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Residential Proximity to Agricultural Fumigant Use and Respiratory Health in 7-year Old Children

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Abstract

Objectives—To examine the relationship between residential proximity to agricultural fumigant use and respiratory symptoms and lung function in 7-year old children.

Methods—Participants were 294 children living in the agricultural Salinas Valley, California and enrolled in the Center for the Health Assessment of Mothers and Children Of Salinas (CHAMACOS) study. We obtained information on respiratory symptoms and asthma medication use from maternal questionnaires and children performed spirometry to determine the forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and forced expiratory flow 25–75% ($FEF_{25–75}$) at 7-years of age. We estimated agricultural fumigant use within 3, 5 and 8 km of residences during pregnancy and from birth to age 7 using California's Pesticide Use Report data. We evaluated the association between prenatal and postnatal residential proximity to agricultural use of methyl bromide, chloropicrin, metam sodium and 1,3-dichloropropene with respiratory symptoms and use of asthma medication with logistic regression models and continuous lung function measurements with linear regression models adjusted for confounders.

Results—There were no significant associations between residential proximity to use of fumigants and respiratory symptoms or use of asthma medication. We did not observe any adverse

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Statement of financial interest

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relationships between residential proximity to fumigant use and lung function measurements. Unexpectedly, we observed suggestive evidence of improved FEV_1 and $FEF_{25–75}$ with higher use of methyl bromide and chloropicrin during the prenatal period. For example, for each 10-fold increase in methyl bromide use during the prenatal development period we observed higher FEV_1 (β=0.06 L/s; 95% CI: 0.00, 0.12) and higher $FEF_{25–75}$ (β=0.15 L/s; 95% CI: 0.03, 0.27). Maternal report of child allergies (runny nose without a cold during the previous year) modified the relationship between FEV_1 and prenatal proximity to methyl bromide use (p = 0.07) and we only observed higher FEV_1 among children without allergies (β=0.08 L/s; 95% CI: 0.02, 0.14 for a 10-fold increase in methyl bromide use during the prenatal period).

Conclusions—Residential proximity to agricultural fumigant use during pregnancy and childhood did not adversely affect respiratory health in the children through 7 years of age. These findings should be explored in larger studies.

Keywords

Child; Fumigants; Lung Function; Pesticides; Respiratory Symptoms

1. Introduction

Metam sodium, 1, 3-dichloropropene (1,3-DCP), methyl bromide, and chloropicrin are high-use agricultural fumigants that account for about 20% of the annual pesticide usage in California (CDPR 2012). These fumigants are known respiratory toxicants and were the top four pesticides ranked by chronic health risk based on a risk assessment conducted in the early 2000s (Lee et al. 2002). Methyl bromide, 1, 3-DCP and chloropicrin have also been identified as the top three pesticides of public health concern used near schools (CDPH 2014). An evaluation of pesticide drift-related illnesses in 11 states found that the largest percentage of cases were related to fumigant applications, indicating the particularly hazardous nature of these substances (Lee et al. 2011).

Methyl bromide was banned by the Montreal Protocol due to harmful effects on the ozone layer and is currently being phased out of use, resulting in increased usage of chloropicrin, metam sodium and 1,3-DCP in recent years (CDPR, 2016). Cases of acute methyl bromide exposure in adults and children have produced symptoms such as shortness of breath, pulmonary edema, cough, respiratory irritation and respiratory arrest (Goldman et al. 1987; Deschamps and Turpin 1996; Squier et al. 1992; Breeman 2009). In the Agricultural Health Study, which examines pesticides and health in a cohort of pesticide applicators and their families, methyl bromide application was associated with higher prevalence of chronic bronchitis in nonsmoking wives of farmers (Valcin et al. 2007).

Metam sodium degrades into methylisothiocyanate, which is known to irritate respiratory tissue (CDPR 2004), and then further breaks down into methylisocyanate, the active ingredient responsible for the Bhopal tragedy that killed more than 3500 people (Dhara 1992). In the Bhopal tragedy the most common and serious problems were related to respiratory symptoms (Mehta et al. 1990). Cases of metam sodium-related illnesses have involved minor respiratory symptoms including coughing and dyspnea (Bretaudeau Deguigne et al. 2011). A metam sodium spill in California resulted in persistent respiratory

health problems (including irritant-induced asthma) for nearby residents (Cone et al. 1994). In a case study of drift from a metam sodium application in California, an association between cases of respiratory illness in nearby residents and proximity to the application area was observed (O'Malley et al. 2005).

