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Residential agricultural pesticide exposures and risks of preeclampsia

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Abstract

We investigated risks of preeclampsia phenotypes from potential residential pesticide exposures, including 543 individual chemicals and 69 physicochemical groupings that were applied in the San Joaquin Valley of California during the study period, 1998–2011. The study population was derived from birth certificate data linked with Office of Statewide Health Planning and Development maternal and infant hospital discharge data. The following numbers of women with preeclampsia phenotypes were identified: 1045 with superimposed (pre-existing hypertension with preeclampsia) preeclampsia (265 with gestational weeks 20–31 and 780 with gestational weeks 32–36); 3471 with severe preeclampsia (824 with gestational weeks 20–31 and 2647 with gestational weeks 32–36); and 2780 with mild preeclampsia (207 with gestational weeks 20–31 and 2573 with gestational weeks 32–36). The reference population for these groups was 197,461 women who did not have diabetes (gestational or pre-existing), did not have any hypertensive disorder, and who delivered at 37 weeks or later. The frequency of *any* exposure was lower or about the same in each preeclampsia case group (further delineated by gestational age), and month time period, relative to the frequency in reference population controls. Nearly all odds ratios were below 1.0 for these *any* vs no exposure comparisons. This study showed a general lack of increased risks between a range of agriculture pesticide exposures near women's residences and various preeclampsia phenotypes.

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1. INTRODUCTION

Preeclampsia, commonly defined as high blood pressure and proteinuria after 20 weeks of pregnancy, affects upwards of 5% of pregnancies and contributes substantially to maternal morbidity and mortality in the United States (Mol et al. 2016). Factors contributing to elevated risks of preeclampsia include nulliparity, African-American race, obesity, nonsmoking, a clinical history of preeclampsia, hypertension, diabetes, and autoimmune conditions (Jeyabalan 2013). Gene variants in selected pathways such as oxidative stress, inflammation, and angiogenesis have also been put forward as contributors to the risk profile of women who develop preeclampsia (Jebbink et al. 2012).

Environmental exposures have been rarely investigated for their potential etiologic contribution to preeclampsia. Certain pesticide exposures (e.g., organochlorines, have been suggested to elevate risk of hypertensive disorders in general (Morgan et al. 1980; Siddiqui et al. 2002; Rosenbaum et al. 2017) and in pregnancy specifically, preeclampsia (Saldana et al. 2009; Nugteren JJ et al. 2012). Despite a few studies suggesting associations, though not all (Willis et al. 1993; Nordby et al. 2006; Saunders et al. 2014), between pesticide exposures and preeclampsia, the scant literature is insufficient to draw clear inferences. In general, such studies have been nonspecific to the pesticide chemical (e.g., any pesticide exposure yes vs no), small in sample size, varied in how women's activities may have facilitated pesticide exposure (e.g., employment or self-reported activities), or did not consider pertinent comorbidities like gestational diabetes.

To substantially extend the limited extant information, we investigated population-based data on >200,000 births and proximal residential exposures to more than 500 commercial agricultural pesticide active ingredients and adjuvants during multiple gestational time points. The study population derived from the San Joaquin Valley of California, one of the highest agricultural pesticide use areas in the US.

2. MATERIALS AND METHODS

2.1. Study population

This study was approved by the Stanford University Institutional Review Board and the California State Committee for the Protection of Human Subjects.

Data for this case-control study derive from 1998–2011 California births to women residing in the San Joaquin Valley (Fresno, Kern, Kings, Madera, Merced, San Joaquin, Stanislaus, and Tulare counties). In this region and time period there were 892,088 livebirths delivered in non-military hospitals. We restricted the study to those with gestational ages 20–41 weeks (determined by obstetric estimate for 2007–11 and by last menstrual period for 1998–2006), birth weights between 500 and 5000 grams, and singleton births – a total of 771,416 births. This analysis was an opportunistic extension of a previously conducted study specific to

preterm birth (Shaw et al. 2018) whereby the 771,416 eligible births were 78,421 preterm (i.e., <37 weeks gestation) and 692,995 term (i.e., >37 weeks gestation). For analytic efficiency that study was based on a randomly selected group of 235,263 (from the 692,995) term births in a 3:1 ratio of term to preterm infants.

For each of these 313,684 (78,421 + 235,263) births, we obtained the mother's residential address at the time of delivery from the electronic birth certificate. A REST API Geocode Service maintained by the California Department of Public Health Information Technology Services Division was used to geocode addresses. This service standardizes, verifies, and corrects addresses before matching against multiple address-attributed reference databases. Successful geocoding was achieved for 295,387 births (94%).

We further linked the 295,387 births with Office of Statewide Health and Planning (OSHPD) maternal and infant hospital discharge data. This linkage allowed for information on a range of maternal and pregnancy characteristics found on the birth certificate paired with clinical detail from the delivery hospitalization for practically all inpatient live births. The algorithm employed for this linkage is accurate and previously described (Herrchen et al. 1997; Lyndon et al. 2012). Successful linkage was achieved for 99% (n=293,044).

Our analytic goal was to investigate various preeclampsia phenotypes among pregnancies that delivered before 37 weeks gestation. To identify preeclampsia as well as other comorbidities from hospital discharge data, we employed International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. Included as comorbidities were pre-existing diabetes (Type 1 (250.x1, 250.x3) and Type 2 (250.x0, 250.x2, 648.0)) and gestational diabetes (648.8). For hypertensive disorders we identified: pre-existing hypertension (401–405, 642.0, 642.1, 642.2, 642.9); gestational hypertension (642.3); mild preeclampsia (642.4); severe preeclampsia/eclampsia (642.5, 642.6); and preeclampsia or eclampsia superimposed on preexisting hypertension (642.7). Women with multiple ICD9 codes for hypertensive disorders were reclassified to allow for mutually exclusive groups. Specifically, women with multiple codes were classified as: women with a pre-existing hypertension code and a preeclampsia or eclampsia code were classified as having preeclampsia or eclampsia superimposed on preexisting hypertension; women with pre-existing hypertension and gestational hypertension were classified as having pre-existing hypertension; and women with multiple codes for gestational hypertension and preeclampsia or eclampsia were classified as the most severe condition. Thus, for our primary analytic queries women were grouped into one of 3 "case" phenotypic groups: 1) preeclampsia or eclampsia superimposed on pre-existing hypertension; 2) severe preeclampsia/eclampsia; and 3) mild preeclampsia. The 3 preeclampsia phenotypic groups were further stratified by gestational age of delivery as 20–31 weeks or 32–36 weeks. Women who delivered in the study period who did not have diabetes (gestational or pre-existing), did not have any hypertensive disorder (including preeclampsia), and who delivered at 37 weeks or greater served as the referent population (controls).

2.2. Pesticide and adjuvant compounds studied

We assessed exposure to 543 individual chemicals used as pesticides or as adjuvants in pesticide products or application mixtures and 69 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 the 8 San Joaquin Valley counties in any year during the study period, 1998–2011 (California-Department-of-Pesticide-Regulation, Pesticide Use Reporting). Low-toxicity chemicals such as biopesticides (e.g., microbial pesticides, soaps, essential oils), low-toxicity inorganic compounds (e.g., sulfur, kaolin clay), and other compounds determined by US EPA to have low toxicity, as described in US EPA Risk Assessment documents for each chemical were excluded (EPA-U.S.-Environmental-Protection-Agency, Pesticide Chemical Search). 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) or as endocrine disruptors (Colborn T; European-Commission, 2012; Keith 1997). Chemicals with a US EPA-determined Reference Dose based on a toxicological study with a reproductive or developmental endpoint as described in EPA risk assessment documents were included (EPA-U.S.-Environmental-Protection-Agency. Pesticide Chemical Search).

2.3. Pesticide exposure assessment

To estimate pesticide exposures, we assigned a time window of exposure for each case or control woman from one month before conception (B1) to date of delivery by every 4 weeks of pregnancy (P1-P9).

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 1998 and 31 December 2011 (California-Department-of-Pesticide-Regulation. Pesticide Use Reporting). These data are submitted by county agriculture commissioners and are spatially referenced to public land survey sections (PLSS). For the study period, the total number of active ingredient daily production agricultural use records with a PLSS specified, and for the 543 chemicals that were present in PUR records, exceeded 24 million. 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. 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 PLSS 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 1998–2011 for the 543 chemicals of interest, >90% were successfully linked to polygons. For those where no field polygon was specified, no spatial refinement was possible. We determined temporal proximity by comparing recorded dates of applications, believed to be accurate within a few days, to the time window of exposure for each case or control woman.

