**County-level pesticide use and risk of shortened gestation and preterm birth**

Paul Winchester (Paul.Winchester@franciscanalliance.org)¹, Cathy Proctor¹, Jun Ying²

¹Section of Neonatal-Perinatal Medicine, Indiana University School of Medicine, Indianapolis, IN, USA
²Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, OH, USA

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**Correspondence**
P D Winchester, MD, Franciscan St. Francis Health, 8111 South Emerson Avenue, Indianapolis, IN 46237, USA.
Tel: +1 317 528 5595 | Fax: +1 317 528 5433 | Email: Paul.Winchester@franciscanalliance.org

**ABSTRACT**

**Aim:** This study assesses the association between pesticide exposure in pregnancy, preterm birth (PTB) and shortened gestation.

**Methods:** Pregnancy information was abstracted from the Centers for Disease Control (CDC) Non-Public Use Natality Datasets 1990–2005. Pesticide use in maternal county of residence was calculated using California Pesticide Use Reporting (PUR) data 1990–2005. Counties were ranked by pesticide use, and birth months were sorted by peak (May–June) or nonpeak (other months) pesticide use. Multivariate logistical regression models were used.

**Results:** Counties with higher pesticide use were associated with higher PTB (low 8.59 ± 0.11%, moderate 9.25 ± 0.07%, high 10.0 ± 0.06%, p's < 0.001) and shorter gestations (low 39.197 ± 0.014 weeks, moderate 39.126 ± 0.011 weeks, high 39.049 ± 0.011 weeks, p's < 0.001). Peak pesticide months were associated with higher PTB (10.01 ± 0.05% vs. 9.36 ± 0.05%, p < 0.001) and shorter gestations (39.069 ± 0.007 weeks vs. 39.122 ± 0.007 weeks, p < 0.001). The pesticide effect on shortened gestation and higher PTB was found in all racial groups. Pesticide use was highest for fungicides > insecticides > fumigants > herbicides > others. Each pesticide type was found to be associated with higher PTB and shorter gestation.

**Conclusion:** PTB and shortened gestation were significantly associated with pesticide use in maternal county of residence regardless of race, gestation at birth, and in most risk categories.

**INTRODUCTION**

Infants born preterm (<37 weeks of gestation) are the greatest contributors to infant mortality and morbidity in the United States (U.S.) (1). Shorter gestations, even among healthy ‘term’ babies (gestations less than 39 weeks), have been associated with lower cognitive ability (2). In the United States, preterm births (PTB) increased 30% over the past two decades and the length of gestation has declined (3,4). Environmental pesticides may contribute to PTB and shortened gestation.

Associations between pesticides and birth weight were reported, but the relationship between pesticides, PTB and shortened gestation remains controversial (5–7). In utero organophosphate pesticide exposure was found to be associated with higher PTB and shortened gestation in Latina women living in the Salinas Valley, California (6). However, the relevance of their findings at the population level was questioned (6). Our aim was to examine whether pesticide exposure significantly impacted the risk of PTB and shortened gestation at the population level.

**Methods**

California county-level pesticide use between 1990 and 2005 was obtained from the California PUR database (8). Total pounds applied and pounds per acre for all pesticides in each county were abstracted by month and year. Pesticides were classified by type: fungicide, insecticide, fumigant, herbicide or other based on primary use type as indicated in the PAN Pesticides Database.

**Key notes**
- Higher pesticide-use counties are associated with higher preterm birth (PTB) rates and shorter gestations.
- Months of peak pesticide use (May–June) are also associated with higher PTB and shorter gestations.
- Pesticide adverse effects are found in all racial groups and are correlated with each pesticide type (fungicide, insecticide, fumigant or herbicide).

**Abbreviations**

CDC, Centers for Disease Control; PTB, Preterm birth(s); PUR, Pesticide use reporting; U.S., United States.
The study population included California singleton live births between 24 and 42 weeks of gestation from 1990 to 2005. An institutional data-use agreement was approved to obtain the CDC Non-Public Use Natality Datasets with all counties identified. An IRB for Human Subjects Research was not required for this study.

