Residential proximity to agricultural fumigant use and IQ, attention and hyperactivity in 7-year old children

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ABSTRACT

Objectives: Our objective was to examine the relationship between residential proximity to agricultural fumigant use and neurodevelopment in 7-year old children.

Methods: Participants were 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 administered the Wechsler Intelligence Scale for Children (4th Edition) to assess cognition and the Behavioral Assessment System for Children (2nd Edition) to assess behavior. 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 ($n = 285$) and postnatal ($n = 255$) residential proximity to agricultural use of methyl bromide, chloropicrin, metam sodium and 1,3-dichloropropene with neurodevelopment.

Results: We observed decreases of 2.6 points (95% Confidence Interval (CI): $-5.2, 0.0$) and 2.4 points (95% CI: $-4.7, -0.2$) in Full-Scale intelligence quotient for each ten-fold increase in methyl bromide and chloropicrin use within 8 km of the child's residences from birth to 7-years of age, respectively. There were no associations between residential proximity to use of other fumigants and cognition or proximity to use of any fumigant and hyperactivity or attention problems. These findings should be explored in larger studies.

1. Introduction

Methyl bromide, chloropicrin, metam sodium and 1, 3-dichloropropene (1,3-DCP) are common agricultural fumigants used primarily to reduce pathogens and pests in soil prior to planting crops. Approximately 44 – 51 million kilograms (kg) of these four fumigants are applied annually in the United States (Grube et al., 2011), and 13 million kg are applied annually in California (CDPR, 2016c), constituting one sixth of all pesticide use in California. Fumigants are more likely than other pesticides to drift from application sites due to their high vapor pressure (California Department of Pesticide Regulation, 2015, 2016a, 2016b). In 2012, California implemented a pesticide air monitoring network in several agricultural communities. Fumigants were frequently detected at each of the air monitoring sites, indicating repeated, low-level community exposures (CDPR, 2014). Acute human exposure to methyl bromide has produced symptoms including

headaches, seizures, muscle weakness, memory problems (Bishop, 1992; Reidy et al., 1994), and neuropathy (Ben Slamia et al., 2006; Cavalleri et al., 1995). More attention and concentration problems have been reported in workers exposed to methyl bromide (Magnavita, 2009). Residents exposed to metam sodium after a train spill experienced increased psychological problems (e.g., depression and anxiety) (Bowler et al., 1994b). Symptoms of chloropicrin intoxication are also primarily neurologic, including tremors and seizures (TeSlaa et al., 1986). Although there is no evidence of neurotoxicity from limited human and animal research of 1,3-DCP (ATSDR, 2008), increased use of 1,3-DCP as a replacement for methyl bromide warrants further studies on the human health effects of this fumigant. A survey of pesticide related illnesses reported in 11 states from 1998 to 2006 found that soil applications of fumigants were responsible for the largest percentage of acute illnesses (45%) and non-occupational cases (61%) (Lee et al., 2011). In a risk assessment using California air monitoring data, these

Abbreviations: 1, 3-DCP, 1,3-dichloropropene; BASC-2, Behavioral Assessment System for Children 2; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, confidence interval; DAP, dialkyl phosphate; DDT, p, p' -dichlorodiphenyltrichloroethylene; DDE, p, p' -dichlorodiphenyldichloroethylene; HOME, Home Observation for Measurement of the Environment; IQ, intelligence quotient; OP, organophosphate; OR, odds ratio; PBDE, polybrominated diphenyl ether; PPVT, Peabody Picture Vocabulary Test; TVIP, Test de Vocabulario en Imágenes Peabody; WISC-IV, Wechsler Intelligence Scale for Children, 4th edition

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four high-use fumigants (methyl bromide, chloropicrin, metam sodium and 1,3-DCP) were the top four pesticides ranked in terms of chronic health risks and an estimated 5 million U.S. residents live in areas of high agricultural fumigant use (Lee et al., 2002).

Currently, there are no reliable biomarkers to assess human exposure to fumigants in epidemiologic studies (Hustinx et al., 1993; Magnavita, 2009; Verberk et al., 1979). Thus, residential proximity to fumigant use is currently the best method to characterize potential exposure. Since 1990, California has maintained a Pesticide Use Reporting (PUR) system which requires commercial growers to report all agricultural pesticide use to a one square mile (~259 ha) area (CDPR, 2016c). A study using PUR data showed that methyl bromide use within a 7 × 7 square mile area (~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). Several epidemiologic studies have used PUR data and observed associations between higher nearby agricultural pesticide use during pregnancy and adverse neurodevelopmental outcomes including birth defects (Carmichael et al., 2014; Rull et al., 2006; Yang et al., 2014), autism (Roberts et al., 2007; Shelton et al., 2014) and cognitive function (Gunier et al., 2016; Rowe et al., 2016).

