Examining Pesticide Exposure, Dose, and Neurobehavioral Effects among Children and Adolescents Living in California's Salinas Valley

By

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ABSTRACT

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Prenatal organophosphate (OP) pesticide exposure has been associated with adverse neurodevelopment, including decreased cognition, increased hyperactivity and inattention, and higher risk for autism-related traits in multiple studies. However, OP pesticide use has decreased in recent decades and data gaps exist regarding the neurodevelopmental impacts of *current-use* pesticides, such as neonicotinoids, glyphosate, and pyrethroids. Moreover, most people, particularly those living in agricultural areas, are exposed to multiple pesticides and research is needed to examine the effects of these mixtures that may interact synergistically to adversely impact health and neurodevelopment. Mounting evidence also suggests that the effects of environmental toxicants are due in part to causal interactions with social stressors and biologic factors, e.g., genetics, however studies investigating the neurodevelopmental impacts of environmental exposures have typically treated social factors as confounders. Failure to account for potential effect modification by these factors may underestimate the impact of environmental neurotoxicants, particularly among the most vulnerable populations where exposures to environmental and non-chemical stressors are likely to co-occur. Additionally, previous exposure assessment and epidemiology studies investigating pesticide exposures and subsequent health effects have largely relied on the analysis of dialkylphosphate (DAPs) metabolites, non-specific biomarkers of OP pesticide exposure, from random spot urine samples. DAPs have higher inter- and intra-individual variability and data gaps exist regarding the extent to which concentrations from spot samples may approximate internal dose from the "gold standard" 24-hour urine samples, which has implications for pesticide risk assessment and the establishment of regulatory guidelines. This dissertation aims to examine the validity of using DAPs assessed from random spot urine samples to estimate cumulative OP pesticide dose, the associations between applications of mixtures of agricultural pesticides near the home during pregnancy and early childhood with adolescent neurobehavioral functioning, and the joint effects of use of mixtures

of agricultural pesticides near the home during pregnancy and adverse childhood experiences (ACEs) on adolescent neurobehavioral outcomes.

Chapter 1 provides a general introduction to human exposure to agricultural pesticides and highlights the background, significance, and specific aims for each study/chapter.

Chapter 2 examines the validity of using first morning void (FMV) and random non-FMV urine samples to estimate cumulative 24-hr OP pesticide dose among participants in the Child Validation Study (CVS). For this study, investigators collected urine samples over seven consecutive days, including two 24-hr samples, from 25 children living in the agricultural Salinas Valley, California. These analyses employed measurements of urinary DAP metabolites, data on nearby agricultural pesticide applications, and daily dietary intake data to estimate internal dose from exposure to a mixture of OP pesticides according to the United States (US) Environmental Protection Agency (EPA) Cumulative Risk Assessment guidelines. Dose estimates from volume- and creatinine-adjusted same-day FMV and non-FMV spot urine samples were compared to the "gold standard" estimates from 24-hr samples. Non-FMV samples had relatively weak ability to predict 24-hr dose (R^2=0.09-0.38 for total DAPs) and tended to underestimate the percentage of samples exceeding regulatory guidelines. Models with FMV samples or the average of an FMV and non-FMV sample were similarly predictive of 24-hr estimates (R^2 for DAPs=0.40-0.68 and 0.40-0.80, respectively, depending on volume adjustment method). Findings for these analyses suggest that reliance on non-FMV samples for risk assessments may underestimate daily OP dose and the percentage of children with dose estimates exceeding regulatory guidelines.

Chapter 3 examines associations of applications of mixtures of agricultural pesticides within 1 kilometer (km) of the home during pregnancy and early childhood (ages 0-5 years) and adolescent internalizing and externalizing behaviors in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort. These analyses employed linear mixed effects Bayesian Hierarchical Models (BHM) to examine associations with maternal- and youth-reported behavioral and emotional problems from the Behavior Assessment System for Children, 2nd edition (BASC-2) at ages 16 and 18 years (*n*=593). Associations between pesticide applications and neurobehavioral outcomes were largely null. There were some trends of modestly increased internalizing behaviors and attention problems in association with OP insecticide use near the home during the prenatal period. In the postnatal period, a two-fold increase in glyphosate applications was associated with more youth-reported depression (β=1.2; 95% Credible Interval (CrI): 0.2, 2.2) and maternal-reported internalizing behaviors (β=1.23; 95% CrI: 0.2, 2.3) and anxiety (β=1.2; 95% CrI: 0.2, 2.3). There were some protective associations with imidacloprid, a neonicotinoid, during the prenatal period, particularly in sex-specific analyses. This study extends previous work by considering the neurobehavioral effects of potential exposure to mixtures of pesticides.

Chapter 4 examines interactions of applications of pesticide mixtures near the home during pregnancy and childhood adversity with adolescent neurobehavioral outcomes among CHAMACOS participants. These analyses employed linear mixed effects BHM to examine the joint effect of applications of 11 agricultural within 1 km of maternal homes during pregnancy and youth-reported Adverse Childhood Experiences (ACEs) with maternal and youth-reported internalizing behaviors, hyperactivity, and attention problems at ages 16 and 18 years. Overall, there was little evidence of modification of exposure-outcome associations by ACEs. Malathion use near the home during pregnancy with associated with increased internalizing behaviors among those with high ACEs from both maternal report (β = 1.9; 95% CrI: 0.2, 3.7 for high

ACEs [3+] vs. β = -0.1; 95% (CrI): -1.2, 0.9 for low ACEs [0-2]) and youth report (β = 2.1; 95% CrI: 0.4, 3.8 for high ACEs vs. β = 0.2; 95% CrI: -0.8, 1.2 for low ACEs). Results were stronger among males for both maternal and youth report of internalizing behaviors. Applications of malathion and dimethoate were also associated with higher youth-reported hyperactivity and/or inattention among those with high ACEs. There was no evidence of effect modification by ACEs for any other pesticides. This analysis builds upon previous studies by considering co-exposure to mixtures of agricultural pesticides and social adversity. It is the first to examine interactions of chemical and non-chemical stressors on neurobehavioral development assessed during adolescence or early adulthood.

Chapter 5 highlights the major findings for each chapter/study, conclusion, and future directions.

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List of Abbreviations

2,4-D: 2,4-dichlorophenoxy acetic
3-PBA: 3-phenoxybenzoic acid
aPAD: Acute population adjusted dose
AChE: Acetylcholinesterase
ACE: Adverse Childhood Experiences
ADHD: Attention Deficit Hyperactivity Disorder
ASD: Autism Spectrum Disorder
BASC: Behavior Assessment for Children
BHM: Bayesian Hierarchical Modeling
BMD: Benchmark Dose
BMI: Body Mass Index
CDC: Centers for Disease Control and Prevention
CHAMACOS: Center for the Health Assessment of Mothers and Children of Salinas
CES-D: Center for Epidemiologic Studies Depression Scale
Credible Interval: CrI
CVS: Child Validation Study
DAP: Dialkylphosphate
DCPA: Dimethyl tetrachloroterephthalate
DE: Diethyl
DEP: Diethylphosphate
DETP: Diethylthiophosphate
DEDTP: Diethyldithiophosphate
DF: Detection Frequency
DM: Dimethyl
DMDTP: Dimethyldithiophosphate
DMP: Dimethylphosphate
DMTP: Dimethylthiophosphate
DPR: Department of Pesticide Regulation
EPA: Environmental Protection Agency
FCCR: Food Consumption-Chemical Residue
FCID: Food Commodity Intake Database
FFQ: Food Frequency Questionnaire
FMV: First Morning Void
FQPA: Food Quality Protection Act
GEE: Generalized Estimating Equation
HOME-SF: Home Observation Measurement of the Environment-Short
HPA: hypothalamic-pituitary-adrenal
ICC: Intraclass Correlation Coefficient
IQ: Intelligence Quotient
JAGS: Just Another Gibbs Sampler
MCMC: Markov Chain Monte Carlo
nAChR: nicotine acetylcholine receptor
NHANES: National Health and Nutrition Examination Survey
OP: Organophosphate

PLSS: Public Land Survey System
PUR: Pesticide Use Reporting
RMSE: Root Mean Squared Error
RPF: Relative Potency Factor
SDQ: Strengths and Difficulties Questionnaire
SRP: Self-Report of Personality
TCPy: Trichloro-2-pyridinol
US: United States

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CHAPTER 1. Introduction: Health effects of pesticide exposure, pesticide exposure assessment, and research needs

1.1 Health effects of pesticide exposure

According to the latest United States (U.S.) Environmental Protection Agency (EPA) pesticide sales and usage report (2008-2012), over 1 billion pounds of pesticides are applied in the United States and nearly 6 billion pounds are applied worldwide each year, with agricultural use representing nearly 90% of total pesticide usage.[1] The most widely used pesticides include the herbicide glyphosate and the insecticides organophosphates (OPs), pyrethroids, and neonicotinoids.[1]

In agricultural populations, chronic occupational pesticide exposure has been associated with outcomes such as Parkinson's Disease,[2,3] impaired neurobehavioral function,[4,5] and cancer, including prostate,[6-9] brain,[10,11] and thyroid[12] cancers and non-Hodgkin lymphoma.[13,14] There is also sparse evidence that occupational pesticide exposure may be associated with adverse cardiometabolic,[15] endocrine,[16,17] and respiratory outcomes.[18,19]

Pesticide exposure has also been associated with adverse health outcomes among children living in agricultural areas, with some of the most consistent effects observed for poorer neurodevelopment.[20] Previous research has focused primarily on OP pesticide exposure and has found that prenatal and postnatal concentrations of dialkylphosphate (DAP) metabolites, non-specific biomarkers of OPs, and residential proximity to agricultural OP spraying are associated with abnormal neonate reflexes[21,22] and adverse cognitive development,[23-31] attention problems,[32,33] internalizing behaviors,[31] and autistic traits[34] among preschool and school-aged children. Fewer studies have examined the neurodevelopmental impacts of prenatal and childhood exposure to non-OP pesticides. The studies that have been conducted have identified associations between prenatal biomarkers of exposure to pyrethroid pesticides with behavioral and executive functioning deficits;[35,36] postnatal biomarkers of exposure to pyrethroid pesticides with decreased verbal comprehension and working memory scores;[37] and prenatal residential proximity to agricultural glyphosate use with increased odds of Autism Spectrum Disorder (ASD) during childhood.[38]

Research suggests that pregnancy and early childhood are periods of particular vulnerability for exposure to pesticides and other neurotoxicants, as fetuses and young children are undergoing rapid periods of brain growth and development, have higher rates of metabolism, are physiologically immature, and have lower levels of enzymes involved in the detoxification of pesticides such as OPs.[39-42] In addition, children may have increased exposures relative to their bodyweights due to factors such as having higher hand-to-mouth activity, spending more time on the floor where dust-borne pesticide residues settle, and having less varied diets that include foods with higher levels of pesticide residues.[41-43]

There is growing consensus regarding the need to examine the health effects of exposure to multiple co-occurring environmental chemicals. Environmental epidemiology studies have historically fit models with one exposure variable at a time, which may result in confounding by

correlated exposures.[44] For example, children living in agricultural areas are exposed to numerous pesticides with varying degrees of toxicity through multiple sources and routes of exposure,[45-48] yet few studies have attempted to quantify the overall impacts of exposure to pesticide mixtures.

Increasing evidence also suggests that the impacts of environmental neurotoxicants, such as pesticides, may interact synergistically with non-chemical stressors such as poverty and adverse childhood experiences (ACEs).[49-51] Previous studies examining the joint impacts of chemical and non-chemicals stressors have focused primarily on environmental exposures such as lead,[52-57] air pollutants,[58-60] and environmental tobacco smoke.[61,62] Data gaps exist regarding the neurodevelopmental effects of prenatal and early-life co-exposure to pesticides and social adversity, which may have similar or overlapping mechanisms of action. Only two previous studies have examined the neurodevelopmental effects of exposure to pesticides and social adversity. In the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study, investigators found that totally early-life adversity and domain-specific adversity (i.e., poor learning environment and adverse parent-child interactions) magnified previously observed associations of prenatal OP pesticide exposure and decreased Intelligence Quotient (IQ) at age 7 years.[63] In another examination of low-income urban children, investigators observed that the child's home environment assessed at age 3 years did not modify the effects of prenatal chlorpyrifos exposure on working memory age at 7 years.[29]

1.2 Pesticide exposure assessment

The primary source of pesticide exposure in the general population is diet.[64] In addition to consumption of contaminated food and water,[65] those living in agricultural areas may also be exposed to pesticides via drift from treated fields near homes[65,66] and through the take-home exposure pathway (i.e., when workers who have come into contact with pesticide carry residues into the home on their clothing or shoes).[47,67]

Biomonitoring is often considered the "gold standard" for assessing exposure to many environmental chemicals.[68] One of the primary advantages of biological monitoring to assess exposure to pesticides is that it reflects the various sources (e.g., residential, dietary, occupation) and routes (i.e., inhalation, dermal, ingestion) of exposure.[69] Urinary biomonitoring is often used for pesticides with short half-lives that are rapidly excreted from the body;[70] to date, the majority of research on the neurodevelopmental effects of pesticides has been focused on urinary concentrations of OP metabolites or parent chemicals.[20] DAPs, non-specific biomarkers reflecting exposure to OPs as a class, are the most commonly measured metabolites in assessing human OP pesticide exposure.[70,71] While urinary biomarkers of OPs are an important tool to assess exposure, several challenges limit their utility in epidemiologic analyses. For example, since some highly toxic OPs lack pesticide-specific biomarkers, many studies have used class-specific measurements of DAP urinary metabolites as an overall indicator of OP exposure.[72] Limitations of DAP measurements include that: 1) some common OPs do not devolve to DAPs;[73] 2) DAPs reflect exposure to an unknown mix of OPs with varying levels of toxicity;[74] and 3) DAPs have a short half-lives and reflect only recent exposures.[75] These limitations may result in measurement error that could bias epidemiologic analyses toward the null hypothesis.[76] Further, studies have reported associations between nearby agricultural OP pesticide use during

pregnancy and poorer neurodevelopment at 7 years independent of prenatal urinary DAP levels,[27] suggesting that DAPs do not provide a complete measure of OP exposure. Additionally, many non-OPs lack biomarkers or are cost-prohibitive to analyze, resulting in data gaps regarding the health effects of some of the most commonly used pesticides.

In addition to biomarkers, pesticides may also be measured in environmental samples such as house dust or ambient air samples.[77,78] In a previous analysis of 22 pesticides used in the Salinas Valley, investigators found mixed results regarding the reliability of indoor dust sampling to predict potential environmental exposure based on environmental conditions and the physicochemical properties of different pesticides.[77] For example, investigators observed high correlations between agricultural use near the home and dust concentrations for pesticides such as chlorpyrifos, dimethyl tetrachloroterephthalate (DCPA), and iprodione, but weak correlations for pesticides such as diazinon and permethrin.[77]

Given some of the limitations of environmental and biological markers of exposure, recent studies have increasingly used geospatial methods to characterize potential exposure to a range of pesticides.[27,28,79,80] Since 1990, all agricultural pesticide applications in California, including the crop, active ingredient, date, pounds applied, and location of use have been reported to the California Department of Pesticide Regulation (DPR) and compiled into the Pesticide Use Reporting (PUR) database. Employing PUR data allows investigators to assess potential exposure to a range of pesticides, including those for which biomarkers do not exist, using free, publicly available data. One of the primary limitations of relying on PUR data for exposure assessment is that individuals are inevitably exposed to pesticides via other sources of exposure, e.g., food via ingestion, not captured by agricultural pesticide use. Additionally, factors such as the physicochemical properties of individual pesticides, wind speed and direction during applications, precipitation, and other factors will affect the likelihood of actual human exposure to pesticides applied near the home.[77,78]

1.3 Research needs

While there is relatively consistent evidence that prenatal and early-life OP pesticide exposure is associated with adverse child neurodevelopment, a number of data gaps remain regarding the reliability of relying solely on OP biomarkers of exposure for epidemiologic analyses and risk assessments, the health effects of non-OP pesticides, and the impacts of exposure to pesticides mixtures, as the joint effects of exposure to pesticides and non-chemical stressors. Notably, previous studies have largely focused solely on exposure to OP pesticides in isolation and have primarily assessed exposure via DAPs, non-specific biomarkers of OP pesticide exposure, from random spot urine samples. Reliance on these biomarkers with short half-lives and high inter- and intra-individual variability may result in exposure misclassification that could bias epidemiologic analyses towards the null. Few studies have examined the extent to which concentrations from spot samples may approximate internal dose from the "gold standard" 24-hour urine samples or potential implications of reliance on spot samples for risk assessments.

Additional research is also needed examining the health impacts of non-OP pesticides. OP pesticide use has decreased in recent decades and data gaps exist regarding the neurodevelopmental impacts of current-use pesticides, such as neonicotinoids, pyrethroids, and

the herbicide glyphosate. Moreover, most people, particularly those living in agricultural areas, are exposed to multiple pesticides[65,81] and research is needed to examine the effects of these mixtures that may interact synergistically to adversely impact health and neurodevelopment. Mounting evidence also suggests that the effects of environmental toxicants are due in part to causal interactions with social stressors and biologic factors, however studies investigating the neurodevelopmental impacts of environmental exposures have typically treated social factors as confounders and adjusted for them in multivariate analyses.[29] Failure to account for potential effect modification by these factors may underestimate the impact of environmental neurotoxicants,[82] particularly among the most vulnerable populations where exposures to environmental and non-chemical stressors are likely to co-occur.

1.4 Statement of research questions

This dissertation aims to investigate the developmental neurotoxicity of exposure to mixtures of pesticides and non-chemical stressors and examine OP pesticide dose among children living in the Salinas Valley, an area of intensive agricultural pesticide use. To answer these questions, this dissertation employs two datasets examining pesticide exposure among children living in the Salinas Valley.

Chapter 2 aims to examine how well estimates of internal OP dose from spot and first-morning void (FMV) urine samples approximate dose from 24-hour samples from the Child Validation Study (CVS), a study of 25 children living in the Salinas Valley in which urine samples were collected over seven consecutive days, including two 24-hour sampling days, and analyzed for DAP concentrations. Chapter 3 aims to examine associations of mixtures of agricultural pesticide use near the home during the prenatal and early childhood periods (ages 0-5 years) with behavioral and emotional problems at ages 16 and 18 years in the Center for Health Assessment of Mothers and Children of Salinas (CHAMACOS), a birth cohort of 600 Latinx youth. Lastly, Chapter 4 aims to examine whether associations of agricultural pesticide use near the home during the prenatal period with adolescent behavioral and emotional problems are modified by early-life adversity among participants in the CHAMACOS study.

1.5 Significance

This dissertation builds upon previous research from the CHAMACOS cohort that has identified associations of exposure to OP pesticides, based on DAPs, and adverse neurodevelopment by employing novel statistical methods to assess exposure to mixtures of co-occurring neurotoxic pesticides and early-life adversity. Few studies have examined the joint neurodevelopmental effect of exposure to mixtures of pesticides, information that is critical to elucidate which pesticides or groups of pesticides exert the most deleterious impacts. This research also enhances previous work by examining whether the effects of pesticides are modified by other factors that are associated with neurodevelopment, including early-life social adversity. This research has the potential to guide pesticide risk assessments and regulation by providing information regarding the reliability of current exposure assessment methods and examining the neurobehavioral effects of pesticides for which little data on human health exist.

CHAPTER 2. Organophosphate Pesticide Dose Estimation from Spot and 24-hr Urine Samples Collected from Children in an Agricultural Community

2.1 Introduction

Organophosphate (OP) pesticides are commonly used insecticides that inhibit acetylcholinesterase (AChE) enzyme function and have been associated with poorer neurodevelopment in children.[23-26,32,33,83] Children are particularly susceptible to the adverse impacts of pesticides[83-85] and those living in agricultural areas may be exposed via multiple pathways, including diet, drinking water, residential use, drift from agricultural applications, and take-home exposures.[41,47,77,86-91] Assessing exposure to OP pesticides is difficult due to their short biologic half-lives and rapid excretion from the body.[70,92] Dialkylphosphate (DAP) metabolites, the most commonly used biomarker to characterize OP exposure in epidemiologic studies,[93] have biological half-lives of less than 30 minutes to more than 24 hours, depending on the parent OP and route of exposure.[94]

Measurements of metabolites or parent chemicals in 24-hr urine samples are considered the "gold standard" for assessing daily exposure to pesticides and other environmental chemicals that are excreted in urine.[95,96] However, factors such as cost and participant burden make it difficult to collect 24-hr samples.[97] While collection of spot urine samples is a convenient alternative, research suggests that analysis of biomarkers with short half-lives, including DAPs, in spot samples may result in exposure misclassification due to higher inter- and intra-individual variability.[75,98,99] First morning void (FMV) urine samples may reduce exposure misclassification, as they are more concentrated and reflect a longer period of accumulation.[71,75] Few studies have assessed how well either random spot or FMV urine samples approximate internal pesticide dose estimated from 24-hr samples, information that is critical for risk assessment and pesticide regulation.

Estimating dose based on metabolite concentrations from spot samples also requires an accurate measure of urinary dilution and total daily urinary output volume.[100] In adults, 24-hr urinary metabolite excretion has been estimated from spot urine samples by adjusting for creatinine excretion as an index of total daily urinary output volume.[73,97,100,101] However, few studies have evaluated the validity of this approach in children. Due to likely differences in children's urinary creatinine excretion from factors including age, sex, muscle mass, body mass index (BMI), diet, and fluid intake,[97,102,103] adjusting for creatinine to estimate toxicant doses in children may introduce unknown sources of variability.[75] Although not used as widely as creatinine correction, some evidence suggests that adjusting for specific gravity may be a more robust method to account for urinary output among children.[104,105]

The US Environmental Protection Agency (EPA) is mandated by the 1996 Food Quality Protection Act (FQPA) to review and establish health-based standards for pesticide residues in foods and examine the cumulative health effects of exposure to mixtures of pesticides that share a common mechanism of toxicity, with prioritization of pesticides that may pose the greatest risk, such as OPs.[106] The U.S. EPA has selected the Relative Potency Factor (RPF) method to conduct hazard and dose-response assessments. RPFs are calculated as the ratio of the toxic potency of a given chemical, determined by the oral benchmark dose$_{10}$ (BMD$_{10}$) value based on a 10% brain cholinesterase inhibition, to that of an index chemical. Individual OP doses derived from index chemical toxicity equivalent doses can be summed to create cumulative OP dose equivalents.[73]

In this study, we measured DAP metabolites in spot and 24-hr void urine samples collected from 25 preschool-aged children over 7 consecutive days. The objective of this analysis was to evaluate the validity of using volume- and creatinine-adjusted FMV and non-FMV spot urine samples to estimate total 24-hr OP dose in children according to the 2006 US EPA Organophosphorus Cumulative Risk Assessment guidelines. The results of these analyses have implications for policy and risk assessments and could serve as a case study for other non-persistent toxicants measured in urine.

2.2 Methods

2.2.1 Study population

Subject recruitment and procedures have been described previously.[75] Briefly, we enrolled a convenience sample of 25 children (10 boys, 15 girls) recruited from clinics serving low-income families in the Salinas Valley, California. Eligible children were 3-6 years old, in good health with no history of diabetes or renal disease, toilet trained, and free of enuresis, and had English- or Spanish-speaking mothers who were $\geq$ 18 years old. Sampling occurred in March and April 2004. The University of California at Berkeley Committee for the Protection of Human Subjects approved all study procedures and parents provided written informed consent.

2.2.2 Data collection

Each family participated in the study over 7 consecutive days. On the first day, study staff measured the participating child's height and weight, provided the supplies needed to collect urine samples, including specimen trays and jars, gloves, collection jars with blank labels, a small refrigerator, and two 24-hr sampling record forms, and instructed the parents and child on how to collect, record, and store samples. Urine voids were collected either directly into a collection jar or into a sterile pre-cleaned specimen tray placed over the toilet, which was then transferred by parents into the collection jar.

Figure 2.1 shows the timing of study activities. On spot-sampling days (1, 3, 4, 6, and 7), families collected a single void at their convenience, recording the time of collection on the jar labels and identifying the sample as an FMV or non-FMV spot sample. On 24-hr sampling days (2 and 5), families were instructed to collect all urine voids from the 24-hr period as separate specimens, including the child's FMV, all daytime and evening spot voids, and the FMV of the following day (i.e., study days 3 and 6), if it occurred within the 24-hr sampling period. Participants were instructed to record the timing of all voids, including missed voids, on the 24-hr sampling record form. We limited the current analyses to samples collected on 24-hr sampling days (referred to henceforth as 24-hr composites or same-day FMV and non-FMV samples).

Research staff reviewed the 24-hr sampling record with the parents to ensure accuracy and completeness. Urine samples were stored in the sample refrigerator until daily collection by research staff. Trained, bilingual study staff administered daily questionnaires that assessed the child's exposure to pesticides, including questions regarding dietary intake of fruits, vegetables, and juices; time spent indoors/outdoors; parental occupational exposures; and residential pesticide use over the previous 24-hr period.

2.2.3 Sampling process and analysis

Study staff processed the samples at the study field office, recording the weight (grams) and volume (milliliters). On 24-hr sampling days, staff were instructed to select the first FMV sample plus one to three randomly selected additional spot samples for individual analysis. All

remaining voids from the sampling period were pooled prior to analysis. The total volume of the 24-hr composite sample was based on the volume of the individually analyzed samples plus the volume of all samples that were included in the pooled sample. The DAP concentrations were based on volume-weighted averages of concentrations in the individually analyzed samples plus the pooled sample. Samples were stored at -80^{0}C until shipment on dry ice to the Centers for Disease Control and Prevention for analysis in August and September 2004.

Laboratory methods and quality control procedures have previously been described in detail [107]. Urine samples were lyophilized to remove water, re-dissolved in a 1:1 solution of acetonitrile and diethyl ether, and analyzed using gas chromatography-tandem mass spectrometry using isotope dilution to quantify concentrations of six DAP metabolites, including three dimethyl (DM) phosphate metabolites: dimethylphosphate (DMP), dimethylthiophosphate (DMTP), and dimethyldithiophosphate (DMDTP); and three diethyl (DE) phosphates: diethylphosphate (DEP), diethylthiophosphate (DETP), and diethyldithiophosphate (DEDTP). These non-specific metabolites represent the breakdown products of approximately 80% of total OP pesticide use in the Salinas Valley during the study period.[108] Creatinine concentrations were determined using a commercially available diagnostic enzyme method (Vitros CREA slides, Ortho Clinical Diagnostics, Raritan, NJ, USA). The validity of each analytical run was established using Westgard rules for quality control.[109] Sixty blank samples were analyzed, and the average DAP concentration was 0.12 nmol/L.

Limits of detection (LODs) were 0.2 μg/L for all diethyls (DEs), 0.5 μg/L for dimethylphosphate (DMP), 0.4 μg/L for dimethylthiophosphate (DMTP), and 0.1 μg/L for dimethyldithiophosphate (DMDTP). Values below the LOD were assigned a value of LOD/√2 [110]. Total dimethyl (DM), total DE, and total DAP concentrations were calculated within each sample by summing molar concentrations. We computed metabolite levels in 24-hr samples using the volume-weighted average of concentrations in all samples collected in that 24-hr sampling period (which included the FMV sample from the following day for 9 "participant-days" in which the FMV on the mornings of study days 3 and 6 occurred within the 24-hr sampling period).

2.2.4 Statistical analyses

Statistical analyses were performed using Stata 14 for Windows (StataCorp LP, College Station, TX). We characterized the mixture of OPs that participants were potentially exposed to based on: 1) nearby pesticide applications, and 2) diet (described in detail below).

Pesticide use data: In California, all agricultural pesticide use, including crop, active ingredient, date, pounds applied, and location of use within one square mile (1.6 x 1.6 km) sections defined by the Public Lands Survey System (PLSS) are recorded in pesticide use reports (PUR) by the California Department of Pesticide Regulation (DPR; Sacramento, CA). We used the latitude and longitude of the participant's home, geocoded from their street address, to map pesticide applications. We considered pesticide use within three kilometers of the home in the six months prior to each of the two 24-hr urine sampling days for each study participant, as these are within the range of distances and time periods that have been mostly strongly associated with OP concentrations in samples from this region.[77] We included 11 OPs that devolve into DAPs that are used in the Salinas Valley, which is representative of the most commonly used OPs nationally in the same time period.[1] These 11 OPs include eight DM (azinphos-methyl, dimethoate, malathion, methidathion, methyl parathion, naled, oxydemeton-methyl, phosmet)

and three DE (chlorpyrifos, diazinon, disulfoton) pesticides. All estimates were adjusted for the proportion of time the residence was downwind of each pesticide application.[111]

Dietary exposure assessment: At each study visit, study staff asked parents to report (yes/no) whether their child had consumed fresh fruits or vegetables from a 21-item list since the previous visit. Parents were also asked to report their child's consumption of any fruits or vegetables that were not on the list; canned, jarred, or frozen fruits and vegetables; and orange, apple, or other 100% fruit juice (Table S2.1).

Each year since 1991, the United States Department of Agriculture (USDA) Pesticide Data Program (PDP) has tested food commodities, including fruits and vegetables, for approximately 450 pesticides and their breakdown products.[112] Using a food consumption-chemical residue (FCCR) approach described previously,[113,114] we used these publicly available data to calculate the mean concentration of the 11 OPs of interest (µg OP/g food) for each of the food items reported in our study.

To estimate dietary OP exposure, we multiplied the estimated concentration of the 11 OPs in each food item by the estimated intake of that food item. Per the US EPA Cumulative Organophosphorus Risk Assessment guidelines, we also included omethoate, the dimethoate oxon, in our dietary assessment, however it was not detected on any of the food commodities of interest in 2004. We made the assumption that each reported consumption of a particular fruit or vegetable was equal to one serving and used data for children ages 3-6 years from the 2003-2004 National Health and Nutrition Examination Survey (NHANES) "What we Eat in America" study [115] linked to Food Commodity Intake Database (FCID)[116] codes to estimate the weight of each food item. We estimated total exposure for each OP by summing estimated intake (µg) across all food items. We included reported food consumption that we were certain had preceded the urine void. For 24-hr samples, we considered the average exposure from all produce reported on the current day and previous day (i.e., produce consumed on days 1 and 2 for 24-hour sampling on day 2). For spot samples, we considered all produce reported on the day prior to sampling in order to ensure the produce was consumed before the sample was collected. We used USDA pesticide residue data from 2004 (the year of urine sample collection), when available. For commodities not analyzed in 2004, we used data from the most proximate year (Table S2.1). PDP samples with values <LOD were set to 0.

Dose calculations: We used the 2006 U.S. EPA OP Cumulative Risk Assessment guidelines to estimate total OP pesticide dose.[106] These guidelines consider the effects of exposures to mixtures of pesticides and assume that OPs share a common mechanism of toxicity (i.e., the inhibition of cholinesterase activity). We used the approach outlined by Castorina et al. (2003) to calculate cumulative OP dose in units of chlorpyrifos equivalents (µg /kg/day) from nearby agricultural pesticide use, based on PUR data, using Equation 1, where D_{cum} is the cumulative dose equivalent (µg /kg/day), $\mu Mol_{Diethyl}$ is total micromoles of DE metabolites (DEP, DETP, DEDTP), $\mu Mol_{Dimethyl}$ is total micromoles of DM metabolites (DMP, DMTP, DMDTP) excreted over a 24-hr period, P_i is the proportion of pesticide *i* in the mixtures calculated from PUR data for each participant, MW_i is the molecular weight of the *i*th pesticide in micrograms per micromole, and RPF_i is the relative potency factor of the *i*th pesticide in the cumulative assessment group, and BW is the body weight of the child at the time of urine sample collection.

$$D_{cum} = \frac{\mu Mol_{Diethyl} \sum P_i MW_i RPF_i}{BW} + \frac{\mu Mol_{Dimethyl} \sum P_i MW_i RPF_i}{BW} \qquad [1]$$

Using the FCCR approach outlined by Curl et al. (2015), we adapted Equation 1 to estimate cumulative OP dose in units of chlorpyrifos equivalents (μg/kg/day) from diet. After calculating the intake of each of the 11 OPs in μg as described above, we estimated the proportion of each pesticide (P_i) by dividing the estimated dietary concentration of that pesticide by the total concentration of DMs or DEs estimated from diet.

Based on results in a similar population of 40 children ages 3-6 years living in Salinas Valley and Oakland, CA in which investigators observed that Salinas area children's total urinary DAPs decreased by about 40% following an organic diet intervention,[64] we estimated that diet contributed approximately 40% of overall OP exposure to the children in the current study. We assumed the additional 60% of pesticide exposure was derived from nearby pesticide use, represented by PUR data. Total OP exposure in chlorpyrifos equivalents were calculated for total DAPs, DMs, and DEs separately using Equation 2:

$$Total\ dose\ (\mu g\ chlorpyrifos\ equivalents/kg/day) = (Dose_{PUR} * 0.60) + (Dose_{Diet} * 0.40) \quad [2]$$

Underlying our dose estimation models are the following assumptions, adapted from Castorina et al. (2003): 1) urinary concentrations represent steady state conditions over a 24-hr period; 2) 100% of absorbed OP pesticide dose is expressed as urinary diethyl and dimethyl phosphate metabolites; 3) the estimated proportion of pesticides from the PUR and dietary assessments is a reasonable surrogate for the mixture of OPs to which participants were exposed from all sources; and 4) OP metabolite concentrations are equivalent to internal doses on a molar basis.

Volume adjustment: In order to estimate the micromoles of each of the six DAPs excreted over a 24-hr period based on spot samples (Equation 1), we multiplied the observed urinary metabolite concentration in that spot sample by an estimate of the 24-hr urinary output volume (L/day) using four distinct volume-adjustment approaches. First, we used expected 24-hr child urinary output based on reference values (henceforth referred to as volume-adjusted dose estimates based on *expected* daily urinary volume). Previous literature estimates that children have a urinary output of 1-2 mL/kg/hr;[117] we used the average output to estimate each child's urinary output in L/day. Second, we used the mean volume of each individual's two 24-hr composite urine samples (henceforth referred to as volume-adjusted dose estimates based on *observed* daily urine volume). Third, we estimated expected 24-hr urine output based on expected creatinine excretion using the following equation (henceforth referred to as creatinine-adjusted dose estimates based on *expected* daily creatinine excretion):

$$Vi = \frac{Ccr_i}{Cc_i} \quad [3]$$

where Vi is the expected 24-hr urine output for the ith participant (L/day), Ccr_i is the expected daily creatinine excretion (mg/day) based on equations 4 and 5 for the ith participant, and Cc_i is the observed creatinine concentration in the ith participant's urine sample (mg/L). Expected creatinine excretion was calculated based on the following equations,[118] where Ht = height in centimeters:

$$Expected\ creatinine\ (mg/day)\ for\ males = Ht\ \times\ [6.265 + 0.0564\ (Ht - 168)] \quad [4]$$

$$Expected\ creatinine\ (mg/day)\ for\ females = 2.045\ \times Ht^{[0.01552(Ht-90)]} \quad [5]$$

Finally, we estimated 24-hr urine output based on the mean observed 24-hr creatinine excretion from each individual's 24-hr composite samples (henceforth referred to as creatinine-adjusted dose estimates based on *observed* daily creatinine excretion).

