Characterizing Dietary Exposure to Organophosphate Pesticides, Incorporating Organic Food Consumption, for Use in Epidemiological Research

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A dissertation

submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2014

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ABSTRACT

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Concern exists about the potential for low-level exposure to organophosphate pesticides (OPs) to lead to neurological and cognitive health effects. OPs are the most widely used insecticides in American agricultural, and diet is thought to be the primary route by which the general public is exposed to OPs. The United States Department of Agriculture permits food to be certified "organic" when grown according to specific regulations, including prohibitions on the use of most synthetic pesticides. While organic food consumption is known to reduce exposure to OPs, health benefits from choosing organic food have not been demonstrated. We aimed to develop a novel method to assess long-term dietary OP exposure, designed to avoid many of the limitations of the existing methods of OP exposure assessment. Using a combination of individual-level information on dietary intake and national-level data on pesticide residue levels on food items, we estimated long-term dietary OP exposure in a multi-city, multi-ethnic population of over 4,000 adults. We assessed the face validity of this method by evaluating its comparability with urinary biomonitoring in a subset of participants. Among individuals with conventional diets, increasing tertile of estimated dietary OP exposure was associated with higher urinary metabolite

concentrations. We also found that metabolite concentrations were significantly lower in people reporting more frequent consumption of organic produce. We further aimed to better understand the individual- and neighborhood-level characteristics associated with organic food consumption. We observed that women, younger individuals and those with higher education were more likely to consume organic food, and that neighborhood produce availability was also associated with organic food consumption. Our third and final aim was to evaluate the association between the long-term dietary OP exposure we developed and cognitive outcomes, accounting for the individual- and neighborhood-level variables that were associated with organic food consumption. We observed a relationship between increasing dietary OP exposure and decrements in the phonological loop component of working memory as assessed by the Forward Digit Span Test, but did not find OP exposure to be associated with three other cognitive endpoints. The results of this study suggest that the new method we have developed to assess dietary pesticide exposure will be useful in future epidemiological studies of the health effects of low-level exposure to OPs.

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ACKNOWLEDGEMENTS

I am so grateful for the support of so many wonderful people throughout this process. Above all, I am grateful to Joel Kaufman for his remarkable mentorship and encouragement. I am consistently awed by his skill as a teacher, researcher, grant writer, and outside-the-box thinker, and cannot possibly express the degree to which he has helped shape the trajectory of my career and the way I think about science and scientific research. I am also fortunate to have started my career working with another amazing mentor, Richard Fenske, whose guidance, advice and clear insight have continued to benefit me as a doctoral student. In addition, I want to express my sincere appreciation of Annette Fitzpatrick and Shirley Beresford, whose contributions to my dissertation committee have been invaluable.

I would like to acknowledge two key sources of funding, without which this dissertation would not exist. This work benefitted greatly from the EPA's Science to Achieve Results Fellowship program and from the University of Washington's Department of Environmental and Occupational Health Sciences Pilot Study Funding Program. I'd also like to thank participants of the Multi-Ethnic Study of Atherosclerosis; MESA is supported by contracts N01-HC-95159 through N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-TR-000040 and UL1-RR-025005 from NCRR.

Finally, I'd like to thank my friends and family for their patience, love and support. I am especially appreciative of my parents, whose willingness to listen to the day-to-day minutiae of this work has been incredible. I'd also like to thank Berni Kenworthy, Alma Feldpausch, Cristina Valdes, Elizabeth Spalt, and Amanda Gassett, who kept urging me on throughout this long process. Finally, none of this would have been possible without my husband, Adam, whose love, friendship, partnership, and keen sense of humor I am grateful for every day.

DEDICATION

To my daughter, not yet born, but already a source of inspiration and motivation.

CHAPTER I. Introduction

Organophosphate Pesticides (OPs)

Organophosphate pesticides (OPs) constitute the most widely used class of insecticides in the United States. Approximately 33 million pounds of OPs were applied in the US in 2007, representing more than a third of the country's total insecticide use.[1] OPs are applied to a wide variety of crops including berries, tree fruits, leafy green vegetables, root vegetables, mushrooms, nuts, grains, melons, beans, squash and many others.[2] These insecticides are also registered for a limited number of residential uses, such as roach bait, ant control, and pet and lice treatments, as well as for public health purposes, including mosquito and fire ant control. However, agricultural applications dominate total OP usage in the United States.[2]

Collectively, OPs constitute a class of more than 50 chemicals, sharing a common central structure and a primary biological mechanism that affects the nervous system through inhibition of cholinesterase.[2] Although this mechanism of action is common across OPs, individually these compounds demonstrate a wide range of toxicities. As a group, they have been a focus of intense regulatory attention due to the frequency of their use and the high level of toxicity of some individual agents. One of the most significant pieces of pesticide legislation in recent history, the Food Quality Protection Act of 1996, required the US Environmental Protection Agency (EPA) to review all pesticide tolerances and to consider the cumulative effects resulting from exposure to multiple chemicals with a common mechanism of action.[3] OPs were among the first group of chemicals targeted under this act, reflecting both concerns about their toxicity and the central role they play in pest control practices in the US.

