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Elemental Sulfur Use and Associations with Pediatric Lung Function and Respiratory Symptoms in an Agricultural Community (California, USA)

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Background: Elemental sulfur, "the oldest of all pesticides," is the most heavily used agricultural pesticide in California and Europe. Sulfur is considered relatively safe and is used in both conventional and organic farming systems. Adverse respiratory effects have been reported in applicators and animals, but the effect on residential populations, and especially on children living in proximity to fields treated with elemental sulfur, is not known.

Objectives: We evaluated associations between residential proximity to elemental sulfur applications and respiratory symptoms and spirometry of children living in an agricultural community.

Methods: Participants were enrolled in the CHAMACOS longitudinal birth cohort. We collected respiratory symptomatology for 347 children at 7 y of age and measured spirometry on a subset of 279. Of these, estimations of proximity to sulfur application and relevant covariate data were available for 237 and 205 children for whom we had symptomatology information and FEV_1 measurements, respectively. Data from the California Pesticide Use Reporting System were used to estimate the amount of elemental sulfur applied within 0.5, 1, and 3 km of a child's residence during the week, month, and 12 mo prior to pulmonary evaluation. Regression models controlled for maternal smoking during pregnancy; season of birth; $PM_{2.5}$ (particulate matter ≤ 2.5 mm in aerodynamic diameter); breast feeding duration; child's sex, age, and height; technician; and other covariates.

Results: Adverse associations with respiratory outcomes were found for sulfur applications within 0.5- and 1-km radii. Specifically, asthma medication usage and respiratory symptoms increased [$OR = 3.51$; 95% confidence interval (CI): 1.50, 8.23, $p = 0.004$; $OR = 2.09$; 95% CI: 1.27, 3.46, $p = 0.004$, respectively] and FEV_1 decreased ($\beta = -0.143$; 95% CI: -0.248, -0.039, $p = 0.008$) per 10-fold increase in the estimated amount of sulfur used within 1 km of child residence during the year prior to pulmonary evaluation.

Conclusions: This study suggests that elemental sulfur use, allowed in both organic and conventional farming, in close proximity to residential areas, may adversely affect children's respiratory health. https://doi.org/10.1289/EHP528

Introduction

Elemental sulfur, "the oldest of all pesticides" (Klaassen 2013; Kuklińska et al. 2013), is permitted on both conventional as well as organic crops (U.S. Electronic Code of Federal Regulations, https://www.ecfr.gov/) and represents the most heavily used crop protection chemical in California and Europe (CDPR 2015; Klaassen 2013; PAN Germany 2003; Federal Office of Consumer Protection and Food Safety Germany 2014). In California alone, 21,467,908 kg of elemental sulfur were applied in agriculture in 2013 (CDPR 2015).

Although many sulfur compounds [e.g., sulfur dioxide, hydrogen sulfide (Klaassen 2013)] may be toxic to the respiratory system, elemental sulfur is generally considered safe for the environment and human health (EFSA 2009; Klaassen 2013). According to the U.S. EPA (1991a) "elemental sulfur is of low toxicity, and its use as a pesticide poses very little known hazard to people and nontarget species." However, in animals, elemental sulfur can induce contact dermatitis when administered by intradermal injection or topically (Matsushita et al. 1977) and can cause breathing difficulties when administered by gavage (Humphreys 1988; European Commission 2015; Krieger 2001).

The California Pesticide Illness Registry contained 1,698 occupational cases involving elemental sulfur exposure between 1982 and 1995 (Krieger 2001). Of 155 cases involving sulfur pesticide handlers, ocular symptoms were present in 44%, dermatitis in 45%, and respiratory or systemic illness in 32%. Some cases resulted in rhinitis or asthma symptoms (Krieger 2001).

Similar results were reported in 1998–1999 by the Sentinel Event Notification System for Occupational Risks (SENSOR) pesticide surveillance data (Calvert et al. 2004), and among workers exposed to sulfur dust in mines (Stellman 1998; U.S. EPA 1991a). Isolated nonoccupational case reports have been described of contact allergy (Krieger 2001), dyspnea, and hypoxemia resulting from exposure to sulfur that drifted from a nearby sprayed field (Calvert et al. 2004), and of sore throat, chest pain, and acute tracheobronchitis characterized by cough resulting from sulfur inhalation (Ellenhorn and Barceloux 1988).

To our knowledge, no study has investigated possible health effects in residents living near applications despite the wide agricultural use of elemental sulfur and the potential for drift (Calvert et al. 2004). Herein, we present the first report of an association between agricultural use of elemental sulfur and both respiratory symptoms and lung function in children living in an agricultural community.

Methods

Study Setting and Design

The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) is a longitudinal birth cohort study

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All authors certify that their freedom to design, conduct, interpret, and publish research is not compromised by any controlling sponsor. A.B. is a member of the USDA National Organic Standards Board and has participated as a member of the Board for the Organic Center, a nonprofit organization that provides information for scientific research about organic food and farming. A.B. has also consulted with nonprofit organizations on the development of environmental health education curricula for child care providers. R.R. has served as a consultant to a nonprofit organization and expert witness on cases unrelated to the issues in this paper.

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examining environmental exposures in children living in the Salinas Valley, California. Research protocols were approved by the University of California, Berkeley, Committee for the Protection of Human Subjects. Written informed consent was obtained from the mothers and children's oral assent was obtained at age 7 (see Eskenazi et al. 2006 for more details).