Maternal age, race, hypertension, diabetes, tobacco or alcohol use, and birth defects were abstracted. Gestational age was derived from the methods outlined in the CDC Natality Data User and Technical Guidelines (9). Mean PTB and gestational lengths were calculated for each maternal county of residence and each birth month. Gestation <37 weeks was defined as preterm, and gestation ≥37 weeks was defined as term. PTB and gestational lengths were calculated for Hispanic, White, Black and other maternal race.

In a separate analysis, counties were stratified by population size and categorised as large metro, medium metro or small metro (derived from the 2006 NCHS Urban-Rural Classification Scheme for Counties). These are meant to reflect relatively urban versus relatively rural counties. Within each metro category, counties were ranked by pesticide use. PTB and gestation were then calculated for these subcategories of counties within rural/urban populations.

For the dichotomous outcome variable of preterm birth, multivariate logistical regression models were used. In the geographic analysis, pesticide use in maternal county of residence (low vs. moderate vs. high pesticide use) was tested for interactions with each controlling covariate (maternal age, race/ethnicity, maternal tobacco use, hypertension, diabetes and birth defects). To account for clustering correlation within each county, a random effect was used (PROC GLIMMIX). Using the logistical model framework, PTB was estimated for each pesticide-use level and compared between counties at varying pesticide-use levels. Further, such comparisons were performed between pesticide-use levels within subpopulations stratified by the controlling covariates. In the temporal analysis, peak month (a binary variable of months, May–June vs. other months) was used in the multivariate regression model controlling for the same covariates adjusting for county clustering. The same covariates were used for the continuous outcome variable gestational age. Based on these models, means were estimated and compared geographically between pesticide-use levels and temporally between peak vs. non-peak pesticide-use months for both the total population and subpopulations. All statistical analyses were performed using SAS 9.4 software (SAS, Cary, NC, USA) package. P-values <0.05 were considered statistically significant.

### RESULTS

#### Pesticide use

Pesticide use ranged from 53 646 lbs (Alpine county) to 540 057 105 lbs (Fresno County). Total pesticide use was categorised by terciles for low (19 counties; 53 646–4 935 034 lbs applied), moderate (20 counties; 5 302 968–40 096 097 lbs applied) and high (19 counties; 51 188 816–540 057 105 lbs applied). Total pesticide-use mean ± SE was higher in peak months (528 070 ±

### Table 1 Demographic and preterm risk factors

| Risk factor     | Category | Total N | Cases | Incidence (95% CI) |
|-----------------|----------|---------|-------|-------------------|
|                 |          |         |       |                   |
| All             | All      | 7 940 794 | 754 375 | 9.5 (9.4, 9.6)    |
| Race/ethnicity  | Hispanic | 3 695 641 | 362 173 | 9.8 (9.7, 9.9)    |
|                 | White    | 2 771 158 | 238 320 | 8.6 (8.5, 8.7)    |
|                 | Black    | 532 456 | 77 206 | 14.5 (14.3, 14.7) |
|                 | Other    | 941 539 | 85 680 | 9.1 (9.0, 9.2)    |
| Age (years)     | <20      | 867 299 | 89 332 | 10.3 (9.7, 11.0)  |
|                 | 20–35    | 6 151 861 | 485 997 | 7.9 (7.6, 8.2)    |
|                 | >35      | 858 075 | 79 801 | 9.3 (8.7, 10.0)   |
| Hypertension    | Yes      | 178 722 | 43 787 | 24.5 (24.0, 25.0) |
|                 | No       | 7 698 513 | 700 565 | 9.1 (9.1, 9.2)    |
| Diabetes        | Yes      | 161 759 | 21 837 | 13.5 (13.2, 13.7) |
|                 | No       | 7 779 035 | 731 229 | 9.4 (9.3, 9.5)    |
| Tobacco         | Yes      | 1201 | 259 | 21.6 (19.1, 24.2) |
|                 | No       | 7 939 593 | 754 261 | 9.5 (9.4, 9.6)    |
| Alcohol         | Yes      | 407 | 103 | 25.4 (20.7, 30.2) |
|                 | No       | 7 940 387 | 754 337 | 9.5 (9.4, 9.6)    |
| Birth defect    | Yes      | 51 168 | 9978 | 19.5 (17.9, 21.2) |
|                 | No       | 7 889 626 | 646 949 | 8.2 (7.9, 8.5)    |

