Preschool-age children's exposures to pesticides measured in indoor dust in California

By

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ABSTRACT

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This dissertation focuses on young children's exposures to pesticides in indoor environments from dust. Research shows that young children, particularly in California, are exposed to pesticides in their environment, including in their homes and child care / early care and education (ECE) settings. Children are uniquely vulnerable to chemical exposures due to their exposure-prone behaviors and rapidly developing bodies and systems. Chemical exposures during critical windows of development put children are at higher risk since their respiratory, reproductive, digestive, immunological, and central nervous systems are not fully developed and are vulnerable to disruption.

Most children in the U.S. spend a significant amount of time in environments other than their home, but few studies have characterized exposures to pesticides in child care programs. Likewise, there are few studies that derive potential intake doses and characterize risk, despite the effort over the past three decades make risk assessments more protective of vulnerable populations, including young children. In this dissertation, we take a mixtures approach to assessing potential health impacts from early childhood exposures to pesticides in indoor dust, both in assessing cumulative risk for children in ECE settings, and assessing exposures to pesticide mixtures among children in an agricultural community and potential impacts on child cognition.

Chapter 1 reviews literature on determinants of pesticide exposure to young children in indoor environments and their potential health impacts. We present a brief introduction to the pesticides that will be discussed throughout this dissertation, key concepts related to measuring pesticides in dust, as well as the two study populations used in this dissertation.

Chapter 2 aims to identify determinants of pesticide levels in carpet dust samples collected from 51 licensed child care centers in Northern California and analyzed for 14 structural and agricultural pesticides. The most frequently detected pesticides were cis-permethrin (98%), trans-permethrin (98%), bifenthrin (94%), fipronil (94%), and chlorpyrifos (88%). Higher bifenthrin levels were correlated with agricultural applications within 3 kilometers, and higher fipronil levels were correlated with professional pesticide applications in the prior year. In multivariable models, higher Integrated Pest Management (IPM) Checklist scores were associated with lower loading of chlorpyrifos and permethrin. Placement of the sampled area carpet was also a predictor of chlorpyrifos loading. The strongest predictor of higher pesticide loading for the most frequently detected pesticides was location in California's San Joaquin Valley.

Chapter 3 aims to determine if children's exposures to pesticides in child care via non-dietary ingestion and dermal absorption exceed health-protective reference values, and compares traditional risk calculations to methods that account for uncertainty and cumulative risk. Estimated exposures did not exceed EPA-established RfDs or approximated probabilistic RfDs. While potential pesticide exposures in licensed child care centers are unlikely to cause neurotoxic or hepatotoxic effects, these estimates represent only a portion of the total daily exposure. Our tiered approach to producing a comprehensive risk assessment for multiple pesticides in children's ECE settings is an important application of available methods for improved health risk assessment.

Chapter 4 examines the relationship between early life exposure to pesticide mixtures in house dust and children's neurodevelopment, accounting for co-exposures and potential interactions with social factors. We used Bayesian Hierarchical Modeling to evaluate the association between levels of common pesticide classes detected in the dust and neurodevelopmental outcomes assessed by the Wechsler Intelligence Scale for Children at age seven years. A 10-fold increase in pesticide loading was associated with a 3-point deficit on the Processing Speed subscale at age seven years for the organophosphate oxydemeton-methyl (median of posterior: -3.3 (95% CrI: -6.4, -0.2)), but higher iprodione loading was associated with higher Verbal Comprehension subscale scores (2.5 (0.3, 4.6)). Results were null for pyrethroids, herbicides (individual or class effects), and for interaction with the quality of the home environment. Early childhood exposure to pesticide mixtures, especially organophosphates, in indoor environments may negatively impact children's cognition. Our findings support further research into pesticide mixtures effects potentiated by sex of the child and quality of the home environment.

Chapter 5 concludes the dissertation with a summary of the results from each chapter, the strengths and limitations of the current work, and a discussion of future directions for research on children's exposures to pesticides in early childhood environments.

Dedication

For Joaquin.

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That said, while I've collected hundreds of dust samples, conducted probabilistic modeling, and used Bayesian statistics, the most complex and confusing part of my PhD experience has been navigating "momademia." I struggled with post-partum depression, pandemic isolation, and navigating health care, finances, and child care (not being able to access our university child care centers) with a dependent. The EHS division has been incredibly supportive, but it is the culture of academia that is often at odds with being a good parent. As any working mother knows, you are put in the impossible position of trying to parent like you don't work, and trying to work like you don't have children. Throughout my doctoral journey, I attempted to complete several writing challenges that should have been simple enough - just write for a half hour per day. That's what many academics do to stay productive. But not all academics are moms. Finding 30

minutes to myself feels impossible most days. Between demanding schedules and an even more demanding toddler, there's little left at the end of the day. I am privileged to be writing this while my mother-in-law watches my toddler, but other mothers of young children in academia or in environmentalism may not be so lucky. More work needs to be done to make academia a safe place for all families.

Finally, I would like to acknowledge the participating child care directors, teachers, parents, and children from the Healthy Children and Environments Study and the CHAMACOS participants and their families. The entire child care community deserves acknowledgement and as I reflect on my PhD experience, I am called to make a plea for valuing child care providers and the critical service they provide.

We are seeing an unprecedented number of women leaving the workforce, with nearly 2 million fewer women working today than at the start of the pandemic. The pandemic has severed an already fragile and cracking child care system, and has exposed just how ill-equipped we are for the turbulent times ahead of us in a changed climate. I believe that universal access to affordable, high-quality child care is central to science and to a just transition. During WWII, for those families that could access them, the Kaiser shipyard child care centers provided on-site, full-service, quality day care for parents working essential jobs for the war effort. A green new economy needs to replicate that model, expanding opportunities for the entire working class -- and not just for white families this time. Bring child care programs to where jobs are. Ensure the facilities are sustainable and healthful spaces with good indoor air quality, with safer products and materials used throughout, and that can double as essential infrastructure for when climate disasters continue to occur. Pay teaching staff a living wage. Provide children with opportunities for outdoor and environmental education. Send parents home with a healthy, hot meal when they pick up their children, as they did in the Kaiser shipyard child care programs. Do all of this with government subsidies, employer partnerships, and sliding-scale fees so that families aren't putting more than half of their take-home pay toward child care. Child care is an essential service, and both child care providers and working parents deserve dignity in interacting with the system. I am so thankful to have conducted research with child care providers, and I will continue to fight for investment in child care for as long as it takes.

Chapter 1 Introduction to Preschool-Age Children's Exposures to Pesticides in Indoor Dust

1.1 Overview

This dissertation focuses on young children's exposures to pesticides in indoor environments from dust. This introduction reviews determinants of pesticide exposure to young children in indoor environments and their potential health impacts. We present a brief introduction to the pesticides that will be discussed throughout this dissertation, key concepts related to measuring pesticides in dust, as well as the two study populations used in this dissertation.

1.2 Children's exposures to pesticides in early childhood environments

Research shows that young children, particularly in California, are exposed to pesticides in their environment, including in their homes (1-5) and child care / early care and education (ECE) settings (6-9). Children are uniquely vulnerable to chemical exposures due to their exposure-prone behaviors and rapidly developing bodies and systems. Children have higher intake of air, water, and food per unit of body weight compared with adults (10) and may have a less varied diet which often leads to higher exposures to pesticide residues compared with older children and adults (11). Hand-to-mouth activity and time spent on floors can also increase their exposure to contaminants that settle in dust (10, 12). For example, pesticides may transfer from treated surfaces to hands or objects mouthed by children, resulting in non-dietary ingestion (13, 14)Overall, hand-to-mouth behavior is significantly greater indoors compared with outdoors (15). Young children, for whom hand-to-mouth frequency is highest, in child care may spend 60% to 75% of the time indoors (16).

Chemical exposures during critical windows of development put children are at higher risk since their respiratory, reproductive, digestive, immunological, and central nervous systems are not fully developed and are vulnerable to disruption. Children's metabolic pathways are also immature, making them less able to metabolize and remove toxic chemicals from their bodies (17), which is of particular concern when children are exposed to multiple pesticides and other environmental contaminants and are poorly equipped to metabolize these mixtures of compounds.

While diet is a major source of pesticide exposure, young children can also be exposed to pesticides present in their surrounding environments, including homes and ECE facilities. Studies in North Carolina and Ohio found preschool children were concurrently exposed at low levels to a number of past-use (legacy) and current-use pesticides from several sources and routes of exposure at their homes and child care centers. In the North Carolina study, pesticides that were detected ≥50% in several different media at these locations included α-chlordane, γ-chlordane, heptachlor, chlorpyrifos, diazinon, *cis*- and *trans*-permethrin, and 2,4-D (8). In the Ohio study, cis- and trans-permethrin were detected in 100% of dust samples and over 78% of hand wipe samples collected at both homes and child care centers (18). A study in low-income homes from urban and agricultural communities in California detected several pesticides in most homes, including organophosphate (OP) pesticides previously phased-out for residential uses, pyrethroids, and the pesticide synergist piperonyl butoxide (1). The First National Environmental Health Survey of Child Care Centers measured pesticides in indoor floor wipe

samples, with chlorpyrifos, diazinon, and cis- and trans-permethrin detected in more than 67% of the centers. In smaller studies of ECE programs, detectable levels of pesticides were found in all dust samples from 13 centers in North Carolina (8), 22 centers in Ohio (18), and 40 centers in California (9).

There are many sources of pesticide contamination in early childhood environments. Pesticide contamination in children's home and out-of-home care environments may result from nearby agricultural use. More than one billion pounds (or over 450 million kilograms) of pesticides are applied in the U.S. annually, with nearly 90% used for agriculture (19). A systematic review of non-dietary exposure to agricultural pesticides identified key drivers of exposure, including behaviors like housekeeping practices and personal hygiene frequency, and spatial indicators like proximity to fields and total amounts of pesticides applied nearby (20). Children living in agricultural communities may have higher exposures related to take-home exposure from their parents' employment and location of their home relative to agricultural fields (21, 22). In California, some jurisdictions have setback requirements for buildings from agricultural land, but there is no statewide mandate for buffer zones between homes and agriculture. However, there are some limits set for applying pesticides around child care facilities in California – growers cannot apply certain pesticides within 0.25 miles of a schoolsite (public schools and licensed child care centers) on school days (23).

Pesticide contamination in children's environments may also result from structural use. Studies in low-income homes in the U.S. consistently find high detection frequencies of home-use pesticides, particularly pyrethroids, and use of pesticides to manage pest infestations associated with housing disrepair (1, 24-26). A 2008 survey of 637 child care center directors in California found that 90% reported at least one pest problem and half of these center directors reported using pesticides to control pests, with 47% reporting the use of aerosolized pesticides, which pose greater risk of exposure than pesticides applied as baits or gels (27). This survey was conducted shortly after the California Healthy Schools Act expanded in 2007 to include child care facilities. The DPR School and Child Care IPM Program grew again in 2015 after the enactment of state legislation that added mandates for schoolsites, including child care centers, to have an integrated pest management (IPM) plan, schoolsite pesticide use reporting, and IPM training (28). ECE programs may also hire professionals that apply pesticides inside or outside the facility to manage pest problems. In 2017, 98,522 pesticide applications were reported for public K-12 schools and licensed child care centers across California. Insecticides were the most reported pesticide class, followed by herbicides (29).

1.3 Health effects and neurodevelopmental toxicity

Studies suggest that early-life exposure to pesticides, even at low levels, can have a wide range of adverse health effects such as respiratory symptoms and decreased lung function (30, 31), and impacts on neurological and behavioral development (32). A meta-analysis found that exposure to chronic, low-dose indoor residential insecticides during early childhood is associated with an increased risk of leukemia and lymphoma among young children and young adults (33). Most of what is known about pesticides and children's health come from studies within agricultural communities, where pesticide exposures are disproportionately high. Residential proximity to agricultural pesticide applications during both prenatal and postnatal periods has

been linked to poorer cognitive and neurodevelopment later in childhood, and adverse behavioral outcomes such as autism (34), autism-related behaviors, and ADHD (35). The neurodevelopmental effects of prenatal exposure to OP pesticides are well studied (4, 36-48), but gaps in the literature on early childhood exposures to pesticides still exist, particularly in the area of chronic, low-level exposures to non-OP pesticides.

Pregnancy through the first years of life is a critical window for brain growth development and particularly vulnerability to disruption (49). Neurological pathways rapidly develop in early childhood. In the first few years of life, more than 1 million new neural connections form every second (50). Formation of functional neural networks is key to critical cognitive processes such as memory, learning, and attention. Overall brain volume and development of several regions of white matter may be complete by age 5 years (51), underscoring the critical period prenatally to school age.

Neurotoxicity is defined as an adverse change in the structure or function of the central and/or peripheral nervous system following exposure to a chemical, physical, or biologic agent (52). Neurodevelopmental toxicity refers to the harmful effects of xenobiotics on the development and function of the nervous system, often resulting from exposure to various environmental factors such as chemicals, toxins, or other substances during critical stages of prenatal and childhood development.

The developing brain is particularly vulnerable to adverse effects of neurotoxic pesticides. Physiologically-based pharmacokinetic modeling provides evidence of age-related differences of pesticide metabolism and neurotoxic susceptibility (53, 54). Many pesticide compounds target the nervous system of insects. Because of similarities in brain biochemistry, these pesticides pose an inherent risk for human neurotoxicity (55). Despite their recognition of the importance of evaluating developmental neurotoxicity, U.S. Environmental Protection Agency (EPA) safety testing requirements for pesticides typically focus on acute toxicity, carcinogenicity, genotoxicity, and other immediate health effects.

There are a relatively small number of "known developmental neurotoxicants," namely certain metals, solvents, OP pesticides, and, more recently, endocrine-disrupting compounds, and these may not fully represent of all the potential mechanisms by which chemicals may impact neurodevelopment (56). Some chemicals may have multiple modes of action and may affect the nervous system both directly and indirectly (57), such as through damage to hepatic or cardiovascular structures, or endocrine system disruption. Thyroid hormones, a key component of the endocrine system, play a crucial role in brain development (58).

Mechanisms of neurotoxicity have traditionally been recognized as pathways leading to neuronal cell death, neuropathology, or severe neural injury; however, recent research suggests alternative mechanisms of more subtle yet consequential changes in the brain and behavior (56). Critical neurodevelopmental processes include proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis, and evidence shows that interference with one or more of these developmental processes can lead to developmental neurotoxicity (49). The OP pesticide chlorpyrifos provides a compelling example of how the understood mechanism of neurotoxicity may not explain neurodevelopmental impacts. The common mechanism of toxicity for the class of OPs is inhibition of the enzyme acetylcholinesterase (AChE). Literature suggests that early life exposure to chlorpyrifos at doses lower than what would cause AChE inhibition

still result in neurodevelopmental abnormalities (55, 59-61). The mechanisms underlying the developmental neurotoxicity of chlorpyrifos are not well understood, but potential mechanisms include loss of myelin, disruption of axonal transport and outgrowth, and altered synaptic function (62). If neurodevelopmental effects are secondary to the critical effect or main mechanism of neurotoxicity, such as AChE inhibition, then health protective guidance values based on these traditional mechanisms of neurotoxicity may not be protective of neurodevelopment. These reference doses, often derived based on the understood neurotoxic effects describe above, serve as the point of comparison for health risk assessments.

Developmental neurotoxicants may also cause "silent damage" (57), manifesting with age, and may contribute to neurodegenerative diseases such as Parkinson's or Alzheimer's diseases. One hypothesis for the latency of neurotoxic injury involves the brain's natural plasticity being overwhelmed by further exposures to chemical and non-chemical stressors (e.g., chronic stress or natural aging process) (57).

This dissertation will focus on the potential neurotoxicity / neurodevelopmental toxicity of pesticides measured in young children's environments when considering potential health outcomes (Chapter 2 focuses on predictors of contamination, with no associated health outcome measurement). In Chapter 3, we base our assessment of risk on US EPA risk assessment documents and reference doses, which often use neurotoxicity assays in rats to derive the reference dose. The EPA maintains that risk assessments select the most sensitive endpoint, and are protective of other endpoints, such as neurodevelopmental toxicity. In Chapter 4, we evaluated associations of pesticide exposure on child IQ at age 7 years as our outcome of interest to assess potential neurodevelopmental impacts of early childhood exposure to pesticide mixtures in dust.

1.4 Pesticide compounds and classes

Pesticides consist of various chemical classes with different mechanisms of action. OP and pyrethroid pesticides, which are frequently detected in homes and child care centers, are two of the major classes of insecticides applied to control insects in residential and agricultural settings in recent decades. The use of OPs and pyrethroids grew especially after U.S. phase-outs of organochlorine (OC) pesticides such as dichlorodiphenyltrichloroethane (DDT) in the late 1980's, due to concerns about their persistence and bioaccumulation (however, these highly toxic and bioaccumulative pesticides, while banned in high-income nations, are still used in many low-income and middle-income countries for malaria control). Due to concerns about children's exposures to OP pesticides, the U.S. EPA phased-out residential uses of chlorpyrifos and diazinon in the early 2000's. As of 2021, nearly all uses of chlorpyrifos, which was still heavily used in agriculture, are now restricted in California (63).

Pyrethroid insecticides have replaced many of the residential uses of the OP insecticides, and they are also extensively applied on agricultural fields. Pyrethroids are a class of synthetic insecticides, designed to mimic the naturally occurring insecticidal properties of some chrysanthemum flowers (*Chrysanthemum cinerariifolium* and *Chrysanthemum coccineum*). Pyrethroids are thought to be of lower toxicity than OP or OC pesticides. Geometric mean levels of 3-PBA, a non-specific urinary metabolite for pyrethroids, increased significantly among children in the NHANES 2011–2012 population compared to previous cycles, and levels were higher among children than adults (64). While data did not show a clear increase in the period

from 2007 to 2012 for agricultural use of pyrethroids, residential uses of pyrethroids have likely increased over that time. While the harmful effects of OP pesticides are well established (see above), little is known about risks associated with chronic, low-dose pyrethroid exposure.

The pesticide compounds measured in indoor dust samples and discussed in this dissertation include a mix of pesticides used regionally in agricultural and structural pest control (see Table 1.1). In Chapters 2 and 3, the panel of pesticide analytes include those that have been previously measured in California ECE centers, including several pyrethroids, plus newer-use pesticides such as fipronil and chlorfenapyr that have not previously been measured in child care studies. In Chapter 4, analytes include some that are measured in the child care study (cis- and trans-permethrin, chlorpyrifos, diazinon, and chlorthal dimethyl (DCPA, tradename Dacthal)), plus other OPs (phosmet and oxydemeton-methyl), and one fungicide, iprodione, not measured in the child care study. This dissertation does not include analyses of other commonly used pesticides such as glyphosate, 2,4-D, neonicotinoid insecticides, or persistent legacy pesticides such as DDT. In Chapters 3 and 4, we utilize a pesticide class-based approach to evaluate the risks of pesticide exposure (for pyrethroids) and produce effect estimates on neurodevelopment for each pesticide class using Bayesian Hierarchical Modeling (for OP, pyrethroid, phthalate herbicide, and fungicide classes).

1.5 Characterizing potential exposure using indoor dust

Pollutant concentrations can be measured in a variety of environmental or biological media, or estimated via proxies such as geospatial data. This dissertation focuses on pesticides measured in indoor dust, collected with a high-volume small-surface sampler (HVS3). Developed for the U.S. EPA in 1990 to assess risk from lead, pesticides, polyaromatic hydrocarbons, and other pollutants in house dust on bare surfaces and carpets, the HVS3 allowed measurement of both concentration (μg/g) and loading (μg/m^2) of surface dust pollutants by using a cyclone with controlled air flow and pressure drop across the nozzle (65).

Dust concentration and loading are complimentary measures of indoor contamination. Loading (amount of contaminant per unit of flooring sampled) is generally considered to be a better indicator of potential exposure (66) and is more sensitive to recent cleaning practices, while concentration is generally more indicative of sources of contamination (67, 68) and used in risk assessment calculations of potential intake dose. Dust provides a stable matrix for pesticides, showing less variation over time than air or urine measurements (65, 69).

Carpeting is a common dust reservoir where pesticides accumulate. Carpets collect tracked in soil and collect settled dust from indoor air (65). Pesticide residues may persist for years in carpets, where they are protected from sunlight, rain, temperature extremes, and microorganisms (70, 71). Indoor dust is an important route of exposure for young children as they spend more time in close contact with floors and have high hand-to-mouth activity. Young children spend a significant amount of time indoors, and the concentration of pollutants in house dust may be 2–32 times higher than that found in the outdoor soil nearby (65). Child care centers, where many different children spend a significant amount of time, and the homes of farmworkers with children, are two important settings for studying risks of exposure to pesticides in indoor dust.

1.6 Study populations

This dissertation uses data from two children's environmental health studies with pesticide measurements in California. The University of California, San Francisco (UCSF) Healthy Children & Environments Study (HCES) is an ongoing randomized-control trial funded by the National Institute of Environmental Health Sciences (NIEHS) to examine the effect of an IPM intervention for licensed child care centers. Four northern California counties, two in the San Francisco Bay Area and two in the Central Valley, were randomized to the IPM or attention-control health intervention. Carpet dust samples are collected from classrooms at baseline and after the seven-month intervention period. In addition, five families are recruited from each center meeting the following inclusion criteria: (1) aged 3 or 4 years, (2) plan to spend at least 6 hours per day in the center, (3) plan to be enrolled in the center for the next 9 months, and (4) parent is present during enrollment, who can speak English or Spanish.

Because HCES does not collect health outcome data associated with the measured pesticide exposures, Chapter 4 draws upon the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) Study data to examine the association between common pesticide classes measured in indoor dust samples and child neurodevelopmental outcomes. The CHAMACOS Study is a longitudinal birth cohort study examining pesticide and other environmental exposures among children in a farmworker community. The cohort began in 1999, enrolling pregnant women living in California's Salinas Valley, a key agricultural region. The study enrolled English or Spanish-speaking pregnant women who were at less than 20 weeks' gestation, eligible for low-income health insurance (Medicaid), and at least 18 years of age, recruited from prenatal care clinics serving the Salinas Valley's farmworker population.

Both HCES and CHAMACOS include interviews, surveys, and validated observational assessments of the child care or home environment to capture information about outcomes and covariates. For HCES, the director interview, conducted by the assigned child care health consultant, collects information on personal (e.g., education level, years of experience) and center (e.g., staff turnover, facility age) demographics; the center's pest problems, pesticide use practices, and IPM policies and practices; and the center's cleaning products, cleaning routines, and maintenance practices. During the baseline assessment stage, an experienced research assistant completed inspection checklists in each child care center including the IPM Checklist and Health and Safety Checklist for Early Care and Education Programs, utilized in prior studies (72-76). The IPM Checklist includes 73 items with 8 subscales, and for this project, included additional items to identify use of door mats and the pesticides stored on-site by child care or facility staff. The CHAMACOS study includes data on many potential confounders and modifiers of neurodevelopmental and other health outcomes. In Chapter 4, we focus on cognition measured by the Wechsler Intelligence Scale for Children (WISC-IV) at age 7 years as the key endpoint. This outcome measurement is used in many studies examining associations between OP and pyrethroid pesticides and neurodevelopment in preschool-age children and school-age children (36, 77).

Both the UCSF Healthy Children & Environments Study and the CHAMACOS study collected indoor carpet dust samples using a high-volume small surface sampler (HVS3), which is a specially designed vacuum cleaner that collects particles > 5 μm in diameter (HVS3; Cascade Sampling Systems, Bend, OR), and both studies used the same sampling protocol. Although the CHAMACOS cohort is made up of members of an agricultural community that is disproportionately exposed to many pesticides, the levels of the pyrethroids in those homes in

1999-2000 are similar to environmental levels found in children's environments today. A review of pyrethroid measurements from children's homes found that the CHAMACOS measurements were on the lower end of the distribution, likely due to regional differences. 20 years later, the measurements of cis- and trans-permethrin in California child care centers from non-agricultural regions are similar in concentration (see Chapter 2).

1.7 Research needs and dissertation aims

The overall goal of this dissertation is to examine exposures to pesticides in child care environments, characterize health risks of non-dietary pesticide exposures in child care, and examine potential neurodevelopmental effects of pesticides that are most frequently detected in children's environments.

Child care programs are an important setting for environmental health interventions, but there are a limited number of studies conducted there. Children spend a significant amount of time in child care environments, with particularly long hours for working class families. Few studies have characterized exposures to pesticides in child care programs and none have quantitatively examined predictors of the pesticide levels found in environmental samples. Child care providers and families of enrolled children participating in environmental health research may not have a clear understanding of what concentrations of pesticides in classroom carpet dust means for children's health, therefore research translation is important.

Widespread use of OP and pyrethroid pesticides has led to ubiquitous human exposure (37). However, risk is not distributed evenly or equitably, and children, farmworkers and farming communities, and populations experiencing high levels of stress are disproportionately impacted. This dissertation applies novel statistical and risk estimation methods to better account for multiple exposures and differential vulnerability in the population, improving upon traditional methods in environmental epidemiology and human health risk assessment.

Specific Aims:

- Chapter 2 aims to identify determinants of pesticide levels in dust samples collected from child care classroom carpets.
- Chapter 3 aims to determine if children's exposures to pesticides in child care via non-dietary ingestion and dermal absorption exceed health-protective reference values, and compares traditional risk calculations to methods that account for uncertainty and cumulative risk.
- Chapter 4 aims to examine the relationship between early life exposure to mixtures of current-use and legacy pesticides measured in house dust and children's neurodevelopment.

Overall, this dissertation seeks to close these knowledge gaps and aims to promote healthy early childhood environments, for the benefit of children, their care providers and families, and the community at large.

Table 1.1. Pesticides and pesticide classes measured in dust samples included in this dissertation.

Pesticide / Class	HCES (Ch. 2 & Ch. 3)	CHAMACOS (Ch. 4)
Pyrethroids		
Bifenthrin	X	
Cyfluthrin	X	
Cypermethrin	X	
Deltamethrin	X	
Esfenvalerate	X	
ƛ-Cyhalothrin	X	
Permethrin (cis/trans)	X	X
Organophosphates		
Chlorpyrifos	X	X
Diazinon	X	X
Oxydemeton-methyl		X
Phosmet		X
Fungicides		
Iprodione		X
Herbicides		
Chlorthal dimethyl (DCPA / Dacthal)	X	X
Phenylpyrazoles		
Fipronil	X	
Pyrroles		
Chlorfenapyr	X	
Synergists		
Piperonyl butoxide	X	

Chapter 2 Predictors of pesticide levels in carpet dust collected from child care centers in Northern California, USA

2.1 Introduction

The majority of young children in the United States (U.S.) spend time in out-of-home care settings, with many preschool-age children spending half of their waking weekday hours in early care and education (ECE) programs (78). Chemical exposures in ECE environments are of particular concern because young children are uniquely vulnerable to their adverse effects during critical windows of rapid development (12). Previous studies have reported on the presence of pesticides in ECE facilities (6-9). Studies suggest that early-life exposure to pesticides, even at low levels, can have adverse health effects such as respiratory symptoms and decreased lung function (30, 31), and impacts on neurological and behavioral development (32). A meta-analysis found that exposure to chronic, low-dose indoor residential insecticides during early childhood is associated with an increased risk of leukemia and lymphoma among young children and young adults (33). Physiologically-based pharmacokinetic modeling provides evidence of age-related differences of pesticide metabolism and neurotoxic susceptibility (53, 54).

Pesticide contamination may result from nearby agricultural or structural use. More than one billion pounds (or over 450 million kilograms) of pesticides are applied in the U.S. annually, with nearly 90% used for agriculture (19). A survey of 637 child care center directors in California found that 90% reported at least one pest problem and half of these center directors reported using pesticides to control pests, with 47% reporting the use of aerosolized pesticides, which pose greater risk of exposure than pesticides applied as baits or gels (27). ECE programs may also hire professionals that apply pesticides in or outside the facility to manage pest problems. The First National Environmental Health Survey of Child Care Centers measured pesticides in indoor floor wipe samples, with chlorpyrifos, diazinon, cis-permethrin, and trans-permethrin detected in more than 67% of the centers. In smaller studies of ECE programs, detectable levels of pesticides were found in all dust samples from 13 centers in North Carolina (8) and 22 centers in Ohio (18). However, the predictors of pesticide levels in ECE programs have not been quantitatively assessed.