Participants

Women were eligible for the CHAMACOS study if they were ≥18 y of age, at <20 wk gestation, planning to deliver at the county hospital, English or Spanish speaking, and eligible for low income health insurance (Medi-Cal). A total of 601 pregnant women were enrolled in the study and 526 were followed to the delivery of a live-born surviving singleton. Information on respiratory symptoms and use of asthma medication was available for 347 of their children at age 7. Of these, estimates of proximity to sulfur application and relevant covariate data were available for 237 children. Spirometry measurements were conducted for 279 7-y-olds (see below for details). Forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and forced expiratory flow 25–75% ($FEF_{25–75}$) values of adequate quality were available for 279, 250, and 250 children, respectively. Of these, estimations of proximity to sulfur application and relevant covariate data were available for 205, 184, and 184 children for whom we had FEV_1, FVC, and $FEF_{25–75}$ measurements, respectively. Families included in this analysis ($n = 237$) did not differ significantly from the original full cohort on most attributes, including urinary dialkyl phosphate (DAP) metabolite concentrations during childhood, a nonspecific biomarker of organophosphate (OP) pesticide exposure; maternal asthma, education, marital status, and poverty category and maternal age at delivery; and the child's birth weight and breastfeeding duration. In addition, percentage of reported respiratory symptoms did not differ significantly among children who had spirometry measurements (i.e., who had at least one acceptable FEV_1 measurement) compared with those who did not have spirometry measurements (percent with respiratory symptoms 17.0% vs. 19.4%, respectively).

Maternal Interviews and Respiratory Symptoms

Women were interviewed by bilingual bicultural interviewers twice during pregnancy (mean ± SD = 13.4 ± 4.7 and 26.5 ± 2.6 wk gestation), following delivery, and when their children were 0.5, 1, 2, 3.5, 5, and 7 y old. Home visits were conducted by trained personnel when the children were 0.5, 1, 2, 3.5, and 5 y old. Additionally, information from prenatal and delivery records was abstracted by a registered nurse.

For the present study, we used maternal report of the child's respiratory symptoms when the child was 7 y old. Mothers were asked about their child's respiratory symptoms using questions adapted from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (Asher et al. 1995; Holguin et al. 2007; Kraai et al. 2013; Raanan et al. 2015; Stellman et al. 2013). 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 to any of the following during the previous 12 mo: *a*) wheezing or whistling in the chest; *b*) wheezing, whistling, or shortness of breath so severe that the child could not finish saying a sentence; *c*) trouble going to sleep or being awakened from sleep because of wheezing, whistling, shortness of breath, or coughing that was not associated with a cold; or *d*) having to stop running or playing active games because of wheezing, whistling, shortness of breath, or coughing that was not associated with a cold. In addition, a child was included as having respiratory symptoms if the mother reported use of asthma controller or rescue medications, even in the absence of the above symptoms.

We also analyzed separately the binary outcome of use of asthma controller or rescue medications (i.e., asthma medication). Children who were not categorized as positive for asthma medication use but had other respiratory symptoms were classified as noncases for these analyses.

Spirometry

We measured the child's height and weight at the time spirometry was performed. Spirometry was conducted by the same technician for 92% of the assessments. Three identical EasyOne spirometers were used (ndd Medical Technologies, Inc., Andover, MA). Routine calibration was performed every morning.

For training on the spirometry procedure, children practiced blowing into a whistle as loud and long as they could. Then, the technician demonstrated the maneuver by blowing into the spirometer followed by practice trials. Children were instructed to sit up straight on a stool with their feet flat on the floor, and take a deep breath to fill up their lungs with as much air as they could until they felt they could not get any more air in. The children were asked to place the mouthpiece in their mouth and to seal it with their lips, and not to bite or stick their tongue into the hole. Children were instructed not to lean forward. They were then coached to blast the air out as fast and as hard as they could, and not to stop until they were told. The technician kept encouraging the children to blow until the test was completed. After practicing the maneuver sufficiently, the children were coached to blow until the EasyOne signaled that the test had ended. Each child performed a maximum of eight expiratory maneuvers and up to three best acceptable tests were saved by the spirometric software. Each acceptable blow lasted at least 3 s. Quality control was also achieved by verifying that the child did not lean forward, air did not leak out of the side, the child took a deep breath right from the beginning, blew enough air out, did not stop blowing too soon, and took a big smooth breath. All expiratory flow–volume curves were reviewed by two physicians experienced in pediatric spirometry, and only adequate quality data meeting acceptability criteria were included in the statistical analyses.

Geographic-Based Estimates of Nearby Sulfur Use

We determined the location of the home the child lived in at age 7 y. Latitude and longitude coordinates of participants' homes were collected during a home visit when the children were 5 y old using a handheld Global Positioning System (GPS) unit (Garmin, GPS II, Chicago, IL). At the 7-y visit, mothers were asked if the family had moved since the 5-y visit, and if so, the new address was recorded. We used coordinates collected from the GPS unit for the 54% of participants who had not moved since age 5 y, and we used Geographic Information System (GIS) software (ArcInfo 10; ESRI, Redlands, CA) to obtain coordinates for the new residence for the 46% of participants who had moved between 5 and 7 y of age. We excluded children who resided outside of Monterey County ($n = 19$) and children who moved more than one time between their 5- and 7-y visits ($n = 23$).