We previously found that living within 5 km of methyl bromide use in the second trimester of pregnancy was associated with decreased birth weight, length, and head circumference (Gemmill et al., 2013). 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, 2016c). In the present study, we investigate associations between residential proximity to agricultural use of four fumigants during the prenatal and postnatal periods and child neurodevelopment and behavior at age 7 in 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 families living in the agricultural community of the Salinas Valley, California.

2. Methods

2.1. Study population

We enrolled 601 pregnant women between October 1999 and October 2000 as part of the CHAMACOS study. Women were eligible if they were ≥ 18 years of age, < 20 weeks gestation, eligible for California's subsidized low-income prenatal health care, spoke English or Spanish, and were planning to deliver at the county hospital. We followed the women through the delivery of 537 live born children. We excluded children with medical conditions that could affect neurodevelopmental assessment (n = 4, one child each with Down syndrome, autism, deafness, and hydrocephalus). We included children who had a neurodevelopmental assessment at age 7 (n = 336) and excluded two participants who did not have prenatal measurements of dialkyl phosphate (DAP) metabolites of organophosphate pesticides (OPs) because a previous analysis in this cohort found that DAPs were associated with neurodevelopment (Bouchard et al., 2011). For analyses of proximity to fumigant use, we included participants whose residential location was known for at least 80% of the time during pregnancy (n = 285) for the prenatal period and from birth to the 7-year neurodevelopmental assessment (n = 255) for the postnatal period. Written informed consent was obtained from all women and oral assent from all children at age 7; all research was approved by the University of California, Berkeley, Committee for the Protection of Human Subjects prior to commencement of the study.

2.2. Maternal interviews and assessments

Bilingual interviewers conducted maternal interviews in Spanish or English twice during pregnancy (~13 and 26 weeks gestation), after delivery and when the children were 6 months and 1, 2, 3.5, 5 and 7-years of age. Interviews obtained demographic information including maternal age, education, country of birth, number of years lived in the United States, marital status, paternal education, and family income. We collected residential history information by asking participants if they had moved since the last interview and, if so, the dates of all moves. We conducted home visits shortly after enrollment (~16 weeks gestation) and when the child was 6 months and 1, 2, 3.5 and 5-years of age. For each visit, latitude and longitude coordinates of the participant's home were determined using a handheld global positioning system unit.

Mothers were administered the Peabody Picture Vocabulary Test (PPVT) for English speakers or the Test de Vocabulario en Imágenes Peabody (TVIP) for Spanish speakers at the six-month visit to assess verbal intelligence (Dunn and Dunn, 1981). If maternal PPVT or TVIP scores were unavailable from the 6-month visit, we used scores from the re-administration of the test conducted at a 9-year visit (n = 5) or assigned the mean score of the sample (n = 2). A short version of the HOME (Home Observation for Measurement of the Environment) inventory was completed during the 7-year visit (Caldwell and Bradley, 1984).

2.3. Cognitive and behavior assessments

We assessed cognitive abilities when the children were 7-years of age using the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) (Wechsler, 2003). All assessments were completed by a single bilingual psychometrician, who was trained and supervised by a pediatric neuropsychologist. Index scores for four domains were calculated based on the following subtests: Verbal Comprehension (composed of Vocabulary and Similarities subtests), Perceptual Reasoning (Block Design and Matrix Reasoning subtests), Working Memory (Digit Span and Letter-Number Sequencing subtests), and Processing Speed (Coding and Symbol Search subtests). We administered all subtests in the dominant language of the child using either the WISC-IV English or Spanish edition, which was determined through administration of the oral vocabulary subtest of the Woodcock-Johnson/Woodcock-Munoz Tests of Cognitive Ability (Woodcock and Munoz-Sandoval, 1990) in both English and Spanish at the beginning of the assessment as recommended in the WISC-IV Spanish Manual. The psychometrician was blinded to exposure status. We standardized WISC-IV scores against U.S. population-based norms for the English and Spanish versions of WISC-IV. We did not administer Letter-Number Sequencing or Symbol Search subtests for the first 3 months of assessments, therefore 27 participants lack scores for Processing Speed and Working Memory domains. A Full-Scale IQ was available for 255 children.

Children's behavior was assessed by maternal and teacher report at age 7 using the Behavior Assessment System for Children 2 (BASC-2) (Reynolds, 2004). The behavior assessments were interviewer-administered to the mother (due to low literacy rates) and self-administered by the child's teacher. The BASC-2 has been validated in English and Spanish. The BASC-2 Parent Rating Scale asks how often the child exhibits certain behaviors in the home setting (160 questions), while the Teacher Rating Scale asks about similar behaviors at school (139 questions). Scales of interest from the BASC-2 were hyperactivity and attention problems. Standardized T-scores were computed using age-standardized national norms, with higher values indicating more frequent problem behaviors.