In response to this requirement, the EPA's Office of Pesticide Programs completed a comprehensive Cumulative Risk Assessment (CRA) for OPs in 2006.[2] In the years leading up to the publication of this assessment, the Office of Pesticide Programs reviewed the registration

status of 49 individual OPs and implemented numerous mitigation efforts, including restricting usages and cancelling the registrations of a number of individual agents. As part of this process, residential uses of OPs were almost entirely eliminated, most notably through voluntary cancellations of residential uses of two popular OPs, chlorpyrifos and diazinon. The results of the CRA, which considered these registration status changes, led the EPA to conclude that diet is currently the most significant route of OP exposure for non-occupationally exposed individuals, and that overall there is a reasonable certainty of no harm to the general population or any sensitive subgroups as a result of OP exposure.

While this assessment was both thorough and extensive, risk assessments are not – and are not intended to be – direct measures of health effects in a population. Further, cholinesterase inhibition was the only endpoint considered in the risk assessment, yet other, more subtle health outcomes may exist. Epidemiological studies, especially those designed to elucidate these subtle effects, may better evaluate the impact of OP exposure – and particularly long-term dietary exposure – on human health.

Acute OP Toxicity: Cholinesterase Inhibition

The acute toxicity of OPs, and thus their efficacy as pesticides, stems from their ability to act as nerve poisons through the inhibition of acetylcholinesterase (AChE).[4] Acetylcholine (ACh) transmits nerve signals across the synaptic gap; after the signal has reached its target, AChE is produced to catalyze the hydrolysis of the remaining ACh. In unexposed individuals, ACh attaches itself to the hydroxyl group of serine residue 203 at the active center of AChE to form an enzyme intermediate. Breakdown of this enzyme intermediate results in the hydrolysis of ACh and regeneration of the enzyme.[5] OPs inhibit AChE by phosphorylating the same serine residue, preventing the ACh bond. As a result, ACh accumulates, and the stimulation and

eventual paralysis of the ACh receptors account for the clinical symptoms of acute OP poisoning, including muscarinic, nicotinic, and nervous system effects.[5]

The most common manifestations in the parasympathetic nervous system include salivation, lacrimation, urination, diarrhea, gastrointestinal distress, and emesis. Nicotinic effects include muscle fasciculation, weakness, and paralysis, and at the autonomic synapses, hypertension, dilated pupil, and tachycardia. In the central nervous system, headache, drowsiness, confusion, ataxia, tremor and seizure can result. The ability of OPs to inhibit AChE is well understood, and this inhibition can be measured at levels well below that required to observe the health effects described. Toxic symptoms typically do not occur until 40-50% inhibition, with serious neuromuscular effects demonstrated at 80%.[5]

This inhibition of AChE, measured either in plasma, red blood cells (RBC) or in the brain, is the most common outcome measured in animal toxicology studies used to assess risks associated with exposure to OPs. Numerous studies of the relationship between OP exposure and cholinesterase inhibition exist in a number of animal models over a variety of timescales, and the results of such studies demonstrate the wide range of toxic potentials within the OPs.

One method that has been used to compare toxicities across individual OPs is the relative potency factor (RPF) approach, which employs a common response derived only from studies using comparable measurement methodologies, species, and sex for all exposure routes of interest.[4] As part of the 2006 OP CRA, the EPA used the RPF approach to calculate cumulative risk, selecting 10% brain cholinesterase inhibition in female rats as the common endpoint. Data included in this assessment were also required to reflect steady state conditions, in the interest of producing reproducible RPFs with less uncertainty due to time-sensitive measures.[2] Figure I.1 shows the RPFs developed as part of the 2006 CRA for the oral route of exposure.

Methamidophos was selected as the reference chemical, and just two compounds are more toxic (disulfoton and dircrotophos), indicated by RPDs greater than 1. Relative potencies range from malathion (RPF = 0.0003) to dicrotophos (RPF = 1.91), indicating more than a 6000-fold difference based on brain cholinesterase inhibition in female rats. This statistic demonstrates the wide range of toxicities present with the OP class of pesticides, and the RPF methodology provides a consistent way in which to evaluate these toxicities relative to one another.

Effects of Acute Exposure to OPs

Illness and injury resulting from acute exposure to OPs, and subsequent cholinesterase inhibition, is well understood. It is also relatively common among agricultural workers. As part of the National Institute for Occupational Safety and Health's (NIOSH) effort to monitor risks from pesticide exposure, the Sentinel Event Notification System for Occupational Risks-Pesticides program was developed in 1998.[6] Data from this program from 10 states over the period of 1998-2005 identified over 3,000 cases of acute pesticide poisonings; the majority of these poisonings were from cholinesterase inhibitors, particularly the OPs chlorpyrifos, methamidophos, dimethoate, malathion, and diazinon.