We chose to use equations 3-5 to estimate expected 24-hr urinary output volume based on observed and reference creatinine excretion values because these would be the only methods available for use in many epidemiologic studies and risk assessments that make inferences based on the collection of spot samples alone. Dose estimates from 24-hr composites were not corrected for urinary volume, as they already reflected the actual 24-hr urine output.

Comparing spot, FMV, and 24-hr samples: We used generalized estimating equation (GEE) models using DAP, DM, and DE dose estimates from each 24-hr composite as the outcome variable and dose estimates from same-day spot (FMV and non-FMV) as the predictor variable. We also used the combination of each same-day FMV and non-FMV spot sample as a predictor variable by computing the arithmetic average of the dose estimate from the individual samples. Missing voids from 24-hr samples were excluded from the analysis, as both the volume of the sample and DAP concentrations were unknown. Analyses were conducted for volume- and creatinine-adjusted dose estimates. All dose estimates were $\log_{10}$-transformed. We assessed the performance of the models for each predictor variable using the predictive power of the model defined as the coefficient of determination (R^2); the root mean squared error (RMSE), which is a measure of both precision and accuracy of the model; and the intraclass correlation (ICC),[119] which measures agreement between the dose estimates.

2.2.5 Sensitivity analyses

We conducted several sensitivity analyses to examine the robustness of our results: 1) we excluded participants with >1 FMV sample collected during a 24-hr sampling period; 2) we limited analyses to participants with complete collection of all spot samples within a 24-hr urine sampling period; and 3) we varied the proportion of OP exposure from diet and nearby agricultural pesticide use. Based on the results from a recent study that found that DAPs decreased by approximately 70% among nine children ages 4-15 years living in four U.S. urban areas following an organic diet intervention,[120] we attributed 70% of exposure to diet and 30% of exposure to nearby agricultural pesticide use.

2.3 Results

All children were Mexican American and ranged in age from 3 to 6.5 years (mean $\pm$ SD = 4.5 $\pm$ 0.93 years). We included 69 same-day non-FMV spot samples and 54 same-day FMV spot samples (including FMV samples collected on mornings 1 and 2 of 24-hr sampling periods) from 50 "child-days" (n=25 children over two 24-hr sampling periods) in the analysis. Nine participant-days had 24-hr composites that included two FMV samples (2 FMV samples collected from morning of study day 2 to morning study day 3 and 7 FMV samples collected from morning of study day 5 to morning of study day 6). Participants collected 89% (range=50-100%) of reported voids during 24-hr sampling (range=4-12 voids; mean=7.4 voids).

Twenty-two (44%) of 24-hr samples were based on 100% collection of all voids. The maximum number of missed voids for a single participant for a 24-hr sample was 3 (out of 6 total voids reported). Seven participants missed two or more voids during one of the 24-hr

sampling periods. Reasons for missed voids included out-of-home bathroom use and toileting accidents. We collected entire urine voids. The volume of individual spot samples collected during 24-hr sampling periods ranged from 4.8 to 642.2 mL (mean, 157.5 mL) for FMV samples and 16.4 to 238.3 mL (mean, 73.0 mL) for non-FMV samples.

2.3.1 Estimated cumulative OP dose

Tables S2.2 and S2.3 present estimated cumulative OP dose for 24-hr, non-FMV spots, and FMV spot samples assuming that that the exclusive source of OP exposure was either nearby agricultural pesticide use or diet, respectively. Dose estimates were significantly higher and a greater percentage of samples exceeded the benchmark dose in models in which all OP exposure was attributed to nearby agricultural pesticide use.

We observed high detection frequencies of > 90% for DEs, DMs, and total DAPs (Table 2.1). Total DAP levels were driven primarily by DM metabolites.

Table 2.2 reflects the total estimated cumulative OP dose, assuming that nearby agricultural pesticide use and diet contributed to 60% and 40% of total OP exposure, respectively. We observed that both volume- and creatinine-adjusted non-FMV spot samples tended to underestimate dose relative to 24-hour composites (median dose for DAPs from 24-hr composites = 3.18 µg/kg/day; from volume-adjusted estimates based on *expected daily urine volume* = 1.55 µg/kg/day; from volume-adjusted estimates based on *observed daily urine volume* = 2.22 µg/kg/day; from creatinine-adjusted estimates based on *expected daily creatinine excretion* = 3.01 µg/kg/day), and likewise underestimated the percentage of children exceeding the daily benchmark dose relative to estimates based on 24-hr samples. Of the non-FMV samples, those adjusted for *observed daily creatinine excretion* were most similar to estimates from 24-hr composites (median dose for DAPs = 3.20 µg/kg/day), but still tended to underestimate dose at higher percentiles (e.g., dose estimates at 90th percentile for non-FMV and 24-hr composites = 14.76 µg/kg/day and 19.91 µg/kg/day, respectively). Total DAP doses based on the average of a non-FMV and FMV spot sample most closely approximated dose from 24-hr samples.

2.3.2 Comparison of dose estimates from spot and 24-hr urine samples

Table 2.3 presents results of GEE models examining how well dose estimated from same-day FMV and non-FMV spot samples predicted 24-hr OP dose after excluding one participant-day with abnormally high urinary DAP concentrations (>3 SD from mean). For models estimating the association between a single volume- or creatinine-adjusted spot sample and its respective 24-hr composite, the R^2 was highest for FMVs (R^2 for total DAPs = 0.40-0.68 for FMVs and 0.09-0.38 for non-FMVs, depending on method of volume adjustment). While the predictive power tended to be slightly greater for estimates adjusted for observed 24-hr urine volume or observed 24-hr creatinine, the R^2 and RMSE values indicated that models adjusted for expected 24-hr creatinine excretion also had relatively high ability to predict 24-hr dose (R^2 for total DAPs for FMVs and average of non-FMV and FMV=0.65 and 0.72, respectively). ICC values indicated poor reproducibility for non-FMV samples (ICC for total DAPs = 0.14-0.59 for non-FMV and 0.63-0.82 for FMV samples, depending on the volume-adjustment method).

The best-fitting models were obtained when either an FMV sample or the arithmetic mean of an FMV and non-FMV sample was used to predict the 24-hr dose, depending on the metabolite type and volume-adjustment method (R^2=0.40-0.68 for FMV samples and 0.40-0.80 for average of FMV and non-FMV samples for total DAPs; Table 2.2). Similarly, RMSE values indicated

that models with either FMV samples or the average of an FMV and non-FMV samples were the most accurate predictors of 24-hr dose (RMSE=0.28-0.38 for FMV samples and 0.22-0.37 for average of FMV and non-FMV samples for total DAPs). The best model fit for total DAPs was observed for the mean of an FMV and non-FMV sample adjusted for observed 24-hr creatinine excretion (R^2=0.80; RMSE = 0.22). Model fit was strongest for total DAPs and DMs and considerably weaker for DE metabolites.

2.3.3 Sensitivity analyses

Results from sensitivity analyses in which we 1) excluded participants with >1 FMV sample during a 24-hr sampling period (Tables S2.4-S2.5); 2) excluded participants with <100% collection of urine samples during a 24-hr sampling period (Tables S6-S7); and 3) varied the proportion of estimated OP exposure from diet and nearby agricultural pesticide use (Tables S2.8-S2.9) were largely consistent with findings from our main analyses. Dose estimates from sensitivity analyses in which 70% of OP exposure was attributed to diet were considerably lower than dose estimates from main analyses (Table S2.8). Additionally, model fit was slightly better for non-FMV samples in sensitivity analyses in which we limited to participants with 1 FMV sample (Table S2.5) or complete collection of all urine samples during a 24-hr sampling period (Table S2.7). Consistent with results from the main analyses, the best model fit for total DAPs in each sensitivity analysis was observed for the mean of an FMV and non-FMV sample adjusted for observed 24-hr creatinine excretion.

2.4 Discussion

In this study of 25 children living in an agricultural region, we found that volume- and creatinine-adjusted non-FMV spot urine samples had relatively weak ability to predict 24-hr cumulative OP dose. Moreover, our results indicate that reliance on non-FMV spot samples may underestimate daily cumulative OP dose and the percentage of samples exceeding regulatory guidelines, regardless of the method used to account for expected daily urinary excretion. Models including the average of an FMV and non-FMV spot had the greatest ability to predict 24-hr dose, however models containing just an FMV sample were often similarly predictive of daily dose. Our findings are consistent with previous analyses in this population in which we found that spot urine samples had relatively weak ability to predict cumulative exposure over one week and that reliance on spot samples to reflect chronic OP pesticide exposure may result in exposure misclassification that could bias effect estimates towards null findings.[75] Because 24-hr sampling, considered the "gold standard", or the collection of multiple daily spot samples is infeasible in most epidemiologic studies, we recommend that future studies prioritize the collection of FMV samples to most accurately characterize OP dose.

To our knowledge, only two other studies have examined the ability of same-day spot urine samples to predict 24-hr OP pesticide exposure or dose.[71,95] In a study of 13 2-5 year old children, Kissel et al. analyzed OP metabolite concentrations from urine samples collected during each of two 24-hr sampling cycles in two different seasons and found that FMV samples were the best predictor of weighted-average daily metabolite concentration in both creatinine-adjusted and unadjusted analyses.[71] They also observed high intra-child variability in metabolite levels from urine samples collected on the same day.[71] Their findings indicate that full 24-hr sampling may reduce measurement error due to within-person variability, however if spot

sampling is to be conducted, collection of FMV samples are preferable for analytes with short half-lives.[71]

In another analysis of 20 farmers and their children, Scher et al. analyzed agreement between two OP parent compounds/metabolites (2,4-dichlorophenoxy acetic acid (2,4-D) and 3,5,6-trichloro-2-pyridinol (TCPy)) in morning void samples with 24-hr composite exposure and dose estimates from urine collected between 24 hours before through 96 hours after pesticide application.[95] Compared to estimates based on 24-hr samples, investigators found that single morning void urine samples tended to overestimate daily exposure and dose estimates of 2,4-D and chlorpyrifos (the parent compound of the metabolite TCPy).[95] More specifically, four children had chlorpyrifos dose estimates above the acute population adjusted dose (aPAD) regulatory level of 0.5 µg/kg/day based on morning void samples, whereas no 24-hr dose estimates exceeded EPA safety thresholds.[95] Taken together with our results, these findings suggest that reliance solely on non-FMV spot samples may underestimate OP dose, whereas analysis of FMV samples alone may overestimate dose.

Previous epidemiologic analyses among children living in the Salinas Valley have found DMs to drive associations between urinary DAPs and adverse child neurodevelopment.[23,33,83] We observed that DMs had a substantial influence on OP dose estimates and ability of spot samples to predict 24-hr dose. There are a few possible explanations for this. First, of the 11 OPs examined in this analysis, 8 are DMs and only 3 are DEs. These eight DMs had a much higher total molar mass (2,387 g/mol) than the three DEs (929 g/mol). Second, oxydemeton methyl, a highly toxic DM with a large RPF (16.4 for the index chemical chlorpyrifos), increased in use in the Salinas Valley shortly after our study started[121] and may be influencing the associations observed in our study and previous epidemiologic analyses from this region. Pesticide use trends have shifted drastically since we conducted this study and some of the most toxic OPs have largely been phased out of agricultural use in the Salinas Valley and across the United States. Additional investigations are needed to examine cumulative OP dose estimates and potential contributions from DEs and DMs with the current mixture of OPs being applied. In addition to the potential influence of specific OPs, it's possible that DEs are chemically less stable and have higher intrinsic variability than DMs.[108]

We found that estimates adjusted for expected 24-hr creatinine had similar ability to predict daily OP dose as estimates adjusted for observed 24-hr creatinine excretion or urine volume. Conversely, in a study of 109 children living in an agricultural area in Washington State, investigators found that creatinine-adjusted doses tended to be lower than those calculated with daily urine volume.[122] Previous studies have found that creatinine concentrations may be highly variable due to factors such as age, sex, BMI, diet, and fluid intake[97,102,103] and that correcting for specific gravity may introduce less variability and may be a more robust method in studies focusing on children.[104,105] Additional research may be needed to evaluate the validity of creatinine correction in children. Furthermore, we recommend that future studies collect urine specific gravity information, particularly given the ease of measuring this metric.[104]

This study has multiple strengths and implications for future risk assessments and epidemiologic studies. We extended previous examinations that estimated cumulative OP dose from diet[113] and nearby agricultural pesticide use (using PUR data)[73] separately by considering these exposures in conjunction. Additionally, this is one of only a few studies to examine cumulative OP pesticide dose among children living in an agricultural area and to examine the ability of spot samples to predict 24-hr dose. These results have important implications for risk assessments and could be applied to other non-persistent environmental chemicals.

This study also has limitations. We did not have specific gravity measurements and could not compare adjustment for urinary dilution using specific gravity. Notably, while DAPs represent exposure to approximately 80% of the OPs used in the Salinas Valley,[73] children may have been exposed to other OPs that do not devolve into DAPs.

While California's unique and comprehensive PUR database allowed us to estimate the mix of pesticides participants may have been exposed to from nearby agricultural pesticide use, relying solely on these data to estimate all non-dietary exposures may not adequately account for all sources and pathways of exposure. We examined agricultural pesticide applications near participants' residences in the six months prior to each 24-hr sampling in order to try to account for exposures from multiple sources, including agricultural drift and accumulation of pesticides in the home (i.e., in carpets, household surfaces, and dust), however participants may have also been exposed to pesticides via the take-home exposure pathway, particularly if they lived with farmworkers.[47,67] However, because the dose calculations incorporate the proportion of potential exposure to each pesticide in relation to total DEs and DMs applied, rather than a sum of each pesticide, and because we anticipate that children living with farmworkers were likely exposed to a similar mixture of OPs from para-occupational exposures, we do not believe that this impacted our results substantially. No residential use of OPs was reported by participants.

Our assumption that 100% of absorbed OP dose was excreted as urinary diethyl and dimethyl metabolites may underestimate dose, as approximately 20% of the OPs used in the study area do not metabolize to any of the DAP metabolites.[73] Furthermore, the OPs that do devolve into DAP metabolites are not excreted entirely as DAP metabolites within 24 hours, as they may be excreted in other biological media[123] and as non-DAP urinary metabolites.[92,123] Factors such as the route of exposure may also impact the proportion of parent OPs excreted as DAPs, with previous studies finding a higher recovery for oral versus dermal exposures.[123,124]

Another limitation is that we did not administer a comprehensive dietary assessment. We asked mothers to state whether their child had consumed any fruits or vegetables in the previous day. Compared to a more rigorous Food Frequency Questionnaires (FFQs), our assessment may have underestimated dietary exposures. Moreover, the USDA PDP program publishes food residue data from food samples acquired from across the country without regard to region of origin. Employing these data inherently assumes participants consumed fruits and vegetables with similar exposure profiles of produce sold throughout the U.S. It is possible that participants from an agriculture region are more likely to consume locally grown produce, resulting in exposure profiles that may or may not reflect those sold nationwide. For example, we observed that dose estimates based solely on nearby agricultural pesticide use were significantly higher than dietary dose estimates, in part due to the higher proportion of exposure from more toxic pesticides such as oxydemeton methyl and disulfoton in PUR dose estimates. If specific OPs that were sprayed locally in this timeframe were also present to a higher degree on locally consumed produce, our use of national food residue data may have underestimated dietary dose estimates.

When determining the proportion of exposure to attribute to diet, we chose to incorporate data from an organic diet intervention study in a similar population of children living in Salinas and Oakland, CA in 2006.[64] Various studies, including other intervention studies that have observed decreases in DAP concentrations from 70-89% among children and adults following an organic diet intervention[120,125,126], suggest that diet is the primary source of OP exposure among children in non-agricultural areas.[48,113,127,128] It is possible that diet accounted for a greater proportion of exposure than we attributed to it in this analysis. However, longitudinal studies of children living in agricultural and suburban areas in Washington State suggest that DAP

concentrations may vary temporally and that diet may not necessarily be the primary source of OP exposure among agricultural children during spray seasons.[87,129] Furthermore, the overall interpretation regarding the predictive power of FMV and non-FMV spots remained consistent between main analyses and sensitivity analyses in which we varied the proportion of exposure from diet. Additional studies are needed to disentangle the proportion of exposure from diet, nearby agricultural pesticide use, and other sources among children living both in agricultural and non-agricultural regions. Regardless of the proportion of exposure assigned to each source, our overall conclusions that non-FMV spots may underestimate exposure remain the same.

2.5 Tables and Figures

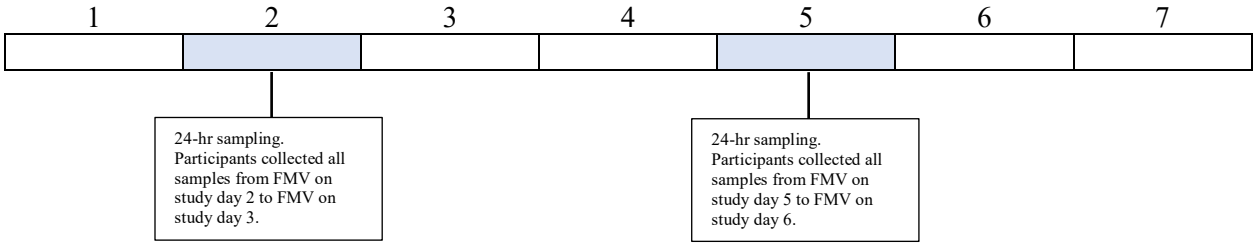

Figure 2.1. Study activities by day. Participants collected all urine voids for a 24-hr period on study days 2 and 5, including the FMV, all daytime and evening spot voids, and the FMV of the following day (study days 3 and 6). The current analyses were limited to samples collected during the 24-hr sampling periods.

Table 2.1. Unadjusted and creatinine-adjusted DAP concentrations in urine samples collected from 2 24-hr sampling periods.

		Unadjusted (nmol/L)				Creatinine adjusted (nmol/g creatinine)			
Type of sample	DF (%)	GM	Mean	Median	Range	GM	Mean	Median	Range
24-hr composite samples (*n*=50)									
Total DAPs	-	158.0	295.5	144.3	34.7-3,698.9	274.5	620.5	244.8	47.5-10,144.5
Total DMs	-	94.6	230.4	89.9	11.8-3,593.0	166.1	507.8	138.5	15.3-9,923.1
Total DEs	-	45.9	65.0	53.3	4.8-248.3	78.9	112.8	93.6	8.6-609.7
Non-FMV spot (*n*=69)									
Total DAPs	98.6	92.5	225.6	87.16	7.8-4.823.8	193.5	692.7	190.9	9.2-20,614.6
Total DMs	92.8	54.3	176.8	50.4	5.2-4,788.9	113.7	602.3	101.8	5.6-20,465.5
Total DEs	94.2	20.7	48.8	22.3	2.5-474.6	43.4	90.5	66.8	3.0-463.2
FMV spot (*n*=54)									
Total DAPs	98.2	177.4	307.7	146.8	7.8-1,617.1	218.8	404.5	212.6	13.1-2,472.7
Total DMs	98.2	99.0	228.9	94.4	5.2-1,519.8	122.0	308.2	122.3	6.2-2,323.8
Total DEs	98.2	50.3	78.8	57.6	2.5-267.9	62.0	96.3	79.2	4.0-355.2

Abbreviations: DF, detection frequency; GM, geometric mean

Table 2.2. Estimated cumulative OP chlorpyrifos equivalent dose (μg/kg/day) based on nearby agricultural pesticide use and diet[a] (*n*=25 children[b]).

Type of spot sample/metabolite excretion units	Metabolite type	n	Percentiles					Range	Estimates exceeding index chemical's BMD_{10}/100 (%)[d]
			10th	25th	50th	75th	90th		
24-hr composite samples[c]									
	Total DAPs	50	1.16	1.60	3.18	10.06	19.91	0.76-146.81	9 (18.0)
	Total DMs	50	0.79	1.11	2.77	10.00	19.07	0.60-146.29	7 (14.0)
	Total DEs	50	0.10	0.30	0.43	0.85	1.01	0.01-2.94	0 (0.0)
Non-FMV spot									
Expected 24-hr urine volume[e]	Total DAPs	69	0.24	0.79	1.55	4.92	10.14	0.12-30.96	4 (5.8)
	Total DMs	69	0.20	0.67	1.29	4.27	8.19	0.07-26.97	3 (4.3)
	Total DEs	69	0.02	0.07	0.26	0.63	1.87	0.01-5.72	0 (0.0)
Observed 24-hr urine volume[f]	Total DAPs	69	0.45	1.17	2.22	6.97	15.17	0.21-195.15	7 (10.1)
	Total DMs	69	0.40	0.80	1.99	6.03	13.06	0.16-194.97	5 (7.2)
	Total DEs	69	0.02	0.05	0.22	0.61	1.25	0.01-3.72	0 (0.0)
Expected 24-hr creatinine excretion[g]	Total DAPs	69	0.51	1.26	3.01	6.92	15.45	0.11-555.50	8 (11.6)
	Total DMs	69	0.35	1.04	2.55	6.56	14.67	0.09-554.99	6 (8.7)
	Total DEs	69	0.03	0.11	0.33	0.72	1.39	0.01-3.04	0 (0.0)
Observed 24-hr creatinine excretion[h]	Total DAPs	69	0.51	1.59	3.20	6.86	14.76	0.19-381.92	6 (8.7)
	Total DMs	69	0.43	1.27	2.33	5.48	13.52	0.14-381.57	6 (8.7)
	Total DEs	69	0.02	0.08	0.33	0.79	1.14	0.01-4.31	0 (0.0)
FMV spot									
Expected 24-hr urine volume[e]	Total DAPs	54	0.69	2.22	4.06	6.32	13.59	0.22-25.28	3 (5.6)
	Total DMs	54	0.53	1.65	3.27	5.95	11.91	0.17-23.48	1 (1.9)
	Total DEs	54	0.08	0.37	0.61	1.08	1.63	0.02-2.59	0 (0.0)
Observed 24-hr urine volume[f]	Total DAPs	54	0.79	1.59	4.33	11.99	24.45	0.18-53.37	11 (20.4)
	Total DMs	54	0.44	1.10	3.61	10.81	23.71	0.15-52.98	11 (20.4)
	Total DEs	54	0.09	0.29	0.51	0.85	1.24	0.01-2.73	0 (0.0)
Expected 24-hr creatinine excretion[g]	Total DAPs	54	0.76	1.11	3.21	7.95	18.75	0.18-80.46	8 (14.8)
	Total DMs	54	0.34	0.78	2.86	7.64	18.20	0.12-79.87	8 (14.8)
	Total DEs	54	0.08	0.24	0.38	0.65	0.93	0.01-1.41	0 (0.0)
Observed 24-hr creatinine excretion[h]	Total DAPs	54	0.74	1.47	3.15	7.17	18.81	0.11-48.75	9 (16.7)
	Total DMs	54	0.34	0.98	2.74	6.75	18.38	0.09-47.02	8 (14.8)
	Total DEs	54	0.10	0.24	0.37	0.63	1.01	0.01-1.74	0 (0.0)
Average of non-FMV and FMV spots[i]									
	Total DAPs	68	0.75	1.67	3.53	5.77	8.03	0.22-21.18	2 (2.9)

Expected 24-hr urine volume[e]	Total DMs	68	0.58	1.39	3.14	4.93	7.17	0.13-18.96	2 (2.9)
	Total DEs	68	0.14	0.32	0.54	0.84	1.27	0.02-3.52	0 (0.0)
Observed 24-hr urine volume[f]	Total DAPs	68	1.01	1.55	4.63	9.59	19.93	0.49-109.80	8 (11.8)
	Total DMs	68	0.86	1.25	4.37	8.95	18.67	0.32-109.34	8 (11.8)
	Total DEs	68	0.13	0.22	0.45	0.73	0.99	0.01-2.27	0 (0.0)
Expected 24-hr creatinine excretion[g]	Total DAPs	68	0.82	1.29	3.67	8.10	19.93	0.24-291.70	9 (13.2)
	Total DMs	68	0.65	1.05	3.30	7.31	19.21	0.16-291.02	9 (13.2)
	Total DEs	68	0.09	0.19	0.41	0.66	0.91	0.01-1.88	0 (0.0)
Observed 24-hr creatinine excretion[h]	Total DAPs	68	1.00	1.50	3.79	8.63	18.80	0.47-200.54	9 (13.2)
	Total DMs	68	0.78	1.26	3.20	8.09	18.38	0.31-200.08	9 (13.2)
	Total DEs	68	0.13	0.24	0.39	0.70	0.91	0.01-2.67	0 (0.0)

[a]n=50 child-days with 24-hour samples; 69 non-FMV and 54 FMV spot samples from either 24-hour sampling period. [b]60% of estimated OP exposure attributed to nearby agricultural use and 40% of estimated OP exposure attributed to diet. [c]24-hour samples reflect collection of all non-FMV and FMV spot samples for that 24-hour period (4 samples lacked non-FMV spot and 5 samples lacked FMV spot). [d]BMD_{10}/100 of index chemical (chlorpyrifos) = 14.8 ug/kg/day. 100-fold uncertainty factor applied to account for intra- and interspecies variability. [e]Dose estimates from spot samples multiplied by expected 24-hr urine output volume based on reference values. [f]Dose estimates from spot pot samples multiplied by observed 24-hr urine output volume (from mean volume of 24-hr urine samples from that participant across the two sampling periods.) [g]Dose estimates from spot pot samples multiplied by expected 24-hr urine output volume based on observed and reference creatinine excretion in spot samples. [h]Dose estimates from spot samples multiplied by expected 24-hr urine output volume based on observed 24-hr creatinine excretion. [i]Average samples reflect collection of 69 non-FMV and 54 FMV spot samples from 41 child-days that provided both a non-FMV and FMV spot sample in the same 24-hour period (n=68 samples with average of non-FMV and FMV spot samples collected in the same 24-hour period).

Table 2.3. Modeling of 24-hour dose using same-day spot urine samples as predictors (log_{10}-transformmed) (n=25 children[a]).

Type of spot sample/metabolite excretion units	Metabolite type	n	β (95% CI)	Intercept	Model R^2	RMSE	ICC
Non-FMV spot							
Expected 24-hr urine volume[b]	Total DAPs	68	0.23 (-0.02, 0.47)	0.53	0.09	0.43	0.14
	Total DMs	68	0.25 (0.00, 0.49)	0.47	0.09	0.46	0.16
	Total DEs	68	0.31 (0.15, 0.47)	-0.21	0.20	0.40	0.36
Observed 24-hr urine volume[c]	Total DAPs	68	0.43 (0.21, 0.65)	0.41	0.25	0.39	0.45
	Total DMs	68	0.47 (0.28, 0.65)	0.36	0.28	0.41	0.48
	Total DEs	68	0.35 (0.17, 0.54)	-0.16	0.28	0.38	0.40
Expected 24-hr creatinine excretion[d]	Total DAPs	68	0.43 (0.23, 0.63)	0.38	0.33	0.37	0.54
	Total DMs	68	0.46 (0.29, 0.63)	0.33	0.36	0.39	0.57
	Total DEs	68	0.28 (0.11, 0.46)	-0.23	0.18	0.41	0.35
Observed 24-hr creatinine excretion[e]	Total DAPs	68	0.51 (0.30, 0.73)	0.34	0.38	0.35	0.59
	Total DMs	68	0.54 (0.36, 0.72)	0.30	0.41	0.37	0.62
	Total DEs	68	0.37 (0.17, 0.57)	-0.18	0.38	0.38	0.44
FMV spot							
Expected 24-hr urine volume[b]	Total DAPs	53	0.64 (0.28, 0.91)	0.26	0.40	0.38	0.63
	Total DMs	53	0.71 (0.46, 0.95)	0.21	0.43	0.41	0.65
	Total DEs	53	0.42 (0.23, 0.62)	-0.26	0.29	0.33	0.51
Observed 24-hr urine volume[c]	Total DAPs	53	0.70 (0.56, 0.84)	0.16	0.68	0.28	0.82
	Total DMs	53	0.66 (0.51, 0.81)	0.17	0.66	0.32	0.80
	Total DEs	53	0.44 (0.24, 0.63)	-0.22	0.32	0.32	0.55
Expected 24-hr creatinine excretion[d]	Total DAPs	53	0.69 (0.56, 0.82)	0.25	0.65	0.29	0.79
	Total DMs	53	0.65 (0.51, 0.79)	0.26	0.63	0.33	0.76
	Total DEs	53	0.43 (0.22, 0.64)	-0.16	0.28	0.33	0.50
Observed 24-hr creatinine excretion[e]	Total DAPs	53	0.73 (0.56, 0.89)	0.23	0.68	0.28	0.81
	Total DMs	53	0.68 (0.51, 0.85)	0.24	0.65	0.32	0.78
	Total DEs	53	0.44 (0.23, 0.64)	-0.16	0.30	0.32	0.51
Average of non-FMV and FMV spot[f]							
Expected 24-hr urine volume[b]	Total DAPs	67	0.73 (0.43, 1.03)	0.23	0.40	0.37	0.47
	Total DMs	67	0.76 (0.43, 1.10)	0.21	0.41	0.41	0.49
	Total DEs	67	0.65 (0.42, 0.88)	-0.20	0.48	0.29	0.54

Observed 24-hr urine volume[c]	Total DAPs	67	0.92 (0.77, 1.06)	0.02	0.78	0.23	0.60
	Total DMs	67	0.91 (0.76, 1.05)	0.02	0.78	0.25	0.80
	Total DEs	67	0.69 (0.46, 0.92)	-0.14	0.53	0.27	0.78
Expected 24-hr creatinine excretion[d]	Total DAPs	67	0.78 (0.60, 0.96)	0.15	0.72	0.26	0.73
	Total DMs	67	0.79 (0.63, 0.96)	0.12	0.74	0.28	0.79
	Total DEs	67	0.62 (0.34, 0.90)	-0.12	0.44	0.31	0.64
Observed 24-hr creatinine excretion[e]	Total DAPs	67	0.89 (0.75, 1.03)	0.07	0.80	0.22	0.79
	Total DMs	67	0.89 (0.76, 1.02)	0.06	0.81	0.23	0.81
	Total DEs	67	0.44 (0.17, 0.71)	-0.20	0.29	0.35	0.48

[a]n=49 child-days with 24-hour samples; 68 non-FMV and 53 FMV spot samples from either 24-hour sampling period. [b]Spot samples multiplied by expected 24-hr urine output volume based on reference values. [c]Spot samples multiplied by observed 24-hr urine output volume (from mean volume of 24-hr urine samples from that participant across the two sampling periods.) [d]Spot samples multiplied by expected 24-hr urine output volume based on observed and reference creatinine excretion in spot samples. [e]Spot samples multiplied by expected 24-hr urine output volume based on observed creatinine excretion (from mean 24-hr creatinine from that participant across the two sampling periods). [f]Average samples reflect collection of 68 non-FMV and 53 FMV spot samples from 41 child-days that provided both a non-FMV and FMV spot sample in the same 24-hour period (n=67 samples with average of non-FMV and FMV spot samples collected in the same 24-hour period).

2.6 Supporting Information

Table S2.1. Year of United States Department of Agriculture (USDA) Pesticide Data Program (PDP) food residue data used for commodities examined in dietary assessment[a]

	Year					
Commodity	2002	2003	2004	2005	2010	2012
Apple			X			
Apple juice[b]	X					
Avocado						X
Banana	X					
Broccoli	X					
Cabbage					X	
Canned/frozen/jar fruit (used canned peaches)			X			
Canned/frozen/jar vegetables (used average of canned green beans and canned spinach)			X			
Cantaloupe			X			
Carrots	X					
Grape			X			
Green beans			X			
Lettuce			X			
Mango					X	
Orange			X	X		
Orange juice			X			
Peach	X	X				
Potatoes	X					
Spinach		X				
Strawberry			X			
Sweet green pepper			X			
Sweet potatoes			X			
Tomatoes			X			
Watermelon				X		
Winter squash			X			

[a]Used data from 2004 (when available) or most proximate year.
[b]Data for the pesticides methyl parathion, disulfoton, methidathion, and oxydemeton methyl used from apple juice measurements in 2012, as these pesticides were not measured in 2002.

Table S2.2. Estimated cumulative OP chlorpyrifos equivalent dose (µg/kg/day) based on nearby agricultural pesticide use (*n*=25 children[a]).

Type of spot sample/metabolite excretion units	Metabolite type	n	Percentiles					Range	Estimates exceeding index chemical's BMD_{10}/100 (%)[c]
			10th	25th	50th	75th	90th		
24-hour urine samples[b]									
	Total DAPs	50	1.27	2.12	4.14	14.31	29.25	0.87-222.71	12 (24.0)
	Total DMs	50	0.97	1.33	3.59	14.25	21.15	0.58-222.29	12 (24.0)
	Total DEs	50	0.11	0.28	0.54	0.99	1.28	0.01-3.92	0 (0.0)
Non-FMV spot									
Expected 24-hr urine volume[d]	Total DAPs	69	0.22	0.44	1.89	4.37	13.36	0.17-43.75	5 (7.2)
	Total DMs	69	0.20	0.36	1.38	3.23	11.50	0.12-35.71	3 (4.3)
	Total DEs	69	0.03	0.08	0.30	0.68	2.06	0.01-8.04	0 (0.0)
Observed 24-hr urine volume[e]	Total DAPs	69	0.68	1.47	3.15	9.70	20.24	0.32-296.42	9 (13.0)
	Total DMs	69	0.59	1.08	3.03	3.63	18.50	0.21-296.28	8 (11.6)
	Total DEs	69	0.02	0.06	0.25	0.77	1.58	0.01-4.52	0 (0.0)
Expected 24-hr creatinine excretion[f]	Total DAPs	69	0.61	1.62	3.76	8.97	23.72	0.18-843.77	11 (15.9)
	Total DMs	69	0.49	1.39	3.72	8.51	23.40	0.15-843.37	9 (13.0)
	Total DEs	69	0.02	0.12	0.34	0.83	1.63	0.01-3.69	0 (0.0)
Observed 24-hr creatinine excretion[g]	Total DAPs	69	0.74	1.99	4.08	9.15	21.76	0.29-580.10	8 (11.6)
	Total DMs	69	0.67	1.58	3.31	8.61	21.26	0.18-579.83	8 (11.6)
	Total DEs	69	0.02	0.09	0.35	0.94	1.33	0.01-5.23	0 (0.0)
FMV spot									
Expected 24-hr urine volume[d]	Total DAPs	54	0.40	2.02	4.89	8.21	16.99	0.22-22.16	6 (11.1)
	Total DMs	54	0.31	1.42	4.30	6.58	14.39	0.13-20.13	5 (9.3)
	Total DEs	54	0.12	0.40	0.77	1.26	2.03	0.02-3.48	0 (0.0)
Observed 24-hr urine volume[e]	Total DAPs	54	1.21	2.09	5.98	17.64	32.37	0.24-82.60	16 (29.6)
	Total DMs	54	0.55	1.51	5.17	15.92	31.47	0.18-82.30	15 (27.8)
	Total DEs	54	0.02	0.06	0.25	0.78	1.58	0.01-4.52	0 (0.0)
Expected 24-hr creatinine excretion[f]	Total DAPs	54	0.89	1.59	4.16	12.08	27.70	0.24-124.52	12 (22.2)
	Total DMs	54	0.45	1.09	3.67	11.85	27.46	0.14-124.07	11 (20.4)
	Total DEs	54	0.09	0.25	0.47	0.78	1.10	0.02-1.53	0 (0.0)
Observed 24-hr creatinine excretion[g]	Total DAPs	54	0.87	1.87	4.17	10.39	26.97	0.14-77.01	10 (18.5)
	Total DMs	54	0.50	1.40	3.77	10.18	26.23	0.12-75.12	10 (18.5)
	Total DEs	54	0.09	0.23	0.45	0.76	1.26	0.02-2.02	0 (0.0)

[a]n=50 child-days with 24-hour samples; 69 non-FMV and 54 FMV spot samples from either 24-hr sampling period. [b]24-hour samples reflect collection of all non-FMV and FMV spot samples for that 24-hr period (4 samples lacked non-FMV spot and 5 samples lacked FMV spot). [c]BMD_{10}/100 of index chemical (chlorpyrifos) = 14.8 ug/kg/day. 100-fold uncertainty factor applied to account for intra- and interspecies variability. [d]Spot samples multiplied by expected 24-hr urine output volume based on reference values. [e]Spot samples multiplied by observed 24-hr urine output volume (from mean volume of 24-

hr urine samples from that participant across the two sampling periods.) [f]Spot samples multiplied by expected 24-hr urine output volume based on observed and reference creatinine excretion in spot samples. [g]Spot samples multiplied by expected 24-hr urine output volume based on observed creatinine excretion (from mean 24-hr creatinine from that participant across the two sampling periods).