2.4. Geographic-based estimates of agricultural fumigant use

To characterize potential exposure, we estimated agricultural

fumigant use near each participant's residence during the prenatal (entire pregnancy) and postnatal (birth to 7-year assessment) time periods using California PUR data from 1999 to 2008 (CDPR, 2016c). We focused on methyl bromide, chloropicrin, metam sodium, and 1,3-DCP because they were the most commonly used agricultural fumigants (in kg applied) in our study area (Monterey County) during our study period (1999–2008). The PUR data included the amount (kg) of active ingredient applied, application date, location to a one-square mile section (1.6 km × 1.6 km) defined by the United States (U.S.) Public Land Survey System (PLSS). We edited the PUR data to correct for likely outliers that had unusually high application rates by replacing the amount of pesticide applied using the acres treated and the median application rate for that pesticide and crop combination (Gunier et al., 2001). Detailed descriptions of the equations and methods that we used to calculate nearby pesticide use have been published previously (Gunier et al., 2011).

For each participant, we estimated the amount of each fumigant used within 3, 5 and 8 km radii of residences during prenatal and postnatal periods using the latitude and longitude coordinates and a geographic information system. In all cases, the buffers around the homes included more than one PLSS section; therefore, we weighted the amount of pesticide applied in each section by the proportion of land area that was included in the buffer. We selected buffer distances of 3, 5 and 8 km for this analysis because these best capture the spatial scale of fumigant use most strongly correlated with measured fumigant concentrations in outdoor air samples (California Department of Pesticide Regulation, 2015; Li et al., 2005). To account for dispersion of fumigants from the application site, we summarized wind direction during the seven days (Cryer and van Wesenbeeck, 2011; Gao et al., 2013) after the application date using available wind direction data (CDWR, 2016), determined the direction of the residence relative to the PLSS section using GIS, and weighted fumigant use in each section by the proportion of time that the residence was downwind of Sections where fumigant applications occurred.

2.5. Data analysis

We log₁₀-transformed continuous prenatal and postnatal fumigant use (kg/year) variables to reduce heteroscedasticity and the influence of outliers. We added one kg/year to the use prior to transforming so that the minimum log₁₀ of use would be zero and all values would be positive. Scores for cognition and behavior were approximately normally distributed and were modeled as continuous outcomes. We used generalized additive models (GAMs) with a three-degrees-of-freedom cubic spline function to test for non-linearity. None of the digression from linearity tests were significant ($p < 0.2$), therefore we expressed fumigant use linearly (on the log₁₀ scale) in separate multivariable linear regression models for each fumigant. Regression coefficients thus represent mean change in cognition or behavior scores for each ten-fold increase in fumigant use.

We selected model covariates *a priori* based on factors associated with child neurodevelopment in previous analyses [i.e., child's exact age at assessment, sex, maternal country of birth (Mexico vs. other) and HOME score at the 7-year visit (continuous)] (Bouchard et al., 2011; Gunier et al., 2016). We considered the following variables as additional covariates in our models: maternal age at delivery, maternal PPVT score (continuous), maternal education ($\leq$ 6th grade vs. $\geq$ 7th grade), marital status at enrollment, and using the Centers of Epidemiological Studies Depression Scale (CES-D) maternal depression (≥ 16 on CES-D) at the child's 7-year visit (Davila et al., 2009). In addition, we considered covariates collected at each visit including housing density (number of persons per room), household poverty ($<$ federal poverty level vs. $\geq$ federal poverty level) (Census, 2008), presence of father in the home (yes/no), maternal work status, location of neurodevelopmental assessment (field office or participant's home), and season of assessment. We imputed missing values ($< 10\%$ missing) at a visit

point using data from the nearest available visit. We evaluated the average of DAP metabolites of OP insecticides measured in maternal urine samples (Bradman et al., 2005) collected during prenatal interviews at 13 weeks and 26 weeks gestation ($n = 283$) in all models since these metabolite levels were related to Full-scale IQ in a previous study of this cohort (Bouchard et al., 2011). We also evaluated agricultural use of OP insecticides within 1 km of the residence during pregnancy in all models because this was related to IQ in a recently published study in this cohort (Gunier et al., 2016). We retained covariates that were significant ($p < 0.2$) in the final multivariate regression models. We included child age, sex, maternal country of birth, HOME score at the 7-year interview, prenatal DAPs and agricultural use of organophosphates within 1 km of the residence during pregnancy in all models. We included maternal depression in all models except for those assessing BASC-2 teacher reports because we believed maternal depression could affect maternal rating of child behavior or cognitive performance of the child. In models for cognition, we also included language of assessment, maternal education, maternal intelligence (PPVT) and household poverty level from the 7-year interview.

