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Early Pregnancy Agricultural Pesticide Exposures and Risk of Gastroschisis among Offspring in the San Joaquin Valley of California

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Abstract

Background—Prevalence of gastroschisis has inexplicably been increasing over the past few decades. Our intent was to explore whether early gestational exposures to pesticides were associated with risk of gastroschisis.

Methods—We used population-based data, accompanied by detailed information from maternal interviews as well as information on residential proximity to a large number of commercial pesticide applications during early pregnancy. The study population derived from the San Joaquin Valley of California (1997–2006). Cases were 156 infants/fetuses with gastroschisis and controls were 785 infants without birth defects.

Results—Among 22 chemical pesticide groups analyzed, none had an elevated odds ratio with an associated confidence interval that excluded 1.0, although exposure to the triazine group showed borderline significance. Among 36 specific pesticide chemicals analyzed, only exposure to petroleum distillates was associated with an elevated risk, odds ratio = 2.5 (1.1–5.6). In general, a substantially different inference was not derived when analyses were stratified by maternal age or when risk estimation included adjustment for race/ethnicity, body mass index, folic acid supplement use, and smoking.

Conclusion—Our study rigorously adds to the scant literature on this topic. Our a priori expectation was that we would observe certain pesticide compounds to be particularly associated with young age owing to the disproportionate risk observed for young women to have offspring with gastroschisis. We did not observe an exposure profile unique to young women.

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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.

Keywords

abdominal wall; birth defects; congenital abnormalities; endocrine disruptors; pesticides

Introduction

Under experimental conditions, several pesticide compounds have been shown to be teratogenic in animals (Shepherd, 1995). Despite this evidence and substantial concern from the public about potential teratogenic risks, relatively few studies have investigated possible associations between gestational pesticide exposures and specific birth defect phenotypes (Wigle et al., 2008). Although a few associations have been observed, the body of data is insufficient to draw clear inferences (Dolk and Vrijheid, 2003; Wigle et al., 2008). The manifold pesticide compounds in use, the complexity of estimating human exposure to such compounds, and the necessity of having and linking to accurate birth defect data are some of the challenges that have contributed to our knowledge gap.

Four recent studies (Mattix et al., 2007; Winchester et al., 2009; Waller et al., 2010; Agopian et al., 2013) have suggested ecological associations between pesticides and gastroschisis, an abdominal wall birth defect. Gastroschisis has a pathophysiology that is not well understood, but several theories exist (Stevenson et al., 2009). Its most consistently observed risk factor is maternal age of <20 years (Rasmussen and Frias, 2008; Vu et al., 2008). Gastroschisis frequency has been inexplicably increasing around the world for several decades (Castilla et al., 2008). This increase has not been exclusive to young mothers (Vu et al., 2008).

With gastroschisis increasing in frequency among various populations, environmental exposures become a target for etiologic inquiry. Here, we have used population-based data, accompanied by detailed information from maternal interviews as well as information on residential proximity to a large number of commercial pesticide applications during early pregnancy, in an effort to extend the limited extant literature on potential etiologies of gastroschisis. The study population derived from the San Joaquin Valley (SJV) of California, one of the highest pesticide use areas in the United States.

Methods

STUDY POPULATION

The California Center of the National Birth Defects Prevention Study (Yoon et al., 2001) is a collaborative partnership between Stanford University and the California Birth Defects Monitoring Program in the Department of Public Health. Since 1997, the Center has been collecting data from women whose residence at the time of delivery was in one of eight counties in the SJV. 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.

Cases included infants or fetuses with gastroschisis confirmed by clinical geneticists to establish study eligibility based on clinical, surgical, or autopsy reports. Cases recognized or strongly suspected to have single-gene conditions or chromosomal abnormalities or with identifiable syndromes were ineligible (Rasmussen et al., 2003), given their presumed distinct underlying etiology. Each case was also classified as isolated (91%) if there was no additional major unrelated congenital anomaly or as nonisolated (9%) if there was at least one unrelated major anomaly.