Increased respiratory symptoms have been reported as a result of community exposure to chloropicrin following application (Barry et al. 2010; CDC 2004). A larger analysis of chloropicrin-related illness in California from 1992–2003 found that 54% of cases involved respiratory irritation (Oriel et al. 2009). Toxicology studies conducted on rodents have shown that 1, 3-DCP exposure is related to benign lung tumor incidence as well as enlargement of the respiratory epithelium (Lomax et al. 1989; Stott et al. 2001; Breslin et al. 1989).

Several epidemiological studies have found an association between occupational exposure to pesticides and an increased risk of respiratory symptoms and asthma (Mamane et al. 2015). No research to date has been conducted on fumigant exposure and respiratory health in children, who are particularly vulnerable to inhalation risk due to relatively higher inhalation-rate-to-body-weight ratios (Lee et al. 2002). There are no biomarkers available to assess human exposure to fumigants in epidemiologic studies (Magnavita, 2009). Residential proximity to fumigant use is currently the best method to characterize potential exposure to fumigants. California has maintained a Pesticide Use Reporting (PUR) system which requires commercial growers to report all agricultural pesticide use since 1990 (CDPR 2016). A study using PUR data showed that methyl bromide use within ~8 km radius around monitoring sites explained 95% of the variance in methyl bromide air concentrations, indicating a direct relationship between nearby agricultural use and potential community exposure (Li et al., 2005). In the present study, we investigate associations of residential proximity to agricultural fumigant usage during pregnancy and childhood with respiratory symptoms and pulmonary function in 7-year-old children participating in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a longitudinal birth cohort study of primarily low-income Latino farmworker families living in the agricultural community of the Salinas Valley, California.

2. Methods

2.1. Study population

We enrolled 601 pregnant women in the CHAMACOS study between October 1999 and October 2000. Women were eligible for the study if they were ≥18 years of age, <20 weeks gestation, planning to deliver at the county hospital, English or Spanish speaking, and eligible for low-income health insurance (Medi-Cal). We followed the women through delivery of 537 live-born children. Research protocols were approved by The University of California, Berkeley, Committee for the Protection of Human Subjects. We obtained written informed consent from the mothers and children’s oral assent at age 7.

Information on respiratory symptoms and use of asthma medication was available for 347 children at age 7. Spirometry was performed by 279 of these 7-year-olds. We excluded participants from the prenatal analyses for whom we had residential history information for

less than 80% of their pregnancy. We excluded participants from the postnatal analyses for whom we had residential history information for less than 80% of the child's lifetime from birth to the date of the 7 year assessment. Prenatal estimates of proximity to fumigant applications and relevant covariate data were available for 257 children and postnatal estimates of proximity to fumigant applications and relevant covariate data were available for 276 children for whom we obtained details of prescribed asthma medications and respiratory symptoms. Prenatal estimates of proximity to fumigant applications and relevant covariate data were available for 229, 208, and 208 children for whom we had FEV_1, FVC and $FEF_{25–75}$ measurements, respectively. Postnatal estimates of proximity to fumigant applications and relevant covariate data were available for 212, 193, and 193 children with FEV_1, FVC and $FEF_{25–75}$ measurements, respectively.

A total of 294 participants were included in either the prenatal or postnatal analyses. Participants included in this analysis did not differ significantly from the original full cohort on most attributes, including maternal asthma, maternal education, marital status, poverty category, and child's birth weight. However, mothers of children included in the present study were slightly older (mean age 26.7 versus 24.9, $p<0.01$) and more likely to be Latino (99.3% versus 93.4%, $p<0.01$) than those from the initial cohort.

2.2. Maternal interviews and respiratory symptoms

Women were interviewed twice during pregnancy (M±SD=13.4±4.7, 26.5±2.6 weeks gestation), following delivery, and when their children were 0.5, 1, 2, 3.5, 5, and 7 years old. Information from prenatal and delivery medical records was abstracted by a registered nurse. Home visits were conducted by trained personnel during pregnancy (~13 weeks gestation) and when the children were 0.5, 1, 2, 3.5 and 5-years old. At the 7-year-old visit, mothers were interviewed about their children's respiratory symptoms, using questions adapted from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (Asher et al. 1995; Raanan et al. 2015). Additionally, mothers were asked whether the child had been prescribed any medication for asthma or wheezing/whistling, or tightness in the chest.

We defined respiratory symptoms as a binary outcome based on a positive response at the 7-year-old visit to any of the following during the previous 12 months: (1) wheezing or whistling in the chest; (2) wheezing, whistling, or shortness of breath so severe that the child could not finish saying a sentence; (3) trouble going to sleep or being awakened from sleep because of wheezing, whistling, shortness of breath, or coughing when the child did not have a cold; or (4) having to stop running or playing active games because of wheezing, whistling, shortness of breath, or coughing when the child did not have a cold. In addition, a child was included as having respiratory symptoms if the mother reported use of asthma medications, even in the absence of the above symptoms.