### Table 2 Preterm birth and gestational length by county fumigant, fungicide, herbicide and insecticide use

| Pesticide-use type | Statistics | Pesticide-use rank | Incidence preterm birth (%) | Mean gestation (weeks) |
|--------------------|------------|---------------------|-----------------------------|------------------------|
| Fumigant           | Low        | SE Mod              | High                        | 8.71 ± 0.10            | 39.181 ± 0.014       |
|                    |            |                    |                             |                        |                      |
|                    | p-Value    | Low vs. Mod         | Low vs. High                | Med vs. High            | 0.001                | 0.001                | 0.001                |
|                    | Low vs. Mod| 0.001               | 0.001                       | 0.001                  |                      |
|                    | Low vs. High| 0.001              | 0.001                       | 0.001                  |                      |
|                    | Med vs. High| 0.001            | 0.001                       | 0.001                  |                      |
| Fungicide          | Low        | SE Mod              | High                        | 8.66 ± 0.10            | 39.192 ± 0.014       |
|                    |            |                    |                             |                        |                      |
|                    | p-Value    | Low vs. Mod         | Low vs. High                | Med vs. High            | 0.001                | 0.001                | 0.001                |
|                    | Low vs. Mod| 0.001               | 0.001                       | 0.001                  |                      |
|                    | Low vs. High| 0.001            | 0.001                       | 0.001                  |                      |
|                    | Med vs. High| 0.001            | 0.001                       | 0.001                  |                      |
| Herbicide          | Low        | SE Mod              | High                        | 8.74 ± 0.10            | 39.159 ± 0.014       |
|                    |            |                    |                             |                        |                      |
|                    | p-Value    | Low vs. Mod         | Low vs. High                | Med vs. High            | 0.001                | 0.001                | 0.001                |
|                    | Low vs. Mod| 0.001               | 0.001                       | 0.001                  |                      |
|                    | Low vs. High| 0.001            | 0.001                       | 0.001                  |                      |
|                    | Med vs. High| 0.001            | 0.001                       | 0.001                  |                      |
| Insecticide        | Low        | SE Mod              | High                        | 8.64 ± 0.10            | 39.205 ± 0.014       |
|                    |            |                    |                             |                        |                      |
|                    | p-Value    | Low vs. Mod         | Low vs. High                | Med vs. High            | 0.003                | 0.001                | 0.001                |
|                    | Low vs. Mod| 0.003               | 0.001                       | 0.001                  |                      |
|                    | Low vs. High| 0.001            | 0.001                       | 0.001                  |                      |
|                    | Med vs. High| 0.001            | 0.001                       | 0.001                  |                      |
20 549 lbs) than nonpeak months (249 960 ± 18 779 lbs) (data not shown). Total pesticide use over the 16-year study period was 3 077 170 355 lbs (fungicides 38.56% > insecticides 23.48% > fumigants 19.07% > herbicides 9.43% > all other 9.39%). Ranking counties by total lbs or by lbs/acre did not change the results; therefore, this study presents all measures as total lbs pesticides used per county. Only county-level birth outcomes were available from the