To assign exposure, we utilized the CEHTP Pesticide Linkage Tool, a custom-developed Java (Oracle, Redwood Shores, CA) application that incorporates the PostGIS spatial and geographic objects library for PostgreSQL (http://www.postgis.net/) and the GeoTools Java

GIS Toolkit, version Release 12 (open source, http://www.geotools.org/) for Geographic information system data management and spatial analysis (California-Environmental-Health-Tracking-Program. Geocoding Service; California-Environmental-Health-Tracking-Program. Agricultural Pesticide Mapping Tool). We characterized pesticides used during each monthly time window (B1-P9) within a 500 m radius of a geocoded point (Roberts et al. 2007), intersecting polygons with the buffer, and assuming homogeneous distribution of pesticides within each polygon.

2.4. Statistical analysis

Risks associated with residential pesticide exposures were estimated using logistic regression. Univariate analyses were conducted to estimate crude odds ratios and 95% confidence intervals (CIs) reflecting associations between pesticide exposures and each of the three preeclampsia phenotypic groups. We performed multivariable analyses adjusting for maternal age (years), race/ethnicity (non-Hispanic white, U.S.-born Hispanic, foreign-born Hispanic, other), education (less than high school, high school, more than high school), parity (1 or ≥2), prenatal care initiated by fifth month (yes vs no), and payer source for care (Medi-Cal, private, or other). Additional analyses based on availability of data beginning with 2007 births were performed adjusting for pre-pregnancy body mass index (BMI in kg/m^2, continuous) and neighborhood poverty derived from US Census data for census tracts. Given that the source of potential covariate information was derived from the birth certificate we determined that women's cigarette smoking was too incomplete to include in analyses.

Comparisons were performed based on the following. For pesticides that had ≥5 exposed case and control women, risks were estimated that compared *any* versus *no* exposure. Risks were not estimated for pesticides that had fewer than 5 exposed case and control women owing to a lack of statistical precision. We also created exposure groupings by flagging studied chemicals as having reproductive or developmental toxicity based on the California Proposition 65 list (California-Office-of-Environmental-Health-Hazard-Assessment) or as endocrine disruptors (Colborn T; European-Commission, 2012; Keith 1997). Chemicals with an EPA-determined reference dose based on an acute toxicological study with a reproductive or developmental endpoint as described in EPA risk assessment documents were also included (EPA-(U.S.-Environmental-Protection-Agency. Pesticide Chemical Search). We created exposure groups by summing total number of chemicals designated as endocrine disruptors, Proposition 65 chemicals, or chemicals in EPA lists. For each group, we explored associations of preeclampsia phenotypes with group sums of chemicals as categorical variables; i.e., exposed subjects were divided into tertiles based on the control distribution sums. Analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, 2016–2017).

An elastic net (EN) algorithm was used for agnostic multivariate analysis (Zou and Hastie 2005). 10% of the data was randomly and uniformly selected for training purposes. The remaining 90% was used as a blinded test-set. For a matrix X of all exposure levels, and a vector of diagnosis results Y, a multivariate model was developed to calculate the coefficients β for each entity in X to minimize the overall differences from Y: $L(\beta)=| Y -$

$X\beta|^2$. A L_1 regularization was applied on the β coefficients to reduce the model complexity, such that $L(\beta)=|\ Y-X\beta|^2+\lambda_1|\beta|_1$ where λ_1 is selected by cross-validation (Tibshirani 1996). This produces a sparse model in which only a limited number of features is utilized. However, this approach is not ideal for the analysis of highly interrelated pesticides, as it would select only representatives of correlated features, while disregarding highly correlated but potentially biologically relevant features. This limitation is addressed by using an additional L_2 regularization to allow the inclusion of highly correlated measurements: $L(\beta)=|\ Y-X\beta|^2+\lambda_1|\beta|_1+\lambda_2|\beta|_2$ where λ_1 and λ_2 are selected by cross-validation (Zou and Hastie 2005).

3. RESULTS

The following numbers of women with preeclampsia phenotypes were identified: 1045 with superimposed preeclampsia (265 with gestational weeks 20–31 and 780 with gestational weeks 32–36); 3471 with severe preeclampsia or eclampsia (824 with gestational weeks 20–31 and 2647 with gestational weeks 32–36); and 2780 with mild preeclampsia (207 with gestational weeks 20–31 and 2573 with gestational weeks 32–36). The reference (controls) population for these groups was 197,461 women who delivered in the study period, did not have diabetes (gestational or pre-existing), did not have any hypertensive disorder, and delivered at 37 weeks or greater. Characteristics of case women and controls are displayed in Table 1.

Frequencies of preeclampsia cases and their controls with *any* vs no pesticide exposure assignments for the B1-P9 month periods are shown in Table 2. The frequency of *any* exposure was lower or about the same in each preeclampsia case group (further delineated by gestational age), and month time period, relative to the frequency in controls. The corresponding odds ratios (crude and adjusted) are shown in Table 3. Nearly all odds ratios were below 1.0 for these *any* vs no exposure comparisons.

As noted in the Methods, we employed a minimum sample size criterion for risk estimation, i.e., pesticides (groups or specific chemicals) that had 5 or more exposed cases *and* controls for each preeclampsia phenotype. This produced >40,000 comparisons based on 6 preeclampsia case groups (superimposed, severe and mild each for the gestational weeks of 20–31 and 32–36), as many as 9 exposure months (i.e., B1-P9), 313 chemical groups with exposure, 61 chemical classes of exposure, and crude and adjusted odds ratios. Owing to this large number of comparisons, we have limited our presentation of results as follows, but summarize in text the general pattern of findings not specifically shown. We show adjusted odds ratios for chemical groups and specific chemicals for which 1) there were >5 cases exposed (this criterion biases toward identifying elevated risks) and 2) only for the exposure month closest to the time of delivery (e.g., for preeclampsia cases delivered at 20–31 weeks, odds ratios are shown for month P6). These results are displayed in Table 4 for chemical groups, and supplementary Table 1 for specific chemicals.

As shown in Table 4, there was only a single comparison (thiophanate) that had an odds ratio above 1.0 and a confidence interval that did not include 1.0. Indeed, many of the adjusted

odds ratios were below 1.0 (crude estimates were similar). Results for the “months of exposure” not shown were not substantially different than those that are shown.

In Supplementary Table 1 we display adjusted odds ratios associated with specific chemicals. Similar to results for chemical groups, only a small number of statistically precise elevated risks was observed (crude estimates were similar). The 20 comparisons observed to have elevated odds ratios ranged in magnitude from 1.36 (copper hydroxide) to 3.57 (hydrogen cyanamide). The observed elevated odds ratios were associated with a variety of chemicals and did not appear to be associated with a specific preeclampsia phenotype.

To estimate potential risks from exposure to multiple pesticides, we summed women’s exposures to various chemical classifications, including number of chemical groups, endocrine disruptors, Proposition 65 listed reproductive toxicants, or EPA listed reproductive or developmental toxicants. Women’s increasing sum of exposures to each of these classifications was not associated with elevated risks (Table 5). Indeed, for superimposed preeclampsia a statistically significant inverse association for increasing sum of exposures was observed.

For a subset (2007–11) of the overall data (1998–2011) we had information about body mass index and poverty (see Table 1 for description and frequency). These additional variables were added as covariates to adjusted models. Results of these additional analyses did not show substantially different findings from those displayed in Tables 2–4 (data not shown).

We also investigated the large amount of data employing an elastic net algorithm. This more agnostic analytic approach also revealed similar results, i.e., showing reduced risks for many of the pesticide exposures and preeclampsia phenotypes. As an example, in Figure 1 we show the results of this approach applied to exposures to chemical groups and any preeclampsia in P5 (other comparisons can be provided upon request). The elastic net model was primarily dominated by negative (in blue) coefficients for several chemical groups. These chemical groups were highly correlated across women (hence, they cluster together in Figure 1, top right). This approach confirms the inverse association with a summary score of the dataset (in this case the summary score is a weighted sum, with the weights objectively calculated using L_1 and L_2 penalties).