2.3. Spirometry

We measured the child's height and weight at the time that spirometry was performed. Three identical EasyOne spirometers were used (ndd Medical Technologies, Inc., Andover, MA). Routine calibration was performed every morning and 92% of tests were conducted by the same technician. The expiratory flow-volume curves were reviewed by two physicians

experienced in pediatric spirometry, and only adequate quality data were included in the statistical analyses. Some participants with adequate quality data for FEV_1 did not provide adequate quality data to calculate FVC or $FEF_{25–75}$. Young children have difficulty sustaining forceful exhalation after a deep breath that is required to produce a plateau in airflow and calculate FVC and subsequently $FEF_{25–75}$. Each child performed a maximum of eight expiratory maneuvers and up to three best acceptable tests were saved by the spirometric device software.

2.4. Geographic-based estimates of nearby fumigant use

Latitude and longitude coordinates of participants' homes were collected during home visits during pregnancy (~13 weeks gestation) and when the children were 0.5, 1, 2, 3.5 and 5 years old using a handheld Global Positioning System (GPS) unit (Garmin, GPS II, Chicago, IL). At the 7-year visit, mothers were asked if the family had moved since the 5-year visit, and if so, the new address was recorded. We used Geographic Information System (GIS) software (ArcInfo 10, ESRI, Redlands, CA) to geocode the new addresses and obtain coordinates. Residential mobility was common in the study population.

We estimated the use of agricultural fumigants near each child's residence using a GIS based on the location of each child's residence and the Pesticide Use Report (PUR) data (CDPR 2016). Mandatory reporting of all agricultural pesticide applications is required in California, including the active ingredient, quantity applied, acres treated, crop treated, and date and location within 1-square-mile sections (approximately 1.6 km by 1.6 km) defined by the Public Land Survey System (PLSS). Before analysis, the PUR data were edited to correct for likely outliers with unusually high application rates using previously described methods (Gunier et al. 2001). We computed nearby fumigant use (i.e., estimates of the total amount of fumigants (kg) applied within each buffer distance) for combinations of distance from the residence (buffer radii of 3, 5, and 8 km) and time periods (prenatal during pregnancy, postnatal from birth to 7-year visit, and the year prior to the 7-year visit). The range of distances best captured the spatial scale that most strongly correlated with concentrations of methyl bromide (Li et al. 2005) and 1,3-DCP in air (van Wesenbeeck et al 2016). We weighted fumigant use near homes based on the proportion of each square-mile PLSS that was within each buffer surrounding a residence. To account for the potential downwind transport of fumigants from the application site, we obtained data on wind direction from the closest meteorological station (CIMIS, 2014). We calculated wind frequency using the proportion of time that the wind blew from each of eight directions during the week after the fumigant application to capture the peak time of fumigant emissions from treated fields (Yates et al. 2015). We determined the direction of each PLSS section centroid relative to residences and weighted fumigant use in a section according to the percentage of time that the wind blew from that direction for the week after application. We summed fumigant use over pregnancy (prenatal), from birth to the 7-year visit (postnatal) and for the year prior to the 7-year visit yielding estimates of the wind-weighted amount of each fumigant (kg) applied within each buffer distance and time period around the corresponding residences for each child.

2.5. Data analysis

We $\log_{10}$ transformed continuous fumigant use variables (1 kg was added to all values to avoid taking the log of 0) to reduce heteroscedasticity and the influence of outliers, and to improve the fit of the models. We used logistic regression models to estimate odds ratios of respiratory symptoms and/or asthma medication use with residential proximity to fumigant use. Our primary outcome was respiratory symptoms defined as positive if during the previous 12 months the mother reported for her child any respiratory symptoms or the use of asthma medications, even in the absence of such symptoms (Raanan et al. 2015). We also examined asthma medication use alone. The continuous lung function measurements (FEV_1, FVC, and $FEF_{25–75}$) were approximately normally distributed, therefore we used linear regression models to estimate the associations with residential proximity to fumigant use. We estimated the associations between the highest spirometric measures for children who had one, two or three maneuvers. We fit separate regression models for each combination of outcome, fumigant, time period, and buffer distance.