| Table 3: Preterm birth by county pesticide use |
|-----------------------------------------------|
| Preterm birth per 10 000 live births          |
| Mean ± SE (L) | Mean ± SE (M) | Mean ± SE (H) | p-Value |
| Low (L) | Moderate (M) | High (H) | L vs. M | L vs. H | M vs. H |
| All | 8.59 ± 0.11 | 9.25 ± 0.07 | 10.00 ± 0.06 | <0.001 | <0.001 | <0.001 |
| No risk factors* | 8.12 ± 0.11 | 8.83 ± 0.07 | 9.68 ± 0.06 | <0.001 | <0.001 | <0.001 |
| Maternal age | | | | | | |
| <20 | 10.07 ± 0.22 | 11.28 ± 0.10 | 11.95 ± 0.08 | <0.001 | <0.001 | <0.001 |
| 20–35 | 8.21 ± 0.11 | 8.84 ± 0.07 | 9.54 ± 0.06 | <0.001 | <0.001 | <0.001 |
| >35 | 10.23 ± 0.21 | 11.28 ± 0.11 | 12.24 ± 0.11 | <0.001 | <0.001 | <0.001 |
| Race/ethnicity | | | | | | |
| Hispanic | 9.15 ± 0.18 | 9.43 ± 0.08 | 10.26 ± 0.06 | 0.149 | <0.001 | <0.001 |
| White | 8.20 ± 0.10 | 8.59 ± 0.07 | 8.90 ± 0.07 | 0.123 | <0.001 | <0.001 |
| Black | 13.93 ± 0.50 | 14.23 ± 0.14 | 14.90 ± 0.14 | 0.563 | 0.062 | 0.001 |
| Hypertension | | | | | | |
| Yes | 21.71 ± 0.63 | 24.87 ± 0.37 | 25.02 ± 0.35 | <0.001 | <0.001 | 0.768 |
| No | 8.22 ± 0.11 | 8.90 ± 0.07 | 9.73 ± 0.06 | <0.001 | <0.001 | <0.001 |
| Diabetes | | | | | | |
| Yes | 13.03 ± 0.45 | 13.51 ± 0.18 | 13.48 ± 0.18 | 0.328 | 0.347 | 0.933 |
| No | 8.50 ± 0.11 | 9.16 ± 0.07 | 9.94 ± 0.06 | <0.001 | <0.001 | <0.001 |
| Tobacco | | | | | | |
| Yes | 25.84 ± 2.47 | 22.44 ± 2.07 | 17.29 ± 2.10 | 0.291 | 0.009 | 0.082 |
| No | 8.56 ± 0.11 | 9.25 ± 0.07 | 10.00 ± 0.06 | <0.001 | <0.001 | <0.001 |
| Alcohol | | | | | | |
| Yes | 15.63 ± 5.78 | 25.21 ± 3.85 | 29.85 ± 3.75 | 0.170 | 0.040 | 0.389 |
| No | 8.59 ± 0.11 | 9.25 ± 0.07 | 10.00 ± 0.06 | <0.001 | <0.001 | <0.001 |

*Excludes risk factors: hypertension, alcohol, tobacco and diabetes.
CDC Natality Datasets; thus, only county-level pesticide data were used.

Preterm birth

A total of 7,940,794 singleton live births from 58 California counties from 1990 to 2005 were analysed for PTB and gestational length. The mean (95% CI) PTB was 9.5% (9.4%, 9.6%) (Table 1). PTB varied significantly by maternal race (Black > Hispanic > other > White) and maternal age [(≤20 years) > (20–35 years) > (20–35 years)]. PTB was significantly increased in pregnancies complicated by hypertension, diabetes, tobacco or alcohol use, and birth defects (Table 1). PTB increased for each race over the study period (data not shown). PTB was significantly increased with increasing total pesticide use and for increasing pesticide-use type (Table 2).

PTB rates were lower in low (8.59 ± 0.11%) than in moderate (9.25 ± 0.07%) and high pesticide-use counties (10.0 ± 0.06%) p’s < 0.001 (Table 3). Births in counties with low vs. high and moderate vs. high pesticide use were significantly more likely to be preterm in Hispanics and Whites, but similar trends did not reach significance for Blacks (Table 3). Trends for increasing PTB with increasing pesticide use remained significant after hypertension, and diabetes, tobacco or alcohol use was excluded. Three levels of preterm birth (≤36, ≤33, <27 weeks) were separately analysed for counties of low, moderate and high pesticide use (Table 3). This was performed to establish whether pesticide use influences differing degrees of prematurity, where extreme prematurity (≤27 weeks) would have the greatest clinical impact. Associations remained significant for <33 and ≤27-week preterm births. All comparisons between low vs. high and moderate vs. high pesticide-use counties were significant for all preterm birth levels for Whites and Hispanics. Blacks in high pesticide-use counties were more likely to be ≤33 weeks premature than in low and moderate pesticide-use counties (Table 3). Pesticides were significantly associated with PTB: slope (SE) = 0.25(0.05), r = 0.53, p < 0.001 (Fig. 1A).