4. DISCUSSION

We investigated population-based data on >200,000 births and proximal residential exposures to >500 commercial agricultural pesticides during multiple gestational time points for potential associations with preeclampsia. Despite a very large study population, consideration of preeclampsia into narrowly-defined phenotypes, and consideration of a variety of gestational exposure definitions such as chemical groups, specific chemicals, and number of pesticides, there was a general lack of association between pesticide exposures and elevated risks of preeclampsia. Given the large number of comparisons made, substantially more elevated risks would have been expected to emerge by chance alone.

Extant research on women's *residential* proximity to pesticide applications and risks of preeclampsia is scant. To our knowledge there has been one study that investigated residential proximity to pesticides. Willis et al. (1993), in a small cohort study of 535 women, indicated that women who reported living near land used for agricultural purposes did not show a significant increased risk to have preeclampsia. Although not directly comparable to exposures in the current study, Saldana and colleagues (2009) observed an increased risk (odds ratio=1.32, 95% CI 1.02–1.60) of preeclampsia among women who reported engaging in activities related to applying pesticides in their home or garden.

Curiously, many of the analytic comparisons (including the agnostic elastic net algorithm) showed reduced risks of preeclampsia and various pesticide exposure estimations. We observed a similar enigmatic direction of findings in a recent study of spontaneous preterm birth and residential pesticide exposures (Shaw et al. 2017); that study excluded women with hypertensive disorders. In that study, as in the current one, we find it difficult to infer that such exposures would be beneficial to reducing the likelihood of either spontaneous preterm birth or preeclampsia given the manifold toxicities pesticide compounds have. Unadjusted confounding influences of cigarette smoking are unlikely to explain the direction of results either owing to 60% of the study population was Hispanic women, a population group known to have very low use of cigarettes.

As a hypothesis for the unexpected direction of some results, it is possible that unobserved early fetal loss hindered our ability to derive unbiased risk estimates. That is, pesticide exposures in pregnancy before 20 weeks, the earliest a birth would be identified in vital statistics files and before preeclampsia would be diagnosed, may selectively increase the odds of earlier loss in pregnancies destined to be preeclamptic and therefore not observable when only live birth data are the target study population. Others have described this construct as left truncation and have specifically done so to characterize some or all of the inverse association between smoking and risk for preeclampsia (Lisonkova and Joseph 2015; Kinlaw et al. 2017). Although such a bias proposition seems reasonable, the extant data investigating potential associations between miscarriage and residential pesticide exposures is too sparse to make meaningful conjectures (Shirangi et al. 2011)

Our study had several strengths, including its population-based design, large sample size, definition of specific maternal hypertensive disorders either included as cases or removed from referents (owing to there likely being different mechanisms underlying such phenotypes), and an exposure assessment that was highly detailed and spatially and temporally specific (to multiple gestational periods), and captured a broad spectrum of pesticide compounds.

Our study also had challenges. Our assessment of residential proximity to agricultural pesticide applications was extensive, but it did not take into account factors such as amounts of pesticides applied or qualities of the pesticides and individuals' behaviors that could affect actual exposures (e.g., chemical half-lives and vapor pressure, wind patterns, accumulative exposures over time a woman may have had before pregnancy, and other sources of pesticide exposure such as occupation or home use). Exposure assignment relied on residence address at delivery rather than at earlier times in pregnancy. Misclassification

of exposure could have occurred for women who moved their residence during gestation. If moving was unrelated to the development of preeclampsia, results would be biased toward the null; if not, the direction cannot be predicted. Further, duration of time spent at the given address is unknown and likely reflective of only a portion of what a woman may encounter in her broader exposome. Although many pesticides are prone to drift and detectable in air samples at locations beyond the application site (Kegley et al. 2012), and residential proximity to pesticide-treated fields has been associated with household dust and urine levels (Fenske et al. 2000; Simcox et al. 1995), there are certainly other exposure sources such as in food or water that were not considered here, whereby individuals could be exposed. These various sources of misclassification would be expected to be non-differential, reducing our precision to estimate potential associations.

Our study rigorously adds to the scant literature on this topic, particularly in its effort to investigate narrower phenotypic groups of preeclampsia as well as numerous pesticide compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Environmental exposures have been rarely investigated for their potential etiologic contribution to preeclampsia, a condition that contributes substantially to maternal morbidity and mortality.
- This study investigated population-based data on >200,000 births and proximal residential exposures to more than 500 commercial agricultural pesticides during multiple gestational time points in one of the highest agricultural pesticide use areas in the US.
- Despite a very large study population, consideration of preeclampsia into narrowly-defined phenotypes, and consideration of a variety of gestational exposure definitions such as chemical groups, specific chemicals, and number of pesticides, there was a general lack of association between pesticide exposures and elevated risks of preeclampsia.
- Nearly all odds ratios were below 1.0 for these *any* vs no exposure comparisons. As a hypothesis for the unexpected direction of some results, it is possible that unobserved early fetal loss hindered our ability to derive unbiased risk estimates.

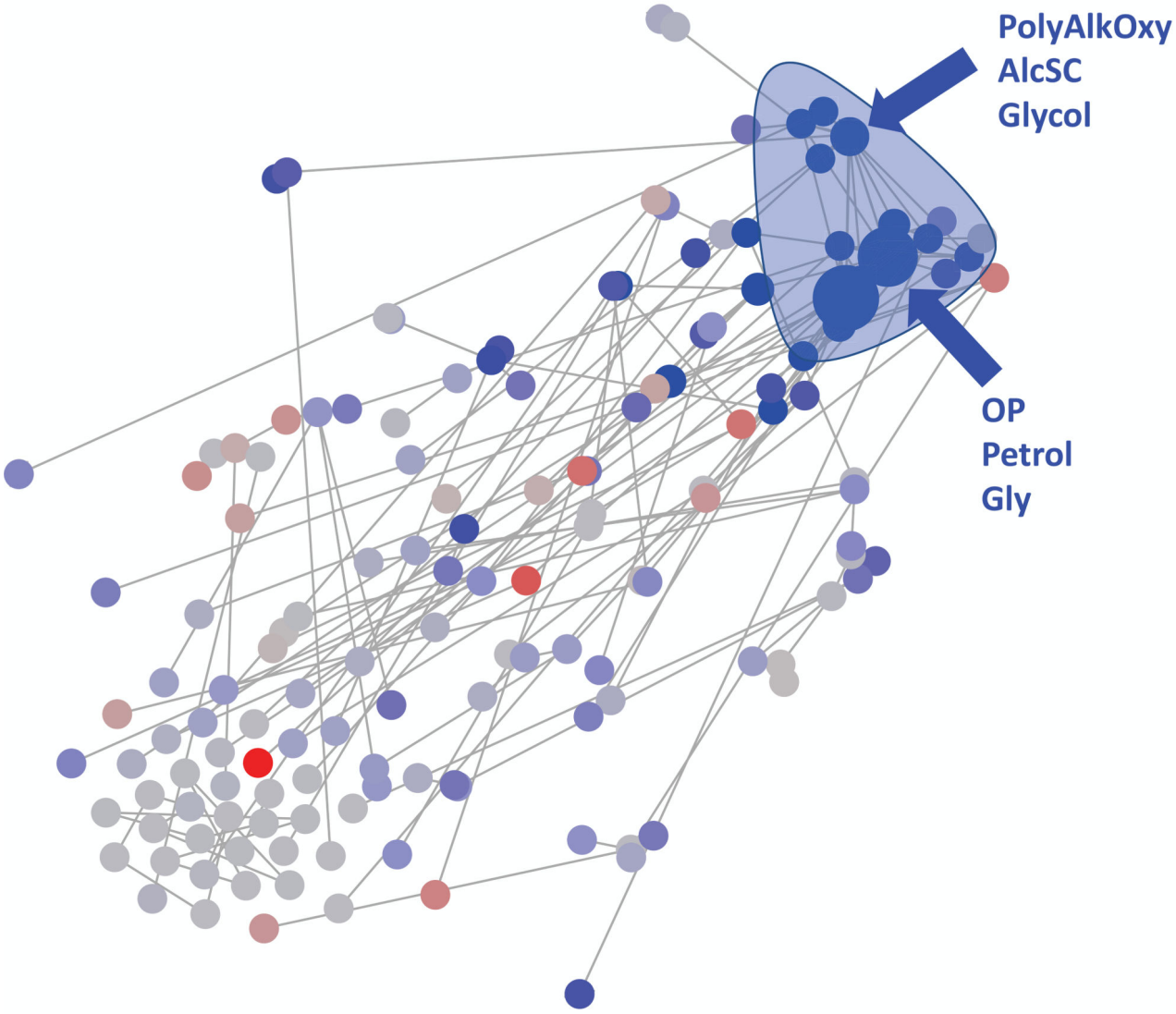

Figure 1.