We estimated the agricultural use of sulfur near each child's residence using a GIS based on the California Pesticide Use Reporting (PUR) system (CDPR 2013a). All agricultural pesticide applications are reported to the state, including the active ingredient, quantity applied, acres treated, crop treated, date, and location to $1\,mi^2$ in area (approximately 1.6 km by 1.6 km) defined by the Public Land Survey System (PLSS) (Figure 1). We edited the PUR data to correct for likely outliers with

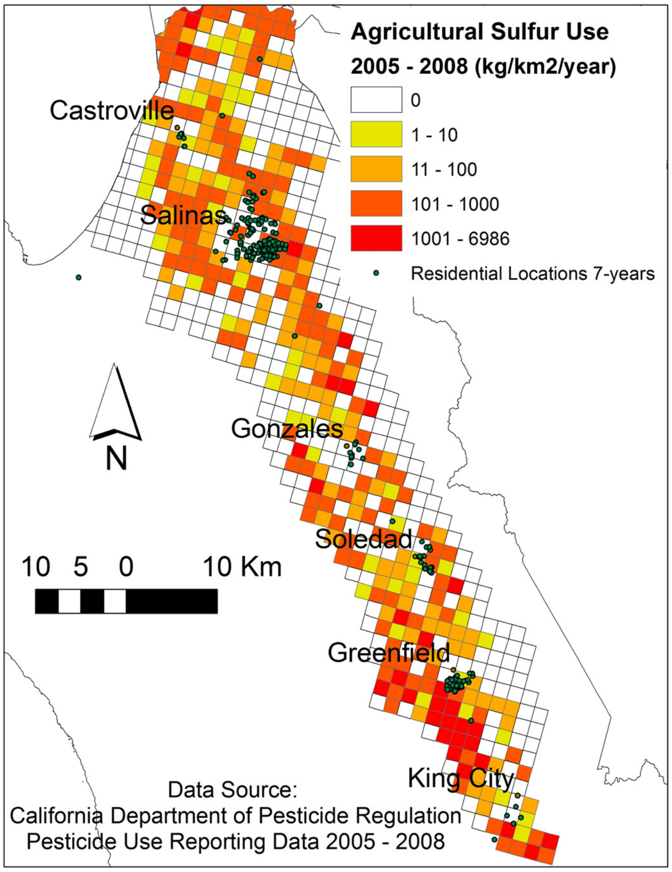

Figure 1. Elemental sulfur use (kg/y) by section of the Public Land Survey System (PLSS) grid in the Salinas Valley, 2005–2008, from the California Pesticide Use Report (PUR) system (CDPR 2013b).

unusually high application rates using previously developed methods (Gunier et al. 2001). We computed nearby sulfur use (i.e., estimates of the total amount of sulfur (kg) applied within each buffer distance) for combinations of distance from the residence (buffer radii of 0.5, 1, and 3 km) and time before the date of the 7-y visit (1 wk, 1 mo, and 12 mo before the visit). This range of buffer distances best captured the spatial scale that most strongly correlated with concentrations of other pesticides in air and house dust in previous studies (Gunier et al. 2011, 2014; Harnly et al. 2005, 2009). We weighted sulfur 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 sulfur from the application site, we obtained data on wind direction from the closest meteorological station; these were located in Arroyo Seco, Castroville, King City, Salinas North, Salinas South, and Pajaro (CIMIS 2014). The dominant wind direction in the Salinas Valley is an onshore breeze from the north or northwest ($\sim 50\%$ of the time) and wind speed does not vary greatly by wind direction; average wind speeds were between 2.5 and 3.8 m/s. We calculated wind frequency using the daily proportion of time the wind blew from each of eight directions during each time period (1 wk, 1 mo, and 12 mo before the visit). We determined the direction of each PLSS centroid relative to residences and weighted sulfur use in a section according to the percentage of time that the wind blew from that direction for each time period (see Figure S1). We summed these totals for each time period prior to the date of the 7-y visit, yielding estimates of the total amount of sulfur (kg) applied around the residence within each buffer distance and time period. Wind-weighted elemental sulfur use near residences was not calculated for the 0.5-km distance because it was not possible to determine the direction of sulfur applications relative to the residence within a section.

Data Analysis

We $\log_{10}$-transformed continuous sulfur use to reduce the influence of outliers and improve the linear fit of the model (1 kg was added to all values to avoid taking the log of 0). We used logistic regressions and generalized linear models (GLM) to estimate the associations of residential proximity to elemental sulfur use with respiratory symptoms and/or asthma medication use, and with the highest FEV_1, FVC, FEV_1/FVC, and $FEF_{25–75}$. Respiratory symptoms were defined as positive if the mother reported her child had any respiratory symptoms or, in the absence of such symptoms, used asthma medications during the previous 12 mo (Raanan et al. 2015). We also examined asthma medication use alone. We used GLM to estimate the association with proximity to sulfur applications for children who had one, two, or three acceptable maneuvers; for children who had at least two acceptable maneuvers; and for children with at least two acceptable reproducible maneuvers (acceptable reproducibility is achieved when the difference between the largest and the next largest FEV_1 is ≤ 0.15 L). We estimated the associations with proximity to sulfur applications 12 mo prior to the respiratory symptoms and asthma medication use assessment (because the symptoms were based on this time period) and with proximity to sulfur applications 1 wk, 1 mo, and 12 mo prior to the spirometry test.