PTB (≤36 weeks) was significantly higher (p < 0.001) in the months of peak pesticide use (10.01 ± 0.05%) vs. nonpeak months (9.56 ± 0.05%) (Table 4). PTB was likewise higher for ≤33 and ≤27 weeks for all races in peak vs. nonpeak months. Mothers with or without hypertension and diabetes were more likely to have preterm births in peak vs. nonpeak months. Pregnancies without reported tobacco or alcohol use were more likely to have preterm births in peak vs. nonpeak months (p < 0.001), but tobacco- or alcohol-use pregnancies did not show significant differences in peak vs. nonpeak months in ≤36 and <33-week PTB. Pregnancies with alcohol or tobacco use were more likely to have PTB at ≤27 weeks in peak vs. nonpeak pesticide months (Table 4).

Gestational length

The overall mean ± SE gestation was 39.0 ± 0.002 weeks among all births in all counties. Counties with low pesticide use had significantly longer gestations than moderate or high pesticide use (p < 0.001); mean ± SE was 39.197 ± 0.014; 39.126 ± 0.011; and 39.049 ± 0.011 weeks, respectively (Table 5). For all races, county pesticide-use comparisons of low vs. high and moderate vs. high were significant. Low vs. moderate pesticide-use comparisons by race was not significant except for Blacks. Generally, no significant trends were found when gestations were compared with county pesticide use in pregnancies complicated by diabetes, tobacco and alcohol use. However, in pregnancies with hypertension, low vs. high and low vs. moderate comparisons were significant. In mothers without diabetes, tobacco or alcohol use, newborns had longer gestations in lower vs. higher pesticide-use counties, (low 39.248 ± 0.014 weeks; moderate 39.170 ± 0.011 weeks; and high 39.086 ± 0.010 weeks) (Table 5). When only term babies (≥37 weeks) were analysed, gestational length was significantly shorter in low vs. high and moderate vs. high infants. The effect was only significant in White mothers and pregnancies without hypertension, diabetes, tobacco and alcohol.

Figure 1 (A) County preterm birth rates versus county pesticide use in California. (B) County gestational lengths versus county pesticide use in California.
Gestations were significantly shorter (p < 0.001) for babies born in the peak pesticide months (39.069 ± 0.007) compared with nonpeak months (39.122 ± 0.007) (Table 6). Shortened gestations in peak months were significant for all races, and in pregnancies with maternal hypertension and maternal diabetes. Mothers with reported use of alcohol or tobacco had no difference in gestations in peak vs. nonpeak months (Table 6). When
term infants were analysed, gestations remained significantly shorter for peak vs. nonpeak months except in high-risk groups (>35 years of age, hypertension, diabetes, alcohol and tobacco use) (Table 6). Pesticides were significantly associated with shortened gestation: slope (SE) = 0.027(0.008), r = 0.41, p = 0.002 (Fig. 1B).

**Pesticide type**

Counties were ranked by pesticide type: fungicides, insecticides, fumigants, herbicides, and others. PTB and gestational length were compared between low, moderate and high pesticide-use counties. Each individual pesticide type was found to be significantly correlated with PTB and gestational length. All low vs. high comparisons were significant (p < 0.001), and all moderate vs. high comparisons were significant except for fungicides. Thus, whether ranked by total pesticides or by individual pesticide type, pesticide use in maternal county of residence predicted higher PTB rate and shorter gestational length in higher pesticide-use counties (Table 2).

**Metro areas**

Counties were analysed as small, medium or large metropolitan (mostly rural to mostly urban). PTB was significantly higher in high pesticide-use counties (small 9.81 ± 0.10, medium 10.78 ± 0.12, large 9.72 ± 0.10) vs. low pesticide-use counties (small 8.95 ± 0.20, medium 8.66 ± 0.13, large 8.86 ± 0.11) within each metro category (p < 0.001). Pesticide use within metro areas had variable effects on gestational length. Only in medium metro counties was gestational length in low pesticide counties significantly longer than in high pesticide counties (low 39.183 ± 0.021, high 38.990 ± 0.02, p < 0.001) (data not shown).