Beyond the immediate impact of OP poisoning, numerous epidemiologic studies have investigated the long-term sequelae of acute poisoning events. In perhaps the first large scale study, Savage et al. evaluated lasting neurological effects of OP poisoning in 100 matched-pairs of individuals with previous acute poisoning and non-poisoned controls.[7] The mean time between acute exposure and neuropsychological exam was 9 years. This study found differences in intellectual function, academic skills, abstraction and flexibility in thinking, and simple motor skills between these two groups. Another study of poisoned individuals in Nicaragua similarly compared neuropsychological results in poisoned individuals and a matched control group two

years after the poisoning events.[8] This study found lasting differences in verbal and visual attention, visual memory, visuomotor speed, sequencing and problem solving, and motor steadiness and dexterity, using assessments including the WAIS-R digit span and digit symbol test and the Trails A test. Later studies of neuropsychological outcomes in migrant farm workers[9], rescue workers in the Tokyo subway sarin attack,[10] and banana workers in Costa Rica[11] showed similar results.

Long-Term, Low-Level OP Toxicity: Non-Cholinergic Mechanisms

Cholinesterase inhibition is the most well-known, and best understood, mechanism by which OPs exercise toxic effects. However, the level of OP exposure required to result in health effects associated with AChE inhibition is relatively high, and a number of observations from both toxicological and epidemiological studies suggest that the neurotoxicity of OPs may not be exclusively the result of cholinergic effects.[12-14] Notably, AChE knockout mice have been shown to exhibit symptoms of neurotoxicity subsequent to OP exposure, similar to wildtype mice.[15] And, as discussed in detail in subsequent sections, epidemiologic evidence suggests health effects at exposure levels far below those that would result in AChE inhibition.[16-19]

Mechanistically, it is possible that other proteins beyond cholinesterases could be targets for OPs, such as serine hydrolase[20] and carboxylesterases, including those found in serum, in the liver, in the central nervous system, the brain and in the lung.[13] OPs have also been shown to form covalent bonds with tyrosine and lysine even in proteins that have no active serine site.[21] By binding to these non-AChE proteins, and in particular those whose functions are dependent on reversible phosphorylation, OPs may effect inflammatory changes, oxidative stress and, potentially, neurodegeneration.[12,20]

While there is no established scientific consensus on the primary mechanism by which long-term low-level OP exposure leads to non-cholinergic neurotoxicity, induction of inflammation leading to neurological effects is among the most compelling explanations. A dermal study of low-dose chlorpyrifos application to adult mice found that exposures at levels too low to produce significant changes in serum cholinesterase resulted in increased glial fibrillary acidic protein (GFAP) expression in the hippocampal regions.[22] GFAP is a protein responsible for the structural integrity of astrocytes, and a number of studies have shown that GFAP is a sensitive and early biomarker of neurotoxicity.[22] The results of this study indicate that prolonged exposure to low-level OPs can trigger inflammatory responses, even in the absence of AChE inhibition and overt clinical symptoms.[12] There is also further experimental evidence that OPs may interact directly with inflammatory cells. For example, rats exposed to single or repeated subclinical doses of the OP sarin have increases in expression of pro-inflammatory cytokines, including IL-6 and TNFα.[23] Overall, emerging evidence suggests that long-term repeated low-level OP exposure up-regulates inflammatory mediators, through pathways not affiliated with cholinergic response and at levels below which such response would occur.

Effects of Long-Term, Low-Level Exposure to OPs: Occupational Studies

The research on the human health effects of long-term, subacute exposure to OPs provides a less consistent picture than the literature on acute effects. For example, a 1997 study of OP-exposed tree fruit farmers with no history of acute poisoning as compared to non-exposed controls found differences in reaction time, but did not observe differences in tests of concentration, visuomotor skills, or memory.[24] An investigation of neurobehavioral performance of Egyptian cotton crop workers who were exposed to a variety of pesticides including several

OPs found significantly lower performance on tests of working memory and mental processing, including the digit symbol and digit span tests, than unexposed controls.[25] A study of greenhouse planting workers exposed to OPs demonstrated differences in central nervous system function, including reaction times, motor steadiness, tension and fatigue.[26] And a study of sheep dippers exposed to OPs as compared to non-exposed quarry workers found differences in sustained attention and speed of information processing.[27] Meanwhile, a prospective cohort study of chlorpyrifos-manufacturing workers found no differences in any measures of central nervous system dysfunction.[28]

For the most part, existing studies of non-acute occupational exposures have been limited by imprecise exposure assessment. A 2003 study of neurobehavioral performance in Florida farm workers found that having done farm work was associated with poor performance on the digit span, tapping, Santa Ana, and postural sway tests, but this exposure characterization could not quantify OP exposure.[16] Similarly, a study utilizing the World Health Organization's Neurobehavioral Core Test Battery (including digit span, digit symbol and simple reaction time tests) in rural Ecuadorians found significant differences in test scores based on farm membership.[29] However, the "farm member" group was a broad classification, including consumers, field workers and applicators, and this categorization does not inform the magnitude of exposure to OPs among these individuals.