Controls included nonmalformed live-born infants randomly selected from birth hospitals to represent the population from which the cases arose (approximately 150 per study year). Maternal interviews were conducted using a standardized, computer-based questionnaire, primarily by telephone, in English or Spanish, between six weeks and 24 months after the infant's estimated date of delivery. Estimated date of conception was derived by subtracting 266 days from expected date of delivery. Expected date of delivery was based on self-report; if unknown, it was estimated from information in the medical record (<2% of participants). Interviews were conducted with mothers of 72% of eligible cases (n = 193) and 69% of controls (n = 974). Interviews were completed within an average of 11 months from estimated date of delivery for cases and 8 months for controls. Because pregestational diabetes (i.e., type I or II) has been associated with birth defects (Waller et al., 2010), cases (n = 0) and controls (n = 7) whose mothers had diabetes were excluded from our analyses. Mothers reported their residential history from three month before conception through delivery, including dates and residences occupied for more than 1 month.

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 U.S. Environmental Protection Agency (EPA) to have low toxicity, as described in U.S. EPA Risk Assessment documents for each chemical (Environmental-Protection-Agency, 2012) were excluded. In addition, compounds were flagged as having reproductive or developmental toxicity based on the California Proposition 65 list (California-Office-of-Environmental-Health-Hazard-Assessment, 2012) or as endocrine disruptors (Colborn, 1996; Keith, 1997; European-Commission, 2000). Chemicals with a U.S. EPA-determined Reference Dose (RfD) based on a toxicological study with a reproductive or developmental endpoint as described in EPA risk assessment documents were included (Environmental-Protection-Agency, 2012).

PESTICIDE EXPOSURE ASSESSMENT

To estimate pesticide exposures, we assigned a time window of exposure for each case or control mother from 1 month before to 2 months after her reported date of conception (B1–P2). The California Environmental Health Tracking Program (CEHTP) Geocoding Service was used to geocode study subjects' residences corresponding to their exposure 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 84% of cases (163/193) and 83% of controls (807/967). Exposure assignments were made for 156 cases and 785 controls whose mothers lived in 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 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 Pesticide Use Reporting 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; i.e., we refined the pesticide application to a specific polygon, which is smaller than the one square mile area of the PLSS polygon. We matched each Pesticide Use Reporting 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 nonagricultural 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 to 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 nonagricultural 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 time window of exposure for each study subject.

To assign exposure, we used 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 subject’s geocoded address (Roberts et al., 2007), intersecting polygons with the buffer, and assuming homogeneous distribution of pesticides within each polygon.

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, 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 (Roberts et al., 2007). We further considered these measures in the current analysis as a means of capturing a more comprehensive environmental exposure burden on study subjects. Briefly, using ambient air quality data collect routinely at over 20 locations in the SJV by the U.S. EPA's Air Quality System database (www.epa.gov/ttn/airs/airsaqs), we estimated quartile levels of CO, NO, NO_2, ozone, PM_{10}, and $PM_{2.5}$, determined by the distribution in the controls. 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 (http://cehtp.org/page.jsp?page_key=136).

STATISTICAL ANALYSIS

Risks associated with pesticide exposures were estimated using logistic regression. Univariate analyses were conducted to estimate crude odds ratios and 95% confidence intervals (CI) reflecting associations between pesticide exposures and gastroschisis. Associations between pesticide exposure (any vs. none) and numerous covariates (maternal education, prepregnancy body mass index, use of folic acid-containing supplements, smoking, or alcohol drinking, parity, plurality, and infant sex) were examined in bivariate analyses among 785 controls with no substantial associations observed (results not shown). However, based on previous reported risk factors for gastroschisis, we performed multivariable analyses adjusting for race/ethnicity (non-Hispanic white, U.S.-born Hispanic, foreign-born Hispanic, and other), prepregnancy body mass index (in kg/m^2, continuous), any (vs. none) use of folic acid-containing supplements, and smoking during the month before and the first 2 months of pregnancy. Analyses were further stratified by maternal age (<20, 20–24, and ≥25 years of age) owing to the known association of young age with gastroschisis.

To focus on comparisons likely to have the most precise estimates and to fully use available data, we did the following. For pesticides that had more than five exposed cases and controls, risks were estimated that compared any versus no exposure. Risks were not estimated for pesticides that had fewer than five exposed cases or controls. We created overall exposure scores by summing the total number of chemicals or groups, endocrine disruptors, Prop 65 chemicals, or EPA reproductive or developmental toxicants to which each case or control was exposed. We examined the association of specific birth defects with these scores specified as continuous variables and as categorical variables (exposed subjects were divided into tertiles based on the control distributions).

Analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, 2012–2013). The study protocol was reviewed and approved by the institutional review boards of Stanford University and the California Department of Public Health.

Results

Relative to controls, mothers of cases were more likely to be U.S.-born Hispanic, younger, less educated, nulliparous, less likely to be obese, and more likely to smoke (Table 1).

Subjects had exposure (based on residential proximity) to 52 groups of chemicals and 233 individual chemicals during the month before or first 2 months of pregnancy within 500 m of their residence. Overall, 35.3% of cases (55/156) and 38.1% of controls (299/785) had any early gestational pesticide exposure. The five chemical groups to which controls were most frequently exposed were polyalkyloxy compounds (polymers made by condensation of ethylene oxide and an alcohol) (25%), glyphosate and its salts (22%), organophosphorus insecticides (17%), simple alcohols/ethers (17%), and pyrethroids (14%).

As noted above, we used a minimum sample size criterion for risk estimation, i.e., pesticides (groups or specific compounds) that had ≥5 exposed cases or controls. We estimated risks for 22 (of 52 total) chemical groups (Table 2) and 36 (of 233 total) specific chemicals (Table 3). As shown in Table 2, none of the 22 chemical groups had an elevated odds ratio with an associated confidence interval that excluded 1.0, although exposure to the triazine group showed borderline significance. Adjustment for race/ethnicity, body mass index, folic acid use, and smoking did not substantially alter observed results. Stratification by maternal age (<20, 20–24, and ≥25 years) did not substantially alter observed results (not shown), with the exception of the chemical group, neonicotinoid, where the adjusted odds ratio for the stratum of women 20 to 24 years old was 6.5 (1.9–22.2).

Among the 36 chemicals shown in Table 3, exposure to oxyfluorfen and petroleum distillates were associated with elevated risks, odds ratios 1.6 (1.0–2.6) and 2.5 (1.1–5.6), respectively. The latter effect was attenuated after adjustment for race/ethnicity, body mass index, folic acid use, and smoking. Stratification by maternal age (<20, 20–24, and ≥25 years) revealed additional elevated risks (confidence not including 1.0) for 20- to 24-year-olds exposed to oxyfluofen of 3.4 (1.4–8.1), for 20- to 24-year-olds exposed to midacloprid of 8.2 (2.2–30.2), and for ≥25-year-olds exposed to petroleum oil (paraffin-based) of 8.1 (2.5–26.9). Owing to previous associations with atrazine and triazine's similarity, the observed odds ratios for triazine for the three age maternal groups (<20, 20–24, and ≥25 years) were: 1.7 (0.6–4.9), 1.2 (0.5–3.0), and 2.1 (0.7–6.5), respectively.

To estimate potential effects associated with cumulative exposures we explored "scores" to various chemical classifications, including number of chemical groups, endocrine disruptors, Proposition 65 listed reproductive toxicants, or EPA listed reproductive or developmental toxicants. Increasing numbers of exposures to any of these classifications did not show elevated risks of gastroschisis either overall or by specific maternal age groups (Table 4). However, small sample sizes in some comparisons do not permit solid conclusions to be drawn about the lack of risks.

We also explored potential risks associated with the combination of pesticide and air pollutant exposures. The case and control mothers for whom we had data on both classes of exposure were a subset of the overall study, i.e., 82 cases and 452 controls. For this subset, any exposure to pesticides (vs. none) had an odds ratio of 0.9 (0.6–1.5), highest quartile air

pollutant exposure (vs. not highest quartile) had an odds ratio of 0.9 (0.5–1.5), and exposure to both (vs. neither) had an odds ratio of 0.8 (0.4–1.7).

Discussion

We explored a potential association between residential pesticide exposures during early pregnancy and risk of gastroschisis. Despite consideration of a variety of exposure definitions such as specific chemicals, groups of chemicals, and cumulative pesticide as well as air pollution exposures, our study showed a general lack of association between these exposures and risk. This study was conducted in an area where agricultural pesticide exposures are likely and where gastroschisis prevalence has been noted to be increasing over time (Vu et al., 2008).

A few chemical-gastroschisis associations emerged, notably triazines and some petroleum compounds. However, owing to the sizable number of comparisons made here, such associations could have emerged by chance alone. The modest association we observed with triazines is compatible with other studies (described below) that reported associations with the related compound, atrazine, and gastroschisis.