(Abreviations, PolyAlkOxy=polyalkyloxy compound, AlcSC=Alcohol ether. OP=organophosphate, Petrol=petroleum derivative-aromatic, Gly=Glycol) Correlation network examining the association between any preeclampsia and pesticide chemical groups exposure during P5. An edge between two nodes indicates a significant correlation (after Bonferroni correction). Node size indicates the -log10 transformed p-value of a univariate Wilcoxon test for each feature. Node color indicates the direction of the correlation (blue and red correspond to higher and lower exposure in preeclamptic women, respectively) and the brightness of the color corresponds to the coefficient of the elastic net model (darker colors have a higher coefficient and therefore are more important).

Table 1

Descriptive characteristics (percentages)[1] of preeclampsia cases and their referent population (controls), California, 1998–2011

Characteristic	Preeclampsia Phenotypes			
	CASES			CONTROLS[2]
	Superimposed n=1045	Severe n=3471	Mild n=2780	37–41 weeks n=197,461
Maternal age (years)				
<20	2.8	16.9	17.2	14.2
20–24	16.5	27.4	26.5	29.9
25–29	23.4	23.7	24.0	28.0
30–34	29.5	17.8	18.0	18.4
>35	27.9	14.2	14.2	9.5
Missing	0	0	<0.1	<0.1
Maternal race/ethnicity				
White, nonHispanic	25.2	25.0	28.6	29.4
White, Hispanic	51.9	59.7	56.7	57.0
Black	12.3	5.9	6.4	4.5
Asian	7.2	6.2	6.0	7.1
Other	2.4	2.4	1.6	1.5
Missing	1.1	0.8	0.8	0.6
Maternal education				
Less than high school	24.3	28.9	28.6	32.6
High school	29.8	31.7	33.0	31.8
More than high school	43.8	37.0	36.4	34.0
Missing	2.1	2.4	2.0	1.6
Prenatal care initiation by fifth month of gestation				
Yes	89.8	89.6	90.5	91.8
No	7.5	7.1	6.5	6.4
Missing	2.8	3.3	3.0	1.8
Parity				
1	32.3	56.4	52.5	34.8
≥2	67.7	43.4	47.4	65.2
Missing	0.1	0.1	0.1	0.1
Payer type for delivery				
Medi-Cal	55.1	56.9	58.4	56.9
Private	41.2	38.7	38.3	39.7
Uninsured	2.9	3.1	1.9	1.7
Other	0.7	1.1	1.1	1.5
Missing	0.2	0.2	0.3	0.2
Infant sex				
Male	48.9	51.8	53.1	50.6

Characteristic	Preeclampsia Phenotypes			
	CASES			CONTROLS[2]
	Superimposed n=1045	Severe n=3471	Mild n=2780	37–41 weeks n=197,461
Female	51.1	48.2	46.8	49.4
Missing	0	0	<0.1	<0.1
Infant Birth Year				
1998	3.1	4.9	6.9	6.7
1999	3.2	4.7	6.2	6.7
2000	2.6	5.5	5.8	6.9
2001	2.6	5.3	5.2	6.9
2002	5.0	5.5	6.5	7.1
2003	5.2	6.8	5.9	7.4
2004	7.0	6.5	7.7	7.9
2005	6.8	7.1	8.4	9.1
2006	7.0	7.4	8.2	9.5
2007	10.7	9.0	9.1	6.8
2008	10.2	8.4	8.0	6.7
2009	10.8	9.6	7.8	6.3
2010	12.7	10.3	7.5	6.1
2011	13.2	9.0	6.7	6.0
Years 2007–2011	603	1609	1086	63021
Prepregnancy body mass index (kg/m^2) (2007–2011)				
Underweight (BMI<18.5)	0.8	1.3	2.1	3.1
Normal (18.5≤BMI<25)	14.6	30.5	27.0	40.2
Overweight (25≤BMI<30)	23.6	24.6	22.5	24.7
Obese (BMI≥30)	48.8	31.5	32.7	20.3
Missing	12.3	12.1	15.8	11.8
Poverty (2007–2011) [3]				
≤107.25	20.9	20.2	16.0	19.4
107.26 – ≤180.14	17.9	19.5	20.2	19.4
180.15 – ≤260.29	19.6	17.6	17.9	19.5
260.30 – ≤365.66	19.1	20.9	23.3	19.6
>365.66	20.4	19.3	20.4	19.3
Missing	2.2	2.5	2.3	2.7

[1] Percentages may not equal 100 owing to rounding

[2] Defined as women who delivered in the study period who did not have diabetes (gestational or pre-existing), did not have any hypertensive disorder, and delivered at 37 weeks or greater.

[3] Quintile cutoffs were determined among term births. The highest quintile reflects the highest degree of poverty.

Table 2

Any (as percentage of total) gestational pesticide exposure per month among women with preeclampsia and their controls

		Count and percentage of any exposure (yes) per month[1]									
	Preeclampsia Phenotype	**B1**	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**
Cases	Superimposed (gestational weeks 20–31) n=265	60 (22.6)	66 (24.9)	63 (23.8)	66 (24.9)	70 (26.4)	66 (24.9)	61 (23.0)			
	Superimposed (gestational weeks 32–36) n=780	198 (25.4)	204 (26.2)	202 (25.9)	203 (26.0)	204 (26.2)	196 (25.1)	207 (26.5)	197 (25.3)	207 (26.5)	
	Severe (gestational weeks 20–31) n=824	207 (25.1)	213 (25.8)	212 (25.7)	212 (25.7)	214 (26.0)	215 (26.1)	226 (27.4)			
	Severe (gestational weeks 32–36) n=2647	715 (27.0)	691 (26.1)	722 (27.3)	699 (26.4)	720 (27.2)	712 (26.9)	723 (27.3)	742 (28.0)	714 (27.0)	
	Mild (gestational weeks 20–31) n=207	58 (28.0)	58 (28.0)	49 (23.7)	58 (28.0)	49 (23.7)	57 (27.5)	57 (27.5)			
	Mild (gestational weeks 32–36) n=2573	717 (27.9)	706 (27.4)	677 (26.3)	698 (27.1)	693 (26.9)	703 (27.3)	698 (27.1)	693 (26.9)	673 (26.2)	
Controls (n=197,461)		55,136 (27.9)	55,507 (28.1)	55,770 (28.2)	56,019(28.4)	55,834 (28.3)	56,029 (28.4)	56,079 (28.4)	56,000 (28.4)	55,662 (28.2)	54,960 (27.8)

[1]B1=month before conception, P1-P9=each successive month from first to ninth month of pregnancy.