In separate sensitivity analyses, we controlled for exposure to other neurotoxicants, which we have previously found to be related to child IQ or attention deficit/hyperactivity disorder in our cohort adjusting for the same covariates listed above (Eskenzazi et al., 2013; Gaspar et al., 2015; Marks et al., 2010), including log₁₀-transformed lipid-adjusted concentrations (ng/g-lipid) of *p*, *p'*-dichlorodiphenyltrichloroethylene (DDT), *p*, *p'*-dichlorodiphenyldichloro-ethylene (DDE) ($n = 219$) (Bradman et al., 2007) and polybrominated diphenyl ether flame retardants (PBDEs) ($n = 221$) measured in prenatal maternal blood samples (Castorina et al., 2011). We used the sum of the four major congeners (BDE-47, -99, -100, and -153) to estimate PBDE exposure (Eskenzazi et al., 2013). In other sensitivity analyses, we excluded outliers identified with studentized residuals greater than three. To control for potential selection bias due to loss to follow-up, we ran regression models with weights determined as the inverse probability of inclusion in our analyses (Hogan and Lancaster, 2004). We determined probability of inclusion using multiple logistic regression models with baseline covariates as potential predictors. Since we evaluated many combinations of fumigants (4), buffer distances (3), time periods (2) and outcomes (3), we assessed adjustment for multiple comparisons to control for type 1 error rate using the Benjamini-Hochberg false discovery rate at $p < 0.05$ (Hochberg and Benjamini, 1990). Finally to assess the effect of methyl bromide and chloropicrin, two fumigants with highly correlated use, in the same model, we calculated the residuals from a regression model with one fumigant as the dependent variable and the other as the independent variable. We then included these residuals as an uncorrelated proxy for exposure in a multivariate model with the fumigant that was the independent variable (Mostofsky et al., 2012). Similarly, we assessed the effect of postnatal fumigant use while controlling for highly correlated prenatal use by calculating residuals from a regression model with postnatal fumigant use as the dependent variable and prenatal use as the independent variable and including the residuals from this model in a multivariate model with prenatal fumigant use.

3. Results

3.1. Demographics, fumigant use and neurodevelopmental scores

Most mothers were born in Mexico (88%), under 30 years of age at delivery (73%) and married or living as married (85%) at the time of enrollment (Table 1). Almost half of the mothers (46%) and most fathers (52%) had a 6th grade education or less, and most families (72%) were living below the poverty level at the time of the 7-year visit. (United States Bureau of the Census, 2008) Slightly more than half of the children were girls (54%) and most children completed their WISC-IV assessment in Spanish (68%). Mothers included in our analyses ($n =$

Table 1
CHAMACOS study cohort characteristics (n = 285).^a

Cohort Characteristic	N (%)
Maternal Country of Birth	
Mexico	251 (88%)
United States and other	34 (12%)
Maternal Age at Delivery	
18 – 24	109 (38%)
25 – 29	99 (35%)
30 – 34	49 (17%)
35 – 45	28 (10%)
Maternal Education	
≤ 6th grade	132 (46%)
7th grade or more	153 (54%)
Marital Status at Enrollment	
Married/Living as married	241 (85%)
Not married	44 (15%)
Paternal Education	
≤ 6th grade	131 (52%)
7th grade or more	119 (48%)
Family Income at 7 y visit	
≤ Poverty level ^b	205 (72%)
> Poverty level ^b	80 (28%)
Maternal Depression at 7 y Visit	
Yes	79 (28%)
No	206 (72%)
Sex	
Girl	153 (54%)
Boy	132 (46%)
Language of WISC-IV tests	
Spanish	193 (68%)
English	92 (32%)

^a Included in analyses for prenatal fumigant use.^b Poverty thresholds for 2008 (Census, 2008).

285) were older at delivery (27 vs. 25 years old), more likely to be Latina (99% vs. 94%) and married (83% vs. 77%), and were less likely to smoke (4% vs. 8%) than mothers with liveborn children that were not included in our analyses (n = 252); otherwise the two populations were demographically similar.

The most heavily used fumigants within 8 km of children's residences during both the prenatal and postnatal periods were methyl

bromide and chloropicrin, with mean ± SD postnatal wind-adjusted use of 89,200 kg ± 59,800 and 97,800 kg ± 67,700, respectively (Table 2). The distributions of WISC-IV and BASC-2 T-scores at 7-years of age are also presented in Table 2. The mean ± SD was 104 ± 14 for Full-scale IQ and similar for the subscales, except for Working Memory which was 93 ± 13. The mean ± SD BASC-2 T-scores for both parent and teacher report of attention and hyperactivity were all around 50 ± 10.