This is the first study we are aware of that has attempted to estimate gastroschisis risk on the basis of individual exposure assessment to pesticides as a result of residential proximity to agricultural use. Five studies inform the scant literature on this topic. In a study of farmers in Norway, parental prenatal exposures to pesticides were not associated with increased risks for gastroschisis among offspring (Kristensen et al., 1997). However, that study included a very small number of such infants ($n = 7$ among farmer offspring and $n = 8$ among nonfarmer offspring). Winchester et al. (2009) did not observe higher prevalences of gastroschisis in the U.S. among infants whose mothers' last menstrual periods were in April and July, months the investigators also indicated were highest in surface water levels of atrazine, and that monthly surface water levels of atrazine, but not nitrates, were positively correlated with gastroschisis prevalence. Mattix et al. (2007) reported a positive correlation between monthly prevalence of abdominal wall defects (classified based on the month of the mother's last menstrual period) and average monthly surface water levels of atrazine, but not nitrate, in Indiana. Such correlation studies with limited individual data are challenging to make meaningful inferences from.

Agopian and colleagues (2013) linked county-based estimates of atrazine use with county address at delivery for 1678 women who delivered infants with gastroschisis and 8390 women who delivered nonmalformed infants from Texas. Observed results were somewhat conflicting, with a lowered risk in counties considered to have medium exposure and an elevated risk (specific only to women >24) in counties considered to have high exposure to atrazine (relative to low exposure counties). This large study was challenged by its use of address at delivery rather than at the earlier more pertinent embryologic time and by its countywide estimation of exposure rather than an individual exposure assessment. Waller et al. (2010) conducted a case-control study based on birth certificates in Washington State. These investigators reported an increased risk of gastroschisis among women whose residence was within 50 km of a water source that had elevated levels of atrazine, but not for

women who lived within 50 km of sites with increased concentrations of nitrates, nitrites, or 2,4-dichlorophenoxyacetic salt or ester. A slight increased risk among Spring conceptions for gastroschisis mothers versus controls was suggested as further evidence of an association with atrazine owing to greater agriculture use of atrazine during Spring months. This study, although based on a large case group (n = 805), had several challenges including a reliance on birth certificates as the case ascertainment tool (known for errors), residential history at birth rather than at the earlier more pertinent embryologic time, and the simple metric of distance to surface water as the single proxy to individuals' exposure assessment. However, it is not readily estimable how these various challenges would influence the study's observed results.

Our study has several strengths, including its population-based design, complete case ascertainment by a well-established active birth defects monitoring program, residential history for the relevant embryonic period, and an exposure assessment that was highly detailed and spatially and temporally specific and captured a broad spectrum of pesticide compounds. Our study also had challenges. Sample sizes for many comparisons were modest contributing to imprecision in potential risk estimation. Cases and control with successful geocoding tended to have somewhat higher education than subjects with unsuccessful geocoding. However, we expect any potential bias to be minimal as both cases and controls had such similar patterns. Our assessment of residential proximity to pesticide applications was thorough, but it does not take into account other factors such as qualities of the pesticides and individuals' metabolism or behaviors that would affect actual exposures (e.g., chemical half-lives and vapor pressure, wind patterns, cumulative exposures over time, an individual's ability to metabolize the various types of chemicals, and other sources of pesticide exposure such as occupation or home use). However, it is also notable 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 (Simcox et al., 1995; Fenske et al., 2005). These factors would be nondifferential with respect to case and control status and, therefore, bias results toward the null.

Our study rigorously adds to the scant literature on this topic. However, its primarily hypothesis-generating focus did not identify any strong candidates for further study. Our a priori expectation was that we would observe certain pesticide compounds to be particularly associated with young age owing to the disproportionate risk observed for young women to have offspring with gastroschisis. We did not observe an exposure profile unique to young women.