$PM_{2.5}$ concentration was calculated using data from the Monterey Unified Air Pollution Control District (MBAPCD) air monitoring station, which uses high-volume Sierra-Andersen gravimetric samplers for 24 h every sixth day (Thermo Scientific, Waltham, MA). Seasons were defined as follows: pollen (mid-January to mid-May 2000), dry (mid-May to mid-August 2000), mold (mid-August to mid-January 2001), wet (mid-January to mid-March 2001), pollen (mid-March to mid-May 2001), and dry (mid-May to October 2001). Discrete seasons of high spore and pollen concentrations were determined by ambient aeroallergen concentrations that were measured throughout the birth periods of the participants. Differences in the date of seasons across years are based on actual rainfall and measured pollen counts for that year. Detailed methods for the differentiation of the four seasons have been described elsewhere (Harley et al. 2009). Allergy was based on the mother's report at the 5-y visit of the child having a runny nose without a cold in the previous 12 mo reported (yes/no) (Downs et al. 2007; Spanier et al. 2014). We used an allergy proxy variable reported on the 5-y visit and not on the 7-y visit because we wanted the allergic symptoms to precede the 12-mo period for reported respiratory symptoms. We also examined interaction between this allergy proxy and the amount of elemental sulfur applied within 0.5, 1, and 3 km of a child's residence and respiratory outcomes.

DAP metabolites were measured by the Division of Laboratory Science at the Centers for Disease Control and Prevention using gas chromatography–tandem mass spectrometry and quantified using isotope dilution calibration (Bravo et al. 2002) (for details, see Bradman et al. 2005). We considered child DAP concentration because it was related to child respiratory health in our previous analyses (Raanan et al. 2015, 2016).

Covariates were selected based on directed acyclic graphs (DAGs) (Greenland et al. 1999) for spirometry measures. For the respiratory symptoms and asthma medication analyses, we first selected variables based on DAGs but only included covariates that changed the coefficient by more than 10%, due to sample size considerations. We considered the following variables as potential confounders in the DAG: maternal smoking and urinary concentrations of DAP metabolites during pregnancy (log_{10}-transformed); signs of moderate or extensive mold in the home (at 6 or 12 mo), distance of home from highway (at 6 or 12 mo), and furry pets currently at home; average $PM_{2.5}$ concentration around residence in the first 3 mo of life; household food insecurity score at age 7 y; child's sex, exact age, season of birth (wet/pollen/dry/mold), breastfeeding duration, height, allergic symptoms, and urinary concentrations of DAP metabolites at age 5 y (log_{10}-transformed); and season of spirometry assessment and technician.

For the respiratory symptoms and asthma medication analyses, in final models, we controlled for maternal smoking during pregnancy (yes/no), signs of moderate or extensive mold noted at either home visit (when child was 6 and 12 mo old) (yes/no), season of birth, and child (at 5 y) urinary log_{10}-transformed concentrations of dialkyl phosphate metabolites (DAPs). In addition, we controlled for allergy and the interaction between this allergy proxy and the amount of elemental sulfur applied within 0.5, 1, and 3 km of a child's residence and respiratory outcomes.

For spirometry analyses, we adjusted for child's sex, age, breastfeeding duration (months), distance ($\leq$150 m vs. >150 m) from highway (at 6 or 12 mo), furry pets at home (5–7 y), household food insecurity score during the previous 12 mo [continuous score ranging from 0 to 6 representing food secure to food insecure with hunger; measured at 7 y using the U.S. Household Food Security Instrument, Spanish version (Harrison et al. 2003)], child's height, season of spirometry assessment, technician, and mean daily $PM_{2.5}$ during first 3 mo of life. Inclusion of maternal prenatal urinary DAP levels did not alter the results and thus were not included in the final spirometry models.

We conducted sensitivity analyses to verify the robustness and consistency of our findings. Because allergy could be on the causal pathway (Krieger 2001), we re-ran all models without adjusting for allergy. Results were similar and therefore only models controlling for allergy are shown. Proximity to any agricultural fields was included as a covariate in sensitivity analyses because we wanted to control for other potential factors in the field (including other pesticides and toxins). In additional analyses of spirometry outcomes, we also excluded those children who reported using any asthma medication in the last 24 h before the spirometry test and who had been prescribed medication for asthma, wheezing, and tightness in the chest during the last 12 mo in order to investigate whether medication use may have altered spirometry results. Potential selection bias due to exclusion of children with missing outcome data or missing covariates was addressed by comparing our results to regression models that included stabilized inverse probability weights (Hernán et al. 2004). Weights were determined using multiple logistic regressions with independent demographic variables selected based on a "Super Learner" algorithm using V-fold cross-validation (van der Laan et al. 2007).

Data were analyzed with Stata (version IC13.0; StataCorp) and R (version 3.1; R Development Core Team). We set statistical significance at $p < 0.05$ for main effects and at $p < 0.1$ for interaction effects.

Results

The cohort participants were primarily born to families of farm workers (63.4% were living with at least one agricultural worker in the household), immigrant families (89.0%), and to mothers who had less than a high school education (81.9%). Food insecurity was reported by 40.5% of mothers at the 7-y visit (Table 1). Based on maternal report, 17.3% of the 7-y-old children had respiratory symptoms and 6.8% had used asthma medication in the previous 12 mo (Table 2).

Table 1. Sociodemographic and household characteristics, CHAMACOS birth cohort, Salinas Valley, California ($n = 237$).

