HHS Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2017 July 25.

Published in final edited form as:

Environ Res. 2014 November ; 135: 133–138. doi:10.1016/j.envres.2014.08.030.

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).

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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.

Keywords

Pesticides; Environment; Birth defects; Endocrine disruptors; Pregnancy

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).

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, perimem-branous 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 PLSS polygons. For the remaining 8.7% of applications (7.9% by poundage), no field polygon was specified and therefore no spatial refinement was possible. We determined temporal proximity by comparing recorded dates of applications (which are believed to be accurate within a few days) to the appropriate time window for each study subject.

To assign exposure, we utilized the CEHTP Pesticide Linkage Tool, a custom-developed Java (Oracle, Redwood Shores, CA) application which incorporates the GeoTools Java GIS Toolkit, version 2.7.1 (open source, http://geotools.codehaus.org/) for GIS data management and spatial analysis (California Environmental Health Tracking Program, 2012a). We calculated pounds of pesticides used during the relevant time window within a 500 m radius of a geocoded point, intersecting polygons with the buffer, and assuming homogeneous distribution of pesticides within each polygon (Roberts et al., 2007).

2.4. Air pollutants exposure assessment

In an earlier investigation we explored daily metrics of the following air pollutants: carbon monoxide (CO), nitrogen oxide (NO), nitrogen dioxide (NO_2), ozone (O_3), particulate matter ≤ 10 μm (PM_{10}), and PM ≤ 2.5 μm ($PM_{2.5}$) in aerodynamic diameter. Details of this work can be found elsewhere (Padula et al., 2013). We further considered these measures in the current analysis as a means of capturing a more comprehensive environmental exposure burden. Briefly, employing ambient air quality data collected routinely at over 20 locations

in the San Joaquin Valley by the US EPA's Air Quality System database (www.epa.gov/ttn/airs/airsaqs), we estimated quartile levels among the controls of CO, NO, NO_2, O_3, PM_{10}, and $PM_{2.5}$. We also estimated traffic density measures from distance-decayed annual average daily traffic volumes within a 300 m radius of geo-coded maternal residences using the CEHTP web-based traffic volume linkage tool (www.cehtp.org/page.jsp?page_key=136).

2.5. Statistical analysis

Risks associated with pesticide exposures were estimated using logistic regression. Analyses estimated odds ratios and 95% confidence intervals (CI) reflecting associations between any versus no exposure to each pesticide or pesticide group of interest and selected CHDs. Associations of any versus no exposure to any pesticide with numerous covariates (maternal education, prepregnancy body mass index, use of folic acid-containing supplements, smoking, or alcohol drinking, parity, plurality) were examined in bivariate analyses among 785 controls; no substantial associations were observed (results not shown). However, based on previous reported risk factors for CHDs, we adjusted odds ratios for race/ethnicity (non-Hispanic white, U.S.-born Hispanic, foreign-born Hispanic, other), education (less than high school, high school, more than high school), age at delivery (year, continuous), any (versus none) intake of folic acid-containing supplements, alcohol, and smoking during the month before or the first two months of pregnancy.

To focus on comparisons likely to have the most precise risk estimates and to fully utilize available data, we did the following. Only heart defect groupings with at least 50 cases (described above; 569 total cases) were included in risk estimation, and adjusted odds ratios (AORs) were estimated only for pesticide chemicals or chemical groups that had at least 5 exposed cases and 5 exposed controls. In addition, we created overall exposure scores by summing the total number of chemicals or groups, endocrine disruptors, Proposition 65 chemicals, or EPA reproductive or developmental toxicants to which each case or control was exposed. We examined the association of specific heart phenotypes with these scores specified as categorical variables (exposed subjects were divided into tertiles based on the control distributions).

After following the sample size criteria described above, we were left with a large number of comparisons (see below). To guard against multiple testing error, we further stipulate that all reportable odds ratios must (1) have confidence intervals excluding 1.0 or (2) be less than or equal to 0.5 or greater than or equal to 2.0. (Results that did not meet these criteria are available upon request.) Analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, 2012–2013).

3. Results

Comparisons of various descriptive factors between the 785 control mothers and the mothers of the overall grouping of 569 CHD case infants did not reveal substantive differences (Table 1).