Some of the most recent research on non-acute exposures to occupationally exposed populations has begun to utilize more refined exposure assessments. Rothlein et al. conducted a study of neurobehavioral performance in Hispanic participants who either did or did not work in agriculture.[30] Their exposure assessment included measurement of urinary biomarkers and of OP residues in environmental samples, in addition to occupational class. These researchers found

that the control group displayed better performance on 12 of 16 tests of neurologic performance, including sustained attention, information processing, and motor speed and coordination.

In general, existing epidemiologic literature (summarized in Table I.1) suggests that there may be neurobehavioral impacts of long-term, sub-acute exposures to OPs in occupationally exposed adults, including deficits in working memory, mental processing, sustained attention, concentration and motor skills. However, these studies have often been limited by relatively small samples sizes (typically on the order of 100-200 participants) and many are challenged by lack of precision in the exposure assessment. Studies with larger sample sizes and better exposure assessment are needed, in order to better understand the association between non-acute OP exposure and health effects.

Effects of Long-Term, Low-Level Exposure to OPs: Non-Occupational Studies

In addition to the extensive body of work on occupational exposure to OPs, more recent studies examine the potential health effects of low-level OP exposures to children. This area of research first focused on children living in agricultural communities. A 2005 study by Rohlman et al. found that children living in agricultural communities had poorer performance on measures of response speed and latency as compared to those children living in non-agricultural communities, and concluded that the observed differences were consistent with the functional effects seen in adults exposed to low concentrations of OPs.[31] A later study of the relationship between OP exposure and neurobehavioral outcomes in a population of children living in an agricultural community in southern Arizona also found a weak association between measures such as speed of attention, sequencing, and mental and conceptual flexibility as compared to controls.[32] However, this study was limited by the fact that exposure was assessed using single

spot urine samples, and the previously defined exposed and non-exposed groups were not consistent with these spot urine sample results.

Several other more recent prospective cohort studies have examined the impact of maternal exposure to OPs on child neurodevelopment. In the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study, a prospective birth cohort recruited between 1999-2000 and aimed at studying the association of pesticides and other environmental agents on the health of pregnant women and their children, researchers found that prenatal maternal urinary metabolite levels of OPs were significantly associated with attention problems and attention deficit/hyperactivity disorder (ADHD) in children at 5 years of age.[33] Within this same cohort, prenatal maternal urinary metabolite levels were associated with poorer intellectual development in these children when they reached 7 years of age.[19]

Two other cohort studies of childhood outcomes related to prenatal exposures were conducted in nonagricultural settings. In the Mount Sinai Children's Environmental Health Cohort study, researchers investigated the relationship between maternal exposure (as assessed by urinary metabolites collected in the third trimester and prenatal maternal blood) and mental development in children at one year of age and at 6-9 years of age.[17] Cognitive development, and particularly perceptual reasoning, was found to be inversely associated with prenatal exposure. Similarly, in the Columbia Center for Children's Environmental Health study, prenatal chlorpyrifos exposure was assessed using umbilical cord blood plasma, and was found to be associated with deficits in both memory and intelligence quotient (IQ) at later timepoints.[18]

Researchers have also evaluated the relationship between neurobehavioral outcomes and OP exposure to children (as opposed to in prenatal maternal samples). In the CHAMACOS study, a 10-fold increase in urinary OP metabolites in children at age 5 was associated with a

doubling of the odds of ADHD.[33] However, this association was weaker and less consistent than the association with prenatal exposure. Using data from the National Health and Nutrition Examination Survey (NHANES) from 2000-2004, Bouchard et al. conducted a cross-sectional analysis of OP metabolites in urine samples collected from a nationally representative sample of 1,139 children aged 8 to 15 years.[34] Children with higher metabolite levels were significantly more likely to be diagnosed with ADHD than children with lower exposure. These studies are summarized in Table I.2.

OP Exposure in the General US Population

Overall, the data on the human health effects of exposure to OPs are conclusive with regard to acute, high-level exposure. The effects of low level pre- and post-natal exposure to children, both in agricultural communities and in the general population, are also fairly consistent. The neurological and cognitive effect of low-level exposure to adults – and particularly adults without occupational exposure – remains unknown.