Indoor dust is an important exposure pathway for young children because they spend more time close to and in direct contact with the ground and have greater hand-to-mouth activity (65). Carpet dust is a good environmental medium for assessing long-term indoor exposure because pesticides and other contaminants collect in dust over years, where they are protected from degradation by sunlight, moisture, and microorganisms (70, 71). Dust concentration and loading are complimentary measures of indoor contamination. Loading (amount of contaminant per unit of flooring sampled) is generally considered to be a better indicator of exposure (66) and is more sensitive to recent cleaning practices, while concentration is generally more indicative of sources of contamination (67, 68).

In California, the Department of Pesticide Regulation (DPR) has enacted policies intended to reduce children's exposures to pesticides in public schools and licensed ECE centers ("schoolsites") by limiting agricultural pesticide applications near schoolsites and encouraging adoption of low-risk pest management practices, known as integrated pest management (IPM). Within 0.25 miles (approximately 402 meters) of a schoolsite, growers cannot apply certain pesticides on school days (23). The California Healthy Schools Act is a right-to-know law that

provides parents and staff with information about pesticide use at schoolsites (79). Additionally, licensed pest management professionals (PMPs) are required to report pesticide applications at schoolsites.

In the present study, we examine behavioral and environmental determinants of pesticide concentrations and loadings in carpet dust collected from 51 ECE centers. We utilize baseline data from an ongoing study examining pesticide use and exposure in Northern California ECE centers. We hypothesize that proximity to agricultural pesticide applications, storing pesticides onsite, fewer IPM practices, older building age, having a PMP apply pesticides in the past year, placement of sampled area carpet on carpeted flooring, and fewer pests observed onsite are associated with higher pesticide concentrations and loading for frequently detected pesticides measured in carpet dust.

2.2 Materials/Subjects and Methods

2.2.1 Study population

Data for this analysis were collected as part of the University of California, San Francisco, Healthy Children & Environments Study (HCES), a randomized-control trial examining the impact of an IPM intervention for ECE centers on pesticide exposure and health risks. The present analysis uses baseline data collected from 51 ECE centers from four northern California counties during the first three years of the study (November 2017-January 2018, August 2018-November 2018, and September 2019-November 2019). Inclusion criteria for the four counties is described by Alkon et al. 2022 (80). Briefly, the two San Francisco Bay Area and two San Joaquin Valley counties were matched on geography, demographics, and agricultural pesticide use. There is high agricultural pesticide use in the San Joaquin Valley counties compared to the more urban / suburban Bay Area counties (81). The Institutional Review Board at the University of California, San Francisco approved all study activities, and written informed consent was obtained from all center directors.

2.2.2 Observational checklist and interview data

We collected information about practices and facility characteristics during ECE director interviews and observational checklists. During the baseline assessment stage, study staff completed two inspection checklists in each ECE center: The Integrated Pest Management Checklist for Early Care and Education Programs (IPM Checklist) and the Health and Safety Checklist for Early Care and Education Programs, both used in previous ECE environment studies (76, 82-84). The IPM Checklist has shown construct, content, face, and criterion validity (83), as well as having predicted change in child care studies (76). The IPM Checklist includes 73 items with 8 subscales (outdoor: garbage, exterior, play area; indoor: kitchen, bathrooms, play areas, storage, staff area). For each subscale pest problems (pest or evidence of pest observed) were recorded in each location. For this project, the IPM Checklist included additional items to identify use of doormats, flooring and carpet types in the classroom, and the pesticide products stored on-site, including product active ingredients and U.S. EPA pesticide registration numbers.

A child care health consultant, a health professional trained to provide health and safety information specific to ECE settings, was assigned to each ECE program and interviewed the director. The interview collected information about the director (e.g., education level, years of experience); center characteristics (e.g., facility age, maintenance information); the center's pest

problems, pesticide use practices, and IPM policies and practices; and cleaning products and routines.

2.2.3 Dust sample collection

Dust samples were collected using a high-volume surface sampler, a specially designed vacuum cleaner that collects particles >5 micrometer (μm) in diameter (85) (HVS3; Cascade Sampling Systems, Bend, OR). Samples were collected from the carpet where children have circle time and / or nap time (often the carpet is used for both). All sites had a carpet or area carpet that was at least 1 square meter (m^2) in area, the minimum area needed for carpet dust sampling.

Study staff used a standard protocol (86) for HVS3 preparation, sampling, and prevention of cross-contamination. The sampling train, vacuum wheels, and collection bottle were cleaned with soap and water, rinsed with distilled water, and washed with isopropyl alcohol between uses. The sample collector wore nitrile gloves and boot covers to sample from an area of 1-2 m^2. The exact area sampled, weather conditions, and GPS coordinates were recorded at the time of the sample collection. Sealed Teflon collection bottles containing the dust samples were labeled with the collection date and sample identification number, stored in a -20 °C freezer, and shipped via overnight mail on dry ice to Southwest Research Institute (SwRI) (San Antonio, TX), where they were stored in freezers until analysis.

2.2.4 Laboratory analysis

SwRI measured concentrations and loadings of 14 pesticides in the dust: bifenthrin, chlorfenapyr, chlorpyrifos, cyfluthrin, cypermethrin, chlorthal-dimethyl (DCPA / Dacthal), deltamethrin, diazinon, esfenvalerate, fipronil, lambda-cyhalothrin, permethrin (cis- and trans-), and piperonyl butoxide. These represent a mix of pesticides used regionally in agricultural and structural pest control that have been previously measured in California ECE centers, plus several newer-use pesticides such as fipronil and chlorfenapyr.

For each dust sample, the total dust mass was passed through a 150-μm stainless steel sieve and the fine dust was weighed. The aliquot of the sample's fine dust mass removed for extraction was: 1.0 gram (g) if this mass exceeded 1.0 g, 0.5 g if 0.5-1.0 g, 0.2 g if 0.2-0.5 g, or the entire fine dust mass if <0.2 g. One duplicate and one matrix spike sample were prepared for every 20 samples in the extraction batch from additional aliquots of the sample with the largest fine dust mass. Each aliquot in the batch was spiked with three labeled extraction surrogates (diazinon-d10, 13C6-cis-permethrin, and p-terphenyl-d14) and Soxhlet-extracted with 200 mL of dichloromethane:hexane (1:1) for 18 hours, and the extract concentrated to 1.0 milliliter. The entire extract was passed for cleanup through a florisil column and the eluent concentrated to a final volume of 1.0 milliliter in hexane for analysis by Gas Chromatography/Mass Spectrometry (GC/MS). One solvent blank was extracted with each extraction batch of dust samples.

Analysis for the 14 targets was performed using an Agilent 6890N/5973 GC/MS in selected ion monitoring mode with a 30-meter x 0.25-millimeter ID x 0.25 μm film thickness Phenomenex ZB-Semi-volatiles GC column. The instrument was scanned to monitor 2 to 4 selected ions per analyte. Quantification was performed using chlorpyrifos-d10 and trans-permethrin-13C6 as internal standards. The percent relative standard deviation of the analytes was maintained within 30% during each initial seven-point standard calibration. The percent

difference of each analyte in the mid-level standard was maintained within 40% of the initial calibration value during continuing calibrations. Pesticide concentrations were determined in nanogram per gram (ng/g) of dust and pesticide loadings were derived by multiplying the concentrations (ng/g-dust) by the dust loading (g-dust/m^2). Detection limits for each target analyte are shown in Supplemental Table 2.1.

2.2.5 California Department of Pesticide Regulation Pesticide Use Information

California Department of Pesticide Regulation (DPR) Pesticide Use Report (PUR) data were used for the geospatial analysis of facility proximity to agricultural pesticide applications and reported structural pesticide applications by PMPs at the schoolsite. PUR agricultural pesticide use data includes application date, pounds of active ingredient applied, pounds of product applied, crop treated, and location geocoded to one-square mile sections defined by the U.S. Public Land Survey System. As part of the Healthy Schools Act, PMPs must report certain pesticide applications made at schoolsites annually to DPR. The PUR data obtained for these school sites via Public Records Request included county, school name, address, product name, active ingredient, location, applicator, and date.

Indoor dust pesticide exposure studies often select a radius of 1 to 4 kilometer (km) around residences to assess associations with nearby agricultural pesticide use (87-90). Harnly et al. (2009) found significant associations within ≈ 23 km^2 around the home which corresponds to a radius of approximately 2.7 km , and Gunier et al. (2014) found concentrations and loadings of manganese in house dust related to agricultural applications of manganese fungicides within 3 km of the residence (89). We estimated agricultural use for each pesticide of interest from 2015 to 2019 within a 3 km radius around each ECE center using GPS coordinates recorded at the time of the sample collection and ArcGIS (ESRI, Redlands, CA). At the time of the analysis, PUR data was publicly available on the California pesticide information portal (calpip.cdpr.ca.gov) for 2015-2018, and 2019 data was provided by DPR staff. We selected 365 days prior to the dust sample collection date to align with questions asked in the director interview (past 12 months) and the time period often correlated with pesticide dust concentrations (88). The density of agricultural pesticide use was estimated using methods described by Nuckols et al. (91). Briefly, for each pesticide, the total reported kilograms applied within the 365 days prior to the date of the dust sampling is weighted by the proportion of the area of the 3 km buffer around the ECE center that intersects with the Public Land Survey System section where the application occurred to determine pesticide use in kg/km^2.

2.2.6 Statistical analyses

We first calculated descriptive statistics for demographic characteristics, pesticide detection frequencies, and distributions of pesticide concentrations and loadings. Among the 14 pesticides measured, we conducted further analyses on those with detection frequencies over 75%: bifenthrin, chlorpyrifos, fipronil, and permethrin (cis- and trans-). The sum of the two concentrations for the isomers cis-permethrin and trans-permethrin were used as a ∑permethrin value for consistency with PUR records. Spearman's correlation coefficients were computed for each pesticide concentration and loading (for samples with measurements below the detection limit, a value was imputed as the limit of detection divided by the square root of two (DL/√2), then all values were natural log transformed) and continuous predictors. Tobit multivariable regression models were developed for each natural log transformed pesticide analyte (both

concentration and loading), setting the lower bound at the detection limit. Tobit regression is an unbiased approach for analyzing truncated data when a portion of the measurements are less than the limit of detection, resulting in left-truncated data (92). The transformed pesticide concentrations or loadings were the dependent variables and the environmental characteristics and behavioral practices were the predictors, controlling for other variables. Statistical analyses were conducted with Stata 15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

Independent variables used in the multivariable models were density of agricultural use of the specific pesticide active ingredient within 3 km over the 12 months preceding the date of the dust sample (continuous, kg/km^2), if an application of the active ingredient was reported to DPR by a PMP within 12 months preceding the date of the dust sample (binary), observation of a product containing the active ingredient during baseline site visit (binary), IPM score based on the IPM checklist (total number of items answered "Yes" over the number of applicable questions), number of types of pests observed at site visit (categorized as none, one, or two or more), geographic region (San Joaquin Valley or Bay Area), and for loading models – placement of sampled carpet (categorized as area carpet on top of hard surface flooring, area carpet on top of carpeted flooring, or carpeted flooring without area rug). Building year (from director interview or county records) was considered in correlations, but excluded from multivariable models because building year was closely correlated with IPM Checklist score.

2.3 Results

2.3.1 ECE characteristics.

Table 2.1 describes the ECE program and facility characteristics. Programs from the first three years of the study were distributed across the four participating counties. There was a mix of program types, including private, non-profit (n=15); private, for-profit (n=10); Head Start (n=6); California State Preschool Programs (n=5); and blended funding (n=15). Programs ranged in size from 10 to 200 children, totaling 3,327 children enrolled in the 51 participating ECE centers. Director experience in the ECE field ranged from 4 to 51 years.

A doormat was present at the entrance to the facility for 47 of 50 centers (94%). Among directors, 62% (n=29) reported knowing about the Healthy Schools Act, 55% (n=26) knew about IPM, 29% (n=15) had an IPM coordinator (as required by the Healthy Schools Act), and 27% (n=14) had a written IPM policy for the program. The average score on the IPM Checklist was 73 (SD=9); scores among the San Joaquin Valley sites were about 10% higher than the Bay Area sites, and their facilities were newer on average. Seventy-eight percent of sites (n=40) had a pest or evidence of pests observed by the researcher completing the IPM Checklist. Most sites had one type of pest observed, and the maximum was four different pests. The most common pests observed by study staff during the completion of the IPM Checklist were flies and spiders. The most common pests observed by directors over the past year were ants (49%), head lice (43%), flies (41%), and spiders (41%) (Supplemental Figure 2.1). Over half of the directors (57%) stated that a PMP had applied pesticides within the previous year and 24% of programs (n=12) had a "non-exempt" pesticide product onsite that requires reporting under the Healthy Schools Act.

Table 2.1 Child care center characteristics

Program and director characteristics		ECE facility characteristics		Characteristics related to IPM / Healthy Schools Act	
Geographic region (n=51)	n (%)	Building age (n=51)		IPM Checklist score (n=51)	
San Francisco Bay Area	25 (49%)	Mean (SD)	1988 (18)	Mean (SD)	73.15 (9.42)
San Joaquin Valley	26 (51%)	Min - Max	1940 - 2018	Min - Max	49.02 - 91.30
Program type (n=51)		Doormat observed at main entrance (n=50)	n (%)	Number of different pests observed (n=51)	n (%)
Non-profit private	15 (29%)	No	3 (6%)	None	11 (21%)
For-profit private	10 (20%)	Yes	47 (94%)	1	28 (55%)
Head Start / Early Head Start	6 (12%)	Doormat observed at classroom exit to outdoors (n=42)		2-4	12 (24%)
California State Preschool Program	5 (10%)	No	13 (31%)	Director knowledge of HSA (n=51)	
Blended	15 (29%)	Yes	29 (69%)	Yes	29 (62%)
Program size (n=51)		Circle-time carpet type (n=50)		No	18 (38%)
10-49 children	21 (41%)	Low pile	42 (84%)	Director knowledge of IPM (n=51)	
50-99 children	20 (39%)	Medium-high pile / plush	8 (16%)	Yes	26 (55%)
100-200 children	10 (20%)	Flooring under sampled carpet (n=51)		No	21 (45%)
Director years of experience in child care (n=51)		Laminate / hardwood / tile	29 (57%)	Center has IPM Coordinator (n=51)	
4-19 years	21 (41%)	Carpet	18 (35%)	Yes	15 (29%)
20-35 years	26 (51%)	NA - Carpet sampled is base flooring	4 (8%)	No	25 (49%)
>36 years	4 (8%)	How often carpets are deep cleaned per year (n=51)		Don't know	11 (22%)

Director education level (n=51)	
Some college	4 (8%)
Associate's	7 (14%)
Bachelor's	29 (57%)
Master's or higher	11 (21%)

<1	1 (2%)
1-2	35 (73%)
3-12	12 (24%)
Agricultural application of pesticide within 3 km, past 12 months (PUR) (n=51)	
Bifenthrin	29 (57%)
Chlorpyrifos	13 (25%)
Permethrin	10 (20%)

Center has written IPM policy (n=51)	
Yes	14 (27%)
No	37 (73%)
PMP or exterminator sprayed in past 12 months (director self-report) (n=51)	
Yes	29 (57%)
No	6 (12%)
Don't know	16 (31%)
Professional structural pesticide application in past 12 months (PUR) (n=51)	
Bifenthrin	6 (12%)
Fipronil	2 (4%)
Permethrin	2 (4%)
Any active ingredient	12 (24%)
Non-exempt pesticide product observed onsite (n=51)	
Bifenthrin	1 (2%)
Permethrin	4 (8%)
Any active ingredient	12 (24%)

Abbreviations:

ECE - early care and education
HSA - California Healthy Schools Act
IPM - integrated pest management
PMP - pest management professional
PUR - California Pesticide Use Report

2.3.2 Pesticide levels in dust.

Table 2.2 summarizes the distributions of all the pesticides analyzed in carpet dust. All ECE centers had at least one detectable pesticide in the carpet dust sample. The most frequently detected pesticides were: cis-permethrin (98%), trans-permethrin (96%), bifenthrin (94%), fipronil (94%), and chlorpyrifos (80%). Among these, chlorpyrifos had the lowest mean concentration and bifenthrin had the highest mean concentration. Piperonyl butoxide, cypermethrin, chlorfenapyr, deltamethrin, lambda-cyhalothrin, esfenvalerate, and cyfluthrin were detected in 10-73% of samples at baseline. Diazinon and DCPA were not detected in any samples. The total number of detected pesticide analytes within each center ranged from three to eleven (Supplemental Figures 2.2-2.4).

2.3.3 Pesticide Use Report (PUR) data.

The amount of pesticide sold for use (agricultural and structural) in California as well as the amount reported in agricultural applications for all 14 pesticides are shown in Table 2.2. Some of the pesticides in this study are primarily or only used in agriculture, such as chlorpyrifos, whereas some are used in primarily non-agricultural applications, such as fipronil, and some pesticides are widely used for both agricultural and structural pest control, such as permethrin.

Most ECE centers were located within 3 km of an agricultural pesticide application in the year prior to the dust sample (Table 2.1). Detailed estimates of agricultural pesticide density are shown by region in Supplemental Table 2.2. In San Joaquin Valley counties, 24 of the 26 centers were within 3 km of at least one agricultural bifenthrin application that took place up to 365 days before the dust collection. The most heavily applied pesticide was chlorpyrifos, with a total of nearly 44 kg/km^2 applied within 3 km of the child care centers, most of which took place in San Joaquin Valley counties.

There were 18 active ingredients applied at the ECE centers reported to DPR within 365 days preceding the dust sampling date (Supplemental Table 2.3). Among these active ingredients, bifenthrin applications accounted for the greatest proportion of applications (36%).

2.3.4 Pesticide concentration correlations.

Spearman's rank correlation coefficients are shown in Table 2.3 for imputed, log-transformed pesticide levels and continuous predictor variables. Density of bifenthrin agricultural pesticide applications within 3 km was significantly correlated ($p<0.05$) with higher bifenthrin dust concentrations ($r=0.38$) and dust loadings ($r=0.44$). Greater number of fipronil applications reported by a PMP was significantly correlated with higher fipronil dust concentrations and loadings ($r=0.30$). Higher IPM Checklist scores were significantly correlated with lower chlorpyrifos concentrations ($r=-0.28$). Other correlation coefficients, including among the pesticide analytes and among the predictors can be found in Supplemental Table 2.4.

2.3.5 Multivariable models.

Results from the multivariable Tobit models for log-transformed pesticide concentrations and loading and predictor variables are shown in Table 2.4 and Figure 2.1. We converted regression coefficients into percent change for the predictors ($\%\Delta = (\exp(\beta)-1)*100$), also shown in Table 4. Location in the San Joaquin Valley was a significant predictor for higher concentrations of bifenthrin (1,166% (95% CI: 274%, 4,185%)) and bifenthrin loading (3,457% (95% CI: 733%,

15,086%)), chlorpyrifos loading (236% (95% CI: 43%, 691%)), fipronil loading (362% (95% CI: 20%, 1,682%)), and ∑permethrin loading (567% (95% CI: 112%, 2,001%)). Lower chlorpyrifos loading was associated with placement of the sampled carpet on carpeted flooring (-57% (95% CI: -81%, -5%)) and sampled base carpeting (-89% (95% CI: -98%, -50%)), compared to the referent placement of area carpet on hard-surface flooring. Higher scoring on the IPM Checklist was associated with lower permethrin dust loading (-8% (95% CI: -14%, -1%)) and lower chlorpyrifos dust loading (-6% (95% CI: -10%, -2%)).

Table 2.2 Distribution of 14 pesticide concentrations and loading in dust (n=51 centers)

Pesticide	DF	Concentration (ng/g)				Loading (ng/m2)				Physicochemical Properties		Statewide Pesticide Use	
	% (n)	Mean (SD)	P50	P95	Max	Mean (SD)	P50	P95	Max	Half-life (days)[a]	LogKow (Octanol-Water)[b]	Kg sold for use in CA, 2018[c]	Kg applied ag. use 2018[d]
cis-Permethrin	98% (50)	1372.58 (6333.28)	131	1130	41400	5063.96 (19883.5)	486.0	8580.0	117000	13*	6.47 to 7.15	261031*	42292*
trans-Permethrin	96% (49)	1755.71 (7760.36)	234	1670	50500	6538.11 (23835.42)	728.0	12700.0	139000		6.47 to 7.43		
Bifenthrin	94% (48)	2153.08 (12211.39)	150	2750	84800	5410.68 (24507.02)	441.0	8520.0	174000	87	6.19 to 8.15	519,812	118,955
Fipronil	94% (48)	170.52 (368.5)	60.5	401	2200	931.72 (1586.77)	199.0	4510.0	7300	142	3.71 to 6.64	86,966	0
Chlorpyrifos	80% (41)	6.71 (5.06)	4.3	18.8	22	34.41 (52.56)	15.8	154.0	274	386	4.66 to 4.96	268,305	272,151
Piperonyl butoxide	73% (37)	269.06 (395.57)	93.1	889	1750	1225.75 (3031.48)	263.0	4156.7	20400	13	4.00 to 4.75	59,427	6,507
Cypermethrin	55% (28)	1556.91 (1386.47)	397	2910	7360	4805.28 (8581.96)	1150.0	25700.0	38700	22	6.05 to 6.60	41,442	300
Deltamethrin	27% (14)	901.01 (1829.47)	<DL	1280	6900	3475.91 (20768.12)	<DL	8790.0	148333	58	6.12 to 6.20	3,789	1
Chlorfenapyr	24% (12)	433.25 (956.23)	<DL	474	3420	388.88 (1100.27)	<DL	2790.0	5950	1	4.76 to 5.51	1,892	83
ƛ-Cyhalothrin	18% (9)	1560.2 (3390.78)	<DL	244	10300	1274.69 (5801.09)	<DL	4250.0	36100	175	6.20 to 6.80	53,472	38,294
Esfenvalerate	18% (9)	643.37 (1269.64)	<DL	333.7	4010	410.22 (1540.76)	<DL	2005.0	8210	67	6.20 to 6.76	17,084	18,114
Cyfluthrin	10% (5)	923.67 (494.56)	<DL	942	1480	988.9 (4393.09)	<DL	4860.0	25800	33	5.74 to 6.29	5,250	4,110
DCPA	0% (0)	--	--	--	--	--	--	--	--	59	3.48 to 4.28	146,956	84345
Diazinon	0% (0)	--	--	--	--	--	--	--	--	9	3.80 to 3.86	31,613	15,161

* Data for permethrin

[a] Soil degradation, aerobic from University of Hertfordshire, Pesticide Properties Database: https://sitem.herts.ac.uk/aeru/ppdb/.

[b] Reports of Pesticide Sold in California, CDPR: https://www.cdpr.ca.gov/docs/mill/nopdsold.htm

[c] California Pesticide Information Portal Application (CalPIP), CDPR: https://calpip.cdpr.ca.gov/main.cfm

[d] University of Hertfordshire, Pesticide Properties Database: https://sitem.herts.ac.uk/aeru/ppdb/

[e] U.S. EPA CompTox Chemicals Dashboard, predicted range values: https://comptox.epa.gov/dashboard/

Table 2.3 Spearman Correlation between pesticide concentrations and loadings and predictors in continuous form

	Bifenthrin		**Chlorpyrifos**		**Fipronil**		**∑Permethrin**	
	Concentration	Loading	Concentration	Loading	Concentration	Loading	Concentration	Loading
Pesticide-specific variables								
Agricultural use of pesticide within 3 km, 1 year (kg/km^2)								
Bifenthrin	0.38**	0.44**						
Chlorpyrifos			0.11	0.10				
Permethrin							0.20	0.06
Number of reported PMP applications of pesticide, 1 year								
Bifenthrin	0.13	0.00						
Fipronil					0.30*	0.30*		
Permethrin							-0.05	0.12
Pesticide products with Active Ingredient observed onsite								
Bifenthrin	0.12	-0.06						
Permethrin							0.23	0.02
Center-specific variables								
IPM Score (# IPM practices observed)	0.23	0.16	-0.28*	-0.21	-0.03	-0.01	-0.26	-0.17
Building year	0.10	0.04	-0.26	-0.18	0.02	0.01	-0.21	-0.10
Pests observed (# types of pests)	-0.10	-0.09	-0.04	-0.03	0.09	0.15	0.13	0.10

Values lower than detection limit were imputed as DL/√2, then all concentrations (ng/g) and loadings (ng/m2) were log-transformed.
*p<0.05
**p<0.01

Table 2.4 Multivariable Tobit model results for pesticide dust concentrations or loadings and predictors.