Table 3

Odds ratios (ORs) for any vs no gestational pesticide exposure (per month) among women with preeclampsia and their controls

Preeclampsia Phenotype	Month of Exposure[1]	Cases (exposed/not-exposed)	Controls (exposed/not-exposed)	Crude OR (95%CI)	Adjusted[2] OR (95%CI)
Superimposed (gestational weeks 20–31) n=265	B1	60/205	55136/142325	0.76 (0.57–1.01)	0.69 (0.51–0.94)
	P1	66/199	55507/141954	0.85 (0.64–1.12)	0.78 (0.58–1.05)
	P2	63/202	55770/141691	0.79 (0.60–1.05)	0.74 (0.55–0.99)
	P3	66/199	56019/141442	0.84 (0.63–1.11)	0.80 (0.60–1.08)
	P4	70/195	55834/141627	0.91 (0.69–1.20)	0.86 (0.64–1.15)
	P5	66/199	56029/141432	0.84 (0.63–1.11)	0.79 (0.59–1.06)
	P6	61/204	56079/141382	0.75 (0.57–1.00)	0.72 (0.53–0.97)
Superimposed (gestational weeks 32–36) n=780	B1	198/582	55136/142325	0.88 (0.75–1.03)	0.88 (0.75–1.05)
	P1	204/576	55507/141954	0.91 (0.77–1.06)	0.92 (0.78–1.09)
	P2	202/578	55770/141691	0.89 (0.76–1.04)	0.91 (0.77–1.07)
	P3	203/577	56019/141442	0.89 (0.76–1.04)	0.92 (0.78–1.08)
	P4	204/576	55834/141627	0.90 (0.77–1.05)	0.94 (0.79–1.10)
	P5	196/584	56029/141432	0.85 (0.72–1.00)	0.88 (0.75–1.04)
	P6	207/573	56079/141382	0.91 (0.78–1.07)	0.94 (0.80–1.11)
	P7	197/583	56000/141461	0.85 (0.73–1.00)	0.88 (0.75–1.04)
	P8	207/573	55662/141799	0.92 (0.78–1.08)	0.94 (0.79–1.10)
Severe (gestational weeks 20–31) n=824	B1	207/617	55136/142325	0.87 (0.74–1.01)	0.89 (0.76–1.05)
	P1	213/611	55507/141954	0.89 (0.76–1.04)	0.91 (0.77–1.07)
	P2	212/612	55770/141691	0.88 (0.75–1.03)	0.89 (0.76–1.05)
	P3	212/612	56019/141442	0.87 (0.75–1.02)	0.89 (0.76–1.05)
	P4	214/610	55834/141627	0.89 (0.76–1.04)	0.92 (0.78–1.08)
	P5	215/609	56029/141432	0.89 (0.76–1.04)	0.92 (0.78–1.08)
	P6	226/598	56079/141382	0.95 (0.82–1.11)	0.99 (0.85–1.16)
Severe (gestational weeks 32–36) n=2647	B1	715/1932	55136/142325	0.96 (0.88–1.04)	0.95 (0.87–1.04)
	P1	691/1956	55507/141954	0.90 (0.83–0.99)	0.90 (0.82–0.98)
	P2	722/1925	55770/141691	0.95 (0.87–1.04)	0.95 (0.87–1.04)
	P3	699/1948	56019/141442	0.91 (0.83–0.99)	0.90 (0.83–0.99)

Preeclampsia Phenotype	Month of Exposure[1]	Cases (exposed/not-exposed)	Controls (exposed/not-exposed)	Crude OR (95%CI)	Adjusted[2] OR (95%CI)
	P4	720/1927	55834/141627	0.95 (0.87–1.03)	0.93 (0.85–1.02)
	P5	712/1935	56029/141432	0.93 (0.85–1.01)	0.91 (0.84–1.00)
	P6	723/1924	56079/141382	0.95 (0.87–1.03)	0.93 (0.85–1.02)
	P7	742/1905	56000/141461	0.98 (0.90–1.07)	0.98 (0.89–1.07)
	P8	714/1933	55662/141799	0.94 (0.86–1.03)	0.94 (0.86–1.03)
Mild (gestational weeks 20–31) n=207	B1	58/149	55136/142325	1.00 (0.74–1.36)	1.07 (0.78–1.46)
	P1	58/149	55507/141954	1.00 (0.73–1.35)	1.08 (0.79–1.48)
	P2	49/158	55770/141691	0.79 (0.57–1.09)	0.84 (0.61–1.17)
	P3	58/149	56019/141442	0.98 (0.73–1.33)	1.01 (0.74–1.39)
	P4	49/158	55834/141627	0.79 (0.57–1.08)	0.84 (0.60–1.17)
	P5	57/150	56029/141432	0.96 (0.71–1.30)	0.99 (0.72–1.36)
	P6	57/150	56079/141382	0.96 (0.71–1.30)	1.04 (0.76–1.43)
Mild (gestational weeks 32–36) n=2573	B1	717/1856	55136/142325	1.00 (0.91–1.09)	1.00 (0.91–1.09)
	P1	706/1867	55507/141954	0.97 (0.89–1.06)	0.96 (0.88–1.06)
	P2	677/1896	55770/141691	0.91 (0.83–0.99)	0.91 (0.83–1.00)
	P3	698/1875	56019/141442	0.94 (0.86–1.03)	0.94 (0.86–1.02)
	P4	693/1880	55834/141627	0.94 (0.86–1.02)	0.92 (0.84–1.01)
	P5	703/1870	56029/141432	0.95 (0.87–1.04)	0.95 (0.87–1.04)
	P6	698/1875	56079/141382	0.94 (0.86–1.02)	0.94 (0.86–1.03)
	P7	693/1880	56000/141461	0.93 (0.85–1.02)	0.93 (0.85–1.02)
	P8	673/1900	55662/141799	0.90 (0.83–0.99)	0.90 (0.82–0.99)

[1] B1=month before conception, P1-P8=each successive month from first to ninth month of pregnancy.

[2] Odds ratio adjusted for maternal age (years), race/ethnicity (non-Hispanic white, U.S.-born Hispanic, foreign-born Hispanic, other), education (less than high school, high school, more than high school), parity (1 or >2), prenatal care initiated by fifth month (yes vs no), payer source for care (Medi-Cal, private, or other).

Table 4

Odds ratios (ORs) for any vs no gestational exposures (per month) for specific pesticide chemical groups among women with preeclampsia and their controls. Shown are adjusted odds ratios for chemical groups where there were >5 cases exposed and for the exposure month closest to the time of delivery (e.g., for preeclampsia cases 32–36 weeks at delivery the odds ratios shown are for month P8).

Chemical Class	Preeclampsia Phenotype	Gestation Weeks at Delivery	Month of Exposure[1]	Cases (exposed/not-exposed)	Control (exposed/not-exposed)	Adjusted OR[2] (95%CI)
2,4 - Dichlorophenoxy acid or ester	superimposed	32–36	P8	13/767	5710/191751	0.61 (0.35–1.06)
2,4 - Dichlorophenoxy acid or ester	severe	20–31	P6	26/798	5754/191707	1.17 (0.79–1.73)
2,4 - Dichlorophenoxy acid or ester	severe	32–36	P8	54/2593	5710/191751	0.72 (0.54–0.94)
2,4 - Dichlorophenoxy acid or ester	mild	20–31	P6	10/197	5754/191707	1.70 (0.87–3.32)
2,4 - Dichlorophenoxy acid or ester	mild	32–36	P8	69/2504	5710/191751	0.90 (0.70–1.15)
2,6-Dinitroaniline	superimposed	20–31	P6	10/255	8657/188804	0.93 (0.50–1.76)
2,6-Dinitroaniline	superimposed	32–36	P8	31/749	8442/189019	0.99 (0.69–1.42)
2,6-Dinitroaniline	severe	20–31	P6	34/790	8657/188804	0.98 (0.69–1.39)
2,6-Dinitroaniline	severe	32–36	P8	100/2547	8442/189019	0.92 (0.75–1.13)
2,6-Dinitroaniline	mild	20–31	P6	7/200	8657/188804	0.86 (0.40–1.83)
2,6-Dinitroaniline	mild	32–36	P8	116/2457	8442/189019	1.07 (0.88–1.29)
Alcohol/Ether	superimposed	32–36	P8	8/772	6273/191188	0.35 (0.18–0.71)
Alcohol/Ether	severe	20–31	P6	24/800	6340/191121	0.97 (0.64–1.46)
Alcohol/Ether	severe	32–36	P8	67/2580	6273/191188	0.80 (0.62–1.03)
Alcohol/Ether	mild	20–31	P6	8/199	6340/191121	1.35 (0.66–2.74)
Alcohol/Ether	mild	32–36	P8	61/2512	6273/191188	0.77 (0.60–1.00)
Amide	severe	20–31	P6	6/818	1214/196247	1.03 (0.43–2.50)
Amide	severe	32–36	P8	16/2631	1232/196229	1.03 (0.63–1.70)
Amide	mild	32–36	P8	18/2555	1232/196229	1.11 (0.69–1.80)
Amine	severe	32–36	P8	12/2635	679/196782	1.03 (0.53–2.00)
Amine	mild	32–36	P8	13/2560	679/196782	1.55 (0.89–2.69)
Anthranilic diamide	superimposed	32–36	P8	6/774	675/196786	2.04 (0.84–4.95)
Anthranilic diamide	severe	20–31	P6	6/818	547/196914	2.25 (0.93–5.47)
Anthranilic diamide	severe	32–36	P8	14/2633	675/196786	1.59 (0.93–2.70)
Anthranilic diamide	mild	32–36	P8	17/2556	675/196786	1.53 (0.88–2.66)