Characteristic	n (%) or Mean ± SD
Maternal characteristics	
Country of birth	
Mexico	208 (87.8)
United States	26 (11.0)
Other	3 (1.3)
Education	
≤6th grade	103 (43.5)
7–12th grade	91 (38.4)
Completed high school	43 (18.1)
History of asthma	
Yes	10 (4.2)
No	227 (95.8)
Smoked during pregnancy	
Yes	10 (4.2)
No	227 (95.8)
Child Characteristics	
Sex	
Male	110 (46.4)
Female	127 (53.6)
Season of birth[a]	
Mold	90 (38.0)
Wet	42 (17.7)
Pollen	49 (20.7)
Dry	56 (23.6)
Breast feeding duration	
Never breastfed	13 (5.5)
≤6 mo	109 (46.0)
>6 mo	115 (48.5)
Age (years)	7.0 ± 0.1
Food insecurity status at age 7 y	
Food secure	141 (59.5)
Food insecure without hunger	59 (24.9)
Food insecure with hunger	37 (15.6)
Height (cm)	123.3 ± 5.7
Weight (kg)	29.5 ± 7.9
Household characteristics	
Home ≤150 m from highway 101 (6 or 12 mo)	
Yes	16 (6.8)
No	221 (93.2)
Mean daily $PM_{2.5}$ near home (0–3 mo)[b]	
<8 $\mu g/m^3$	111 (46.8)
8–12 $\mu g/m^3$	96 (40.5)
≥12 $\mu g/m^3$	30 (12.7)
Signs of moderate/extensive mold at home visit (6 or 12 mo)	
Yes	163 (68.8)
No	74 (31.2)
Furry pets at home at ages 5 to 7 y	
Yes	31 (13.1)
No	206 (86.9)
Agricultural workers in the household at 7 y	
Yes	149 (63.4)
No	86 (36.6)

Note: Information on respiratory symptoms and use of asthma medication was available for 347 of their children at age 7 y. Of these, estimates of proximity to sulfur application and relevant covariate data were available for 237 children. Spirometry measurements were conducted for 279 7-y-olds. FEV_1, FVC, and $FEF_{25–75}$ values of adequate quality were available for 279, 250, and 250 children, respectively. Of these, estimations of proximity to sulfur application and relevant covariate data were available for 205, 184, and 184 children for whom we had FEV_1, FVC, and $FEF_{25–75}$ measurements, respectively.

[a]Season of birth corresponds generally to other potential exposures that might play a causal role in respiratory disease. We defined the seasons as follows: pollen (mid-January to mid-May 2000), dry (mid-May to mid-August 2000), mold (mid-August to mid-January 2001), wet (mid-January to mid-March 2001), pollen (mid-March to mid-May 2001), and dry (mid-May to October 2001). Differences in the date of seasons across years are based on actual rainfall and measured pollen counts for that year.

[b]Average $PM_{2.5}$ concentration in the first 3 mo of life was calculated using data from the Monterey Unified Air Pollution Control District (MBAPCD) air monitoring station, which uses high-volume Sierra-Andersen gravimetric samplers for 24 h every sixth day (Thermo Scientific, Waltham, MA).

Table 2. Respiratory symptoms and lung function measurements at age 7, CHAMACOS birth cohort, Salinas Valley, California ($n = 237$).

Characteristic	n (%) or Mean ± SD
Any respiratory symptoms	
Yes	41 (17.3)
No	196 (82.7)
Wheezing	
Yes	19 (8.0)
No	218 (92.0)
Coughing	
Yes	31 (13.1)
No	206 (86.9)
Asthma medication[a]	
Yes	16 (6.8)
No	221 (93.2)
Lung function measurements at age 7[b,c]	
FEV_1 (L/s)	205 1.66 ± 0.44
FVC (L)	184 1.93 ± 0.50
FEV_1/FVC	184 0.88 ± 0.06
$FEF_{25–75}$ (L/s)	184 2.22 ± 0.84

Note: Information on respiratory symptoms and use of asthma medication was available for 347 of their children at age 7 y. Of these, estimates of proximity to sulfur application and relevant covariate data were available for 237 children. Spirometry measurements were conducted for 279 7-y-olds. FEV_1, FVC, and $FEF_{25–75}$ values of adequate quality were available for 279, 250, and 250 children, respectively. Of these, estimations of proximity to sulfur application and relevant covariate data were available for 205, 184, and 184 children for whom we had FEV_1, FVC, and $FEF_{25–75}$ measurements, respectively.
[a]Reported use of asthma medication was included under the respiratory symptoms variable—all children with maternal report of asthma medication use were also classified as having respiratory symptoms. Children that were not categorized as positive for asthma medication use but had other respiratory symptoms were classified as noncases for these analyses. Of the 237 children, 37 reported respiratory symptoms and 16 reported use of asthma medication (12 reported on both respiratory symptoms and asthma medication intake).
[b]Average values.
[c]Each child performed a maximum of eight expiratory maneuvers, and up to three best acceptable tests were kept by the spirometric software.

Table 3 presents the distribution of wind-weighted elemental sulfur use (kg) near CHAMACOS residences in the 12 mo prior to the spirometry test. The proportion of children living near agricultural elemental sulfur use during the previous 12 mo was 43.5%, 73.8%, and 99.2% for within 0.5-, 1-, and 3-km buffers, respectively. For the 1-km buffer distance, the estimated 50th percentile of wind-weighted elemental sulfur use was 8.9 kg/y.

Proximity to sulfur applications within both 0.5- and 1-km radii during the 12 mo prior to respiratory assessment was associated with increased odds of respiratory symptoms and asthma medication use (Table 4). For a 10-fold increase in the nearby amount of elemental sulfur applied, the adjusted odds ratio (aOR) for respiratory symptoms was 1.71 [95% confidence interval (CI): 1.14, 2.57; $p = 0.009$] for a 0.5-km buffer, and 2.09 (95% CI: 1.27, 3.46; $p = 0.004$) for a 1-km buffer. The aOR for asthma medication use was 2.23 (95% CI: 1.19, 4.21; $p = 0.01$) for 0.5-km buffer, and 3.51 (95% CI: 1.50, 8.23; $p = 0.004$) for 1-km buffer. Sulfur applications within a 3-km radius during the 12 mo prior to respiratory assessment were not associated with increased odds of respiratory symptoms or asthma medication use.