	Concentration (ng/g)				Loading (ng/m2)			
Pesticide	Predictor	β (95% CI)	Percent change (95% CI)	Pseudo R^2	Predictor	β (95% CI)	Percent change (95% CI)	Pseudo R^2
Bifenthrin				0.08				0.10
	Density of Ag Use (kg/km 2)	-0.46 (-1.18, 0.25)	-37% (-69%, 29%)		Density of Ag Use (kg/km 2)	-0.24 (-1.09, 0.6)	-21% (-66%, 83%)	
	PMP reported application in past year	0.17 (-1.42, 1.75)	18% (-76%, 478%)		PMP reported application in past year	-0.43 (-2.3, 1.45)	-35% (-90%, 325%)	
	Active ingredient observed onsite	-0.93 (-4.54, 2.68)	-61% (-99%, 1356%)		Active ingredient observed onsite	-2.62 (-6.94, 1.71)	-93% (-100%, 450%)	
	IPM Checklist score	-0.03 (-0.09, 0.04)	-2% (-8%, 4%)		IPM Checklist score	-0.05 (-0.12, 0.03)	-4% (-12%, 3%)	
	1 pest observed vs. no pests observed	1.12 (-0.26, 2.5)	206% (-23%, 1117%)		1 pest observed vs. no pests observed	0.84 (-0.85, 2.53)	132% (-57%, 1153%)	
	2+ pests observed vs. no pests observed	0.51 (-1.08, 2.11)	67% (-66%, 723%)		2+ pests observed vs. no pests observed	0.73 (-1.22, 2.67)	107% (-70%, 1350%)	
	Region: San Joaquin Valley	2.54 (1.32, 3.76)	1166% (274%, 4185%)		Region: San Joaquin Valley	3.57 (2.12, 5.02)	3457% (733%, 15086%)	
					Area sampled: Area rug on carpeted floor	0.13 (-1.19, 1.45)	14% (-70%, 327%)	
					Area sampled: Carpeted base flooring	0.41 (-1.89, 2.72)	51% (-85%, 1412%)	
Chlorpyrifos				0.08				0.15
	Density of Ag Use (kg/km 2)	0.05 (-0.07, 0.18)	5% (-7%, 20%)		Density of Ag Use (kg/km 2)	0.06 (-0.13, 0.26)	6% (-12%, 29%)	
	IPM Checklist score	-0.04 (-0.07, -0.01)	-4% (-7%, -1%)		IPM Checklist score	-0.06 (-0.11, -0.02)	-6% (-10%, -2%)	
	1 pest observed vs. no pests observed	-0.56 (-1.17, 0.05)	-43% (-69%, 5%)		1 pest observed vs. no pests observed	-0.85 (-1.82, 0.12)	-57% (-84%, 13%)	
	2+ pests observed vs. no pests observed	-0.5 (-1.23, 0.23)	-39% (-71%, 26%)		2+ pests observed vs. no pests observed	-0.34 (-1.5, 0.82)	-29% (-78%, 128%)	
	Region: San Joaquin Valley	0.26 (-0.29, 0.81)	30% (-25%, 124%)		Region: San Joaquin Valley	1.21 (0.36, 2.07)	236% (43%, 691%)	
					Area sampled: Area rug on carpeted floor	-0.84 (-1.64, -0.05)	-57% (-81%, -5%)	
					Area sampled: Carpeted base flooring	-2.23 (-3.77, -0.69)	-89% (-98%, -50%)	
Fipronil				0.03				0.06

	PMP reported application in past year	1.87 (-0.49, 4.23)	547% (-39%, 6748%)		PMP reported application in past year	2.62 (-0.52, 5.77)	1279% (-41%, 31976%)	
	IPM Checklist score	-0.02 (-0.07, 0.04)	-2% (-7%, 4%)		IPM Checklist score	-0.04 (-0.11, 0.04)	-4% (-11%, 4%)	
	1 pest observed vs. no pests observed	0.82 (-0.33, 1.96)	126% (-28%, 609%)		1 pest observed vs. no pests observed	1.05 (-0.54, 2.64)	185% (-42%, 1299%)	
	2+ pests observed vs. no pests observed	0.69 (-0.73, 2.12)	100% (-52%, 729%)		2+ pests observed vs. no pests observed	1.77 (-0.19, 3.72)	485% (-17%, 4039%)	
	Region: San Joaquin Valley	0.6 (-0.4, 1.6)	83% (-33%, 395%)		Region: San Joaquin Valley	1.53 (0.18, 2.88)	362% (20%, 1682%)	
					Area sampled: Area rug on carpeted floor	-0.49 (-1.79, 0.8)	-39% (-83%, 123%)	
					Area sampled: Carpeted base flooring	0.79 (-1.5, 3.07)	119% (-78%, 2051%)	
∑Permethrin				0.03				0.07
	Density of Ag Use (kg/km 2)	0.46 (-0.48, 1.39)	58% (-38%, 303%)		Density of Ag Use (kg/km 2)	0.27 (-0.81, 1.36)	32% (-56%, 290%)	
	PMP reported application in past year	-0.33 (-2.67, 2.02)	-28% (-93%, 652%)		PMP reported application in past year	0.14 (-2.56, 2.84)	15% (-92%, 1615%)	
	Active ingredient observed onsite	-0.16 (-1.91, 1.59)	-15% (-85%, 388%)		Active ingredient observed onsite	-0.75 (-2.78, 1.27)	-53% (-94%, 257%)	
	IPM Checklist score	-0.06 (-0.12, 0)	-6% (-12%, 0%)		IPM Checklist score	-0.08 (-0.15, -0.01)	-8% (-14%, -1%)	
	1 pest observed vs. no pests observed	0.05 (-1.14, 1.24)	5% (-68%, 246%)		1 pest observed vs. no pests observed	0.05 (-1.34, 1.44)	5% (-74%, 324%)	
	2+ pests observed vs. no pests observed	-0.16 (-1.54, 1.22)	-15% (-79%, 239%)		2+ pests observed vs. no pests observed	0.5 (-1.11, 2.12)	65% (-67%, 734%)	
	Region: San Joaquin Valley	0.84 (-0.16, 1.83)	131% (-15%, 524%)		Region: San Joaquin Valley	1.9 (0.75, 3.05)	567% (112%, 2001%)	
					Area sampled: Area rug on carpeted floor	-0.51 (-1.6, 0.58)	-40% (-80%, 79%)	
					Area sampled: Carpeted base flooring	-0.78 (-2.7, 1.13)	-54% (-93%, 210%)	

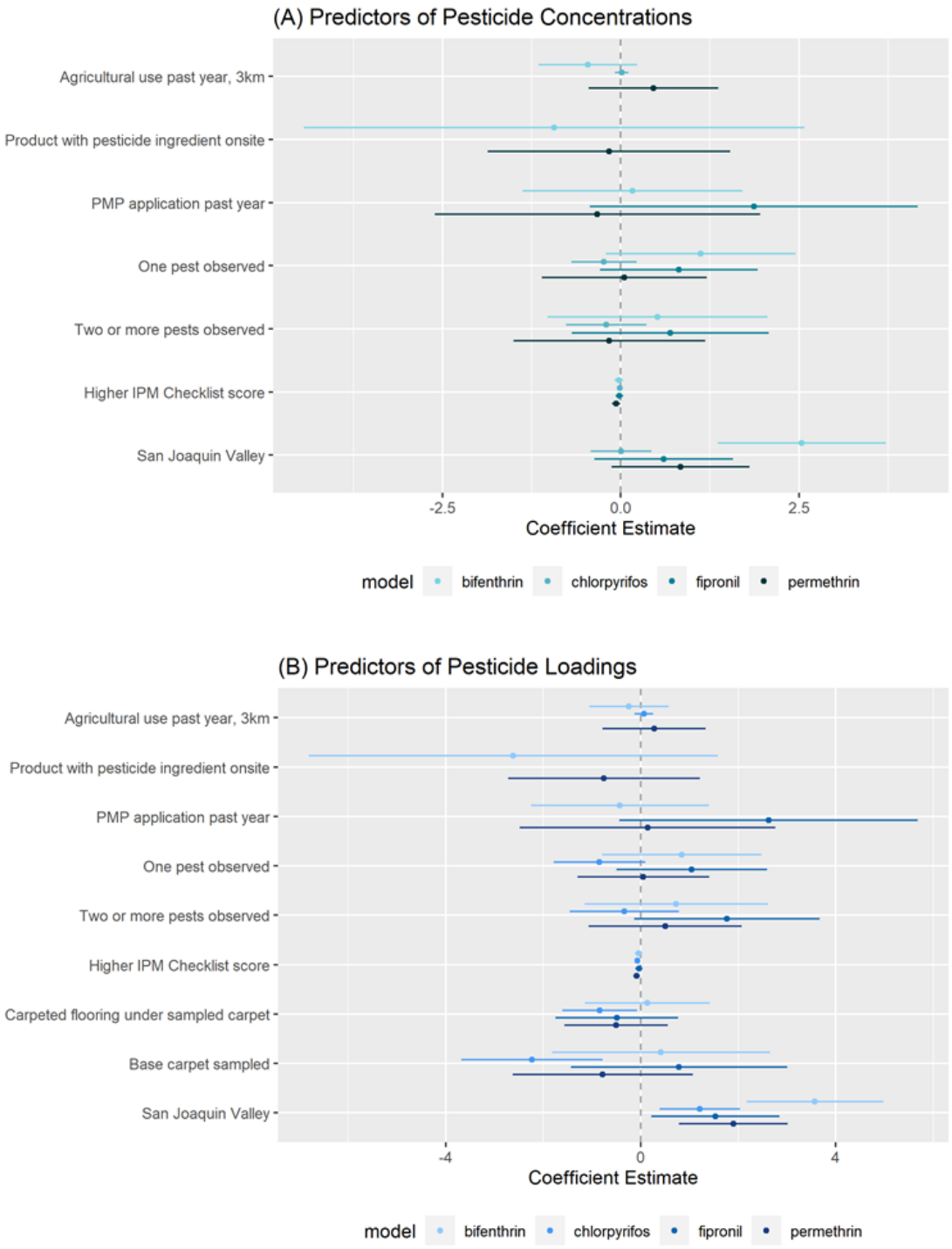


Figure 2.1 Coefficients and 95% confidence intervals for predictors of pesticide levels in ECE carpet dust. **A** Predictors modeled against four pesticide concentrations. **B** Predictors modeled against four pesticide loadings.

2.4 Discussion

Our results indicated that, for specific pesticides, geographic region, proximity to agricultural pesticide applications, applications of structural pesticides, fewer IPM practices, and placement of sampled carpet on hard surface flooring were predictors of higher pesticide levels in carpet dust Northern California ECE centers. The strongest predictor of higher pesticide loading for all the most frequently detected pesticides was location in the San Joaquin Valley. Correlations were strongest for bifenthrin levels and agricultural bifenthrin use within 3 km of the ECE center in the past year; fipronil levels and PMP applications of fipronil at the ECE center; and lower chlorpyrifos levels with better IPM practices. Overall, we saw stronger associations between our selected predictors with the pesticide loading than with concentration. We did not find associations between observed pesticide products stored onsite, pests observed, or age of the facility. Our findings contribute to the growing knowledge that pesticides are ubiquitous in the environments in which California's youngest and most vulnerable populations are cared for.

The distribution of pesticides in our study were consistent with that of a study in California child care centers reported by Bradman et al. 2012 (9) which examined 10 of the same target analytes from samples collected in 2010 and 2011 (Figure 2.2 and Supplemental Table 2.5). Overall, the detection frequencies were similar aside from diazinon and DCPA, which were lower in our study. Chlorpyrifos was found at lower concentrations in the current study than other ECE studies. This is consistent with the declining use of OP pesticides after a voluntary phase-out for indoor uses of chlorpyrifos and diazinon between 2001 and 2004 (1), and declining agricultural use in California which dropped more than 50% since 2005, and all sales of chlorpyrifos ceased in 2020 (63). Median concentrations were similar for permethrin and piperonyl butoxide, and higher for bifenthrin and cypermethrin in our study, which may reflect increasing use of pyrethroids for pest control. In a study of 13 ECE programs in North Carolina, cis- and trans-permethrin were also highly frequently detected in dust samples (8) (Figure 2). To our knowledge, this is the first study to measure fipronil and chlorfenapyr in carpet dust from ECE programs, two relatively new insecticides that are increasing in popularity (93, 94), and were detected in 94% and 33% of our samples, respectively.

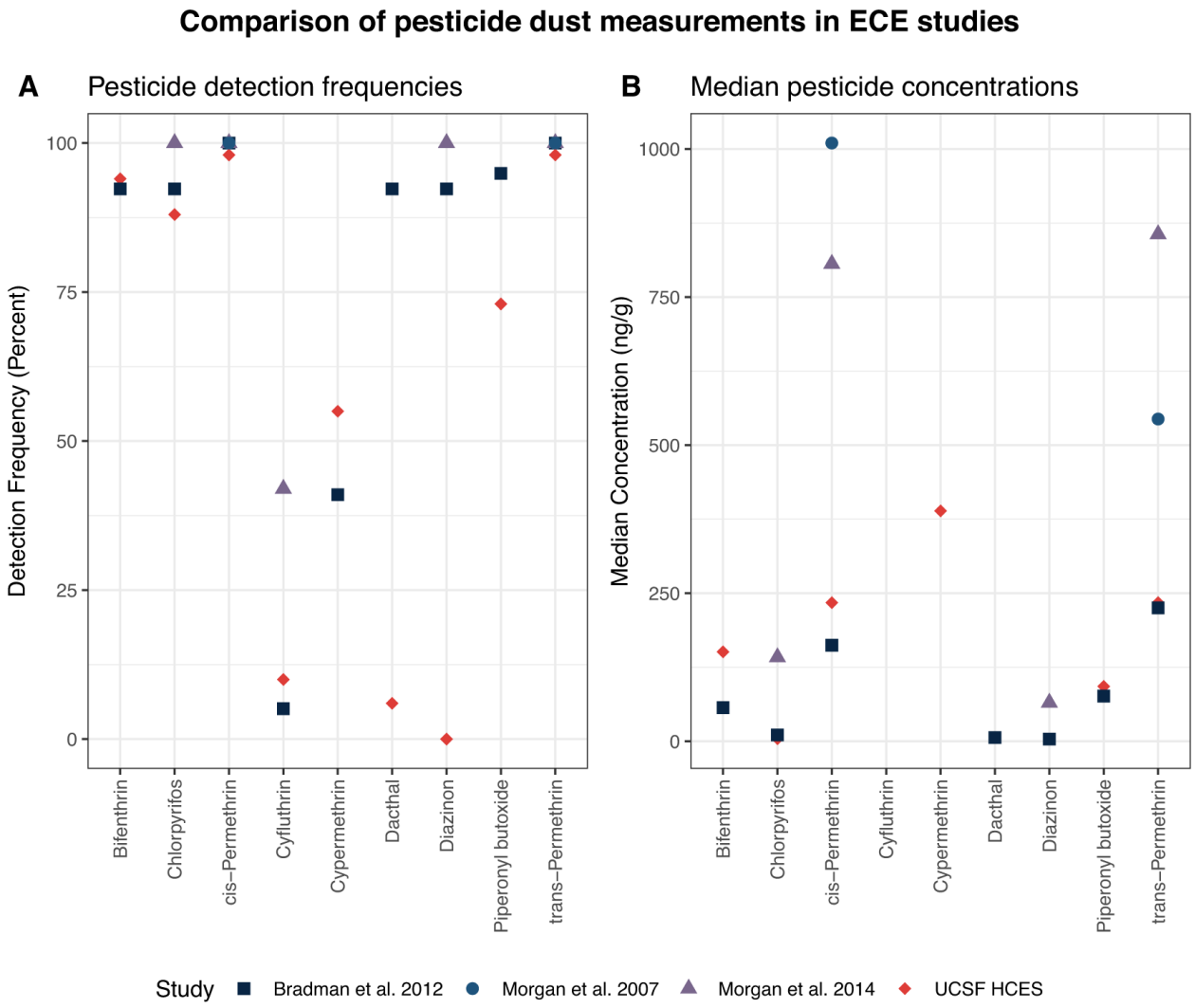


Figure 2.2 Comparison of pesticide measurements among studies with dust samples from early care and education (ECE) programs. **A** Comparison of pesticide detection frequencies among four ECE studies. **B** Comparison of median pesticide concentrations among four ECE studies. UCSF HCES = University of California, San Francisco, Healthy Children and Environments Study.

Predictors of pesticide dust contamination were generally consistent with predictors of pesticide concentrations in passive sampling silicone wristbands worn by preschool-age children in the same study population (80). Having a professional exterminator used in last 6 months at home was associated with higher levels of bifenthrin in wristbands worn by children. Pounds of agricultural pesticide use at the county-level was associated with cypermethrin, fipronil, and permethrin levels in the child wristbands, which is consistent with our findings of strong associations between region and higher concentration of bifenthrin and all pesticide dust loadings. In the silicone wristbands, having no pests observed at the ECE facility was associated

with higher levels of bifenthrin, fipronil, and trans-permethrin, but we found no association between pests observed and pesticide levels in dust.

Most of what is known about determinants of non-dietary exposure to pesticides comes from studies in residential environments and suggest that both nearby agricultural pesticide use and individual behaviors are associated with pesticide exposures. A systematic review of non-dietary exposure to agricultural pesticides identified key determinants of exposure, including behaviors like housekeeping practices, and spatial indicators like proximity to fields and total amounts of pesticides applied near homes (20). Harley et al. (2019) reported that living within 100 m of active agricultural fields, having carpeting in the home, and having an exterminator treat the home in the past six months were associated with higher odds of detecting certain pesticides in silicone wristbands, while concentrations were lower for participants who cleaned their homes daily and had doormats in the entryway of their home (95). Several studies have reported that closer proximity to agricultural pesticide applications is associated with higher concentrations and loadings of pesticides in residential carpet dust (22, 88, 90, 96).

The correlation between bifenthrin levels and agricultural use within 3 km in the present study is consistent with associations in residential settings. We did not find an association with chlorpyrifos levels and agricultural use, despite chlorpyrifos only having agricultural uses in California during the study period. The half-life of chlorpyrifos can exceed one year (see Table 2), therefore we may need to examine associations with applications made within two or more years prior to the dust sample. To our knowledge, this is the first examination of agricultural proximity to child care centers and pesticide exposures. Further investigation is needed to determine if California's regulatory buffer of <500 meters around schoolsites will sufficiently reduce exposure to agricultural pesticides.

We were not able to thoroughly examine other known predictors of residential pesticide contamination (20, 95). For example, we were not able to examine heterogenous patterns for doormats, carpet deep cleaning, or daily cleaning practices. Most ECE programs had their carpets deep cleaned (steam cleaned, shampooed, sent out to cleaner, or other wet cleaning method) at least once per year, only three programs did not have a doormat at their entrance, and routine cleaning, sanitizing, and disinfecting is required by California child care licensing. We did not find any correlation between frequency of deep carpet cleaning and pesticide levels in preliminary analyses. It is notable that there are still measurable concentrations of at least one pesticide in dust from all ECE centers in this study, despite many common practices that should reduce contamination.

We found lower levels of permethrin and chlorpyrifos associated with higher scores on the IPM Checklist. Considering that chlorpyrifos has not been used indoors for more than two decades, this finding suggests that IPM practices may reduce exposure to legacy pesticides that persist in the indoor environment, in addition to preventing pest infestations and reducing the need for new pesticide applications. The IPM Checklist captures some information about building quality, doormats, ventilation, and cleaning practices, which may influence presence of persistent contaminants indoors.

Flooring type and presence of carpets are predictors of total indoor dust loading (97). We found no difference in loading by the type of carpet sampled (low pile vs. medium and high pile). We hypothesized that pesticide levels would be lower in ECE centers with hard surface flooring types, however it appears that the placement of the sampled area carpet on

laminate/hardwood/tile flooring in 29 of the 51 centers permitted ready entrainment of fine dust from the hard flooring with activity in the room and subsequent settling and collection on the sampled area carpet, producing the elevated chlorpyrifos and permethrin loading on these carpets. By contrast, less entrainment of fine dust may have occurred in the 18 centers where the sampled area carpet was placed on carpeted flooring and in the 4 centers where the carpet sampled was the base carpeting. This finding does not suggest that carpeted flooring is better than non-carpeted flooring for reducing exposure, but supports the notion that all carpets, particularly area carpets on which children come in close contact with, serve as reservoirs for indoor dust (98), and therefore should be targeted for frequent cleaning, and children's hands should be washed after contact with carpets to reduce exposure. We were not able to determine the overall ratio of different flooring types in the classroom, and we relied on self-reported cleaning practices and frequencies. Placement of sampled carpets on different flooring types is a novel investigation in exposure assessment literature, and more research is needed.

It is of note that we found poor concordance between the director interview and data on PMP applications provided by DPR. There were instances when the ECE director reported that a PMP sprayed pesticides in the past year, but no PUR record was provided, and vice versa. For over 40% of centers (n=21), the PUR data contradicted the self-reported data from the director interview. We used DPR data assuming it would be more accurate, but that is unconfirmed. A potential limitation of the PUR data is that it includes pesticide applications reported to DPR by licensed PMPs and does not include applications by unlicensed center staff; additionally, some ECE centers are located on a school campus, so applications may be reported for those schools and not shown for the childcare center. However, the PMP records include detailed information about application dates, location, and active ingredient(s). Overall, we found that using the PUR data returned stronger and more precise effect estimates compared to director reported information about PMP practices. Our findings suggest that self-report of PMP pesticide use is not as reliable as statewide PUR data, and that there may be an overall need for better communication between PMPs and ECE directors.

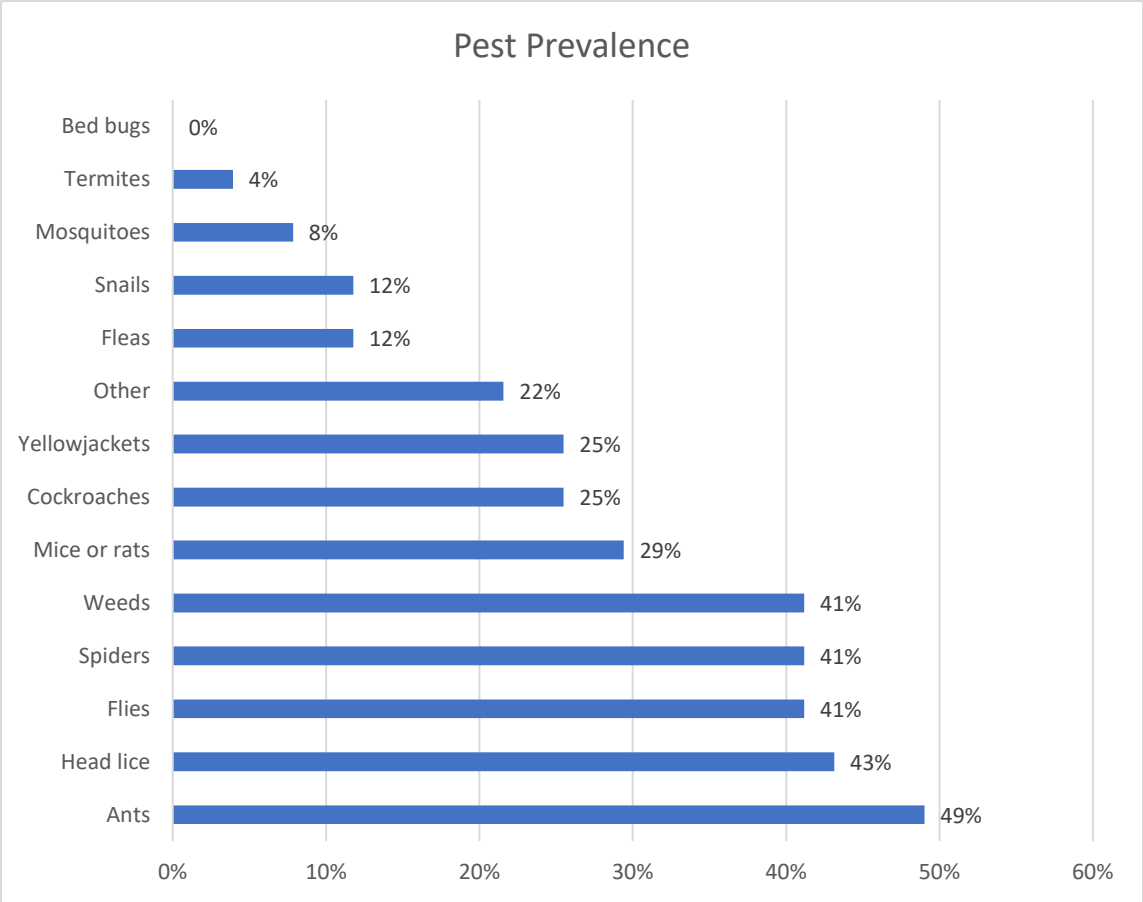
Limitations of this study include the relatively small number of baseline dust samples available from the first three years of HCES (sampling was curtailed due to COVID-19 restrictions) which limited our power to detect associations between pesticide levels and predictors. We enrolled a convenience sample of ECE programs and assessed exposure during a limited period (Fall to early Winter), therefore results are limited in generalizability. Data for certain predictors of pesticide levels were not collected or analyzed, such as measures of classroom ventilation, efficiency of vacuum used in classroom, or wind direction at time of agricultural pesticide applications. We also collected a single sample from one area of the classroom, rather than multiple samples throughout the center. Lastly, this analysis considers center-level predictors and single pesticide outcomes individually and does not account for chemical-specific characteristics such as vapor pressure or persistence, nor considers predictors of pesticide mixtures.

2.5 Conclusion

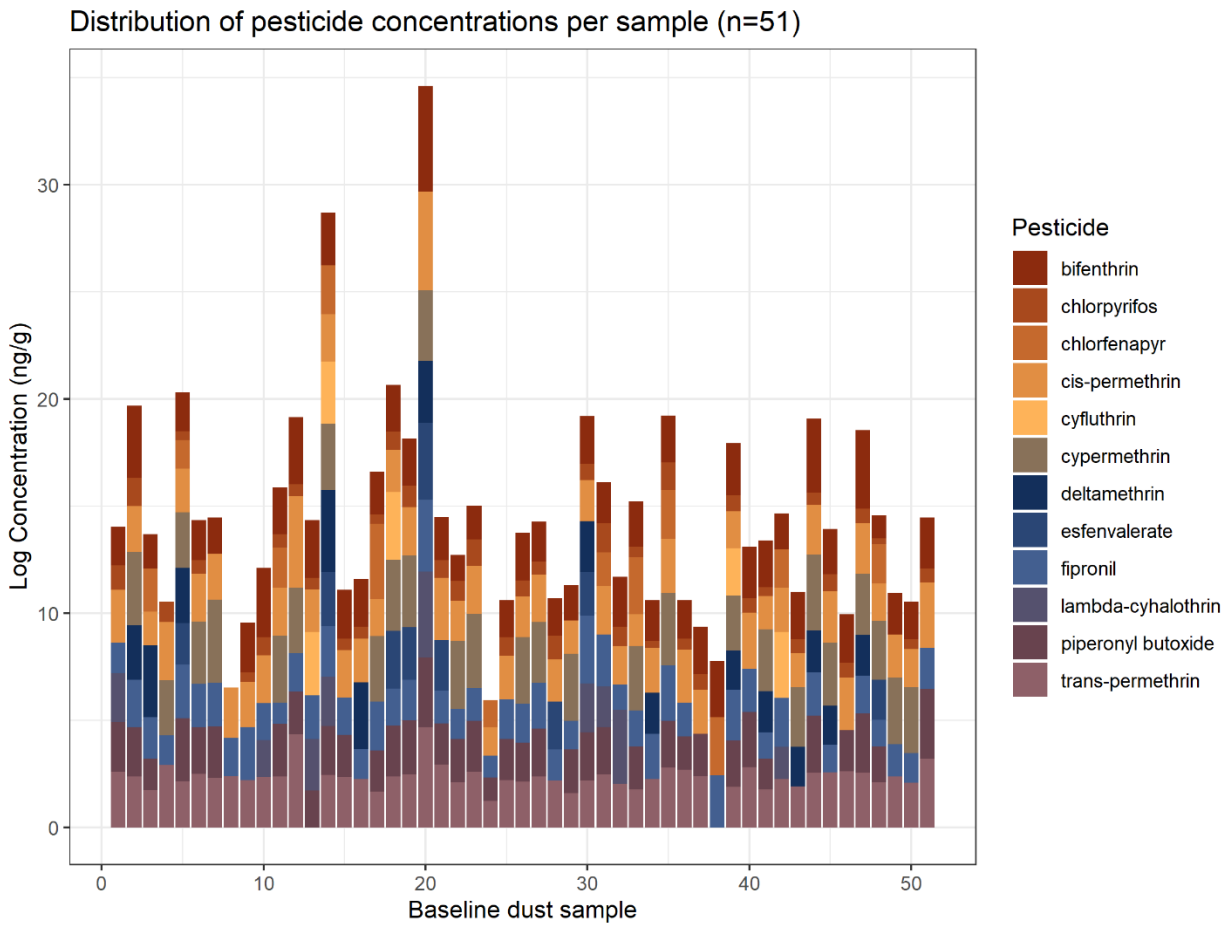
In conclusion, we found that pesticide levels in classroom carpet dust were associated with some factors that ECE directors may have control over (IPM practices and the use of a pest management professional) and others that are beyond their control (geographic location and proximity to agricultural pesticide applications). Children's care environments are generally

understudied, but are a critical point for intervention as chronic, low-level exposures in early childhood can influence lifelong health and development.

