maternal residence in close proximity (500 meters or less) to agricultural applications of specific pesticides during the periconceptional period and certain types of congenital heart defects (Carmichael et al., 2014). While occupational exposures can occur at much higher dose and frequency than residential and environmental exposures, this might not be true for the majority of mothers in this study. Most women rated as possibly exposed to pesticides were not actively engaged in pesticide applications and were estimated to have very low intensity and frequency occupational exposures. Residential pesticide applications can incur fairly substantial pesticide exposures, and have even been associated with acute pesticide poisoning. Paternal occupational exposures are often overlooked, as well, but can also be relevant to congenital malformations. Pesticides can impact spermatogenesis, concentrate in semen, or be carried home on clothes and shoes (Pant et al., 2007; Martenies and Perry, 2013). We plan to examine the effects of paternal and combined parental exposure in additional analyses in the future.

Due to the costs and time burden of performing expert rater assessments, only NBDPS births 1997 to 2002 were included in the NIOSH-conducted exposure assessment for pesticides and other chemicals. This analysis, along with other analyses of chemicals included in the NBDPS occupational exposure assessment, can guide prioritization of chemicals for exposure assessment of 2003 to 2012 births in the future. Future studies should focus on both parents' occupational and residential pesticide exposures and focus on improved exposure assessments. Despite the limitations of this study, however, it improves on prior studies in both exposure assessment quality and ability to examine specific subtypes of CHDs, and can be used to guide future research.

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Disclaimer

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