When San Francisco and Los Angeles counties (the two largest metro areas) were excluded, higher PTB (low 8.60 ± 0.11, moderate 9.24 ± 0.07, high 9.97 ± 0.07) and

| Table 5 Gestational length by county pesticide use |
|-----------------------------------------------|
| **Gestational length** | **Mean ± SE** | **p-Value** | **Mean ± SE** | **p-Value** | **Mean ± SE** | **p-Value** |
| **Gestation** | **Low (L)** | **Moderate (M)** | **High (H)** | **L vs. M** | **L vs. H** | **M vs. H** |
| All gestations | | | | | | |
| All | 39.197 ± 0.014 | 39.126 ± 0.011 | 39.049 ± 0.011 | 0.000 | 0.000 | <0.001 |
| No risk factors* | 39.248 ± 0.014 | 39.170 ± 0.011 | 39.086 ± 0.010 | 0.000 | 0.000 | <0.001 |
| Maternal age | | | | | | |
| <20 | 39.287 ± 0.023 | 39.105 ± 0.013 | 39.018 ± 0.011 | 0.000 | 0.000 | <0.001 |
| 20–35 | 39.227 ± 0.014 | 39.166 ± 0.011 | 39.093 ± 0.010 | 0.001 | 0.000 | <0.001 |
| >35 | 38.880 ± 0.022 | 38.760 ± 0.014 | 38.683 ± 0.013 | 0.000 | 0.000 | <0.001 |
| Race/ethnicity | | | | | | |
| Hispanic | 39.095 ± 0.020 | 39.120 ± 0.011 | 39.046 ± 0.009 | 0.280 | 0.025 | <0.001 |
| White | 39.235 ± 0.015 | 39.214 ± 0.012 | 39.141 ± 0.012 | 0.288 | 0.000 | <0.001 |
| Black | 38.707 ± 0.045 | 38.603 ± 0.014 | 38.533 ± 0.014 | 0.028 | 0.000 | <0.001 |
| Hypertension | Yes | 38.125 ± 0.049 | 37.869 ± 0.031 | 37.853 ± 0.029 | 0.000 | 0.000 | <0.001 |
| No | 39.233 ± 0.014 | 39.159 ± 0.011 | 39.079 ± 0.010 | 0.000 | 0.000 | <0.001 |
| Diabetes | Yes | 38.567 ± 0.036 | 38.553 ± 0.017 | 38.575 ± 0.016 | 0.715 | 0.840 | 0.330 |
| No | 39.209 ± 0.014 | 39.137 ± 0.011 | 39.059 ± 0.011 | 0.000 | 0.000 | <0.001 |
| Tobacco | Yes | 37.998 ± 0.230 | 38.211 ± 0.198 | 38.322 ± 0.201 | 0.485 | 0.290 | 0.693 |
| No | 39.202 ± 0.014 | 39.126 ± 0.011 | 39.050 ± 0.011 | 0.000 | 0.000 | <0.001 |
| Alcohol | Yes | 38.778 ± 0.493 | 37.888 ± 0.320 | 37.485 ± 0.308 | 0.132 | 0.027 | 0.365 |
| No | 39.198 ± 0.014 | 39.126 ± 0.011 | 39.049 ± 0.010 | 0.000 | 0.000 | <0.001 |

*Excludes risk factors: hypertension, alcohol, tobacco and diabetes.*
shorter gestations \((low\ 39.197 \pm 0.014, \mod\ 39.134 \pm 0.011, \high\ 39.058 \pm 0.011)\) in lower to higher pesticide-use counties remained significant \((p < 0.001)\) (data not shown).

**Summary**

Pesticide use in maternal county of residence was associated with higher PTB rates and shorter gestations (Fig. 2A and B). *Peak* pesticide months were associated with greater PTB and shorter gestations within moderate and high pesticide-use counties (Fig. 2A and B).