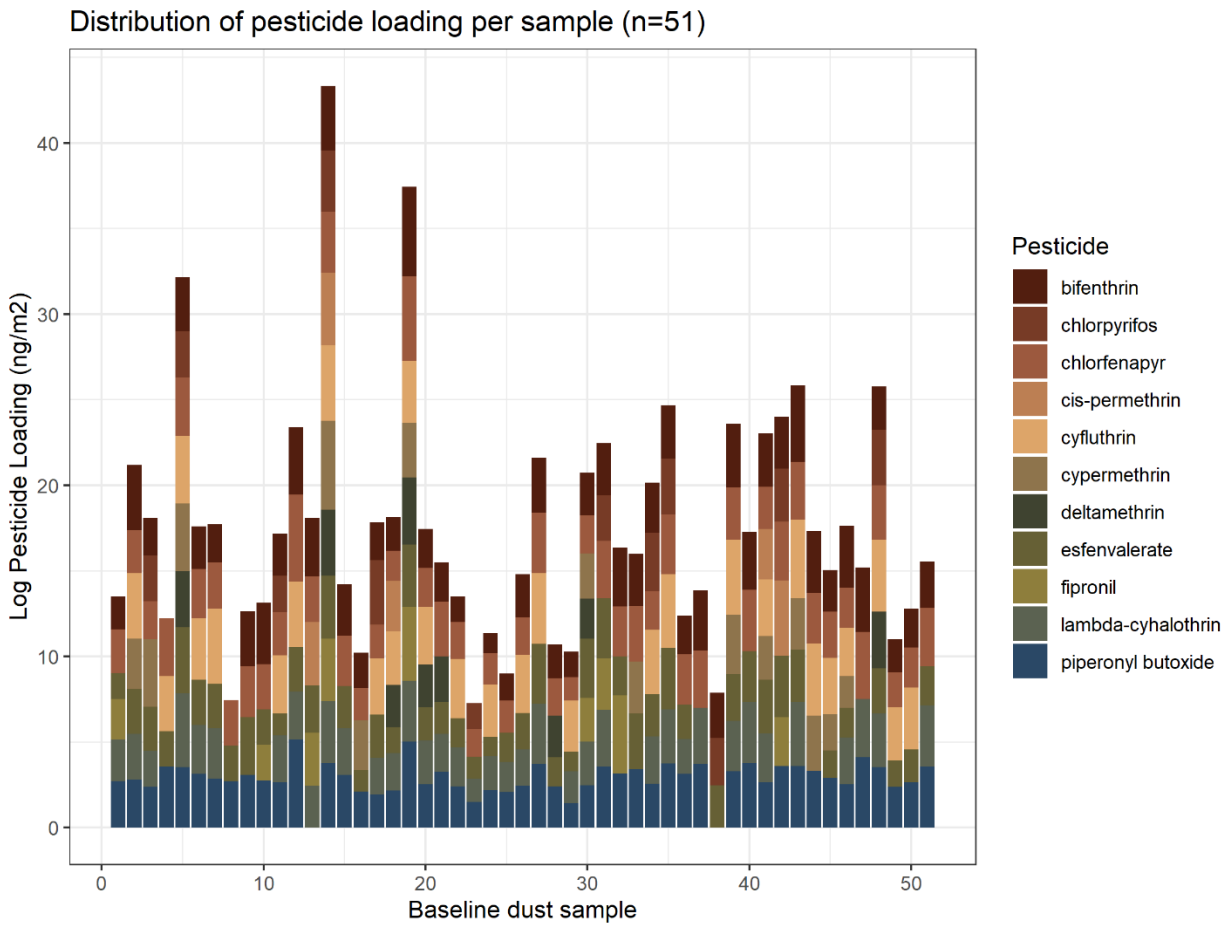
2.6 Supplement to Chapter 2



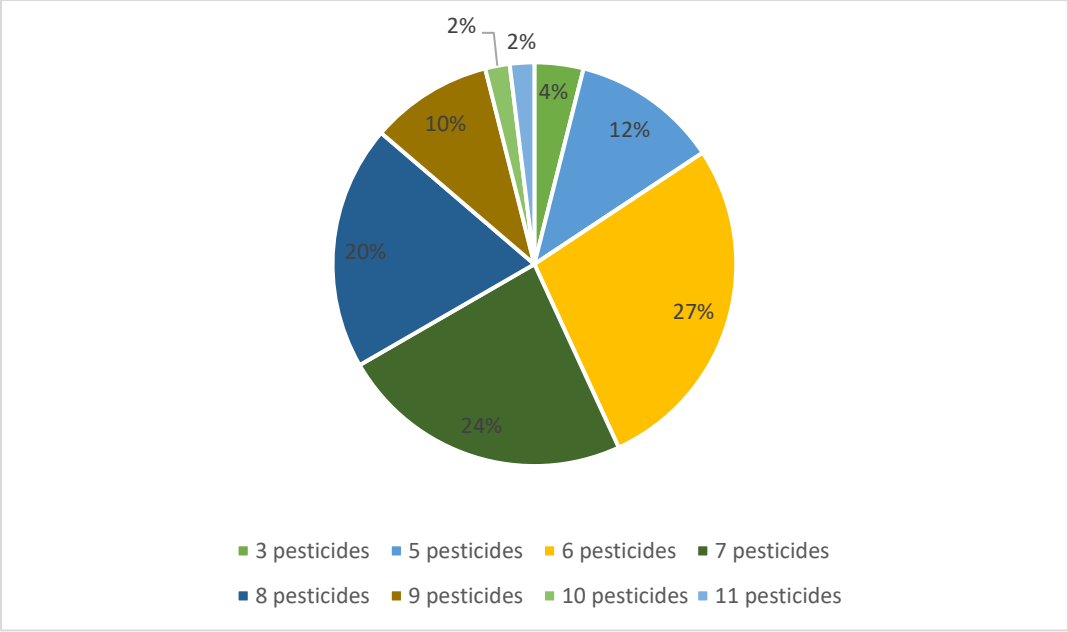
Supplemental Figure 2.1 Director-reported pests observed, past year (director interview)



Supplemental Figure 2.2 Distribution of pesticide concentrations per dust sample (concentrations are log10-transformed)



Supplemental Figure 2.3 Distribution of pesticide loading per dust sample (log10-transformed)



Supplemental Figure 2.4 Total number of detected pesticides per dust sample (n=51)

Supplemental Table 2.1 Laboratory Analytical Data: Recovery of spiked pesticide amount in seven matrix spikes, and detection limits.

Pesticide	Recovery (%)	Limit of Detection (ng/g)		
	Mean (SD)	Min	Median	95th percentile
cis-Permethrin	78 (15)	0.379	3.9	37.5
trans-Permethrin	88 (25)	1.52	12.6	121
Bifenthrin	97 (27)	1.26	1.66	16.3
Fipronil	91 (11)	2.53	3.31	16.5
Chlorpyrifos	92 (12)	1.26	1.65	3.26
Piperonyl butoxide	102 (27)	1.26	16.3	82.3
Cypermethrin	96 (73)	12.6	82.1	412
Chlorfenapyr	110 (39)	2.53	3.31	16.5
Deltamethrin	74 (17)	6.31	40.7	79.5
λ-Cyhalothrin	109 (33)	6.31	8.27	16.6
Esfenvalerate	92 (38)	6.31	41.1	79.5
Cyfluthrin	109 (46)	12.6	81.5	159
DCPA	79 (5)	1.26	1.65	3.26
Diazinon	85 (7)	1.26	1.65	3.26

Measurement accuracy for each pesticide was assessed by the percent recovery of the spiked amount of each targeted pesticide in the seven matrix spike samples. Measurement precision was assessed by degree of agreement between the concentrations of each pesticide measured in the dust sample and its laboratory-split duplicate over the seven duplicate samples. Agreement was within a factor of two for 59 (95%) of the 62 pairs with detected concentrations in both the sample and its duplicate. Agreement was within 20% for 47 (76%) of these 62 duplicate pairs.

LODs were sometimes raised due to inseparable coeluting analytical interference compounds. We report the minimum, median and an upper percentile of the LODs for each target analyte across all of the baseline samples. Comparing the upper percentile and median to the minimum will indicate the prevalence of raised detection limits for each target pesticide.

Supplemental Table 2.2 Estimated density of agricultural pesticide use by region, 3 km around center, 365 days prior to sampling

Pesticide	Region	# ECE Centers with application within 3 km, past year	Median (kg/km^2)*	Range (kg/km^2)*
Bifenthrin	SF Bay Area	5	1.79	0.57 - 2.21
	San Joaquin Valley	24	0.65	0.01 - 3.28
	Total	29	0.69	
Chlorpyrifos	SF Bay Area	2	4.60	4.03 - 5.16
	San Joaquin Valley	11	2.54	0.01 - 8.01
	Total	13	3.08	
Permethrin	SF Bay Area	2	1.18	1.17 - 1.19
	San Joaquin Valley	8	0.24	0.001 - 2.72
	Total	10	0.40	

*Among non-zero values

Supplemental Table 2.3 Pest Management Professional (PMP) pesticide applications reported to DPR – at child care address, 365 days prior to sampling – by active ingredient

Active Ingredient	Number of applications reported n (%)
Alpha-(para-nonylphenyl)-omega-hydrox..	1 (1%)
Bifenthrin	29 (36%)
Bromadiolone	3 (4%)
Chlorfenapyr	1 (1%)
Cyfluthrin	2 (2%)
Cypermethrin	3 (4%)
Deltamethrin	16 (20%)
Dinotefuran	1 (1%)
Edta, tetrasodium salt	1 (1%)
Esfenvalerate	1 (1%)
Fipronil	3 (4%)
Hydroprene	2 (2%)
Indoxacarb	3 (4%)
Permethrin	2 (2%)
Piperonyl butoxide	5 (6%)
Prallethrin	1 (1%)
Pyrethrins	4 (5%)
S-methoprene	3 (4%)
Total	81 (100%)

Supplemental Table 2.1 Correlations among pesticide concentrations and loadings, and among continuous predictors

Correlation among pesticide levels								
	Bifenthrin (BIF)		Chlorpyrifos (CPF)		Fipronil (FIP)		Permethrin (PERM)	
	Concentration	Loading	Concentration	Loading	Concentration	Loading	Concentration	Loading
BIF Concentration	1.00							
BIF Loading	0.78	1.00						
CPF Concentration	0.00	-0.09	1.00					
CPF Loading	0.05	0.44	0.44	1.00				
FIP Concentration	0.32	0.30	-0.10	-0.07	1.00			
FIP Loading	0.24	0.48	-0.27	0.21	0.81	1.00		
PERM Concentration	0.26	0.06	0.37	-0.01	0.16	0.05	1.00	
PERM Loading	0.27	0.61	0.01	0.55	0.25	0.53	0.49	1.00

Correlation among continuous predictors											
	IPM score	Building year	Pests observed (# types of pests)	Density of BIF Ag Use (kg/km^2)	Density of CPF Ag Use (kg/km^2)	Density of PERM Ag Use (kg/km^2)	BIF applications by PMP	FIP applications by PMP	PERM applications by PMP	BIF product onsite	PERM product onsite
IPM average score	1.00										
Building year	0.49	1.00									
Pests observed	-0.36	-0.30	1.00								
Density of BIF Ag Use	0.28	0.19	-0.05	1.00							
Density of CPF Ag Use	0.15	0.24	-0.07	0.39	1.0						
Density of PERM Ag Use	0.15	0.24	-0.07	0.45	0.6	1.00					
BIF applications by PMP	0.17	0.26	-0.11	0.12	-0.1	0.14	1.00				
FIP applications by PMP	-0.14	-0.17	0.27	-0.01	-0.1	-0.10	-0.07	1.00			
PERM applications by PMP	0.14	0.22	-0.30	0.07	0.1	0.17	-0.07	-0.04	1.00		
BIF product onsite	0.01	-0.02	-0.01	0.04	-0.1	-0.07	-0.05	-0.03	-0.03	1.00	
PERM product onsite	-0.33	-0.26	0.12	-0.06	0.0	-0.14	-0.11	-0.06	-0.06	0.48	1.00

Supplemental Table 2.2 Comparison of pesticide measurements in early care and education (ECE) studies. Detection frequencies (DF%) and concentrations (ng/g)

	UCSF Healthy Children & Environments Study (2017-2019) (n=51)				**Bradman et al. 2012 (n=39)**				**Morgan et al. 2014 (n=13)**				**Morgan et al. 2007 (n=22)**			
	Location: California, USA				Location: California, USA				Location: North Carolina, USA				Location: Ohio, USA			
Pesticide Analyte	DF %	p50	p95	Range	DF%	p50	p95	Range	DF%	p50	p95	Range	DF%	p50	p95	Range
cis-Permethrin	98%	131	1,130	<DL-41,400	100%	162	940	47-12,712	100%	806	19,700	113–29,000	100%	1,010	3,830	127-4,630
trans-Permethrin	96%	234	1,670	<DL-50,500	100%	225	1,501	48-21,058	100%	856	20,900	125–29,900	100%	544	3,420	126-3,950
Chlorpyrifos	80%	4	19	<DL-22	92%	11	217	<DL-563	100%	142	921	12.4–921	-	-	-	-
Cyfluthrin	10%	<DL	942	<DL-1,480	5%	<DL	434	<DL-739	42%	<DL	1,750	<DL-1750	-	-	-	-
Diazinon	0%	<DL	<DL	<DL	92%	4	61	<DL-74	100%	65	6,880	3.06–6,880	-	-	-	-
Bifenthrin	94%	151	2,750	<DL-84,800	92%	57	897	<DL-928	-	-	-	-	-	-	-	-
Piperonyl butoxide	73%	93	889	<DL-1,750	95%	76	1,376	<DL-24,629	-	-	-	-	-	-	-	-
Cypermethrin	55%	397	2,910	<DL-7,360	41%	<DL	2,969	<DL-35,898	-	-	-	-	-	-	-	-
DCPA	0%	<DL	<DL	<DL	92%	6	51	<DL-74	-	-	-	-	-	-	-	-
Fipronil	94%	61	401	<DL-2,200	-	-		-	-	-	-	-	-	-	-	-
Chlorfenapyr	24%	<DL	474	<DL-3,420	-	-		-	-	-	-	-	-	-	-	-
Deltamethrin	27%	<DL	1,280	<DL-6,900	-	-		-	-	-	-	-	-	-	-	-
ƛ-Cyhalothrin	18%	<DL	244	<DL-10,300	-	-		-	-	-	-	-	-	-	-	-
Esfenvalerate	18%	<DL	334	<DL-4,010	-	-		-	-	-	-	-	-	-	-	-

Chapter 3 Health risks associated with preschool-age children's exposure to pesticides in carpet dust from child care centers in Northern California: A tiered cumulative risk assessment

3.1 Introduction

Research shows that young children are exposed to pesticides in their environment, including in child care settings (6-9, 99). Most children in the U.S. spend a significant amount of time in environments other than their home. One million children in California under six years of age attend child care programs (100) where they may spend up to 30–40 hours per week (78).

Children are uniquely vulnerable to chemical exposures. Young children spend a large portion of their time on the floor or ground and have frequent hand-to-mouth activity, increasing their exposure to contaminants that settle in dust (10, 12). Overall hand-to-mouth behavior is significantly greater indoors than outdoors (15) and young children often spend 60% to 75% of their time indoors (16). Young children are particularly vulnerable to chemical exposures during critical windows of development because their respiratory, reproductive, digestive, immunological, and central nervous systems are not yet fully matured, causing them to be more susceptible to potential disruptions (12). Few studies have assessed potential health risks associated with pesticide exposures in child care settings (6, 8). One study of exposure to chlorpyrifos and dichlorvos suggested excess cancer risk among children in South Korean child care facilities (6).

Traditional chemical health risk assessment and regulation are often done one chemical at a time (Figure 3.1) (101). However, environmental samples show that children are exposed to mixtures of pesticides as well as other contaminants (8, 9, 102). The U.S. Environmental Protection Agency (EPA) has made some progress in assessing cumulative risks from chemicals thought to act via a common biologic mechanism (for example, organophosphate (OP) pesticides causing acetylcholinesterase inhibition) (103). The U.S. EPA has developed relative potency factors that allow cumulative risk assessments for five classes of pesticides that share a common mechanism of toxicity, including pyrethroids. However, current EPA frameworks are still limited by a lack of attention to variability in human susceptibility, use of deterministic rather than risk-specific, probabilistic approaches to defining reference values, and failure to incorporate interactions between chemical and nonchemical stressors in assessments (104-107).

Risk assessments for non-cancer outcomes, such as neurotoxicity, assume a "safe" level of exposure, operationalized by the use of EPA oral reference doses (RfD), which are defined as levels of exposure "likely to be without an appreciable risk of deleterious effects." The National Research Council of the National Academies' (NRC) report *Science and Decisions* stressed the importance of applying probabilistic approaches and challenging the "bright-line" approach of the reference dose for non-cancer outcomes (104). In 2023, a group of scientists released a consensus statement for health-protective chemical assessments and decisions, outlining key principles for using science in hazard and risk assessment to reflect real-world risks. The accompanying publications provide frameworks and methods to address variability, uncertainty, and differential susceptibility in estimating risks for non-cancer health effects (105-107), which we apply in the present study. Advancements in probabilistic modeling and recent calls for

improved risk assessment approaches have made the application of newer methods for risk assessment more widely accessible and imperative to use.

In the present study, we take a tiered approach to assessing potential health risks from children's exposure to pesticides in indoor dust: First, we aim to generate contextual risk estimates that can inform and empower study participants in the reporting back of research results phase of environmental health studies by offering meaningful insights into potential risks. Child care providers and families involved in environmental health research may not easily understand what levels of pesticides in classroom carpet dust mean for children's health. Calculating potential doses and comparing them to established health benchmarks may support reporting research results to participants. Second, we apply probabilistic risk assessment methods to better account for variability within the diverse general population and describe risk beyond the RfD threshold (105, 106). This comprehensive approach acknowledges the complexity of real-world risks and strives to provide a more accurate and nuanced assessment of pesticide-related health concerns.

In this paper, we assessed children's cumulative exposures to pesticides in child care facilities via non-dietary ingestion and dermal absorption using deterministic and probabilistic models and compared them to health-based reference values.

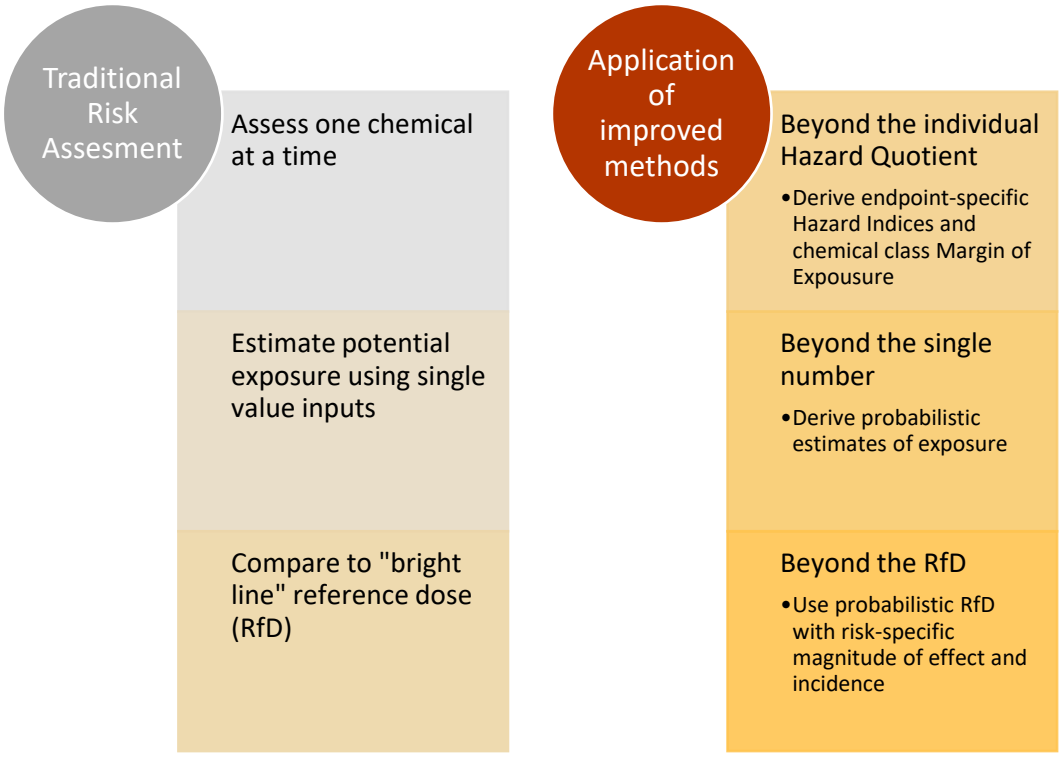


Figure 3.1 Traditional and recommended risk assessment paradigm

3.2 Methods and Materials

3.2.1 Study population

The University of California, San Francisco (UCSF) Healthy Children & Environments Study (HCES) is an ongoing randomized-control trial examining the effect of an integrated pest management (IPM) intervention to reduce pesticide exposures in licensed child care centers (74, 80, 99). Four northern California counties, two in the San Francisco Bay Area and two in the San Joaquin Valley, were randomized to a IPM or attention-control intervention. Carpet dust samples were collected from classrooms at baseline and after a seven-month intervention period. Three to seven children were recruited from each center, meeting the following inclusion criteria: aged 3 or 4 years; plan to spend at least 6 hours per day in the center; plan to be enrolled in the center for the next 9 months; and have a parent present during enrollment who spoke either English or Spanish. Anthropometric measurements were collected on the enrolled children, including age and weight, by a child care health consultant at baseline and after the seven-month intervention period.

3.2.2 Dust sample collection

We collected indoor carpet dust samples using a high-volume small surface sampler (HVS3) (HVS3; Cascade Sampling Systems, Bend, OR). Collection procedures, quality control, and laboratory analytic details are described in Hazard et al., 2023 (99). Dust samples were tested for 14 pesticide analytes, including: pyrethroids (bifenthrin, cyfluthrin, lambda-cyhalothrin, cypermethrin, deltamethrin, esfenvalerate, and cis- and trans-permethrin), OP pesticides (chlorpyrifos and diazinon), and others including the phenylpyrazole fipronil, the synergist piperonyl butoxide, the pyrrole chlorfenapyr, and the herbicide chlorthal-dimethyl (DCPA, tradename Dacthal). In this analysis, we evaluate concentrations of pesticides in dust from 52 child care centers measured at baseline from 2017-2019 (99). We excluded DCPA and diazinon from analysis, which had no detects at baseline, and imputed samples below the limit of detection as LOD/$\sqrt{2}$ (108). We summed cis- and trans-permethrin to derive a total permethrin concentration used in subsequent analyses.

3.2.3 Deterministic Risk Calculations and Individual Hazard Quotients

We first conducted a screening-level deterministic risk assessment using measured pesticide concentrations from the baseline dust samples and body weight measurements for a subset of children from each center. One center had dust data, but no child data, so we imputed one child record for this site, using the mean body weight of all other children (n=253).

We estimated children's potential daily intake doses through dermal and non-dietary incidental ingestion exposure pathways for each pesticide analyte. We developed two potential daily doses deterministically: a central tendency (CT) and upper estimate. For the CT estimates, we used the mean default values listed in the U.S. EPA Exposure Factors Handbook (EFH) for ingestion rate and skin surface area, and assumed one year of exposure within the child care center. For the upper estimates, we used 95th percentile values listed in the EFH and assumed two years of exposure within the child care center. See Table 3.1 for assumptions and defaults used. We calculated potential daily intake dose (mg/kg/day) per pesticide as:

$$Dose_{Dust\text{-}Ingest} = (C_{dust} \times IR \times EF \times ED) / (BW_{child} \times AT)$$

$$Dose_{Derm} = (C_{dust} \times AF \times SA \times ABS \times EF \times ED) / (BW_{child} \times AT)$$

$$\text{Potential Daily Intake (PDI) (mg/kg/day)} = \text{Dose}_{\text{Dust-Ingest}} + \text{Dose}_{\text{Derm}}$$

Where C_{dust} is the analyte dust concentration in the child's child care center (mg/kg), BW_{child} is the child's body weight (kg) obtained at baseline (within days of the dust sample), EF is exposure frequency (days per year), ED is exposure duration (years), IR is dust ingestion rate (mg per day), AF is adherence factor (mg/cm^2), SA is skin surface area (cm^2), ABS is absorption factor for pesticides (unitless), and AT is averaging time (365 days per year). Input values and corresponding assumptions and sources are described in Table 3.1.

Table 3.1 Exposure factors (Deterministic calculations)

Input	Value used	Source
EF = Exposure frequency (day/yr.)	60 (approx. 1,440 hrs/yr)	Assumption: in care 6 hours, 5 days, 48 weeks
ED = Exposure duration (yrs.)	1 (Central Tendency) 2 (Upper)	Assumption: children ages 3-5 yrs. enrolled for 1 or 2 years before entering kindergarten
IR = Dust ingestion rate (mg/day)	30 (Mean) 100 (Upper)	Table 5-1. Recommended Values for Daily Soil, Dust, and Soil + Dust Ingestion (2 to <6y) Exposure Factors Handbook (2017 update)
AF = Weighted Soil Adherence Factor (mg/cm^2)	0.04	Table 7-4. Recommended Values for Mean Solids Adherence to Skin (Daycare Indoors and Outdoors) and Eqn. 7-1 (AF_{wtd}) Exposure Factors Handbook (2011)
SA = Skin surface area available for contact (cm^2)	3870 (Mean) 4840 (Upper)	Table 7-2. Recommended Values for Surface Area of Body Parts (Arms Hands Legs Feet) (3 to <6y) Exposure Factors Handbook (2011)
ABS = Absorption factor (chemical specific)	10%	U.S. EPA Region 3 Technical Guidance Manual, Risk Assessment (conservative assumption of ABS for pesticides) https://www.epa.gov/risk/assessing-dermal-exposure-soil

After estimating the potential daily intake (PDI) for each modeled child, these single-pesticide doses were compared to established Reference Dose (RfD) values to derive a hazard quotient (HQ), such that: HQ = PDI / RfD. An HQ greater than 1 indicates daily exposure that exceeds established health protective reference values.

In general, we used RfDs listed in the U.S. EPA 2021 Human Health Benchmarks for Pesticides (HHBP) Table (109). The HHBP Table includes noncancer benchmarks for exposure to pesticides that the EPA has determined may be found in drinking water. Noncancer benchmarks for acute (one/day) and chronic (lifetime) drinking water exposures to each pesticide were derived for the most sensitive life stage, based on the available information. We selected the chronic RfD when available. In some cases, we used the minimum RfD identified via EPA's CompTox Chemicals Dashboard. For example, for chlorpyrifos, we used California's Office of Environmental Health Hazard Assessment (OEHHA) child-specific RfD of 1.00e-4.

3.2.4 Probabilistic Dose Calculations and Hazard Quotients

We carried out probabilistic dose calculations using Monte Carlo simulations of exposure to account for uncertainty and variability of measured chemical concentrations and assigned exposure factors. We used the EnviroPRA Package (110) available for the R environment to generate dermal and non-dietary ingestion doses for a probabilistic potential daily intake (PDI_{pr}) distributions for each pesticide analyte, with 10,000 Monte Carlo simulations.

The EnviroPRA package allows the user to fit theoretical distributions to observed data and generate a set of random numbers that follow the distribution function selected by the user. We fitted distributions to our measured pesticide concentrations in dust and to our measured body weights of enrolled children based on lowest Bayesian Information Criteria for the distribution fit test and with visual confirmation with Q-Q plots, P-P plots, and density plots via the EnviroPRA package (107). For body weight, we used a log-normal distribution and truncated at one kg less than the minimum observed body weight and one kg greater than the maximum observed body weight. For pesticide concentrations, we used a log-normal distribution for all pesticide analytes except cypermethrin and ∑permethrin, which were fit to a Weibull distribution. We set truncation limits to 0.1 ng/g less than the minimum concentration (which would be imputed at LOD/√2), and 0.1 ng/g greater than the maximum concentration. For three pesticide analytes, the distribution fit test and random number generator within the EnviroPRA package would not converge for pesticide analytes with extreme outliers (bifenthrin, chlorfenapyr, and lambda-cyhalothrin). To address this, we first fit the theoretical distribution to a set of concentrations that excluded the outliers and generated random numbers based on that, and then imputed the values at the extreme.

We assumed children attended day care for 30 hours per week, with a minimum of 15 hours and a maximum of 50 hours, with most children attending between 30-36 hours per week, using a trapezoidal distribution. These assumptions are supported by data collected for the wristband passive samplers also used with participating children (80). We then converted these hours to 24-hour days in our dose calculations. Similarly, we assumed that children would attend for 0.8 to 3.2 years with most attending 1 or 2 years. This assumption supported by the age ranges for the enrolled children. We generated log-normally distributed exposure factors for surface area exposed, soil adherence factor, and dust ingestion rate based on the U.S. EPA Exposure Factor Handbook recommendations and ATSDR Exposure Dose Guidance for Soil/Sediment Dermal Absorption.

3.2.5 Cumulative Risk Characterization

In general, there are two approaches to characterizing cumulative risk: the Hazard Index (HI) and Margin of Exposure (MOE) (104). We employed both methods to characterize cumulative

risk for both the deterministic and probabilistic estimates of exposure: by health endpoints and by pesticide class.

The HI approach sums the HQs when different chemicals that an individual may be exposed to have similar impacts to the same target organ. An HI less than 1 is indicative of a lack of appreciable risk, and an HI greater than 1 indicates some increased risk (the larger the HI, the greater the risk).

$$HI = \sum(Exposure / RfD)$$

In the present study, we sum across health endpoints to derive a Hazard Index (HI) for neurotoxicity and for hepatotoxicity based on the critical effects listed in documentation for the pesticides RfD. For permethrin and piperonyl butoxide, we used two different RfDs for the neurotoxicity HI and hepatotoxicity HI (see Table 4). The MOE approach, used by the U.S. EPA for their cumulative risk assessments of pesticide classes, determines a margin between the point of departure (POD) and the exposure. An MOE smaller than the product of uncertainty factors reflects a potential health concern.

$$MOE = POD / Exposure$$

In the present study, we include eight pyrethroid pesticide analytes in our analysis and apply the same frameworks used in the EPA's cumulative risk assessment for pyrethroids (103) to our measured and modeled data including the relative potency factors and margin of exposure target level.

$$MOE = \frac{BMD_{index}}{CumDoseEq}$$

Where BMD_{index} is the benchmark dose (BMD) of the index chemical, deltamethrin, and CumDoseEq is the cumulative dose equivalent, derived by applying relative potency factors (RPFs) to calculated PDIs per individual pyrethroid analyte:

$$CumDoseEq = \sum RPF_p \times PDI_p$$

$$RPF_p = \frac{BMD_{20-index}}{BMD_{20-p}}$$

U.S. EPA used a 20% change from controls as the BMD threshold (BMD_{20}) for pyrethroids. Additionally, EPA used a target MOE of 300 for children ages 0 to 6 years. Derived MOEs of less than 300 would indicate increased health risk. We computed MOEs from a cumulative pyrethroid dose equivalent by applying EPA's RPFs our estimations of exposure.