Table 4. Associations [OR (95% CI)] of proximity to elemental sulfur use within 0.5-, 1- and 3-km radii of a child's residence 1 y before the respiratory questionnaire with respiratory symptoms and asthma medication at age 7, CHAMACOS study, Salinas Valley, California ($n = 237$), 2006–2007.

Group	Exposed/total	Respiratory symptoms	p-Value	Asthma medication[a]	p-Value
0.5 km	103/237	1.71 (1.14, 2.57)	0.009	2.23 (1.19, 4.21)	0.01
1 km	175/237	2.09 (1.27, 3.46)	0.004	3.51 (1.50, 8.23)	0.004
3 km	235/237	0.96 (0.40, 2.26)	0.92	2.10 (0.39, 11.30)	0.39

Note: Associations reflect change per 10-fold increase in the estimated amount of elemental sulfur applied within 0.5, 1, or 3 km of a child's residence (the amounts were modeled as log_{10}-transformed variables). Adjusted for maternal smoking during pregnancy, season of birth (wet/pollen/dry mold), signs of moderate/extensive mold at home visit (6 or 12 mo), urinary dialkylphosphate (DAP) metabolites of organophosphate pesticides measured at age 5, runny nose without a cold reported at age 5 and its interaction with sulfur use within 0.5-, 1-, or 3-km radii of a child's residence.
[a]Any report on asthma medication also included under the respiratory symptoms variable, i.e., all children classified as positive for "asthma medication" were also classified as having respiratory symptoms.

We also found inverse associations between sulfur applications during the prior 1 wk, 1 mo, and 12 mo within 0.5 km (see Table S1) and 1 km (Table 5, Figure 2; see also Table S1) of a child's residence and highest FEV_1, FVC, and $FEF_{25–75}$. Specifically, the highest FEV_1 measured from children who had at least two reproducible acceptable maneuvers was inversely associated with the amount of elemental sulfur applied within both a 0.5-km radius (adjusted β per 10-fold increase in the amount of elemental sulfur applied (aβ) = –0.108; 95% CI: −0.193, −0.024; $p = 0.01$) and a 1-km radius (aβ = −0.143; 95% CI: −0.248, −0.039; $p = 0.008$) in the previous 12 mo. Similarly, elemental sulfur applied within 0.5 km and 1 km during 1 wk (aβ = −0.222; 95% CI: −0.465, 0.020, $p = 0.07$; aβ = −0.254; 95% CI: −0.622, 0.113, $p = 0.2$ respectively) and 1 mo (aβ = −0.185; 95% CI: −0.327, −0.043, $p = 0.01$; aβ = −0.187; 95% CI: −0.380, 0.006, $p = 0.06$, respectively) before the spirometry test were also inversely related with FEV_1. Results were similar when we used alternative spirometry criteria.

The highest FVC and $FEF_{25–75}$ measured from children who had at least two acceptable maneuvers were inversely associated with the amount of elemental sulfur applied within 0.5-km and 1-km radii of their residence during the previous 12-mo period (Table 5; see also Table S1). Specifically, FVC and $FEF_{25–75}$ were inversely associated with the amount of elemental sulfur applied within 1-km during the previous 12-mo period (FVC: aβ = −0.127; 95% CI: −0.230, −0.024; $p = 0.02$ and $FEF_{25–75}$: aβ = −0.165; 95% CI: −0.338, 0.007; $p = 0.06$). We also found inverse associations between sulfur applications during the prior 1 wk and 1 mo within 0.5 km and 1 km (see Table S1). In general, regression coefficients for the association between all of the above spirometric parameters and amount of sulfur were stronger at 1 wk following application compared with 1 mo, and stronger at 1 mo compared with 1 y, albeit with wider confidence limits and borderline or above borderline significance values (see Table S1).

Table 3. Distribution of elemental sulfur use (kg) near residences of participants 1 y before the respiratory questionnaire and the spirometry test at 7 y of age, CHAMACOS study, Salinas Valley, California.

Group	n	n (%) with nearby sulfur use	Percentiles 25th	50th	75th	90th	95th
0.5-km radius	237	103 (43.5)	0	0	56.0	211.9	442.1
1-km-radius	237	175 (73.8)	0	73.4	521.9	1208.1	2235.4
3-km radius	237	235 (99.2)	2294.9	6229.3	9999.0	13189.5	14876.9
1-km-radius wind-weighted	237	175 (73.8)	0	8.9	46.2	146.1	223.5
3-km radius wind-weighted	237	235 (99.2)	246.7	701.3	1083.4	1465.4	1730.4

Note: Distribution of wind-weighted elemental sulfur use near residences is not presented for 0.5-km distance because it was not possible to determine the direction of sulfur applications relative to the residence within a section.

Table 5. Associations [β (95% CI)] of proximity to elemental sulfur use within 1-km radius of a child's residence 1 y before spirometry with lung function at age 7, CHAMACOS study, Salinas Valley, California, 2006–2007.