We selected covariates *a priori* based on our previous studies of respiratory symptoms (Raanan et al. 2014; Raanan et al. 2017) and respiratory function (Raanan et al. 2016; Raanan et al. 2017) in this cohort. For logistic regression models of respiratory symptoms and asthma medication use, we included maternal smoking during pregnancy (yes/no) and signs of moderate or extensive mold noted at either home visit (when child was six and 12 months old). We also included season of birth (wet/pollen/dry/mold) to control for other potential exposures that might play a causal role in respiratory disease (i.e., wetness (winter), pollen (spring), dryness (summer), and mold (fall)). We defined the seasons of birth as follows: pollen (mid-January to mid-May), dry (mid-May to mid-August), mold (mid-August to mid-January) based on measured pollen and mold counts during the years the children were born (Harley et al. 2009). In addition, we controlled for allergy (Downs et al. 2007; Spanier et al. 2014) using a proxy variable: runny nose without a cold in the previous 12 months reported at age 7. Because allergy could be on the causal pathway, we also re-ran all models without adjusting for allergy. Results were similar and therefore we only present models controlling for allergy.

Additionally, for spirometry analyses only, we adjusted for the technician performing the test, and child's age, sex and height. We included household food insecurity score during the previous 12 months (using the U.S. Household Food Security Instrument, Spanish Version) (Harrison et al. 2003), breastfeeding duration (months), and whether furry pets were in the home at the 7 year visit to control for other factors related to lung function. We also adjusted for mean daily particulate matter concentrations with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$) during the first 3 months of life and whether the home was located ≤150m from a highway in first year of life determined using GIS, to control for air pollution exposures related to lung function. We calculated average $PM_{2.5}$ concentration in the first 3 months of life using data from the Monterey Unified Air Pollution Control District air monitoring station. In all lung function models of postnatal fumigant use, we included prenatal use of that fumigant as a confounder.

To test for non-linearity, we used generalized additive models (GAMs) with three-degrees-of-freedom cubic spline functions including all the covariates included in the final lung

function models. None of the digression from linearity tests were significant ($p<0.1$); therefore, we expressed fumigant use on the continuous $\log_{10}$ scale in multivariable linear regression models. Regression coefficients represent the mean change in lung function for each 10-fold increase in wind-weighted fumigant use.

We conducted sensitivity analyses to verify the robustness and consistency of our findings. We included other estimates of pesticide exposure in our models that have been related to respiratory symptoms or lung function in previous analyses of the CHAMACOS cohort. Specifically, we included child urinary concentrations of dialkylphosphate metabolites (DAPs), a non-specific biomarker of organophosphate (OP) pesticide exposure using the area under the curve calculated from samples collected at 6-months, 1, 2, 3.5 and 5 years of age (Raanan et al. 2015; Raanan et al. 2016). We also included agricultural sulfur use within 1-km of residences during the year prior to lung function measurement (Raanan et al. 2017). We used similar methods as described above for fumigants to calculate wind-weighted sulfur use, except with a 1-km buffer and the proportion of time that the wind blew from each of eight directions during the previous year. The inclusion of these two pesticide exposures reduced our study population with complete data for respiratory symptoms (n= 204) and lung function (n = 165 for FEV_1 and n = 148 for FVC and $FEF_{25–75}$). Previous studies have observed an increased risk of respiratory symptoms and asthma with higher levels of *p, p'*-dichlorodiphenyltrichloroethylene (DDT) or *p, p'*-dichlorodiphenyldichloro-ethylene (DDE) measured in cord blood (Mamane et al. 2015). As a sensitivity analysis, we included $\log_{10}$-transformed lipid-adjusted concentrations (ng/g-lipid) of DDT and DDE measured in prenatal maternal blood samples (Eskenazi et al. 2006). We also used Poisson regression to calculate adjusted risk ratios for respiratory symptoms and asthma medication use for comparison with the ORs estimated using logistic regression because ORs can overestimate risk in cohort studies (Knol et al. 2012).

In additional analyses of spirometry outcomes, we also excluded those children who reported using any prescribed medication for asthma, wheezing, or tightness in the chest during the last 12 months to investigate whether medication use may have altered spirometry results. We ran models including only those children with at least two acceptable reproducible maneuvers (acceptable reproducibility is achieved when the difference between the largest and the next largest FEV1 is ≤0:15 L). We ran all models excluding outliers identified with studentized residuals greater than three. We assessed whether asthma medication or child allergies modified the relationship between lung function and fumigant use by creating interaction terms and running stratified models. To assess potential selection bias due to loss to follow-up, we ran regression models that included stabilized inverse probability weights (Hernan et al. 2004). We determined the weights using multiple logistic regression with inclusion as the outcome and independent demographic variables as the predictors. Data were analyzed with Stata (version IC13.0; StataCorp, College Station, TX) and R (v.3.1; R Foundation for Statistical Computing, Vienna, Austria). We set statistical significance at $p<0.05$ for all analyses, but since we evaluated many combinations of outcomes, fumigants, distances and time periods we assessed adjustment for multiple comparisons using the Benjamini-Hochberg false discovery rate at $p<0.05$ (Hochberg and Benjamini 1990).