Women were exposed to 53 groups of chemicals and 248 individual chemicals during the month before or first two months of pregnancy based on residential proximity within 500 m

of pesticide applications. Overall, 38.1% of control mothers (299/785) and 38.0% of case mothers (216/569) had any periconceptional pesticide exposure. The five chemical groups to which control mothers were most frequently exposed (i.e., any versus no use near their residence) were polyalkyloxy compounds (polymers made by condensation of ethylene oxide and an alcohol, used as adjuvants) (25%), phosphonoglycine herbicides (22%), organophosphorus insecticides (17%), simple alcohols/ethers (17%), and pyrethroids (14%).

We estimated AORs only for chemicals or chemical groups for which at least 5 case mothers and 5 control mothers were exposed. Table 2 shows the number of chemical groups and specific chemicals that met this criterion for risk estimation by specific CHD phenotype.

Table 2 also shows the number of cases per phenotype, which ranged from 53 to 132.

Tables 3 and 4 show AORs that met our criteria of being ≥ 2.0 or ≤ 0.5 or having confidence intervals that excluded 1.0. 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.

Chemical groups with confidence intervals that excluded 1.0 were observed for: tetralogy of Fallot with neonicotinoids, hypoplastic left heart syndrome with strobins, coarctation of the aorta with pyridazinones, pulmonary valve stenosis with bipyridyliums and organophosphates, ventricular septal defects with avermectins, and atrial septal defects with dichlorophenoxy acid salts or esters (Table 3). AORs ranged from 2.3 to 2.9.

Specific chemicals that had AORs with confidence intervals excluding 1.0 ranged from 1.9 to 7.1 and were observed for tetralogy of Fallot (imidacloprid, a neonicotinoid), hypoplastic left heart syndrome (azoxystrobin, a strobin), coarctation of the aorta (norflurazon, a pyridazinone), pulmonary valve stenosis (2,4-D, dimethylamine salt, a dichlorophenoxy acid salt; and paraquat dichloride, a bipyridylium compound); ventricular septal defects (abamectin, an avermectin); and atrial septal defects (hexazinone; 2,4-D, dimethylamine salt, a dichlorophenoxy acid or ester; chlorpyrifos, an organophosphate; fenbutatin-oxide, an organotin; and lambda-cyhalothrin, a pyrethroid) (Table 4).

Scores reflecting the number of pesticides to which women were exposed did not suggest an increasing risk associated with increasing numbers of pesticides (data not shown). Analyses examining combinations of pesticide and air pollutant exposures also did not suggest increasing risk with these combined exposures relative to neither (data not shown).

4. Discussion

We examined the association of residential proximity to commercial applications of pesticides with risks of specific types of CHDs among offspring of women living in the San Joaquin Valley of California, one of the highest pesticide-use areas in the U.S. Thirty-eight percent of women lived within 500 m of a pesticide application during the periconceptional period and were classified as having exposure to 53 groups of chemicals and 248 specific chemicals. Among the chemicals with sufficiently common exposure to merit risk estimation few were associated with substantially increased risk. Among those that were, results should

be interpreted with caution, given the possibility of chance as an alternate explanation because of the relatively large number of comparisons that were made.

Few studies have examined risks of CHDs and pesticide exposures. Their results as well as their methods have varied. For example, a study in Finland reported that occupation-related exposure to pesticides was not associated with hypoplastic left heart syndrome (Tikkanen and Heinonen, 1990). A U.S. study reported that overall prevalence of heart malformations was not higher in high wheat-producing counties (a proxy for exposure to chorophenoxy herbicides) (Schreinemachers, 2003). Other U.S. studies suggested conotruncal heart defects (which include D-transposition of the great arteries and tetralogy of Fallot) were associated with self-reported pesticide exposures via household or occupational use (Loffredo et al., 2001; Shaw et al., 1999). We are unaware of previous epidemiologic investigations of associations of more specific pesticide chemical exposures with CHDs overall or their specific sub-phenotypes. One study reported an association of the antifungal medication fluconazole with certain heart defects (Molgaard-Nielsen et al., 2013). We observed an association of azoles, a group of widely used crop fungicides, with coarctation of the aorta; this phenotype was not examined in the fluconazole study. We observed associations of tetralogy of Fallot with neonicotinoids and of hypoplastic left heart syndrome with strobins. Use of these two classes of chemicals has increased in recent years (DPR, 2014). We were unable to find published animal teratology studies that observed the specific phenotype-chemical associations reported in our current study. Some animal studies have observed teratogenic effects of pesticide exposures on the developing heart, but they are highly variable with regard to specific chemicals and specific heart defects investigated (Kopf and Walker, 2009). Given this variability, as well as limitations inherent to applying animal studies to humans, we do not propose more specific connections between our findings and experimental studies.