Table S2.3. Estimated cumulative OP chlorpyrifos equivalent dose (µg/kg/day) based on diet (*n*=25 children[a]).

Type of spot sample/metabolite excretion units	Metabolite type	n	Percentiles					Range	Estimates exceeding index chemical's BMD_{10}/100 (%)[c]
			10th	25th	50th	75th	90th		
24-hour urine samples[b]									
	Total DAPs	50	0.45	0.79	1.72	3.57	6.67	0.28-32.97	1 (2.0)
	Total DMs	50	0.30	0.53	1.38	2.90	5.75	0.12-32.29	1 (2.0)
	Total DEs	50	0.07	0.18	0.35	0.57	0.76	0.01-2.59	0 (0.0)
Non-FMV spot									
Expected 24-hr urine volume[d]	Total DAPs	69	0.10	0.46	0.90	3.04	6.49	0.00-63.06	2 (2.9)
	Total DMs	69	0.07	0.32	0.69	2.40	6.31	0.00-62.72	1 (1.4)
	Total DEs	69	0.02	0.06	0.15	0.41	1.35	0.00-2.22	0 (0.0)
Observed 24-hr urine volume[e]	Total DAPs	69	0.10	0.41	1.15	2.95	6.49	0.00-43.25	1 (1.4)
	Total DMs	69	0.09	0.29	0.63	1.65	5.56	0.00-43.01	1(1.4)
	Total DEs	69	0.01	0.04	0.15	0.45	1.07	0.00-2.52	0 (0.0)
Expected 24-hr creatinine excretion[f]	Total DAPs	69	0.12	0.59	1.25	2.90	7.28	0.00-123.11	3 (4.3)
	Total DMs	69	0.10	0.43	0.90	2.37	6.61	0.00-122.43	3 (4.3)
	Total DEs	69	0.01	0.04	0.27	0.46	0.98	0.00-2.06	0 (0.0)
Observed 24-hr creatinine excretion[g]	Total DAPs	69	0.11	0.57	1.11	3.00	5.33	0.00-84.64	2 (2.9)
	Total DMs	69	0.09	0.40	0.89	1.90	4.75	0.00-84.17	2 (2.9)
	Total DEs	69	0.01	0.05	0.25	0.46	0.74	0.00-2.92	0 (0.0)
FMV spot									
Expected 24-hr urine volume[d]	Total DAPs	54	0.44	0.97	1.75	5.95	9.07	0.00-35.73	2 (3.7)
	Total DMs	54	0.11	0.60	1.34	5.30	7.73	0.00-34.12	2 (3.7)
	Total DEs	54	0.03	0.25	0.50	0.82	1.24	0.00-1.90	0 (0.0)
Observed 24-hr urine volume[e]	Total DAPs	54	0.26	0.71	1.87	4.20	9.03	0.00-17.95	1 (1.9)
	Total DMs	54	0.07	0.47	1.18	3.82	7.74	0.00-17.15	1 (1.9)
	Total DEs	54	0.03	0.16	0.34	0.60	1.09	0.00-2.23	0 (0.0)
Expected 24-hr creatinine excretion[f]	Total DAPs	54	0.25	0.56	1.30	2.77	2.45	0.00-17.70	1 (1.9)
	Total DMs	54	0.07	0.34	0.91	2.45	5.24	0.00-16.91	1 (1.9)
	Total DEs	54	0.02	0.12	0.30	0.48	0.71	0.00-1.23	0 (0.0)
Observed 24-hr creatinine excretion[g]	Total DAPs	54	0.21	0.57	1.26	3.14	5.85	0.00-14.06	0 (0.0)
	Total DMs	54	0.06	0.37	1.05	2.66	5.12	0.00-13.43	0 (0.0)
	Total DEs	54	0.02	0.14	0.27	0.43	0.72	0.00-1.51	0 (0.0)

[a]n=50 child-days with 24-hour samples; 69 non-FMV and 54 FMV spot samples from either 24-hr sampling period. [b]24-hour samples reflect collection of all non-FMV and FMV spot samples for that 24-hr period (4 samples lacked non-FMV spot and 5 samples lacked FMV spot). [c]BMD_{10}/100 of index chemical (chlorpyrifos) = 14.8 ug/kg/day. 100-fold uncertainty factor applied to account for intra- and interspecies variability. [d]Spot samples multiplied by expected 24-hr urine output volume based on reference values. [e]Spot samples multiplied by observed 24-hr urine output volume (from mean volume of 24-

hr urine samples from that participant across the two sampling periods.) [f]Spot samples multiplied by expected 24-hr urine output volume based on observed and reference creatinine excretion in spot samples. [g]Spot samples multiplied by expected 24-hr urine output volume based on observed creatinine excretion (from mean 24-hr creatinine from that participant across the two sampling periods).

Table S2.4. Estimated cumulative OP pesticide dose equivalents (ug/kg/day) from sensitivity analyses (limited to participants with 1 FMV per 24-hr sampling period (*n*=24 children[a]).

Type of spot sample/metabolite excretion units	Metabolite type	n	Percentiles					Range	Estimates exceeding index chemical's BMD_{10}/100 (%)[c]
			10th	25th	50th	75th	90th		
24-hour urine samples[b]									
	Total DAPs	41	1.15	1.67	3.03	7.17	19.85	0.76-146.81	6 (14.6)
	Total DMs	41	0.79	1.11	2.68	6.41	17.02	0.60-146.29	5 (11.9)
	Total DEs	41	0.10	0.26	0.42	0.87	0.98	0.01-2.94	0 (0.0)
Non-FMV spot									
Expected 24-hr urine volume[d]	Total DAPs	58	0.24	0.72	1.54	4.43	10.14	0.12-30.96	4 (6.7)
	Total DMs	58	0.21	0.61	1.29	4.27	8.19	0.07-26.97	3 (5.0)
	Total DEs	58	0.02	0.06	0.21	0.61	1.88	0.01-5.72	0 (0.0)
Observed 24-hr urine volume[e]	Total DAPs	58	0.46	1.17	2.02	5.68	14.75	0.29-195.15	5 (8.6)
	Total DMs	58	0.41	0.80	1.86	4.68	12.62	0.16-194.97	3 (5.0)
	Total DEs	58	0.02	0.05	0.22	0.60	1.30	0.01-3.72	0 (0.0)
Expected 24-hr creatinine excretion[f]	Total DAPs	58	0.57	1.26	2.91	5.88	14.26	0.30-555.50	5 (8.6)
	Total DMs	58	0.39	1.04	2.52	5.53	14.15	0.16-554.99	3 (5.0)
	Total DEs	58	0.03	0.11	0.33	0.72	1.39	0.01-3.04	0 (0.0)
Observed 24-hr creatinine excretion[g]	Total DAPs	58	0.54	1.59	3.08	5.47	10.66	0.25-381.92	4 (6.7)
	Total DMs	58	0.47	1.27	2.31	4.78	10.12	0.14-381.57	4 (6.7)
	Total DEs	58	0.03	0.07	0.31	0.62	1.01	0.01-3.61	0 (0.0)
FMV spot									
Expected 24-hr urine volume[d]	Total DAPs	37	0.52	1.99	3.41	6.32	12.02	0.23-15.06	1 (2.8)
	Total DMs	37	0.44	1.33	2.80	5.95	10.94	0.19-13.50	0 (0.0)
	Total DEs	37	0.08	0.37	0.62	1.01	1.56	0.02-2.59	0 (0.0)
Observed 24-hr urine volume[e]	Total DAPs	37	1.02	1.47	3.45	11.63	22.45	0.27-53.37	8 (22.2)
	Total DMs	37	0.49	1.10	3.16	10.81	23.71	0.15-52.98	8 (22.2)
	Total DEs	37	0.09	0.31	0.51	0.81	1.24	0.01-2.29	0 (0.0)
Expected 24-hr creatinine excretion[f]	Total DAPs	37	0.76	1.11	2.11	7.96	18.75	0.35-80.46	5 (13.9)
	Total DMs	37	0.39	0.78	3.09	7.64	18.20	0.12-79.87	5 (13.9)
	Total DEs	37	0.08	0.24	0.40	0.58	0.85	0.01-1.11	0 (0.0)
Observed 24-hr creatinine excretion[g]	Total DAPs	37	0.71	1.47	2.67	6.89	18.81	0.34-43.09	7 (19.4)
	Total DMs	37	0.34	0.98	2.40	6.56	18.38	0.12-42.78	6 (16.7)
	Total DEs	37	0.07	0.20	0.33	0.50	0.87	0.01-1.12	0 (0.0)
Average of non-FMV and FMV spots[h]									
	Total DAPs	48	0.52	1.54	3.30	5.00	7.95	0.22-21.18	2 (4.0)

Expected 24-hr urine volume[d]	Total DAPs	48	0.40	1.18	2.67	4.10	6.70	0.13-18.96	2 (4.0)
	Total DMs	48	0.09	0.23	0.51	0.82	1.42	0.02-3.52	0 (0.0)
	Total DEs	48	1.01	1.44	3.70	8.92	20.37	0.77-109.80	5 (10.0)
Observed 24-hr urine volume[e]	Total DAPs	48	0.88	1.18	3.17	7.25	18.67	0.44-109.34	5 (10.0)
	Total DMs	48	0.08	0.18	0.47	0.77	1.04	0.01-2.27	0 (0.0)
	Total DEs	48	0.94	1.29	2.81	2.58	14.45	0.71-291.70	4 (8.3)
Expected 24-hr creatinine excretion[f]	Total DAPs	48	0.69	1.05	2.44	6.38	13.43	0.43-291.02	4 (8.3)
	Total DMs	48	0.08	0.19	0.41	0.65	0.91	0.01-1.89	0 (0.0)
	Total DEs	48	1.00	1.55	2.86	7.04	15.99	0.61-200.55	5 (10.0)
Observed 24-hr creatinine excretion[g]	Total DAPs	48	0.87	1.30	2.63	6.54	15.72	0.32-200.08	5 (10.0)
	Total DMs	48	0.09	0.16	0.34	0.58	0.74	0.01-2.24	0 (0.0)
	Total DEs	48							

[a]n=41 child-days with 24-hour samples; 58 non-FMV and 37 FMV spot samples from either 24-hour sampling period.[b]24-hour samples reflect collection of all non-FMV and FMV spot samples for that 24-hour period. [c]BMD_{10}/100 of index chemical (chlorpyrifos) = 14.8 ug/kg/day. 100-fold uncertainty factor applied to account for intra- and interspecies variability. [d]Dose estimates from spot samples multiplied by expected 24-hr urine output volume based on reference values. [e]Dose estimates from spot samples multiplied by observed 24-hr urine output volume (from mean volume of 24-hr urine samples from that participant across the two sampling periods.) [e]Dose estimates from spot samples multiplied by expected 24-hr urine output volume based on observed and reference creatinine excretion in spot samples. [f]Dose estimates from spot samples multiplied by expected 24-hr urine output volume based on observed 24-hr creatinine excretion. [h]Average samples reflect collection of 69 non-FMV and 54 FMV spot samples from 41 child-days that provided both a non-FMV and FMV spot sample in the same 24-hour period (n=68 samples with average of non-FMV and FMV spot samples collected in the same 24-hour period).

Table S2.5. Modeling of 24-hour dose using same-day spot urine samples as predictors (log_{10}-transformmed) from sensitivity analyses (limited to participants with 1 FMV per 24-hr sampling period) (*n*=24 children[a]).

Type of spot sample/metabolite excretion units	Metabolite type	n	β (95% CI)	Intercept	Model R^2	RMSE	ICC
Non-FMV spot							
Expected 24-hr urine volume[b]	Total DAPs	57	0.26 (0.03, 0.48)	0.49	0.12	0.40	0.20
	Total DMs	57	0.26 (0.03, 0.50)	0.43	0.12	0.43	0.20
	Total DEs	57	0.37 (0.23, 0.52)	-0.18	0.27	0.41	0.44
Observed 24-hr urine volume[c]	Total DAPs	57	0.46 (0.23, 0.70)	0.37	0.28	0.36	0.47
	Total DMs	57	0.49 (0.30, 0.69)	0.33	0.31	0.38	0.50
	Total DEs	57	0.41 (0.24, 0.59)	-0.14	0.37	0.38	0.49
Expected 24-hr creatinine excretion[d]	Total DAPs	57	0.53 (0.31, 0.75)	0.30	0.40	0.33	0.61
	Total DMs	57	0.54 (0.36, 0.72)	0.27	0.42	0.35	0.63
	Total DEs	57	0.36 (0.20, 0.51)	-0.22	0.25	0.41	0.43
Observed 24-hr creatinine excretion[e]	Total DAPs	57	0.64 (0.43, 0.86)	0.25	0.47	0.31	0.67
	Total DMs	57	0.64 (0.46, 0.83)	0.24	0.49	0.33	0.68
	Total DEs	57	0.44 (0.26, 0.62)	-0.16	0.36	0.38	0.53
FMV spot							
Expected 24-hr urine volume[b]	Total DAPs	36	0.61 (0.34, 0.88)	0.25	0.37	0.38	0.61
	Total DMs	36	0.65 (0.39, 0.92)	0.20	0.40	0.41	0.63
	Total DEs	36	0.54 (0.28, 0.79)	-0.25	0.36	0.36	0.59
Observed 24-hr urine volume[c]	Total DAPs	36	0.70 (0.56, 0.84)	0.11	0.70	0.26	0.82
	Total DMs	36	0.63 (0.44, 0.83)	0.13	0.64	0.31	0.78
	Total DEs	36	0.56 (0.29, 0.83)	-0.21	0.39	0.35	0.62
Expected 24-hr creatinine excretion[d]	Total DAPs	36	0.69 (0.55, 0.82)	0.21	0.65	0.29	0.79
	Total DMs	36	0.61 (0.43, 0.79)	0.23	0.59	0.33	0.75
	Total DEs	36	0.62 (0.35, 0.88)	-0.10	0.39	0.35	0.61
Observed 24-hr creatinine excretion[e]	Total DAPs	36	0.75 (0.60, 0.90)	0.18	0.69	0.26	0.83
	Total DMs	36	0.66 (0.45, 0.87)	0.21	0.63	0.32	0.77
	Total DEs	36	0.62 (0.38, 0.87)	-0.10	0.42	0.34	0.64
Average of non-FMV and FMV spots[f]							
Expected 24-hr urine volume[b]	Total DAPs	49	0.59 (0.32, 0.86)	0.26	0.34	0.37	0.57
	Total DMs	49	0.60 (0.31, 0.90)	0.23	0.34	0.40	0.56
	Total DEs	49	0.66 (0.43, 0.90)	-0.21	0.49	0.32	0.69
	Total DAPs	49	0.89 (0.73, 1.05)	-0.01	0.79	0.21	0.88

Observed 24-hr urine volume[c]	Total DMs	49	0.87 (0.70, 1.04)	0.00	0.78	0.23	0.88
	Total DEs	49	0.69 (0.44, 0.45)	-0.17	0.54	0.30	0.74
Expected 24-hr creatinine excretion[d]	Total DAPs	49	0.85 (0.66, 1.03)	0.08	0.75	0.23	0.87
	Total DMs	49	0.85 (0.68, 1.02)	0.07	0.77	0.23	0.88
	Total DEs	49	0.67 (0.38, 0.95)	-0.14	0.45	0.33	0.68
Observed 24-hr creatinine excretion[e]	Total DAPs	49	0.97 (0.79, 1.14)	0.00	0.83	0.19	0.91
	Total DMs	49	0.95 (0.79, 1.12)	0.00	0.83	0.19	0.91
	Total DEs	49	0.70 (0.42, 0.98)	-0.08	0.47	0.33	0.67

[a]n=40 child-days with 24-hour samples; 57 non-FMV and 36 FMV spot samples from either 24-hour sampling period. [b]Spot samples multiplied by expected 24-hr urine output volume based on reference values. [c]Spot samples multiplied by observed 24-hr urine output volume (from mean volume of 24-hr urine samples from that participant across the two sampling periods.) [d]Spot samples multiplied by expected 24-hr urine output volume based on observed and reference creatinine excretion in spot samples. [e]Spot samples multiplied by expected 24-hr urine output volume based on observed creatinine excretion (from mean 24-hr creatinine from that participant across the two sampling periods). [f]Average samples reflect collection of 68 non-FMV and 53 FMV spot samples from 41 child-days that provided both a non-FMV and FMV spot sample in the same 24-hour period (n=67 samples with average of non-FMV and FMV spot samples collected in the same 24-hour period).

Table S2.6. Estimated cumulative OP pesticide dose equivalents (ug/kg/day) from sensitivity analyses (limited to participants with collection of 100% of samples within a 24-hr sampling period) (*n*=15 children[a]).

Type of spot sample/metabolite excretion units	Metabolite type	n	Percentiles					Range	Estimates exceeding index chemical's BMD_{10}/100 (%)[c]
			10th	25th	50th	75th	90th		
24-hour urine samples[b]									
	Total DAPs	22	1.17	1.71	3.07	6.78	19.85	0.89-146.81	3 (13.6)
	Total DMs	22	0.83	1.00	2.77	6.22	17.02	0.68-146.29	3 (13.6)
	Total DEs	22	0.12	0.30	0.43	0.63	0.97	0.05-2.94	0 (0.0)
Non-FMV spot									
Expected 24-hr urine volume[d]	Total DAPs	31	0.45	1.13	2.32	8.16	10.14	0.12-27.23	2 (6.5)
	Total DMs	31	0.37	1.02	1.94	6.38	8.19	0.07-26.97	2 (6.5)
	Total DEs	31	0.06	0.16	0.42	0.87	1.88	0.04-2.72	0 (0.0)
Observed 24-hr urine volume[e]	Total DAPs	31	0.77	1.17	3.21	8.27	11.42	0.36-195.15	2 (6.5)
	Total DMs	31	0.41	0.76	1.91	7.37	9.94	0.25-194.97	1 (3.3)
	Total DEs	31	0.05	0.18	0.41	1.13	1.30	0.02-3.72	0 (0.0)
Expected 24-hr creatinine excretion[f]	Total DAPs	31	0.71	1.55	3.44	7.32	11.37	0.32-555.50	3 (9.7)
	Total DMs	31	0.39	1.01	2.48	7.28	9.98	0.24-554.99	1 (3.3)
	Total DEs	31	0.04	0.23	0.64	0.96	1.47	0.03-3.04	0 (0.0)
Observed 24-hr creatinine excretion[g]	Total DAPs	31	0.77	1.66	3.20	7.54	10.89	0.42-381.92	2 (6.5)
	Total DMs	31	0.43	1.09	2.02	5.70	10.82	0.26-381.57	2 (6.5)
	Total DEs	31	0.06	0.15	0.51	0.74	1.14	0.02-3.61	0 (0.0)
FMV spot									
Expected 24-hr urine volume[d]	Total DAPs	21	0.96	1.70	3.17	5.70	6.32	0.31-13.59	0 (0.0)
	Total DMs	21	0.53	1.33	2.63	4.78	5.95	0.19-11.27	0 (0.0)
	Total DEs	21	0.12	0.38	0.60	0.81	1.08	0.04-2.32	0 (0.0)
Observed 24-hr urine volume[e]	Total DAPs	21	1.33	1.67	4.14	9.80	19.01	0.74-36.29	3 (14.3)
	Total DMs	21	0.62	1.16	3.75	9.43	16.28	0.39-35.88	3 (14.3)
	Total DEs	21	0.12	0.35	0.51	0.72	0.85	0.06-2.73	0 (0.0)
Expected 24-hr creatinine excretion[f]	Total DAPs	21	0.78	1.09	2.53	5.31	14.07	0.63-39.07	2 (9.5)
	Total DMs	21	0.41	1.01	2.52	4.78	13.13	0.33-38.63	2 (9.5)
	Total DEs	21	0.09	0.24	0.37	0.59	0.76	0.02-0.93	0 (0.0)
Observed 24-hr creatinine excretion[g]	Total DAPs	21	0.80	1.47	3.42	5.40	14.83	0.36-26.95	3 (14.3)
	Total DMs	21	0.38	1.14	3.40	4.99	13.79	0.25-26.64	2 (9.5)
	Total DEs	21	0.08	0.20	0.31	0.38	0.87	0.02-0.99	0 (0.0)
Average of non-FMV and FMV spots[h]									
	Total DAPs	25	0.46	1.55	3.18	5.75	8.92	0.22-19.63	1 (4.0)

Expected 24-hr urine volume[d]	Total DAPs	25	0.97	1.45	4.28	7.22	13.97	0.91-109.80	2 (8.0)
	Total DMs	25	0.86	0.98	3.40	6.91	12.22	0.44-109.34	2 (8.0)
	Total DEs	25	0.09	0.44	0.52	0.82	0.98	0.08-2.27	0 (0.0)
Observed 24-hr urine volume[e]	Total DAPs	25	0.82	1.33	2.47	8.07	12.52	0.71-291.70	2 (8.0)
	Total DMs	25	0.67	0.89	1.76	6.57	11.25	0.43-291.02	2 (8.0)
	Total DEs	25	0.10	0.39	0.52	0.81	1.14	0.06-1.88	0 (0.0)
Expected 24-hr creatinine excretion[f]	Total DAPs	25	1.00	1.53	2.99	7.99	15.99	0.61-200.55	3 (12.0)
	Total DMs	25	0.84	0.96	2.75	8.31	15.72	0.32-200.08	3 (12.0)
	Total DEs	25	0.13	0.24	0.50	0.61	0.84	0.08-2.24	0 (0.0)
Observed 24-hr creatinine excretion[g]									

[a]n=22 child-days with 24-hour samples; 31 non-FMV and 21 FMV spot samples from either 24-hour sampling period. [b]24-hour samples reflect collection of all non-FMV and FMV spot samples for that 24-hour period. [c]BMD_{10}/100 of index chemical (chlorpyrifos) = 14.8 ug/kg/day. 100-fold uncertainty factor applied to account for intra- and interspecies variability. [d]Dose estimates from spot samples multiplied by expected 24-hr urine output volume based on reference values. [e]Dose estimates from spot samples multiplied by observed 24-hr urine output volume (from mean volume of 24-hr urine samples from that participant across the two sampling periods.) [e]Dose estimates from spot samples multiplied by expected 24-hr urine output volume based on observed and reference creatinine excretion in spot samples. [f]Dose estimates from spot samples multiplied by expected 24-hr urine output volume based on observed 24-hr creatinine excretion. [h]Average samples reflect collection of 69 non-FMV and 54 FMV spot samples from 41 child-days that provided both a non-FMV and FMV spot sample in the same 24-hour period (n=68 samples with average of non-FMV and FMV spot samples collected in the same 24-hour period).

Table S2.7. Modeling of 24-hour dose using same-day spot urine samples as predictors (log_{10}-transformmed) from sensitivity analyses (limited to participants with collection of 100% of samples within a 24-hr sampling period) (*n*=14 children[a]).

Type of spot sample/metabolite excretion units	Metabolite type	n	β (95% CI)	Intercept	Model R^2	RMSE	ICC
Non-FMV spot							
Expected 24-hr urine volume[b]	Total DAPs	30	0.33 (0.06, 0.59)	0.42	0.21	0.35	0.40
	Total DMs	30	0.34 (0.07, 0.62)	0.35	0.22	0.38	0.42
	Total DEs	30	0.34 (0.03, 0.66)	-0.20	0.25	0.32	0.47
Observed 24-hr urine volume[c]	Total DAPs	30	0.55 (0.33, 0.77)	0.30	0.46	0.29	0.65
	Total DMs	30	0.58 (0.39, 0.79)	0.27	0.53	0.30	0.68
	Total DEs	30	0.32 (0.01, 0.63)	-0.21	0.25	0.32	0.46
Expected 24-hr creatinine excretion[d]	Total DAPs	30	0.53 (0.28, 0.78)	0.29	0.43	0.30	0.64
	Total DMs	30	0.55 (0.33, 0.79)	0.26	0.48	0.31	0.66
	Total DEs	30	0.27 (-0.03, 0.57)	-0.24	0.18	0.34	0.40
Observed 24-hr creatinine excretion[e]	Total DAPs	30	0.59 (0.35, 0.84)	0.25	0.49	0.28	0.69
	Total DMs	30	0.61 (0.40, 0.82)	0.23	0.54	0.29	0.71
	Total DEs	30	0.28 (-0.02, 0.59)	-0.24	0.17	0.34	0.40
FMV spot							
Expected 24-hr urine volume[b]	Total DAPs	20	0.32 (-0.20, 0.85)	0.39	0.10	0.39	0.32
	Total DMs	20	0.38 (-0.08, 0.84)	0.32	0.13	0.43	0.36
	Total DEs	20	0.41 (0.21, 0.61)	-0.29	0.21	0.34	0.46
Observed 24-hr urine volume[c]	Total DAPs	20	0.67 (0.42, 0.92)	0.11	0.57	0.27	0.74
	Total DMs	20	0.63 (0.35, 0.91)	0.12	0.58	0.30	0.75
	Total DEs	20	0.44 (0.20, 0.67)	-0.26	0.22	0.33	0.48
Expected 24-hr creatinine excretion[d]	Total DAPs	20	0.63 (0.41, 0.85)	0.26	0.55	0.28	0.72
	Total DMs	20	0.61 (0.37, 0.84)	0.25	0.57	0.31	0.72
	Total DEs	20	0.38 (0.14, 0.63)	-0.21	0.25	0.33	0.46
Observed 24-hr creatinine excretion[e]	Total DAPs	20	0.67 (0.44, 0.90)	0.23	0.61	0.26	0.76
	Total DMs	20	0.64 (0.40, 0.88)	0.22	0.62	0.29	0.76
	Total DEs	20	0.38 (0.19, 0.56)	-0.22	0.20	0.34	0.43
Average of non-FMV and FMV spots[f]							
Expected 24-hr urine volume[b]	Total DAPs	24	0.39 (0.02, 0.75)	0.30	0.20	0.36	0.46
	Total DMs	24	0.39 (0.04, 0.74)	0.25	0.20	0.40	0.45
	Total DEs	24	0.73 (0.55, 0.91)	-0.21	0.57	0.25	0.71

Observed 24-hr urine volume[c]	Total DAPs	24	0.80 (0.59, 1.01)	0.03	0.67	0.23	0.81
	Total DMs	24	0.79 (0.55, 1.02)	0.03	0.71	0.24	0.83
	Total DEs	24	0.74 (0.58, 0.89)	-0.19	0.56	0.25	0.72
Expected 24-hr creatinine excretion[d]	Total DAPs	24	0.74 (0.47, 1.00)	0.10	0.68	0.23	0.82
	Total DMs	24	0.75 (0.51, 1.00)	0.08	0.73	0.24	0.85
	Total DEs	24	0.70 (0.40, 1.01)	-0.18	0.53	0.26	0.72
Observed 24-hr creatinine excretion[e]	Total DAPs	24	0.81 (0.59, 1.02)	0.06	0.76	0.20	0.87
	Total DMs	24	0.81 (0.63, 0.99)	0.05	0.80	0.20	0.89
	Total DEs	24	0.72 (0.46, 0.99)	-0.13	0.45	0.28	0.68

[a]n=21 child-days with 24-hour samples; 30 non-FMV and 20 FMV spot samples from either 24-hour sampling period. [b]Spot samples multiplied by expected 24-hr urine output volume based on reference values. [c]Spot samples multiplied by observed 24-hr urine output volume (from mean volume of 24-hr urine samples from that participant across the two sampling periods.) [d]Spot samples multiplied by expected 24-hr urine output volume based on observed and reference creatinine excretion in spot samples. [e]Spot samples multiplied by expected 24-hr urine output volume based on observed creatinine excretion (from mean 24-hr creatinine from that participant across the two sampling periods). [f]Average samples reflect collection of 68 non-FMV and 53 FMV spot samples from 41 child-days that provided both a non-FMV and FMV spot sample in the same 24-hour period (n=67 samples with average of non-FMV and FMV spot samples collected in the same 24-hour period).

Table S2.8. Estimated cumulative OP pesticide dose equivalents (ug/kg/day) from sensitivity analyses (in which 70% of OP pesticide exposure was attributed to diet) (*n*=25 children[a]).

Type of spot sample/metabolite excretion units	Metabolite type	n	Percentiles					Range	Estimates exceeding index chemical's BMD_{10}/100 (%)[c]
			10th	25th	50th	75th	90th		
24-hour urine samples[b]									
	Total DAPs	50	0.87	1.23	2.50	6.72	12.99	0.56-89.89	3 (6.0)
	Total DMs	50	0.60	0.83	2.28	6.39	12.28	0.39-89.29	3 (6.0)
	Total DEs	50	0.09	0.25	0.38	0.66	0.83	0.01-2.65	0 (0.0)
Non-FMV spot									
Expected 24-hr urine volume[d]	Total DAPs	69	0.19	0.72	1.32	4.27	8.92	0.08-45.15	3 (4.3)
	Total DMs	69	0.17	0.60	1.01	3.55	7.67	0.04-44.85	2 (2.9)
	Total DEs	69	0.03	0.07	0.18	0.52	1.39	0.01-3.97	0 (0.0)
Observed 24-hr urine volume[e]	Total DAPs	69	0.27	0.81	1.61	4.41	10.63	0.12-119.20	2 (2.9)
	Total DMs	69	0.26	0.63	1.33	3.85	9.84	0.10-118.99	2 (2.9)
	Total DEs	69	0.02	0.04	0.19	0.56	1.09	0.01-3.12	0 (0.0)
Expected 24-hr creatinine excretion[f]	Total DAPs	69	0.26	1.06	2.45	4.84	10.89	0.05-339.30	5 (7.2)
	Total DMs	69	0.20	0.75	1.61	4.56	9.80	0.04-338.71	5 (7.2)
	Total DEs	69	0.02	0.06	0.34	0.66	1.13	0.01-2.55	0 (0.0)
Observed 24-hr creatinine excretion[g]	Total DAPs	69	0.33	1.01	2.34	4.43	10.24	0.11-233.28	4 (5.8)
	Total DMs	69	0.26	0.87	1.89	4.04	9.52	0.09-232.87	3 (4.3)
	Total DEs	69	0.08	0.31	0.62	1.01	1.14	0.01-3.61	0 (0.0)
FMV spot									
Expected 24-hr urine volume[d]	Total DAPs	54	0.73	1.86	3.18	6.62	10.55	0.17-30.50	2 (3.7)
	Total DMs	54	0.59	1.22	2.18	6.06	8.93	0.09-28.80	1 (1.9)
	Total DEs	54	0.06	0.34	0.53	0.97	1.41	0.02-2.11	0 (0.0)
Observed 24-hr urine volume[e]	Total DAPs	54	0.64	1.24	3.03	8.26	15.52	0.14-31.45	7 (13.0)
	Total DMs	54	0.35	0.79	2.52	7.80	14.52	0.11-30.99	5 (9.3)
	Total DEs	54	0.06	0.22	0.45	0.70	1.15	0.01-2.48	0 (0.0)
Expected 24-hr creatinine excretion[f]	Total DAPs	54	0.59	0.89	2.46	5.89	12.20	0.13-47.41	5 (9.3)
	Total DMs	54	0.24	0.64	1.93	5.22	11.72	0.10-46.72	5 (9.3)
	Total DEs	54	0.06	0.17	0.36	0.54	0.83	0.01-1.32	0 (0.0)
Observed 24-hr creatinine excretion[g]	Total DAPs	54	0.60	1.13	2.33	5.47	11.82	0.08-27.56	4 (7.4)
	Total DMs	54	0.23	0.71	2.21	4.53	11.35	0.06-25.94	4 (7.4)
	Total DEs	54	0.07	0.20	0.33	0.64	0.87	0.01-1.62	0 (0.0)
Average of non-FMV and FMV spots[h]									
	Total DAPs	68	0.77	1.23	3.14	5.41	6.67	0.15-27.85	2 (2.9)

Expected 24-hr urine volume[d]	Total DMs	68	0.59	0.96	2.63	4.50	5.99	0.06-27.06	1 (1.5)
	Total DEs	68	0.09	0.29	0.48	0.71	1.12	0.02-2.44	0 (0.0)
Observed 24-hr urine volume[e]	Total DAPs	68	0.79	1.11	3.15	6.44	11.27	0.24-67.27	4 (5.9)
	Total DMs	68	0.60	0.85	2.70	5.94	10.60	0.16-66.73	4 (5.9)
	Total DEs	68	0.08	0.22	0.40	0.66	0.95	0.01-1.90	0 (0.0)
Expected 24-hr creatinine excretion[f]	Total DAPs	68	0.62	1.00	2.51	5.53	11.27	0.12-178.40	5 (7.4)
	Total DMs	68	0.43	0.71	2.20	4.97	10.60	0.08-177.61	5 (7.4)
	Total DEs	68	0.08	0.18	0.34	0.60	0.79	0.01-1.58	0 (0.0)
Observed 24-hr creatinine excretion[g]	Total DAPs	68	0.62	1.12	2.92	6.08	12.22	0.24-122.65	4 (5.9)
	Total DMs	68	0.47	0.85	2.46	5.51	11.73	0.15-122.11	4 (5.9)
	Total DEs	68	0.09	0.17	0.34	0.58	0.82	0.01-2.24	0 (0.0)

[a]n=50 child-days with 24-hour samples; 69 non-FMV and 54 FMV spot samples from either 24-hour sampling period.[b]24-hour samples reflect collection of all non-FMV and FMV spot samples for that 24-hour period (4 samples lacked non-FMV spot and 5 samples lacked FMV spot). [c]BMD_{10}/100 of index chemical (chlorpyrifos) = 14.8 ug/kg/day. 100-fold uncertainty factor applied to account for intra- and interspecies variability. [d]Dose estimates from spot samples multiplied by expected 24-hr urine output volume based on reference values. [e]Dose estimates from spot samples multiplied by observed 24-hr urine output volume (from mean volume of 24-hr urine samples from that participant across the two sampling periods.) [e]Dose estimates from spot samples multiplied by expected 24-hr urine output volume based on observed and reference creatinine excretion in spot samples. [f]Dose estimates from spot samples multiplied by expected 24-hr urine output volume based on observed 24-hr creatinine excretion. [h]Average samples reflect collection of 69 non-FMV and 54 FMV spot samples from 41 child-days that provided both a non-FMV and FMV spot sample in the same 24-hour period (n=68 samples with average of non-FMV and FMV spot samples collected in the same 24-hour period).

