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Residential agricultural pesticide exposures and risk of selected congenital heart defects among offspring in the San Joaquin Valley of California

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ABSTRACT

Background: Pesticide exposures are ubiquitous and of substantial public concern. We examined the potential association of congenital heart defects with residential proximity to commercial agricultural pesticide applications in the San Joaquin Valley, California.

Methods: Study subjects included 569 heart defect cases and 785 non-malformed controls born from 1997 to 2006 whose mothers participated in a population-based case-control study. Associations with any versus no exposure to physicochemical groups of pesticides and specific chemicals were assessed using logistic regression adjusted for relevant covariates, for 8 heart defect phenotypes that included ≥ 50 cases and pesticide exposures with ≥ 5 exposed cases and controls, which resulted in 235 comparisons.

Results: 38% of cases and controls were classified as exposed to pesticides within a 500 m radius of mother's address during a 3-month periconceptional window. Adjusted odds ratios (AORs) with 95% CIs excluding 1.0 were observed for 18 comparisons; all were >1 and ranged from 1.9 to 7.1. They included tetralogy of Fallot ($n=101$ cases) and neonicotinoids; hypoplastic left heart syndrome ($n=59$) and strobins; coarctation of the aorta ($n=74$) and pyridazinones; pulmonary valve stenosis ($n=53$) and bipyridyliums and organophosphates; ventricular septal defects ($n=93$) and avermectins and pyrethroids; and atrial septal defects ($n=132$) and dichlorphenoxy acid or esters, organophosphates, organotins, and pyrethroids. No AORs met both of these criteria for D-transposition of the great arteries ($n=58$) or heterotaxia ($n=53$).

Conclusions: Most pesticides were not associated with increased risk of specific heart defect phenotypes. For the few that were associated, results should be interpreted with caution until replicated in other study populations.

1. Introduction

Congenital heart defects (CHDs) are the most common broad grouping of structural birth defects, affecting close to one percent of infants and comprising close to a third of all infants with birth defects (Bjornard et al., 2013). CHDs include a variety of phenotypes with differing pathogeneses and likely etiologies. In general, a combination of environmental and genetic factors likely contributes to the etiologies of CHDs, but beyond that, our knowledge is relatively limited. Some known risk factors for CHDs include maternal race-ethnicity, age, smoking, diabetes, and use of some medications, but specific associations vary for different specific phenotypes (Patel and Burns, 2013).

Abbreviations: AOR, adjusted odds ratio; OR, odds ratio; CHD, congenital heart defects; NBDPS, National Birth Defects Prevention Study; VSD, ventricular septal defect; ASD, atrial septal defect; EPA, Environmental Protection Agency; RfD, Reference Dose; CEHTP, California Environmental Health Tracking Program; PUR, Pesticide Use Reporting; PLSS, public land survey sections; CO, carbon monoxide; NO, nitrogen oxide; NO_2, nitrogen dioxide; O_3, ozone; PM_{10}, particulate matter ≤ 10 μm; $PM_{2.5}$, particulate matter ≤ 2.5 μm; CI, confidence intervals

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Exposure to pesticides is ubiquitous, and public concern regarding their potential harmful effects is extensive. Some experimental studies suggest that certain pesticides are teratogenic (Kopf and Walker, 2009). However, associations from human studies are few and not clear (Wigle et al., 2008). Pesticides comprise a variety of different chemicals, with varying biologic effects, and with varied routes of exposure, making it challenging to study human exposure. Pesticides and other environmental chemical exposures have been suggested to be associated with CHDs but evidence is too limited to draw conclusions (Wigle et al., 2008). Few studies have examined specific CHD phenotypes (Correa-Villasenor et al., 1991; Erickson et al., 1984; Loffredo et al., 2001; Shaw et al., 1999; Tikkanen and Heinonen, 1990; Wilson et al., 1998), which is important given potential etiologic heterogeneity by phenotype. Previous studies relied on self-reported, broad categories of exposure (e.g., lived near agricultural crops or used pesticides at home or work). None of them examined exposure to specific chemicals.