3.2. Correlation of fumigant use

Agricultural fumigant use (log10-transformed) was moderately to highly correlated ($p < 0.001$) at the three buffer distances we evaluated (Table 3). There was moderate to high correlation between postnatal fumigant use within 3 and 5 km (0.54 – 0.9), moderate to high correlation between fumigant use within 3 and 8 km (0.23 – 0.84) and high correlation between use within 5 and 8 km (0.78 – 0.99). Correlations were similar for prenatal fumigant use at different buffer distances (data not shown). Correlation was relatively high between prenatal and postnatal time periods for individual fumigants. For use within 8 km of residences, there was high correlation ($p < 0.001$) between prenatal and postnatal use for chloropicrin ($r = 0.82$) and methyl bromide ($r = 0.82$), but no correlation for metam sodium and a negative correlation ($r = -0.47$) for 1,3-DCP. There was weak to high correlation ($p < 0.05$) between the use of different fumigants. Postnatal use of metam sodium was weakly correlated with methyl bromide and chloropicrin (0.15 – 0.22), there was moderate correlation between 1,3-DCP and the other three fumigants (0.56 – 0.73), while methyl bromide and chloropicrin use was highly correlated (0.96).

3.3. Fumigant use and neurodevelopment

Table 4 shows the associations of wind-adjusted prenatal and postnatal fumigant use within 8 km of the home and IQ (associations within 3 and 5 km are shown in Supplemental Tables S1 and S2). There were no significant relationships between wind-adjusted prenatal fumigant use within 5 or 8 km and Full-Scale IQ or any of the WISC-IV subscales (Table 4 and Supplemental Table S1). However, we observed some associations between prenatal fumigant use within 3 km and IQ. Specifically, a ten-fold increase in wind-adjusted prenatal methyl

Table 2
Distributions of wind-weighted agricultural fumigant use (kg) within 8-km of residence and neurodevelopmental assessment scores at 7-years of age.

	N	Mean ± SD	25th	50th	75th	Max.
Prenatal^a pesticide use (kg)						
Methyl bromide	285	13,400 ± 10,900	2350	13,600	21,100	56,400
Chloropicrin	285	8690 ± 7120	1210	8690	13,800	35,000
Metam sodium	285	525 ± 1500	0	0	6	8640
1,3-DCP	285	914 ± 1810	5	52	806	8230
Postnatal^b pesticide use (kg)						
Methyl bromide	255	89,200 ± 59,800	20,500	111,000	136,000	349,000
Chloropicrin	255	97,800 ± 67,700	10,600	128,000	152,000	287,000
Metam sodium	255	9940 ± 9440	1180	5240	21,400	54,600
1,3-DCP	255	60,200 ± 45,100	17,500	60,300	99,200	154,000
WISC-IV						
Full-scale IQ	257	104 ± 14	92	105	114	144
Perceptual Reasoning	285	103 ± 16	92	100	112	141
Processing Speed	258	109 ± 13	100	109	118	136
Verbal Comprehension	285	107 ± 17	95	108	121	152
Working Memory	258	93 ± 13	83	91	99	132
BASC-2 Parent Report^c						
Attention	284	50 ± 11	42	50	59	78
Hyperactivity	284	46 ± 9	40	44	50	79
BASC-2 Teacher Report^c						
Attention	234	51 ± 8	45	51	56	69
Hyperactivity	234	49 ± 10	41	47	55	86

^a Prenatal period during pregnancy (1999 – 2001).^b Postnatal period from birth to 7-year visit (2000 – 2008).^c BASC-2 general sex combined T-scores. Abbreviation: 1,3-DCP = 1,3-dichloropropene.

Table 3

Pearson correlations of log-transformed agricultural fumigant use (kg) by distance, time period and active ingredients.

Comparison	N	Methyl Bromide	Chloropicrin	Metam Sodium	1,3-DCP
<i>Correlations by distance</i>					
Postnatal 3 and 5 km	255	0.86**	0.90**	0.54**	0.74**
Postnatal 3 and 8 km	255	0.79**	0.84**	0.23**	0.47**
Postnatal 5 and 8 km	255	0.99**	0.97**	0.73**	0.86**
<i>Correlations by time period</i>					
Prenatal and Postnatal 8 km	255	0.82**	0.82**	−0.01	−0.47**
<i>Correlations between fumigants</i>					
Methyl Bromide Postnatal 8 km	255	–	–	–	–
Chloropicrin Postnatal 8 km	255	0.96**	–	–	–
Metam Sodium Postnatal 8 km	255	0.15*	0.22**	–	–
1,3-DCP Postnatal 8 km	255	0.68**	0.73**	0.56**	–

Abbreviation: 1,3-DCP = 1,3-dichloropropene.

* p < 0.05.

** p < 0.001.

bromide use within 3 km (Supplemental Table S1) was marginally associated with lower Full-scale IQ ($\beta = -1.3$; 95% CI: $-2.7, 0.1$), and reduced Processing Speed [$\beta = -1.5$; 95% confidence interval (CI): $-2.9, -0.2$], while a ten-fold increase in prenatal chloropicrin use within 3 km was marginally associated with a lower Processing Speed ($\beta = -1.4$; 95% CI: $-2.8, 0.1$).