We do know that these exposures are prevalent. In 2011, Barr and colleagues published the results of a comprehensive effort to characterize OP exposure in the general population as part of NHANES.[35] Urinary OP biomarkers were analyzed in nearly 7,500 samples collected over three two-year cycles of the NHANES study, from 1999-2004. While this work showed that OP exposures are on the decline – likely attributable to the passage of the Food Quality Protection Act of 1996 – the authors still found detectable levels of OP metabolites in a majority of the urine samples. Of note, potentially sensitive subpopulations including both adolescents and older adults had the highest levels of exposure.

Diet is one potentially important route of OP exposure to the non-occupationally exposed US population. OP residues can be present on food items at point-of-sale locations (e.g., grocery

stores) at the time that food is purchased by consumers. This is demonstrated by comprehensive residue data collected by the United States Department of Agriculture (USDA). In 1991, the USDA's Agricultural Marketing Service began implementation of a program to collect data on pesticide residues in foods, called the Pesticide Data Program (PDP).[36] Since then, the PDP has repeatedly tested over 95 different commodities, including fresh, frozen and canned fruit and vegetables, fruit juices, dairy products, grains, corn syrup, nuts, peanut butter, honey, poultry, beef, pork, catfish and various water sources for residues of more than 450 pesticides, including all of the OPs registered for use in the US or for which there are tolerances on imported items. These data are accessible in publically available electronic databases, which include nearly 2 million records per year, and represent perhaps the best available estimates of pesticide residue levels on food items at the time that they are purchased by consumers.

PDP samples are collected by eleven participating states, which represent all US regions and about 50% of the nation's population.[37] Sample collection occurs regularly throughout the year, and is intended to represent purchases made by consumers. Once selected, samples are shipped to central laboratories where they are prepared emulating consumer practices (washed, with inedible portions removed). The EPA's 2006 CRA[2] employed PDP data collected from 1994-2004, and determined representative distributions of OPs on 44 commodities (primarily fresh, frozen and canned fruits and vegetables). At least one OP was detected in 91% of the commodity types analyzed.

Given the presence of OP residues on food items at the time of consumption, and the cancellation of residential uses of OPs, it follows that diet may be the most significant and perhaps the only OP exposure route for non-occupationally exposed individuals, particularly for those who do not live in agricultural communities. This is consistent with the findings of the

EPA's 2006 CRA[2] and with some of the more sophisticated findings from the NHANES analysis of urinary OP biomarkers in the US population.[35] The authors of the NHANES study observed high correlations among several of the biomarkers measured, suggesting common pathways for both exposure and excretion. Because the biomarkers represented exposure to compounds that are unlikely to be sprayed together in non-agricultural settings, they concluded that this correlation points to dietary exposures from produce on which both groups of pesticides are used regularly.[35] The hypothesis that diet is responsible for a significant portion of OP exposure is further supported by studies examining predictors of urinary OP biomarker concentrations. The number of daily servings of produce consumed (in general, or as specific items such as apples or apple juice) is reliably found to be associated with OP exposure.[38,39]

Effects of Organic Food Consumption on OP Exposure

If diet is responsible for the majority of OP exposure in most Americans, consumption of foods grown without the use of OPs should have a significant impact on total exposure. The National Organic Program of the USDA permits food to be certified "organic" when grown without use of specified pesticides and synthetic fertilizers, including OPs.[40] In keeping with the theory that diet is an important route of OP exposure to the general population, several studies have shown that consumption of organic food, and particularly organic produce, can significantly reduce total OP exposure.[41-43] In the first study to examine the influence of organic diets on OP exposure, we assessed OP metabolite levels in 24-hr urine samples from children with organic and conventional diets.[41] We found that children with conventional diets had 9 times higher average levels of OP metabolites in their urine than children with organic diets.

Following our small study, Lu and colleagues conducted an elegant intervention study in which they repeatedly measured metabolite levels in a group of 23 children with conventional

diets.[43] The researchers then introduced an organic diet and continued to monitor the OP biomarkers. They found that the median urinary concentrations of the metabolites decreased to below the detection limit immediately after the introduction of organic diets and remained undetectable until conventional diets were reintroduced. Primarily on the basis of these studies, the American Academy of Pediatrics released a report concluding that organic diets expose consumers to fewer pesticides associated with human disease.[44]

These studies suggest that substitution of organically grown foods is a successful strategy for reducing dietary exposures to OPs. It is worth noting that food items labeled "organic" are not always found to be completely free of pesticide residues. In a study of pyrethroid and OP residues in composite diet samples from adults in Georgia, 47 of the samples were described by the study participants as organic.[45] However, half of these samples were found to contain one or more of the pesticides measured, albeit at lower concentrations. The authors describe their findings as consistent with the work of Baker et al., who compared pesticide residues in foods either grown conventionally, grown using integrated pest management techniques, or grown organically.[46] In this study, approximately a quarter of the food items labeled as organic were found to contain at least one pesticide at a detectable level, as compared to approximately three-quarters of those with no market claim (and thus most likely conventionally grown). Thus, while it is still possible for food labeled "organic" to contain pesticide residues, measurement of these residues on organic food is far less frequent and typically in lower concentrations than on conventional food.