Chemical Class	Preeclampsia Phenotype	Gestation Weeks at Delivery	Month of Exposure[1]	Cases (exposed/not-exposed)	Control (exposed/not-exposed)	Adjusted OR[2] (95%CI)
Aryloxyphenoxy propionic acid	severe	32–36	P8	5/2642	296/197165	1.32 (0.54–3.21)
Avermectin	superimposed	32–36	P8	16/764	5232/192229	0.77 (0.46–1.28)
Avermectin	severe	20–31	P6	16/808	5249/192212	0.72 (0.43–1.21)
Avermectin	severe	32–36	P8	66/2581	5232/192229	0.96 (0.74–1.23)
Avermectin	mild	20–31	P6	5/202	5249/192212	0.79 (0.29–2.13)
Avermectin	mild	32–36	P8	70/2503	5232/192229	1.03 (0.81–1.31)
Azole	superimposed	20–31	P6	8/257	8914/188547	0.62 (0.29–1.31)
Azole	superimposed	32–36	P8	28/752	8588/188873	0.82 (0.55–1.21)
Azole	severe	20–31	P6	45/779	8914/188547	1.27 (0.94–1.73)
Azole	severe	32–36	P8	106/2541	8588/188873	0.90 (0.74–1.11)
Azole	mild	20–31	P6	10/197	8914/188547	1.19 (0.63–2.25)
Azole	mild	32–36	P8	105/2468	8588/188873	0.92 (0.75–1.12)
Benzoic acid	superimposed	32–36	P8	9/771	1425/196036	1.56 (0.77–3.15)
Benzoic acid	severe	20–31	P6	5/819	1453/196008	0.88 (0.37–2.13)
Benzoic acid	severe	32–36	P8	17/2630	1425/196036	0.83 (0.50–1.38)
Benzoic acid	mild	32–36	P8	17/2556	1425/196036	0.91 (0.55–1.49)
Bipyridylium	superimposed	20–31	P6	10/255	9839/187622	0.73 (0.38–1.43)
Bipyridylium	superimposed	32–36	P8	24/756	9717/187744	0.60 (0.39–0.91)
Bipyridylium	severe	20–31	P6	41/783	9839/187622	0.98 (0.71–1.37)
Bipyridylium	severe	32–36	P8	99/2548	9717/187744	0.76 (0.62–0.93)
Bipyridylium	mild	20–31	P6	10/197	9839/187622	1.08 (0.57–2.04)
Bipyridylium	mild	32–36	P8	113/2460	9717/187744	0.91 (0.75–1.10)
Botanical	superimposed	32–36	P8	12/768	3304/194157	1.02 (0.58–1.82)
Botanical	severe	20–31	P6	14/810	3393/194068	0.99 (0.57–1.72)
Botanical	severe	32–36	P8	36/2611	3304/194157	0.77 (0.55–1.09)
Botanical	mild	20–31	P6	6/201	3393/194068	1.92 (0.85–4.35)
Botanical	mild	32–36	P8	39/2534	3304/194157	0.90 (0.65–1.25)
Chloroacetanilide	superimposed	32–36	P8	5/775	890/196571	1.50 (0.62–3.63)
Chloroacetanilide	severe	32–36	P8	15/2632	890/196571	1.24 (0.73–2.10)
Chloroacetanilide	mild	32–36	P8	11/2562	890/196571	0.91 (0.49–1.70)

Chemical Class	Preeclampsia Phenotype	Gestation Weeks at Delivery	Month of Exposure[1]	Cases (exposed/not-exposed)	Control (exposed/not-exposed)	Adjusted OR[2] (95%CI)
Copper compound	superimposed	20–31	P6	11/254	11537/185924	0.70 (0.37–1.31)
Copper compound	superimposed	32–36	P8	29/751	11486/185975	0.59 (0.40–0.88)
Copper compound	severe	20–31	P6	55/769	11537/185924	1.23 (0.93–1.62)
Copper compound	severe	32–36	P8	148/2499	11486/185975	0.98 (0.83–1.17)
Copper compound	mild	20–31	P6	12/195	11537/185924	1.11 (0.62–2.00)
Copper compound	mild	32–36	P8	143/2430	11486/185975	0.95 (0.80–1.13)
Cyclohexenone derivative	superimposed	32–36	P8	5/775	1375/196086	0.93 (0.39–2.26)
Cyclohexenone derivative	severe	32–36	P8	20/2627	1375/196086	1.09 (0.69–1.71)
Cyclohexenone derivative	mild	32–36	P8	18/2555	1375/196086	0.94 (0.57–1.54)
Diacylhydrazine	superimposed	20–31	P6	5/260	2906/194555	1.11 (0.41–2.98)
Diacylhydrazine	superimposed	32–36	P8	10/770	2907/194554	0.82 (0.42–1.58)
Diacylhydrazine	severe	20–31	P6	13/811	2906/194555	0.97 (0.53–1.76)
Diacylhydrazine	severe	32–36	P8	36/2611	2907/194554	0.90 (0.64–1.27)
Diacylhydrazine	mild	32–36	P8	36/2537	2907/194554	0.96 (0.68–1.34)
Dicarboximide	superimposed	32–36	P8	13/767	3825/193636	0.84 (0.47–1.49)
Dicarboximide	severe	20–31	P6	18/806	4085/193376	1.12 (0.70–1.79)
Dicarboximide	severe	32–36	P8	51/2596	3825/193636	1.01 (0.76–1.35)
Dicarboximide	mild	32–36	P8	53/2520	3825/193636	1.05 (0.79–1.40)
Dithiocarbamate–ETU	superimposed	32–36	P8	10/770	4290/193171	0.57 (0.29–1.10)
Dithiocarbamate-ETU	severe	20–31	P6	25/799	4364/193097	1.44 (0.96–2.16)
Dithiocarbamate-ETU	severe	32–36	P8	54/2593	4290/193171	1.00 (0.76–1.31)
Dithiocarbamate-ETU	mild	32–36	P8	60/2513	4290/193171	1.04 (0.80–1.37)
Dithiocarbamate-MITC	severe	32–36	P8	16/2631	1142/196319	1.05 (0.63–1.76)
Dithiocarbamate-MITC	mild	32–36	P8	18/2555	1142/196319	1.22 (0.75–1.98)
Glycol	severe	20–31	P6	13/811	3201/194260	1.06 (0.61–1.84)
Glycol	severe	32–36	P8	32/2615	3308/194153	0.73 (0.51–1.05)
Glycol	mild	32–36	P8	31/2542	3308/194153	0.75 (0.53–1.07)
Halogenated organic	severe	20–31	P6	8/816	2054/195407	0.99 (0.49–2.00)
Halogenated organic	severe	32–36	P8	20/2627	1939/195522	0.76 (0.49–1.20)
Halogenated organic	mild	32–36	P8	20/2553	1939/195522	0.83 (0.53–1.29)