With postnatal exposure, IQ scores were generally lower across all domains with increasing wind-adjusted use of methyl bromide, chloropicrin, and 1,3-DCP within 8 km (Table 4), with a marginally significant decrease of 2.6 points (95% CI: $-5.2, 0.0$) in Full-scale IQ for each ten-fold increase in postnatal methyl bromide use and a decrease of 2.4 points (95% CI: $-4.7, -0.2$) for each ten-fold increase in postnatal chloropicrin use. Results were similar for postnatal use of methyl bromide and chloropicrin within 5 km and generally null for postnatal use of all fumigants within 3 km and use of metam sodium or 1,3-DCP at any distance (Supplemental Table 2).

Since postnatal use of methyl bromide and chloropicrin within 8 km of residences were both associated with Full-scale IQ, we assessed the effect of postnatal chloropicrin use controlling for methyl bromide use to determine which fumigant is driving the association with Full-scale IQ since methyl bromide and chloropicrin are often used together and are highly correlated; importantly, methyl bromide is currently being replaced by chloropicrin throughout California (CDPR, 2016c). In the model evaluating residuals of postnatal methyl bromide when controlling for postnatal chloropicrin use, the effect of a ten-fold increase in postnatal chloropicrin use within 8 km of residences changed directions and was no longer significant ($\beta = 1.2$; 95% CI: $-7.7, 10.1$). In the model evaluating residuals of postnatal chloropicrin when controlling for postnatal methyl bromide use, however, the effect of a ten-fold increase in postnatal chloropicrin use within 8 km of residences was similar in direction and magnitude to the original single fumigant model for chloropicrin, but with much wider confidence intervals ($\beta = -3.4$; 95% CI: $-11.1, 4.3$) suggesting that proximity to use of chloropicrin was more influential. The relationship between postnatal chloropicrin use and Full-scale IQ was also similar ($\beta = -3.0$; 95% CI: $-6.7, 0.7$) when controlling for highly correlated prenatal use of chloropicrin ($\beta = -1.1$; 95% CI: $-2.6, 0.4$), suggesting that postnatal use may capture the more critical time period.

There was no relationship between wind-adjusted prenatal or postnatal fumigant use within 8 km of residences and BASC-2 maternal or teacher report of hyperactivity or attention problems (Table 5). There were no associations between prenatal (Supplemental Table 3) or postnatal (Supplemental Table 4) fumigant use within 3 or 5 km of the residence and hyperactivity or attention problems.

Results were similar for fumigant use within 8 km and WISC-IV cognition scales with and without the inclusion of DDT, DDE and PBDEs (not shown) even though the sample sizes were smaller for the models that included these covariates (e.g., $n = 176$ for Full-scale IQ).

Excluding the relatively few outliers for postnatal metam sodium use ($n = 2$) and 1,3-DCP use ($n = 3$) did not change our results and there were no outliers with studentized residuals > 3 for models with methyl bromide or chloropicrin use. Associations between postnatal fumigant use and Full-scale IQ were slightly weaker, but similar for both methyl bromide ($\beta = -2.3$; 95% CI: $-4.7, 0.1$) and chloropicrin ($\beta = -2.2$; 95% CI: $-4.2, -0.3$) when we used inverse probability weighting to adjust for potential selection bias. After adjusting for multiple comparisons, which is not common practice in environmental epidemiological studies, none of our associations reached significance at the critical p-value = 0.003.

4. Discussion

We observed a suggestive association between Full-Scale IQ and postnatal proximity to agricultural use of methyl bromide and chloropicrin during childhood. Adjusted for covariates and other exposures, a ten-fold increase in methyl bromide or chloropicrin use within 8 km of the residence during the child's lifetime was associated with an approximately 2.5 point decrease in Full-Scale IQ. In our population, fumigant use increased 100-fold from the 5th to the 95th percentiles of the distribution for both methyl bromide and chloropicrin suggesting a potentially five point decrease in Full-Scale IQ, or one third of a standard deviation, for children with the highest use of these fumigants near their residences during their lifetime. Including both methyl bromide and chloropicrin in the same model using residuals suggests that use of chloropicrin is more influential, but the use of these fumigants was highly correlated and difficult to disentangle in this cohort. We observed a marginal association between proximity to higher prenatal use of methyl bromide and chloropicrin within 3 km and poorer Processing Speed; there were no other relationships between prenatal fumigant use and cognition. There were no associations between prenatal or postnatal fumigant use and attention or hyperactivity. These results need to be replicated in a larger study with sufficient power to evaluate multiple comparisons of fumigant use and neurodevelopment.