**DISCUSSION**

This study found increased PTB and shortened gestation with increasing pesticide use *geographically* in maternal county of residence and *temporally* in *peak* pesticide-use months. Babies born in *peak* pesticide months were more likely to be preterm and have shorter gestations (Table 5, Fig. 2A and B).

The association between prenatal exposure and foetal growth or gestational duration in humans has been reviewed (6). Organophosphate pesticides, especially at the end of pregnancy, significantly correlated with shortened gestation in a population of Latina women in the Salinas Valley, California (6). As this population had relatively low PTB, the authors concluded that the association between shortened gestation and pesticides ‘did not seem to have clinical implications for this (Latina) population.’ Women with hypertension, diabetes, twins and prior stillbirths were excluded (6).

In another study, male exposure to combinations of activities with a variety of pesticides [atrazine, glyphosate, organophosphates, 4-(2,4-dichlorophenox) butyric acid and insecticides] was associated with odds ratios of two or greater for preterm delivery (10).
Additional studies have correlated urinary biomarkers of pesticide exposure with PTB and shortened gestation (11–13). Pesticides have been linked to altered choline-terase enzyme expression and endocrine disruption (6,13,14). Pesticides such as vinclozolin, methoxychlor, permethrin and the insect repellant DEET can alter DNA methylation and cause transgenerational effects in rodents (15–17).

In our study, pesticide exposure was estimated with geospatial and temporal California PUR data. Other studies in California correlated urinary organophosphate pesticide levels with season and location of exposure (18), which suggests that the California PUR data (while not as definitive as biomarker data) will likely correlate with population exposure.

This study has several limitations. Increasing risk with increasing exposure may result from other unmeasured variables. Risk factors such as poverty, air pollution and nitrates might be correlated with pesticide use in California counties.

An approximate increase in PTB by 16% and shorter gestations by 0.135%, though statistically significant, might be interpreted as clinically insignificant. This increased PTB represents 112 000 more infants at risk of hospitalisation, mortality and morbidity in the California population. After controlling for risk factors, county pesticide exposure increased the risk of having a <27-week preterm infant by 35%. These infants have the highest mortality and morbidity of all preterm infants. The average 25- to 26-week preterm will require ~100 days of NICU care (costing between $350 000 and $800 000 per baby). Foetal and developmental origins of adult disease research suggested that the life-time risks of preterm birth may be underestimated (19). Prematurity has adverse effects on basic mathematic processing following birth at all gestations <36 weeks and on IQ and mathematic attainment <34 weeks GA (20). Global methylation across multiple organs has been reported in pregnancies with differing gestations (21). Through epigenetic mechanisms, pesticide exposure in pregnancy may alter lifetime risks of diseases. Epidemiological studies have already reported shorter life spans in Americans with birth months in peak pesticide months of May and June (22).

Many preterm birth risk factors were confirmed by this study. Maternal race, age, maternal hypertension, diabetes, tobacco or alcohol use, and infants with birth defects are known to be associated with preterm birth. In pregnancies with hypertension and diabetes, PTB were higher in peak vs. nonpeak pesticide months.

In conclusion, PTB and shortened gestation were found to be significantly related to pesticide use in maternal county of residence and to peak pesticide months. These geotemporal data suggest that pesticide exposure shortens the length of gestation and increases preterm birth risk across most demographic groups.

DISCLAIMERS
The views expressed in this article are that of the authors and not that of the institution or data providers.

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The authors declare no financial conflict of interest.