Strengths of the current study include the population-based design, large numbers of infants with specific heart defect phenotypes, maternal residential addresses from the relevant embryonic time period, data on many potential covariates, and pesticide exposure assessment that was spatially and temporally specific and encompassed a broad spectrum of specific pesticide compounds. An important limitation was the modest sample sizes for many comparisons, which limited the precision of the estimates and their attendant inferences. In addition, the exposure assessment did not take into account other factors that may affect actual exposures (e.g., chemical half-lives and vapor pressure, wind patterns, an individual's ability to metabolize the chemicals, and other sources of pesticide exposure such as occupation or home use). It is notable however that most pesticides are prone to drift and detectable in air samples at locations beyond the application site (Kegley et al., 2011), and residential proximity to pesticide-treated fields has been associated with household dust and urine levels (Fenske et al., 2005; Simcox et al., 1995). Errors in exposure assessment may have occurred due to variable amounts of time away from home but we do not have reason to believe that this time would have varied systematically for cases versus controls.

We made 235 comparisons (although the number per phenotype ranged from 16 to 50). Given our goal to perform a hypothesis-generating study, we did not correct results for multiple comparisons or restrict presentation of results to strict criteria of statistical

significance. Thus, the results we have highlighted should be interpreted with caution. We would also like to note, however, that a fundamental property of false positive findings generated through multiple testing is that the resulting coefficients should be distributed symmetrically around zero. Our results depart from this symmetry, i.e., no negative coefficients meeting our reporting criteria. Although the departure from symmetry does not exclude the possibility that some results may arise from multiple testing, it adds some credibility to the idea that residential proximity to pesticide applications or some unknown confounding variable may be associated with cardiac organogenesis.

Results of this study do not in general indicate strong associations of specific CHDs with residential proximity to pesticide applications. These findings were in the context of a high-pesticide use area of the U.S. The study investigated several specific CHD phenotypes and exposure to specific chemicals, which has not been the case for most previous studies of CHDs and environmental exposures. Results regarding observed associations with specific chemicals or groups of chemicals require further inquiry and verification before firm conclusions can be reached regarding potential teratogenicity.

Acknowledgments

We thank the California Department of Public Health Maternal Child and Adolescent Health Division for providing data. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the California Department of Public Health. This work would not have been possible without the tremendous intellectual contribution of our dear colleague Craig Wolff, who passed away during the course of this research.

Funding source

This project was partially supported by Gerber Foundation (11NC-010-1359-2988-02), CDC (6U01DD000489), and NIH (P20ES018173, P01ES022849, and K99ES021470). The sponsors had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

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

References

Agency, U.E.P., Pesticide Chemical Search. [accessed 15.08.14] U.S. Environmental Protection Agency, Office of Pesticide Programs. 2012. ⟨http://www.epa.gov/pesticides/chemicalsearch⟩

Bjornard K, Riehle-Colarusso T, Gilboa SM, Correa A. Patterns in the prevalence of congenital heart defects, metropolitan Atlanta, 1978 to 2005. Birth Defects Res. A Clin. Mol. Teratol. 2013; 97:87–94. [PubMed: 23404870]

California Environmental Health Tracking Program. Agricultural Pesticide Mapping Tool. 2012a [accessed 15.08.14] ⟨http://cehtp.org/p/tools_pesticide⟩.

California Environmental Health Tracking Program, Geocoding Service. 2012b [accessed 15.08.14] ⟨http://cehtp.org/geocoding⟩.