Previous studies observed poorer neurologic test scores (Acuna et al., 1997) more concentration and attention problems (Magnavita, 2009) and memory impairment (Acuna et al., 1997; Magnavita, 2009) in workers exposed to methyl bromide. A case study found problems with concentration, memory and processing as well as increased anxiety after exposure to methyl bromide from home fumigation (Reidy et al., 1994). Among pesticide applicators, those that applied fumigants had higher odds of reporting more neurologic symptoms including difficulty concentrating and absentmindedness [odds ratio (OR) = 1.5; 95% CI: 1.2–1.8] than those that did not apply fumigants (Kamel et al., 2005). Residents exposed to metam sodium after a spill reported higher levels of depression and anxiety than those that were not exposed (Bowler et al., 1994a). This is the first study to evaluate prenatal and

Table 4
Adjusted^a association between a ten-fold increase in wind-adjusted fumigant use (kg) within 8 km of residence and 7-year WISC Scales.

	Full-Scale IQ			Verbal Comprehension			Working Memory			Perceptual Reasoning			Processing Speed		
	N	β	(95%CI)	N	β	(95%CI)	N	β	(95%CI)	N	β	(95%CI)	N	β	(95%CI)
<i>Prenatal Exposure</i>															
Methyl Bromide	257	-0.9	(-2.5, 0.7)	285	-0.8	(-2.4, 0.7)	258	-0.3	(-2.0, 1.3)	285	-1.0	(-2.8, 0.9)	258	-0.7	(-2.3, 0.9)
Chloropicrin	257	-0.7	(-2.1, 0.6)	285	-0.6	(-1.9, 0.7)	258	-0.3	(-1.7, 1.1)	285	-0.9	(-2.5, 0.7)	258	-0.4	(-1.8, 1.0)
Metam Sodium	257	1.0	(-0.4, 2.3)	285	0.4	(-0.8, 1.6)	258	0.7	(-0.7, 2.0)	285	0.6	(-0.9, 2.1)	258	0.8	(-0.6, 2.2)
1,3-DCP	257	0.4	(-1.0, 1.8)	285	0.3	(-0.9, 1.6)	258	0.7	(-0.7, 2.2)	285	0.8	(-0.7, 2.4)	258	0.1	(-1.3, 1.5)
<i>Postnatal Exposure</i>															
Methyl Bromide	228	-2.6	(-5.2, 0.0)	255	-1.1	(-3.5, 1.4)	229	-1.5	(-4.1, 1.1)	255	-2.7	(-5.6, 0.3)	229	-2.0	(-4.6, 0.6)
Chloropicrin	228	-2.4	(-4.7, -0.2)	255	-0.9	(-3.0, 1.2)	229	-1.8	(-4.1, 0.4)	255	-2.4	(-5.0, 0.2)	229	-1.8	(-4.0, 0.4)
Metam Sodium	228	-0.4	(-2.7, 1.9)	255	-0.8	(-2.9, 1.4)	229	0.0	(-2.2, 2.3)	255	-0.4	(-3.0, 2.2)	229	0.1	(-2.2, 2.3)
1,3-DCP	228	-2.8	(-6.5, 1.0)	255	-2.5	(-6.1, 1.2)	229	-1.7	(-5.4, 2.1)	255	-3.9	(-8.3, 0.5)	229	-0.4	(-4.2, 3.3)

^a Adjusted for age at assessment, language of assessment, sex, maternal intelligence, maternal education, maternal depression at 7 years, maternal country of birth, HOME score, household poverty level at 7 years, prenatal DAPs and prenatal proximity to agricultural OP use.

postnatal residential proximity to agricultural fumigant use and cognitive development in children.

One challenge in utilizing PUR data to characterize exposure is selecting appropriate distances from the residence to summarize pesticide use. In this cohort, we previously reported associations between Full-scale IQ at 7-years of age and prenatal OP insecticide use within 1 km of maternal residences during pregnancy (Gunier et al., 2016; Rowe et al., 2016) and also with other potentially neurotoxic pesticides including carbamates, neonicotinoids, pyrethroids and maneb (Gunier et al., 2016). A study utilizing California PUR data observed higher odds of autism spectrum disorder (OR = 1.6; 95% CI: 1.0 – 2.5) with any use of OP insecticides within 1.5 km of their residence during the prenatal period (Shelton et al., 2014). Previous studies that have evaluated prenatal residential proximity to fumigant use using PUR data found no association with autism (Roberts et al., 2007) or neural tube defects (Rull et al., 2006) using a buffer distance of 1 km from the residence. However, for methyl bromide, reported use from PUR data within a 7 × 7 square mile area (~ 8 km) of the residence explained the largest amount of the variation (95%) in measured concentrations of methyl bromide in community air (Li et al., 2005). Other studies have also demonstrated fumigant drift far (5 – 20 km) from application sites (Cryer and van Wesenbeeck, 2011; van Wesenbeeck et al., 2016), suggesting that using smaller buffer distances (< 3 km) to summarize fumigant use underestimates exposure by excluding applications farther from the residence that influence air concentrations, resulting in exposure misclassification.