Study Aims

The primary goal of this dissertation was to develop a novel means of predicting long-term dietary exposures to OP pesticides by combining information on individual dietary habits with average pesticide residue levels on food. This methodology was intended to be an improvement over other exposure assessment methods, and specifically was developed: 1) to allow quantification of risk from OP exposure; 2) to be representative of appropriate timeframes of exposure; 3) to be transferable across populations and pesticide classes; and 4) to be relevant for epidemiologic analyses. We then aimed to assess the face validity of this new method by evaluating its comparability with urinary dialkylphosphate biomonitoring in a subset of participants. Finally, we aimed to employ these new estimates in an epidemiologic analysis in which we assess the relationship between estimated long-term dietary OP exposure and results of a battery of tests reflecting different cognitive domains, accounting for relevant confounders and potential effect modifiers.

Study Population

This project utilizes data collected in the Multi-Ethnic Study of Atherosclerosis (MESA) to evaluated the aims in this study. MESA, sponsored by the National Heart, Lung, and Blood Institute (NHLBI) in 1999, was designed to investigate the prevalence, correlates and progression of subclinical cardiovascular disease in a multi-city, multi-ethnic population-based cohort.[47] MESA includes 6,814 participants from six US communities: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County (Winston-Salem), North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota (see Figure I.2). Participants were recruited by staff at "field centers" in each area, each based out of

a local university, using random-digit dialing, door-to-door visits and brochures mailed to households in targeted areas. MESA participants were aged 45 to 84 years at enrollment, with an approximately equal gender ratio. Four racial/ethnic groups were targeted for inclusion and the recruitment protocol required overlapping ethnic groups among communities. The MESA cohort is 39% non-Hispanic Caucasian, 28% African American, 22% Hispanic, and 12% Chinese. Selected demographic and socioeconomic characteristics of this cohort at enrollment are shown in Table I.3.

The structure of MESA is similar to that of other large cardiovascular cohort studies. Repeated clinical exams are scheduled at approximately two year intervals, and are supplemented with follow up phone calls, the primary function of which is to ascertain information about clinical cardiovascular disease events (e.g., acute myocardial infarction, congestive heart failure, etc.). The first clinical exam ("Exam 1") occurred between July 2000 and July 2002, and the fifth clinical exam ("Exam 5") occurred between April 2010 and April 2012. During each exam, participants provided extensive interview data, including medical history, personal history, demographics, and information on socioeconomic status (SES), medication use, and physical activity habits. They also completed anthropometry measurements, blood pressure readings, and provide blood samples. Additional tests occurred at some, but not all, visits, including electrocardiography, flow-mediated brachial artery endothelial vasodilation, carotid ultrasound, cardiac magnetic resonance imaging (MRI), and cardiac computed tomography (CT) scanning. Follow-up phone calls took place every nine to twelve months, and in addition to documenting clinical events, interviewers recorded changes in health status, including hospitalizations, nursing home admissions, or diagnoses of new cardiovascular conditions which were followed-up for ascertainment of events.

Components of the exams with most relevance to this project were collected at MESA Exam 5. These include a food frequency questionnaire (FFQs), collection of a urine sample, and a battery of cognitive tests, including the Digit Symbol Coding Test (DSCT), the Forwards and Backwards Digit Span Tests (FDST and BDST) and the Cognitive Abilities Screening Instrument (CASI). In addition to asking about food and beverage intake, the FFQ also included questions about the frequency with which they consumed organic food. Each of these components will be discussed in more detail in the following chapters.

Summary of Chapters

The analyses described in the following chapters make use of the rich set of demographic and socioeconomic data, dietary information and cognitive outcomes available in MESA. Because organic food consumption has the potential to play such a critical role in dietary OP exposure, we first conducted a comprehensive analysis of the individual- and neighborhood-level characteristics that may influence the frequency with which organic food is consumed (Chapter II). We then employed a combination of individual dietary intake data from Food Frequency Questionnaires, OP residue data from national databases, and self-reported information on organic food consumption to estimate long-term dietary OP exposure within the MESA cohort (Chapter III). Finally, we conducted an epidemiologic analysis of the relationship between long-term dietary OP exposure and cognitive outcomes, accounting for the individual- and neighborhood-level variables previously found to be associated with organic food consumption (Chapter IV). Ultimately, this work provides new information about the factors associated with organic food consumption, demonstrates a novel means of estimating an important and widespread environmental exposure, and provides additional insight on the health effects of long-term, low-level exposure to OPs.