3. Results

3.1. Demographics and distributions

Most mothers were born in Mexico (87.8%), below age 30 at time of delivery (73.5%), and married or living as married (82.3%) at the time of study enrollment (Table 1). Nearly all mothers (95.9%) did not smoke during pregnancy. When cohort participants were 6 and 12 months old, most households (66.7%) showed signs of moderate or extensive mold at either visit. At age 7, based on maternal report, the majority (71.1%) of families was living below the Federal Poverty Level, 15.7% of cohort children experienced a runny nose without a cold within the past year, 16.3% displayed asthma symptoms, and 6.1% were currently taking asthma medication.

Table 2 shows the distributions of wind-weighted fumigant use within 8 km of CHAMACOS residences during the prenatal and postnatal exposure periods. Methyl bromide and chloropicrin were the most heavily used fumigants during the prenatal period, with mean ± SD wind-adjusted use of 13,380 ± 10,437 and 8,665 ± 6,816 kg, respectively. Reflecting declines in methyl bromide use, the use of chloropicrin was greater than the use of methyl bromide during the postnatal period, with median values of 127,977 and 109,616 kg during the 7 years, respectively. When we examined correlations within each fumigant, use within 3, 5, and 8 km from the home was highly correlated ($p<0.001$) for each fumigant (Supplemental Table 1). Fumigant use during the prenatal and postnatal periods was also highly correlated ($r = 0.8$) for methyl bromide and chloropicrin, but was not correlated for metam sodium use and was inversely correlated for 1,3-DCP use ($r = -0.4$). We also examined correlations among fumigants and observed high correlations between prenatal methyl bromide and chloropicrin use ($r = 0.96$) and between prenatal metam sodium and 1,3-DCP use ($r = 0.7$). There were negative correlations between prenatal methyl bromide and chloropicrin use with prenatal metam sodium and 1,3-DCP use (Supplemental Table 1).

The distributions of lung function measurements at 7 years of age are presented in Table 2. The mean ± SD for FEV_1, FVC and $FEF_{25–75}$ were 1.81 ± 0.47 L/s, 2.08 ± 0.54 L and 2.54 ± 0.88 L/s, respectively.

3.2. Respiratory symptoms and asthma medication use

The adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for respiratory symptoms and use of asthma medication with prenatal and postnatal fumigant use within 8 km of residences are presented in Table 3. There were no significant relationships with either prenatal or postnatal fumigant use. Results within 3 and 5 km of the home are shown in Supplemental Table 2. We observed borderline significant increased odds of asthma medication use with postnatal metam sodium use within 3 and 5-km with OR=1.5 (95% CI: 1.0–2.2, p=0.05) and OR=2.2 (95% CI: 0.8–6.0, p=0.11), respectively.

3.3. Lung function

Adjusted associations between a 10-fold increase in the amount of fumigants applied within 8 km of the home and the highest lung function measurements are presented in Table 4. We did not observe any significant adverse relationships between prenatal or postnatal fumigant

use within 8 km and lung function. A 10-fold increase in wind-adjusted prenatal methyl bromide use within 8 km was associated with higher FEV_1 (β=0.06; 95% CI: 0.0, 0.12; p=0.05) and $FEF_{25–75}$ (β=0.15; 95% CI: 0.03, 0.27; p=0.01). Additionally, a 10-fold increase in wind-adjusted prenatal chloropicrin use within 8 km was positively associated with $FEF_{25–75}$ (β=0.11; 95% CI: 0.0, 0.21; p=0.05). Associations between methyl bromide and chloropicrin use and lung function observed in the prenatal exposure period were not observed in the postnatal period. Results were similar, although no longer statistically significant, for prenatal methyl bromide and chloropicrin use within 5 km of residences (Supplemental Table 3). There were no associations between fumigant use within 3 km of residences and lung function (Supplemental Table 3). We did not observe associations between postnatal fumigant use at any distance and lung function measurements (Table 4 and Supplemental Table 4) or between fumigant use during the year prior to the assessment and lung function measurements (Supplemental Table 5).