3.2.6 Probabilistic RfD

We also compared the probabilistic dose estimates (PDIpr) to a probabilistically derived reference dose. The probabilistic RfD represents the lower confidence limit of the HD_M^I defined as the human dose at which a fraction I of the population shows an effect of magnitude (severity) M for the critical effect considered. In this application, the probabilistic RfD (PrRfD) is the dose that protects 99% of the population from neurotoxic/hepatotoxic effects of 5% or more, with a confidence of 95%. For example, the PrRfD for deltamethrin is 0.008 mg/kg/day, an estimate of

the dose at which, with 95% confidence, at most 1% of the population will have decreased locomotor activity of magnitude 5% change or greater.

We used the World Health Organization (WHO) APROBAplus tool (available at https://www.rivm.nl/en/aproba-plus), to produce PrRfDs for each pesticide analyte (111). In general, we used points of departure from the EPA risk assessments used in the determination of the established RfD (112), and used the defaults included in the APROBAplus tool. More details about inputs used in APROBAplus can be found in Supplemental Table 3.1. Using the PrRfDs, we again derived neurotoxicity and hepatotoxicity Hazard Indices by summing HQs (PDI_{pr}/PrRfD).

3.2.7 Sensitivity analysis

This analysis uses data from baseline of the HCES study. As a sensitivity analysis, we generated distributions of pesticide concentrations based on measured data at up to three time points per center (baseline, approx. 7 months later, and 1-2 years from baseline in the same season).

3.2.8 Hypothetical aggregate exposure scenarios

In an exploratory analysis, we considered the possibility that exposure to pesticides in dust at home would be similar to exposures in child care centers (1, 8, 18, 113). We approximated aggregate PDIs for incidental dust ingestion and dermal exposure by using an exposure frequency of 365 24-hr days (Supplemental Table 3.2). As a test case for fipronil, we added an estimated chronic dietary intake taken from EPA's risk assessment documentation for fipronil to approximate a more complete aggregate exposure for one pesticide.

3.3 Results

3.3.1 Pesticide concentrations in dust and estimated exposure

The baseline detection frequency and geometric mean values for 12 pesticide analytes measured in 52 child care centers are shown in Table 3.2. The most frequently detected pesticides were cis- and trans-permethrin, bifenthrin, fipronil, and chlorpyrifos. The highest geometric mean concentrations (ng/g) were found for cypermethrin (1205.8) and cyfluthrin (740.6). Deltamethrin, esfenvalerate, trans-permethrin, and lambda-cyhalothrin had geometric mean concentrations between 200-300 ng/g, and bifenthrin, cis-permethrin, piperonyl butoxide, and chlorfenapyr had geometric mean concentrations between 100-200 ng/g. While among the most frequently detected pesticides, fipronil had a geometric mean concentration less than 100 ng/g (72.4), and chlorpyrifos less than 10 ng/g (5.5).

Distributions of the estimated exposures are shown in Table 3.3. The 95th percentiles of the probabilistic estimates were greater than the 95th percentile of the deterministic estimates for most pesticides, and were similar to the upper deterministic estimate for deltamethrin, esfenvalerate, lambda-cyhalothrin, and piperonyl butoxide. The highest estimated dose at the 99.9th percentile was the probabilistic estimate of bifenthrin exposure, while the lowest was the central tendency deterministic estimate of chlorpyrifos exposure.

3.3.2 Deterministic (screening-level) risk assessment

Under both the mean estimate and upper estimate exposure scenarios, neither of the individual HQs exceeded 1 (Table 3.4), nor any of the cumulative HIs for neurotoxicity or hepatotoxicity (Table 3.5). Likewise, all MOEs for the cumulative pyrethroid doses for both the mean estimate and upper estimate exposure scenarios were greater than three hundred (Table 5).

3.3.3 Probabilistic cumulative risk estimates by endpoint and by class

Distributions of neurotoxicity and hepatotoxicity HIs (summed HQs by endpoint) are shown in Table 5. When using the probabilistic PDI over the established RfD, the maximum total HI for neurotoxicity was 0.27, and the maximum HI for hepatotoxicity was 0.01. Distributions of MOEs for cumulative pyrethroid exposure are shown in Table 5. All estimated MOEs (minimum=5,843) were greater than the target MOE of 300 for children under 6 years old (114). Our probabilistic and cumulative estimates of daily exposure to pesticides in child care carpet dust do not exceed levels that the EPA would consider to appreciable risk of adverse effects over a lifetime.

3.3.4 Application of probabilistic reference dose

When using the lower confidence limit (5^{th} percentile) of the approximate probabilistic HD_{05}^{01} as the point of reference for comparing estimated exposure (probabilistic PDI) to derive HQs and summed HIs by endpoint, we observe risk estimates nearly twice as high as using the established RfDs. However, none of the HIs exceeded one for the neurotoxicity or hepatotoxicity.

3.3.5 Sensitivity analysis

Using concentration distributions based on up to three carpet dust measurements from each child care center did not change the overall proportion of HQs>1 at the 99.9^{th} percentile, but the maximum neurotoxicity HQ based on concentration distributions fit to the three time points was greater than 1 (max HQ = 2.62).

3.3.6 Secondary analyses of additional scenarios

Under the assumption that pesticide levels at home would be similar to child care, changing the exposure frequency to 365 24-hr days resulted in the neurotoxicity HI exceeding 1 for a small percentage of the total simulated sample (0.2%), with an HI exceeding 1 at the 99.9^{th} percentile of cumulative exposure to pesticides in dust with neurotoxic effects (Supplemental Table 3.3).

In our test case using fipronil, we examined the effects of incorporating FQPA safety factors into the APROBAplus tool to derive a PrRfD for fipronil (the pesticide most highly correlated with the overall neurotoxicity hazard index, rho=0.93) that is even more conservative, and compare this to a crude estimate of aggregate exposure. With an upper confidence limit of 10x for a child safety factor, the estimated chronic dietary intake alone of fipronil for children 3-5 years old exceed the PrRfD of 0.00003 mg/kg/day. Using 3x as the upper confidence limit, we see aggregate exposure to fipronil exceed the PrRfD of 0.00007 mg/kg/day for 6.4% of the simulated exposures.

Table 3.2 Pesticide concentrations and program / child characteristics

Distributions of pesticides in carpet dust (n=52 child care centers enrolled in HCES)		
Pesticide Analyte	Detection Frequency n (%)	Geometric Mean (SD) (ng/g)
Bifenthrin	49 (94%)	168.45 (4.52)
Chlorfenapyr	12 (23%)	125.69 (4.45)
Chlorpyrifos	42 (81%)	5.45 (1.86)
Cyfluthrin	5 (10%)	740.56 (2.43)
Cypermethrin	28 (54%)	1205.81 (2.01)
Deltamethrin	14 (27%)	260.04 (4.57)
Esfenvalerate	9 (17%)	258.56 (3.35)
Fipronil	48 (92%)	72.44 (3.25)
Lambda-cyhalothrin	10 (19%)	229.08 (6.14)
Permethrin (cis-)	51 (98%)	157.48 (3.78)
Permethrin (trans-)	50 (96%)	253.03 (3.7)
Piperonyl butoxide	37 (71%)	147.87 (2.88)
Program and Child Characteristics (n=253 children enrolled in HCES)		
Characteristic	Mean (SD)	Range
Age (years)	4.2 (0.6)	2.82-5.18
Body weight (kg)	18.0 (3.1)	11.20-34.20
Sex	n (%)	
Male	125 (49%)	
Female	128 (51%)	
Parent-reported child race / ethnicity	n (%)	
Asian	11 (4.4%)	
Black / African American	21 (8.3%)	
Hispanic / Latino	68 (26.9%)	
Native American / Native Alaskan	5 (2%)	
Pacific Islander / Native Hawaiian	1 (0.4%)	
White	60 (23.7%)	
Multi-Racial	43 (17%)	
Other	4 (1.6%)	
No answer	40 (15.8%)	
Region	n (%)	
San Francisco Bay Area	25 (48%)	
San Joaquin Valley	27 (52%)	
Program type	n (%)	
Non-profit private	16 (31%)	
For-profit private	10 (19%)	
Head Start / Early Head Start	6 (11%)	
California State Preschool Program	5 (10%)	
Blended	15 (29%)	

Table 3.3 Distributions of estimated potential daily intake doses for each pesticide analyte and estimation method

		Potential Daily Intake (ng/kg/day)[a]				
Analyte	Estimation Method	25th %	50th %	75th%	95th%	99.9th %
Bifenthrin	Deterministic: Central Tendency	0.024	0.055	0.088	1.138	42.215
Bifenthrin	Deterministic: Upper Estimate	0.259	0.596	0.949	12.267	455.196
Bifenthrin	Probabilistic	0.314	0.802	2.159	9.486	553.166
Chlorfenapyr	Deterministic: Central Tendency	0.001	0.001	0.006	0.182	1.888
Chlorfenapyr	Deterministic: Upper Estimate	0.010	0.012	0.065	1.961	20.362
Chlorfenapyr	Probabilistic	0.026	0.061	0.164	1.480	45.155
Chlorpyrifos	Deterministic: Central Tendency	0.001	0.002	0.003	0.008	0.011
Chlorpyrifos	Deterministic: Upper Estimate	0.011	0.019	0.033	0.091	0.122
Chlorpyrifos	Probabilistic	0.013	0.023	0.042	0.111	0.434
Cyfluthrin	Deterministic: Central Tendency	0.005	0.022	0.027	0.401	0.684
Cyfluthrin	Deterministic: Upper Estimate	0.054	0.232	0.290	4.324	7.378
Cyfluthrin	Probabilistic	0.140	0.279	0.603	2.123	14.130
Cypermethrin	Deterministic: Central Tendency	0.014	0.182	0.530	1.232	4.054
Cypermethrin	Deterministic: Upper Estimate	0.154	1.968	5.712	13.280	43.715
Cypermethrin	Probabilistic	0.899	2.388	6.047	21.208	105.081
Deltamethrin	Deterministic: Central Tendency	0.003	0.012	0.027	0.415	3.373
Deltamethrin	Deterministic: Upper Estimate	0.030	0.132	0.295	4.471	36.368
Deltamethrin	Probabilistic	0.119	0.282	0.724	3.200	33.098
Esfenvalerate	Deterministic: Central Tendency	0.003	0.012	0.015	0.138	1.996
Esfenvalerate	Deterministic: Upper Estimate	0.030	0.127	0.160	1.493	21.525
Esfenvalerate	Probabilistic	0.095	0.200	0.453	1.789	14.938
Fipronil	Deterministic: Central Tendency	0.010	0.025	0.060	0.182	1.095

Fipronil	Deterministic: Upper Estimate	0.113	0.271	0.645	1.964	11.809
Fipronil	Probabilistic	0.173	0.397	0.935	3.508	19.594
Lambda-Cyhalothrin	Deterministic: Central Tendency	0.002	0.003	0.004	0.100	5.128
Lambda-Cyhalothrin	Deterministic: Upper Estimate	0.025	0.028	0.047	1.082	55.289
Lambda-Cyhalothrin	Probabilistic	0.049	0.088	0.170	0.550	55.234
Permethrin	Deterministic: Central Tendency	0.007	0.040	0.091	0.350	0.871
Permethrin	Deterministic: Upper Estimate	0.079	0.427	0.980	3.775	9.394
Permethrin	Probabilistic	0.210	0.498	1.216	4.421	27.865
Piperonyl Butoxide	Deterministic: Central Tendency	0.081	0.146	0.237	0.895	45.750
Piperonyl Butoxide	Deterministic: Upper Estimate	0.869	1.575	2.559	9.646	493.308
Piperonyl Butoxide	Probabilistic	1.461	3.939	10.618	44.768	320.068
[a]Uptake from non-dietary ingestion and dermal routes of exposure. 1,000,000 ng/kg = 1 mg/kg.						
Assumptions:						
Deterministic: Central Tendency	In care 6 hours, 5 days, 48 weeks for 1 year, mean dust ingestion rate and skin surface area, observed pesticide concentrations and body weight, 10% absorption					
Deterministic: Upper Estimate	In care 6 hours, 5 days, 48 weeks for 2 years, 95th% dust ingestion rate and skin surface area, observed pesticide concentrations and body weight, 10% absorption					
Probabilistic	In care 15-50 hours per week for 0.8 to 3.2 years, log-normally distributed ingestion rate, skin surface area with mean and 95th% at values provided by EPA, log-normal distribtution fit to observed body weight and log-normal or Weibull distribution fit to pesticide concentration, 10% absorption					

Table 3.4 Chemical properties, reference dose (RfD), inputs for probabilistic reference dose (PrRfD), and resulting maximum individual Hazard Quotients (HQ)

Class	Analyte	Endpoint	RfD (mg/kg/day)	Source	Max HQ (PDI_{pr}/RfD)	*PrRfD*[a]	Effect	Safety Factor[b]	Max HQ_{pr} (PDI_{pr}/*PrRfD*)
Organophosphate	Chlorpyrifos	Neurotoxicity	0.0001	OEHHA, 2010	0.01	0.0001	cholinesterase inhibition	10	0.01
Pyrethroid	Bifenthrin	Neurotoxicity	0.0310	HHBP, 2021	0.08	0.0150	decreased locomotor activity	1	0.16
Pyrethroid	Cyfluthrin	Neurotoxicity	0.0117	HHBP, 2021	<0.01	0.0051	decreased locomotor activity	1	<0.01
Pyrethroid	Cypermethrin	Neurotoxicity	0.0716	HHBP, 2021	<0.01	0.0398	decreased locomotor activity	1	<0.01
Pyrethroid	Deltamethrin	Neurotoxicity	0.0150	HHBP, 2021	0.01	0.0088	decreased locomotor activity	1	0.01
Pyrethroid	Esfenvalerate	Neurotoxicity	0.0110	HHBP, 2021	<0.01	0.0064	decreased locomotor activity	1	0.01
Pyrethroid	Lambda-Cyhalothrin	Neurotoxicity	0.0009	HHBP, 2021	0.26	0.0008	clinical signs of neurotoxicity	3	0.32
Pyrethroid	Permethrin	Neurotoxicity	0.4400	HHBP, 2021	<0.01	0.2252	decreased locomotor activity	1	<0.01
		Hepatotoxicity	0.0500	IRIS, 1987	0.01	0.0310	increased liver weights	1	0.02
Other: Phenylpyrazole	Fipronil	Neurotoxicity	0.0002	HHBP, 2021	0.26	0.0001	convulsions	1	0.45
Other: Pyrrole	Chlorfenapyr	Neurotoxicity	0.0500	HHBP, 2021	<0.01	0.0310	decreased locomotor activity	1	<0.01
Other: Synergist	Piperonyl Butoxide	Neurotoxicity	5.0000	HHBP, 2021	<0.01	3.1080	grip strength, ambulation/fine movement,	1	<0.01

							gate abnormality		
		Hepatotoxicity	0.1600	HHBP, 2021	<0.01	0.2550	hepatocellular hypertrophy, alkaline phosphatase activity, decreased liver weight	1	<0.01
[a]*PrRfD = Lower confidence level of estimated dose (mg/kg/day) at which, with 95% confidence, 1% of the population will have effect of magnitude ≥5%*									
[b]*Used as upper confidence level in APROBAplus (LCL=1), value taken from US EPA/CalEPA risk assessment documentation for established RfD*									

Table 3.5 Summary of cumulative risk estimates by each exposure estimation method and point of comparison

				Hazard Index (HI)		
Cumulative Risk Grouping	Exposure Estimation	Comparison	Indication of risk	p50	p95	Max
Neurotoxicity	$PDI_{D\text{-}Central}$	RfD	HI>1	<0.01	<0.01	0.01
Neurotoxicity	$PDI_{D\text{-}Upper}$	RfD	HI>1	<0.01	0.02	0.14
Neurotoxicity	PDI_{Pr}	RfD	HI>1	<0.01	0.02	0.27
Neurotoxicity	PDI_{Pr}	*PrRfD*	HI>1	<0.01	0.03	0.44
Hepatotoxicity	$PDI_{D\text{-}Central}$	RfD	HI>1	<0.01	<0.01	<0.01
Hepatotoxicity	$PDI_{D\text{-}Upper}$	RfD	HI>1	<0.01	<0.01	0.01
Hepatotoxicity	PDI_{Pr}	RfD	HI>1	<0.01	<0.01	0.01
Hepatotoxicity	PDI_{Pr}	*PrRfD*	HI>1	<0.01	<0.01	0.02
				Margin of Exposure (MOE)		
Cumulative Risk Grouping	Exposure Estimation	Comparison	Indication of risk	p50	p05	Min
Pyrethroid Pesticides	$CDE_{D\text{-}Central}$	$BMD_{Deltamethrin}$	MOE<300	>1mil	>1mil	253,325
Pyrethroid Pesticides	$CDE_{D\text{-}Upper}$	$BMD_{Deltamethrin}$	MOE<300	>1mil	624,889	23,494
Pyrethroid Pesticides	CDE_{Pr}	$BMD_{Deltamethrin}$	MOE<300	>1mil	750,676	5,843

3.4 Discussion

We found that estimated pesticides exposures to young children in child care centers, using both deterministic and probabilistic methods to estimate exposures distributions, were not likely to exceed established RfDs, even when assessing cumulative risks across endpoints (neurotoxicity and hepatotoxicity), or within classes of pesticides (pyrethroids).

Few other studies have assessed risks associated with pesticide exposures in child care settings, and these studies assess single chemicals without considering cumulative risk. Morgan et al. (2014) estimated children's median potential aggregate (home and child care) intake doses by dietary ingestion, nondietary ingestion, and inhalation routes for chlorpyrifos (4.6 ng/kg/day) and cis/trans-permethrin (12.5 ng/kg/day) (8). The median PDIs in our study were lower for chlorpyrifos (probabilistic 0.023 ng/kg/day, deterministic 0.002-0.019) and for ∑permethrin (0.498 ng/kg/day, deterministic 0.04-0.427), although the routes of exposure differ. Our estimates do not include dietary ingestion or inhalation routes.

Kim et al. (2013) assessed health risks of two OP pesticides in child care facilities in South Korea, but did not report specific estimated doses (6). They did calculate an HQ greater than 1 at the 95th percentile for dichlorvos (not measured in the present study), and focused on excess cancer risk for chlorpyrifos (out of scope for the present study). We did not identify any more recent (less than 10 years) assessments of health risks associated with exposure to pesticides in child care environments, which underscores the need for more research on this environment where children spend significant amounts of time.

We employed a tiered approach to pesticide risk assessment. The first step involves a screening risk assessment, which we argue serves a critical purpose in translating research findings to child care providers and families participating in environmental health studies. These stakeholders are often eager to understand the implications of measured pesticide levels on their children's health. Given the absence of established standards or regulations for pesticide exposures in such settings, employing a screening-level deterministic risk assessment approach enables us to effectively communicate research results to the child care community. Reporting results often involves comparing a participant's chemical concentrations to that of others in the study (115). Within current EPA frameworks, all our deterministic dose estimates suggest the exposures would be without appreciable risk of adverse effects during a lifetime. As of this writing, study staff are returning carpet dust results to participants. Using the deterministic risk estimates, we can communicate to child care providers that, while pesticide exposure is ubiquitous and steps can and should be taken to reduce exposure, the levels measured in their carpets at baseline are not likely to harm children's health according to U.S. EPA guidelines and defaults.

Subsequently, the refinement phase of our approach incorporates probabilistic modeling with distributions of realistic assumptions, assessments of cumulative risk, and comparisons to probabilistic reference values. This step goes beyond the screening phase to provide a deeper understanding of the risks posed by pesticide exposures. Unlike traditional risk assessments that often focus on individual chemicals, we examined cumulative risk by computing distributions for endpoint-specific Hazard Indices (HIs) and Margins of Exposure (MOEs) specifically for pyrethroids.

Aligning with the NRC's recommendation to consider non-threshold dose-response relationships for non-cancer endpoints and to better account for variability and uncertainty in hazard characterization, we applied WHO-IPCS methods to derive PrRfDs to use in derivation of neurotoxicity HI instead of the established RfDs. These PrRfDs are expressed as the lower 95% confidence bound of the dose associated with an effect of magnitude 5% for a population incidence of 1%. Using probabilistic dose estimates with PrRfDs did not result in individual HQs or endpoint-specific HI exceeding 1, suggesting that the assumed exposures were generally below levels of concern. In our thought experiment assuming children are exposed to similar levels at home and in child care, we observed a small percentage of the simulated sample (0.42%) with a neurotoxicity HI>1 using the PrRfD as the point of comparison, nearly doubling the number when comparing to the existing EPA RfDs. Use of the approximate PrRfD also provides more information to express risk as a probability, rather than a bright-line with an undefined level of increased risk.

It's important to note that we did not modify the pyrethroid Cumulative Risk Assessment (CRA) methodology based on the redefinition of reference doses in this analysis. The EPA used benchmark dose modeling to determine relative potency based on a 20% change from controls (BMD_{20}), which the EPA determined was "the most conservative estimate able to predict a significant change from control values" (114). Other pesticide CRAs have used a benchmark dose threshold of 10%, which is more in line with EPA practices for cancer (non-threshold) risk assessments (104, 116), and may change the distribution of MOEs in the present study. This would be a valuable direction for further exploration.

Another potential departure from current U.S. EPA risk assessment methods that can greatly impact the overall determination of risk is in the application of child-specific safety factors. The Food Quality Protection Act of 1996 (FQPA) mandated that the EPA establish safe levels for pesticides to ensure no harm to infants and children from aggregate pesticide exposure. This requirement included applying a 10x safety margin to account for data gaps on potential prenatal and postnatal toxicity. In 2011, this safety margin was reduced to 3x for pyrethroid pesticides, and in 2019, the EPA reevaluated the scientific evidence and concluded that the FQPA safety factor for all pyrethroids could be further reduced from 3x to 1x while still protecting infants and children. This decision has been criticized by some NGOs as heavily influenced by industry lobbying (117, 118).

Of the ten EPA risk assessment documents reviewed for derivation of the RfD and PrRfD in the present study, only one, lambda-cyhalothrin, applied a child health safety factor greater than 1x. We matched the upper confidence limit of an additional child safety factor to what was used in the published EPA risk assessment documentation in the APROBAplus tool. However, further analyses could explore the effect of different distributions of child safety factors, consistent with the FQPA original mandate, to better incorporate considerations of age-specific differences across life stages of development (106). For example, in our examination using fipronil as a test case, we assessed the impact of incorporating various FQPA safety factors into the APROBAplus tool to derive the PrRfD. Changes to the child safety factors from 1x to 3x to 10x had wide implications for the PrRfD and overall risk, particularly when considering aggregate risk from multiple sources. Given that fipronil is just one of many neurotoxic pesticides children may encounter, there are concerns about cumulative and aggregate exposure risks to children's

health, particularly without the use of a child health safety factor, adding uncertainty to the point of comparison.

This study is limited in that we only examined exposures via dermal absorption and non-dietary ingestion while in the child care center. We did not calculate aggregate exposure from all possible relevant sources, which may underestimate overall risk (119). In reality, children are exposed at home to similar levels of pesticides in dust (1), are exposed through diet (120), and may be exposed through other pathways such as take-home occupational exposures from adults in the home, or pesticide drift, particularly in agricultural communities (21). Additional research is needed to identify the best available methods for estimating aggregate exposures to multiple pesticides when a study's focus is measuring a specific source of exposure. Future studies could make use of aggregate and cumulative exposure models used by the U.S. EPA Office of Pesticide Programs to assess how these exposures within this specific environment contribute to overall cumulative and aggregate exposure, for example, comparing our estimated doses to results from Stochastic Human Exposure and Dose Simulation (SHEDS) models.

Additionally, we did not consider possible distributions for some default assumptions. We assumed a default value of 10% for dermal absorption for all analyses based on U.S. EPA guidance for pesticides, though there may be differences between pesticides based on individual physicochemical properties. We also assumed that once in the body, there was 100% absorption in the gastrointestinal tract. These assumptions could result in over- or under-estimation of exposure and risk. With a dozen pesticides included in the present study, we did not complete a thorough assessment of certain parameters to examine impact on our exposure estimates, such as correlation with model inputs or contribution by exposure route.

Utilizing probabilistic estimates of exposure and of risk better incorporates uncertainty and differential susceptibility in exposed populations, especially where exposures can produce non-cancer effects that are likely to be compounded by other chemicals or other non-chemical stressors that exert similar health effects (104, 107). A key assumption of both methods we used to estimate cumulative risk, the endpoint-specific HI and cumulative pyrethroid dose using relative potency, is dose-additivity. For pyrethroids, dose-additivity implies multiple pyrethroids can interact with voltage-gated sodium channels simultaneously, and the overall toxic response will be a summation of all the individual pyrethroids. For the neurotoxicity HI, we used RfDs corresponding to critical effects on the central nervous system. More research is needed to test these dose-additivity assumptions and explore potential synergistic effects.

To our knowledge, this study is the first to apply probabilistic risk assessment methods to a large panel of pesticides measured in child care facilities. By integrating measured environmental concentrations and child-level anthropometric data with probabilistic estimates of exposure based on established U.S. EPA guidelines, our research provides a robust analysis of potential risks associated with pesticide exposures in child care settings. As noted above, young children can spend a significant amount of time in child care environments, with particularly long hours for working class families.

Moving forward, more research is needed to validate assumptions and explore cumulative risk effects, allowing for better understanding of the uncertainty and differential susceptibility of children, particularly considering these children's different chemical and non-chemical exposures that may act on neurodevelopmental pathways. Our study contributes to the

understanding of pesticide risks in child care environments, providing valuable insights for improving children's health and safety.

3.5 Conclusion

Within licensed child care centers in Northern California, we do not observe potential pesticide exposures via dermal and incidental ingestion pathways that would likely cause neurotoxic or hepatotoxic effects in young children. However, these estimated exposures represent just a portion of the true potential total daily exposure for young children. When considering the total impact of cumulative and aggregate pesticide exposures in early childhood, it is critical to reduce exposure in every environment where children spend time. Deterministic exposure estimates and derivation of risk estimates using established U.S. EPA frameworks can also serve as an important starting point for returning environmental health research results to participants. Probabilistic approaches to estimating exposure and reference doses provide realistic risk scenarios that can aid in decision making that is ultimately more health-protective for our youngest and most vulnerable populations.

3.6 Supplement to Chapter 3

Supplemental Table 3.1 APROBAplus inputs

Established RfD basis (per EPA documentation)	Input used
RfD based on NOAEL or LOAEL	APROBA defaults[a]
RfD based on BMDL	Derive BMDU (BMDU = 2 * BMD1sd - BMDL1sd)
RfD based on acute study with NOAEL	NOAEL to BMD adjustment: used same defaults as chronic (LCL 0.07, UCL 1.57)

[a]APROBA defaults: WHO-IPCS. Guidance on Evaluating and Expressing Uncertainty in Hazard Assessment, 2017 (Ref(121)).

Supplemental Table 3.2 Distribution of probabilistic estimated potential daily intake (ng/kg/day) using exposure frequency of 365 days (PDI_{365})

Pesticide	p50	p75	p95	p99.9	p100
Bifenthrin	5.71	17.89	105.50	1297.68	7796.26
Chlorfenapyr	0.07	0.11	0.24	1.40	34.97
Chlorpyrifos	0.14	0.26	0.68	2.62	3.72
Cyfluthrin	1.83	3.98	14.28	101.48	224.36
Cypermethrin	9.99	29.27	144.52	942.23	1893.46
Deltamethrin	1.61	4.25	18.22	173.72	359.56
Esfenvalerate	1.25	2.92	11.45	99.00	159.02
Fipronil	2.30	5.71	24.05	271.55	1153.02
Lambda-cyhalothrin	0.49	0.94	2.92	203.03	664.46
Piperonyl Butoxide	3.07	6.79	24.61	142.80	217.09
∑Permethrin	15.13	36.38	135.49	1239.27	2494.89

Supplemental Table 3.3 Risk estimates using PDI_{365}

Risk estimates using PDI_{365}	50%	95%	99.9%	100% (Max)	# HI>1
Hepatotoxicity HI	<0.01	<0.01	0.02	0.08	0
Hepatotoxicity HI using *PrRfD*	<0.01	<0.01	0.04	0.12	0
Neurotoxicity HI	0.02	0.13	1.41	5.84	18 (of 10,000)
Neurotoxicity HI using *PrRfD*	0.03	0.21	2.27	9.74	42 (of 10,000)

Chapter 4 Early childhood exposures to pesticide mixtures in house dust, the home environment, and IQ at age 7 years

4.1 Introduction

Young children are uniquely vulnerable to chemical exposures due to their behaviors and developing bodies and systems (10, 12), and are frequently exposed to pesticides in their environment (1, 2). There is disproportionate exposure to pesticides across California -- it is estimated that 95% of agricultural pesticide use in California occurs in 60% of zip codes with the highest proportion of residents of color (122). Children residing in agricultural regions are disproportionately exposed to mixtures of pesticides via multiple pathways, such as take-home exposures from farm-working family members, drift from nearby applications, diet, and residential use (21, 123, 124).