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References
1. Callaghan WM, MacDorman MF, Rasmussen SA, Qin C, Lackritz EM. The contribution of preterm birth to infant mortality rates in the United States. Pediatrics 2006; 118: 1566–73.
2. Yang S, Platt R, Kramer M. Variation in child cognitive ability by week of gestation among health term births. Am J Epidemiol 2010; 171: 359–406.
3. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, et al. National vital statistics report, births: final data for 2006, vol 57 no 7. Hyattsville, MD: National Center for Health Statistics, 2009: 17.
4. Donahue SMA, Kleinman KP, Gillman MW, Oken E. Trends in birth weight and gestational length among singleton term births in the United States: 1990–2005. Obstet Gynecol 2010; 115: 557–64.
5. Behrman RE, Adashi EY, Allen MC, Loch Caruso R, Culhane J, Dunkel Schetter C, et al. Preterm birth: causes, consequences, and prevention. Washington, DC: National Academies Press, 2007: 790.
6. Eskenazi B, Harley K, Bradman A, Weltzien E, Jewell NP, Barr DB, et al. Association of in utero organophosphate pesticide exposure and fetal growth and length of gestation in an agricultural population. Environ Health Perspect 2004; 112: 1116–24.
7. Ochoa-Acuna H, Frankenberger J, Hahn L, Carbajo C. Drinking-water herbicide exposure in Indiana and prevalence of small-for-gestational-age and preterm delivery. Environ Health Perspect 2009; 117: 1619–24.
8. California Department of Pesticide Regulation. California Pesticide Use Reports [Internet] 1990–2005. Available at: http://www.cdpr.ca.gov/docs/put/putmain.htm (accessed on July 23, 2009).
9. CDC/National Center for Health Statistics. U.S. Natality Non-Public Use Data Files and Documentation. 1990–2005.
10. Savitz DA, Arbuckle T, Kaczor D, Curtis KM. Male pesticide exposure and pregnancy outcome. Am J Epidemiol 1997; 146: 1025–36.
11. Wang P, Tian Y, Wang XJ, Gao Y, Shi R, Wang GQ, et al. Organophosphate pesticide exposure and perinatal outcomes in Shanghai, China. Environ Int 2012; 42: 100–4.
12. Kadhel P, Monfort C, Costet N, Rouget F, Thomé J-P, Multigner L, et al. Chlordecone exposure, length of gestation, and risk of preterm birth. Am J Epidemiol 2014; 179: 536–44.
13. Chevrier C, Limon G, Monfort C, Rouget F, Garlantezec R, Petit C, et al. Urinary biomarkers of prenatal atrazine exposure and adverse birth outcomes in the PELAGIE birth cohort. Environ Health Perspect 2011; 119: 1034–41.
14. Hayes TB, Case P, Chui S, Chung D, Haefele C, Haston K. Pesticide mixtures, endocrine disruption, and amphibian declines: are we understanding the impact? Environ Health Perspect 2006; 114(Suppl 1): 40–50.
15. Manikkam M, Guerrero-Bosagna C, Tracey R, Haque MM, Skinner MK. Transgenerational actions of environmental compounds on reproductive disease and identification of epigenetic biomarkers of ancestral exposures. PLoS ONE 2012; 7: e31901.
16. Anway MD, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors. Endocrinology 2006; 147: S43–9.
17. Rusiecki JA, Baccarelli A, Bollati V, Tarantini L, Moore LE, Bonefeld-Jørgensen EC. Global DNA hypomethylation is associated with high serum-persistent organic pollutants in Greenlandic Inuit. Environ Health Perspect 2008; 116: 1547–52.
18. Bradman A, Castorina R, Barr DB, Chevrier J, Harnly M, Eisen E, et al. Determinants of organophosphorus pesticide urinary metabolite levels in young children living in an agricultural community. Int J Environ Res Public Health 2011; 8: 1061–83.
19. Hofman PL, Regan F, Jackson WE, Jeffries C, Knight DB, Robinson EM, et al. Premature birth and later insulin resistance. N Engl J Med 2004; 351: 2179–86.
20. Wolke D, Yu-Chun Strauss V, Johnson S, Gilmore C, Marlow N, Jaekel J. Universal gestational age effects on cognitive and basic mathematical processing: 2 cohorts in 2 countries. J Pediatr 2015; 166: 1410–6.
21. Michels KB, Harris HR, Barault L. Birthweight, maternal weight trajectories and global DNA methylation of LINE-1 repetitive elements. PLoS ONE 2011; 6: e25254.
22. Dohlehammer G, Vaupel JW. Lifespan depends on month of birth. Proc Natl Acad Sci USA 2001; 98: 2934–9.