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TABLE 1

Characteristics (as %) of Subjects, Eight Counties in the San Joaquin Valley of California, 1997 to 2006

	Cases[a] (n = 156)	Controls[a] (n = 785)
Maternal race/ethnicity		
White	25	33
U.S.- born Hispanic	34	25
Foreign-born Hispanic	19	28
Other	21	14
Maternal age at delivery (years)		
<20	41	17
20–24	38	28
>25	21	55
Maternal education (years)		
<12	39	30
12	37	28
>12	22	41
Parity		
0	62	37
1	26	31
2+	12	32
Prepregnancy BMI (kg/m^2)		
Underweight BMI (<18.5)	6	5
Normal weight (18.5 ≤ BMI <25)	66	47
Overweight (25 ≤ BMI <30)	19	24
Obese (≥30)	6	18
Multi-vitamin Use[b]		
Yes	59	64
No	39	34
Smoking[b]		
None	77	85
Any	23	15
Drinking[b]		
None	70	69
Any	30	31
Plurality		
Singletons	100	99
Infant sex		
Male	50	53
Female	50	47

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

[b]During the month before and the first 2 months of pregnancy.

TABLE 2

Odds Ratios for Gastroschisis Associated with Residential Proximity to Pesticide Applications by Chemical Groups, Eight Counties in the San Joaquin Valley of California, 1997 to 2006

Chemical group	Cases (n = 156) Any/no exposure	Controls (n = 785) Any/no exposure	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Dichlorophenoxy salt or ester	11/145	41/744	1.4 (0.7–2.7)	1.6 (0.8–3.2)
Alcohol/ether	31/125	131/654	1.2 (0.8–1.9)	1.3 (0.8–2.1)
Avermectin	7/149	31/754	1.1 (0.5–2.6)	1.3 (0.6–3.2)
Azole	14/142	61/724	1.2 (0.6–2.1)	1.2 (0.6–2.2)
Bipyridylium	20/136	89/696	1.2 (0.7–1.9)	1.1 (0.6–2.0)
Copper-containing compound	19/137	98/687	1.0 (0.6–1.6)	1.0 (0.6–1.7)
2,6-Dinitroaniline	15/141	70/715	1.1 (0.6–2.0)	1.1 (0.6–2.0)
Dicarboximide	11/145	49/736	1.1 (0.6–2.2)	1.1 (0.5–2.2)
Dithiocarbamate	10/146	52/733	1.0 (0.5–1.9)	1.2 (0.6–2.4)
Phosphonoglycine	32/124	169/616	0.9 (0.6–1.4)	1.0 (0.6–1.5)
Halogenated organic	6/150	32/753	0.9 (0.4–2.3)	0.9 (0.3–2.3)
N-Methyl carbamate	12/144	61/724	1.0 (0.5–1.9)	1.1 (0.6–2.2)
Neonicotinoid	9/147	35/750	1.3 (0.6–2.8)	1.4 (0.6–3.0)
Organophosphate	29/127	137/648	1.1 (0.7–1.7)	1.0 (0.6–1.7)
Petroleum derivative	23/133	102/683	1.2 (0.7–1.9)	1.2 (0.7–2.0)
Polyalkyloxy compound	41/115	194/591	1.1 (0.7–1.6)	1.2 (0.8–1.8)
Pyrethroid	18/138	108/677	0.8 (0.5–1.4)	0.8 (0.4–1.4)
Pyridazinone	8/148	23/762	1.8 (0.8–4.1)	1.6 (0.6–3.8)
Silicone	22/134	95/690	1.2 (0.7–2.0)	1.2 (0.7–2.1)
Strobin	5/151	33/752	0.8 (0.3–2.0)	0.7 (0.3–1.8)
Triazine	18/138	57/728	**1.7 (1.0–2.9)**	1.7 (0.9–3.1)
Urea	13/143	53/732	1.3 (0.7–2.4)	1.2 (0.6–2.5)

OR, odds ratio; CI, confidence interval. Boldface values denote odds ratios with associated confidence intervals that do not include 1.0.

[a]Odds ratio adjusted for race/ethnicity, body mass index, folic acid supplement use, and smoking.