Organophosphate (OP) and pyrethroid pesticides are two of the major classes of pesticides that are used to control insects in residential and agricultural settings and are frequently found in children's environments (99, 113). Use of OP pesticides, such as chlorpyrifos, has declined in recent decades (125), following regulatory efforts in the 1990s, voluntary cancellation of residential uses of chlorpyrifos and diazinon in the early 2000s, and a near total restriction on chlorpyrifos in California in 2020. There is strong evidence linking prenatal exposures to OPs to cognitive and behavioral deficits in children (36, 37, 126).

Pyrethroid pesticides, thought to be relatively safe due to lower acute mammalian toxicity, have increased in use in recent decades (127). Pyrethroids are used in agriculture, structural pest control, and consumer products (128), and are increasingly found in children's environments and bodies (64, 129). Data on the potential health effects of low-level pyrethroid exposure, particularly for children, are limited. However, some epidemiologic studies show associations between early life (prenatal and early childhood) pyrethroid exposure and poorer neurodevelopmental and behavioral outcomes, while others have shown inconsistent results (55, 77, 127, 130-135).

The study of complex exposure mixtures has led to the development of novel statistical methods, with marked improvement over examining associations with single chemical exposures in isolation. Relatively few other studies have applied mixture methods to examining pesticides and neurodevelopmental outcomes (39, 40, 48, 136-138). Of particular interest are approaches that can examine effects by pesticide class within mixtures, as whole classes of pesticides can increase or decrease in use over time, and can be regulated as entire classes as well.

Measurement of urinary metabolites is often used to assess pesticide exposure, but this approach has limitations. For example, OP metabolites in child urine are highly variable (139). OPs and pyrethroids are also metabolized quickly in the human body (half-life is less than 24 hours) (140), indicating that urine biomarkers provide a short-term snapshot of exposure, mostly driven by recent dietary exposure (139). As an alternative, investigators have used reported pesticide applications near homes as an indicator of potential exposure. In California, this information is accessible through the Pesticide Use Report (PUR) data system. However, the PUR system mainly records agricultural applications, while pyrethroids are also used for non-agricultural purposes not geocoded in the PUR database. Indoor dust can provide a stable, long-term estimate of pesticide contamination that young children are likely to be exposed to (65, 70,

71), due to their frequent hand-to-mouth activity and time spent crawling on floors (10, 12). Studies show associations between contaminants in dust and exposure; for example, blood lead concentrations were found to be strongly associated with lead loading in dust (66).

Biological and social factors may alter or exacerbate the harm caused by neurotoxicants. Adverse social conditions may potentiate the harmful effects of chemical exposures as suggested by studies on lead (141), air pollution (142, 143), and tobacco smoke (144) exposure. However, limited research has explored the impact of interaction with pesticide exposure. The quality of the home environment is an important social factor and source of psychosocial stress that plays a significant role in predicting child neurodevelopment. The home quality of the home could potentially exacerbate or buffer neurodevelopmental impacts from pesticide exposures (145). A supportive home, characterized by enrichment, positive interactions, and access to resources, can potentially mitigate the negative impacts of pesticides on child cognition. Conversely, an impoverished or stressful home environment may amplify these effects. It is posited that poor home environments impact child health through increased exposure to stress, resulting in dysregulation of the neuroendocrine and immune systems, which are particularly sensitive in childhood.

Evidence suggests that many current and past-use pesticides, including the OPs, pyrethroids, dicarboximide fungicides, and phthalate herbicides included in the present study, may act as hormone-disrupting agents (146-151) with the potential to act on the same neuroendocrine pathways for which social factors become biologically embedded and for which sex-dimorphic effects are produced (152). Failing to examine potential effect modification may underestimate the impact of neurodevelopmental toxicants, particularly among more vulnerable populations where exposures to environmental and non-chemical stressors are likely to co-occur.

In the present study, we examine the association between child cognition and potential non-dietary exposure to pyrethroid, OP, and other pesticide classes found in house dust among participants in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study. We also evaluate potential effect modification by sex of the child and potential synergistic effects with the quality of the home environment.

4.2 Methods

4.2.1 Study Population

Participants were enrolled in the CHAMACOS study, a longitudinal birth cohort study of pesticide exposure and neurodevelopment in children residing in an agricultural area. Beginning in 1999, the study enrolled English or Spanish-speaking pregnant women attending prenatal care clinics who were less than 20 weeks gestation, eligible for low-income health insurance (Medicaid), and at least 18 years of age. Detailed Information about participant recruitment and study procedures have been described previously (153).

In the present study, we included 185 participants who had a dust sample collected from their home (Supplemental Figure 4.1). We excluded 37 that did not complete a Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV) assessment at age 7y. We excluded children diagnosed with Down Syndrome, Autism, deafness, hydrocephalus, or who experienced seizures in their first year (n=2 children with seizures). A total of 146 participants were included with Verbal Comprehension and Perceptual Reasoning scores and 128 with Working Memory,

Processing Speed, and Full-Scale IQ scores. Participants included in this analysis did not differ significantly from the original full cohort on most attributes. However, participants in the present analysis were younger at the seven-year assessment (7.08 versus 7.11, p=0.03), had higher HOME scores at 6 months (32.08 versus 31.42, p= 0.02), mothers had slightly higher Peabody Picture Vocabulary Test (PPVT) scores at 6 months (87. 84 versus 85.38, p=0.07), and mothers were more likely to be married during pregnancy than those from the initial cohort (86% versus 80%, p=0.04). All study activities were approved by the University of California, Berkeley Committee for the Protection of Human Subjects.

4.2.2 Exposure Characterization

For this analysis, we used pesticide concentrations measured in indoor dust collected from the home when the children were 6 and 12 months of age (2, 90) from 1999 to 2002. This analysis focuses on eight pesticides from four pesticide classes: pyrethroids (cis- and trans-permethrin), OPs (chlorpyrifos, diazinon, oxydemeton-methyl, and phosmet), one phthalate herbicide (chlorthal-dimethyl (DCPA)), and one dicarboximide fungicide (iprodione). While 22 analytes were measured in CHAMACOS dust samples, these eight analytes represent those pesticides with >5% detection frequency in samples and meeting quality control criterion for this cohort (90). Note that iprodione and DCPA are not generally considered neurotoxic by authoritative bodies, but research suggests neurotoxic / neurodevelopmental effects for iprodione (154, 155) and DCPA is a known endocrine disrupting agent; therefore we included it for potential effects on the neuroendocrine system (156).

We utilized both concentration (ng/g of dust) and loading (ng/m^2 of sampled area) to classify characterize potential exposure. Several studies suggest that loading (amount of contaminant per area sampled) is a better indicator of human exposure (66). Concentrations and loadings under the limit of detection (LOD) were imputed at LOD/√2. The 6- and 12-month samples were averaged if both samples were taken (n=132), or the single value was used if only one sample was available (n=2 missing at 6m, n=12 missing at 12m). Values were log10 transformed for analyses.

4.2.3 Outcome Assessment

We used the Wechsler Intelligence Scale for Children (WISC-IV) to assess neurodevelopment at age 7 years. This scale consisted of eight subtests, which yielded four subscale scores – the Perceptual Reasoning Index (PRI), Verbal Comprehension Index (VCI), Working Memory Index (WMI), and Processing Speed Index (PSI) – as well as an overall score, the Full-Scale Intelligence Quotient (FSIQ). Detailed information on data collection in the CHAMACOS cohort is explained in Bouchard et al. (38). Briefly the assessments were carried out in English or Spanish by bilingual, bicultural psychometricians blinded to children's pesticide exposures.

4.2.4 Statistical Analysis

We used two-stage Bayesian Hierarchical Models (BHM) to examine exposure-outcome associations simultaneously with all eight pesticide co-exposures measured in dust and to examine effects by pesticide classes. Employing BHM as a principled approach to examine associations with all pesticides, providing some adjustment of estimates based on prior knowledge, produces estimates that are more stable and interpretable than with other approaches

to multiple exposure modeling (157). For comparison, we ran a generalized linear model (GLM) on the FSIQ outcome using just the first stage model.

In the first stage model, we regressed each outcome on the exposures and covariates in a single linear model as: $(E[Y \mid X,W]) = \alpha + X\beta + W\gamma$; where X is the vector of all pesticides, and W is the vector of confounders. In the second stage, the exposure effects (β) were modeled as a function of an exchangeability matrix Z, coefficient vector π, and vector of residual errors δ 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, with the same mechanism of toxicity, would yield similar effects on the outcome (see Supplemental Table 4.1). We specified vague priors on parameters (α, γ, π) with independent normal distribution with mean 0 and precision 0.001. We specified independent normal distribution for each δ with mean 0 and pre-specified the precision to correspond to the assumption that the resulting β parameters would lie within an 8-fold interval (precision $\tau_b = 1/(8/(2*1.96))^2 = 0.24$). We present mean β effect estimates and 95% Credible Intervals (CrIs) for each pesticide predicted from the first-stage model and each pesticide class from the second-stage model.

Concentration and loading models were specified in a Fully Bayesian framework and the posterior distribution of all model parameters was estimated via Markov Chain Monte Carlo (MCMC) sampling. Just Another Gibbs Sampler (JAGS) was used to sample from the posterior distributions of these parameters and we estimated the posterior mean and 95% CrIs. We ran models with 100,000 iterations after an initial burn-in of 30,000 and thinning rate of 5. We assessed convergence graphically using trace plots, autocorrelation plots, and density plots, and statistically using the Geweke test. All analyses were conducted using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) with packages "R2jags" (Yu-Sung Su and Masanao Yajima, (2021). R2jags: Using R to Run 'JAGS'. R package version 0.7-1.) and "coda" (Martyn Plummer, Nicky Best, Kate Cowles and Karen Vines (2006). CODA: Convergence Diagnosis and Output Analysis for MCMC, R News, vol 6, 7-11).

Models were adjusted for the following confounders identified using a directed acyclic graph (DAG; see Supplemental Figure 4.2) based on factors associated with infant neurodevelopment in previous analyses: total prenatal urinary dialkyl phosphate (DAP) metabolite concentrations (a measure of prenatal OP exposure, log10 of average DAPS in pregnancy (nmol/gL)), maternal education (≤ 6th grade, 7-12th grade, ≥ high school graduate), maternal verbal intelligence (Peabody Picture Vocabulary Test (PPVT) score), maternal depression (>=16 on Center for Epidemiologic Studies Depression Scale (CES-D)), language of assessment (Spanish or English), age at assessment (in months), and farmworkers in household (Yes/No). We controlled for Infant-Toddler Home Observation for Measurement of the Environment (HOME) inventory scores assessed at six months (z-score) in non-interaction analyses, and sex of the child in non-stratified analyses.

4.2.5 Interaction and Effect Modification

The Home Observation for the Measurement of the Environment (HOME) (158) is a well-validated instrument for assessing the quality and quantity of stimulation and support available to a child in their home environment (159, 160). We examined whether the HOME score modified the association of pesticide exposure and neurodevelopment outcomes, hypothesizing that

negative associations would be stronger among children with low HOME scores. Product terms were added to the first-stage model (161) and an additional column was added to the Z-matrix (see Supplemental Table 4.2). We used the same approach to evaluate child's sex as an effect measure modifier by including a product term between sex and each pesticide. We present male- and female-specific estimates and examined if the 95% CrI for the product term included or excluded the null.

4.2.6 Sensitivity Analysis

We ran models changing the precision for δ under the assumption that β parameters would lie within a 6-fold and 4-fold interval, rather than our pre-specified 8-fold assumption. Acknowledging that we have many more OP pesticides than the other classes of pesticides measured in dust, we applied a modified z-matrix that groups pesticides by OP or non-OP, and also incorporates relative potency factors (RPFs) from the U.S. EPA. RPFs are calculated as the ratio of the toxic potency of a given chemical to that of the index chemical, ultimately expressing exposures of all chemicals in the group into exposure equivalents of the index chemical. Deriving RPFs is common for determining joint risk associated with mixtures. In an application drawn from using nutrient profiles for diet epidemiologic BHM analyses (162), we specified indicator variables (0/1) for non-OP pesticides, and specified RPFs with chlorpyrifos as the index chemical from EPA's Organophosphorus Cumulative Risk Assessment (163). We applied this modified z-matrix in analyses of pesticide loading and FSIQ and subscales, for all participants and stratified by sex (see Supplemental Table 3).

4.3 Results

4.3.1 Participant characteristics

Most mothers of children included in this analysis were born in Mexico (89%), had less than a High School graduate level education (84%), and were at or below federal poverty level at time of birth (63%) (Table 4.1). The average maternal age at delivery was 27 years (SD=5.3). Most households had agricultural workers in the home during pregnancy (74%). These demographics are consistent with other analyses from the CHAMACOS cohort using neurodevelopmental outcomes. Detection frequencies and mean concentrations for the 6-month and 12-month dust samples are shown in Table 4.2. Consistent with the dust sample distributions published in Harnly et al. 2009, cis- and trans-permethrin and DCPA were detected in over 90% of samples, and phosmet was the least detected.

Table 4.1 Sociodemographic characteristics of CHAMACOS study participants with data on WISC-IV outcome

	Overall n=146
Demographics at delivery	
Mother's age (mean (SD))	27.5 (5.3)
Maternal education (%)	
≤ 6th grade	69 (47%)
7-12th grade	52 (36%)
≥ HS graduate	25 (17%)
Maternal country of birth: Mexico	133 (91%)
Years lived in USA (mean (SD))	8.0 (7.3)
At or below poverty (%)	93 (64%)
Child sex: Female	78 (53%)
Agricultural workers in home: Yes (%)	107 (73%)
Married (%)	126 (86%)
Childhood characteristics	
Language at 7y WISC-IV assessment: English (%)	51 (35%)
Exact age (years) at assessment (mean (SD))	7.1 (0.2)
Months breastfed (mean (SD))	9.5 (9.16)
Attended preschool (%)	103 (73%)

Table 4.2 Distributions of pesticides measured in house dust of CHAMACOS study participants with data on WISC-IV outcome

	6m		**12m**	
Pesticide Analyte	Detection n (%)	Mean (SD) concentration (ng/g)	Detection n (%)	Mean (SD) concentration (ng/g)
Chlorpyrifos	111 (77%)	272 (911)	111 (83%)	4 (43)
Chlorthal-dimethyl (DCPA)	132 (92%)	41 (62)	124 (93%)	40 (57)
Diazinon	114 (79%)	104 (384)	109 (81%)	125 (559)
Iprodione	62 (43%)	103 (328)	59 (44%)	70 (178)
Oxydemeton-methyl	65 (56%)	10 (14)	74 (67%)	13 (18)
*cis*Permethrin	139 (96%)	819 (1990)	124 (93%)	1947 (14566)
*trans*Permethrin	139 (96%)	1209 (4125)	127 (95%)	2979 (22953)
Phosmet	9 (6%)	60 (470)	16 (12%)	90 (460)

4.3.2 Full-Scale IQ – comparison of GLM and BHM

Table 4.3 shows results from adjusted single-stage GLM and the adjusted two-stage BHM for the 8 pesticide dust concentrations and loadings for the FSIQ outcome. Results are shown for all participants and models stratified by sex. BHM resulted in more precise and stable estimates for the first-stage coefficients and intervals than GLM. BHM also produced effect estimates for the four pesticide classes. When using pesticide concentration (ng/g) for the exposures, all individual and class 95% confidence intervals (CI) and credible intervals (CrI) crossed the null. In the adjusted GLM model, chlorpyrifos loading (ng/m^2) was associated with higher FSIQ (95% CI: 1.0, 8.1), but not in the BHM analyses. When stratified by sex, the associated held among males for diazinon in the GLM model (-11.4, -0.4), and in general, effect estimates tended to be negative for male children, compared to female children for whom nearly all effect estimates were positive.

4.3.3 WISC-IV Subscales.

Table 4.4 shows results from BHM for pesticide loading (ng/m^2) for the four subscales (Verbal Comprehension, Working Memory, Processing Speed, and Perceptual Reasoning), for all participants and stratified by sex. A 10-fold increase in oxydemeton-methyl loading was associated with a deficit of 3.3 points on the Processing Speed subscale (95% CrI: -6.4, -0.2). We observe a borderline effect for the class of OP pesticides and Processing Speed deficits, particularly among male children (95% CrI: -6.1, 0.2) (see Figure 4.1). A 10-fold increase in iprodione loading was associated with higher Verbal Comprehension scores (95% CrI: 0.3, 4.6).

In analyses using pesticide concentrations (ng/g), all 95% CrIs crossed the null for the four subscales (shown in Supplemental Table 4.4). While all 95% CrI cross the null for concentrations of individual pesticides and pesticide classes, we observed a trend toward positive associations with pyrethroids for Working Memory and Processing Speed, and a trend toward adverse associations associated with OPs for Processing Speed. This trend toward adverse associations among OPs on Processing Speed was more pronounced among male children.

4.3.4 Interaction with home environment

All 95% CrI for the pesticide concentration-HOME score interaction product terms crossed the null for the Full-Scale IQ and the four subscales (Supplemental Table 4.5). We observed borderline effects between higher chlorthal-dimethyl (DCPA) loading levels and lower quality home environment on FSIQ (95% CrI of product term: -8.0, 0.2 and Working Memory (-8.7, 0.1). We then observed that there was a borderline association of lower FSIQ scores and higher DCPA loading among those with lower HOME scores (β= -7.1 (95% CrI -14.7, 0.5) among low HOME scores, β= -0.5 (95% CrI -6.0, 5.0) among higher HOME scores). For Working Memory, the effect estimate was negative among those with low HOME scores and positive for those with higher HOME scores, but the 95% CrIs widely spanned the null.

4.3.5 Sensitivity Analyses

When we adjusted the second stage residual precision under the assumption that the β parameters would lie within a narrower interval, we did see changes in the 95% CrI (see Supplemental Table 4.6). In particular, the Processing Speed subscale was sensitive to the assumption on the 2^{nd} stage precision. With a 4-fold assumption, the individual and overall class effects for pyrethroids were significant (indicating an increase in pyrethroid loading was

associated with better Processing Speed scores), while we observe significant adverse effects for the class of OPs on Processing Speed. Confidence intervals from similar analyses of child cognition often range 4-to-10 fold (38, 40, 46, 77), and we feel confident in using an 8-fold or 6-fold interval, but results may be too sensitive to selection of a 4-fold interval prior.

Our application of the modified z-matrix with indicators for OP and non-OP pesticides, and incorporation of RPFs for the OP pesticides yielded intriguing results, shown in Table 4.5. A ten-fold increase in oxydemeton-methyl loading was associated with deficits for Full-Scale IQ (not observed in primary analysis) (95% CrI: -8.4, -0.1) and Processing Speed (consistent with primary analysis) (-9.9, -1.5). Effects on Processing Speed were observed among both male children (95% CrI: -14.9, -0.03) and female children (95% CrI: -10.8, -0.3) We also observed a modest, borderline association for the class of OPs and Processing Speed deficits (95% CrI: -0.7, 0.005) (see Figure 4.2). Application of RPFs pulled estimates towards the more toxic pesticides, and produced narrower 95% CrIs for the class (OP or non-OP) effect estimates.

Table 4.3 Adjusted[a] associations of 10-fold increase in pesticide concentration (ng/g) and loading (ng/m2) with Full Scale IQ using generalized linear models (GLM) and Bayesian Hierarchical Models (BHM)

Concentration (ng/g)	GLM						BHM					
	All		Male		Female		All		Male		Female	
	β	95% CI	β	95% CI	β	95% CI	β	95% CrI	β	95% CrI	β	95% CrI
Class: Pyrethroid							2.51	-1.07, 6.1	1.59	-2.79, 6.05	2.7	-1.91, 7.32
cis-Permethrin	3.93	-3.74, 11.63	-1.11	-13.87, 11.66	9.57	-5.97, 25.1	2.65	-0.93, 6.19	1.38	-3.15, 5.93	3.05	-1.73, 7.76
trans-Permethrin	0.99	-6, 7.96	4.42	-6.69, 15.52	-2.92	-16.86, 11.03	2.39	-0.92, 5.7	1.79	-2.48, 6.05	2.35	-2.07, 6.79
Class: OP							0.42	-2.33, 3.21	-1.3	-4.94, 2.37	0.85	-2.71, 4.35
Chlorpyrifos	3.39	-0.15, 6.85	1.31	-4.14, 6.76	4.35	-1.34, 10.05	1.88	-0.9, 4.69	-0.13	-4.05, 3.74	0.5	-3.08, 4.09
Phosmet	2.08	-3.02, 7.23	-0.44	-8.09, 7.2	2.63	-6.16, 11.43	1.07	-2.56, 4.63	-1.06	-5.44, 3.37	1.4	-3.26, 5.97
Diazinon	-2.98	-6.74, 0.8	-4.83	-10.7, 1.05	-3.18	-9.66, 3.31	-1.32	-4.24, 1.61	-2.52	-6.54, 1.61	-0.5	-4.47, 3.55
Oxydemeton-methyl	-0.67	-6.55, 5.19	-2.34	-13.16, 8.49	-0.97	-9.18, 7.23	0.06	-3.65, 3.76	-1.54	-6.19, 3.16	2.01	-2.54, 6.48
Class: Fungicide							0.94	-3.87, 5.76	0.19	-5.52, 5.91	2.47	-3.24, 8.18
Iprodione	1.09	-1.65, 3.86	0.29	-3.82, 4.4	2.16	-2.17, 6.48	0.94	-1.79, 3.66	0.18	-3.93, 4.32	2.47	-1.68, 6.57
Class: Herbicide							-1.55	-8.69, 5.54	-2.28	-11.31, 6.84	2.37	-8.3, 13.24
Chlorthal-dimethyl (DCPA)	-1.59	-7.42, 4.25	-3.44	-11.87, 4.98	-1.15	-11.65, 9.35	-1.55	-7.54, 4.4	-2.29	-10.36, 5.93	2.37	-7.64, 12.43
Loading (ng/m2)	GLM						BHM					
	All		Male		Female		All		Male		Female	
	β	95% CI	β	95% CI	β	95% CI	β	95% CrI	β	95% CrI	β	95% CrI
Class: Pyrethroid							1.75	-1.58, 5.13	2.16	-1.85, 6.15	1.82	-2.44, 6.1
cis-Permethrin	1.9	-6.24, 10.09	-1.84	-16.5, 12.82	9.38	-5.31, 24.08	1.8	-1.5, 5.12	1.96	-2.02, 5.97	2.33	-1.96, 6.62
trans-Permethrin	1.28	-6.49, 8.97	6.85	-7.07, 20.78	-6.01	-20.24, 8.21	1.71	-1.49, 4.91	2.37	-1.51, 6.26	1.35	-2.81, 5.63
Class: OP							-0.18	-2.74, 2.37	-1.37	-4.43, 1.71	0.13	-3.28, 3.52
Chlorpyrifos	4.6	**1.01, 8.14**	3.63	-1.57, 8.82	3.94	-2.48, 10.35	2.09	-0.74, 4.88	0.45	-3.12, 3.96	-0.15	-4.14, 3.86
Phosmet	2.72	-1.22, 6.67	0.79	-5.28, 6.85	3.75	-2.34, 9.84	1.12	-1.95, 4.17	-0.91	-4.78, 2.96	1.06	-3.01, 5.08
Diazinon	-3.89	-7.88, 0.13	-5.91	**-11.41, -0.42**	-1.26	-8.35, 5.84	-1.95	-4.93, 1.07	-2.79	-6.38, 0.9	-0.48	-4.62, 3.68
Oxydemeton-methyl	-4.22	-8.39, 0.02	-4.91	-12.43, 2.62	-4.33	-10.29, 1.64	-1.99	-5.07, 1.14	-2.23	-6.21, 1.79	0.13	-3.89, 4.15
Class: Fungicide							1.66	-2.96, 6.37	1.01	-4.42, 6.47	2.38	-2.95, 7.75
Iprodione	1.8	-0.61, 4.25	0.93	-2.74, 4.59	2.08	-1.75, 5.91	1.67	-0.83, 4.16	1.01	-2.71, 4.73	2.4	-1.23, 6.04
Class: Herbicide							-4.44	-10.62, 1.77	-3.36	-10.87, 4.06	-2.48	-11.6, 6.74
Chlorthal-dimethyl (DCPA)	-3.98	-8.61, 0.6	-3.52	-9.91, 2.88	-4.76	-13.27, 3.74	-4.46	-9.14, 0.25	-3.37	-9.71, 2.9	-2.51	-10.75, 5.84

[a]Adjusted for: maternal education, maternal intelligence, maternal depression, total prenatal urinary DAPs, assessment language (VC only), age at assessment, HOME score, agricultural workers in house, and sex* (in non-stratified models). *95% CrI of sex of child by pesticide analyte interaction terms crossed the null in all cases.

Table 4.4 Adjusted[a] association (Beta and 95% Credible Intervals) of ten-fold increase in ng/m2 loading of pesticides in dust and WISC-IV Subscales using Bayesian Hierarchical Modeling

	Working Memory (WM)						Verbal Comprehension (VC)					
	All		Male		Female		All		Male		Female	
Pesticide	β	95% CrI	β	95% CrI	β	95% CrI	β	95% CrI	β	95% CrI	β	95% CrI
Pyrethroid	1.54	-1.99, 5.03	1.43	-2.79, 5.6	0.88	-3.49, 5.24	0.45	-2.77, 3.63	1.09	-2.58, 4.74	0.32	-3.37, 3.97
cis-Permethrin	1.42	-2.06, 4.85	1.2	-3.07, 5.46	1.12	-3.29, 5.49	1.13	-2.02, 4.27	1.06	-2.69, 4.78	0.88	-2.78, 4.5
trans-Permethrin	1.63	-1.74, 4.98	1.66	-2.45, 5.8	0.64	-3.67, 4.99	-0.23	-3.27, 2.81	1.11	-2.52, 4.64	-0.24	-3.86, 3.37
Organophosphate	-0.19	-2.9, 2.52	-0.7	-3.92, 2.59	0.6	-3.15, 4.33	-0.11	-2.56, 2.34	-1.16	-4.05, 1.73	0.62	-2.35, 3.62
Chlorpyrifos	1.03	-1.98, 4.04	1.21	-2.53, 4.86	0.3	-3.99, 4.6	1.91	-0.69, 4.5	0.21	-3.11, 3.47	1.47	-1.97, 4.86
Phosmet	1.02	-2.31, 4.32	-0.98	-5.1, 3.16	1.79	-2.76, 6.29	-0.14	-2.93, 2.67	-1.23	-4.88, 2.4	0.91	-2.66, 4.47
Diazinon	-1.46	-4.68, 1.78	-1.86	-5.68, 2.04	0.47	-3.97, 4.87	-0.97	-3.71, 1.8	-1.59	-4.93, 1.82	0.32	-3.29, 3.95
Oxydemeton-methyl	-1.36	-4.68, 1.96	-1.21	-5.38, 3	-0.14	-4.42, 4.24	-1.26	-4.18, 1.69	-2.03	-5.78, 1.77	-0.24	-3.92, 3.45
Fungicide	1.91	-2.94, 6.76	1.16	-4.63, 7	2.97	-2.77, 8.71	2.45	-2.07, 7.01	2.97	-2.1, 8.08	2.13	-3.05, 7.3
Iprodione	1.92	-0.84, 4.68	1.17	-3.08, 5.43	2.99	-1.18, 7.09	2.46	**0.28, 4.64**	2.98	-0.24, 6.21	2.12	-1.17, 5.37
Herbicide	-2.26	-8.82, 4.37	-2.75	-10.99, 5.59	-1.74	-11.8, 8.18	-2.53	-8.33, 3.18	-3.47	-10.48, 3.6	-0.27	-8.17, 7.59
Chlorthal-dimethyl (DCPA)	-2.28	-7.59, 3.05	-2.77	-10.04, 4.57	-1.76	-10.95, 7.43	-2.55	-6.78, 1.67	-3.49	-9.29, 2.42	-0.28	-7.09, 6.54

Table 4.4 continued.