Spirometry	*n*	β (95% CI)	*p*-Value
Highest FEV_1 for children who had one, two, or three maneuvers	205	−0.127 (−0.204, −0.049)	0.002
Highest FEV_1 for children with at least two reproducible[a] maneuvers	106	−0.143 (−0.248, −0.039)	0.008
Highest FVC for children who had one, two, or three maneuvers	184	−0.161 (−0.255, −0.066)	0.001
Highest FVC for children who had at least two maneuvers	157	−0.127 (−0.230, −0.024)	0.02
Highest $FEF_{25–75}$ for children who had one, two, or three maneuvers	184	−0.248 (−0.414, −0.083)	0.003
Highest $FEF_{25–75}$ for children who had at least two maneuvers	157	−0.165 (−0.338, 0.007)	0.06
Highest FEV_1/FVC for children who had one, two, or three maneuvers	184	−0.006 (−0.017, 0.005)	0.3
Highest FEV_1/FVC for children who had at least two maneuvers	157	−0.005 (−0.017, 0.007)	0.4

Note: Associations [β (95% CI)] reflect change per 10-fold increase in the estimated amount of elemental sulfur applied within 1 km of a child's residence (the amounts were modeled as log_{10}-transformed variables). Adjusted for child's sex, age, height; maternal smoking during pregnancy; season of birth (wet/pollen/dry mold); mean daily $PM_{2.5}$ during first 3 mo of life; breast feeding duration; signs of moderate/extensive mold at home visit (6 or 12 mo); distance (≤150 m) from highway (6 or 12 mo); pets at home (5–7 y); urinary dialkylphosphate (DAP) metabolites of organophosphate pesticides measured at age 5; household food insecurity score (7 y); runny nose without a cold reported at age 5 and its interaction with sulfur use within 1-km radii of a child's residence; season of spirometry; and technician.

[a]Measured from children who had at least two reproducible acceptable maneuvers. Acceptable reproducibility is achieved when the difference between the largest and the next largest FEV_1 is ≤0.15 L.

No statistically significant adverse associations were found for any time period or distance from sulfur application and the FEV_1/FVC ratio (Table 5; see also Table S1). In addition, no statistically significant adverse associations were found for any spirometry measurement or any time period for the amount of elemental sulfur applied within 3 km of residence.

Results were similar when we adjusted for residential proximity to agricultural fields, restricted our analyses to residences located using handheld GPS units, or excluded children who may have taken medication for asthma symptoms in the last 24 h before spirometry (data not shown). Estimates for inverse probability weighted regression models yielded similar results (data not shown), suggesting that selection bias did not substantially alter our results.

Discussion

We have previously reported that exposure to organophosphate pesticides (OPs) as measured by dialkyl phosphate metabolites in the urine of the children was adversely associated with respiratory health in this population of children living in the Salinas Valley, California (Eskenazi et al. 1999; Raanan et al. 2015; Raanan et al. 2016). We now present the first report of an association between poorer respiratory health and nearby agricultural use of elemental sulfur—one of the most heavily used agricultural pesticides. Specifically, we found poorer lung function (FEV_1, FVC, and $FEF_{25–75}$) and higher odds of reported respiratory symptoms and asthma medication use assessed at 7 y of age in children living within 0.5 km and 1 km of elemental sulfur applications during the previous week, month, and year. These findings were independent of exposure to OPs. Our results are suggestive of an acute effect given stronger coefficients (albeit with wider confidence intervals and borderline or above borderline significance values given small numbers) for sulfur use within the previous week following application compared with 1 mo, and for sulfur use within the previous month compared with 1 y.

Our current study findings suggest a restrictive effect of low-level elemental sulfur exposure on children's lungs. This is similar to the restrictive effect suggested by our findings on early-life exposure to OPs (Raanan et al. 2016). Our findings agree with previous reports on adverse respiratory effects associated with elemental sulfur in animal models (Humphreys 1988; European Commission 2015; Krieger 2001), in workers (Calvert et al. 2004; Lee et al. 2005; Sama et al. 1997), and in case reports of poisoning (Ellenhorn and Barceloux 1988; Krieger 2001). This study also lends credibility to reports of drift of elemental sulfur after agricultural application (U.S. EPA 1991a; Calvert et al. 2004).

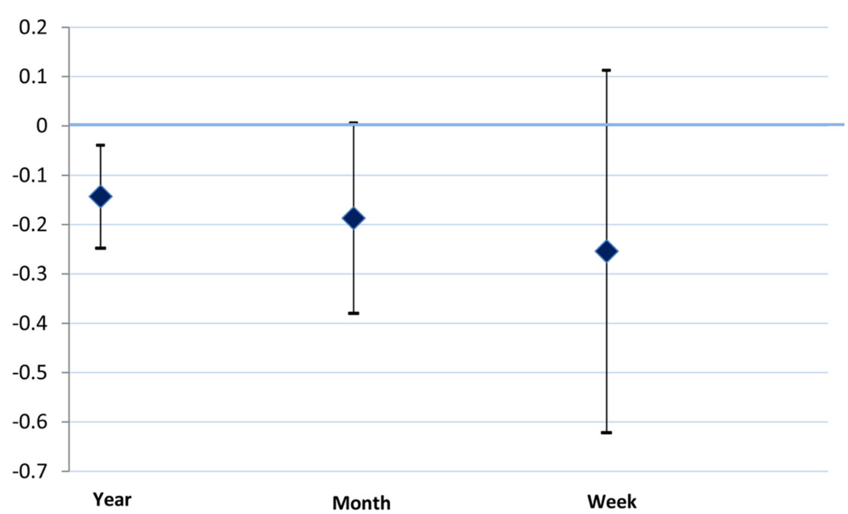

Figure 2. Associations of proximity to elemental sulfur use within 1-km radius of a child's residence 1 y, 1 mo, and 1 wk before the spirometry test with FEV_1 at age 7, CHAMACOS study, Salinas Valley, California, 2006–2007.