For this study, we examined whether residential proximity to applications of specific pesticide chemicals was associated with risk of specific CHD phenotypes. To do this, we linked detailed data on CHD phenotypes from a population-based birth defects registry with detailed publicly available data regarding commercial agricultural applications of pesticides. We determined which specific pesticides were applied within a 500 m radius of the mother's residential address during early pregnancy, when heart development takes place. Births occurred in the San Joaquin Valley of California, one of the highest pesticide use areas in the U.S.

2. Methods

2.1. Study population

The California Center of the National Birth Defects Prevention Study (NBDPS) is a collaborative partnership between Stanford University and the California Birth Defects Monitoring Program in the Department of Public Health (Yoon et al., 2001). Since 1997, the Center has collected data from women whose residence at the time of delivery was one of eight counties in the San Joaquin Valley. The California Birth Defects Monitoring Program is a well-known surveillance program that is population-based (Croen et al., 1991). To identify cases with birth defects, data collection staff visit all hospitals with obstetric or pediatric services, cytogenetic laboratories, and all clinical genetics prenatal and postnatal outpatient services. This analysis included study subjects with estimated dates of delivery from October 1, 1997 to December 31, 2006. The study protocol was reviewed and approved by the institutional review boards of Stanford University and the California Department of Public Health.

Cases included infants or fetuses with CHDs confirmed by echocardiography, cardiac catheterization, surgery, or autopsy reports. Most diagnoses occurred in the first year. A central team of clinicians with expertise in pediatric cardiology and medical genetics reviewed the available clinical documentation to code and classify the CHDs of each case infant, as described (Rasmussen et al., 2003). Briefly, each infant's CHDs were classified into one of three categories: simple, association, or complex, depending on the cardiac phenotype. For example, an infant with perimembranous ventricular septal defect but without any other cardiac abnormality would be classified as simple. If a secundum atrial septal defect was also present, it would be classified as an association. A ventricular septal defect in the context of a single ventricle phenotype (e.g., double inlet left ventricle) would not be classified or counted as a ventricular septal defect, but only as a single ventricle, double inlet left ventricle type. The complex category includes a small group of phenotypes with multiple structural cardiac findings, as can occur for heterotaxy or certain single ventricle phenotypes (Rasmussen et al., 2003). Eligible cases of heterotaxy were those with major eligible CHDs associated with situs ambiguous or situs inversus. To improve case homogeneity, analyses focused on CHDs classified as simple, with the inclusion of heterotaxy, which was classified as complex. Cases recognized or strongly suspected to have single-gene disorders, chromosomal aneuploidy, or identifiable syndromes were ineligible, assuming that their etiologies are known. We included eight CHD phenotypes for which we had maternal interviews and pesticide exposures data (see below) for at least 50 cases: heterotaxia, tetralogy of Fallot, D-transposition of the great arteries, hypoplastic left heart syndrome, coarctation of the aorta, pulmonary valve stenosis, perimembranous ventricular septal defect (VSD), and atrial septal defect (ASD) secundum.

Controls included non-malformed live-born infants randomly selected from birth hospitals to represent the population from which the cases arose. That is, we selected approximately 150 controls per study year, such that their distribution by hospital was proportional to the underlying birth population. Maternal interviews were conducted using a standardized, computer-based questionnaire, primarily by telephone, in English or Spanish, between 6 weeks and 24 months after the infant's estimated date of delivery. Interviews were conducted with mothers of 70% of eligible cases ($n=704$) and 69% of controls ($n=974$). Interviews were completed within an average of 12 months from estimated date of delivery for cases and 8 months for controls. Because poorly managed pregestational diabetes (i.e. type I or II) has been associated with increased risk of birth defects (Correa et al., 2008), cases ($n=30$) and controls ($n=7$) whose mothers had diabetes were excluded from analyses. Mothers reported their residential history from 3 months before conception through delivery, including dates and residences occupied for more than 1 month.