	Processing Speed (PS)						Perceptual Reasoning (PR)					
	All		Male		Female		All		Male		Female	
	β	95% CrI	β	95% CrI	β	95% CrI	β	95% CrI	β	95% CrI	β	95% CrI
Pyrethroid	2.48	-0.89, 5.9	2.02	-2.09, 6.12	2.07	-1.7, 5.83	0.15	-3.32, 3.6	0.49	-3.77, 4.73	-0.41	-4.57, 3.76
cis-Permethrin	2.58	-0.77, 5.89	2.19	-1.92, 6.3	2.26	-1.49, 5.97	0.11	-3.33, 3.57	0.36	-3.95, 4.68	-0.29	-4.45, 3.91
trans-Permethrin	2.4	-0.81, 5.59	1.86	-2.18, 5.86	1.91	-1.77, 5.65	0.19	-3.16, 3.54	0.6	-3.63, 4.75	-0.52	-4.63, 3.66
Organophosphate	-2.05	-4.64, 0.53	-3	-6.14, 0.18	-1.76	-4.87, 1.37	1.48	-1.26, 4.25	0.17	-3.34, 3.68	2.55	-0.95, 6.04
Chlorpyrifos	-1.19	-3.98, 1.58	-2.46	-6.01, 1.09	-0.88	-4.52, 2.7	2.59	-0.49, 5.69	0.93	-3.03, 4.85	2.89	-1.16, 6.96
Phosmet	-1.53	-4.66, 1.57	-3.21	-7.18, 0.82	-1.45	-5.19, 2.31	2.72	-0.64, 6.06	0.75	-3.59, 5.1	3.31	-0.88, 7.55
Diazinon	-2.14	-5.15, 0.9	-2.91	-6.7, 0.83	-1.49	-5.24, 2.2	-0.08	-3.36, 3.22	-0.92	-4.93, 3.19	2.11	-2.07, 6.34
Oxydemeton-methyl	-3.33	**-6.44, -0.18**	-3.45	-7.54, 0.68	-3.25	-6.83, 0.38	0.72	-2.71, 4.16	-0.08	-4.47, 4.34	1.88	-2.38, 6.2
Fungicide	1.04	-3.68, 5.69	-0.24	-5.89, 5.35	1.94	-3.12, 7.01	0.32	-4.62, 5.23	1.36	-4.54, 7.32	-0.63	-6.41, 5.24
Iprodione	1.04	-1.44, 3.53	-0.23	-4.27, 3.83	1.94	-1.25, 5.08	0.34	-2.54, 3.2	1.37	-3.06, 5.7	-0.63	-4.83, 3.62
Herbicide	-1.88	-8.1, 4.37	0.59	-7.35, 8.49	-1.25	-9.38, 6.74	-4.33	-11.1, 2.43	-3.95	-12.77, 4.88	-4	-13.7, 5.74
Chlorthal-dimethyl (DCPA)	-1.89	-6.57, 2.88	0.58	-6.33, 7.52	-1.26	-8.27, 5.71	-4.37	-9.86, 1.15	-3.95	-11.92, 4	-4.01	-12.86, 4.96

[a]Adjusted for: maternal education, maternal intelligence, maternal depression, total prenatal urinary DAPs, assessment language (VC only), age at assessment, HOME score, agricultural workers in house, and sex* (in non-stratified models).
*95% CrI of sex of child by pesticide analyte interaction terms crossed the null in all cases.

Table 4.5 Adjusted[a] association (Beta and 95% Credible Intervals) of ten-fold increase in ng/m2 loading of pesticides in dust and WISC-IV Full-Scale and Subscales using Bayesian Hierarchical Modeling using modified z-matrix incorporating organophosphate relative potency factors (RPFs)

Pesticide	**Full-Scale IQ (FSIQ)**		**Verbal Comprehension (VC)**		**Working Memory (WM)**		**Processing Speed (PS)**		**Perceptual Reasoning (PR)**	
	All		All		All		All		All	
	β	95% CrI	β	95% CrI	β	95% CrI	β	95% CrI	β	95% CrI
cis-Permethrin	1.23	-1.92, 4.38	0.98	-2.06, 4.01	1.11	-2.11, 4.37	1.75	-1.43, 4.91	-0.02	-3.25, 3.22
trans-Permethrin	1.3	-1.73, 4.34	-0.3	-3.22, 2.64	1.39	-1.75, 4.53	1.7	-1.36, 4.77	0.12	-3.01, 3.28
Chlorpyrifos	2.04	-0.66, 4.68	1.79	-0.71, 4.29	1.02	-1.79, 3.8	-0.47	-3.11, 2.18	1.88	-1.03, 4.74
Phosmet	1.5	-1.32, 4.32	0.12	-2.46, 2.7	1.31	-1.67, 4.28	-0.32	-3.14, 2.52	2.07	-0.97, 5.06
Diazinon	-1.72	-4.56, 1.14	-0.81	-3.46, 1.83	-1.27	-4.24, 1.72	-1.12	-3.95, 1.72	-0.7	-3.72, 2.35
Oxydemeton-methyl	-4.31	**-8.41, -0.12**	-2.46	-6.23, 1.34	-3.21	-7.83, 1.43	-5.69	**-9.93, -1.48**	-0.28	-5.21, 4.73
Iprodione	1.41	-0.71, 3.5	1.99	**0.06, 3.89**	1.65	-0.64, 3.91	0.9	-1.23, 3.01	0.23	-2.13, 2.6
Chlorthal-dimethyl (DCPA)	-1.14	-4.32, 2.08	-0.74	-3.73, 2.27	0.06	-3.28, 3.42	0.02	-3.17, 3.22	-1.43	-4.88, 2
Class: Non-OP	0.7	-1.6, 2.97	0.49	-1.75, 2.72	1.05	-1.28, 3.4	1.09	-1.18, 3.4	-0.28	-2.67, 2.11
OP (Relative potency weighted)	-0.25	-0.6, 0.1	-0.14	-0.48, 0.19	-0.19	-0.56, 0.18	-0.35	**-0.7, 0**	-0.01	-0.39, 0.38

Table 4.5 continued

Pesticide	FSIQ		Verbal Comprehension (VC)		Working Memory (WM)		Processing Speed (PS)		Perceptual Reasoning (PR)	
	Male β (95% CrI)	Female β (95% CrI)	Male β (95% CrI)	Female β (95% CrI)	Male β (95% CrI)	Female β (95% CrI)	Male β (95% CrI)	Female β (95% CrI)	Male β (95% CrI)	Female β (95% CrI)
cis-Permethrin	0.92 (-2.5, 4.42)	1.92 (-1.61, 5.47)	0.54 (-2.84, 3.93)	1.21 (-2.13, 4.55)	0.52 (-3.06, 4.07)	1.51 (-2.08, 5.07)	1.3 (-2.23, 4.82)	1.52 (-1.86, 4.91)	-0.14 (-3.76, 3.46)	0.17 (-3.34, 3.69)
trans-Permethrin	1.38 (-1.95, 4.68)	0.99 (-2.53, 4.49)	0.57 (-2.69, 3.82)	0.19 (-3.11, 3.49)	1 (-2.4, 4.46)	1.2 (-2.35, 4.75)	0.88 (-2.52, 4.29)	1.42 (-1.96, 4.8)	0.14 (-3.36, 3.63)	0.03 (-3.5, 3.58)
Chlorpyrifos	1.22 (-1.91, 4.27)	-0.57 (-3.82, 2.71)	0.75 (-2.25, 3.74)	0.98 (-2.11, 4.07)	1.65 (-1.62, 4.87)	-0.52 (-3.9, 2.86)	-0.74 (-3.87, 2.42)	-0.35 (-3.48, 2.81)	0.78 (-2.51, 4.12)	1.25 (-2.14, 4.63)
Phosmet	0.14 (-3.15, 3.44)	1.06 (-2.2, 4.33)	-0.27 (-3.51, 2.94)	0.67 (-2.41, 3.74)	-0.37 (-3.82, 3.04)	1.53 (-1.96, 5.01)	-1.1 (-4.48, 2.32)	-0.02 (-3.2, 3.18)	0.72 (-2.81, 4.21)	1.61 (-1.78, 5.02)
Diazinon	-1.87 (-5.09, 1.35)	-0.57 (-4.02, 2.84)	-0.79 (-3.87, 2.32)	0.12 (-3.14, 3.34)	-1.31 (-4.64, 2.07)	0.08 (-3.48, 3.63)	-0.89 (-4.19, 2.46)	-0.3 (-3.59, 3.03)	-0.97 (-4.36, 2.46)	0.45 (-3.06, 3.96)
Oxydemeton-methyl	-6.1 (-12.87, 0.72)	0.15 (-5.97, 6.27)	-5.06 (-11.17, 1.14)	-1.49 (-6.71, 3.84)	-3.93 (-11.7, 3.89)	-2.06 (-8.87, 4.7)	-7.46 **(-14.92, -0.03)**	-5.54 **(-10.83, -0.27)**	-1.31 (-9.56, 6.98)	0.32 (-6.73, 7.41)
Iprodione	0.97 (-1.8, 3.73)	1.89 (-0.83, 4.61)	2.07 (-0.53, 4.61)	1.8 (-0.79, 4.37)	0.9 (-2.11, 3.92)	2.32 (-0.65, 5.29)	0.29 (-2.63, 3.18)	1.47 (-1.1, 4.03)	0.6 (-2.52, 3.74)	-0.06 (-3.09, 3.01)
Chlorthal-dimethyl (DCPA)	-0.14 (-3.64, 3.41)	0.62 (-3.3, 4.52)	-0.37 (-3.82, 3.06)	0.82 (-2.91, 4.54)	0.01 (-3.73, 3.72)	1.1 (-3.02, 5.22)	0.92 (-2.69, 4.54)	0.62 (-3.22, 4.48)	-0.69 (-4.53, 3.21)	-0.48 (-4.52, 3.6)
Not OP	0.79 (-1.69, 3.26)	1.35 (-1.28, 3.98)	0.7 (-1.7, 3.1)	1 (-1.49, 3.49)	0.61 (-1.96, 3.2)	1.52 (-1.2, 4.28)	0.85 (-1.68, 3.39)	1.26 (-1.25, 3.82)	-0.02 (-2.69, 2.64)	-0.08 (-2.76, 2.64)
OP (Relative potency weighted)	-0.37 (-0.84, 0.11)	0.01 (-0.43, 0.45)	-0.31 (-0.75, 0.13)	-0.09 (-0.49, 0.32)	-0.23 (-0.76, 0.3)	-0.12 (-0.6, 0.35)	-0.46 (-0.96, 0.05)	-0.34 (-0.73, 0.06)	-0.08 (-0.63, 0.48)	0.03 (-0.47, 0.52)

[a]Adjusted for: maternal education, maternal intelligence, maternal depression, total prenatal urinary DAPs, assessment language (FSIQ and VC), age at assessment, HOME score, agricultural workers in house, and sex (in non-stratified analyses).
*All 95% CrI for interaction terms for child sex included null.

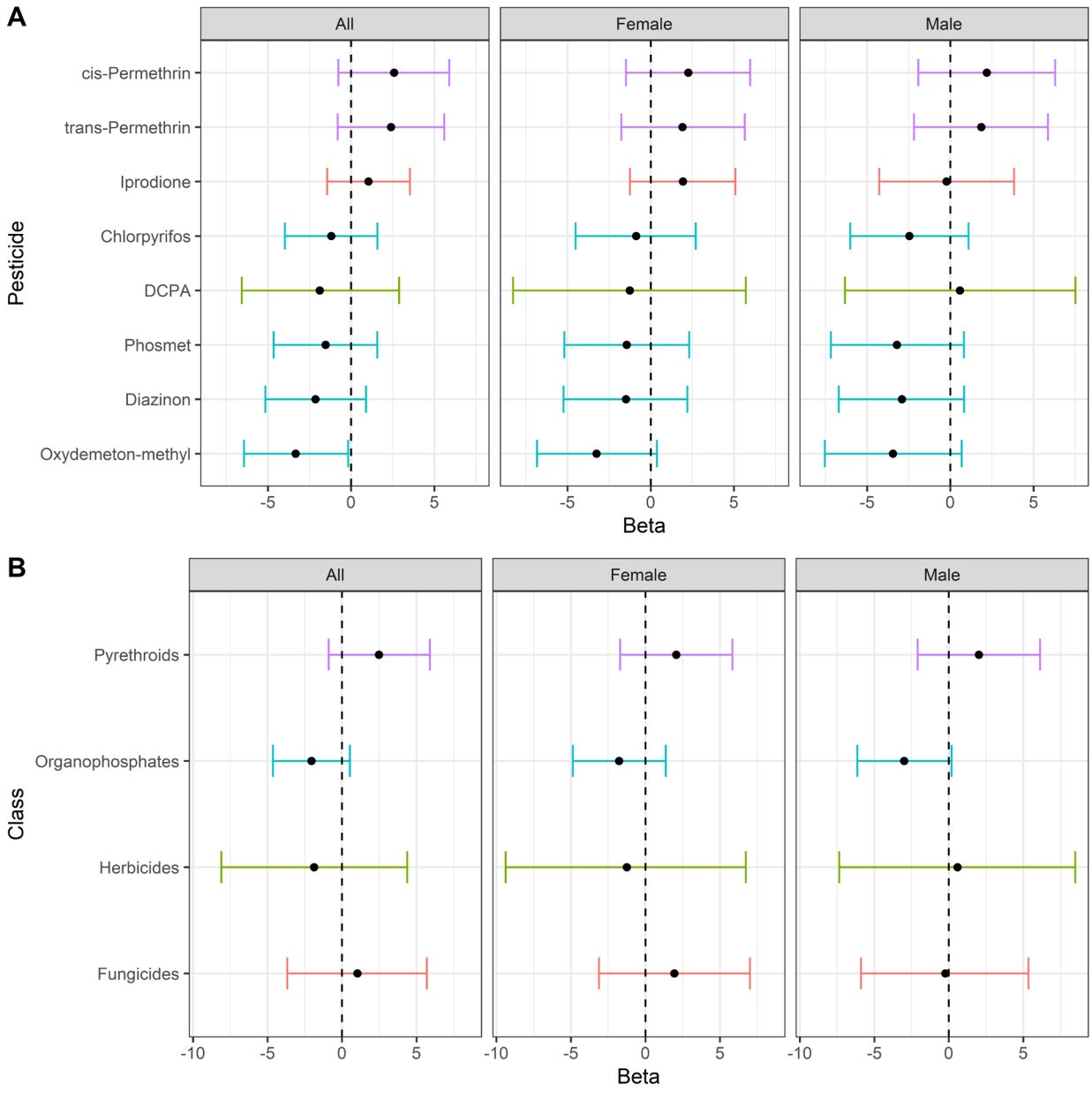


Figure 4.1 Processing Speed subscale BHM results by (A) individual pesticides and (B) pesticide class. Models adjusted for: maternal education, maternal intelligence, maternal depression, total prenatal urinary DAPs, age at assessment, HOME score, agricultural workers in house, and sex (in non-stratified models).

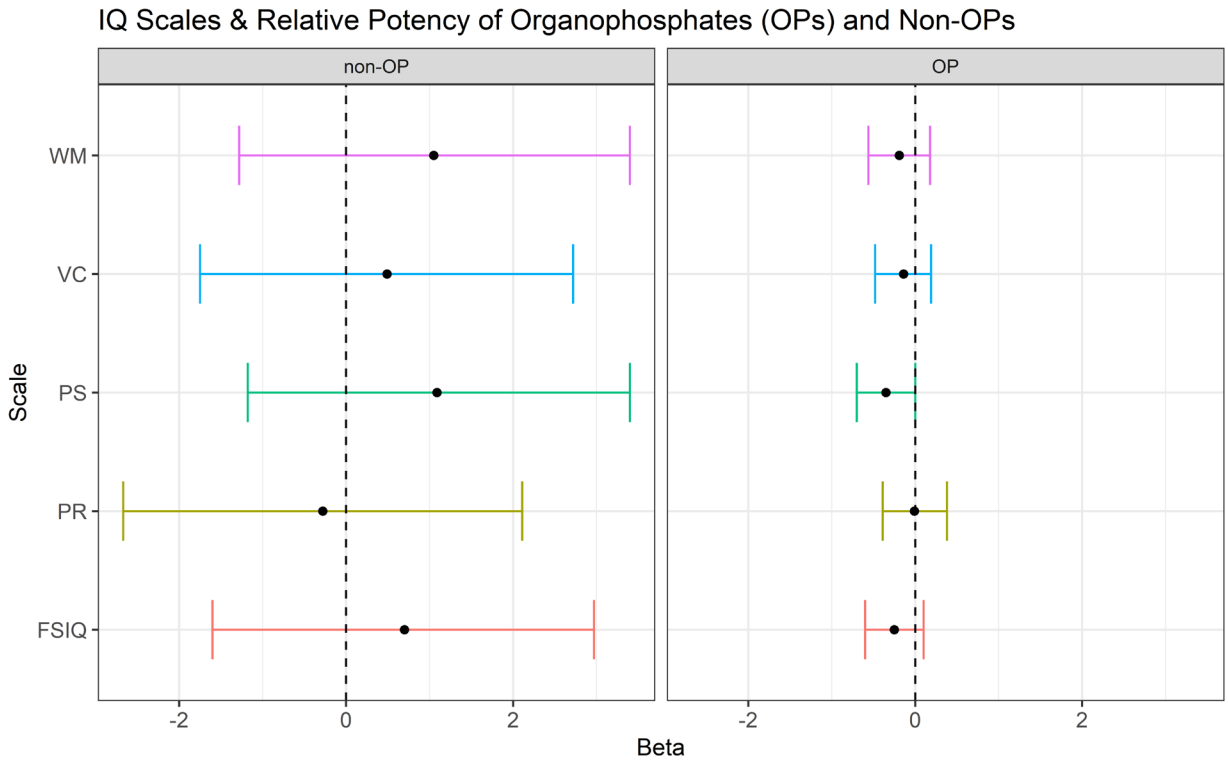


Figure 4.2 Class effects of Organophosphate (OP) pesticides on Full-Scale IQ (FSIQ), Verbal Comprehension (VC), Working Memory (WM), Processing Speed (PS), Perceptual Reasoning (PR) at age seven years using Relative Potency Factors in Bayesian Hierarchical Models. Models adjusted for: maternal education, maternal intelligence, maternal depression, total prenatal urinary DAPs, assessment language (VC and FSIQ), age at assessment, HOME score, agricultural workers in house, and sex (in non-stratified models).

4.4 Discussion

We did not observe significant associations between pesticide concentrations (ng/g) in house dust measured in early childhood with cognitive scores at age seven. Our results showed largely null associations between pesticide dust loading (ng/m^2) and child cognition at age seven, however, we did observe a 10-fold increase in oxydemeton-methyl loading associated with modest deficits on the Processing Speed subscale, consistent across primary and sensitivity analyses, with stronger effects among male children. We also observed higher Verbal Comprehension scores associated with higher iprodione loading in dust. We produced effect estimates for four pesticide classes using BHM, but did not observe more than borderline effects on cognition by pesticide class. Overall OP levels trended toward cognition deficits, while pyrethroid levels trended toward higher cognition.

We observed stronger effect estimates associated with pesticide dust loading than for pesticide concentrations, which is consistent with existing exposure assessment literature. In studies evaluating blood lead concentrations and lead dust levels, the associations were much stronger with dust loading (66). After observing null results for primary analyses using

concentration, we focused our analyses on loading as the exposure characterization of interest. Concentration measurements can be useful for assessing indoor contamination and in exposure estimation calculations. However, in some situations, there may be higher concentrations but with very little surface dust available for exposure. Loading measurements can provide a more directly relevant metric for exposure assessment for use in epidemiology.

We found the strongest, most consistent association between higher levels of oxydemeton in dust and cognition deficits at age 7 years, especially when incorporating prior information on the potency of oxydemeton-methyl relative to other OP pesticides. Previous CHAMACOS analyses have also identified this association for prenatal exposure and childhood cognition. Bouchard et al. 2011 found that urinary dimethyl (DM) phosphate metabolite concentrations averaged during pregnancy were associated with poorer cognitive scores (38). The investigators noted that the stronger associations with DM metabolites for most cognitive measures could be explained by higher toxicity pesticides, particularly oxydemeton-methyl, devolving to DM. Gunier et al. 2017 used multiple tests of association with neurodevelopment for both individual pesticides and pesticide classes with relative potency weighting (35). They found that IQ scores generally decreased across all domains with increasing use of OP pesticides within 1 km of the maternal residence during pregnancy, and that use of oxydemeton-methyl near child homes was one of the individual OP pesticides that had the strongest inverse relationship with Full-Scale IQ.

In a study that used a different approach to evaluating the impact of pesticide mixtures on child cognition, using pesticide profiles of agricultural pesticides applied near maternal residences during pregnancy, investigators also identified oxydemeton-methyl, in addition to acephate, and maneb, as important contributors to the inverse associations with Full-Scale IQ in the CHAMACOS cohort (39). Their findings suggested potential sub-additive effects in the magnitude of these associations. It is logical that our results for oxydemeton-methyl in house dust align with analyses based on PUR data, given that these indicators of exposure are often correlated, and makes these findings more compelling (88, 90).

The literature on early childhood pyrethroid exposure and neurobehavioral outcomes is sparse with overall mixed findings. We initially selected our statistical methods and exposure assessment to best uncover associations between pyrethroid pesticides and neurodevelopment while accounting for effects of other neurotoxic pesticide classes. The literature suggesting links between neurobehavioral deficits and childhood pyrethroid exposure (77, 134, 135, 164, 165) or prenatal exposure (130, 135, 166, 167) have measured exposure via urine samples, while our study focuses on early childhood non-dietary exposure to pesticides in dust. Our observed null associations between early life pyrethroid exposure and cognition are consistent with the other epidemiologic studies that also did not report inverse associations (133, 168, 169). These studies were cross-sectional and/or were limited by small sample sizes. Future analyses could draw upon environmental measures, geospatial analyses, and urine biomarkers for a more robust exposure assessment.

Few other studies have examined pesticide exposures and interactions with psychosocial stress. Within the CHAMACOS cohort, one study found that one OP pesticide (malathion) was associated with worse internalizing behaviors among those with high Adverse Childhood Experiences (ACEs), another source of psychosocial stress (170). Another examination of early childhood adversity in the CHAMACOS study found stronger associations between prenatal OP

exposure and child IQ with more life stress (171). We selected quality of the home environment as a key social factor and potential source of psychosocial stress. In addition to influencing neurodevelopment, the home environment is also a more modifiable social factor than, say, exposure to racism or living in historically marginalized communities, as many families provide positive psychosocial environments, despite experiencing poverty or other challenges posed by socio-economic status. We posit that psychosocial stress acts on the same neuroendocrine stress response pathway (hypothalamic-pituitary-adrenal axis) (172) as environmental contaminants such as pesticides (173).

While analyses on pesticides and interaction with HOME scores were null, we observed borderline effects suggesting the potential for interaction between the phthalate herbicide, chlorthal-dimethyl or DCPA (trade name Dacthal) and the quality of the home environment, for WISC-IV Full-Scale IQ and Working Memory, suggesting that higher levels of DCPA and lower quality home environments can synergistically impact child cognitive outcomes. DCPA is a suspected endocrine-disrupting chemical, and the U.S. Environmental Protection Agency concluded that DCPA demonstrated a potential for thyroid hormone interaction (151). Note that while the EPA does not consider DCPA neurotoxic, disruptions in thyroid function are suspected causes of neurodevelopmental deficits. Our findings of borderline synergistic effects warrant further exploration of the hypothesis that pesticides and social stress operate within the same neuroendocrine system.

Similar to the present study, Horton et al. examined the potential of the home environment and the child's sex to modify the adverse effects of prenatal exposure to the OP pesticide chlorpyrifos on child working memory. They also found that a good quality home environment did not moderate the adverse effects of chlorpyrifos (45). They did observe that males experience a greater deficit in working memory than females following prenatal chlorpyrifos exposure, and that male children benefit more from a nurturing home environment than females. We also observed an overall trend of poorer cognition associated with higher OP levels among male children. This is consistent with the epidemiologic literature (174), although the strongest evidence exists for prenatal, rather than early childhood, OP exposures.

There are some important limitations to note. While this analysis draws on methods that do not require a large sample size, we were only able to include a subset of the larger CHAMACOS cohort that had dust measured in the home and the outcome assessment. Other epidemiologic studies that use dust for exposure assessment had sample sizes of more than 350 to over 1,000 participants (175-177). There were also a limited number of pesticides within each pesticide class used in this analysis. We had house dust measurements for two pyrethroid isomers, but many more compounds in this class of pesticides are likely to be present in homes. This analysis only focused on certain pesticide exposures, and not legacy pesticides such as DDT or other chemical exposures that can impact neurodevelopment, such as lead. In addition, homes are not the only environment young children spend time, and this analysis does not account for potential exposures outside of the home (about 30% of participants stayed 15+ hours outside home and average was about 40 hours/week among those). We also acknowledge that a more accurate accounting of psychosocial stress than just HOME scores would better serve this interaction analysis, but additional measures of psychosocial stress were limited within our exposure-outcome subpopulation. The home environment is but one potential contributor to psychosocial stress. Other measurable contributors to early life adversity include Adverse Childhood

Experiences (ACEs) (170) or a total adversity index, such as that used in Stein et al., 2016 (171), or biomarkers of stress; future studies of pesticide exposures and child cognition should explore effect modification by these measures.

The present study is, to our knowledge, the first to examine associations between early childhood exposures to pesticide mixtures in house dust and later child cognition. We drew on a robust longitudinal cohort and the ability to control for several measured confounders and applied principled approaches for considering exposure to pesticide mixtures. Overall, these methods move the field forward toward a class-based approach to chemical assessment and regulatory control. This analysis also aimed to treat the quality of the home environment, a social factor that can contribute to psychosocial stress, as a co-exposure, rather than just another variable to control for, thereby moving toward consideration of the cumulative impacts of chemical and non-chemical exposures on children's health.

4.4.1 Breaking the cycle of children's health disparities.

This research was conducted as part of the 2022-2023 Break the Cycle Program and aims to break the cycle of children's environmental health disparities by focusing on the cumulative impact of chemical and non-chemical exposures within a disproportionately burdened community (see Cycle Diagram – Figure 4.3). The widespread use of neurotoxic pesticides has resulted in ubiquitous human exposure. However, this exposure is not distributed evenly, and children, farmworkers, and farming communities bear a disproportionate burden of exposure to pesticides and susceptibility to their effects. By investigating the connections between early childhood exposure to mixtures of different pesticide classes, the quality of the home environment, and neurodevelopmental outcomes in a particularly vulnerable population (young children from low-income households within an agricultural community), we can identify potential points of intervention. This includes the regulation of chemicals by class, agricultural policies that promote integrated pest management, enhancements to housing quality, interventions in child care facilities and schools focused on education and reducing environmental exposures, and the provision of social and economic support to historically disadvantaged families and communities.