Note: Associations reflect change per 10-fold increase in the estimated amount of elemental sulfur; highest FEV_1 for children with at least two acceptable reproducible maneuvers. Acceptable repeatability is achieved when the difference between the largest and the next largest FEV_1 is ≤0.15 L.

Elemental sulfur, when applied as a pesticide, is thought to be incorporated into the natural sulfur cycle (U.S. EPA 1991a; 2015). It has been speculated that under certain environmental conditions sulfur can be oxidized into other sulfur oxides (European Commission 2015; Kuklińska et al. 2013; Lee et al. 2005), which have known adverse respiratory effects (Klaassen 2013; U.S. EPA 1991a; 2015). No lung inflammatory response (Lee et al. 2005) was reported following injection of elemental sulfur dust in animals, but it is plausible that inhalation of sulfur dust or sulfur oxides generated from dusted elemental sulfur (Lee et al. 2005) may be more likely to cause respiratory effects. We did not observe a significant adverse association between sulfur use within 3 km and respiratory symptoms or lung function, likely because sulfur is applied as a dust and transport is limited to distances shorter than 3 km, resulting in exposure misclassification and attenuation of the risk estimates.

This study has several strengths. We used both questionnaire and spirometry data in a longitudinal birth cohort, and adjusted for relevant environmental agents and sociodemographic confounders. Moreover, sulfur applications were estimated at 1 wk, 1 mo, and 12 mo prior to lung function testing performed at age 7. Another strength of our study is that our models were adjusted for exposure to OPs using a biomarker of exposure (Raanan et al. 2015, 2016).

This study also has some limitations. It is challenging to achieve high quality spirometry in young children and thus our results should be interpreted with some caution (Hall and Brookes 2005). The largest FEV_1 and the largest FVC are ideally selected from three technically satisfactory maneuvers. However, because of this well-known challenge, and because of sample size considerations, we determined the associations for children who had one, two, or three maneuvers (i.e., they may have had only one or two acceptable maneuvers) and for children who had at least two maneuvers. We also presented associations for the highest FEV_1 for children with at least two reproducible maneuvers among those who had at least two reproducible acceptable maneuvers (acceptable reproducibility is achieved when the difference between the largest and the next largest FEV_1 is ≤ 0.15 L).

Another limitation is that assessing elemental sulfur exposure remains a challenge for epidemiological studies because exposure biomarkers are not available; even the few occupational reports on sulfur exposure have used surveillance data (Calvert et al. 2004; Lee et al. 2005; Sama et al. 1997; Stellman 1998; U.S. EPA 1991b). Using residential proximity for sulfur exposure assessment has some limitations. The relationship between agricultural use and personal exposure has not been evaluated for sulfur; however, previous studies have shown that PUR data is correlated with environmental pesticide concentrations in house dust and outdoor air (Harnly et al. 2005, 2009; Gunier et al. 2011), suggesting it is a meaningful indicator of pesticide exposure. Also, we did not consider sulfur exposure near the child's school or other locations in our estimates of exposure and we did not account for meteorological factors that could affect exposure other than wind direction. Such exposure misclassification would presumably be nondifferential and would serve to underestimate the effects. We suggest that future analyses include applications near child care, preschool, and school locations to capture a more complete picture of potential exposure.

Our study had other limitations. We assessed children's exposure to OPs by measurement of urinary DAPs. DAPs as a biomarker of exposure is limited because of the short half-life of OP pesticides, and thus DAP measurements reflect only recent OP exposures (Bradman et al. 2005). Another limitation is that the DAP concentrations were based on measurements from urines collected at the 5-y visit because we did not measure DAPs at older ages. We also used an allergy proxy variable reported on the 5-y visit because we wanted to use information on allergy that was reported before the outcome measurements were assessed. This may lead to covariate misclassification, which would presumably be nondifferential.

In summary, our findings suggest that childhood exposure to elemental sulfur was associated with poorer respiratory health among school-age children living in an agricultural community. We found that each 10-fold increase in the amount of elemental sulfur applied in the previous 12 mo within a 0.5-km radius and a 1-km radius of the home was associated with an average decrease of 108 mL/s and 143 mL/s, respectively, in FEV_1 in 7-y-old children. In comparison, passive pediatric exposure to maternal cigarette smoke was found to be associated with a decrease in FEV_1 of 101 mL/s after 5 y of exposure (Tager et al. 1983), and we recently reported (Raanan et al. 2016) that each 10-fold increase in time-weighted average concentrations of OP urinary metabolites measured through early childhood (0.5–5 y of age) was associated with an average decrease of 159 mL/s in FEV_1 in these children at age 7 y.

Conclusions

Our results suggest that elemental sulfur, considered relatively safe in Europe (EFSA 2009) and in the United States (U.S. EPA 1991a; 2015), and one of the most heavily used agricultural pesticides in Europe and the United States (CDPR 2015; Klaassen 2013; PAN Germany 2003; Federal Office of Consumer Protection and Food Safety Germany 2014), may contribute to nonoccupational respiratory disease in agricultural communities. Future studies should attempt to replicate these findings in other study populations. Given the widespread use worldwide, we believe that the potential respiratory toxicity of elemental sulfur deserves more regulatory attention.

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