[accessed 15.08.14] California Office of Environmental Health Hazard Assessment, Proposition 65. 2012. ⟨http://www.oehha.ca.gov/prop65.html⟩

Colborn T. Widespread pollutants with reproductive and endocrine-disrupting effects. Our Stolen Future web site. 1996 [accessed 15.08.14] ⟨http://www.ourstolenfuture.org/basics/chemlist.htm⟩.

Correa-Villasenor A, Ferencz C, Boughman JA, Neill CA. Total anomalous pulmonary venous return: familial and environmental factors. The Baltimore-Washington Infant Study Group. Teratology. 1991; 44:415–428. [PubMed: 1962287]

Correa A, Gilboa SM, Besser LM. Diabetes mellitus and birth defects. Am. J. Obstet. Gynecol. 2008; 199:231–239.

Croen LA, Shaw GM, Jensvold NG, Harris JA. Birth defects monitoring in California: a resource for epidemiological research. Paediatr. Perinat. Epidemiol. 1991; 5:423–427. [PubMed: 1754501]

DPR, Pesticide Use Reporting Data. [accessed 15.08.14] California Department of Pesticide Regulation. 2014. ⟨http:/www.cdpr.ca.gov/docs/pur/purmain.htm⟩

Erickson JD, et al. Vietnam veterans' risks for fathering babies with birth defects. J. Am. Med. Assoc. 1984; 252:903–912.

European Commission, Towards the Establishment of a Priority List of Substances for Further Evaluation of Their Role in Endocrine Disruption, Appendix 1. 2000

Fenske RA, et al. Biologic monitoring to characterize organophosphorus pesticide exposure among children and workers: an analysis of recent studies in Washington State. Environ. Health Perspect. 2005; 113:1651–1657. [PubMed: 16263526]

Kegley, S., Hill, B., Orme, S., Choi, A. Pesticide Action Network. San Francisco, CA: 2011. PAN Pesticide Database.

Keith, LH. Environmental Endocrine Disruptors: A Handbook of Property Data. New York: Wiley Interscience; 1997.

Kopf PG, Walker MK. Overview of developmental heart defects by dioxins, PCBs, and pesticides. J. Environ. Sci. Health C Environ. Carcinog. Ecotoxicol. Rev. 2009; 27:276–285. [PubMed: 19953399]

Loffredo CA, Silbergeld EK, Ferencz C, Zhang J. Association of transposition of the great arteries in infants with maternal exposures to herbicides and rodenticides. Am. J. Epidemiol. 2001; 153:529–536. [PubMed: 11257060]

Molgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. N. Engl. J. Med. 2013; 369:830–839. [PubMed: 23984730]

Padula AM, et al. Ambient air pollution and traffic exposures and congenital heart defects in the San Joaquin Valley of California. Paediatr. Perinat. Epidemiol. 2013; 27:329–339. [PubMed: 23772934]

Patel SS, Burns TL. Nongenetic risk factors and congenital heart defects. Pediatr. Cardiol. 2013; 34:1535–1555. [PubMed: 23963188]

Rasmussen SA, et al. Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Res. A Clin. Mol. Teratol. 2003; 67:193–201. [PubMed: 12797461]

Roberts EM, et al. Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley. Environ. Health Perspect. 2007; 115:1482–1489. [PubMed: 17938740]

Rull RP, Ritz B. Historical pesticide exposure in California using pesticide use reports and land-use surveys: an assessment of misclassification error and bias. Environ. Health Perspect. 2003; 111:1582–1589. [PubMed: 14527836]

Schreinemachers DM. Birth malformations and other adverse perinatal outcomes in four U.S. Wheat-producing states. Environ. Health Perspect. 2003; 111:1259–1264. [PubMed: 12842783]

Shaw GM, et al. Maternal pesticide exposure from multiple sources and selected congenital anomalies. Epidemiology. 1999; 10:60–66. [PubMed: 9888281]

Simcox NJ, et al. Pesticides in household dust and soil: exposure pathways for children of agricultural families. Environ. Health Perspect. 1995; 103:1126–1134. [PubMed: 8747019]

Tikkanen J, Heinonen OP. Risk factors for cardiovascular malformations in Finland. Eur. J. Epidemiol. 1990; 6:348–356. [PubMed: 2091934]

Wigle DT, et al. Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. J. Toxicol. Environ. Health B Crit. Rev. 2008; 11:373–517. [PubMed: 18470797]

Wilson PD, Loffredo CA, Correa-Villasenor A, Ferencz C. Attributable fraction for cardiac malformations. Am. J. Epidemiol. 1998; 148:414–423. [PubMed: 9737553]

Yoon PW, et al. The National Birth Defects Prevention Study. Public Health Rep. 2001; 116(Suppl 1):S32–S40.