2.2. Selection of pesticide compounds

We assessed exposure to 461 individual chemicals and 62 physicochemical groupings having the same chemical classification and proven or putative mechanism of action (e.g., organophosphates) that were applied at >100 lb in any of eight SJV counties in any year during the study period (1997–2006) (Kegley et al., 2011). Low-toxicity chemicals such as biopesticides (e.g., microbial pesticides, soaps, essential oils), low-toxicity inorganic compounds (e.g., sulfur), and other compounds determined by US EPA to have low toxicity, as described in US EPA Risk Assessment documents for each chemical were excluded (Agency, 2012). In addition, compounds were flagged as having reproductive or developmental toxicity based on the California Proposition 65 list or as endocrine disruptors (California Office of Environmental Health Hazard Assessment, 2012; Colborn, 1996; European-Commission, 2000; Keith, 1997). Chemicals with a US EPA-determined Reference Dose (RfD) based on a toxicological study with a reproductive or developmental endpoint as described in EPA risk assessment documents were also included (Agency, 2012).

2.3. Pesticide exposure assessment

Off-site transport of pesticides occurs via airborne drift of aerosols and dust particles from spray applications (spray drift), post-application volatilization drift from evaporation of semi-volatile and volatile pesticides from leaf and soil surfaces, and leaching through soils into groundwater. Thus, proximity to pesticide use is one measure of exposure that can occur through inhalation of volatilized pesticides and spray drift and incidental oral exposures from contaminated house dust. For this analysis, pesticide use is considered to be a proxy for exposure via spray drift and volatilization drift.

For each case or control mother, we estimated pesticide exposure from 1 month before to 2 months after her reported date of conception (B1-P2), which is inclusive of the time period of heart development. The California Environmental Health Tracking Program (CEHTP) Geocoding Service was used to geocode study each subject's residences corresponding to this time window (California Environmental Health Tracking Program, 2012b). The CEHTP Geocoding Service standardizes, verifies, and corrects addresses before matching against multiple address-attributed reference databases. Geocoding was successful for 87% of cases (585 of 674) and 83% of controls (807 of 967). Exposure assignments were made for 569 heart defect cases and 785 controls whose mothers lived at the geocoded addresses more than 68 days during B1-P2 (i.e., at least 75% of the 3-month window). For those mothers who reported multiple addresses, days at each address were used as the weighting for exposure assignment.

To estimate pesticide applications, we obtained statewide Pesticide Use Reporting (PUR) records from the California Department of Pesticide Regulation describing agricultural pesticide applications occurring between 1 January 1997 and 31 December 2006. These data are submitted by county agriculture commissioners and are spatially referenced to public land survey sections (PLSS). During the 10-year study period, the total number of active ingredient daily production agricultural use records with a public land survey section specified, and for the 461 chemicals that were present in PUR records, was 23,883,704. Following the method of Rull and Ritz (2003), we spatially refined PLSS polygons through overlay of matched land-use survey field polygons provided by the California Department of Water Resources; that is, we refined the pesticide application to a specific polygon, which is smaller than the 1-square-mile area of the PLSS polygon. We matched each PUR record to the land-use survey conducted closest in time to the application date (surveys are conducted roughly every 5–7 years in each California county). Matching is based on location and crop type as specified in records. Infrequently rotated crops, such as orchard crops and vineyards, were matched one-to-one, while frequently rotated crops, such as field and truck crops, were grouped together in a single category, and non-agricultural land-uses were subtracted from PLSS polygons when no crop types were matched to available polygons. Of the total applications (and active-ingredient poundage) recorded spanning 1997–2006 for the 461 chemicals of interest, 91.3% (92.1% by poundage) were successfully linked to polygons – 31.8% (42.0% by poundage) were matched on individual crop, 56.4% (46.9% by poundage) were under the “frequently rotated” category, and 3.0% (3.1% by poundage) were refined, subtracting non-agricultural land-use polygons from