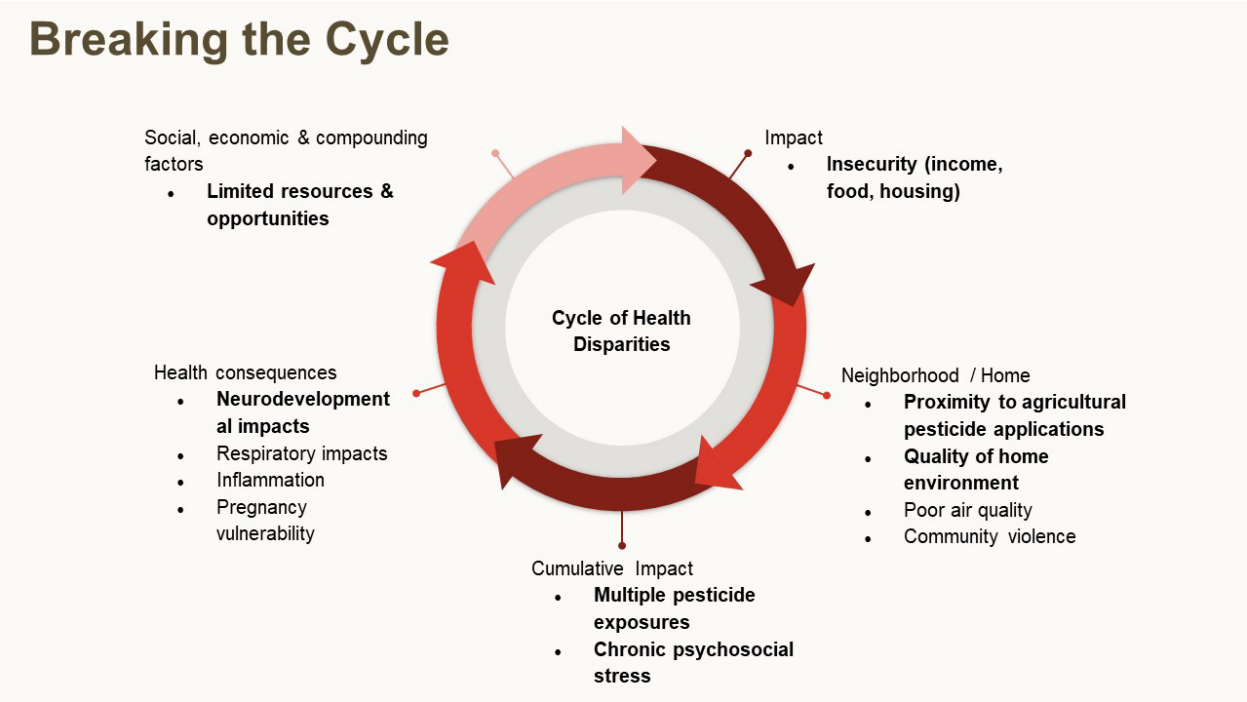


Figure 4.3 Cycle Diagram for children's environmental health in California's Salinas Valley

Advancements in statistical approaches to studying complex environmental chemical mixtures (157, 178) allow researchers the opportunity to further elucidate the complex interactions between psychosocial stressors, environmental neurotoxicants, and cognitive outcomes. Conventional epidemiological methods have been limited in their capacity to address the challenge of multiple exposures. However, to break the cycle of children's environmental health disparities, we must acknowledge that children from historically underserved communities are more likely to be exposed to a combination of chemical and non-chemical stressors, and therefore use statistical methods to account for these co-exposures. This research emphasizes the examination of current and past-use pesticides, both individually and as entire classes. Furthermore, chemical regulations should transition towards regulating classes of chemicals collectively, rather than addressing them one at a time, to prevent regrettable substitution.

Our results suggest that there may be interactive joint effects between the quality of the home environment and some pesticides, resulting in greater cognitive deficits among particularly vulnerable children. Potential interventions to improve the quality of the home environment include those that aim to enhance parental interactions and create a more stimulating learning environment in the child's home. Again, these can be bolstered through social and economic supports for families. The quality of the home environment can be improved through interventions at multiple levels – for example, providing families with age-appropriate toys and access to stimulating experiences (such as museum passes), but also creating conditions that lower parental stress (such as higher wages and safer workplaces), resulting in greater capacity for quality interactions with children at home. Research suggests interventions aimed at reducing

psychosocial stress in children significantly decreased inflammation, in part due to improved parenting in the treated group (179), but assessment of such interventions on cognition is limited and deserves greater study.

Another strategy to break the cycle of children's environmental health disparities is to engage youth around environmental health literacy and research. CHAMACOS cohort researchers have successfully engaged Latino youth in Salinas, CA to become environmental health researchers, leaders, and advocates (180). This should not be overlooked when conducting secondary data analyses as in the present study.

4.5 Conclusion

Using a mixtures approach, we observed associations between lower cognition (namely Processing Speed) and early childhood exposure to OP pesticides, particularly oxydemeton-methyl, among Mexican-American children living in an agricultural region in California. This research highlights the issue of exposure to complex pesticide mixtures in early childhood and its potential impacts on children's neurodevelopment. It contributes to our understanding by advancing class-based approaches to chemical assessment and emphasizing the importance of considering both chemical and non-chemical stressors. Our findings support existing research on the impacts of OPs and the particularly toxic oxydemeton-methyl on neurodevelopment, but finds this association for exposure in the important early childhood window, rather than prenatal exposure. Future research should further explore mixtures of current and past-use pesticides, utilize additional exposure assessment methods, and assess the cumulative impacts of these exposures. Targeted interventions should be considered to break the cycle of children's environmental health disparities for vulnerable children who are exposed to toxic chemicals as well as to non-chemical stressors.

4.6 Supplement to Chapter 4

Supplemental Table 4.1 Z-Matrix used in primary analysis

	Pyrethroid	OP	Fungicide	Herbicide
cis-Permethrin	1	0	0	0
trans-Permethrin	1	0	0	0
Chlorpyrifos	0	1	0	0
Phosmet	0	1	0	0
Diazinon	0	1	0	0
Oxydm	0	1	0	0
Iprodione	0	0	1	0
DCPA	0	0	0	1

Supplemental Table 4.2 Z-Matrix for interaction analysis

	Pyrethroid	OP	Fungicide	Herbicide	HOME
cis-Permethrin	1	0	0	0	0
trans-Permethrin	1	0	0	0	0
Chlorpyrifos	0	1	0	0	0
Phosmet	0	1	0	0	0
Diazinon	0	1	0	0	0
Oxydm	0	1	0	0	0
Iprodione	0	0	1	0	0
DCPA	0	0	0	1	0
HOME Score	0	0	0	0	1
cisPerm*HOME	1	0	0	0	1
transPerm*HOME	1	0	0	0	1
Chlorpyrifos*HOME	0	1	0	0	1
Phosmet*HOME	0	1	0	0	1
Diazinon*HOME	0	1	0	0	1
Oxydm*HOME	0	1	0	0	1
Iprodione*HOME	0	0	1	0	1
DCPA*HOME	0	0	0	1	1

Supplemental Table 4.3 Z-Matrix for sensitivity analysis using Relative Potency Factors (RPFs)

	Not OP	OP Relative Potency
cis-Permethrin	1	0
trans-Permethrin	1	0
Chlorpyrifos	0	1
Phosmet	0	0.42
Diazinon	0	0.24
Oxydm	0	16.44
Iprodione	1	0
DCPA	1	0

Supplemental Table 4.4 Adjusted[a] association (Beta and 95% Credible Intervals) of ten-fold increase in ng/g concentration of pesticides in dust using and WISC-IV Subscales using Bayesian Hierarchical Modeling

	Working Memory		Verbal Comprehension		Processing Speed		Perceptual Reasoning	
Pesticide	Beta	95% CrI	Beta	95% CrI	Beta	95% CrI	Beta	95% CrI
cis-Permethrin	2.08	-1.65, 5.79	1.4	-1.88, 4.66	2.92	-0.63, 6.48	0.82	-2.83, 4.48
trans-Permethrin	2.22	-1.3, 5.75	-0.15	-3.2, 2.93	2.71	-0.64, 6.06	1.18	-2.3, 4.69
Chlorpyrifos	0.62	-2.39, 3.63	1.8	-0.73, 4.32	-0.93	-3.68, 1.86	2.15	-0.87, 5.18
Phosmet	1.23	-2.57, 5.03	-0.29	-3.36, 2.76	-1.54	-5.12, 2.05	2.7	-0.91, 6.32
Diazinon	-0.62	-3.76, 2.57	-0.79	-3.5, 1.91	-1.8	-4.73, 1.16	-0.41	-3.62, 2.83
Oxydemeton-methyl	0.42	-3.49, 4.3	0.38	-3.15, 3.87	-1.99	-5.7, 1.69	1.46	-2.53, 5.47
Iprodione	1.01	-2.09, 4.12	2.49	0.08, 4.88	0.18	-2.6, 2.94	0.04	-3.14, 3.16
DCPA	-0.9	-7.59, 5.74	-0.76	-6.12, 4.6	0.01	-5.95, 5.94	-0.1	-7.11, 6.91
Class: Pyrethroid	2.16	-1.55, 5.89	0.63	-2.69, 3.93	2.81	-0.78, 6.41	1	-2.64, 4.64
Class: OP	0.42	-2.51, 3.36	0.27	-2.31, 2.87	-1.57	-4.35, 1.17	1.48	-1.42, 4.41
Class: Fungicide	1.01	-4.02, 6.02	2.46	-2.18, 7.13	0.19	-4.65, 5.01	0.05	-5.04, 5.1
Class: Herbicide	-0.9	-8.6, 6.87	-0.75	-7.46, 5.91	0.03	-7.11, 7.2	-0.11	-8.15, 7.92

[a]Adjusted for: maternal education, maternal intelligence, maternal depression, total prenatal urinary DAPs, assessment language (verbal comprehension), age at assessment, HOME score, agricultural workers in house, and sex.

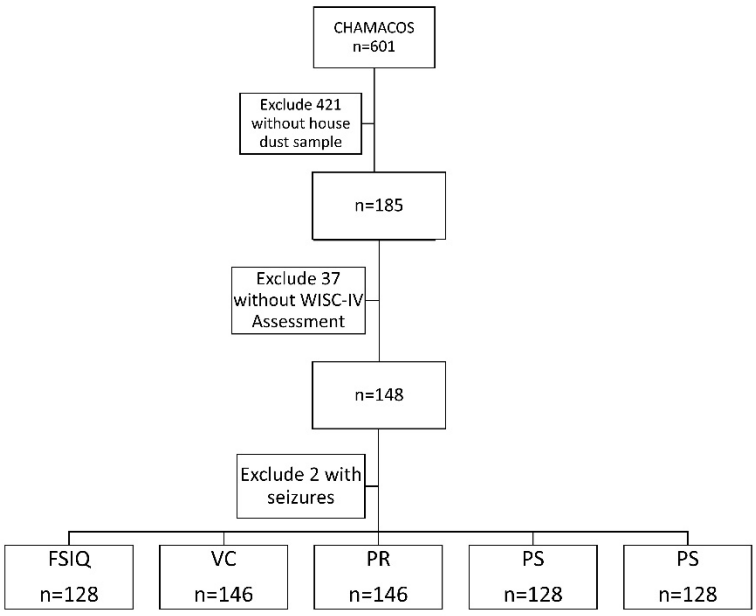
Supplemental Table 4.5 Interaction term 95% Credible Intervals (Pesticide x inverse HOME z-score) for adjusted[a] Bayesian Hierarchical Models for Full-Scale IQ (FSIQ), Verbal Comprehension (VC), Working Memory (WM), Processing Speed (PS), Perceptual Reasoning (PR) using concentration (conc.) (ng/g) and loading (load.) (ng/m^2)

Pesticide used in interaction with HOME Scores	**FSIQ**		**VC**		**WM**		**PS**		**PR**	
	Conc.	Load.	Conc.	Load.	Conc.	Load.	Conc.	Load.	Conc.	Load.
cis-Permethrin	-3.56, 3.29	-3.05, 3.78	-2.57, 4.38	-2.59, 4.04	-2.88, 4.74	-2.71, 4.25	-0.36, 4.83	-2.45, 4.39	-4.1, 3.15	-4.32, 2.82
trans-Permethrin	-3.6, 3.08	-3.23, 3.36	-2.29, 4.4	-3.19, 3.25	-2.75, 4.6	-2.85, 3.96	-0.5, 4.5	-2.55, 4.1	-3.81, 3.31	-3.97, 2.98
Chlorpyrifos	-2.07, 4.55	-1.69, 4.13	-3.72, 3.41	-2.04, 3.6	-4.27, 3.04	-1.09, 5.09	-1.88, 3.09	-3.21, 2.62	-4.37, 3.16	-2.88, 3.54
Phosmet	-3.8, 3.45	-3.73, 2.44	-4.92, 2.72	-5.03, 0.85	-3.67, 4.17	-3.47, 2.92	-2.99, 2.39	-4.87, 1.29	-3.97, 4.24	-2.72, 4.09
Diazinon	-2.66, 4.05	-1.94, 4.36	-3.79, 2.72	-2.6, 3.41	-3.54, 3.25	-3.2, 3.39	-1.78, 2.89	-1.83, 4.57	-4.03, 2.98	-2.56, 4.3
Oxydemeton-methyl	-5.36, 2.26	-4.34, 2.16	-5.21, 2.62	-4.29, 1.99	-6.59, 1.49	-4.62, 2.18	-2.79, 2.73	-5.19, 1.32	-5.74, 2.56	-3.07, 3.96
Iprodione	-2.88, 4.07	-1.55, 2.89	-3.69, 3.04	-0.46, 3.54	-5.06, 1.96	-2.17, 2.67	-2.26, 2.7	-1.57, 2.94	-2.27, 5.52	-1.49, 3.66
Chlorthal-dimethyl (DCPA)	-6.79, 2.77	-7.98, 0.21[b]	-8.02, 1.25	-6.19, 1.3	-7.57, 2.73	-8.65, 0.11[c]	-3.31, 3.94	-6.53, 1.67	-6.65, 4.23	-5.94, 3.27

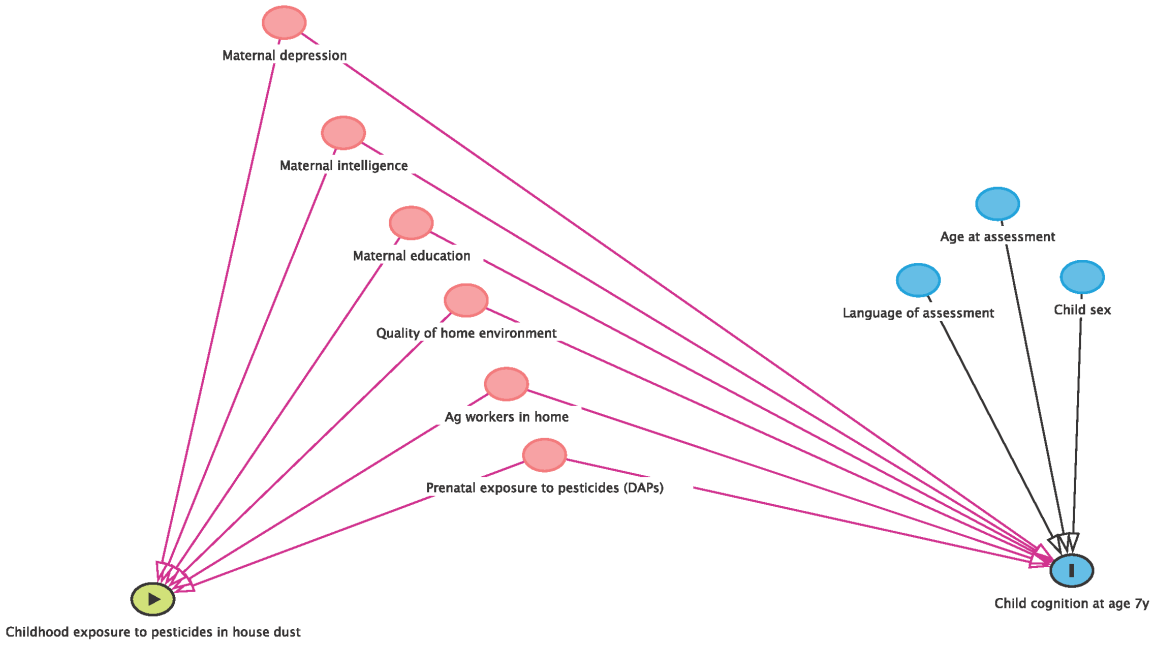
[a]Adjusted for: maternal education, maternal intelligence, maternal depression, total prenatal urinary DAPs, assessment language (FSIQ and VC), age at assessment, HOME score, agricultural workers in house, and sex.
[b]Stratified DCPA loading and FSIQ: lower HOME scores: β= -7.07 (95% CrI: -14.65, 0.51); higher HOME scores: β= -0.51 (-6.03, 5.0)
[c]Stratified DCPA loading and WM: lower HOME scores: β= -5.57 (95% CrI: -13.13, 2.08); higher HOME scores: β= 3.52 (-3.07, 10.12)

Supplemental Table 4.6 Sensitivity analysis of changing precision parameter

	Full-Scale IQ (FSIQ)		WM	VC	PS	PR
	95% CrI using 6-fold assumption	95% CrI using 4-fold assumption	95% CrI using 4-fold assumption	95% CrI using 4-fold assumption	95% CrI using 4-fold assumption	95% CrI using 4-fold assumption
cis-Permethrin	-0.44, 5.65	-0.01, 5.22	-0.97, 3.95	-1.42, 3.17	0.3, 4.85	-2.36, 2.58
trans-Permethrin	-0.41, 5.38	0.04, 5.09	-0.89, 4.01	-1.75, 2.69	0.28, 4.79	-2.27, 2.56
Chlorpyrifos	-1.12, 3.97	-1.29, 3.25	-2.13, 2.55	-1.02, 2.99	-3.86, 0.44	-0.5, 4.22
Phosmet	-2.25, 3.97	-1.97, 3.26	-2.29, 2.72	-2.14, 2.44	-4.19, 0.49	-0.57, 4.47
Diazinon	-3.49, 1.87	-2.57, 2.08	-3.07, 1.78	-2.14, 2.04	-4.34, 0.22	-1.49, 3.38
Oxydemeton-methyl	-3.02, 3.43	-2.32, 2.91	-3.05, 1.84	-2.07, 2.79	-4.78, -0.19	-1.27, 3.77
Iprodione	-1.84, 3.65	-1.91, 3.61	-0.89, 4.66	-0.06, 4.75	-1.49, 3.49	-2.67, 3.07
Chlorthal-dimethyl (DCPA)	-7.45, 4.46	-7.33, 4.5	-7.69, 2.76	-5.78, 4.94	-6.67, 2.67	-10.04, 0.99
Class: Pyrethroid	-0.52, 5.58	-0.01, 5.16	-0.96, 4	-1.59, 2.95	0.31, 4.84	-2.3, 2.55
Class: OP	-1.99, 2.87	-1.71, 2.56	-2.3, 1.91	-1.53, 2.22	-3.96, -0.11	-0.65, 3.6
Class: Fungicide	-3.18, 4.95	-2.55, 4.24	-1.55, 5.28	-0.79, 5.45	-2.17, 4.16	-3.3, 3.72
Class: Herbicide	-8.13, 5.2	-7.64, 4.79	-8.07, 3.19	-6.12, 5.25	-7.01, 3.08	-10.44, 1.28



Supplemental Figure 4.1 Inclusion criteria



Supplemental Figure 4.2 Directed Acyclic Graph

Chapter 5 Conclusion

5.1 Summary

The purpose of this dissertation was to 1) characterize and identify determinants of pesticide levels in carpet dust in California child care centers, 2) assess the risk of these potential exposures, through non-dietary ingestion and dermal absorption, surpassing health-protective reference values, and 3) examine early childhood exposures to pesticide mixtures in house dust, the home environment, and child cognition. This research addresses critical gaps in our understanding of the determinants and health implications of pesticide exposure in early childhood environments.

Methods

Our methodology is grounded in analysis of two important children's environmental health studies. This dissertation includes some of the first findings from the UCSF Healthy Children and Environments Study, a randomized-control trial of licensed child care centers in four Northern California counties aiming to examine the effect of an Integrated Pest Management (IPM) intervention on pesticide levels in child care. Indoor dust is an important source of exposure for young children. We utilized dust samples collected via High Volume Small Surface Sampler (HVS3). This dissertation provides the first characterization of contamination for certain new-use pesticides in early childhood environments, including fipronil and chlorfenapyr. To understand how exposures to pesticides in indoor dust can influence child health, we applied probabilistic methods to both health risk assessment and epidemiologic investigation. In an effort to establish links to health impacts through an epidemiologic investigation, we applied innovative methods for examining mixtures by chemical class and incorporating prior knowledge into a dataset sourced from the robust CHAMACOS birth cohort study. Our statistical approaches utilize probabilistic risk assessment methods and Bayesian hierarchical modeling that incorporates consideration of pesticide classes and relative potency.

Key findings

In Chapter 2, our research yielded important insights into the factors influencing pesticide levels in carpet dust within child care centers in Northern California. Specifically, we identified correlations with and predictors of levels of chlorpyrifos, bifenthrin, fipronil, and ∑permethrin. Important predictors included geographic region, proximity to agricultural pesticide applications, application of structural pesticides, fewer IPM practices, and placement of carpets on hard surface flooring. Notably, location within the San Joaquin Valley emerged as the strongest predictor of elevated pesticide loading for frequently detected pesticides. Many of our findings supported our hypotheses, including the positive association between bifenthrin levels and the density of agricultural bifenthrin use within 3 km, lower chlorpyrifos levels with better IPM practices, and increased fipronil levels with Pest Management Professional (PMP) applications of fipronil at child care centers in the past year. On the other hand, we did not find associations between higher concentrations of pesticides and observed pesticide products stored on-site, observed pests, or the age of the facility…

Results from Chapter 3 indicated that, within licensed child care centers in Northern California, potential pesticide exposures through dermal and incidental ingestion pathways are

unlikely to cause neurotoxic or hepatotoxic effects in young children. However, these estimates represent only part of potential daily exposure. In hypothetical thought exercises, we observed that similar environmental exposures at home could result in risk for neurotoxic effects for the most highly exposed children, and exposures from dietary sources could also result in overall exposure levels of concern for neurotoxic effects. We found that application of probabilistic methods for exposure estimation and risk-specific reference doses was feasible and should be applied widely in risk assessments.

In Chapter 4, we hypothesized that higher levels of pyrethroids and OPs in house dust in early childhood would be associated with lower IQ scores at age 7y and the effect would vary by sex of the child and quality of the home environment, however, results regarding pesticide dust levels and child cognition at age seven showed largely null associations. Nevertheless, a 10-fold increase in oxydemeton-methyl loading was linked to modest deficits on the Processing Speed subscale, particularly among male children, at age 7 years. Oxydemeton-methyl was the most toxic OP in the mixture. Other CHAMACOS researchers have also identified stronger associations with dimethyl metabolites for cognitive deficits explained by higher toxicity pesticides like oxydemeton-methyl. Interestingly, overall OP levels trended toward cognition deficits, while pyrethroid levels trended toward higher cognition. There was some evidence suggesting that effects of OPs vary by the sex of the child, with worse cognitive outcomes for male children. While we did not observe significant interactive effects with the quality of the home environment, borderline interactions support further analysis and the routine consideration of social factors contributing to psychosocial stress in pesticide neurodevelopmental investigations.

5.2 Limitations and Direction for Future Research

This dissertation focuses on pesticides in indoor dust, but there is a broad spectrum of potential contaminants in house dust, such as metals, phthalates, flame retardants, fluorinated compounds, and allergens. While this research applies mixture methods and considers cumulative risk to pesticide exposure, these could and should be applied to a broader set of contaminants present in children's environments. Another limitation is the relatively small number of baseline dust samples available for analysis from the HCES study due to COVID-19 disruptions. We produced novel findings regarding carpet placement on different flooring types, suggesting an avenue for further exploration in exposure assessment literature.

Both the cumulative health risk assessment for the class of pyrethroids and the Bayesian second-stage model outputs for the class of pyrethroids did not yield results that indicate adverse neurodevelopmental or other health impacts. We have compelling results incorporating relative potency factors for OPs in our Bayesian hierarchical model framework, and future research should aim to continue to apply this method to other pesticide classes as well, particularly newer-use pesticides.

This research was limited by the lack of health outcome data from the HCES study and the inclusion of only two pyrethroid isomers in the CHAMACOS dust analysis. In many ways, pesticides are a moving target for exposure assessment and epidemiology. Patterns of use for individual pesticides and pesticide classes change over time and differ by region. The permethrin levels in CHAMACOS homes 1999 to 2002 are similar to what we find in Northern California child care centers 18 years later, but we do not have similar measurements of the same

pyrethroids found in HCES child care centers for the CHAMACOS homes. These limitations underscore the necessity for well-designed studies with robust exposure assessment methods and a comprehensive panel of analytes in future research.

Additional areas for further exploration in pesticide risk assessment include better understanding the implications of changes to Food Quality Protection Act (FQPA) mandated child-specific safety factors, and better accounting for aggregate and cumulative exposure. For the present study, we relied on established U.S. EPA methods for the pyrethroid cumulative health risk assessment and did not apply the probabilistic reference dose approach to deriving the margin of exposure for pyrethroids. Further exploration into other ways to incorporate relative potency to assess cumulative risk, not just for pyrethroids, but for all neurotoxic pesticides, is warranted. We also relied on the FQPA safety factors used by U.S. EPA in its determination of the reference dose. However, over the past two decades, the FQPA safety factor for pyrethroids has been reduced from a tenfold to a threefold margin of safety, to a complete elimination of the safety factor for young children. The impact of these changes warrant further exploration.

5.3 Significance

This research makes several contributions to the field of environmental health sciences. Child care programs, vital environments for over a million California children, are under-researched in environmental health studies. Children may be spending a significant amount of time in child care environments, with particularly long hours for working class families. Children are not the only vulnerable population in child care settings. California's early care and education workforce includes approximately 130,000 people, predominantly female, with ethnic diversity consistent with that of the children they care for (181). Nationwide, child care workers earn wages that put them barely above the poverty level for a family of three (78). Prioritizing environmental health in child care protects the health of children and promotes health equity for many women of color.

Our findings suggest that IPM practices may reduce exposure to legacy pesticides that persist in the indoor environment, in addition to preventing pest infestations and reducing the need for new pesticide applications. IPM is an important health intervention in child care settings, and better IPM practices within our food systems can help reduce pesticide exposures for the general public, residents of agricultural communities, and farmworkers and their families. We are encouraged by the recent release of California's Sustainable Pest Management roadmap that will hopefully reduce children's exposures to pesticides at school and at home.

Several methodologies used in this research should continue to be applied in environmental health studies. Probabilistic risk assessment and use of probabilistic reference doses as points of comparison should be the standard for chemical risk assessment. Bayesian statistical methods can answer multiple questions from one data set and incorporate prior knowledge. We produced class-specific effect estimates, and incorporated relative potency factors, which is a unique feature of this research. This study adds to the limited knowledge about how pesticide exposures and psychosocial stress interact. The quality of the home environment and exposure to pesticides during early life are both linked to neurodevelopmental issues. Although there is evidence connecting either psychosocial stress or chemical exposures to negative neurodevelopmental outcomes, their combined effects have not been extensively studied. When data are available, particularly when researching disproportionately impacted communities, researchers should

routinely analyze potential interactions, in the same way epidemiologists routinely control for confounding. Social factors contributing to psychosocial stress that might affect the same neuroendocrine pathways as pesticides should be treated as co-exposures with the potential for synergistic effects. Bayesian statistical methods allow researchers to incorporate this with relative ease. Finally, our findings underscore the importance of using dust loading to characterize potential exposure.

Pesticide use restrictions and right-to-know regulations provide some protection from exposures at schools and child care centers. Growers cannot apply certain pesticides within 0.25 miles (approx. 402 meters) during the school day. We observed correlation between bifenthrin levels in carpet dust and the density of agricultural bifenthrin use within 3 km of the site. Further investigation is needed to determine if California's regulatory buffer around schoolsites will sufficiently reduce exposure to agricultural pesticides. As of this writing, and after decades of advocacy, the California Department of Pesticide Regulation is developing the infrastructure and technology to support a statewide notification system for agricultural pesticide applications. This is a critical development as a tool to help communities protect their health, and for researchers to study potential adverse health outcomes.

Overall, our research contributes to filling gaps in knowledge around chronic, low-level exposure to pesticide mixtures to promote healthier early childhood environments.

5.4 Conclusion

This dissertation aimed to assess pesticide exposures in children's environments, and examine health risks and potential neurodevelopmental effects associated with those exposures. Our findings reveal the ubiquitous presence of pesticides in children's care environments, influenced by various factors, both within and beyond the control of child care operators. While pesticide levels within our child care study population did not raise significant concerns, we still advocate for the reduction of exposures as children are exposed to mixtures of pesticides both within child care and beyond. Our findings supporting the extant literature on the neurodevelopmental effects of OP pesticides underscore the need to move away from this class of pesticides and toward truly safer alternatives, rather than potentially regrettable substitutes.

Looking ahead, our research emphasizes the imperative of exploring low-dose effects of pesticide mixtures, particularly newer-use pesticides, with a focus on disproportionately burdened communities and vulnerable subpopulations. We advocate for support systems promoting thriving developing brains, emphasizing high-quality early care and education, and adoption of IPM practices. Recognizing the significance of early childhood exposures, our study calls for ongoing efforts to safeguard children's developing brains and create healthier environments.

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