Table 1

Characteristics of subjects, San Joaquin Valley of California, 1997–2006.

	***Percent of cases*[a] (*n* = 569)**	***Percent of controls*[a] (*n* = 785)**
Maternal race/ethnicity		
White	31	33
U.S.-born Hispanic	22	25
Foreign-born Hispanic	33	28
Other	14	14
Maternal age at delivery (years)		
<20	12	17
20–24	25	28
25–29	31	26
30–34	20	18
>35	11	10
Maternal education (years)		
< 12	33	30
12	29	28
> 12	37	41
Parity		
0	33	37
1	30	31
2+	37	32
Prepregnancy BMI (kg/m^2)		
Underweight BMI (< 18.5)	5	5
Normal weight (18.5 ≤ BMI < 25)	44	47
Overweight (25 ≤ BMI < 30)	23	24
Obese (≥ 30)	22	18
Multi-vitamin Use[b]		
Yes	64	64
No	35	34
Smoking[b]		
None	86	85
Any	14	15
Drinking[b]		
None	73	69
Any	27	31
Plurality		
Singletons	95	99

[a]Percentages may not equal 100 owing to rounding or missing data.

[b] During the month before or the first two months of pregnancy.

Table 2

Percent of cases exposed to pesticides and number of chemical groups and specific chemicals that met case count criteria for risk estimation[a], San Joaquin Valley of California, 1997–2006.

Heart defect	No. of cases	No. (percent) of cases with any pesticide exposure	No. of chemical groups	No. of specific chemicals
Heterotaxia	53	21(39.6%)	9	7
Tetralogy of Fallot	101	37(36.6%)	18	22
D-Transposition of the great arteries	58	20(34.5%)	11	9
Hypoplastic left heart syndrome	59	24(40.7%)	15	12
Coarctation of the aorta	74	27(36.5%)	13	16
Pulmonary valve stenosis	53	22(41.5%)	11	10
VSD perimembranous	93	35(37.6%)	15	17
ASD secundum	132	52(39.4%)	20	30

[a]For each phenotype, the table shows the number of chemical groups and specific chemicals that had at least 5 exposed cases. Risks were only estimated for these chemical groups and specific chemicals. For reference, the study included 785 controls, 299 (38.1%) of whom were exposed to pesticides, and a total of 569 cases.

Table 3

Odds ratios for pesticide chemical groups and congenital heart defects, San Joaquin Valley of California, 1997–2006.[a]

Heart defect	Pesticide group	No. cases exposed/not exposed	No. controls exposed/not exposed	AOR (95% CI)
Heterotaxia	Avermectin	5/48	31/754	2.8(1.0–7.6)
Tetralogy of Fallot	Neonicotinoid	10/91	35/750	**2.4(1.1–5.1)**
Hypoplastic left heart syndrome	Strobin	7/52	33/752	**2.9(1.2–7.0)**
	Triazine	8/51	57/728	2.2(1.0–5.1)
Coarctation of the aorta	Pyridazinone	6/68	23/762	**2.9(1.1–7.5)**
Pulmonary valve stenosis	Dichlorophenoxy acid or ester	6/47	19/383	2.9(1.0–7.9)
	Bipyridylium	11/42	40/362	**2.3(1.1–4.9)**
	Organophosphate	15/38	57/345	**2.5(1.2–5.0)**
	Triazine	6/47	24/378	2.2(0.8–6.0)
Ventricular septal defect, perimembranous	Avermectin	10/83	31/754	**2.8(1.2–6.2)**
Atrial septal defect, secundum	Dichlorophenoxy acid or ester	14/118	41/744	**2.3(1.2–4.5)**

[a]AORs are presented for chemicals for which the AOR was ≤ 0.5 or ≥ 2.0 or for which the confidence interval excluded 1.0. ORs were adjusted for maternal race/ethnicity, education, age (continuous), and any (versus none) intake of folic acid-containing supplements, alcohol, and smoking during the month before and the first two months of pregnancy.