Table S2.9. Modeling of 24-hour dose using same-day spot urine samples as predictors (log_{10}-transformmed) from sensitivity analyses (in which 70% of OP pesticide exposure was attributed to diet) (*n*=25 children[a]).

Type of spot sample/metabolite excretion units	Metabolite type	n	β (95% CI)	Intercept	Model R^2	RMSE	ICC
Non-FMV spot							
Expected 24-hr urine volume[b]	Total DAPs	68	0.23 (0.01, 0.45)	0.41	0.10	0.40	0.21
	Total DMs	68	0.24 (0.04, 0.44)	0.34	0.10	0.43	0.22
	Total DEs	68	0.27 (0.11, 0.42)	-0.28	0.16	0.40	0.31
Observed 24-hr urine volume[c]	Total DAPs	68	0.37 (0.15, 0.58)	0.35	0.21	0.37	0.40
	Total DMs	68	0.40 (0.21, 0.59)	0.30	0.24	0.40	0.42
	Total DEs	68	0.32 (0.14, 0.50)	-0.23	0.24	0.38	0.35
Expected 24-hr creatinine excretion[d]	Total DAPs	68	0.37 (0.17, 0.56)	0.32	0.28	0.35	0.48
	Total DMs	68	0.39 (0.23, 0.56)	0.27	0.31	0.38	0.51
	Total DEs	68	0.25 (0.08, 0.42)	-0.30	0.15	0.40	0.31
Observed 24-hr creatinine excretion[e]	Total DAPs	68	0.45 (0.24, 0.66)	0.30	0.34	0.34	0.54
	Total DMs	68	0.47 (0.29, 0.65)	0.25	0.36	0.36	0.56
	Total DEs	68	0.33 (0.14, 0.52)	-0.24	0.24	0.38	0.40
FMV spot							
Expected 24-hr urine volume[b]	Total DAPs	53	0.63 (0.43, 0.82)	0.18	0.44	0.35	0.67
	Total DMs	53	0.66 (0.46, 0.86)	0.13	0.46	0.38	0.68
	Total DEs	53	0.39 (0.19, 0.58)	-0.30	0.35	0.33	0.48
Observed 24-hr urine volume[c]	Total DAPs	53	0.65 (0.52, 0.78)	0.15	0.53	0.28	0.78
	Total DMs	53	0.62 (0.48, 0.75)	0.15	0.61	0.32	0.76
	Total DEs	53	0.41 (0.21, 0.60)	-0.26	0.28	0.32	0.52
Expected 24-hr creatinine excretion[d]	Total DAPs	53	0.64 (0.50, 0.77)	0.24	0.59	0.30	0.74
	Total DMs	53	0.60 (0.47, 0.74)	0.23	0.57	0.34	0.72
	Total DEs	53	0.40 (0.20, 0.60)	-0.21	0.25	0.33	0.46
Observed 24-hr creatinine excretion[e]	Total DAPs	53	0.68 (0.53, 0.83)	0.22	0.62	0.29	0.76
	Total DMs	53	0.64 (0.49, 0.79)	0.22	0.60	0.33	0.74
	Total DEs	53	0.42 (0.21, 0.61)	-0.21	0.27	0.33	0.48
Average of non-FMV and FMV spots[f]							
Expected 24-hr urine volume[b]	Total DAPs	67	0.68 (0.39, 0.97)	0.18	0.42	0.34	0.64
	Total DMs	67	0.67 (0.33, 1.02)	0.16	0.40	0.38	0.63
	Total DEs	67	0.59 (0.34, 0.83)	-0.23	0.40	0.30	0.63
	Total DAPs	67	0.82 (0.63, 1.01)	0.07	0.70	0.24	0.84

Observed 24-hr urine volume[c]	Total DMs	67	0.82 (0.63, 1.01)	0.05	0.70	0.27	0.84
	Total DEs	67	0.63 (0.39, 0.87)	-0.17	0.46	0.29	0.68
Expected 24-hr creatinine excretion[d]	Total DAPs	67	0.69 (0.48, 0.90)	0.17	0.64	0.27	0.79
	Total DMs	67	0.71 (0.51, 0.91)	0.13	0.65	0.29	0.80
	Total DEs	67	0.55 (0.28, 0.82)	-0.17	0.36	0.31	0.59
Observed 24-hr creatinine excretion[e]	Total DAPs	67	0.82 (0.65, 0.99)	0.10	0.73	0.23	0.85
	Total DMs	67	0.82 (0.66, 0.99)	0.08	0.74	0.25	0.86
	Total DEs	67	0.64 (0.39, 0.89)	-0.14	0.43	0.29	0.65

[a]n=49 child-days with 24-hour samples; 68 non-FMV and 53 FMV spot samples from either 24-hour sampling period. [b]Spot samples multiplied by expected 24-hr urine output volume based on reference values. [c]Spot samples multiplied by observed 24-hr urine output volume (from mean volume of 24-hr urine samples from that participant across the two sampling periods.) [d]Spot samples multiplied by expected 24-hr urine output volume based on observed and reference creatinine excretion in spot samples. [e]Spot samples multiplied by expected 24-hr urine output volume based on observed creatinine excretion (from mean 24-hr creatinine from that participant across the two sampling periods). [f]Average samples reflect collection of 68 non-FMV and 53 FMV spot samples from 41 child-days that provided both a non-FMV and FMV spot sample in the same 24-hour period (n=67 samples with average of non-FMV and FMV spot samples collected in the same 24-hour period).

CHAPTER 3. Associations between pesticide mixtures applied near home during pregnancy and early childhood with adolescent behavioral and emotional problems in the CHAMACOS study

3.1 Introduction

Evidence from longitudinal cohort studies indicates that biomarkers of pesticide exposure and residential proximity to agricultural pesticide applications during pregnancy and early childhood may be associated with adverse child neurodevelopment, including poorer cognition[23-25,27,28,37] and increased hyperactivity/inattention[26,33,130] and traits related to autism spectrum disorders (ASD).[34,38,80,131] Despite relatively consistent findings for outcomes assessed during early and middle childhood, previous studies have only followed children up to age 12 years, and data gaps exist regarding the persistence of pesticide-neurodevelopment associations into adolescence and young adulthood.

Epidemiologic studies to date have focused primarily on exposure to single pesticides or pesticide classes at a time, which may result in biased measures of association due to co-pollutant confounding by other pesticides.[132] In particular, previous research has examined the neurodevelopmental impacts of exposure to organophosphate (OP) pesticides in isolation. These studies have largely relied on urinary biomarkers such as dialkylphosphate metabolites (DAPs), which are non-specific, to characterize exposure; less is known about the effects of specific OPs with varying levels of toxicity.[74] Additionally, agricultural use of pesticides such as pyrethroids, neonicotinoids, and glyphosate has increased substantially in the United States and globally in recent decades,[133-135] yet few longitudinal studies have examined their potential impacts on human health and neurobehavioral development.[28]

Bayesian methods have become increasingly utilized in epidemiologic analyses of chemical mixtures due to their ability to simultaneously model multiple highly correlated exposure variables.[132,136,137] A particular advantage of Bayesian Hierarchical Modeling (BHM) is that it allows correlated exposures to "borrow" information from each other,[138] resulting in more precise effect estimates.[136,137,139] These estimators also reduce the potential for extreme exposure-outcome associations, addressing concerns regarding multiple comparisons,[136,140,141] and produce highly interpretable results.

Because many pesticides lack biomarkers or are cost-prohibitive to analyze in biological samples, recent analyses have used geospatial methods to characterize potential exposure to a range of pesticides.[27,28,79,80] In the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort study, we are able to leverage California's unique and comprehensive Pesticide Use Reporting (PUR) database to characterize agricultural pesticide applications near participants' residences, allowing us to examine associations with potential exposure to mixtures of pesticides, including those that are now the most widely used in agriculture. In a previous analysis in our cohort, we found that participants living in the areas of highest cumulative pesticide use during the prenatal period had intelligence quotient (IQ) deficits of approximately 7 points at age 7 compared to those living in areas of the lowest pesticide use.[28]

Here, we investigate associations of agricultural applications of neurotoxic pesticides within 1 km of the home during pregnancy and early childhood with maternal- and self-reported behavioral and emotional problems at ages 16 and 18 years in the CHAMACOS cohort. This analysis extends previous research by employing BHM to examine associations with specific

pesticides while accounting for correlated co-exposures. This is the first study to examine associations of prenatal or early-life pesticide exposure with behavioral or emotional problems measured longitudinally into adolescence and young adulthood.

3.2 Methods

3.2.1 Study Population

CHAMACOS is a longitudinal birth cohort study investigating the developmental impacts of environmental exposures among children born in the Salinas Valley, an agricultural region of Monterey County, California. The initial cohort (CHAM1) included pregnant women who met eligibility criteria (≥18 years old, <20 weeks gestation, Spanish- or English-speaking, qualified for low-income health insurance, and planning to deliver at the county hospital). CHAM1 participants were recruited in community clinics serving predominantly low-income Latino patients in 1999-2000. Of the 1,130 eligible women, 601 (53.2%) agreed to participate in the study. Of the 601 women enrolled at baseline, 527 (88%) remained in the study and delivered a live-born singleton and 337 (56%) remained in the study through the child's 9-year assessment. In 2009-2011, we expanded the cohort and recruited an additional 305 9-year-old Salinas Valley residents whose mothers met eligibility criteria (≥18 years at delivery, Spanish- or English-speaking, qualified for low-income health insurance during pregnancy, delivered child in local hospital, and had sought prenatal care in the first trimester). CHAM2 participants were recruited via newspaper and radio announcements advertising a study on the health effects of pesticides and environmental chemicals at local elementary schools, churches, libraries, food banks, and community events. A total of 595 CHAMACOS participants (CHAM1 and CHAM2) remained in the cohort through the 16-year study visit. As of March 2020, when data collection was paused due to the COVID-19 pandemic, 478 CHAMACOS participants had also completed their 18-year study visits.

Mothers of CHAM1 participants were interviewed twice during pregnancy, after delivery, and throughout childhood. CHAM2 mothers completed a comprehensive baseline interview when their children were 9 years old. Mothers of CHAM1 and CHAM2 participants completed identical assessments when their children were 10.5, 12, 14, 16, and 18 years of age; CHAMACOS youth participants were interviewed directly starting at age 10.5 years. We restricted the current analyses to participants whose prenatal (n=814) or early childhood (n=443) residential history could be geocoded for pesticide exposure assessment and who had a maternal- or youth- reported neurobehavioral assessment from the 16-year (n=594) or 18-year (n=494) study visits. We excluded participants with medical conditions such as Down's syndrome, autism, and hydrocephalus that could affect neurodevelopmental assessments (n=6). The total sample size with data on the exposure and outcome for the 16-year analyses was 578 for prenatal and 428 for postnatal; the total for 18-year analyses was 476 for prenatal and 381 for postnatal.

The University of California Berkeley Committee for the Protection of Human Subjects approved all study activities and we obtained written informed consent from all mothers at all study visits. We obtained youth written assent at age 16 years and written consent at age 18 years.

3.2.2 Behavioral assessment

At the 16- and 18-year assessments, bilingual psychometricians administered the Behavior Assessment for Children, second edition (BASC-2) [142] to mothers in their dominant language and the youth completed the BASC-2 Self-Report of Personality (SRP). We examined

maternal- and youth-reported scores for four individual scales (hyperactivity, attention problems, depression, and anxiety) and the internalizing problems composite scale. In addition, we examined maternal-reported scores for the externalizing problems composite scale (there is no externalizing composite score for the youth-reported BASC-2 SRP). We examined BASC-2 age- and sex-standardized T-scores (M=50, SD=10).

3.2.3 Estimation of agricultural pesticide use

In order to characterize potential exposure to a range of pesticides, including those for which biomarkers do not exist, we used California's PUR database to characterize agricultural pesticide use near each participant's residence during the prenatal and early childhood (0-5 years) periods, as has been described previously.[27,28] We characterized agricultural applications of pesticides that 1) have evidence of neurotoxicity in humans or animals, 2) had more than 4,500 kg applied in Monterey County in the time period of interest, and 3) were used within 1 km of the home of at least 50% of CHAMACOS participants in the time period of interest (11 pesticides for prenatal period and 12 pesticides for postnatal period). We used the latitude and longitude coordinates from geocoded residential addresses, reported prospectively at all study visits for CHAM1 participants, and retrospectively at the 9- and 16-year visits from CHAM2 participants. We estimated the total amount of each pesticide that met these criteria applied within a 1 km radius of each residence. We selected a 1 km buffer because this distance has been used in previous epidemiologic analyses[27,28] and has been shown to be most strongly correlated with concentrations of agricultural pesticides from house-dust samples.[77,143] To account for the potential downwind transport of pesticides 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.[144] We calculated wind frequency using the daily proportion of time the wind blew from each of eight directions during each time period (pregnancy and 0-5 years). We determined the direction of each Public Land Survey System (PLSS) centroid relative to residences and weighted pesticide use in a section according to the percentage of time that the wind blew from that direction for each time period. All pesticide use estimates were $\log_2$-tranformed and thus measures of association correspond to a two-fold increase in pesticide use.

3.2.4 Covariate information

At each study visit, bilingual study staff administered structured questionnaires to ascertain participant characteristics. The following confounders were selected *a priori* using a directed acyclic graph [145]: maternal age (continuous), years spent in the United States (categorical: $\leq$5 years, >5 years but not born in US, born in US), education (categorical: $\leq 6^{th}$ grade, 7^{th}-12^{th} grade, completed high school), and marital status (dichotomous: not married/living as married vs. married/living as married) at the time of delivery. We also included the following predictors of the outcome *a priori*: maternal depression status at the 9-year assessment (categorical: yes vs. no) assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) [146], child sex (dichotomous) and exact age at assessment (continuous), Home Observation Measurement of the Environment-Short Form (HOME-SF)[147] z-score at the 10.5-year visit (continuous) to assess enrichment in the home, household income at the time of assessment (categorical: at or below poverty line vs. above poverty line), and language of interview assessment for maternal-reported outcomes (dichotomous: English vs. Spanish; all youth completed assessments in English).

3.2.5 Statistical analyses

We implemented a two-stage BHM[136,148-154] to examine exposure-outcome associations with all pesticides included simultaneously. In the first stage, we regressed each BASC outcome on the exposures and covariates in a single linear mixed-effects model with a random subject-specific effect as: $(E[Y \mid X,W, u]) = \alpha + X\beta + W\gamma + u$; where X is the vector of all pesticides, W is the vector of confounders, and u is a normally distributed subject-specific random effect. In the second stage, we modeled the exposure effects (β) as a function of an exchangeability matrix Z, coefficient vector π, and residual error δ (normally distributed with mean zero and variance τ^2) as: $\beta = Z\pi + \delta$. We used a Z matrix with indicator variables (0/1) for the class to which each individual pesticide belongs, incorporating our *a priori* expectation that pesticides from the same class would exert similar effects of the outcome. For the primary analyses, we included only pesticide classes that had >1 pesticide in the Z matrix (i.e., OPs). We specified vague second-stage priors for individual pesticides not included in the Z matrix. For the postnatal analyses, we included a second Z matrix in which we adjusted for the 11 pesticides that were included in the prenatal analyses. The Bayesian framework allowed us to automatically account for missing outcomes for any participants missing data from a particular BASC domain, but who completed a neurobehavioral assessment at 16 and/or 18 years. We present median β effect estimates and 95% Credible Intervals (CrIs) for each pesticide predicted from the first-stage model.

As suggested by previous work,[155] we specified vague priors on some model parameters (α, γ, π) and pre-specified the variance for δ (i.e., τ^2) based on background information. We selected a value of τ that assumed that β parameters would lie within $\pm$ 0.5 SD of the mean of the BASC outcome of interest in our population (i.e., from -5 to 5 in the normative sample). We specified models in a Fully Bayesian framework[138] and estimated the posterior distribution of all model parameters via Markov Chain Monte Carlo (MCMC) sampling.[156] We summarized the posterior distributions of these parameters by estimating the posterior median and 95% CrIs using Just Another Gibbs Sampler (JAGS).[157] Models were run with 50,000 iterations after an initial burn-in of 10,000. Convergence was assessed graphically using trace plots, autocorrelation plots, and density plots,[156] and statistically using the Geweke test[158] and Gelman-Rubin test statistic.[159] All analyses were conducted using R Version 3.6.2.

We conducted sex-specific analyses by including an interaction term between each pesticide and child sex in the first stage model. For sex-specific analyses, we included all pesticides in the second-stage model, as all pesticides would benefit from shrinkage due to the pesticide $\times$ sex interaction term (as compared to the primary analyses, where we only included pesticides with >1 pesticide in a class in the second-stage model, as described previously).

3.2.6 Sensitivity analyses

We examined the robustness of our results by conducting sensitivity analyses in which we varied the specification of the Z matrix. First, we used a Z matrix in which we included indicator variables (0/1) for the class to which each individual pesticide belongs (i.e., OPs, carbamates, pyrethroids, neonicotinoids, fungicides, herbicides; Table S3.1) for all pesticide classes, as opposed to excluding classes with only one pesticide from the Z matrix, as in the main analyses. In the second sensitivity analysis, we indicated whether each OP was a diethyl (DE) or dimethyl (DM) using a 0/1 indicator variable and incorporated the benchmark dose$_{10}$ (BMD$_{10}$), as used by the U.S. Environmental Protection Agency (EPA) for cumulative OP risk assessments[160] (Table S3.2). In addition to the hierarchical models, we also ran multivariable linear mixed-effects regression models in which we included all exposures simultaneously without specifying a

second-stage model.

3.3 Results

A total of 593 participants completed a maternal- or youth-reported BASC assessment at the 16 and/or 18-year study visits and provided residential history during pregnancy and/or childhood (ages 0-5 years). Most mothers were born in Mexico (87%) and nearly half had spent less than 5 years in the U.S. prior to delivery and had a sixth-grade education or less (Table 3.1). About 51% of the youth participants included in these analyses were girls.

The distributions of wind-adjusted neurotoxic pesticide applications within 1 km of the home during the prenatal and postnatal periods, as well as the total kilograms of pesticides applied in Monterey County in the years 2000 and 2005 (reflecting general trends in pesticide use during the prenatal and postnatal periods), are shown in Table 3.2. In general, applications of pesticides were highly correlated with each other during both the prenatal (Figure S3.1) and postnatal (Figure S3.2) periods. Individual OPs had some of the highest correlation coefficients (ρ=0.4-0.9 during both prenatal and postnatal periods). Correlations coefficients for individual pesticides ranged from 0.50-0.71 across the prenatal and postnatal periods (Table 3.2).

3.3.1 Associations with pesticide use during the prenatal period

We observed largely negligible associations between pesticide use near the home during pregnancy and neurobehavioral outcomes. There were some subtle associations of chlorpyrifos use and increased internalizing behaviors from both maternal- and youth-report. More specifically, each two-fold increase in chlorpyrifos applications was associated with increased BASC-2 T-scores for maternal-reported depression (β=1.0, 95% CrI: -0.2, 2.1; Table 3.3) and youth-reported depression and internalizing problems (β =1.1, 95% CrI: -0.1, 2.3; β = 1.0, 95% CrI: -0.2, 2.2; respectively; Table 3.4). For maternal depression only, we observed stronger associations among girls than boys (boys: β=0.7, 95% CrI: -0.7, 2.1; girls: β=1.7, 95% CrI: 0.1, 3.3; Table S3). We also observed some isolated associations of increased youth-reported attention problems in association with applications of the OPs diazinon and dimethoate during pregnancy (β=1.2, 95% CrI: 0.0, 2.5 and β=1.9, 95% CrI: 0.0, 3.6, respectively; Table 3.4).

In contrast, we found associations of use of the neonicotinoid imidacloprid with fewer maternal- and youth-reported behavioral and emotional problems (Tables 3.3 and3. 4), particularly for girls (Supplemental Tables S3.3 and S3.4). Among all participants, each two-fold increase in imidacloprid use during the prenatal period was associated with decreased maternal-reported attention problems (β=-2.4, 95% CrI: -5.3, 0.4; Table 3.3), with evidence of stronger inverse associations among girls (boys: β=-2.2, 95% CrI: -4.8, 0.5; girls: β=-4.5, 95% CrI: -7.9, -0.9; Table S3.3). Imidacloprid use was also associated with decreased maternal-reported internalizing problems and depression among girls, as well as youth-reported internalizing problems and anxiety among girls. We also observed that use of the pyrethroid permethrin was associated with fewer youth-reported attention problems among all participants (β=-1.9, 95% CrI: -4.2, 0.3; Table 3.4).

3.3.2 Associations with pesticide use during childhood

The most consistent associations we observed for pesticide use during the postnatal period were for glyphosate and maternal-and youth-reported internalizing behaviors. Each two-fold increase in glyphosate applications was associated with increased maternal-report of

internalizing problems and anxiety (β=1.3, 95% CrI: 0.2, 2.3 and β=1.2, 95% CrI: 0.2, 2.3, respectively; Table 3.5) and youth-report of depression (β=1.2, 95% CrI: 0.2, 2.2; Table 3.6), with trends of stronger associations among girls (Tables S3.5 and S3.6). Notably, in contrast, chlorpyrifos and naled were each associated with decreased maternal-reported anxiety (β=-1.7, 95% CrI: -3.3, -0.1 and β=-1.2, 95% CrI: -2.5, 0.0, respectively; Table 5), with stronger inverse associations for chlorpyrifos and maternal-reported anxiety among girls (boys: β=-0.9, 95% CrI: -2.7, 0.9; girls: β=-2.2, 95% CrI: -4.1, -0.3; Table S3.5).

We observed some associations of OP use postnatally and increased externalizing problems, though there were no consistent trends. For example, dimethoate was associated with increased youth-reported hyperactivity (β=2.0, 95% CrI: 0.0, 3.9) and naled was associated with increased youth-reported attention problems (β=1.2, 95% CrI: 0.1, 2.4). Additionally, acephate was associated with increased maternal-reported hyperactivity (β=1.6, 95% CrI: 0.1, 3.0). We also observed some inverse associations, with the OPs oxydemeton methyl and malathion associated with decreased maternal- and youth-reported attention problems, respectively (β=-2.3, 95% CrI: -4.6, 0.2 and β=-0.9, 95% CrI: -1.8, 0.1; respectively).

3.3.3 Sensitivity analysis

Results from our sensitivity analyses were robust to variations of the specification of the Z matrix, and our overall interpretations were qualitatively the same (data not shown). Results were also very similar from multivariable models in which we included all exposure variables simultaneously without specifying the second-stage model (Tables S3.7-S3.8 for prenatal analyses and Tables S3.9-S3.10 for postnatal analyses). Confidence intervals were slightly wider for some pesticides in multivariable linear mixed-effects regression models; however, our overall interpretation of the results was consistent with findings from the hierarchical analyses.

3.4 Discussion

We observed mostly null associations of agricultural pesticide use near the home during critical periods of brain development and behavioral and emotional problems at ages 16 and 18 years among participants living in an intensive agricultural region. We observed some associations of use of the OP chlorpyrifos near the home during pregnancy and use of glyphosate near the home during early childhood with increased internalizing problems, however effect estimates were small. We also observed trends of fewer maternal- and youth-reported internalizing behaviors and attention problems in association with imidacloprid use near the home during pregnancy. This is the first study to examine longitudinal associations of agricultural pesticide use near the home during pregnancy or early childhood with behavioral problems during adolescence or young adulthood, a critical time for the manifestation of these outcomes [161]. Our work also extends previous research by investigating potential exposure to multiple classes of pesticides.

Previous studies examining associations of prenatal or postnatal OP exposure and child neurodevelopment have largely assessed exposure using non-specific DAP metabolites, limiting inferences regarding associations with specific OP pesticides. In this analysis, we found associations of agricultural use of chlorpyrifos, a diethyl (DE) OP, during pregnancy with increased report of internalizing problems, depression, and anxiety from both mothers and youth, however effect estimates were quite small. In the longitudinal Mount Sinai Children's Environmental Health Center study, investigators found that higher prenatal dimethyl (DM) OP

concentrations were associated with more BASC parent-reported internalizing problems among 141 children from ages 4-9 years.[31] In addition to studies of children, chronic occupational OP exposure and history of acute OP poisonings have been associated with increased self-reported depression among farmworkers,[162-167] and the Agricultural Health Study has observed some of the strongest associations for pesticides such as malathion, diazinon, and chlorpyrifos.[166]

We observed some isolated associations of increased youth-reported attention problems in association with applications of the OPs diazinon and dimethoate during the prenatal period. In previous analyses in this cohort, prenatal DAPs were associated with higher maternal-reported attention problems and psychometrician-assessed Attention Deficit Hyperactivity Disorder (ADHD) at age 5, but not 3.5 years.[33] Additionally, in a longitudinal analysis of inner-city mothers and children in New York City, investigators found that prenatal chlorpyrifos concentrations were associated with increased attention and hyperactivity problems at 3 years.[26] Notably, we did not observe associations of chlorpyrifos use during the prenatal or postnatal period with maternal- or youth-reported attention problems or hyperactivity in this analysis. Cross-sectional and case-control studies have also found associations between childhood OP exposure and more behavioral and attention problems [168] and higher odds of having an ADHD diagnosis.[32,169]

We observed largely null associations of permethrin use near the home during either pregnancy or early childhood with maternal- or youth-reported behavioral or emotional problems. This is in contrast with previous studies showing associations of prenatal pyrethroid exposure with child behavior problems. Specifically, longitudinal studies in New York City and France have identified associations of prenatal biomarkers of pyrethroid exposure and more parent-reported behavioral and emotional problems, including internalizing problems, depression, and externalizing problems, among children ages 4-9 years.[35,36] Results of cross-sectional studies investigating childhood pyrethroid exposure and behavioral outcomes have been more inconsistent. While one analysis of 1999-2002 data from the National Health and Nutrition Examination Survey (NHANES) found no association of pyrethroid exposure and parental report of ADHD among children ages 6-15 years,[170] another analysis of NHANES participants ages 8-15 years from 2001-2002 found that higher urinary levels of a non-specific pyrethroid biomarker, 3-phenoxybenzoic acid (3-PBA), were associated with higher odds of an ADHD diagnosis and more hyperactive-impulsive symptoms.[171] In the cross-sectional Canadian Health Measures Survey, two other pyrethroid biomarkers were associated with increased odds of parent-reported global total difficulties assessed using the Strengths and Difficulties Questionnaire (SDQ) among 779 children ages 6-11 years.[172] It is possible that inconsistencies in findings from our study and previous analyses may be due to different exposure assessment methods or the age at which the outcome was assessed. Notably, each of these previous studies assessed exposure using urinary biomarkers, which are a more integrated measure of total pyrethroid exposure than PUR data. Residential pesticide use is one of the biggest risk factors for pyrethroid exposure,[173] which would not be captured with our exposure assessment method.

We also observed associations of applications of the neonicotinoid imidacloprid during the prenatal period with fewer maternal- and youth-reported internalizing behaviors and attention problems, particularly among girls. While neonicotinoids are intended to be highly selective to insects[174] and are thought to have low mammalian toxicity due to a lower affinity for binding to the nicotine acetylcholine receptor (nAChR),[175,176] few epidemiologic studies have examined their impacts on human health and significant data gaps exist.[176,177] Toxicological studies suggest that gestational imidacloprid exposure may be associated with sensorimotor deficits in the

offspring[178] and case studies indicate that acute neonicotinoid poisoning can result in adverse respiratory, cardiovascular, and neurologic outcomes.[176] However, no studies to date have examined associations of prenatal or early-life neonicotinoid exposure with adolescent neurobehavior, using either frequentist or Bayesian mixtures models. It is possible that we observed null or protective effects for imidacloprid because our exposure assessment method – agricultural pesticide use - did not adequately capture imidacloprid exposure due to the physical properties and mode of application of neonicotinoids.[134,176,179,180] Neonicotinoids are commonly applied as seed treatments,[181,182] and more integrated exposure assessment methods, such as urinary biomarkers, may be needed to accurately characterize exposure. Neonicotinoids are now the most widely used class of insecticides worldwide and use continues to rise.[134,183] Additional studies, potentially using biomarkers of exposure, are needed to examine the neurodevelopmental impacts of neonicotinoids.

We observed relatively consistent associations of glyphosate use near the home during the postnatal period across maternal- and youth-reported internalizing problems, depression, and anxiety. Very few epidemiologic studies have examined neurodevelopmental outcomes associated with glyphosate exposure, though toxicology studies have shown neurotoxic effects such as depressive behavior[184,185] and poorer locomotor activity[185-188] and recognition memory.[186,189] In one previous case-control study using PUR data, investigators found that glyphosate use within 2 km of the mother's residence during pregnancy was associated with increased odds of ASD.[38] Additionally, case studies of acute poisoning have also suggested that glyphosate may have direct impacts on neurotoxicity and Parkinsonism after chronic exposures.[190-192] Glyphosate is the most widely used pesticide in the U.S. and worldwide, with global use increasing about 15-fold since the introduction of genetically engineered glyphosate-tolerant crops in 1996.[135] Agricultural and non-agricultural use of glyphosate has continued to skyrocket since the exposure periods of interest for the present analysis, and additional studies are needed to investigate whether early exposure to current levels of glyphosate use may be associated with child or adolescent neurodevelopment.

We did not observe consistent trends over prenatal and postnatal analyses. Previous examinations of urinary biomarkers of OP pesticides and neurodevelopment in CHAMACOS and other studies have observed stronger effects for exposures occurring prenatally.[23,33,193,194] Notably, the exposure period of interest was 9 months for pregnancy and 5 years for childhood exposures, and thus prenatal and postnatal effect estimates are not directly comparable in the present analysis.

We did observe some consistencies for associations with specific pesticides across maternal- and youth-report. For example, effect estimates for internalizing behaviors in association with chlorpyrifos use during pregnancy and glyphosate use during early childhood were similar across maternal- and youth-report. Previous studies have reported relatively poor agreement between maternal- and youth-report of adolescent psychopathology,[195] particularly for internalizing behaviors.[196-198] Mothers may be more reliable reporters of adolescent externalizing behaviors, which may be more easily observed by others, as opposed to depression or anxiety, which the participant may choose not to disclose to caregivers.[196]

Although it is difficult to elucidate potential mechanisms of actions of specific pesticides from epidemiology studies in which humans are exposed to a mixture of pesticides, evidence from animal studies suggest that possible mechanisms may include changes in levels of neurotransmitters,[185] inhibition of axonal growth,[199,200] alteration of voltage-gated sodium channel function,[201-203] increased oxidative stress,[204-206] and damage to or decreased synthesis of

brain DNA.[207-210] The inhibition of acetylcholinesterase (AChE) was long proposed as one of the primary neurodevelopmental mechanisms of action of OP and carbamate pesticides; however, there is growing evidence from human and animal studies that these pesticides may exert deleterious impacts on neurodevelopment at levels of exposure below which AChE inhibition would occur.[193,211] For example, OPs may disrupt neurotransmitter systems including norepinephrine, dopamine, and serotonin,[212-217] which could influence emotional and behavioral problems such as aggression, depression, and ADHD that have been associated with OP exposure in previous epidemiologic studies.[32,33,218] Toxicology studies have shown that developmental glyphosate exposure may also impact cholinergic and glutamatergic neurotransmission, increase oxidative stress, and induce neural cell death in the hippocampus.[184] There is consistent evidence from epidemiologic and animal studies that fetuses and young children, who are undergoing periods of rapid brain and nervous system development,[219] are particularly susceptible to the potential neurotoxic effects of pesticides[83,219] and may experience neurobehavioral abnormalities at doses that would not be toxic to adults.[220-222]

Our study has several strengths and limitations. One of the biggest limitations is that applications of pesticides near the home are not a direct measure of exposure and reliance on PUR data may result in measurement error. Previous analyses suggest that PUR data are correlated with environmental concentrations of OPs, but not pyrethroids, in homes,[77,78] and data gaps exist regarding how well how well reliance on PUR may capture exposure to other pesticides such as neonicotinoids or glyphosate. The precision of the exposure assessment was likely independent of the outcomes of interest and would thus result in non-differential misclassification that may have contributed to our mostly null findings. We were also only able to characterize potential exposure to pesticides based on use near the maternal residence, and not in other areas the mothers and children may have spent time during the prenatal and postnatal periods, such as work and childcare. Additionally, while CHAM1 participants reported their residential address at all study visits, addresses and timing of household moves were reported retrospectively for CHAM2 participants and may be prone to error.

Strengths include a well-characterized cohort with rich collection of data, including longitudinal neurobehavioral measures from two reporters (i.e., mothers and youth). While it has been well established that prenatal and, to a lesser extent, postnatal OP pesticide exposure is associated with adverse child neurodevelopment, a number of data gaps exist. Previous studies have examined associations among children followed up to age 12 years, and ours is the first to examine the persistence of pesticide-neurodevelopment associations into adolescence and young adulthood. Moreover, previous investigations have largely examined single pesticides or pesticide classes in isolation, which may result in bias from co-pollutant confounding.[132] Many studies have also relied on DAPs or other non-specific biomarkers that reflect only very recent exposures,[75] resulting in data gaps regarding the impact of specific pesticides with varying degrees of toxicity. By leveraging California's unique and comprehensive PUR database, we were able to examine associations with multiple neurotoxic pesticides, including those that lack biomarkers. We employed BHM as a principled approach to examine associations with all pesticides included in a single model, allowing for estimation of mutually adjusted exposure effects that are more stable and interpretable than with other approaches to multiple exposure modeling (e.g., simultaneous inclusion of all exposure variables).[136,137,139] While multiple methods are being developed to examine environmental mixtures, BHM has many advantages in that it allows the incorporation of *a priori* information; facilitates a "borrowing" of information across similar exposures[138] that results in estimates with lower mean squared error and interval

estimate coverage closer to the nominal level; reduces the potential for extreme exposure-outcome associations, addressing concerns regarding multiple comparisons;[136,140,141] and produces highly interpretable results.

3.5 Tables and Figures

Table 3.1. Sociodemographic characteristics of CHAMACOS study participants with 16 or 18-year neurobehavioral assessments and data on agricultural pesticide use near home during prenatal or postnatal (0-5 years) periods (*n*=593).

Characteristic	*n* (%) or median (P25-P75)
Maternal/household characteristics	
Age at enrollment (years)	26.0 (22.0-30.0)
Country of birth	
Mexico or other	519 (88.6)
U.S.	67 (11.4)
Years in the U.S. at delivery	
≤5 years	280 (47.7)
>5 years, but not born in U.S.	254 (43.3)
Born in U.S.	53 (9.0)
Education at baseline	
≤6th grade	258 (44.0)
7th-12th grade	194 (33.0)
≥High school graduate	135 (23.0)
Marital status at baseline	
Not married/living as married	106 (18.1)
Married/living as married	481 (81.9)
Maternal depression at 9-year visit (≥16 CES-D score)[a]	
No	417 (71.0)
Yes	170 (29.0)
Household income at 16-year assessment[a]	
At or below poverty level	333 (56.7)
Above poverty level	254 (43.3)
Language of 16-year maternal assessment[a]	
English	72 (12.5)
Spanish	506 (87.5)
HOME z-score at 10.5-year assessment[b]	0.2 (-0.6 – 0.6)
Child characteristics	
Child's sex	
Boy	286 (48.7)
Girl	301 (51.3)
Exact age at 16-year assessment	16.3 (16.1-16.5)
Exact age at 18-year assessment	18.0 (18.0-18.1)

[a]Missing data filled in from data collected at earlier or later time points. *n*=41 participants missing maternal depression at 9-year assessment; 7 missing poverty status at 16-year assessment; 16 missing maternal language of 16-year assessment.
[b]Missing data filled in from earlier or later assessments for 13 participants missing HOME score at 10.5-year assessment; filled in as median HOME score observed for population included in this analysis for one participant missing HOME score at all visits.