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Chemical Class	Preeclampsia Phenotype	Gestation Weeks at Delivery	Month of Exposure[1]	Cases (exposed/not-exposed)	Control (exposed/not-exposed)	Adjusted OR[2] (95%CI)
Hydroxybenzonitrile	severe	32–36	P8	16/2631	1117/196344	1.14 (0.69–1.88)
Hydroxybenzonitrile	mild	32–36	P8	10/2563	1117/196344	0.73 (0.39–1.36)
Imidazolinone	severe	32–36	P8	9/2638	664/196797	1.08 (0.56–2.09)
Insect growth regulator (Chitin)	superimposed	32–36	P8	7/773	1496/195965	1.06 (0.47–2.38)
Insect growth regulator (Chitin)	severe	20–31	P6	9/815	1444/196017	1.45 (0.72–2.91)
Insect growth regulator (Chitin)	severe	32–36	P8	16/2631	1496/195965	0.71 (0.42–1.20)
Insect growth regulator (Chitin)	mild	32–36	P8	23/2550	1496/195965	1.16 (0.76–1.77)
Monochlorophenoxy acid or ester	severe	20–31	P6	5/819	1518/195943	0.85 (0.35–2.06)
Monochlorophenoxy acid or ester	severe	32–36	P8	16/2631	1506/195955	0.73 (0.43–1.23)
Monochlorophenoxy acid or ester	mild	32–36	P8	24/2549	1506/195955	1.28 (0.86–1.93)
N-Methyl Carbamate	superimposed	32–36	P8	13/767	5382/192079	0.60 (0.34–1.07)
N-Methyl Carbamate	severe	20–31	P6	17/807	5436/192025	0.79 (0.49–1.28)
N-Methyl Carbamate	severe	32–36	P8	68/2579	5382/192079	0.92 (0.71–1.18)
N-Methyl Carbamate	mild	20–31	P6	7/200	5436/192025	1.16 (0.51–2.61)
N-Methyl Carbamate	mild	32–36	P8	56/2517	5382/192079	0.80 (0.61–1.05)
Neonicotinoid	superimposed	32–36	P8	19/761	5317/192144	0.77 (0.46–1.28)
Neonicotinoid	severe	20–31	P6	24/800	5197/192264	1.15 (0.75–1.74)
Neonicotinoid	severe	32–36	P8	65/2582	5317/192144	0.88 (0.68–1.14)
Neonicotinoid	mild	20–31	P6	5/202	5197/192264	0.81 (0.30–2.19)
Neonicotinoid	mild	32–36	P8	58/2515	5317/192144	0.84 (0.65–1.10)
Organoarsenic	severe	32–36	P8	6/2641	310/197151	1.49 (0.66–3.35)
Organoarsenic	mild	32–36	P8	7/2566	310/197151	1.82 (0.86–3.87)
Organochlorine	severe	20–31	P6	5/819	1326/196135	0.99 (0.41–2.39)
Organochlorine	severe	32–36	P8	17/2630	1309/196152	1.02 (0.63–1.64)
Organochlorine	mild	32–36	P8	10/2563	1309/196152	0.62 (0.33–1.15)
Organophosphate	superimposed	20–31	P6	14/251	16763/180698	0.55 (0.31–0.98)
Organophosphate	superimposed	32–36	P8	55/725	17033/180428	0.84 (0.63–1.10)
Organophosphate	severe	20–31	P6	69/755	16763/180698	1.03 (0.80–1.32)
Organophosphate	severe	32–36	P8	215/2432	17033/180428	0.95 (0.82–1.09)
Organophosphate	mild	20–31	P6	17/190	16763/180698	1.01 (0.60–1.69)

Chemical Class	Preeclampsia Phenotype	Gestation Weeks at Delivery	Month of Exposure[1]	Cases (exposed/not-exposed)	Control (exposed/not-exposed)	Adjusted OR[2] (95%CI)
Organophosphate	mild	32–36	P8	171/2402	17033/180428	0.74 (0.63–0.87)
Petroleum derivative-Aromatic	superimposed	20–31	P6	7/258	11398/186063	0.42 (0.19–0.94)
Petroleum derivative-Aromatic	superimposed	32–36	P8	32/748	11470/185991	0.73 (0.51–1.05)
Petroleum derivative-Aromatic	severe	20–31	P6	45/779	11398/186063	0.95 (0.69–1.29)
Petroleum derivative-Aromatic	severe	32–36	P8	132/2515	11470/185991	0.87 (0.73–1.04)
Petroleum derivative-Aromatic	mild	20–31	P6	15/192	11398/186063	1.33 (0.77–2.30)
Petroleum derivative-Aromatic	mild	32–36	P8	132/2441	11470/185991	0.86 (0.71–1.03)
Phosphine	severe	32–36	P8	13/2634	974/196487	1.06 (0.61–1.84)
Phosphine	mild	32–36	P8	8/2565	974/196487	0.65 (0.32–1.31)
Phosphonoglycine	superimposed	20–31	P6	22/243	25816/171645	0.62 (0.40–0.98)
Phosphonoglycine	superimposed	32–36	P8	101/679	25416/172045	1.05 (0.85–1.31)
Phosphonoglycine	severe	20–31	P6	105/719	25816/171645	1.02 (0.82–1.25)
Phosphonoglycine	severe	32–36	P8	295/2352	25416/172045	0.86 (0.76–0.98)
Phosphonoglycine	mild	20–31	P6	29/178	25816/171645	1.17 (0.78–1.76)
Phosphonoglycine	mild	32–36	P8	288/2285	25416/172045	0.85 (0.75–0.96)
Piperonyl	severe	32–36	P8	5/2642	465/196996	0.86 (0.36–2.09)
Piperonyl	mild	32–36	P8	6/2567	465/196996	1.04 (0.46–2.33)
Polyalkyloxy Compound	superimposed	32–36	P8	18/762	11641/185820	0.37 (0.22–0.61)
Polyalkyloxy Compound	severe	20–31	P6	45/779	11826/185635	0.94 (0.69–1.28)
Polyalkyloxy Compound	severe	32–36	P8	124/2523	11641/185820	0.80 (0.67–0.97)
Polyalkyloxy Compound	mild	20–31	P6	17/190	11826/185635	1.58 (0.96–2.61)
Polyalkyloxy Compound	mild	32–36	P8	130/2443	11641/185820	0.87 (0.73–1.04)
Pyrethroid	superimposed	20–31	P6	9/256	12452/18500	0.49 (0.24–0.99)
Pyrethroid	superimposed	32–36	P8	52/728	12541/184920	1.09 (0.82–1.45)
Pyrethroid	severe	20–31	P6	45/779	12452/185009	0.86 (0.63–1.18)
Pyrethroid	severe	32–36	P8	143/2504	12541/184920	0.85 (0.72–1.01)
Pyrethroid	mild	20–31	P6	17/190	12452/185009	1.27 (0.75–2.15)
Pyrethroid	mild	32–36	P8	132/2441	12541/184920	0.79 (0.66–0.94)
Pyridazinone	severe	20–31	P6	8/816	1994/195467	1.03 (0.51–2.08)
Pyridazinone	severe	32–36	P8	17/2630	2029/195432	0.65 (0.40–1.05)

Chemical Class	Preeclampsia Phenotype	Gestation Weeks at Delivery	Month of Exposure[1]	Cases (exposed/not-exposed)	Control (exposed/not-exposed)	Adjusted OR[2] (95%CI)
Pyridazinone	mild	32–36	P8	25/2548	2029/195432	0.99 (0.66–1.47)
Quaternary Ammonium Compound	severe	32–36	P8	20/2627	1570/195891	0.89 (0.56–1.43)
Quaternary Ammonium Compound	mild	32–36	P8	15/2558	1570/195891	0.77 (0.46–1.28)
Silicone	severe	20–31	P6	14/810	4322/193139	0.84 (0.49–1.43)
Silicone	severe	32–36	P8	43/2604	4358/193103	0.73 (0.53–1.00)
Silicone	mild	32–36	P8	46/2527	4358/193103	0.84 (0.62–1.13)
Soap	severe	20–31	P6	6/818	987/196474	1.57 (0.70–3.53)
Soap	severe	32–36	P8	13/2634	946/196515	0.84 (0.45–1.56)
Soap	mild	32–36	P8	17/2556	946/196515	1.46 (0.90–2.37)
Spinosyn	superimposed	32–36	P8	11/769	4287/193174	0.64 (0.34–1.21)
Spinosyn	severe	20–31	P6	20/804	4304/193157	1.19 (0.76–1.85)
Spinosyn	severe	32–36	P8	58/2589	4287/193174	1.02 (0.79–1.34)
Spinosyn	mild	20–31	P6	7/200	4304/193157	1.49 (0.66–3.37)
Spinosyn	mild	32–36	P8	44/2529	4287/193174	0.73 (0.53–1.00)
Streptomycin	severe	32–36	P8	7/2640	473/196988	1.18 (0.56–2.49)
Strobin	superimposed	20–31	P6	6/259	6165/191296	0.76 (0.34–1.71)
Strobin	superimposed	32–36	P8	22/758	6117/191344	0.87 (0.55–1.35)
Strobin	severe	20–31	P6	23/801	6165/191296	0.91 (0.60–1.40)
Strobin	severe	32–36	P8	86/2561	6117/191344	1.00 (0.80–1.26)
Strobin	mild	20–31	P6	5/202	6165/191296	0.85 (0.35–2.06)
Strobin	mild	32–36	P8	89/2484	6117/191344	1.11 (0.89–1.38)
Sulfonylurea	superimposed	32–36	P8	8/772	1346/196115	1.61 (0.80–3.24)
Sulfonylurea	severe	32–36	P8	20/2627	1346/196115	1.14 (0.72–1.79)
Sulfonylurea	mild	32–36	P8	17/2556	1346/196115	0.92 (0.55–1.53)
Thiocarbamate	severe	32–36	P8	8/2639	776/196685	0.81 (0.40–1.64)
Thiocarbamate	mild	32–36	P8	14/2559	776/196685	1.45 (0.85–2.47)
Thiophanate, benzimidazole precursor	severe	20–31	P6	8/816	854/196607	**2.35 (1.16–4.74)**
Thiophanate, benzimidazole precursor	severe	32–36	P8	6/2641	783/196678	0.60 (0.27–1.35)
Thiophanate, benzimidazole precursor	mild	32–36	P8	8/2565	783/196678	0.83 (0.41–1.66)
Thiophthalimide	severe	20–31	P6	5/819	1246/196215	1.00 (0.41–2.42)