Table 4

Odds ratios for specific pesticide chemicals and congenital heart defects, San Joaquin Valley of California, 1997–2006.[a]

Heart defect	Pesticide name	Pesticide group	No. cases exposed/ not exposed	No. controls exposed/ not exposed	*AOR* (95% *CI*)
Heterotaxia	Abamectin	Avermectin	5/48	31/754	2.8(1.0–7.6)
	Petroleum oil, unclassified	Petroleum derivative	7/46	52/733	2.3(1.0–5.5)
Tetralogy of Fallot	Methomyl	N-methyl carbamate	7/94	23/762	2.3(0.9–5.5)
	Imidacloprid	Neonicotinoid	9/92	31/754	**2.4(1.1–5.4)**
	Ethephon	Organophosphate	6/95	20/765	2.4(0.9–6.2)
	Polyoxyethylene polyoxypropylene	Polyalkyloxy compound	6/95	17/768	2.5(1.0–6.7)
Hypoplastic left heart syndrome	Azoxystrobin	Strobin	6/53	21/764	**4.0(1.5–10.6)**
	Simazine	Triazine	7/52	50/735	2.1(0.9–5.0)
Coarctation of the aorta	Propiconazole	Azole	5/69	19/766	2.6(0.9–7.2)
	Petroleum oil, unclassified	Petroleum derivative	10/64	52/733	2.0(1.0–4.2)
	Norflurazon	Pyridazinone	6/68	23/762	**2.9(1.1–7.5)**
Pulmonary valve stenosis	Oxyfluorfen	n.a.	9/44	39/363	2.0(0.9–4.6)
	2,4-D, dimethylamine salt	Dichlorophenoxy acid or ester	6/47	12/390	**4.5(1.5–13.2)**
	Paraquat dichloride	Bipyridylium	11/42	39/363	**2.3(1.1–5.1)**
	Chlorpyrifos	Organophosphate	7/46	26/376	2.4(1.0–6.3)
	Alpha-[para-(1,1,3,3-tetramethylbutyl)phenyl]-omega-hydroxypoly(oxyethylene)	Polyalkyloxy compound	7/46	24/378	2.2(0.9–5.8)
	Simazine	Triazine	6/47	22/380	2.4(0.9–6.4)
Ventricular septal defect, perimembranous	Abamectin	Avermectin	10/83	31/754	**2.8(1.2–6.2)**
	Permethrin	Pyrethroid	7/86	23/762	2.2(0.8–5.7)
Atrial septal defect, secundum	Hexazinone	n.a.	5/127	5/780	**7.1(1.9–26.0)**
	2,4-D, dimethylamine salt	Dichlorophenoxy acid or ester	11/121	26/759	**3.0(1.4–6.5)**
	Chlorpyrifos	Organophosphate	19/113	67/718	**1.9(1.1–3.4)**
	Fenbutatin-oxide	Organotin	7/125	16/769	**3.0(1.2–7.8)**

Heart defect	Pesticide name	Pesticide group	No. cases exposed/ not exposed	No. controls exposed/ not exposed	*AOR* (95% *CI*)
	Petroleum oil, paraffin based	Petroleum derivative	7/125	25/760	2.0(0.8–5.0)
	Cyfluthrin	Pyrethroid	6/126	13/772	2.6(0.9–7.1)
	Lambda-cyhalothrin	Pyrethroid	6/126	15/770	**2.9(1.1–7.9)**

[a]AORs are presented for chemicals for which the AOR was ≤ 0.5 or ≥ 2.0 or for which the confidence interval excluded 1.0. ORs were adjusted for maternal race/ethnicity, education, age (continuous), and any (versus none) intake of folic acid-containing supplements, alcohol, and smoking during the month before and the first two months of pregnancy.