Table 3.2. Total pesticide use in Monterey County in 2000 and 2005 and distributions of wind-adjusted agricultural pesticide applications within 1 km of maternal residence during prenatal and postnatal periods[a].

	Kilograms used (2000)	Kilograms used (2005)	Prenatal				Postnatal				Spearman Correlation Coefficients for Prenatal and Postnatal Periods
			P25	P50	P75	Max	P25	P50	P75	Max	
Organophosphate insecticides											
Acephate	40,077	22,340	0.22	1.12	2.07	6.29	1.69	3.09	4.35	6.98	0.60
Chlorpyrifos	30,691	30,459	0.19	0.92	2.03	6.76	1.11	2.67	4.22	7.59	0.63
Diazinon	50,999	73,707	1.07	1.95	3.02	7.01	2.53	3.79	5.43	8.47	0.55
Malathion	30,490	29,513	0.00	0.31	1.47	6.68	0.92	2.14	3.89	7.86	0.31
Oxydemeton methyl	31,084	33,330	0.20	1.00	1.97	5.77	1.55	2.94	4.19	8.32	0.64
Naled[b]	13,090	7,839	0.00	0.00	0.54	3.93	0.00	0.98	2.48	6.37	0.50
Dimethoate	20,259	18,948	0.10	0.53	1.50	5.01	0.89	2.08	3.56	6.73	0.71
Carbamate insecticides											
Methomyl	35,371	28,843	0.22	0.82	1.86	4.91	1.50	2.71	3.77	7.33	0.51
Pyrethroid insecticides											
Permethrin	11,869	10,467	0.10	0.47	1.16	4.12	0.59	1.49	2.85	5.70	0.61
Neonicotinoid insecticides											
Imidacloprid	8,729	5,753	0.15	0.41	0.89	3.32	0.71	1.42	2.33	4.74	0.55
Fungicides											
Mn-fungicides	161,154	169,887	1.62	3.13	4.32	5.30	3.85	5.43	6.76	10.02	0.60
Herbicides											
Glyphosate	44,236	55,886	0.00	0.07	1.23	4.51	0.91	2.01	3.23	6.75	0.53

[a]Prenatal period accounts for 9 months of pregnancy and postnatal period accounts for child ages 0-5 years.
[b]Included in postnatal, but not prenatal analysis.

Table 3.3. Adjusted[a] associations [β (95% CrI)] of two-fold increase in pesticide use within 1 km of residence *during pregnancy* with *maternal-reported* behavioral and emotional problems at age 16 and 18 years using linear mixed effects Bayesian Hierarchical Modeling (BHM) (*n*=1,049; *k*=587).

	Internalizing problems	Depression	Anxiety	Externalizing problems	Hyperactivity	Attention problems
Organophosphates						
Acephate	0.1 (-1.4, 1.5)	-0.1 (-1.6, 1.3)	0.5 (-0.9, 2.9)	-0.5 (-1.5, 0.7)	-0.3 (-1.5, 0.8)	-0.7 (-2.1, 0.7)
Chlorpyrifos	0.7 (-0.5, 1.9)	1.0 (-0.2, 2.1)	0.5 (-0.6, 1.6)	0.3 (-0.6, 1.1)	0.3 (-0.6, 1.2)	-0.1 (-1.2, 0.9)
Diazinon	0.0 (-1.4, 1.4)	-0.2 (-1.6, 1.2)	0.4 (-0.9, 1.8)	0.2 (-0.8, 1.3)	0.1 (-1.0, 1.1)	0.3 (-1.0, 1.6)
Malathion	0.2 (-0.6, 1.0)	0.6 (-0.2, 1.4)	-0.4 (-1.2, 0.4)	-0.1 (-0.7, 0.5)	-0.1 (-0.8, 0.5)	0.1 (-0.6, 0.9)
Oxydemeton methyl	-0.1 (-2.2, 2.0)	0.3 (-1.8, 2.4)	-0.3 (-2.4, 1.8)	-0.1 (-1.6, 1.5)	-0.4 (-2.1, 1.3)	0.2 (-1.8, 2.2)
Dimethoate	0.5 (-1.4, 2.4)	0.4 (-1.5, 2.3)	0.0 (-1.9, 1.9)	0.4 (-1.0, 1.9)	0.8 (-0.8, 2.3)	1.2 (-0.6, 3.0)
Carbamates						
Methomyl	0.0 (-1.2, 1.2)	-0.2 (-1.3, 1.1)	0.1 (-1.0, 1.3)	0.4 (-0.5, 1.3)	0.3 (-0.7, 1.2)	0.0 (-1.1, 1.1)
Pyrethroid						
Permethrin	-1.5 (-3.9, 0.9)	-1.3 (-3.8, 1.1)	-1.4 (-3.8, 0.9)	0.2 (-1.6, 2.1)	0.1 (-1.8, 2.0)	0.5 (-1.8, 2.7)
Neonicotinoid						
Imidacloprid	-0.2 (-3.3, 2.8)	0.0 (-3.1, 3.1)	-1.1 (-4.2, 1.8)	-0.3 (-2.5, 2.0)	-0.6 (-3.1, 1.8)	-2.4 (-5.3, 0.4)
Fungicide						
Mn-Fungicides	0.0 (-1.3, 1.2)	-0.1 (-1.3, 1.1)	0.1 (-1.1, 1.3)	-0.3 (-1.2, 0.6)	0.0 (-1.0, 0.9)	0.1 (-1.1, 1.2)
Herbicide						
Glyphosate	0.2 (-0.5, 0.9)	-0.1 (-0.9, 0.6)	0.4 (-0.4, 1.1)	0.3 (-0.2, 0.9)	0.4 (-0.2, 1.0)	0.4 (-0.3, 1.1)

Notes: *k*, number of participants with data for at least one time point; *n*, number of observations from both time points. Higher score for each BASC outcome indicates more symptomatic behavior.

[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment

Table 3.4. Adjusted[a] associations [β (95% CrI)] of two-fold increase in pesticide use within 1 km of residence *during pregnancy* with *youth-reported* behavioral and emotional problems at age 16 and 18 years using linear mixed effects Bayesian Hierarchical Modeling (BHM) (*n*=1,032; *k*=584).

	Internalizing problems	Depression	Anxiety	Hyperactivity	Attention problems
Organophosphates					
Acephate	0.0 (-1.5, 1.6)	0.2 (-1.3, 1.7)	-0.6 (-2.2, 1.0)	-0.1 (-1.5, 1.2)	0.2 (-1.2, 1.6)
Chlorpyrifos	1.0 (-0.2, 2.2)	1.1 (-0.1, 2.3)	0.6 (-0.7, 1.9)	-0.1 (-1.2, 1.0)	0.0 (-1.1, 1.1)
Diazinon	0.5 (-1,0, 1.9)	0.4 (-1.0, 1.8)	0.4 (-1.1, 1.9)	0.1 (-1.1, 1.3)	1.2 (0.0, 2.5)
Malathion	0.6 (-0.2, 1.4)	0.6 (-0.3, 1.4)	0.6 (-0.3, 1.5)	-0.1 (-0.8, 0.7)	0.0 (-0.7, 0.8)
Oxydemeton methyl	-1.1 (-3.3, 1.1)	-0.8 (-3.0, 1.4)	-0.5 (-2.9, 1.8)	-0.6 (-2.6, 1.3)	-1.4 (-3.3, 0.6)
Dimethoate	-0.6 (-2.6, 1.4)	-1.2 (-3.1, 0.8)	-0.4 (-2.5, 1.8)	0.6 (-1.2, 2.4)	1.9 (0.0, 3.6)
Carbamates					
Methomyl	0.0 (-1.3, 1.2)	-0.6 (-1.8, 0.6)	-0.1 (-1.5, 1.2)	0.3 (-0.8, 1.4)	-0.3 (-1.4, 0.8)
Pyrethroid					
Permethrin	-0.6 (-3.2, 1.9)	-0.9 (-3.3, 1.7)	-1.3 (-4.0, 1.4)	-0.7 (-3.0, 1.5)	-1.9 (-4.2, 0.3)
Neonicotinoid					
Imidacloprid	-0.4 (-3.6, 2.7)	0.2 (-2.9, 3.3)	-0.8 (-4.1, 2.5)	0.4 (-2.3, 3.2)	-1.6 (-4.4, 1.3)
Fungicide					
Mn-Fungicides	0.1 (-1.2, 1.4)	0.3 (-1.0, 1.6)	0.6 (-0.8, 2.0)	-0.1 (-1.2, 1.0)	0.1 (-1.0, 1.3)
Herbicide					
Glyphosate	0.3 (-0.5, 1.0)	0.4 (-0.4, 1.1)	0.4 (-0.4, 1.2)	0.4 (-0.3, 1.1)	0.2 (-0.5, 0.8)

Notes: *k*, number of participants with data for at least one time point; *n*, number of observations from both time points. Higher score for each BASC outcome indicates more symptomatic behavior.

[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment

Table 3.5. Adjusted[a] associations [β (95% CrI)] of two-fold increase in pesticide use within 1 km of residence *during childhood (0-5 years*) with *maternal-reported* behavioral and emotional problems at age 16 and 18 years using linear mixed effects Bayesian Hierarchical Modeling (BHM) (*n*=797; *k*=427).

	Internalizing problems	Depression	Anxiety	Externalizing problems	Hyperactivity	Attention problems
Organophosphates						
Acephate	0.8 (-1.0, 2.6)	0.5 (-1.3, 2.3)	1.0 (-0.9, 2.8)	0.8 (-0.6, 2.1)	1.6 (0.1, 3.0)	0.5 (-1.1, 2.1)
Chlorpyrifos	-1.0 (-2.5, 0.6)	-0.1 (-1.7, 1.6)	-1.7 (-3.3, -0.1)	0.1 (-1.1, 1.3)	0.1 (-1.2, 1.3)	0.9 (-0.6, 2.3)
Diazinon	1.1 (-0.9, 3.1)	1.3 (-0.8, 3.3)	0.1 (-1.9, 2.2)	0.0 (-1.5, 1.5)	0.2 (-1.3, 1.8)	1.2 (-0.7, 3.0)
Malathion	0.2 (-0.7, 1.3)	0.1 (-0.9, 1.1)	0.7 (-0.3, 1.7)	-0.4 (-1.1, 0.4)	-0.5 (-1.3, 0.3)	-0.9 (-1.8, 0.0)
Oxydemeton methyl	0.3 (-2.5, 3.0)	-0.4 (-3.1, 2.3)	0.5 (-2.2, 3.1)	-1.0 (-3.0, 1.0)	-2.4 (-4.5, -0.2)	-2.3 (-4.6, 0.2)
Naled	-0.7 (-2.0, 0.6)	-0.2 (-1.4, 1.1)	-1.2 (-2.5, 0.0)	0.4 (-0.5, 1.4)	0.3 (-0.7, 1.3)	0.8 (-0.4, 1.9)
Dimethoate	0.9 (-1.2, 3.1)	-0.3 (-2.4, 1.9)	1.0 (-1.2, 3.2)	0.7 (-1.0, 2.4)	0.8 (-0.9, 2.5)	-1.1 (-3.1, 0.9)
Carbamates						
Methomyl	0.1 (-1.6, 1.7)	0.6 (-1.1, 2.2)	-0.6 (-2.2, 1.0)	-0.2 (-1.5, 1.0)	-0.5 (-1.8, 0.8)	-0.9 (-2.4, 0.6)
Pyrethroid						
Permethrin	0.2 (-2.1, 2.6)	-0.2 (-2.6, 2.1)	0.5 (-1.8, 2.9)	0.0 (-1.8, 1.7)	-0.8 (-2.6, 1.1)	-0.8 (-2.9, 1.3)
Neonicotinoid						
Imidacloprid	-0.1 (-2.9, 2.7)	-0.5 (-3.3, 2.2)	1.0 (-1.7, 3.7)	0.1 (-2.0, 2.2)	1.2 (-1.0, 3.3)	1.5 (-0.9, 4.0)
Fungicide						
Mn-Fungicides	-1.8 (-3.9, 0.4)	-0.9 (-3.1, 1.3)	-1.0 (-3.2, 1.1)	-0.3 (-2.0, 1.3)	0.2 (-1.5, 1.9)	0.9 (-1.1, 2.8)
Herbicide						
Glyphosate	1.3 (0.2, 2.3)	0.6 (-0.5, 1.6)	1.2 (0.2, 2.3)	0.1 (-0.7, 0.9)	0.1 (-0.8, 0.9)	0.0 (-0.9, 1.0)

Notes: *k*, number of participants with data for at least one time point; *n*, number of observations from both time points. Higher score for each BASC outcome indicates more symptomatic behavior.

[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, language of assessment, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment, agricultural applications of 11 pesticides included in prenatal assessment during the prenatal period.

Table 3.6. Adjusted associations [β (95% CrI)] of two-fold increase in pesticide use within 1 km of residence *during childhood (0-5 years)* with *youth-reported* behavioral and emotional problems at age 16 and 18 years using linear mixed effects Bayesian Hierarchical Modeling (BHM) (*n*=786; *k*=426).

	Internalizing problems	Depression	Anxiety	Hyperactivity	Attention problems
Organophosphates					
Acephate	0.3 (-1.6, 2.1)	0.1 (-1.7, 1.8)	-0.8 (-2.8, 1.2)	0.8 (-0.9, 2.4)	-0.2 (-1.9, 1.5)
Chlorpyrifos	-1.1 (-2.7, 0.5)	-1.4 (-2.9, 0.2)	-0.9 (-2.6, 0.8)	0.1 (-1.4, 1.5)	0.1 (-1.4, 1.6)
Diazinon	0.3 (-1.7, 2.3)	0.4 (-1.5, 2.3)	0.7 (-1.5, 2.8)	0.3 (-1.6, 2.1)	-0.2 (-2.0, 1.7)
Malathion	-0.7 (-1.7, 0.3)	-0.4 (-1.3, 0.6)	-0.4 (-1.5, 0.7)	-0.3 (-1.3, 0.6)	-0.9 (-1.8, 0.1)
Oxydemeton methyl	-0.1 (-2.8, 2.7)	0.5 (-2.1, 3.1)	0.7 (-2.3, 3.5)	-1.8 (-4.3, 0.6)	-1.1 (-3.6, 1.4)
Naled	0.5 (-0.8, 1.7)	0.3 (-0.9, 1.5)	-0.3 (-1.7, 1.1)	0.0 (-1.1, 1.2)	1.2 (0.1, 2.4)
Dimethoate	2.0 (-0.2, 4.2)	1.5 (-0.6, 3.6)	1.5 (-0.8, 3.9)	2.0 (0.0, 3.9)	1.2 (-0.8, 3.2)
Carbamates					
Methomyl	-1.4 (-3.0, 0.2)	-1.1 (-2.6, 0.5)	-0.3 (-2.1, 1.5)	-0.8 (-2.3, 0.7)	-0.9 (-2.4, 0.6)
Pyrethroid					
Permethrin	0.3 (-2.0, 2.6)	0.0 (-2.2, 2.3)	0.5 (-2.0, 3.0)	-0.1 (-2.2, 2.1)	0.1 (-2.1, 2.3)
Neonicotinoid					
Imidacloprid	-0.7 (-3.4, 2.0)	-1.3 (-3.9, 1.2)	-1.5 (-4.4, 1.5)	-0.5 (-3.0, 2.0)	0.4 (-2.1, 3.0)
Fungicide					
Mn-Fungicides	0.1 (-2.0, 2.3)	0.1 (-2.0, 2.2)	0.3 (-2.0, 2.6)	0.8 (-1.1, 2.8)	0.7 (-1.3, 2.7)
Herbicide					
Glyphosate	0.9 (-0.1, 2.0)	1.2 (0.2, 2.2)	0.9 (-0.3, 2.0)	-0.5 (-1.5, 0.4)	0.0 (-1.0, 1.0)

Notes: *k*, number of participants with data for at least one time point; *n*, number of observations from both time points. Higher score for each BASC outcome indicates more symptomatic behavior.

[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, language of assessment, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment, agricultural applications of 11 pesticides included in prenatal assessment during the prenatal period.

3.6 Supporting Information

Table S3.1. Exchangeability matrix for Bayesian Hierarchical Model (BHM) for prenatal analyses from Sensitivity Analysis 1[a].

	OP	Carbamate	Pyrethroid	Neonicotinoid	Fungicide	Herbicide
Acephate	1	0	0	0	0	0
Chlorpyrifos	1	0	0	0	0	0
Diazinon	1	0	0	0	0	0
Malathion	1	0	0	0	0	0
Oxydemeton methyl	1	0	0	0	0	0
Dimethoate	1	0	0	0	0	0
Methomyl	0	1	0	0	0	0
Permethrin	0	0	1	0	0	0
Imidacloprid	0	0	0	1	0	0
Maneb & Mancozeb	0	0	0	0	1	0
Glyphosate	0	0	0	0	0	1

[a]Sensitivity analysis in which all pesticide classes were included in the Z matrix.

Table S3.2. Exchangeability matrix for Bayesian Hierarchical Model (BHM) for prenatal analyses, Sensitivity Analysis 2[a].

	DE	DM	BMD_{10}
Acephate	0	1	0.99
Chlorpyrifos	1	0	1.48
Diazinon	1	0	6.24
Malathion	0	1	313.91
Oxydemeton methyl	0	1	0.09
Dimethoate	0	1	0.25

[b]Sensitivity analysis in which only OP pesticides were included in the Z matrix (with designation of whether OP was a diethyl or dimethyl pesticide and benchmark dose) and null priors implemented for remaining pesticides.

Table S3.3. Adjusted associations [β (95% CrI)] of two-fold increase in pesticide use within 1 km of residence *during pregnancy* with *maternal-reported* behavioral and emotional problems at age 16 and 18 years using linear mixed effects Bayesian Hierarchical Modeling (BHM), stratified by sex (boys: *n*=506, *k*=286; girls: *n*=543, *k*=301).

	Internalizing problems		Depression		Anxiety		Externalizing Problems		Hyperactivity		Attention Problems	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
OPs												
Acephate	-0.3 (-2.0, 1.3)	-1.0 (-3.1, 1.1)	-0.2 (-1.9, 1.4)	-0.9 (-3.1, 1.3)	0.4 (-1.1, 2.0)	-0.3 (-2.4, 1.8)	-0.1 (-1.3, 1.0)	-0.3 (-1.8, 1.3)	0.1 (-1.2, 1.3)	-0.2 (-1.8, 1.4)	-0.9 (-2.3, 0.6)	0.3 (-1.5, 2.3)
Chlorpyrifos	0.6 (-0.7, 2.0)	0.8 (-0.8, 2.5)	0.7 (-0.7, 2.1)	1.7 (0.1, 3.3)	0.1 (-1.2, 1.5)	1.1 (-0.5, 2.6)	0.3 (-0.7, 1.3)	0.9 (-0.2, 2.0)	0.1 (-0.9, 1.1)	0.9 (-0.2, 2.1)	-0.6 (-1.8, 0.6)	0.6 (-0.7, 2.0)
Diazinon	0.3 (-1.3, 1.9)	-0.2 (-2.1, 1.8)	-0.5 (-2.1, 1.2)	-0.9 (-2.8, 1.2)	0.3 (-1.3, 1.9)	-0.2 (-2.1, 1.8)	0.3 (-0.9, 1.4)	-0.5 (-2.0, 0.9)	0 (-1.2, 1.1)	-0.5 (-2.0, 0.9)	0.8 (-0.7, 2.1)	-0.1 (-1.9, 1.6)
Malathion	0.6 (-0.5, 1.6)	0.0 (-1.1, 1.2)	0.9 (-0.1, 2)	0.7 (-0.5, 1.8)	0.1 (-0.9, 1.2)	-0.7 (-1.8, 0.5)	-0.3 (-1.1, 0.4)	0.5 (-0.3, 1.4)	-0.2 (-0.9, 0.6)	0.0 (-0.8, 0.9)	0.1 (-0.8, 1.0)	0.4 (-0.5, 1.4)
Oxydemeton methyl	-0.6 (-2.9, 1.7)	0.1 (-3.0, 3.2)	-0.2 (-2.6, 2.1)	0.8 (-2.4, 4.0)	-0.7 (-3.1, 1.6)	0.5 (-2.6, 3.5)	-0.3 (-2.0, 1.3)	0.0 (-2.2, 2.3)	-0.6 (-2.4, 1.1)	-0.5 (-2.9, 1.8)	-0.6 (-2.6, 1.5)	-0.4 (-3.1, 2.4)
Dimethoate	0.8 (-1.4, 3.0)	0.2 (-2.4, 2.7)	1.4 (-0.8, 3.6)	-1.1 (-3.8, 1.5)	0.1 (-2.0, 2.3)	-1 (-3.5, 1.5)	1.4 (-0.2, 3.0)	-1.5 (-3.4, 0.4)	1.9 (0.3, 3.6)	-0.9 (-2.9, 1.0)	2.0 (0.1, 4.0)	1.1 (-1.2, 3.4)
Carbamates												
Methomyl	-0.8 (-2.2, 0.6)	0.9 (-0.7, 2.6)	-1.4 (-2.8, 0.0)	1.4 (-0.3, 3.0)	-0.4 (-1.8, 1.0)	0.1 (-1.5, 1.8)	-0.2 (-1.2, 0.9)	1.9 (0.7, 3.1)	-0.2 (-1.3, 0.8)	1.5 (0.2, 2.7)	0.0 (-1.3, 1.3)	0.3 (-1.2, 1.7)
Pyrethroid												
Permethrin	-0.9 (-3.3, 1.6)	0.7 (-2.3, 3.7)	-0.3 (-2.9, 2.2)	1.0 (-2.0, 4.1)	-1.3 (-3.8, 1.1)	1.2 (-1.8, 4.2)	0.3 (-1.5, 2.1)	2.6 (0.5, 4.8)	-0.4 (-2.4, 1.4)	1.7 (-0.6, 4.0)	0.1 (-2.1, 2.4)	1.0 (-1.8, 3.7)
Neonicotinoid												
Imidacloprid	0.3 (-2.7, 3.3)	-4.7 (-8.6, -0.8)	0.7 (-2.2, 3.8)	-4.4 (-8.3, -0.4)	-0.2 (-3.2, 2.7)	-3.0 (-6.8, 0.9)	-0.5 (-2.6, 1.7)	-2.8 (-5.7, 0.0)	-0.1 (-2.4, 2.2)	-2.6 (-5.6, 0.4)	-2.2 (-4.8, 0.5)	-4.5 (-7.9, -0.9)
Fungicide												
Mn-Fungicides	0.4 (-1.1, 1.9)	0.5 (-1.1, 2.0)	0.4 (-1.1, 1.9)	0.3 (-1.3, 1.9)	0.6 (-0.9, 2.1)	0.3 (-1.3, 1.8)	-0.5 (-1.6, 0.6)	-0.6 (-1.8, 0.5)	-0.3 (-1.4, 0.8)	0.2 (-1, 1.4)	-0.1 (-1.4, 1.3)	-0.2 (-1.6, 1.1)
Herbicide												
Glyphosate	-0.5 (-1.5, 0.4)	0.0 (-1.0, 1.1)	-1.2 (-2.2, -0.3)	-0.1 (-1.1, 0.9)	0.3 (-0.6, 1.2)	-0.1 (-1.1, 0.9)	0.0 (-0.7, 0.6)	0.3 (-0.4, 1.0)	0.0 (-0.7, 0.7)	0.5 (-0.3, 1.2)	-0.1 (-0.9, 0.7)	0.5 (-0.4, 1.4)

Notes: *k*, number of participants with data for at least one time point; *n*, number of observations from both time points. Higher score for each BASC outcome indicates more symptomatic behavior.

[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, language of assessment, depression at 9Y assessment; child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment, agricultural applications of 11 pesticides included in prenatal assessment during the prenatal period.

Table S3.4. Adjusted associations [β (95% CrI)] of two-fold increase in pesticide use within 1 km of residence *during pregnancy* with *youth-reported* behavioral and emotional problems at age 16 and 18 years using linear mixed effects Bayesian Hierarchical Modeling (BHM), stratified by sex (boys: *n*=495, *k*=285; girls: *n*=537, *k*=299).

	Internalizing problems		Depression		Anxiety		Hyperactivity		Attention problems	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
OPs										
Acephate	0.3 (-1.4, 2.1)	0.4 (-1.7, 2.7)	0.1 (-1.5, 1.8)	-0.4 (-2.4, 1.7)	0.7 (-1.1, 2.5)	-0.6 (-2.9, 1.7)	0.4 (-1.1, 1.9)	-0.8 (-2.7, 1.1)	0.2 (-1.3, 1.7)	-0.4 (-2.4, 1.5)
Chlorpyrifos	1.3 (-0.1, 2.7)	1.2 (-0.3, 2.7)	1.0 (-0.3, 2.3)	1.4 (-0.2, 2.9)	0.0 (-1.4, 1.5)	0.9 (-0.7, 2.6)	-0.3 (-1.5, 0.9)	-0.2 (-1.6, 1.2)	0.3 (-1.0, 1.5)	0.2 (-1.2, 1.6)
Diazinon	0.1 (-1.5, 1.7)	1.4 (-0.6, 3.4)	0 (-1.5, 1.6)	1 (-0.9, 3)	-0.4 (-2.1, 1.3)	1.1 (-1.0, 3.1)	0.0 (-1.4, 1.4)	0.8 (-1.0, 2.6)	1.0 (-0.5, 2.4)	1.4 (-0.5, 3.2)
Malathion	0.9 (-0.2, 2.0)	-0.3 (-1.5, 0.8)	0.7 (-0.3, 1.7)	-0.3 (-1.4, 0.8)	0.9 (-0.2, 2.1)	-0.2 (-1.5, 0.9)	-0.9 (-1.8, 0.1)	0.5 (-0.5, 1.5)	0.4 (-0.6, 1.3)	-0.7 (-1.7, 0.3)
Oxydemeton methyl	-1.1 (-3.5, 1.3)	-1.6 (-4.7, 1.5)	-0.9 (-3.2, 1.5)	-0.3 (-3.3, 2.7)	-0.9 (-3.5, 1.5)	-0.7 (-4, 2.6)	0.3 (-1.9, 2.4)	-0.2 (-2.9, 2.6)	-1.1 (-3.2, 1.1)	-1.5 (-4.4, 1.3)
Dimethoate	-0.9 (-3.1, 1.3)	-1.3 (-4.0, 1.3)	-0.8 (-2.9, 1.4)	-3 (-5.5, -0.4)	-0.6 (-3, 1.7)	0.5 (-2.3, 3.4)	-0.2 (-2.1, 1.9)	0.5 (-1.7, 2.9)	1.5 (-0.5, 3.6)	1.0 (-1.4, 3.2)
Carbamates										
Methomyl	-0.4 (-1.9, 1.1)	1.2 (-0.5, 3.0)	-0.8 (-2.3, 0.6)	0.9 (-0.7, 2.5)	-0.7 (-2.2, 0.9)	0.0 (-1.8, 1.8)	0.4 (-0.8, 1.8)	0.6 (-0.9, 2.1)	0.0 (-1.3, 1.4)	0.2 (-1.3, 1.7)
Pyrethroid										
Permethrin	-0.4 (-2.9, 2.2)	-1.0 (-4.1, 2.2)	-0.3 (-2.8, 2.2)	0.0 (-3, 3)	-0.6 (-3.4, 2.1)	-1.9 (-5.3, 1.3)	-0.4 (-2.7, 1.9)	-0.7 (-3.5, 2.0)	-1.8 (-4.0, 0.6)	-1.0 (-3.8, 1.9)
Neonicotinoid										
Imidacloprid	-0.8 (-4.0, 2.3)	-3.9 (-7.9, 0.0)	-0.1 (-3.0, 2.8)	-2.0 (-5.9, 1.9)	-0.5 (-3.7, 2.7)	-4.3 (-8.4, 0.0)	1.9 (-0.8, 4.6)	-1.2 (-4.7, 2.3)	-1.5 (-4.3, 1.1)	-2.1 (-5.5, 1.4)
Fungicide										
Mn-Fungicides	0.7 (-0.9, 2.2)	0.1 (-1.4, 1.5)	0.8 (-0.7, 2.3)	0.2 (-1.3, 1.7)	1.4 (-0.2, 3.0)	0.8 (-0.9, 2.5)	-0.6 (-2.0, 0.7)	-0.4 (-1.8, 1.0)	0.3 (-1.0, 1.7)	0.3 (-1.1, 1.8)
Herbicide										
Glyphosate	-0.2 (-1.1, 0.8)	0.5 (-0.5, 1.5)	0.3 (-0.6, 1.2)	0.1 (-0.8, 1.1)	0.0 (-1.0, 1.0)	0.6 (-0.5, 1.7)	0.3 (-0.5, 1.1)	0.5 (-0.4, 1.4)	-0.3 (-1.1, 0.5)	0.3 (-0.7, 1.2)

Notes: *k*, number of participants with data for at least one time point; *n*, number of observations from both time points. Higher score for each BASC outcome indicates more symptomatic behavior.
[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, depression at 9Y assessment; child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment, agricultural applications of 11 pesticides included in prenatal assessment during the prenatal period.

Table S3.5. Adjusted associations [β (95% CrI)] of two-fold increase in pesticide use within 1 km of residence *during childhood (0-5 years)* with *maternal-reported* behavioral and emotional problems at age 16 and 18 years using linear mixed effects Bayesian Hierarchical Modeling (BHM), stratified by sex (boys: *n*=379, *k*=204; girls: *n*=418, k=223).

	Internalizing problems		Depression		Anxiety		Externalizing Problems		Hyperactivity		Attention Problems	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
OPs												
Acephate	-0.5 (-2.4, 1.4)	1.7 (-0.6, 3.9)	-0.4 (-2.2, 1.5)	1.5 (-0.7, 3.7)	0.0 (-1.9, 1.8)	1.2 (-1.1, 3.4)	0.6 (-0.8, 2.0)	1.6 (0.0, 3.3)	1.0 (-0.5, 2.6)	1.9 (0.1, 3.8)	0.4 (-1.3, 2.2)	-0.1 (-2.2, 2.0)
Chlorpyrifos	0.0 (-1.8, 1.8)	-1.5 (-3.4, 0.3)	0.6 (-1.2, 2.3)	-0.8 (-2.7, 1.0)	-0.9 (-2.7, 0.9)	-2.2 (-4.1, -0.3)	0.5 (-0.9, 1.8)	-0.6 (-2.0, 0.8)	0.3 (-1.2, 1.7)	-0.6 (-2.1, 0.8)	0.2 (-1.5, 1.8)	1.0 (-0.8, 2.7)
Diazinon	1.4 (-0.5, 3.2)	0.2 (-2.5, 2.8)	1.4 (-0.5, 3.3)	0.9 (-1.7, 3.6)	0.9 (-0.9, 2.8)	-1.1 (-3.7, 1.6)	0.1 (-1.3, 1.5)	-0.4 (-2.4, 1.6)	0.8 (-0.6, 2.3)	-0.2 (-2.3, 1.9)	2.1 (0.4, 3.9)	0.7 (-1.8, 3.1)
Malathion	0.4 (-0.8, 1.5)	0.0 (-1.1, 1.1)	0.7 (-0.4, 1.8)	0.0 (-1.1, 1.1)	0.6 (-0.5, 1.7)	0.1 (-1.0, 1.2)	-0.1 (-1.0, 0.7)	-0.2 (-1.0, 0.6)	-0.2 (-1.1, 0.7)	-0.2 (-1.1, 0.6)	-0.1 (-1.1, 1.0)	-0.6 (-1.7, 0.4)
Oxydemeton methyl	-0.5 (-3.1, 2.1)	1.4 (-1.8, 4.5)	-0.9 (-3.6, 1.8)	0.1 (-3.0, 3.2)	-0.1 (-2.7, 2.6)	1.2 (-2.0, 4.4)	-1.6 (-3.6, 0.3)	0.2 (-2.2, 2.5)	-2.8 (-5.0, -0.7)	-0.6 (-3.1, 1.9)	-2.0 (-4.5, 0.5)	-0.3 (-3.2, 2.6)
Naled	-0.6 (-2.1, 0.8)	-0.7 (-2.1, 0.8)	-0.6 (-2.0, 0.9)	0.3 (-1.1, 1.7)	-1.3 (-2.7, 0.2)	-0.8 (-2.3, 0.6)	0.1 (-1.0, 1.2)	0.3 (-0.8, 1.4)	0.2 (-1.0, 1.3)	0.3 (-0.9, 1.5)	0.0 (-1.4, 1.3)	1.3 (-0.1, 2.7)
Dimethoate	1.1 (-1.2, 3.5)	1.1 (-1.4, 3.7)	0.2 (-2.1, 2.5)	0.3 (-2.3, 2.8)	1.0 (-1.3, 3.3)	0.9 (-1.7, 3.5)	0.2 (-1.4, 2.0)	1.2 (-0.7, 3.1)	0.8 (-1.0, 2.6)	0.9 (-1.3, 2.9)	-1.5 (-3.6, 0.6)	-1.1 (-3.5, 1.3)
Carbamates												
Methomyl	0.4 (-1.3, 2.1)	-0.5 (-2.6, 1.7)	1.2 (-0.5, 2.8)	-0.8 (-2.9, 1.3)	-0.5 (-2.3, 1.1)	-0.8 (-2.9, 1.3)	0.6 (-0.7, 1.9)	-2.0 (-3.5, -0.4)	0.5 (-0.9, 1.8)	-1.5 (-3.2, 0.2)	0.6 (-0.9, 2.2)	-3.0 (-5.0, -1.0)
Pyrethroid												
Permethrin	-0.7 (-2.8, 1.4)	2.9 (-0.2, 5.9)	-0.8 (-2.9, 1.3)	1.1 (-1.9, 4.2)	-0.8 (-2.9, 1.3)	2.8 (-0.2, 5.9)	0.0 (-1.5, 1.6)	-0.3 (-2.6, 1.9)	-1.0 (-2.7, 0.7)	-1.9 (-4.4, 0.5)	-0.6 (-2.6, 1.4)	-2.5 (-5.3, 0.3)
Neonicotinoid												
Imidacloprid	1.0 (-1.5, 3.5)	-0.4 (-3.8, 3.0)	0.4 (-2.1, 2.9)	-0.5 (-3.9, 2.9)	2.1 (-0.5, 4.6)	1.6 (-1.8, 5.0)	0.4 (-1.5, 2.3)	1.8 (-0.8, 4.3)	1.2 (-0.8, 3.2)	3.2 (0.5, 5.9)	1.0 (-1.4, 3.4)	3.9 (0.7, 7.1)
Fungicide												
Mn-Fungicides	-1.4 (-3.5, 0.7)	-2.8 (-5.3, -0.3)	-1.2 (-3.3, 0.8)	-1.6 (-4.1, 0.8)	-0.6 (-2.7, 1.5)	-1.5 (-4.0, 1.1)	-0.6 (-2.1, 1.0)	-0.9 (-2.8, 0.9)	-0.4 (-2.1, 1.2)	-0.6 (-2.5, 1.3)	-0.2 (-2.1, 1.8)	0.8 (-1.4, 3.0)
Herbicide												
Glyphosate	0.2 (-0.9, 1.4)	1.9 (0.7, 3.2)	0.0 (-1.1, 1.2)	1.0 (-0.2, 2.2)	0.4 (-0.7, 1.6)	1.6 (0.3, 2.8)	-0.2 (-1.0, 0.7)	0.9 (-0.1, 1.8)	-0.3 (-1.2, 0.6)	0.8 (-0.2, 1.8)	-0.4 (-1.4, 0.7)	0.4 (-0.8, 1.6)

Notes: *k*, number of participants with data for at least one time point; *n*, number of observations from both time points. Higher score for each BASC outcome indicates more symptomatic behavior.
[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, language of assessment, depression at 9Y assessment; child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment, agricultural applications of 11 pesticides included in prenatal assessment during the prenatal period.