3.4 Sensitivity analyses

In sensitivity analyses using multivariable models including other pesticide exposures that have been previously related to respiratory symptoms and lung function including childhood urinary DAP metabolites (Raanan et al. 2015; Raanan et al. 2016), proximity to agricultural sulfur use during the year prior to lung function assessment (Raanan et al. 2017) and prenatal DDT/DDE blood concentrations (Mamane et al. 2015), the results were very similar to those presented in Tables 3 and 4. For example, the relationships between prenatal methyl bromide use within 8 km were very similar for FEV_1 (β=0.07; 95% CI: −0.01, 0.14) and $FEF_{25–75}$ (β=0.18; 95% CI: 0.03, 0.34). Prenatal fumigant use was generally not correlated with other pesticide exposures that we found to be associated with lung function in this cohort, except for weak correlations between agricultural sulfur use within 1 km during the year prior to spirometry and prenatal use of metam sodium and 1,3 – DCP with r = 0.14 and r=0.26 respectively. The results were very similar when we only included children with two acceptable reproducible maneuvers in the analyses (data not shown). The results were also similar when we excluded those currently using asthma medication, excluded the one outlier for FEV_1 models or used inverse probability weighting to adjust for participation bias (data not shown). Risk ratios estimated for asthma symptoms and medication using Poisson regression were nearly identical to the ORs presented in Table 3 and Supplemental Table 2. We did not observe effect modification by asthma medication use. Maternal report of child allergies (runny nose without a cold during the previous year) modified the relationship between FEV_1 and prenatal proximity to methyl bromide use (p = 0.07) and we only observed higher FEV_1 among children without allergies (β=0.08 L/s; 95% CI: 0.02, 0.14 for a 10-fold increase in methyl bromide use during the prenatal period). After adjusting for multiple comparisons, none of the associations reached significance at the critical p-value 0.002 based on the Benjamini-Hochberg false discovery rate.

4. Discussion

This is the first study to examine lung function or respiratory symptoms in relation to residential proximity to agricultural fumigant use. We found no significant evidence of reductions in lung function or increased odds of respiratory symptoms or use of asthma

medication in 7-year-old children with increased use of agricultural fumigants within 3 – 8 km of their prenatal or postnatal residences. We unexpectedly observed a slight improvement in lung function at 7 years of age with residential proximity to higher methyl bromide and chloropicrin use during the prenatal period and this improvement was limited to children without allergies. Although these results remained after adjustment for other pesticide exposure measures previously related to respiratory symptoms and lung function in our cohort, they do not remain significant after adjustment for multiple comparisons. There is a strong spatial pattern of methyl bromide and chloropicrin use during the pregnancy period for our study because of heavy use on strawberry fields near the coast at the northern portion of the Salinas Valley (Gemmill et al. 2013). There could be other unmeasured environmental or other factors that are confounding the relationship we observed between higher prenatal fumigant use and improved lung function. We explored the use of location (Coast, Salinas or South Valley) as a proxy variable but the results remained similar. Previously published studies of prenatal exposure to air pollutants and lung function have generally observed links to alterations in lung development and function and to other negative respiratory conditions in childhood, and plausible mechanisms include changes in maternal physiology and DNA alterations in the fetus (Veras et al. 2017). Improved lung function was associated with higher estimates of recent ambient exposure to hydrogen sulfide in a study of adults living in a geothermal area of New Zealand (Bates et al. 2015). However, hydrogen sulfide has been shown to be an endogenously produced “gasotransmitter”, with anti-inflammatory and cytoprotective functions (Calvert et al. 2010), and is being explored for its use for protection against ventilator-induced lung injury (Faller et al. 2010; Otulakowski et al 2010).

In previous studies of this cohort, we found increased odds of respiratory symptoms (OR= 2.5; 95% CI: 1.3, 4.9) and lower FEV_1, (L/s) (β=−0.16, 95% CI −0.30 to −0.02) and FVC (L) (β=−0.17, 95% CI −0.34 to 0.01) per 10-fold increase of childhood average urinary concentrations of metabolites of organophosphate pesticides (Raanan et al. 2015; Raanan et al. 2016). Other studies of prenatal pesticide exposure and respiratory health in children have mostly evaluated exposure using cord blood concentrations of DDE, a breakdown product of DDT, and have observed an increased risk of respiratory symptoms and asthma with higher levels of DDE (Mamane et al. 2015). Most studies of postnatal pesticide exposure and respiratory health in children have utilized self-reported information from mothers to assess pesticide exposure and have observed higher odds of respiratory disease and asthma with reported pesticide exposure (Mamane et al. 2015). None of the previous studies of pesticide exposure and respiratory health have specifically evaluated fumigants. Another strength of the study is that CHAMACOS is a prospective cohort followed since pregnancy with extensive data on potential confounders of respiratory health and other measures of pesticide exposure.