Tables and Figures

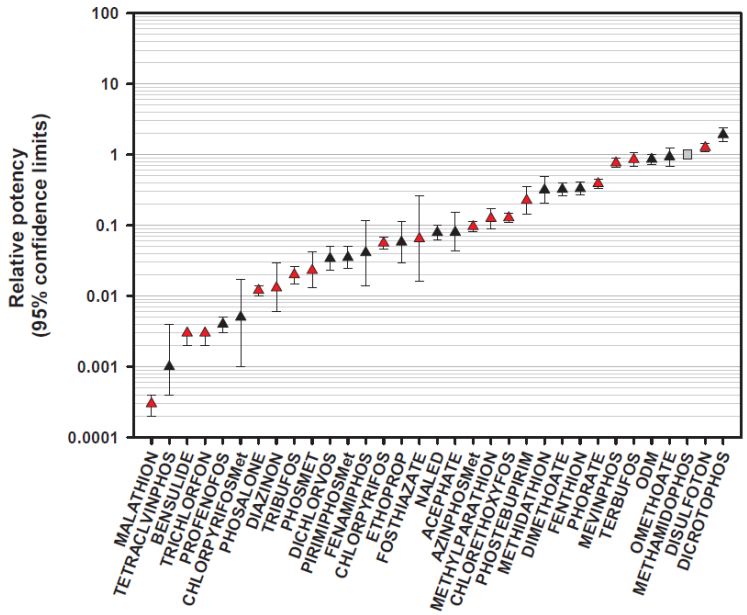

Figure I.1. Relative potency factors for oral ingestion of 33 OPs considered in the EPA's Organophosphorus Cumulative Risk Assessment – 2006 update.

Table I.1. Summary of epidemiologic results of occupational exposure to OPs on neurological and cognitive outcomes in adults.

Reference	Population	Exposure Assessment	Results*		
			Digit span	***Digit symbol***	***Other tests***
Daniell et al. 1992 [48]	Apple orchard pesticide applicators	Comparison with slaughterhouse workers	-	+	No other differences observed
Stephens et al. 1995 [27]	Sheep dippers in the UK	Comparison with quarry workers	-	+	Differences observed in processing speed and attention, but not memory or learning
Cole et al. 1997 [29]	Rural Ecuadorian farmers	Comparison with controls in the local population	+	-	Differences observed in several neurobehavioral tests, esp. visual-spatial tasks
Fiedler et al. 1997 [24]	Tree fruit farmers	Comparison with berry growers, store owners	-	-	Differences observed in reaction time, but not concentration, visuomotor skills, or memory
Bazylewicz-Walczak et al. 1999 [26]	Greenhouse workers	Measures of levels of OPs in air, skin, and clothes	-	-	Differences in reaction times and motor steadiness observed
Farahat et al. 2003 [25]	Egyptian cotton crop workers	Comparison with clerks, administrators	+	+	Differences also observed in tests of visual attention, task switching and vocabulary
Kamel et al. 2003 [16]	Florida farmworkers	Comparison with controls in the local population	+	-	Differences also observed in tests of psychomotor function and balance, but not sensory or motor function
Rothlein et al. 2006 [30]	Hispanic immigrant farmworkers	Urinary metabolites, OPs in dust, work practices	+	-	Poorer performance by farmworkers on most tests, though few were statistically significant

*A "+" indicates a statistically significant difference on this test based on exposure to OPs; a "-" indicates that such an association was not found.

Table I.2. Summary of epidemiologic results of non-occupational exposure to OPs on neurological and cognitive outcomes in children.

Reference	Population	Exposure Assessment	Results
Rohlman et al. 2005 [31]	Children in agricultural communities in North Carolina and Oregon	Comparison with controls from non-agricultural communities	Significantly poorer performance on studies of response speed and latency
Lizardi et al. 2008 [32]	Children in agricultural communities in Arizona	Urinary dialkylphosphate levels at age 7	Non-significant decrease in speed of attention, sequencing, mental flexibility, visual search, concept formation and conceptual flexibility
Marks et al. 2010 [33]	Mother-child pairs in the Salinas Valley, CA	Prenatal and child urinary dialkylphosphate levels	Significant increase in ADHD at 5 years
Bouchard et al. 2010 [34]	Nationally representative sample of children (NHANES)	Urinary dialkylphosphate metabolite levels in spot urines from children	Significant increase in ADHD at 8 to 15 years
Bouchard et al. 2011 [19]	Mother-child pairs in the Salinas Valley, CA	Prenatal urinary dialkylphosphate levels	Significant decrement in cognitive development (IQ) at 7 years
Engel et al. 2011 [17]	Mother-child pairs in New York (Mt. Sinai)	Prenatal urinary dialkylphosphate levels	Significant decrement in cognitive development (IQ) at 12 months and 6-9 years
Rauh et al. 2011[18]	Mother-child pairs in New York (Columbia)	Prenatal urinary levels of chlorpyrifos metabolites	Significant decrement in cognitive development (memory and IQ) at 7 years