Table S3.6. Adjusted associations [β (95% CrI)] of two-fold increase in pesticide use within 1 km of residence *during childhood (0-5 years)* with *youth-reported* behavioral and emotional problems at age 16 and 18 years[a] using linear mixed effects Bayesian Hierarchical Modeling (BHM), stratified by sex (boys: *n*=370, *k*=203; girls: *n*=416, k=223).

	Internalizing problems		Depression		Anxiety		Hyperactivity		Attention problems	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
OPs										
Acephate	0.3 (-1.6, 2.2)	0.3 (-2.1, 2.7)	0.3 (-1.6, 2.2)	0.6 (-1.8, 2.8)	-1.1 (-3.2, 1.0)	-0.8 (-3.2, 1.7)	1.4 (-0.4, 3.2)	1.4 (-0.7, 3.5)	0.2 (-1.6, 2.1)	-0.9 (-3.1, 1.3)
Chlorpyrifos	-0.2 (-2.1, 1.7)	-1.2 (-3.1, 0.7)	0.2 (-1.5, 2.0)	-1.5 (-3.3, 0.3)	-0.9 (-2.9, 1.1)	-0.7 (-2.7, 1.3)	0.3 (-1.3, 2.0)	-0.6 (-2.3, 1.1)	0.8 (-0.9, 2.4)	-0.5 (-2.2, 1.2)
Diazinon	-0.4 (-2.4, 1.6)	1.8 (-1.0, 4.5)	-0.4 (-2.3, 1.4)	1.8 (-0.8, 4.5)	0.0 (-2.0, 2.1)	1.4 (-1.5, 4.3)	0.0 (-1.8, 1.7)	0.2 (-2.3, 2.6)	-0.3 (-2.1, 1.5)	0.3 (-2.2, 2.8)
Malathion	-0.4 (-1.6, 0.7)	-0.3 (-1.4, 0.9)	-0.2 (-1.4, 0.9)	-0.5 (-1.6, 0.6)	-0.1 (-1.4, 1.2)	-0.3 (-1.5, 0.9)	-0.3 (-1.4, 0.7)	0.1 (-0.9, 1.1)	-0.5 (-1.5, 0.6)	-1.1 (-2.1, 0.0)
Oxydemeton methyl	-0.9 (-3.6, 1.8)	-0.8 (-4.1, 2.4)	0.0 (-2.6, 2.7)	-0.3 (-3.4, 2.9)	0.2 (-2.7, 3.1)	0.1 (-3.3, 3.4)	-2.5 (-4.9, -0.1)	-2.5 (-5.4, 0.3)	-1.6 (-4.1, 0.9)	-2.0 (-5.0, 0.9)
Naled	0.1 (-1.4, 1.6)	-0.2 (-1.7, 1.3)	-0.7 (-2.1, 0.7)	0.9 (-0.5, 2.4)	-0.3 (-1.9, 1.3)	-0.3 (-1.9, 1.2)	-0.2 (-1.5, 1.2)	0.3 (-1.0, 1.7)	0.2 (-1.2, 1.6)	2.0 (0.6, 3.4)
Dimethoate	1.2 (-1.2, 3.6)	3.0 (0.3, 5.7)	0.0 (-2.2, 2.3)	1.8 (-0.7, 4.2)	1.0 (-1.5, 3.5)	2.2 (-0.6, 5.0)	1.8 (-0.3, 3.9)	2.6 (0.2, 4.9)	0.4 (-1.8, 2.5)	3.2 (0.8, 5.7)
Carbamates										
Methomyl	-0.5 (-2.3, 1.3)	-1.4 (-3.5, 0.7)	0.0 (-1.7, 1.7)	-1.4 (-3.4, 0.6)	0.8 (-1.0, 2.7)	-0.9 (-3.1, 1.4)	-1.2 (-2.8, 0.3)	-1.0 (-2.9, 0.9)	-0.6 (-2.3, 1.0)	-2.0 (-3.9, -0.1)
Pyrethroid										
Permethrin	0.2 (-2.1, 2.3)	0.4 (-2.8, 3.5)	-0.3 (-2.4, 1.8)	0.8 (-2.2, 3.9)	0.2 (-2.1, 2.5)	0.7 (-2.6, 3.9)	-0.4 (-2.3, 1.6)	-0.3 (-3.0, 2.5)	-0.6 (-2.6, 1.4)	0.2 (-2.7, 3.2)
Neonicotinoid										
Imidacloprid	-0.2 (-2.7, 2.5)	-3.3 (-6.8, 0.3)	0.5 (-1.9, 3.0)	-3.2 (-6.6, 0.1)	-0.6 (-3.3, 2.2)	-3.7 (-7.3, 0.0)	1.5 (-0.8, 3.8)	-1.1 (-4.3, 2.0)	1.4 (-1.0, 3.8)	0.3 (-2.9, 3.5)
Fungicide										
Mn-Fungicides	0.7 (-1.5, 2.8)	0.1 (-2.5, 2.6)	0.0 (-2.1, 2.1)	-0.1 (-2.4, 2.3)	0.9 (-1.3, 3.2)	0.7 (-1.9, 3.4)	1.2 (-0.7, 3.1)	0.9 (-1.3, 3.2)	1.3 (-0.7, 3.2)	1.1 (-1.2, 3.4)
Herbicide										
Glyphosate	0.2 (-1.0, 1.4)	1.8 (0.5, 3.1)	0.7 (-0.4, 1.8)	1.6 (0.4, 2.8)	0.5 (-0.8, 1.7)	1.3 (-0.1, 2.7)	-0.5 (-1.6, 0.5)	-0.7 (-1.8, 0.5)	-0.3 (-1.4, 0.8)	-0.4 (-1.6, 0.8)

Notes: *k*, number of participants with data for at least one time point; *n*, number of observations from both time points. Higher score for each BASC outcome indicates more symptomatic behavior.
[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, depression at 9Y assessment; child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment, agricultural applications of 11 pesticides included in prenatal assessment during the prenatal period.

Table S3.7. Adjusted[a] associations [β (95% CI)] of two-fold increase in pesticide use within 1 km of residence *during pregnancy* with *maternal-reported* behavioral and emotional problems at age 16 and 18 years using linear mixed effects regression with all exposure variables included simultaneously.

	Internalizing problems[b]	Depression[b]	Anxiety[c]	Externalizing problems[c]	Hyperactivity[d]	Attention problems[d]
Organophosphates						
Acephate	0.1 (-1.4, 1.7)	-0.2 (-1.7, 1.4)	0.6 (-1.0, 2.1)	-0.5 (-1.6, 0.7)	-0.3 (-1.5, 0.9)	-0.7 (-2.2, 0.7)
Chlorpyrifos	0.7 (-0.6, 1.9)	0.9 (-0.3, 2.2)	0.5 (-0.7, 1.7)	0.2 (-0.7, 1.1)	0.2 (-0.7, 1.2)	-0.3 (-1.4, 0.9)
Diazinon	-0.1 (-1.5, 1.4)	-0.3 (-1.7, 1.2)	0.4 (-0.9, 1.8)	0.2 (-0.8, 1.3)	0.0 (-1.1, 1.2)	0.3 (-1.0, 1.6)
Malathion	0.2 (-0.6, 1.0)	0.6 (-0.3, 1.4)	-0.4 (-1.2, 0.4)	-0.1 (-0.7, 0.5)	-0.1 (-0.8, 0.5)	0.1 (-0.7, 0.8)
Oxydemeton methyl	-0.1 (-2.4, 2.2)	0.4 (-1.9, 2.8)	-0.4 (-2.7, 1.9)	0.0 (-1.8, 1.7)	-0.4 (-2.3, 1.4)	0.2 (-2.0, 2.4)
Dimethoate	0.5 (-1.6, 2.5)	0.2 (-1.9, 2.3)	0.0 (-2.1, 2.0)	0.4 (-1.2, 1.9)	0.8 (-0.8, 2.4)	1.3 (-0.6, 3.3)
Carbamates						
Methomyl	0.1 (-1.1, 1.3)	-0.1 (-1.3, 1.1)	0.2 (-1.0, 1.4)	0.5 (-0.4, 1.3)	0.3 (-0.6, 1.3)	0.0 (-1.1, 1.1)
Pyrethroid						
Permethrin	-1.4 (-3.8, 1.1)	-1.2 (-3.7, 1.4)	-1.4 (-3.8, 1.0)	0.3 (-1.5, 2.2)	0.2 (-1.8, 2.1)	0.5 (-1.8, 2.8)
Neonicotinoid						
Imidacloprid	-0.3 (-3.3, 2.8)	0.0 (-3.1, 3.1)	-1.1 (-4.1, 1.9)	-0.3 (-2.6, 1.9)	-0.7 (-3.1, 1.7)	-2.4 (-5.3, 0.5)
Fungicide						
Mn-Fungicides	-0.1 (-1.4, 1.1)	-0.2 (-1.4, 1.1)	0.0 (-1.2, 1.2)	-0.4 (-1.3, 0.6)	-0.1 (-1.1, 0.9)	0.0 (-1.2, 1.1)
Herbicide						
Glyphosate	0.3 (-0.5, 1.0)	-0.1 (-0.8, 0.7)	0.4 (-0.3, 1.1)	0.4 (-0.2, 0.9)	0.4 (-0.1, 1.0)	0.4 (-0.2, 1.1)

Notes: *k*, number of participants with data for at least one time point; *n*, number of observations from both time points. Higher score for each BASC outcome indicates more symptomatic behavior.

[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, language of assessment, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment.

[b]*n*=1,044; *k*=583

[c]*n*=1,048; *k*=587

[d]*n*=1,049; *k*=587

Table S3.8. Adjusted[a] associations [β (95% CI)] of two-fold increase in pesticide use within 1 km of residence *during pregnancy* with *youth-reported* behavioral and emotional problems at age 16 and 18 years using linear mixed effects regression with all exposure variables included simultaneously.

	Internalizing problems[b]	Depression[c]	Anxiety[c]	Hyperactivity[d]	Attention problems[d]
Organophosphates					
Acephate	0.1 (-1.5, 1.8)	0.3 (-1.4, 1.9)	-0.6 (-2.4, 1.1)	-0.1 (-1.5, 1.4)	0.4 (-1.0, 1.9)
Chlorpyrifos	1.1 (-0.2, 2.4)	1.2 (-0.1, 2.4)	0.6 (-0.8, 2.0)	-0.1 (-1.3, 1.0)	-0.1 (-1.2, 1.1)
Diazinon	0.4 (-1.1, 1.9)	0.3 (-1.1, 1.8)	0.3 (-1.3, 1.9)	0.0 (-1.3, 1.3)	1.2 (-0.1, 2.5)
Malathion	0.6 (-0.3, 1.4)	0.5 (-0.3, 1.4)	0.6 (-0.3, 1.5)	-0.1 (-0.9, 0.6)	0.0 (-0.7, 0.8)
Oxydemeton methyl	-1.3 (-3.7, 1.2)	-0.9 (-3.4, 1.5)	-0.6 (-3.2, 2.0)	-0.7 (-2.9, 1.5)	-1.8 (-4.0, 0.4)
Dimethoate	-0.6 (-2.8, 1.6)	-1.2 (-3.4, 0.9)	-0.3 (-2.7, 2.0)	0.7 (-1.2, 2.7)	2.3 (0.3, 4.2)
Carbamates					
Methomyl	0.1 (-1.2, 1.3)	-0.5 (-1.8, 0.7)	-0.1 (-1.4, 1.3)	0.4 (-0.7, 1.5)	-0.3 (-1.4, 0.8)
Pyrethroid					
Permethrin	-0.5 (-3.1, 2.1)	-0.7 (-3.3, 1.8)	-1.2 (-4.0, 1.6)	-0.6 (-2.9, 1.6)	-1.9 (-4.2, 0.4)
Neonicotinoid					
Imidacloprid	-0.3 (-3.5, 2.9)	0.3 (-2.9, 3.4)	-0.8 (-4.2, 2.6)	0.4 (-2.4, 3.3)	-1.6 (-4.5, 1.2)
Fungicide					
Mn-Fungicides	0.0 (-1.3, 1.3)	0.2 (-1.1, 1.5)	0.5 (-0.9, 1.9)	-0.2 (-1.3, 1.0)	0.1 (-1.1, 1.2)
Herbicide					
Glyphosate	0.3 (-0.4, 1.1)	0.4 (-0.4, 1.1)	0.4 (-0.4, 1.3)	0.4 (-0.2, 1.1)	0.2 (-0.5, 0.8)

Notes: *k*, number of participants with data for at least one time point; *n*, number of observations from both time points. Higher score for each BASC outcome indicates more symptomatic behavior.

[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment.

[b]*n*=1,027; *k*=584

[c]*n*=1,031; *k*=584

[d]*n*=1,030; *k*=584

Table S3.9. Adjusted[a] associations [β (95% CI)] of two-fold increase in pesticide use within 1 km of residence *during childhood (0-5 years)* with *maternal-reported* behavioral and emotional problems at age 16 and 18 years using linear mixed effects regression with all exposure variables included simultaneously.

	Internalizing problems[b]	Depression[b]	Anxiety[c]	Externalizing problems[c]	Hyperactivity[d]	Attention problems[d]
Organophosphates						
Acephate	1.1 (-0.9, 3.1)	0.9 (-1.1, 2.9)	1.2 (-0.8, 3.2)	1.1 (-0.4, 2.6)	2.2 (0.6, 3.8)	1.0 (-0.8, 2.8)
Chlorpyrifos	-1.1 (-2.8, 0.7)	0.0 (-1.7, 1.7)	-1.8 (-3.6, -0.1)	0.2 (-1.1, 1.5)	0.1 (-1.2, 1.5)	1.1 (-0.5, 2.6)
Diazinon	1.2 (-1.0, 3.4)	1.4 (-0.8, 3.6)	0.1 (-2.1, 2.3)	0.0 (-1.7, 1.7)	0.4 (-1.3, 2.1)	1.4 (-0.6, 3.4)
Malathion	0.3 (-0.8, 1.3)	0.1 (-0.9, 1.2)	0.8 (-0.2, 1.8)	-0.4 (-1.2, 0.4)	-0.6 (-1.4, 0.2)	-1.1 (-2.0, -0.1)
Oxydemeton methyl	0.5 (-2.9, 3.8)	-0.4 (-3.7, 2.9)	0.8 (-2.5, 4.1)	-1.3 (-3.8, 1.2)	-3.3 (-5.9, -0.6)	-2.5 (-5.5, 0.5)
Naled	-0.8 (-2.2, 0.5)	-0.2 (-1.5, 1.1)	-1.4 (-2.7, -0.1)	0.5 (-0.5, 1.5)	0.4 (-0.6, 1.4)	1.0 (-0.2, 2.2)
Dimethoate	1.1 (-1.4, 3.7)	-0.4 (-2.9, 2.1)	1.3 (-1.2, 3.7)	0.8 (-1.1, 2.7)	1.0 (-1.0, 3.0)	-1.5 (-3.7, 0.8)
Carbamates						
Methomyl	0.2 (-1.5, 1.9)	0.7 (-1.0, 2.4)	-0.6 (-2.3, 1.1)	-0.2 (-1.5, 1.1)	-0.5 (-1.8, 0.8)	-0.9 (-2.4, 0.7)
Pyrethroid						
Permethrin	0.3 (-2.2, 2.8)	-0.1 (-2.6, 2.4)	0.7 (-1.8, 3.1)	-0.1 (-2.0, 1.8)	1.0 (-1.0, 3.0)	-0.9 (-3.2, 1.3)
Neonicotinoid						
Imidacloprid	0.0 (-3.0, 2.9)	-0.3 (-3.2, 2.6)	0.9 (-1.9, 3.7)	0.3 (-1.8, 2.5)	1.6 (-0.6, 3.9)	1.9 (-0.7, 4.4)
Fungicide						
Mn-Fungicides	-2.5 (-4.8, -0.3)	-1.6 (-3.9, 0.6)	-1.7 (-3.9, 0.5)	-0.6 (-2.3, 1.1)	0.0 (-1.8, 1.7)	0.4 (-1.6, 2.4)
Herbicide						
Glyphosate	1.4 (0.3, 2.4)	0.6 (-0.5, 1.7)	1.3 (0.3, 2.4)	0.1 (-0.7, 0.9)	0.0 (-0.8, 0.9)	-0.1 (-1.0, 0.9)

Notes: *k*, number of participants with data for at least one time point; *n*, number of observations from both time points. Higher score for each BASC outcome indicates more symptomatic behavior.

[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, language of assessment, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment, agricultural applications of 11 pesticides included in prenatal assessment during the prenatal period.

[b]*n*=793; *k*=427

[c]*n*=796; *k*=427

[d]*n*=797; *k*=427

Table S3.10. Adjusted associations [β (95% CI)] of two-fold increase in pesticide use within 1 km of residence *during childhood (0-5 years)* with *youth-reported* behavioral and emotional problems at age 16 and 18 years using linear mixed effects regression with all exposure variables included simultaneously.

	Internalizing problems[b]	Depression[c]	Anxiety[c]	Hyperactivity[d]	Attention problems[d]
Organophosphates					
Acephate	0.5 (-1.5, 2.5)	0.2 (-1.7, 2.1)	-0.8 (-3.0, 1.4)	1.2 (-0.7, 3.0)	-0.1 (-1.9, 1.8)
Chlorpyrifos	-1.2 (-2.9, 0.5)	-1.5 (-3.1, 0.1)	-1.1 (-2.9, 0.8)	0.0 (-1.5, 1.6)	0.1 (-1.4, 1.7)
Diazinon	0.4 (-1.8, 2.6)	0.5 (-1.6, 2.6)	0.7 (-1.7, 3.1)	0.4 (-1.6, 2.3)	-0.2 (-2.2, 1.8)
Malathion	-0.7 (-1.7, 0.3)	-0.3 (-1.3, 0.7)	-0.3 (-1.5, 0.8)	-0.4 (-1.3, 0.6)	-0.9 (-1.8, 0.1)
Oxydemeton methyl	-0.1 (-3.4, 3.2)	0.6 (-2.5, 3.8)	1.0 (-2.6, 4.6)	-2.3 (-5.3, 0.6)	-1.1 (-4.1, 1.9)
Naled	0.5 (-0.8, 1.8)	0.3 (-1.0, 1.5)	-0.4 (-1.8, 1.0)	0.1 (-1.1, 1.3)	1.4 (0.2, 2.6)
Dimethoate	2.5 (0.0, 5.0)	1.9 (-0.5, 4.3)	1.9 (-0.8, 4.7)	2.4 (0.2, 4.7)	1.3 (-1.0, 3.6)
Carbamates					
Methomyl	-1.4 (-3.1, 0.2)	-1.1 (-2.7, 0.5)	-0.2 (-2, 1.6)	-0.9 (-2.4, 0.6)	-1.0 (-2.6, 0.5)
Pyrethroid					
Permethrin	0.3 (-2.2, 2.8)	0.1 (-2.3, 2.4)	0.6 (-2.1, 3.3)	-0.3 (-2.5, 1.9)	0.0 (-2.3, 2.3)
Neonicotinoid					
Imidacloprid	-0.8 (-3.7, 2.1)	-1.6 (-4.3, 1.2)	-1.7 (-4.8, 1.4)	-0.2 (-2.8, 2.3)	0.7 (-1.9, 3.4)
Fungicide					
Mn-Fungicides	-0.3 (-2.6, 1.9)	-0.3 (-2.4, 1.8)	-0.2 (-2.6, 2.2)	0.6 (-1.5, 2.6)	0.5 (-1.6, 2.5)
Herbicide					
Glyphosate	1.0 (-0.1, 2.0)	1.3 (0.3, 2.3)	0.9 (-0.3, 2.1)	-0.6 (-1.6, 0.4)	-0.1 (-1.1, 0.9)

Notes: *k*, number of participants with data for at least one time point; *n*, number of observations from both time points. Higher score for each BASC outcome indicates more symptomatic behavior.

[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment, agricultural applications of 11 pesticides included in prenatal assessment during the prenatal period.

[b]*n*=783; *k*=426

[c]*n*=786; *k*=426

[d]*n*=785; *k*=426

[e]*n*=784; *k*=426

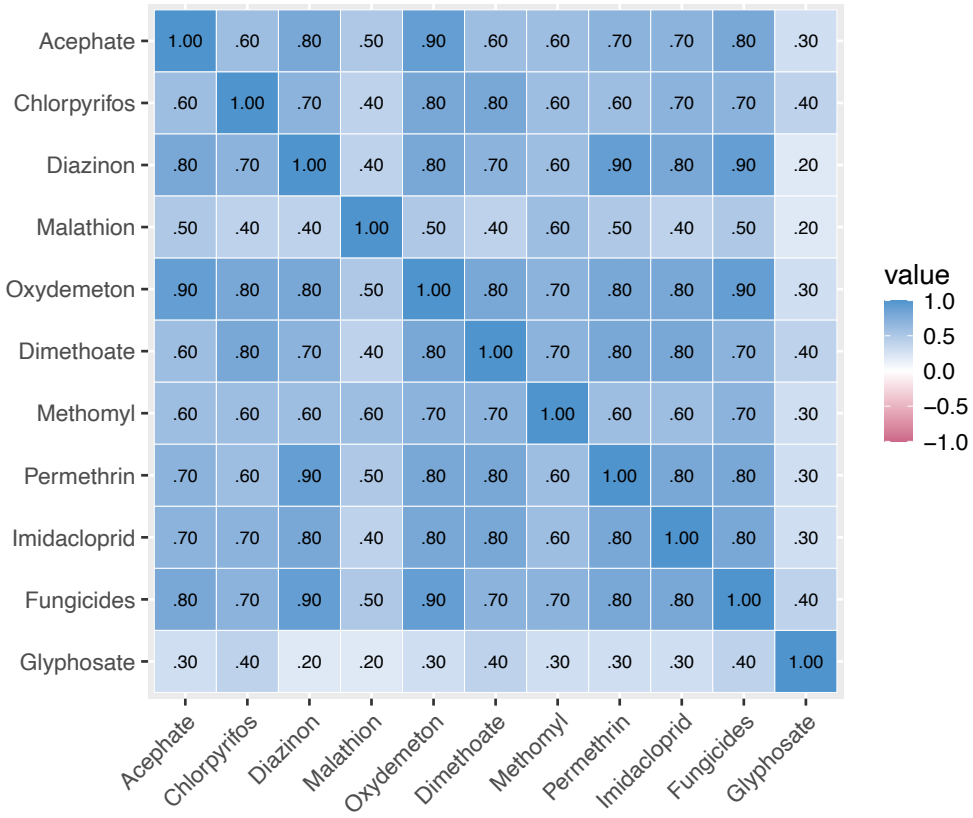

Figure S3.1. Spearman correlation coefficients of agricultural pesticide use within 1 km of home during the prenatal period.

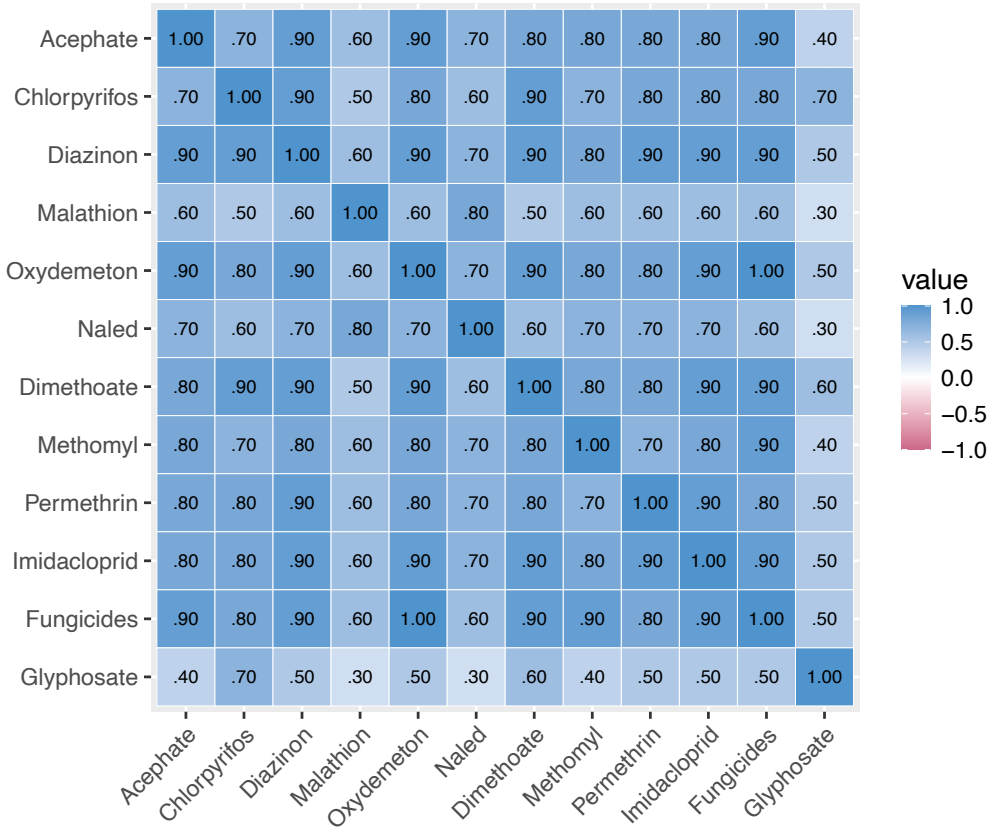

Figure S3.2. Spearman correlation coefficients of agricultural pesticide use within 1 km of home during the postnatal period.

CHAPTER 4. Interactions of agricultural pesticide use near home during pregnancy and adverse childhood experiences on adolescent neurobehavioral development in the CHAMACOS cohort

4.1 Introduction

Previous research has consistently shown that prenatal and early-life exposure to organophosphate (OP) pesticides is associated with poorer neurodevelopment, including cognitive function,[23-25,27,28,30] traits related to autism spectrum disorder (ASD),[34,38,131,223] and behavioral problems.[26,33,130] Specifically, research has identified associations of OP pesticide exposure and increased hyperactivity/inattention[26,33] and internalizing behaviors such as depression and anxiety[218,224,225] during childhood and adolescence. Studies have also shown associations of early-life adversity, or "toxic stress", with poorer cognitive and neurobehavioral development.[226-229] However, studies to date have largely examined environmental and social exposures separately.[230] Growing evidence suggests that the detrimental effects of environmental neurotoxicants may be magnified by early-life adversity[49-51,231,232] and that these exposures are likely to co-occur,[29,233] underscoring the importance of examining their joint effects.

Research examining joint exposures to social adversity and environmental toxicants has shown synergistic associations on cognitive and behavioral outcomes. However, these studies have focused primarily on lead,[52-57] air pollutants,[58-60] and environmental tobacco smoke.[61,62] There are gaps in the literature on potential interactions of early-life adversity and other environmental neurotoxicants, such as pesticides. In previous analyses from the Center for the Health Assessment for Mothers and Children of Salinas (CHAMACOS), we found that greater total adversity and domain-specific adversity (i.e., poor learning environment for boys and adverse parent-child interactions for girls) magnified associations between prenatal OP pesticide exposure -- assessed via dialkylphosphate (DAP) metabolites -- and decreased Intelligence Quotient (IQ) at age 7 years.[63]

In addition to considering the joint impacts of chemical and non-chemical stressors, emerging evidence highlights the importance of employing statistical methods to efficiently evaluate the impacts of exposure to mixtures of highly correlated environmental chemicals.[234] In recent analyses, we employed Bayesian Hierarchical Modeling (BHM) to evaluate associations of applications of multiple agricultural pesticide within 1 km of the home during the prenatal and early childhood (ages 0-5) periods and maternal- and youth-reported internalizing and externalizing behaviors in CHAMACOS, a cohort of low-income Mexican-American youth living in the agricultural Salinas Valley, California.[235] We observed modest associations of higher internalizing behaviors and attention problems in association with a two-fold increase in applications of OP pesticides such as chlorpyrifos, diazinon, and dimethoate near the home during the prenatal period. Here, we extend this analysis to examine potential interactions of agricultural pesticide use with adverse childhood experiences (ACEs) and hypothesize that associations of pesticides with neurodevelopment are stronger among those experiencing more ACEs.

4.2 Methods

4.2.1 Study Population

Information about participant recruitment and study procedures have been described previously.[236] Briefly, CHAMACOS is a longitudinal cohort study examining the health impacts

of prenatal and early-life exposure to pesticides and environmental chemicals among children born in the agricultural Salinas Valley, California. We recruited pregnant women who met eligibility criteria (≥18 years old, <20 weeks gestation, Spanish- or English-speaking, qualified for low-income health insurance, and planning to deliver at the county hospital) from community clinics serving low-income Latino patients in 1999-2000. Of the 601 women enrolled at baseline, 527 (88%) remained in the study through delivery of a live-born singleton and 337 (56%) remained in the study through the child's 9-year assessment (referred to henceforth as CHAM1). We expanded the cohort in 2009-2011 and recruited an additional 305 9-year-old Salinas Valley residents whose mothers met eligibility criteria (were ≥18 years at delivery, Spanish- or English-speaking, qualified for low-income health insurance during pregnancy, delivered child in local hospital, and had sought prenatal care in the first trimester) (referred to henceforth as CHAM2). In total, 595 participants (CHAM1 and CHAM2) remained in the cohort through the 16-year study visit and 478 participants had also completed the 18-year study visit by March 2020, when data collection was paused due to the COVID-19 pandemic.

Study staff administered detailed questionnaires in either English or Spanish to mothers of CHAM1 participants at two time points during pregnancy, after delivery, and at multiple points throughout childhood. CHAM2 mothers were administered a comprehensive baseline interview when their children were enrolled at 9 years, and all mothers (CHAM1 and CHAM2) completed identical assessments when their children were 10.5, 12, 14, 16, and 18 years of age. CHAMACOS youth were interviewed in English directly starting at age 10.5 years. We limited the current analysis to participants with 1) a prenatal address that could be geocoded (n=814), 2) maternal- or youth-reported behavioral outcomes at the 16- or 18-year visit (n=473), and 3) childhood adversity reported retrospectively at the 18-year assessment (n=466) (total n=458).

The University of California Berkeley Committee for the Protection of Human Subjects approved all study activities. We obtained written informed consent from all mothers at all study visits. Youth provided written assent at age 16 years and written consent at age 18 years.

4.2.2 Estimation of agricultural pesticide use near home

Exposure assessment procedures have been described elsewhere.[235] Briefly, we used California's Pesticide Use Reporting (PUR) database to characterize wind-adjusted use of agricultural pesticides within 1 km of each participant's residences during the prenatal period. We included 11 pesticides that met the following criteria: 1) have evidence of neurotoxicity in humans or animals; 2) had more than 4,500 kg applied in Monterey County during the prenatal period; and 3) were used within 1 km of the home of at least 50% of CHAMACOS participants during the prenatal period. We $\log_2$-tranformed all pesticide use estimates and measures of association correspond to a two-fold increase in pesticide use.

4.2.3 Behavioral assessment

At the 16- and 18-year study visits, mothers were interviewed on the emotional and behavioral problems of their child using the Behavior Assessment for Children, second edition (BASC-2)[142]. Youth independently completed the BASC-2 Self-Report of Personality (SRP). We considered maternal- and youth-reported scores from the internalizing problems composite scale, as well as the hyperactivity and inattention subscales. We examined BASC-2 scores as age- and sex-standardized T-scores (M=50, SD=10).

4.2.4 Adverse Childhood Experiences

At the 18-year visit, young adult participants completed an adaptation of the Centers for Disease Control and Prevention (CDC) Adverse Childhood Experiences (ACE) survey,[237] which inquires retrospectively about adverse events in the first 18 years of life (e.g., parent separation), and has shown good predictive validity.[238] Participants used Computer Assisted Personal Interviews (CAPIs) to confidentially answer questions about ACEs. The survey included two parts: in the first, we listed seven events and asked participants to report whether they had experienced 0, 1, 2, 3, 4 or 5+ of these events; in the second part, we listed an additional seven events and asked participants to respond to each question individually indicating whether they had experienced that event. We summed the number of events reported from these two categories and considered interactions with ACEs dichotomized as low as (0-2) or high (3+).[239,240]

4.2.5 Covariate information

We collected detailed covariate information about the prenatal period and selected the following confounders *a priori* using a directed acyclic graph:[145] maternal age (continuous), years spent in the US (categorical: ≤5 years, >5 years but not born in US, born in US), education (categorical: ≤6th grade, 7th-12th grade, completed high school), and marital status (dichotomous: not married/not living as married vs. married/living as married). We also adjusted models for the following predictors of the outcomes selected *a priori*: maternal depression status at the 9-year assessment (categorical: yes vs. no) assessed using the Center for Epidemiologic Studies Depression Scale (CES-D),[146] child sex (dichotomous), exact age at assessment (continuous), Home Observation Measurement of the Environment-Short Form (HOME-SF)[147] z-score at the 10.5-year visit (continuous) to assess enrichment in the home, household income at the time of assessment (categorical: at or below poverty line vs. above poverty line), and language of maternal interview for the BASC outcomes (English vs. Spanish).

4.2.6 Statistical analyses

We used a two-stage linear mixed effects BHM[136,148-154] to examine associations of all 11 pesticides included simultaneously with BASC scores assessed at the 16- and 18-year study visits. Details of the analysis have been described previously.[235] Briefly, in the first stage, we regressed each BASC outcome on the exposures and covariates in a single linear mixed-effects model with a random subject-specific effect as: $E[Y \mid X,W,u] = \alpha + X\beta + W\gamma + u$; where X is the vector of all pesticides, W is the vector of confounders, and u is a normally distributed subject-specific random effect. In the second stage, we modeled the exposure effects (β) as a function of an exchangeability matrix Z, coefficient vector π, and residual error δ (normally distributed with mean zero and precision τ) as: $\beta = Z\pi + \delta$. We incorporated a Z matrix with indicator variables (0/1) for the class to which each individual pesticide belongs (i.e., OPs, carbamates, pyrethroids, neonicotinoids, fungicides, and herbicides), asserting our *a priori* expectation that pesticides from the same class would have similar associations with the outcome (Table S4.1).

We extended our previous analyses examining associations of applications of these 11 pesticides within 1 km of the home during the prenatal period and neurobehavioral outcomes by considering interactions with ACEs. We included an interaction term between each pesticide and the number of ACEs (categorized as 0-2 or 3+) in the first stage model. ACEs were reported by participants retrospectively at the 18-year assessment, and we made the assumption that all events occurred prior to age 16 years and thus preceded the outcome of interest (behavioral

outcomes assessed at the 16- and 18-year visits). We considered there to be meaningful evidence of modification if the 95% credible intervals (CrIs) for the product-interaction term did not cross the null value, following similar criterion previously used in environmental BHM analyses.[153] We examined sex-specific effects by stratifying models by child sex.