Our study also had some limitations. We did not have information on maternal occupational exposure to fumigants or the geographic location of maternal workplaces during pregnancy, and we did not have the location of schools during childhood. These limitations likely resulted in some exposure misclassification during both the prenatal and postnatal periods. An important consideration in this study is that we estimated fumigant exposure using proximity to agricultural fumigant applications reported in the PUR data, which is not a

direct measure of exposure. However, the PUR data explains a large amount of the variability (R^2 = 95% for methyl bromide) of measured fumigant concentrations in outdoor air (Li et al. 2005).

In conclusion, we did not observe adverse associations between residential proximity to agricultural fumigant use during pregnancy or childhood and respiratory health in the children through 7 years of age. Although we did not observe adverse effects of fumigants on lung function or respiratory symptoms in this analysis, we have seen adverse associations in previous analyses of the CHAMACOS cohort between residential proximity to higher fumigant use and child development. We observed an association between higher methyl bromide use during the second trimester of pregnancy and lower birthweight and restricted fetal growth (Gemmill et al. 2013). We also observed decreases of ~2.5 points in Full-Scale intelligence quotient at 7 years of age for each 10-fold increase in methyl bromide or chloropicrin use within 8 km of the child's residences from birth to 7 years of age (Gunier et al. 2017). Future studies are needed in larger and more diverse populations with a greater range of agricultural fumigant use to further explore the relationship with respiratory function and health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

1,3-DCP	1,3 – dichloropropene (Telone)
CHAMACOS	Center for the Health Assessment of Mothers and Children of Salinas
CI	confidence interval
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
$FEF_{25–75}$	forced expiratory flow 25–75%
OR	odds ratio
PUR	Pesticide Use Report

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Highlights

- Respiratory symptoms were not related to prenatal residential proximity to fumigant use.
- Respiratory symptoms were not related to postnatal residential proximity to fumigant use.
- Lung function improved slightly with prenatal residential proximity to fumigant use.
- Lung function was not associated with postnatal residential proximity to fumigant use.

Table 1

CHAMACOS study cohort characteristics (n=294).

Cohort Characteristic	N	%
Maternal Country of Birth		
Mexico	258	87.8%
United States and other	36	12.2%
Maternal Age at Delivery		
18 – 24	112	38.1%
25 – 29	104	35.4%
30 – 34	50	17.0%
35 – 45	28	9.5%
Maternal Education		
≤ 6th grade	133	45.2%
7th grade or more	161	54.8%
Marital Status at enrollment		
Married/Living as married	242	82.3%
Not married	52	17.7%
Mother smoked during pregnancy		
Yes	12	4.1%
No	282	95.9%
Maternal body mass index at 7y visit (kg/m^2)[a]	276	30.8 (27.5 – 34.5)
Sex		
Girl	153	52.0%
Boy	141	48.0%
Child body mass index at 7y visit (kg/m^2)[a]	294	18.0 (16.1 – 21.2)
Mold at 6m or 12m visit		
Yes	196	66.7%
No	98	33.3%
Family income at 7y visit[b]		
< Poverty level	209	71.1%
≥ Poverty level	85	28.9%
Runny nose without cold in past year at 7y visit		
Yes	46	15.7%
No	248	84.4%
Wheezing in the past year at 7y visit		
Yes	20	6.8%
No	274	93.2%
Any respiratory symptoms in past year at 7y visit		
Yes	48	16.3%
No	246	83.7%
Current asthma medication use at 7y visit		
Yes	18	6.1%

Cohort Characteristic	N	%
No	276	93.9%

[a] Body mass index (kg/m^2)= median (25th – 75th percentiles).

[b] Poverty level at 7 year visit was imputed from the nearest available visit for n=3 participants.

Table 2

Distributions of wind-weighted agricultural fumigant use (kg) within 8 km of residence and lung function measurements at 7 years of age.