TABLE 3

Odds Ratios for Gastroschisis Associated with Residential Proximity to Pesticide Applications by Specific Chemicals, Eight Counties in the San Joaquin Valley of California, 1997 to 2006

Chemical name	Chemical group[a]	Cases (n = 156) Any/no exposure	Controls (n = 785) Any/no exposure	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
Propargite	n.a.	5/151	47/738	0.5 (0.2–1.3)	0.7 (0.3–1.9)
Oxyfluorfen	n.a.	24/132	80/705	**1.6 (1.0–2.6)**	**1.8 (1.0–3.0)**
Cyprodinil	n.a.	5/151	16/769	1.6 (0.6–4.4)	1.7 (0.6–5.0)
2,4-D,dimethylaminesalt	Dichlorophenoxy salt or ester	8/148	26/759	1.6 (0.7–3.6)	1.7 (0.7–4.1)
Isopropylalcohol	Alcohol/ether	29/127	125/660	1.2 (0.8–1.9)	1.3 (0.8–2.1)
Abamectin	Avermectin	7/149	31/754	1.1 (0.5–2.6)	1.3 (0.6–3.2)
Myclobutanil	Azole	9/147	45/740	1.0 (0.5–2.1)	1.1 (0.5–2.4)
Tebuconazole	Azole	5/151	20/765	1.3 (0.5–3.4)	1.1 (0.4–3.2)
Paraquatdichloride	Bipyridylium	20/136	87/698	1.2 (0.7–2.0)	1.2 (0.7–2.1)
Copper hydroxide	Copper	16/140	78/707	1.0 (0.6–1.8)	1.1 (0.6–2.0)
Copper oxide(Ous)	Copper	5/151	14/771	1.8 (0.6–5.1)	1.8 (0.6–5.4)
Oryzalin	2,6-Dinitroaniline	9/147	26/759	1.8 (0.8–3.9)	1.7 (0.7–4.1)
Pendimethalin	2,6-Dinitroaniline	5/151	14/771	1.8 (0.6–5.1)	1.8 (0.6–5.9)
Iprodione	Dicarboximide	10/146	49/736	1.0 (0.5–2.1)	1.0 (0.5–2.1)
Maneb	Dithiocarbamate	5/151	19/766	1.3 (0.5–3.6)	1.9 (0.7–5.4)
Glyphosate, isopropylamine Salt	Phosphonoglycine	30/126	166/619	0.9 (0.6–1.4)	0.9 (0.6–1.5)
Methylbromide	Halogenated organic	6/150	27/758	1.1 (0.5–2.8)	1.1 (0.4–2.9)
Methomyl	N-Methyl carbamate	5/151	23/762	1.1 (0.4–2.9)	1.4 (0.5–3.8)
Imidacloprid	Neonicotinoid	8/148	31/754	1.3 (0.6–2.9)	1.4 (0.6–3.2)
Diazinon	Organophosphate	5/151	34/751	0.7 (0.3–1.9)	0.7 (0.2–2.0)
Dimethoate	Organophosphate	5/151	16/769	1.6 (0.6–4.4)	1.9 (0.6–5.4)
Chlorpyrifos	Organophosphate	15/141	67/718	1.1 (0.6–2.1)	1.0 (0.5–1.8)
Petroleum distillates	Petroleum derivative	9/147	19/766	**2.5 (1.1–5.6)**	2.1 (0.9–5.1)
Petroleum oil, unclassified	Petroleum derivative	16/140	52/733	1.6 (0.9–2.9)	1.7 (0.9–3.3)
Petroleum oil, paraffin based	Petroleum derivative	7/149	25/760	1.4 (0.6–3.4)	1.7 (0.7–4.2)

Chemical name	Chemical group[a]	Cases (n = 156) Any/no exposure	Controls (n = 785) Any/no exposure	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
Alpha-alkylaryl-omega-hydroxypoly(oxyethylene)	Polyalkyloxy compound	9/147	48/737	0.9 (0.5–2.0)	1.0 (0.5–2.2)
Alpha-octylphenyl-omega-hydroxypoly(oxyethylene)	Polyalkyloxy compound	11/145	50/735	1.1 (0.6–2.2)	1.2 (0.6–2.5)
Alpha-(para-nonylphenyl)-omega-hydroxypoly(oxyethylene)	Polyalkyloxy compound	38/118	148/637	1.4 (0.9–2.1)	1.5 (1.0–2.3)
4–Nonylphenol, formaldehyderesin, propoxylated	Polyalkyloxy compound	7/149	39/746	0.9 (0.4–2.0)	0.9 (0.4–2.2)
Alpha-[para-(1,1,3,3-tetramethylbutyl)phenyl]-omega-hydroxypoly(oxyethylene)	Polyalkyloxy compound	11/145	53/732	1.0 (0.5–2.1)	1.2 (0.6–2.5)
Esfenvalerate	Pyrethroid	10/146	52/733	1.0 (0.5–1.9)	0.9 (0.4–2.0)
Norflurazon	Pyridazinone	8/148	23/762	1.8 (0.8–4.1)	1.6 (0.6–3.8)
Dimethylpolysiloxane	Silicone	19/137	80/705	1.2 (0.7–2.1)	1.3 (0.8–2.3)
Silicone defoamer	Silicone	6/150	20/765	1.5 (0.6–3.9)	1.2 (0.4–3.4)
Simazine	Triazine	15/141	50/735	1.6 (0.9–2.9)	1.6 (0.9–3.1)
Diuron	Urea	13/143	51/734	1.3 (0.7–2.5)	1.3 (0.6–2.6)