We specified vague priors on nuisance parameters (α, γ, π) and pre-specified the precision for δ (i.e., τ) under the assumption that the β parameters would lie within $\pm$ 0.5 SD of the mean of the BASC outcome of interest in our population (i.e., from -5 to 5 in the normative sample). Models were specified in a Fully Bayesian framework[138] and the posterior distribution of all model parameters was estimated via Markov Chain Monte Carlo (MCMC) sampling,[156] and summarized via posterior medians and 95% CrIs. We used Just Another Gibbs Sampler (JAGS)[157], obtaining 50,000 samples after an initial burn-in of 10,000. We assessed convergence graphically using trace plots, autocorrelation plots, and density plots,[156] and statistically using the Geweke test[158] and Gelman-Rubin test statistic.[159] All analyses were conducted using R Version 3.6.2.

4.2.7 Sensitivity analyses

Because ACEs retrospectively reported at age 18 years may not have occurred prior to the 16-year assessment (and thus prior to the 16-year behavioral outcomes included in linear mixed effects models), we ran the same hierarchical models with 18-year outcome data only.

4.3 Results

Table 4.1 shows the sociodemographic characteristics of the participants included in this analysis (n=458). Mothers were predominantly born in Mexico (89%) and had low levels of education (43% had <6th grade education at baseline) and high household poverty levels (56% at or below poverty level at 16-year assessment). Maternal- and youth-report of internalizing behaviors, hyperactivity, and attention problems were similar across most sociodemographic characteristics (Table S4.2). Notably, participants with high ACEs tended to have higher scores for maternal- and youth-report of all outcomes compared to those with low ACEs (Table S4.2).

4.3.1 Internalizing problems

The only pesticide for which we observed modification of exposure-outcome associations for internalizing problems was malathion (Table 4.2). Specifically, we found that a two-fold increase in malathion applications within 1 km of the home during pregnancy was associated with a 1.9-point increase (95% CrI: 0.2, 3.7) in maternal-report of internalizing problems among youth who experienced high ACEs (3+), compared with -0.1 points (95% CrI: -1.2, 0.9) among youth who experienced low ACEs (0-2) (95% CrI for interaction term: 0.1, 4.0; Table S4.3). Malathion use was associated also associated with a 2.1-point increase (95% CrI: 0.4, 3.8) in youth-reported internalizing problems among those with high ACEs, compared with 0.2 points (95% CrI: -0.8, 1.2) among those with low ACEs (Table 4.3) (95% CrI for interaction term: 0.1, 3.8; Table S3). Associations for both maternal- and youth-report were largely driven by males (Table S4.4). For example, the effect of a two-fold increase in malathion applications with youth-reported internalizing problems was 1.2 (95% CrI: 0.0, 2.5) among males, compared to -0.1 (95% CrI: -1.4, 1.3) among females (Table S4). This effect was even more pronounced when considering interactions with ACEs; for boys, malathion use near the home was associated with a 4.9-point increase (95% CrI: 1.9, 8.0) in self-reported internalizing problems among those with

high ACEs, compared to a 0.8-point increase (95% CrI: -0.4, 2.1) among those with low ACEs. For girls, the effect was 1.4 (95% CrI: -0.8, 3.4) among those with high ACEs and -0.3 (95% CrI: -1.8, 1.2) among those with low ACEs (Table S4).

In addition to malathion, a two-fold increase in Mn-containing fungicides within 1 km of the home during pregnancy was associated with increased youth report of internalizing problems among participants with high ACEs (β = 2.1; 95% CrI: -0.1, 4.3), but not low ACES (β = 0.4; 95% CrI: -1.0, 1.8; Table 3); however, the 95% CrI for the interaction term included the null (-0.7, 4.1; Table S4.3). We did not observe evidence of modification by ACEs for associations of any other pesticides with maternal- or youth-reported internalizing problems.

4.3.2 Hyperactivity and attention problems

Results examining interactions of pesticide use near the home and childhood ACEs were largely null for maternal-reported hyperactivity and attention problems among all participants (Table 2) and in sex-stratified analyses (Tables S5 and S6). Notably, a two-fold increase in imidacloprid applications within 1 km of the home during pregnancy was associated with decreased maternal-reported attention problems among those with high ACEs (β = -6.3, 95% CrI: -11.5, -1.1), but not low ACES (β = -2.5; 95% CrI: -5.4, 0.4; Table 4.2); the 95% CrI for the interaction term included the null (-8.5, 0.8; Table S4.3). The inverse association of imidacloprid and ACEs on maternal-reported hyperactivity was stronger among girls (Table S5). We did not observe associations of imidacloprid and youth-reported attention problems.

A two-fold increase in malathion applications was associated with increased youth-reported hyperactivity among those with high ACEs (β = 1.7; 95% CrI: 0.1, 3.2), but not low ACEs (β = -0.7; 95% CrI: -1.6, 0.3) (95% CrI for interaction term: 0.6, 4.0) (Table 3). Additionally, a two-fold increase in dimethoate applications was associated with increased youth-reported hyperactivity and attention problems among those with high ACEs. For hyperactivity, the effect was an increase of 2.9 points (95% CrI: -0.1, 5.8) among those with high ACEs and -0.1 points (95% CrI: -2.1, 2.0) among those with low ACEs (Table 4.3); 95% CrI for interaction term: 0.1, 6.3 (Table S4.3). For attention problems, the effect was 4.0 points (95% CrI: 0.9, 6.9) among those with high ACEs and 0.8 points (95% CrI: -1.3, 3.0) among those with low ACEs (Table 4.3); 95% CrI for interaction term: 0.0, 6.2 (Table S4.3). There was not meaningful evidence of sex-specific effects for youth-reported hyperactivity (Table S4.5) or attention problems (Table S4.6).

4.3.3 Sensitivity analyses

Results from models in which we included only outcome data reported at the 18-year assessment, thus ensuring the ACEs occurred prior to the outcome, were similar to results from mixed-effects models including 16 and 18-year outcome data (Table S4.7 for maternal-reported outcomes; Table S4.8 for youth-reported outcomes); however, credible intervals from models employing just the 18-year outcome data were much wider given the smaller sample size. Overall, our interpretations were qualitatively similar.

4.4 Discussion

In previous analyses in this population, we observed some associations of OP pesticide use (i.e., chlorpyrifos, dimethoate, diazinon) near the home during pregnancy and modestly increased maternal- and youth-reported internalizing and externalizing problems at ages16 and 18 years.[235]

In this paper, we extend these analyses by considering interactions of nearby agricultural pesticide use and ACEs. We observed little evidence of modification of associations between agricultural pesticide use near maternal homes during pregnancy and maternal-and youth-reported behavioral and emotional problems during adolescence by ACEs. For internalizing problems, only associations with malathion were modified by ACEs; results were consistent across maternal- and youth-report. There was some evidence of increased youth-, but not maternal-, reported hyperactivity and attention problems in association with malathion and dimethoate applications near the home among those with high ACEs. We did not observe meaningful evidence of modification by ACEs for any other pesticides.

Previous studies have shown that factors such as the child's home environment, maternal stress, psychological distress, and poor social support may amplify associations of environmental exposures such as lead, air pollution, environmental tobacco smoke, and heavy metals with childhood cognitive and behavioral outcomes.[52-62,232,241] Nevertheless, only two previous studies to date have examined the joint effects of exposure to pesticides and to social adversity.[29,63] Previous analyses from our cohort indicate that the adverse effects of prenatal metabolites of OP pesticides, DAPs, and IQ at age 7 years were stronger among those with higher levels of total childhood adversity and domain-specific adversity (i.e., poor learning environment for boys and adverse parent-child relationships for girls).[63] In the only other previous study to investigate the impact of co-exposure to pesticides and social factors on neurobehavioral outcomes, investigators found that the child's home environment assessed at age 3 years did not modify the effects of prenatal chlorpyrifos exposure on working memory age at 7 years.[29]

Synergistic effects of early-life exposure to social stressors and environmental chemicals on neurodevelopment have been demonstrated in animal studies.[242-245] These studies, which have largely focused on lead as an environmental exposure, suggest that mechanisms may include altered hypothalamic-pituitary-adrenal (HPA) axis function,[246,247] changes in levels of neurotransmitters and proteins in regions of the brain known to mediate learning/behavioral flexibility,[245] and impaired hippocampal volume, functioning, and neurogenesis.[248-251]

In this analysis, we observed that malathion use was associated with increased report of internalizing problems from both mothers and youth among participants experiencing high ACEs, and that effects were stronger among males. Previous studies have identified associations of occupational OP pesticide use and depression or depressive symptoms among farmworkers;[162-167,252,253] fewer studies have examined the role of OP pesticide exposure and internalizing behaviors such as depression or anxiety among children or adolescents. In a previous longitudinal study of 141 children from the Mount Sinai Children's Environmental Health Center study, investigators reported that prenatal dimethyl (DM) OP concentrations were associated with parent-report of BASC internalizing problems at ages 4-9 years.[218] Additionally, a cross-sectional analysis of 529 adolescents ages 11-17 years living in an floricultural community in Ecuador found that that lower acetylcholinesterase (AChE) activity, reflecting greater exposure to the cholinesterase-inhibiting pesticides OPs and carbamates, was associated with higher depression symptoms, particularly among girls.[225] Notably, we observed that associations were much stronger among boys; however, credible intervals from sex-stratified analyses were quite wide given the smaller sample size. Surprisingly, we only observed associations with the pesticide malathion, which is one of the least toxic OP pesticides based on levels of AChE inhibition.[160]

In addition to interactions of malathion and ACEs with maternal- and youth-reported internalizing problems, we observed that malathion and dimethoate were associated with

increased youth-reported hyperactivity and attention problems, respectively, among participants with high ACEs; we did not observe interactions of any pesticides and ACEs for maternal-reported hyperactivity or attention problems. Notably, while youth tend to be more reliable reports or their own internalizing behaviors, mothers may be more reliable reporters of behaviors such as hyperactivity and inattention that can be more easily observed by others.[196] One previous study found that prenatal biomarkers of exposure to chlorpyrifos, another OP pesticide, were associated with increased hyperactivity and inattention at age 3 years among 354 inner-city children.[26] In previous analyses in our cohort, we also found that higher prenatal concentrations of DAPs, non-specific biomarkers of OP pesticide exposure, were associated adversely associated with attention ascertained via maternal report, psychometrician observation, and direct assessment at age 5 years, with stronger effects among boys.[33]

Findings from this study should be interpreted in light of some limitations. First, we did not collect data regarding all specific ACEs participants experienced or the age at which each event occurred, but rather asked participants to retrospectively report the number of ACEs prior to the 18-year study visit. Previous studies suggest that adverse events experienced earlier in childhood (e.g., ages 0-5 years[254]) may have stronger effects on behavioral outcomes than events occurring later in childhood or adolescence. Moreover, it is possible that the retrospective assessment of ACEs at age 18 could have resulted in recall bias, and events occurring earlier in childhood may be particularly prone to bias. Additionally, we cannot say with certainty that the ACEs reported at age 18 occurred prior to the 16-year behavioral outcomes. However, results from sensitivity analyses in which we included only 18-year outcome data were similar to results from main analyses. Second, as discussed in previous analyses,[235] use of nearby agricultural pesticide use to characterize potential pesticide exposure may result in exposure misclassification. Although several studies show significant relationships between nearby use of some agricultural pesticides and residential contamination,[77,143] the physical-chemical properties of individual pesticides, wind speed and direction during applications, precipitation, and other factors will affect the likelihood of actual human exposure.[255-257] Future studies should consider interactions of exposures to pesticides and adversity using more accurate methods of exposure assessment, such as repeated biomarker measurements. Third, we did not examine interactions with pesticide use near the home during early childhood, which we may consider in future analyses.

This study also has notable strengths and builds upon the literature in a number of ways. Previously, we examined associations between applications of mixtures of agricultural pesticides near the home during pregnancy and maternal- and youth-reported internalizing and externalizing behavior during adolescence; here we extend these analyses by considering interactions with childhood adversity. CHAMACOS is a large, well-characterized cohort with rich collection of exposure, covariate, and outcome data assessed longitudinally. We collected behavioral measures from two reporters (i.e., mothers and youth) and adversity measures from youth using validated scales. We leveraged California's unique and comprehensive PUR database to create detailed exposure estimates of nearby agricultural pesticide use during pregnancy, allowing us to examine associations with mixtures of pesticides. While some previous studies have evaluated interactions of chemical and non-chemical stressors using frequentist methods, we are the first to examine potential exposure to mixtures of pesticides (assessed via agricultural pesticide use near the home) and social adversity. Additionally, this study is the first to examine interactions of environmental neurotoxicants and adversity on behavioral outcomes measured longitudinally into adolescence and young adulthood.

4.5 Tables and Figures

Table 4.1. Sociodemographic characteristics of CHAMACOS study participants with data on 16 or 18-year behavioral outcomes, agricultural pesticide use near home during prenatal period, and Adverse Childhood Experiences (*n*=458).

	n (%) or median (P25-P75)
Maternal/household characteristics	
Age at enrollment (years)	26 (22-30)[c]
Country of birth	
Mexico or other	407 (88.9)
U.S.	51 (11.1)
Years in the U.S. at delivery	
≤5	222 (48.5)
>5, but not born in U.S.	196 (42.8)
Born in U.S.	40 (8.7)
Education at baseline	
≤6th grade	195 (42.6)
7th-12th grade	158 (34.5)
≥High school graduate	105 (22.9)
Marital status at baseline	
Not married/not living as married	81 (17.7)
Married/living as married	377 (82.3)
Maternal depression at 9-year visit (≥16 CES-D score)[a]	
No	325 (71.0)
Yes	133 (29.0)
Household income at 16-year assessment[a]	
At or below poverty level	258 (56.3)
Above poverty level	200 (43.7)
Language of 16-year maternal interview[a]	
English	56 (12.2)
Spanish	402 (87.8)
HOME z-score at 10.5-year assessment[b]	0.2 (-0.6, 0.6)[c]
Child characteristics	
ACEs	1 (0-3)[c]
Low (0-2)	331 (72.3)
High (3+)	127 (27.7)
Child's sex	
Boy	216 (47.2)
Girl	242 (52.8)
Exact age at 16-year assessment	16.3 (16.1, 16.5)[c]
Exact age at 18-year assessment	18.0 (18.0, 18.1)[c]

[a]Missing data filled in from data collected at earlier or later time points. *n*=40 participants missing maternal depression at 9-year assessment; 7 missing poverty status at 16-year assessment; 16 missing maternal language of 16-year assessment.
[b]Missing data filled in from earlier or later assessments for 13 participants missing HOME z-score at 10.5-year assessment; filled in as median HOME z-score observed for population included in this analysis for one participant missing HOME z-score at all visits.
[c]Median (P25, P75) of continuous variables

Table 4.2. Adjusted[a] associations [β (95% CrI)] of interaction of two-fold increase in neurotoxic pesticide use within one kilometer of residence during pregnancy and childhood ACEs[b] with *maternal report* of behavioral and emotional problems at age 16 and 18 years using Bayesian Hierarchical Modeling (BHM) (all participants: *n*=458, *k*=916; low ACEs: *n*=331, *k*=662; high ACEs: *n*=127, *k*=254).

	Internalizing problems			Hyperactivity			Attention problems		
	All participants	Low ACEs	High ACEs	All participants	Low ACEs	High ACEs	All participants	Low ACEs	High ACEs
OPs									
Acephate	0.0 (-1.7, 1.6)	0.0 (-1.8, 1.8)	0.0 (-2.7, 2.7)	-0.3 (-1.6, 1.0)	-0.4 (-1.8, 0.9)	0.0 (-2.1, 2.0)	-0.3 (-1.9, 1.2)	-0.3 (-1.9, 1.4)	-0.5 (-3.0, 1.9)
Chlorpyrifos	1.0 (-0.3, 2.3)	0.4 (-1.1, 1.8)	0.8 (-1.5, 3.1)	0.4 (-0.6, 1.4)	0.2 (-0.9, 1.3)	0.3 (-1.4, 2.1)	0.0 (-1.2, 1.1)	-0.2 (-1.5, 1.1)	0.0 (-2.1, 2.1)
Diazinon	-0.7 (-2.2, 0.9)	-0.4 (-2.0, 1.2)	-1.0 (-3.9, 1.9)	-0.3 (-1.5, 0.9)	-0.6 (-1.8, 0.7)	0.5 (-1.8, 2.6)	0.1 (-1.3, 1.5)	0.2 (-1.3, 1.7)	-0.6 (-3.3, 2.0)
Malathion	0.3 (-0.6, 1.3)[c]	-0.1 (-1.2, 0.9)	1.9 (0.2, 3.7)	-0.1 (-0.8, 0.6)	0.0 (-0.8, 0.8)	-0.2 (-1.5, 1.2)	0.2 (-0.7, 1.0)	0.3 (-0.7, 1.2)	0.0 (-1.6, 1.6)
Oxydemeton methyl	-0.1 (-2.5, 2.3)	0.5 (-2.0, 3.0)	-0.4 (-4.2, 3.3)	-0.3 (-2.2, 1.5)	-0.5 (-2.4, 1.4)	0.4 (-2.5, 3.2)	-0.1 (-2.3, 2.0)	-0.2 (-2.5, 2.1)	0.4 (-3.0, 3.8)
Dimethoate	0.2 (-1.9, 2.4)	0.2 (-2.1, 2.6)	0.8 (-2.7, 4.2)	0.4 (-1.3, 2.1)	0.5 (-1.3, 2.3)	0.3 (-2.3, 2.9)	1.4 (-0.6, 3.4)	1.2 (-1.0, 3.3)	2.0 (-1.1, 5.1)
Carbamates									
Methomyl	-0.2 (-1.6, 1.1)	0.0 (-1.4, 1.5)	-1.8 (-4.4, 0.8)	0.5 (-0.5, 1.6)	0.5 (-0.6, 1.6)	0.2 (-1.7, 2.1)	0.1 (-1.2, 1.3)	0.2 (-1.1, 1.6)	-0.7 (-3.0, 1.6)
Pyrethroid									
Permethrin	-0.7 (-3.5, 2.1)	-1.1 (-3.7, 1.5)	0.5 (-4.6, 5.5)	0.3 (-1.8, 2.4)	0.0 (-2.1, 2.0)	1.6 (-2.3, 5.4)	0.2 (-2.2, 2.8)	0.0 (-2.4, 2.4)	2.5 (-2.1, 7.2)
Neonicotinoid									
Imidacloprid	-0.8 (-4.2, 2.7)	-1.0 (-4.2, 2.2)	-1.9 (-7.6, 3.9)	-0.3 (-2.9, 2.3)	-0.5 (-2.9, 2.0)	-2.8 (-7.3, 1.6)	-2.9 (-6.0, 0.2)	-2.5 (-5.4, 0.4)	-6.3 (-11.5, -1.1)
Fungicide									
Mn-Fungicides	0.4 (-1.0, 1.8)	0.3 (-1.3, 1.8)	1.1 (-1.2, 3.4)	0.1 (-1.0, 1.2)	0.5 (-0.7, 1.6)	-0.4 (-2.1, 1.4)	0.1 (-1.2, 1.4)	0.2 (-1.2, 1.6)	0.5 (-1.7, 2.6)
Herbicide									
Glyphosate	0.3 (-0.6, 1.1)	0.1 (-0.7, 1.1)	0.6 (-1.2, 2.4)	0.3 (-0.3, 1.0)	0.3 (-0.4, 1.0)	0.6 (-0.8, 1.9)	0.3 (-0.5, 1.0)	0.2 (-0.6, 1.1)	0.1 (-1.5, 1.7)

Notes: *n*, number of participants with data for at least one time point; *k*, number of observations from both time points. Higher BASC scores indicate more symptomatic behavior.

[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, language of assessment, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment.

[b]Low ACEs = 0-2 events; High ACEs = 3+ events

[c]95% CrI for product-interaction term of pesticides and ACEs did not cross the null (95% CrIs available in Table S3).

Table 4.3. Adjusted[a] associations [β (95% CrI)] of interaction of two-fold increase in neurotoxic pesticide use within one kilometer of residence during pregnancy and childhood ACEs[b] with *youth report* of behavioral and emotional problems at age 16 and 18 years using Bayesian Hierarchical Modeling (BHM) (all participants: *n*=458, *k*=916; low ACEs: *n*=331, *k*=662; high ACEs: *n*=127, *k*=254).

	Internalizing problems			Hyperactivity			Attention problems		
	All participants	Low ACEs	High ACEs	All participants	Low ACEs	High ACEs	All participants	Low ACEs	High ACEs
OPs									
Acephate	0.2 (-1.5, 1.8)	0.3 (-1.4, 2.0)	-0.5 (-3.0, 2.1)	-0.2 (-1.7, 1.3)	0.2 (-1.3, 1.8)	-1.9 (-4.1, 0.5)	-0.1 (-1.5, 1.5)	-0.1 (-1.8, 1.5)	0.0 (-2.4, 2.4)
Chlorpyrifos	1.1 (-0.2, 2.4)	0.1 (-1.3, 1.5)	1.0 (-1.3, 3.2)	-0.4 (-1.6, 0.8)	-0.9 (-2.1, 0.4)	-1.0 (-3.1, 1.0)	0.1 (-1.0, 1.3)	-0.5 (-1.7, 0.8)	0.2 (-1.8, 2.3)
Diazinon	0.5 (-1.1, 2.0)	0.8 (-0.7, 2.4)	0.3 (-2.5, 3.0)	0.3 (-1.0, 1.8)	0.1 (-1.3, 1.6)	1.9 (-0.6, 4.6)	0.7 (-0.7, 2.1)	0.9 (-0.5, 2.4)	0.2 (-2.4, 2.8)
Malathion	0.6 (-0.4, 1.5)[c]	0.2 (-0.8, 1.2)	2.1 (0.4, 3.8)	-0.1 (-1.0, 0.7)[c]	-0.7 (-1.6, 0.3)	1.7 (0.1, 3.2)	0.0 (-0.9, 0.8)	-0.2 (-1.2, 0.7)	0.5 (-1.0, 2.0)
Oxydemeton methyl	-1.0 (-3.3, 1.4)	-0.2 (-2.7, 2.2)	-0.8 (-4.4, 2.8)	0.0 (-2.1, 2.2)	0.3 (-2.0, 2.5)	0.9 (-2.4, 4.1)	-0.9 (-3.1, 1.3)	-0.4 (-2.6, 1.9)	-1.4 (-4.7, 2.0)
Dimethoate	-0.6 (-2.8, 1.6)	-0.6 (-2.8, 1.6)	0.7 (-2.5, 4.0)	0.3 (-1.6, 2.3)	-0.1 (-2.1, 2.0)	2.9 (-0.1, 5.8)	1.5 (-0.5, 3.5)[c]	0.8 (-1.3, 3.0)	4.0 (0.9, 6.9)
Carbamates									
Methomyl	-0.4 (-1.7, 1.0)	-0.2 (-1.6, 1.1)	-1.6 (-4.0, 0.9)	0.3 (-0.9, 1.6)	0.4 (-0.9, 1.7)	-0.6 (-2.8, 1.6)	-0.4 (-1.6, 0.9)	-0.3 (-1.6, 1)	-0.6 (-2.9, 1.6)
Pyrethroid									
Permethrin	-0.5 (-3.2, 2.3)	-1.2 (-3.7, 1.3)	-1.4 (-6.2, 3.4)	-1.1 (-3.6, 1.4)	-1.9 (-4.2, 0.4)	-2.7 (-7.2, 1.8)	-1.7 (-4.2, 0.8)	-2.2 (-4.6, 0.1)	-1.4 (-6.1, 3.0)
Neonicotinoid									
Imidacloprid	-1.6 (-5.0, 1.7)	-1.7 (-4.7, 1.3)	-1.6 (-6.9, 3.9)	0.7 (-2.4, 3.8)	0.4 (-2.4, 3.2)	1.0 (-4.0, 6.0)	-1.9 (-5.0, 1.3)	-1.8 (-4.7, 1.0)	-2.5 (-7.6, 2.5)
Fungicide									
Mn-Fungicides	0.6 (-0.8, 2.0)	0.4 (-1.0, 1.8)	2.1 (-0.1, 4.3)	-0.2 (-1.5, 1.0)	0.2 (-1.1, 1.6)	-0.6 (-2.5, 1.4)	0.7 (-0.6, 2.0)	1.0 (-0.4, 2.3)	0.9 (-1.2, 2.9)
Herbicide									
Glyphosate	0.0 (-0.8, 0.8)	0.2 (-0.7, 1.0)	-0.9 (-2.5, 0.8)	0.4 (-0.3, 1.2)	0.7 (-0.1, 1.5)	-0.5 (-2.0, 1.1)	-0.2 (-0.9, 0.6)	0.0 (-0.8, 0.8)	-1.2 (-2.7, 0.4)

Notes: *n*, number of participants with data for at least one time point; *k*, number of observations from both time points. Higher BASC scores indicate more symptomatic behavior.

[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment.

[b]Low ACEs = 0-2 events; High ACEs = 3+ events

[c]95% CrI for product-interaction term of pesticides and ACEs did not cross the null (95% CrIs available in Table S3).

4.6 Supporting Information

Table S4.1. Exchangeability matrix for Bayesian Hierarchical Model (BHM).

	OP	Carbamate	Pyrethroid	Neonicotinoid	Fungicide	Herbicide	ACE
Acephate	1	0	0	0	0	0	0
Chlorpyrifos	1	0	0	0	0	0	0
Diazinon	1	0	0	0	0	0	0
Malathion	1	0	0	0	0	0	0
Oxydemeton methyl	1	0	0	0	0	0	0
Dimethoate	1	0	0	0	0	0	0
Methomyl	0	1	0	0	0	0	0
Permethrin	0	0	1	0	0	0	0
Imidacloprid	0	0	0	1	0	0	0
Mn-Containing Fungicides	0	0	0	0	1	0	0
Glyphosate	0	0	0	0	0	1	0
ACE	0	0	0	0	0	0	1
Acephate * ACE	1	0	0	0	0	0	1
Chlorpyrifos * ACE	1	0	0	0	0	0	1
Diazinon * ACE	1	0	0	0	0	0	1
Malathion * ACE	1	0	0	0	0	0	1
Oxydemeton methyl * ACE	1	0	0	0	0	0	1
Dimethoate * ACE	1	0	0	0	0	0	1
Methomyl * ACE	0	1	0	0	0	0	1
Permethrin * ACE	0	0	1	0	0	0	1
Imidacloprid * ACE	0	0	0	1	0	0	1
Mn-Containing Fungicides * ACE	0	0	0	0	1	0	1
Glyphosate * ACE	0	0	0	0	0	1	1

Table S4.2. Mean ± SD BASC scores[a] from maternal and youth-report by sociodemographic characteristics.

	Maternal internalizing	Maternal hyperactivity	Maternal attention	Youth internalizing	Youth hyperactivity	Youth attention
All participants	49.9 ± 10.8	45.4 ± 8.5	48.7 ± 10.1	49.1 ± 10.8	46.8 ± 10.0	49.0 ± 9.9
Maternal/household characteristics						
Country of birth						
Mexico or other	50.1 ± 10.7	45.2 ± 8.5	48.5 ± 10.1	48.8 ± 10.7	46.5 ± 9.9	48.9 ± 10.1
U.S.	48.2 ± 11.6	46.8 ± 8.6	51.2 ± 9.8	50.9 ± 11.2	49.1 ± 10.3	49.8 ± 8.7
Years in the U.S. at delivery						
≤5	50.4 ± 10.0	44.7 ± 8.2	48.1 ± 10.0	48.8 ± 10.7	46.1 ± 9.9	48.9 ± 9.9
>5, but not born in U.S.	49.7 ± 11.5	46.0 ± 9.0	49.0 ± 10.2	49.1 ± 10.6	47.2 ± 10.1	49.1 ± 10.1
Born in U.S.	47.8 ± 11.5	45.9 ± 8.1	51.5 ± 9.5	50.4 ± 12.4	48.8 ± 9.7	49.8 ± 9.2
Education at baseline						
≤6th grade	49.6 ± 10.9	44.6 ± 8.8	48.4 ± 10.5	48.8 ± 11.1	45.9 ± 9.9	48.6 ± 10.0
7th-12th grade	50.4 ± 10.8	45.4 ± 8.1	48.8 ± 9.7	49.0 ± 10.8	45.8 ± 9.1	49.1 ± 9.8
≥High school graduate	49.6 ± 10.8	46.7 ± 8.7	49.3 ± 9.9	49.8 ± 10.3	49.8 ± 10.8	49.7 ± 9.9
Marital status at baseline						
Not married/living as married	49.1 ± 10.8	46.4 ± 9.7	48.5 ± 10.3	49.8 ± 9.7	48.2 ± 9.5	50.3 ± 10.4
Married/living as married	50.0 ± 10.8	45.2 ± 8.3	48.8 ± 10.1	49.9 ± 11.0	46.5 ± 10.1	48.8 ± 9.8
Maternal depression at 9-year visit (≥16 CES-D score)						
No	48.4 ± 10.5	44.8 ± 8.3	47.9 ± 9.9	48.7 ± 10.6	46.7 ± 9.8	48.5 ± 9.5
Yes	53.5 ± 10.9	46.8 ± 9.1	50.9 ± 10.1	50.0 ± 11.3	47.0 ± 10.6	50.5 ± 10.7
Household income at 16-year assessment						
At or below poverty level	50.0 ± 10.5	45.9 ± 9.2	48.9 ± 10.1	49.1 ± 10.7	46.9 ± 9.9	49.1 ± 9.9
Above poverty level	49.5 ± 9.4	46.4 ± 8.5	50.0 ± 10.0	48.8 ± 11.1	48.1 ± 10.1	49.6 ± 10.2
Language of 16-year maternal assessment						
English	48.5 ± 10.6	47.7 ± 8.9	51.2 ± 9.8	51.2 ± 11.6	49.6 ± 10.8	50.7 ± 10.0
Spanish	50.0 ± 9.9	45.9 ± 8.9	49.2 ± 10.1	48.7 ± 10.7	47.1 ± 9.9	49.1 ± 10.0
Child characteristics						
ACEs						
Low (0-2)	48.8 ± 9.7	44.5 ± 7.0	47.9 ± 9.7	47.0 ± 9.7	45.5 ± 9.4	47.6 ± 9.3
High (3+)	52.8 ± 12.9	47.8 ± 9.7	51.0 ± 10.8	54.7 ± 11.5	50.1 ± 10.8	52.8 ± 10.5
Child's sex						

Boy	50.5 ± 9.2	44.6 ± 7.9	48.5 ± 10.0	48.8 ± 10.7	47.7 ± 10.0	48.5 ± 10.0
Girl	49.3 ± 12.1	46.1 ± 9.1	48.9 ± 10.2	49.4 ± 10.9	46.0 ± 10.0	49.5 ± 9.8

[a]Average score across 16 and 18Y assessments (except for household income and language of maternal assessment, which are reported from the 16Y assessment only)

Table S4.3. 95% CrI from product-interaction term for associations of two-fold increase in neurotoxic pesticide use within one kilometer of residence during pregnancy and ACEs with maternal- and youth-report of behavioral and emotional problems at age 16 and 18 years using Bayesian Hierarchical Modeling (BHM).