	N	Mean ± SD	25th	50th	75th	Max
Prenatal pesticide use (kg)						
Methyl bromide	257	13,380 ± 10,437	3,293	13,567	21,009	56,433
Chloropicrin	257	8,665 ± 6,816	1,551	8,756	13,672	34,990
Metam sodium	257	466 ± 1,451	0	0	0	8,577
1,3-DCP	257	867 ± 1,770	4	29	554	8,232
Postnatal pesticide use (kg)						
Methyl bromide	276	88,449 ± 59,061	22,331	109,616	134,086	348,958
Chloropicrin	276	97,869 ± 67,513	11,405	127,977	152,276	287,351
Metam sodium	276	10,166 ± 9,558	1,682	5,246	21,519	54,621
1,3-DCP	276	60,773 ± 45,929	17,196	59,634	101,730	154,018
Lung function measurements at age 7y						
FEV_1 (L/s), Mean ± SD	262	1.81 ± 0.47	1.44	1.75	2.21	2.72
FVC (L), Mean ± SD	239	2.08 ± 0.54	1.62	2.07	2.56	3.09
$FEF_{25–75}$ (L/s), Mean ± SD	239	2.54 ± 0.88	1.85	2.44	3.30	5.10

Table 3

Adjusted* odds ratios (95% Confidence Interval) for a 10-fold increase in wind-adjusted fumigant use (kg) within 8-km radius of a child's residence during prenatal and postnatal periods with respiratory symptoms and asthma medication at 7 years of age,CHAMACOS study, 1999 – 2007.

Exposure	Respiratory symptoms OR (95% CI)	p	Asthma medication OR (95% CI)	p
Prenatal (n = 257)				
Methyl bromide	1.1 (0.8–1.6)	0.55	1.0 (0.6–1.8)	0.87
Chloropicrin	1.1 (0.8–1.4)	0.66	1.0 (0.6–1.5)	0.94
Metam sodium	1.0 (0.8–1.3)	0.88	1.2 (0.8–1.8)	0.35
1,3-DCP	1.1 (0.8–1.4)	0.58	1.3 (0.9–2.0)	0.17
Postnatal (n = 276)				
Methyl bromide	1.0 (0.6–1.6)	0.93	0.8 (0.4–1.7)	0.63
Chloropicrin	1.0 (0.6–1.5)	0.87	0.9 (0.5–1.6)	0.61
Metam sodium	0.9 (0.6–1.4)	0.72	1.3 (0.7–2.7)	0.41
1,3-DCP	1.2 (0.6–2.4)	0.64	1.3 (0.4–3.6)	0.66

*Adjusted for maternal smoking during pregnancy, season of birth (wet/pollen/dry mold), signs of moderate/extensive mold at home visit (6 or 12 months), and runny nose without a cold reported at age 7y.

Table 4

Adjusted* association between a 10-fold increase in wind-adjusted fumigant use (kg) within 8 km of residences and lung function measurements at 7 years of age, CHAMACOS study, 1999 – 2007.

	Highest FEV_1				Highest FVC				Highest $FEF_{25–75}$			
	N	β	(95% CI)	p	N	β	(95% CI)	p	N	β	(95% CI)	p
Prenatal Exposure												
Methyl bromide	229	0.06	(0.00, 0.12)	0.05	208	0.06	(−0.01, 0.13)	0.09	208	0.15	(0.03, 0.27)	0.01
ChloroPicrin	229	0.04	(−0.01, 0.09)	0.09	208	0.05	(−0.01, 0.11)	0.14	208	0.11	(0.00, 0.21)	0.05
Metam sodium	229	−0.03	(−0.08, 0.02)	0.19	208	−0.02	(−0.08, 0.04)	0.57	208	−0.08	(−0.18, 0.03)	0.16
1,3-DCP	229	−0.02	(−0.07, 0.02)	0.31	208	−0.03	(−0.09, 0.03)	0.34	208	−0.08	(−0.18, 0.02)	0.11
Postnatal Exposure												
Methyl bromide	212	−0.10	(−0.28, 0.08)	0.29	193	−0.04	(−0.25, 0.18)	0.75	193	−0.14	(−0.51, 0.23)	0.45
ChloroPicrin	212	−0.01	(−0.16, 0.13)	0.84	193	0.00	(−0.17, 0.18)	0.96	193	0.05	(−0.25, 0.35)	0.74
Metam sodium	212	0.04	(−0.04, 0.13)	0.33	193	0.05	(−0.05, 0.16)	0.31	193	0.05	(−0.12, 0.23)	0.55
1,3-DCP	212	0.00	(−0.15, 0.14)	0.95	193	0.04	(−0.13, 0.22)	0.63	193	−0.0 1	(−0.31, 0.29)	0.97

*Adjusted for child's sex, age, height, maternal smoking during pregnancy, season of birth (wet/pollen/dry mold), mean daily PM2.5 during first 3 months of life, breast feeding duration, signs of moderate/extensive mold at home visit (6 or 12 months), distance (≤150m) from highway (6 or 12 months), pets at home (5–7 years), household food insecurity score (7 years), runny nose without a cold reported at age 7y and postnatal exposure adjusted for prenatal exposure.