n.a., not applicable; OR, odds ratio; CI, confidence interval. Boldface values denote odds ratios with associated confidence intervals that do not include 1.0.

[a] n.a. (not applicable) indicates that the chemical was not part of a larger group.

[b] Odds ratio adjusted for race/ethnicity, body mass index, folic acid supplement use, and smoking.

TABLE 4

Adjusted Odds Ratios (ORs) for Sums of Specific Classifications of Pesticide Exposures and Gastroschisis by Maternal Age Groupings, Eight Counties in the San Joaquin Valley of California, 1997 to 2006

	All			<20 years			20–24 years			≥ 25 years		
	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[a]
No. of chemical groups with any exposure												
0	96	450	Reference	39	77	Reference	35	135	Reference	22	238	Reference
1–3	12	83	0.7 (0.3–1.3)	5	15	0.7 (0.2–2.1)	6	18	1.2 (0.4–3.2)	1	50	NC
4–8	22	103	1.0 (0.6–1.7)	11	15	1.5 (0.6–3.7)	8	28	1.1 (0.4–2.6)	3	60	0.7 (0.2–2.3)
9–21	18	84	1.0 (0.6–1.8)	5	20	0.6 (0.2–1.7)	9	23	1.5 (0.6–3.7)	4	41	1.1 (0.4–3.6)
No. of endocrine disruptors with any exposure												
0	101	481	Reference	42	83	Reference	37	143	Reference	22	255	Reference
1	9	62	0.6 (0.3–1.3)	1	11	NC	6	16	1.2 (0.4–3.4)	2	35	NC
2–3	18	82	1.0 (0.6–1.8)	12	13	1.9 (0.8–4.7)	4	20	0.7 (0.2–2.3)	2	49	NC
4–13	20	95	1.1 (0.6–1.9)	5	20	0.6 (0.2–1.7)	11	25	1.8 (0.8–4.2)	4	50	1.0 (0.3–3.2)
No. of Prop. 65 reproductive toxicants with any exposure												
0	125	593	Reference	52	102	Reference	49	178	Reference	24	313	Reference
1	10	82	0.6 (0.3–1.2)	3	15	0.5 (0.1–1.7)	5	18	1.0 (0.3–2.8)	2	49	NC
2–6	13	45	1.5 (0.8–3.0)	5	10	1.2 (0.4–3.8)	4	8	2.4 (0.6–8.8)	4	27	1.9 (0.6–6.3)
No. of reproductive or developmental toxicants with any exposure												
0	98	457	Reference	41	79	Reference	35	138	Reference	22	240	Reference
1–2	16	78	0.9 (0.5–1.6)	8	11	1.4 (0.5–3.9)	7	22	1.2 (0.5–3.1)	1	45	NC

	All			<20 years			20–24 years			≥ 25 years		
	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI) [a]	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[a]
3–6	16	102	0.8 (0.4–1.4)	5	18	0.5 (0.2–1.5)	8	23	1.3 (0.5–3.4)	3	61	0.7 (0.2–2.4)
7–24	18	83	1.1 (0.6–1.9)	6	19	0.8 (0.3–2.1)	8	21	1.5 (0.6–3.9)	4	43	1.1 (0.3–3.4)

OR, odds ratio; CI: confidence interval; NC, not calculated.

[a]ORs not calculated (NC) for cell count <3 in cases or controls. ORs were adjusted for maternal race–ethnicity, body mass index, folic acid supplement use, and smoking. Analyses included subjects with complete date on adjusted covariates.