Chemical Class	Preeclampsia Phenotype	Gestation Weeks at Delivery	Month of Exposure[1]	Cases (exposed/not-exposed)	Control (exposed/not-exposed)	Adjusted OR[2] (95%CI)
Thiophthalimide	severe	32–36	P8	11/2636	1203/196258	0.72 (0.40–1.31)
Thiophthalimide	mild	32–36	P8	19/2554	1203/196258	1.28 (0.81–2.03)
Triazine	superimposed	32–36	P8	17/763	6626/190835	0.66 (0.40–1.08)
Triazine	severe	20–31	P6	30/794	6676/190785	1.19 (0.82–1.71)
Triazine	severe	32–36	P8	77/2570	6626/190835	0.89 (0.70–1.12)
Triazine	mild	20–31	P6	8/199	6676/190785	1.31 (0.64–2.65)
Triazine	mild	32–36	P8	84/2489	6626/190835	0.98 (0.79–1.23)
Urea	superimposed	20–31	P6	5/260	5243/192218	0.78 (0.32–1.90)
Urea	superimposed	32–36	P8	21/759	5139/192322	0.97 (0.61–1.56)
Urea	severe	20–31	P6	29/795	5243/192218	1.42 (0.97–2.08)
Urea	severe	32–36	P8	73/2574	5139/192322	1.10 (0.86–1.39)
Urea	mild	20–31	P6	6/201	5243/192218	1.26 (0.56–2.84)
Urea	mild	32–36	P8	60/2513	5139/192322	0.85 (0.65–1.12)
Xylylalanine	severe	20–31	P6	5/819	1664/195797	0.62 (0.23–1.66)
Xylylalanine	severe	32–36	P8	22/2625	1591/195870	1.07 (0.70–1.63)
Xylylalanine	mild	32–36	P8	24/2549	1591/195870	1.10 (0.72–1.68)
Zinc,inorganic	severe	32–36	P8	9/2638	971/196490	0.75 (0.39–1.46)
Zinc,inorganic	mild	32–36	P8	12/2561	971/196490	1.02 (0.58–1.81)

[1] B1=month before conception, P1-P8=each successive month from first to ninth month of pregnancy.

[2] Odds ratio adjusted for maternal age (years), race/ethnicity (non-Hispanic white, U.S.-born Hispanic, foreign-born Hispanic, other), education (less than high school, high school, more than high school), parity (1 or >2), prenatal care initiated by fifth month (yes vs no), payer source for care (Medi-Cal, private, or other).

Table 5

Adjusted odds ratios (ORs) for sums of specific classifications of pesticide exposures and preeclampsia phenotypes.

	Superimposed 20–31 weeks	Superimposed 32–36 weeks	Severe 20–31 weeks	Severe 32–36 weeks	Mild 20–31 weeks	Mild 32–36 weeks
	OR (95%CI)[1]	OR (95%CI)[1]	OR (95%CI)[1]	OR (95%CI)[1]	OR (95%CI)[1]	OR (95%CI)[1]
No. of chemical groups with any exposure[2]						
0	Reference	Reference	Reference	Reference	Reference	Reference
1–2	0.93 (0.63–1.36)	1.14 (0.92–1.41)	0.90 (0.71–1.13)	1.01 (0.90–1.15)	0.84 (0.51–1.37)	0.91 (0.80–1.03)
3–5	0.53 (0.30–0.92)	0.85 (0.65–1.12)	1.09 (0.86–1.39)	0.92 (0.80–1.06)	1.37 (0.88–2.14)	0.89 (0.77–1.03)
>5	0.43 (0.21–0.87)	0.63 (0.44–0.91)	1.10 (0.84–1.45)	0.82 (0.70–0.98)	1.10 (0.63–1.91)	0.85 (0.71–1.00)
Continuous	0.88 (0.81–0.95)	0.95 (0.91–0.98)	1.00 (0.98–1.03)	0.98 (0.96–1.00)	1.02 (0.97–1.08)	0.98 (0.96–1.00)
No. of endocrine disruptors with any exposure						
0	Reference	Reference	Reference	Reference	Reference	Reference
1	0.85 (0.54–1.34)	0.74 (0.55–0.99)	1.04 (0.81–1.33)	1.04 (0.91–1.19)	1.33 (0.84–2.10)	0.92 (0.80–1.06)
2	0.31 (0.12–0.84)	1.06 (0.77–1.47)	1.20 (0.88–1.63)	0.81 (0.66–0.99)	1.06 (0.54–2.08)	0.72 (0.58–0.90)
>2	0.40 (0.18–0.89)	0.70 (0.49–1.02)	1.16 (0.86–1.55)	0.89 (0.74–1.06)	1.30 (0.73–2.29)	0.83 (0.69–1.00)
Continuous	0.75 (0.63–0.91)	0.91 (0.84–0.98)	1.02 (0.96–1.09)	0.96 (0.92–1.00)	1.10 (0.99–1.22)	0.93 (0.90–0.97)
No. of Prop. 65 reproductive toxicants with any exposure						
0	Reference	Reference	Reference	Reference	Reference	Reference
1	0.69 (0.38–1.23)	0.73 (0.52–1.01)	0.95 (0.72–1.27)	0.93 (0.79–1.09)	1.34 (0.81–2.21)	0.85 (0.72–1.01)
>1	N/A	N/A	0.90 (0.53–1.54)	0.93 (0.69–1.25)	N/A	0.82 (0.60–1.13)
Continuous	0.60 (0.37–0.96)	0.64 (0.50–0.84)	0.94 (0.78–1.13)	0.95 (0.85–1.05)	1.08 (0.78–1.50)	0.89 (0.80–0.99)
No. of reproductive or developmental toxicants with any exposure						
0	Reference	Reference	Reference	Reference	Reference	Reference
1–2	1.02 (0.71–1.47)	1.10 (0.89–1.36)	0.94 (0.75–1.17)	0.92 (0.81–1.04)	0.94 (0.60–1.48)	0.91 (0.80–1.03)
3–4	0.63 (0.34–1.15)	0.97 (0.72–1.30)	1.17 (0.90–1.53)	1.02 (0.87–1.18)	1.11 (0.64–1.93)	0.91 (0.77–1.07)
>4	0.46 (0.23–0.89)	0.73 (0.53–1.01)	0.95 (0.72–1.26)	0.81 (0.69–0.96)	1.08 (0.63–1.84)	0.85 (0.72–1.00)
Continuous	0.91 (0.84–0.98)	0.96 (0.92–0.99)	1.00 (0.97–1.03)	0.98 (0.96–1.00)	1.02 (0.96–1.08)	0.98 (0.96–1.00)

[1]Odds ratio adjusted for maternal age (years), race/ethnicity (non-Hispanic white, U.S.-born Hispanic, foreign-born Hispanic, other), education (less than high school, high school, more than high school), parity (1 or >2), prenatal care initiated by fifth month (yes vs no), payer source for care (Medi-Cal, private, or other).

[2]This categorization reflects the total number of chemical groups (total possible=67) that an individual was considered exposed to.