There are several limitations of this study. Residential proximity to agricultural fumigant use is not a direct measure of personal exposure. More research is needed to evaluate the relationship between reported fumigant use and measured concentrations in ambient and personal air samples. Additionally, we were unable to include potential exposure from fumigant use near schools, workplaces, or other locations where mothers and children spend significant amounts of time. Our samples size for this analysis was relatively small when restricted to participants with mostly complete residential history. We also made numerous statistical comparisons with four fumigants, two time periods, three distances and three health outcomes; therefore the associations we observed should be interpreted with caution.

Our study also had several strengths. Reporting agricultural fumigant applications is mandatory and closely regulated in California because these fumigants are restricted use pesticides, minimizing potential reporting bias. We incorporated wind direction for the seven days after fumigant applications to account for dispersion from the application site for these highly volatile compounds. Since validated biomarkers of environmental exposure are not available for these fumigants, residential proximity to agricultural applications from PUR data is one of the only methods for characterizing exposure. The CHAMACOS cohort is a relatively homogeneous population with extensive data on covariates and other environmental exposures that are related to cognition and behavior in children, allowing for better control of confounding. Our results were similar using inverse probability weighting; therefore we do not believe that there was a large impact from selection bias.

Future research is needed to develop better prediction models for human exposure using PUR data and existing measurements of fumigant concentrations in outdoor air. These fumigant exposure models could be used in larger epidemiological studies that combine cohorts or use available data to assess the relationship between agricultural fumigant use and neurodevelopment in children. There is also a need for further development of statistical methods for analyzing environmental exposures to highly correlated chemical mixtures (Rider et al., 2013).

5. Conclusions

We observed decreases in Full-scale intelligence quotient with increasing methyl bromide and chloropicrin use within 8 km of

Table 5

Adjusted association between a ten-fold increase in wind-adjusted fumigant use (kg) within 8-km of residences and BASC Attention Problems and Hyperactivity Standardized Scores at 7-years.

	Maternal Report ^a							Teacher Report ^b						
	Attention Problems				Hyperactivity			Attention Problems				Hyperactivity		
	N	β	(95%CI)	p	β	(95%CI)	p	N	β	(95%CI)	p	β	(95%CI)	p
<i>Prenatal Exposure</i>														
Methyl Bromide	284	0.1	(−1.1, 1.4)	0.83	0.0	(−0.9, 1.0)	0.95	234	0.0	(−1.0, 1.1)	0.94	0.1	(−1.2, 1.5)	0.87
Chloropicrin	284	−0.2	(−1.3, 0.9)	0.71	0.1	(−0.7, 0.9)	0.77	234	0.0	(−0.9, 0.9)	0.96	0.2	(−1.0, 1.3)	0.78
Metam Sodium	284	0.0	(−1.0, 0.9)	0.93	0.5	(−0.3, 1.2)	0.23	234	0.5	(−0.3, 1.2)	0.23	−0.3	(−1.4, 0.7)	0.53
1,3-DCP	284	−0.1	(−1.1, 0.9)	0.86	0.4	(−0.5, 1.2)	0.39	234	−0.1	(−1.0, 0.7)	0.73	−0.5	(−1.6, 0.6)	0.39
<i>Postnatal Exposure</i>														
Methyl Bromide	255	−0.5	(−2.5, 1.4)	0.60	−0.5	(−2.1, 1.0)	0.49	211	−0.6	(−2.3, 1.1)	0.51	−0.5	(−2.6, 1.6)	0.66
Chloropicrin	255	−0.4	(−2.1, 1.3)	0.64	0.2	(−1.0, 1.5)	0.72	211	−0.1	(−1.6, 1.3)	0.85	0.0	(−1.8, 1.8)	1.00
Metam Sodium	255	0.5	(−1.2, 2.3)	0.55	−0.1	(−1.4, 1.2)	0.88	211	−0.2	(−1.7, 1.2)	0.75	0.4	(−1.4, 2.3)	0.64
1,3-DCP	255	0.7	(−2.1, 3.6)	0.61	−1.1	(−3.2, 1.1)	0.34	211	−0.7	(−3.1, 1.8)	0.59	−0.2	(−3.2, 2.8)	0.89

^a Adjusted for sex, age at assessment, maternal country of birth, maternal depression and HOME score at 7-years, prenatal DAPs and OP use.

^b Adjusted for sex, age at assessment, maternal country of birth, HOME score at 7-years, prenatal DAPs and OP use.

residences during the child's lifetime. However, these results should be interpreted with caution until further explored in larger studies.

Statement of financial interest

Dr. Asa Bradman is a volunteer member of the Board for The Organic Center, a non-profit organization addressing scientific issues around organic food and agriculture. None of the other authors declares any actual or potential competing financial interest.

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Appendix A. Supplementary material

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