	Maternal Report			Youth Report		
	Internalizing Problems	Hyperactivity	Attention problems	Internalizing Problems	Hyperactivity	Attention problems
OPs						
Acephate	-2.9, 2.7	-1.8, 2.6	-2.9, 2.3	-3.5, 2.0	-4.5, 0.4	-2.5, 2.6
Chlorpyrifos	-2.0, 3.0	-1.9, 2.1	-2.1, 2.5	-1.6, 3.2	-2.4, 2.0	-1.5, 2.9
Diazinon	-3.5, 2.3	-1.3, 3.2	-3.5, 1.9	-3.4, 2.3	-0.9, 4.4	-3.4, 2.0
Malathion	0.1, 4.1	-1.6, 1.3	-2.1, 1.5	0.1, 3.8	0.6, 4.0	-1.0, 2.4
Oxydemeton methyl	-4.6, 2.8	-2.0, 3.8	-2.8, 4.1	-4.1, 3.0	-2.7, 4.0	-4.4, 2.3
Dimethoate	-3.0, 4.0	-2.9, 2.5	-2.3, 4.0	-2.0, 4.7	-0.1, 6.0	0.0, 6.2
Carbamates						
Methomyl	-4.6, 0.9	-2.4, 1.8	-3.5, 1.5	-3.9, 1.3	-3.4, 1.3	-2.7, 2.1
Pyrethroid						
Permethrin	-3.0, 6.1	-1.9, 5.1	-1.8, 6.7	-4.7, 4.2	-4.9, 3.3	-3.4, 4.8
Neonicotinoid						
Imidacloprid	-5.8, 4.2	-6.3, 1.5	-8.5, 0.8	-4.8, 4.8	-3.9, 5.0	-5.1, 3.7
Fungicide						
Mn-Fungicides	-1.7, 3.4	-2.7, 1.1	-2.0, 2.6	-0.7, 4.1	-3.0, 1.4	-2.3, 2.2
Herbicide						
Glyphosate	-1.6, 2.3	-1.2, 1.8	-1.9, 1.7	-2.9, 0.8	-2.9, 0.5	-2.9, 0.6

Table S4.4. Adjusted[a] associations [β (95% CrI)] of interaction of two-fold increase in neurotoxic pesticide use within one kilometer of residence during pregnancy and childhood ACEs[b] with maternal and youth report of behavioral and *internalizing problems* at age 16 and 18 years using Bayesian Hierarchical Modeling (BHM), stratified by child sex[c]

	Maternal-Report						Youth-Report					
	Boys			Girls			Boys			Girls		
	All	Low ACEs	High ACEs	All	Low ACEs	High ACEs	All	Low ACEs	High ACEs	All	Low ACEs	High ACEs
OPs												
Acephate	0.1 (-1.8, 1.9)	0.6 (-1.3, 2.5)	0.1 (-2.9, 3.3)	-0.3 (-3.0, 2.3)	-0.5 (-3.3, 2.2)	0.1 (-4.0, 4.4)	0.0 (-2.0, 2.1)	0.6 (-1.5, 2.7)	0.5 (-3.0, 3.9)	-0.1 (-2.5, 2.4)	-0.2 (-2.6, 2.2)	-1.2 (-4.9, 2.4)
Chlorpyrifos	0.5 (-1.0, 1.9)	0.1 (-1.4, 1.6)	-0.5 (-3.5, 2.5)	1.8 (-0.2, 3.9)	1.2 (-1.2, 3.6)	2.0 (-1.2, 5.2)	1.2 (-0.5, 2.9)	0.3 (-1.4, 2.0)	1.0 (-2.3, 4.4)	0.7 (-1.1, 2.7)	-0.4 (-2.5, 1.6)	0.7 (-2.1, 3.6)
Diazinon	-0.4 (-2.1, 1.4)	0.4 (-1.4, 2.1)	-0.7 (-4.2, 2.6)	-0.2 (-2.8, 2.4)	-0.9 (-3.7, 1.8)	0.6 (-3.5, 4.7)	-0.2 (-2.1, 1.8)	1.0 (-1.0, 2.9)	1.1 (-2.7, 5.0)	1.7 (-0.8, 4.0)	0.8 (-1.5, 3.3)	1.6 (-1.9, 5.2)
Malathion	0.4 (-0.7, 1.5)	0.0 (-1.2, 1.1)	2.8 (0.1, 5.6)	-0.1 (-1.6, 1.3)	-0.4 (-2.1, 1.4)	0.6 (-1.8, 3.0)	1.2 (0.0, 2.5)	0.8 (-0.4, 2.1)	4.9 (1.9, 8.0)	-0.1 (-1.4, 1.3)	-0.3 (-1.8, 1.2)	1.4 (-0.8, 3.4)
Oxydemeton methyl	-0.8 (-3.3, 1.7)	-0.8 (-3.4, 1.8)	-1.2 (-5.2, 3.0)	0.3 (-3.3, 3.9)	1.0 (-2.7, 4.7)	-0.7 (-6.0, 4.5)	-0.8 (-3.6, 2.0)	-0.6 (-3.4, 2.2)	-0.6 (-5.3, 4.0)	-0.5 (-3.9, 2.7)	0.6 (-2.7, 3.9)	-0.5 (-5.1, 4.2)
Dimethoate	1.0 (-1.4, 3.5)	1.0 (-1.4, 3.4)	2.6 (-1.4, 6.6)	-1.5 (-4.7, 1.7)	-1.0 (-4.2, 2.4)	-2.4 (-7.2, 2.4)	-0.9 (-3.7, 1.9)	-0.6 (-3.4, 2.1)	0.6 (-3.9, 4.9)	-0.4 (-3.3, 2.6)	0.1 (-2.8, 3.1)	1.3 (-2.9, 5.6)
Carbamates												
Methomyl	-1.2 (-2.9, 0.4)	-1.1 (-2.6, 0.6)	-0.7 (-4.0, 2.7)	1.4 (-0.9, 3.7)	1.6 (-0.7, 3.9)	-0.4 (-4.2, 3.3)	-1.0 (-2.9, 0.9)	-0.9 (-2.6, 0.9)	-0.3 (-3.9, 3.4)	0.1 (-2.0, 2.2)	-0.1 (-2.2, 1.9)	-2.4 (-5.6, 0.9)
Pyrethroid												
Permethrin	-1.7 (-5.2, 1.8)	-2.3 (-5.5, 1.0)	-3.0 (-10.0, 4.0)	-0.4 (-4.7, 3.7)	0.0 (-3.9, 3.9)	1.5 (-5.3, 8.3)	-1.6 (-5.5, 2.4)	-2.9 (-6.4, 0.5)	-6.2 (-13.8, 1.7)	-0.6 (-4.5, 3.3)	-0.6 (-4, 2.7)	-0.6 (-6.5, 5.4)
Neonicotinoid												
Imidacloprid	2.5 (-1.7, 6.7)	1.3 (-2.5, 5.0)	3.7 (-4.2, 11.6)	-4.8 (-10.2, 0.6)	-3.9 (-8.5, 0.9)	-8.0 (-16.2, 0.2)	0.8 (-3.8, 5.5)	-0.6 (-4.6, 3.6)	-0.4 (-8.9, 8.1)	-4.2 (-9.2, 0.8)	-2.5 (-6.6, 1.5)	-3.2 (-10.3, 4.0)
Fungicide												
Mn-Fungicides	0.4 (-1.3, 2.2)	0.2 (-1.5, 1.9)	0.0 (-3.2, 3.3)	0.7 (-1.4, 2.8)	0.5 (-1.8, 2.8)	1.4 (-1.7, 4.6)	1.2 (-0.8, 3.2)	0.9 (-1.0, 2.7)	0.7 (-2.9, 4.3)	0.2 (-1.8, 2.2)	0.0 (-2.0, 2.0)	2.2 (-0.6, 4.9)
Herbicide												
Glyphosate	-0.1 (-1.1, 0.9)	-0.1 (-1.1, 1.0)	0.7 (-1.9, 3.3)	0.9 (-0.4, 2.3)	0.6 (-0.8, 2.1)	1.5 (-1.1, 4.2)	-0.2 (-1.3, 1.0)	0.0 (-1.1, 1.2)	0.6 (-2.3, 3.4)	0.1 (-1.1, 1.3)	0.0 (-1.3, 1.3)	-1.3 (-3.6, 1.0)

Notes: *n*, number of participants with data for at least one time point; *k*, number of observations from both time points. Higher BASC scores indicate more symptomatic behavior.
[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment.
[b]Low ACEs = 0-2 events; High ACEs = 3+ events
[c]Boys: *n*=216, *k*=432; low ACES: *n*=169, *k*=338; high ACES: *n*=47, *k*=94. Girls: *n*=242, *k*=484; low ACEs: *n*=162, *k*=324; high ACEs: *n*=80, *k*=160.

Table S4.5. Adjusted[a] associations [β (95% CrI)] of interaction of two-fold increase in neurotoxic pesticide use within one kilometer of residence during pregnancy and childhood ACEs[b] with maternal and youth report of *hyperactivity* at age 16 and 18 years using Bayesian Hierarchical Modeling (BHM), stratified by child sex[c]

	Maternal-Report						Youth-Report					
	Boys			Girls			Boys			Girls		
	All	Low ACEs	High ACEs	All	Low ACEs	High ACEs	All	Low ACEs	High ACEs	All	Low ACEs	High ACEs
OPs												
Acephate	-0.2 (-1.7, 1.3)	0.1 (-1.5, 1.7)	-1.6 (-4.2, 1.1)	-0.4 (-2.4, 1.4)	-0.9 (-2.9, 1.1)	0.8 (-2.2, 3.9)	0.3 (-1.6, 2.2)	0.8 (-1.1, 2.8)	-1.2 (-4.4, 2.1)	-0.7 (-2.9, 1.4)	-0.8 (-3.0, 1.3)	-2.0 (-5.3, 1.3)
Chlorpyrifos	0.0 (-1.2, 1.2)	0.1 (-1.1, 1.4)	0 (-2.5, 2.6)	1.0 (-0.5, 2.5)	0.8 (-0.9, 2.5)	1.4 (-1.0, 3.7)	-0.2 (-1.7, 1.4)	-0.4 (-2.0, 1.2)	-0.4 (-3.5, 2.9)	-0.6 (-2.3, 1.1)	-1.5 (-3.3, 0.3)	-1.4 (-3.9, 1.1)
Diazinon	0.3 (-1.1, 1.7)	0.1 (-1.4, 1.5)	2.1 (-0.8, 4.9)	-0.4 (-2.3, 1.5)	-0.7 (-2.7, 1.3)	-0.8 (-3.8, 2.2)	0.1 (-1.7, 1.9)	0.0 (-1.9, 1.8)	1.7 (-1.9, 5.4)	1.1 (-1.0, 3.2)	0.5 (-1.5, 2.6)	1.4 (-1.8, 4.6)
Malathion	-0.4 (-1.3, 0.5)	-0.3 (-1.2, 0.7)	-0.7 (-2.9, 1.7)	-0.1 (-1.2, 1.0)	0.2 (-1.1, 1.4)	-0.3 (-2.0, 1.5)	-0.7 (-1.9, 0.5)	-1.0 (-2.2, 0.2)	0.5 (-2.4, 3.4)	0.4 (-0.8, 1.6)	-0.2 (-1.5, 1.2)	1.7 (-0.1, 3.6)
Oxydemeton methyl	-0.6 (-2.6, 1.5)	-0.8 (-2.9, 1.4)	-0.6 (-4.0, 2.9)	-0.3 (-3.0, 2.4)	-0.5 (-3.2, 2.2)	-0.1 (-4.0, 3.7)	0.7 (-2.0, 3.3)	0.5 (-2.2, 3.2)	2.2 (-2.2, 6.6)	-0.2 (-3.1, 2.7)	0.8 (-2.1, 3.8)	-0.1 (-4.2, 4.1)
Dimethoate	2.1 (0.1, 4.1)	2.0 (-0.1, 4.0)	2.9 (-0.4, 6.1)	-1.9 (-4.2, 0.5)	-1.5 (-3.8, 1.0)	-2.6 (-6.1, 1.0)	-1.1 (-3.7, 1.5)	-1.2 (-3.9, 1.4)	-0.5 (-4.7, 3.6)	1.3 (-1.3, 3.8)	1.3 (-1.3, 3.9)	3.4 (-0.3, 7.1)
Carbamates												
Methomyl	-0.3 (-1.7, 1.0)	-0.3 (-1.7, 1.0)	0.1 (-2.7, 2.9)	1.7 (0.0, 3.3)	1.7 (0.0, 3.4)	1.2 (-1.5, 4.0)	0.4 (-1.3, 2.1)	0.8 (-0.9, 2.5)	-1.1 (-4.6, 2.5)	0.3 (-1.6, 2.0)	-0.5 (-2.3, 1.3)	0.4 (-2.5, 3.3)
Pyrethroid												
Permethrin	-1.6 (-4.4, 1.3)	-1.8 (-4.4, 0.8)	-4.1 (-9.9, 1.8)	1.4 (-1.7, 4.5)	1.2 (-1.6, 4.0)	4.7 (-0.3, 9.6)	-1.6 (-5.4, 2.1)	-2.6 (-5.9, 0.8)	-4.5 (-11.8, 2.9)	-0.8 (-4.2, 2.7)	-1.0 (-3.9, 1.9)	-0.6 (-5.9, 4.6)
Neonicotinoid												
Imidacloprid	1.5 (-1.8, 4.9)	1.4 (-1.8, 4.6)	3.1 (-3.3, 9.6)	-2.6 (-6.6, 1.4)	-2.4 (-5.8, 1.0)	-6.7 (-12.6, -0.6)	4.5 (0.1, 9.0)	3.3 (-0.5, 7.3)	7.4 (-0.8, 15.7)	-2.9 (-7.3, 1.4)	-1.8 (-5.4, 1.9)	-2.5 (-8.7, 3.7)
Fungicide												
Mn-Fungicides	-0.3 (-1.7, 1.1)	-0.1 (-1.5, 1.3)	-0.8 (-3.5, 1.9)	0.6 (-1.0, 2.2)	0.8 (-0.9, 2.5)	0.7 (-1.5, 2.9)	-0.8 (-2.6, 1.1)	-0.2 (-2.0, 1.5)	-0.9 (-4.4, 2.6)	0.0 (-1.7, 1.7)	0.4 (-1.4, 2.2)	0.2 (-2.2, 2.6)
Herbicide												
Glyphosate	0.3 (-0.6, 1.1)	0.2 (-0.6, 1.1)	0.1 (-2.1, 2.2)	0.6 (-0.3, 1.6)	0.3 (-0.8, 1.3)	1.0 (-0.9, 3.0)	0.4 (-0.6, 1.5)	0.9 (-0.2, 2.0)	-1.5 (-4.3, 1.2)	0.5 (-0.6, 1.5)	0.1 (-1.0, 1.2)	0.3 (-1.6, 2.4)

Notes: *n*, number of participants with data for at least one time point; *k*, number of observations from both time points. Higher BASC scores indicate more symptomatic behavior.
[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment.
[b]Low ACEs = 0-2 events; High ACEs = 3+ events
[c]Boys: *n*=216, *k*=432; low ACES: *n*=169, *k*=338; high ACES: *n*=47, *k*=94. Girls: *n*=242, *k*=484; low ACEs: *n*=162, *k*=324; high ACEs: *n*=80, *k*=160.

Table S4.6. Adjusted[a] associations [β (95% CrI)] of interaction of two-fold increase in neurotoxic pesticide use within one kilometer of residence during pregnancy and childhood ACEs[b] with maternal and youth report of *attention problems* at age 16 and 18 years using Bayesian Hierarchical Modeling (BHM), stratified by child sex[c]

	Maternal-Report						Youth-Report					
	Boys			Girls			Boys			Girls		
	All	Low ACEs	High ACEs	All	Low ACEs	High ACEs	All	Low ACEs	High ACEs	All	Low ACEs	High ACEs
OPs												
Acephate	-0.9 (-2.8, 1.1)	-0.5 (-2.5, 1.6)	-2.5 (-5.9, 0.8)	0.2 (-1.9, 2.4)	0.1 (-2.2, 2.4)	1.4 (-2.1, 4.8)	0.1 (-1.8, 2.1)	0.2 (-1.7, 2.2)	1.5 (-1.8, 4.7)	-0.5 (-2.7, 1.6)	-0.4 (-2.6, 1.8)	-1.0 (-4.4, 2.4)
Chlorpyrifos	-0.5 (-2.0, 1.0)	-0.5 (-2.1, 1.1)	-1.2 (-4.4, 2.1)	0.8 (-0.9, 2.5)	0.7 (-1.2, 2.7)	1.7 (-0.9, 4.4)	0.3 (-1.3, 1.8)	-0.3 (-1.9, 1.3)	-0.5 (-3.7, 2.7)	-0.1 (-1.9, 1.6)	-0.9 (-2.9, 1.0)	0.1 (-2.7, 2.7)
Diazinon	0.9 (-0.9, 2.8)	1.1 (-0.8, 3.0)	1.7 (-1.9, 5.4)	-0.2 (-2.4, 1.9)	-0.3 (-2.5, 2)	-1.3 (-4.6, 2.1)	0.6 (-1.2, 2.4)	1.0 (-0.9, 2.8)	2.5 (-1.1, 6.2)	1.0 (-1.2, 3.1)	0.9 (-1.3, 3.1)	0.3 (-3.1, 3.6)
Malathion	-0.1 (-1.2, 1.1)	0.0 (-1.3, 1.3)	0.6 (-2.4, 3.6)	0.4 (-0.8, 1.6)	0.7 (-0.7, 2.1)	-0.1 (-2.0, 1.9)	0.5 (-0.7, 1.7)	0.3 (-0.9, 1.5)	3.0 (0.1, 6.0)	-0.6 (-1.8, 0.7)	-0.7 (-2.1, 0.7)	-0.1 (-2.1, 1.9)
Oxydemeton methyl	-0.7 (-3.3, 2.0)	-0.7 (-3.4, 2.1)	-1.4 (-5.9, 3.1)	-0.1 (-3.0, 3.0)	-0.4 (-3.5, 2.6)	-0.4 (-4.7, 3.9)	-0.5 (-3.2, 2.2)	-0.2 (-2.9, 2.5)	0.6 (-3.8, 5.0)	-0.6 (-3.6, 2.3)	0.0 (-3.1, 3.1)	-1.2 (-5.5, 3.1)
Dimethoate	2.3 (-0.4, 4.9)	2.3 (-0.4, 5.0)	3.3 (-1.0, 7.6)	0.0 (-2.6, 2.6)	-0.2 (-2.9, 2.5)	0.5 (-3.5, 4.4)	1.6 (-1.0, 4.2)	1.3 (-1.4, 3.9)	3.7 (-0.5, 7.9)	1.0 (-1.7, 3.6)	0.9 (-1.8, 3.6)	3.1 (-0.9, 7.0)
Carbamates												
Methomyl	0.2 (-1.6, 1.9)	0.1 (-1.6, 1.9)	0.6 (-2.9, 4.2)	0.1 (-1.8, 2.0)	0.4 (-1.5, 2.3)	-0.6 (-3.6, 2.5)	-0.5 (-2.3, 1.3)	-0.3 (-1.9, 1.4)	-0.7 (-4.1, 2.8)	-0.3 (-2.1, 1.6)	-0.6 (-2.6, 1.3)	-0.6 (-3.7, 2.4)
Pyrethroid												
Permethrin	-0.2 (-3.9, 3.4)	-0.8 (-4.3, 2.6)	-2.9 (-10.5, 4.6)	0.2 (-3.2, 3.7)	0.1 (-3.0, 3.3)	4.1 (-1.6, 9.6)	-2.4 (-6.1, 1.2)	-3.2 (-6.5, 0.1)	-5.7 (-13.2, 1.6)	-1.8 (-5.4, 1.7)	-1.7 (-4.8, 1.5)	-1.3 (-7.0, 4.3)
Neonicotinoid												
Imidacloprid	-1.6 (-5.9, 2.8)	-1.2 (-5.2, 2.9)	-1.7 (-10.0, 6.8)	-4.2 (-8.7, 0.3)	-3.6 (-7.6, 0.3)	-8.9 (-15.7, -2.2)	-1.6 (-6.1, 2.7)	-2.5 (-6.3, 1.5)	-4.3 (-12.8, 4)	-1.6 (-6.1, 2.8)	-1.0 (-4.8, 2.8)	-1.4 (-8.1, 5.4)
Fungicide												
Mn-Fungicides	-0.4 (-2.2, 1.5)	-0.4 (-2.2, 1.5)	0.5 (-3.0, 4.1)	0.6 (-1.1, 2.3)	0.7 (-1.2, 2.6)	0.8 (-1.8, 3.3)	0.8 (-1.1, 2.6)	0.9 (-0.9, 2.6)	-0.2 (-3.6, 3.2)	0.9 (-0.9, 2.6)	0.9 (-1.0, 2.8)	1.3 (-1.3, 3.8)
Herbicide												
Glyphosate	0.0 (-1.1, 1.1)	-0.1 (-1.3, 1.0)	0.3 (-2.6, 3.1)	0.7 (-0.4, 1.8)	0.8 (-0.4, 2.1)	-0.1 (-2.2, 2.1)	-0.5 (-1.6, 0.5)	-0.2 (-1.2, 0.9)	-0.9 (-3.6, 1.8)	0.1 (-1.0, 1.2)	-0.1 (-1.3, 1.1)	-0.7 (-2.8, 1.5)

Notes: *n*, number of participants with data for at least one time point; *k*, number of observations from both time points. Higher BASC scores indicate more symptomatic behavior.
[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment.
[b]Low ACEs = 0-2 events; High ACEs = 3+ events
[c]Boys: *n*=216, *k*=432; low ACES: *n*=169, *k*=338; high ACES: *n*=47, *k*=94. Girls: *n*=242, *k*=484; low ACEs: *n*=162, *k*=324; high ACEs: *n*=80, *k*=160.

Table S4.7. Adjusted[a] associations [β (95% CrI)] interaction of two-fold increase in neurotoxic pesticide use within one kilometer of residence during pregnancy and childhood ACEs[b] with *maternal report* of behavioral and emotional problems *at age 18 years only* using Bayesian Hierarchical Modeling (BHM) (all participants: *n*=464; low ACEs: *n*=337; high ACEs: *n*=127).

	Internalizing problems			Hyperactivity			Attention problems		
	All participants	Low ACEs	High ACEs	All participants	Low ACEs	High ACEs	All participants	Low ACEs	High ACEs
OPs									
Acephate	-0.3 (-2.2, 1.6)	-0.1 (-2.2, 1.9)	-0.7 (-3.7, 2.3)	-0.1 (-1.4, 1.2)	-0.1 (-1.5, 1.3)	0.1 (-2.0, 2.1)	0.2 (-1.4, 1.9)	0.3 (-1.5, 2.0)	0.3 (-2.3, 2.9)
Chlorpyrifos	0.8 (-0.6, 2.3)	0.2 (-1.4, 1.8)	0.5 (-2.0, 3.2)	0.1 (-0.9, 1.1)	0.0 (-1.1, 1.1)	0.0 (-1.8, 1.8)	0.2 (-1.1, 1.4)	-0.1 (-1.5, 1.3)	0.2 (-2.1, 2.5)
Diazinon	-0.8 (-2.6, 1.0)	-0.6 (-2.5, 1.2)	-0.9 (-4.1, 2.4)	-0.5 (-1.8, 0.7)	-0.7 (-1.9, 0.6)	-0.4 (-2.7, 1.8)	-0.1 (-1.7, 1.5)	0.2 (-1.4, 1.9)	-1.4 (-4.2, 1.5)
Malathion	0.7 (-0.4, 1.8)	0.2 (-0.1, 1.4)	2.6 (0.6, 4.6)	0.1 (-0.6, 0.9)	0.2 (-0.6, 1.0)	0.5 (-0.9, 1.8)	0.0 (-0.9, 0.9)	0.1 (-0.9, 1.2)	-0.1 (-1.9, 1.6)
Oxydemeton methyl	0.5 (-2.2, 3.1)	1.0 (-1.7, 3.8)	0.8 (-3.2, 4.9)	0.2 (-1.6, 2.0)	0.0 (-1.9, 1.9)	1.4 (-1.4, 4.3)	0.2 (-2.2, 2.4)	0.1 (-2.3, 2.6)	0.8 (-2.8, 4.5)
Dimethoate	0.4 (-2.0, 2.9)	0.4 (-2.1, 3.0)	1.0 (-2.8, 4.8)	0.4 (-1.2, 2.1)	0.6 (-1.1, 2.4)	0.1 (-2.4, 2.7)	1.4 (-0.7, 3.6)	1.1 (-1.2, 3.3)	2.7 (-0.5, 6.1)
Carbamates									
Methomyl	-0.8 (-2.3, 0.8)	-0.4 (-2.0, 1.3)	-2.6 (-5.5, 0.3)	0.4 (-0.7, 1.4)	0.6 (-0.6, 1.7)	-0.8 (-2.8, 1.2)	-0.3 (-1.7, 1.1)	-0.2 (-1.6, 1.3)	-0.8 (-3.4, 1.7)
Pyrethroid									
Permethrin	-0.6 (-3.8, 2.6)	-1.0 (-3.9, 1.9)	0.6 (-5.0, 6.3)	-0.2 (-2.4, 1.9)	-0.4 (-2.5, 1.6)	1.9 (-2.1, 5.9)	-0.5 (-3.2, 2.3)	-0.6 (-3.2, 1.9)	0.9 (-4.1, 5.9)
Neonicotinoid									
Imidacloprid	-0.9 (-4.8, 3.1)	-1.1 (-4.7, 2.5)	-2.9 (-9.4, 3.6)	0.1 (-2.6, 2.8)	-0.3 (-2.8, 2.1)	-2.3 (-6.9, 2.2)	-2.7 (-6.2, 0.8)	-2.5 (-5.6, 0.7)	-5.3 (-11.1, 0.5)
Fungicide									
Mn-Fungicides	0.3 (-1.3, 2.0)	0.1 (-1.6, 1.8)	1.2 (-1.4, 3.8)	0.0 (-1.1, 1.1)	0.3 (-0.9, 1.5)	-0.1 (-1.9, 1.7)	-0.3 (-1.7, 1.1)	-0.2 (-1.8, 1.3)	0.0 (-2.3, 2.4)
Herbicide									
Glyphosate	0.3 (-0.7, 1.2)	0.2 (-0.8, 1.2)	0.8 (-1.3, 2.8)	0.2 (-0.4, 0.9)	0.2 (-0.5, 0.9)	0.6 (-0.8, 2.0)	0.2 (-0.6, 1.0)	0.2 (-0.7, 1.1)	0.0 (-1.8, 1.8)

Notes: *n*, number of participants with data for at least one time point; *k*, number of observations from both time points. Higher BASC scores indicate more symptomatic behavior.
[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment.
[b]Low ACEs = 0-2 events; High ACEs = 3+ events
[c]95% CrI for product-interaction term of pesticides and ACEs did not cross the null (95% CrIs available in Table S3).

Table S4.8. Adjusted[a] associations [β (95% CrI)] interaction of two-fold increase in neurotoxic pesticide use within one kilometer of residence during pregnancy and childhood ACEs[b] with *youth report* of behavioral and emotional problems *at age 18 years only* using Bayesian Hierarchical Modeling (BHM) (all participants: *n*=464; low ACEs: *n*=337; high ACEs: *n*=127).

	Internalizing problems			Hyperactivity			Attention problems		
	All participants	Low ACEs	High ACEs	All participants	Low ACEs	High ACEs	All participants	Low ACEs	High ACEs
OPs									
Acephate	-0.2 (-2.0, 1.7)	0.0 (-1.9, 1.9)	-0.8 (-3.7, 2.0)	-0.5 (-2.1, 1.1)	0.0 (-1.7, 1.7)	-2.2 (-4.8, 0.3)	-0.1 (-1.8, 1.5)	-0.3 (-2.0, 1.4)	0.1 (-2.5, 2.8)
Chlorpyrifos	1.3 (-0.1, 2.8)	0.2 (-1.4, 1.7)	1.5 (-1.0, 3.9)	0.0 (-1.3, 1.3)	-0.5 (-1.9, 0.8)	-0.2 (-2.4, 2.1)	0.5 (-0.8, 1.8)	-0.3 (-1.7, 1.1)	1.4 (-1.0, 3.6)
Diazinon	1.0 (-0.7, 2.8)	1.5 (-0.3, 3.2)	1.1 (-1.9, 4.2)	1.0 (-0.5, 2.6)	0.8 (-0.8, 2.4)	2.1 (-0.7, 4.8)	1.2 (-0.4, 2.8)	1.3 (-0.3, 3.0)	1.0 (-1.8, 3.7)
Malathion	0.7 (-0.4, 1.8)	0.4 (-0.7, 1.5)	2.4 (0.5, 4.3)	0.0 (-0.9, 0.9)	-0.2 (-1.2, 0.7)	1.0 (-0.7, 2.7)	0.1 (-0.9, 1.0)	-0.1 (-1.1, 1.0)	0.8 (-0.9, 2.6)
Oxydemeton methyl	-0.6 (-3.3, 2.0)	-0.1 (-2.7, 2.6)	0.1 (-3.8, 4.0)	0.2 (-2.1, 2.5)	0.4 (-2.0, 2.8)	1.2 (-2.4, 4.7)	-0.8 (-3.2, 1.5)	-0.3 (-2.8, 2.1)	-0.7 (-4.3, 2.9)
Dimethoate	-0.9 (-3.3, 1.5)	-0.9 (-3.4, 1.6)	0.3 (-3.3, 3.9)	0.4 (-1.7, 2.6)	-0.2 (-2.3, 2.0)	2.7 (-0.6, 5.9)	0.4 (-1.7, 2.6)	-0.1 (-2.4, 2.1)	2.6 (-0.7, 5.9)
Carbamates									
Methomyl	-0.5 (-2.0, 1.1)	-0.2 (-1.8, 1.3)	-1.9 (-4.6, 0.8)	0.4 (-1.0, 1.8)	0.5 (-0.8, 1.9)	-0.6 (-3.0, 1.8)	-0.4 (-1.8, 1.0)	-0.1 (-1.5, 1.3)	-1.8 (-4.3, 0.7)
Pyrethroid									
Permethrin	0.4 (-2.7, 3.6)	-0.5 (-3.3, 2.2)	-0.1 (-5.6, 5.2)	-1.3 (-4.1, 1.4)	-2.2 (-4.7, 0.3)	-1.7 (-6.5, 3.3)	-0.3 (-3.1, 2.5)	-0.9 (-3.4, 1.7)	0.2 (-4.8, 5.2)
Neonicotinoid									
Imidacloprid	-2.6 (-6.5, 1.3)	-2.6 (-5.9, 0.8)	-3.9 (-9.9, 2.2)	0.5 (-2.9, 4.0)	0.1 (-3.0, 3.0)	0.1 (-5.3, 5.7)	-2.4 (-5.9, 1.1)	-2.4 (-5.5, 0.7)	-5.2 (-10.8, 0.5)
Fungicide									
Mn-Fungicides	0.0 (-1.6, 1.6)	-0.1 (-1.7, 1.5)	1.2 (-1.3, 3.6)	-0.7 (-2.1, 0.7)	-0.3 (-1.8, 1.1)	-0.3 (-2.4, 2.0)	0.1 (-1.3, 1.6)	0.3 (-1.2, 1.8)	0.6 (-1.7, 2.8)
Herbicide									
Glyphosate	0.7 (-0.3, 1.6)	0.6 (-0.3, 1.6)	0.5 (-1.3, 2.4)	0.7 (-0.1, 1.5)	0.9 (0.0, 1.8)	-0.3 (-1.9, 1.5)	0.0 (-0.9, 0.8)	0.1 (-0.8, 1.0)	-0.7 (-2.5, 1.0)

Notes: *n*, number of participants with data for at least one time point; *k*, number of observations from both time points. Higher BASC scores indicate more symptomatic behavior.
[a]Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment.
[b]Low ACEs = 0-2 events; High ACEs = 3+ events
[c]95% CrI for product-interaction term of pesticides and ACEs did not cross the null (95% CrIs available in Table S3).

CHAPTER 5. Summary of finings, concussions, and future research needs

5.1 Summary of research findings

The purpose of this dissertation was to 1) examine the validity of using FMV and random non-FMV urine samples to estimate cumulative 24-hr OP pesticide dose among children living in an agricultural region., 2) examine associations between mixtures of agricultural pesticides applied near the home during pregnancy and early childhood with adolescent neurobehavioral development, and 3) examine whether associations of pesticide use near the home during pregnancy and adolescent neurobehavioral development are modified by early-life adversity using two datasets of children living in the agricultural Salinas Valley.

Research suggests that assessment of DAPs, which have high inter- and intra-individual variability,[75,98,99] in spot urine samples may not accurately reflect chronic OP pesticide exposure and that reliance solely on spot urine samples may bias epidemiologic analyses and risk assessments.[75] However, because collection of 24-hr urine samples is cumbersome and often cost prohibitive, many risk assessments and pesticide regulations are informed from studies that rely on one or two random spot samples to approximate chronic OP exposure and internal dose. Results of this study suggest that non-FMV spot samples tend to underestimate daily OP dose and may underestimate the percentage of children with dose estimates exceeding regulatory guidelines, which could impact regulatory decision-making. If 24-hr sampling is infeasible, future studies should prioritize the collection of FMV samples to most accurately characterize OP dose in children. The results of these analyses may help inform future epidemiologic study design and risk assessments and could be extended beyond OPs to other non-persistent chemicals.

Previous studies have identified adverse associations of prenatal and early-life exposure to pesticides, predominantly OP pesticides measured by non-specific biomarkers of exposure, and childhood neurodevelopment.[23-26,32,33,83] Fewer studies have examined the impacts of these exposures on neurodevelopmental outcomes measured during adolescence or the impacts of exposure to mixtures of co-occurring pesticides. This study employed BHM to examine associations between applications of mixtures of agricultural pesticide near maternal residences during pregnancy and early childhood with internalizing and externalizing behaviors measured at ages 16 and 18 years in the CHAMACOS cohort. This study found largely null associations of agricultural pesticide use near the home with adolescent neurobehavioral outcomes, with some evidence of modest associations for OPs applied during the prenatal period and glyphosate applications during the early childhood period. During the prenatal period, a two-fold increase in applications of the OP chlorpyrifos during pregnancy was associated with modestly increased report of internalizing behaviors from both mothers and youth; applications of the OPs diazinon and dimethoate during pregnancy were each associated with increased youth-reported attention problems. A two-fold increase in the use of glyphosate during the early childhood period (ages 0-5 years) was associated with increased maternal- and youth-reported internalizing behaviors.

Few studies have assessed the neurodevelopmental effects of exposure to both environmental and social stressors. The studies that have been conducted have largely focused on environmental chemicals such as lead,[52-57] air pollutants,[58-60] and environmental tobacco smoke;[61,62] few have considered exposure to pesticides. This study examined interactions of pesticide mixtures used within 1km of the home during pregnancy and ACEs on adolescent

neurobehavioral outcomes. Overall, there was little evidence of modification of exposure-outcome associations by ACEs. A two-fold increase in use of the OP malathion within 1km of the home was associated with increased report of internalizing problems from both mothers and youth among participants who experienced high, but not low ACEs; these associations with malathion were largely driven by boys. Additionally, there was some evidence of interactions of ACEs and malathion for youth-reported hyperactivity, and of ACEs and dimethoate for youth-reported hyperactivity and attention problems.

5.2 Conclusions

This dissertation employed data from CVS and CHAMACOS, two studies of pesticide exposure among children living in the agricultural Salinas Valley, California. Although CVS has a relatively small sample size, investigators collected urine voids over seven consecutive days, including all urine voids from two separate 24-hr sampling cycles, allowing for comparisons of the reliability of OP dose estimates from spot and 24-hr urine samples. The CHAMACOS study has numerous strengths, including a prospective design, relatively large sample size, assessment of neurobehavioral data from two reporters at multiple time points, rich collection of data on potential confounders, and the comprehensive assessment of maternal residences during pregnancy and early childhood, which can be linked with California's rich PUR database to estimate potential exposure to pesticides.

This work extends previous research showing that that reliance on DAPs assessed from spot urine samples may understatement OP exposure and bias epidemiologic analyses[75] by examining the impacts of reliance on spot urine samples to estimate total OP dose, which has more direct implications for risk assessments. Additionally, few studies have examined cumulative OP pesticide dose among children living in an agricultural area. The results of this work could be applied to other non-persistent environmental chemicals.

This is the first study to examine associations of applications of mixtures of neurotoxic pesticides near the home during pregnancy or early childhood, critical periods of brain development, and neurobehavioral outcomes assessed during adolescence or young adulthood. Adolescence is an important time for the manifestation of these behavioral outcomes[161] and may have important downstream effects on other outcomes, including impaired school performance, juvenile delinquency, increased risk-taking behavior, substance abuse, adult crime, and future psychopathology.[258-260] This study found mostly null or modest associations between pesticides and neurobehavioral outcomes. Pesticide use trends have shifted drastically since the prenatal and postnatal exposure periods for children in this study. As many OPs are being phased out from residential and agricultural use due to evidence of neurotoxicity to the developing brain, it is increasingly important to study the safety of their replacements.

This study found little evidence of interactions between applications of agricultural pesticides near the home during the prenatal period and childhood adversity, assessed via ACEs, with maternal- or youth-reported behavioral and emotional outcomes among CHAMACOS participants at ages 16 and 18 years. There is increasing consensus regarding the need to examine the joint neurodevelopmental impact of environmental toxicants and social factors, as these exposures are likely to co-occur,[29,233] and failure to account for potential effect modification may underestimate the impact of environmental neurotoxicants.[82] Future studies should consider examining interactions of additional chemical and non-chemical stressors using biomarker-based exposure assessment methods.

5.3 Future research needs

While employing PUR data allows for the analysis of the impacts of potential exposure to mixtures of pesticides, including those for which biomarkers do not exist or are cost-prohibitive to analyze, data gaps remain regarding how well PUR data alone may approximate true pesticide exposure. While this study highlighted some concerns regarding the reliability of the assessment of non-persistent pesticides, such as OPs, in random spot urine samples, PUR data largely reflects potential exposure from inhalation and dermal routes of exposure and does not capture dietary sources, a major contributor to total pesticide exposure among children. Future research may consider examining associations of mixtures of agricultural pesticides, as well as the joint impacts of pesticides and social adversity, using biomarker-based methods of exposure assessment. Taken together with findings from Chapter 2, this research suggests that future studies employing biomonitoring should attempt to prioritize the collection of FMV or, if possible, 24-hr urine samples in order to minimize exposure misclassification.

Additional studies are needed examining associations of pesticide mixtures and social adversity and child/adolescent neurodevelopment for exposures occurring at different points during pregnancy (e.g., separate trimesters) or childhood (e.g., earlier versus later childhood) in order to identify potential critical windows of exposure. It would also be informative to examine associations with nearby agricultural pesticide use or biomarkers of pesticide exposure measured prior to pregnancy.

Future research should also consider examining interactions with additional measures of adversity (e.g., childhood poverty, food insecurity), potentially in a population with greater variation in social adversity. Studies are also needed examining potential protective social factors that may attenuate the adverse impacts of environmental neurotoxicants, such as having a cognitively or emotionally stimulating home environment.

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