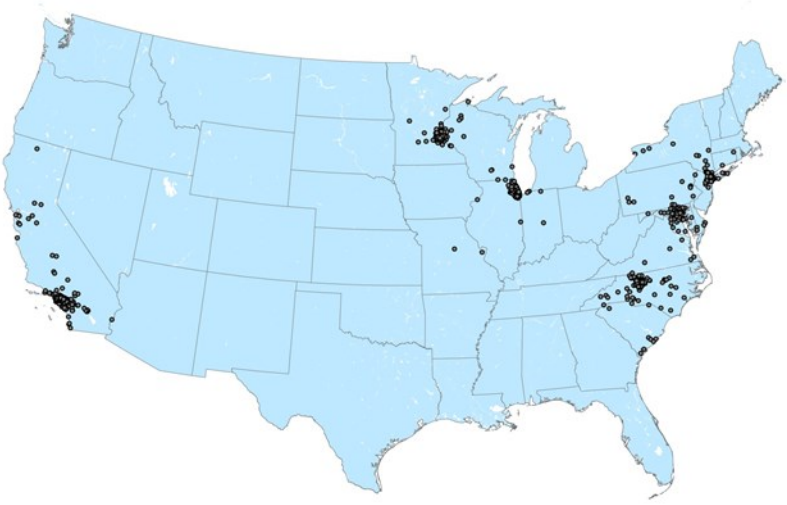

Figure I.2. Residential locations of MESA participants at enrollment.

Table I.3. Demographic, socioeconomic, and health characteristics of the MESA cohort at enrollment.

	MESA Population
n	*6814*
Sex	
Female	3601 (53%)
Male	3213 (47%)
Race/Ethnicity	
White	2622 (38%)
African-American	1893 (28%)
Hispanic	1496 (22%)
Chinese	803 (12%)
Age at enrollment (years)	
≤59	2915 (43%)
60-69	2075 (30%)
70-79	1536 (23%)
≥80	288 (4%)
Socioeconomic status indicators	
≥ High school education	5566 (82%)
Currently married	4119 (61%)
Family income ≥$30,000	4090 (63%)
Health status	
Body mass index (kg/m^2), median (std dev)	27.6 (5.5)
Diabetes Mellitus[a]	859 (13%)

[a]Defined either as treated diabetes or fasting glucose >125 mg/dL.

End Notes

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CHAPTER II. Organic Produce Consumption, SES and the Local Food Environment

Background

The National Organic Program (NOP) of the United States Department of Agriculture (USDA) permits food to be certified "organic" when grown without the use of specified pesticides and synthetic fertilizers.[1] In the US, sales of organic food have grown steadily in the past two decades, from $1 billion in 1990 to $26.7 billion in 2010.[2] Little research to date has examined the direct effect of organic food consumption on health,[3] but several studies have shown that consumption of organic food, and particularly organic produce, can significantly reduce pesticide exposure.[4-6] The American Academy of Pediatrics recently released a report concluding that organic diets expose consumers to fewer pesticides associated with human disease.[7] This conclusion was based, in part, on several studies of pesticide exposure in children and pregnant women that suggest even relatively low exposures to certain agricultural pesticides may be associated with developmental, neurological and cognitive effects, such as decreased gestational age at birth and birth weight, and increased attention deficit-hyperactivity disorder and decrements in memory and IQ.[8-13] Choice of organic food is also an opportunity to support farming practices that can reduce risks to farmworkers and promote ecological health.[7,14]

Everyone may not have equal access to organic food, and thus may not have equal ability to make these choices. Organic food is more expensive than conventionally grown food, and it is not equally available in all communities. Research suggests that residents of neighborhoods with better access to healthy foods tend to have healthier diets.[15] We hypothesize a parallel with respect to organic food consumption – specifically, we hypothesize that residents of neighborhoods with better access to organic food may be more likely to eat organic food.

The purpose of this study was to examine the relationship between organic produce consumption and individual demographic and socioeconomic factors including sex,

race/ethnicity, age, income, education, metropolitan area and employment status in a multi-city, multi-ethnic cohort. We further explored the relationship between organic produce consumption and three complementary measures of the local food environment intended to represent food accessibility: 1) geographic information system (GIS) based supermarket density, 2) self-reported assessments, and 3) aggregated survey responses of independent informants.

While this work is valuable in its own right, it also has other implications in the context of this dissertation. A growing body of research indicates the importance of an individual's neighborhood on a variety of health outcomes,[16,17] and if these neighborhood-level characteristics are also related to organic food consumption habits, they have the potential to act as confounders in epidemiologic studies of the health effects of dietary exposure to pesticides. Thus, it is critical that we understand both the individual- and neighborhood-level characteristics associated with organic food consumption.

Methods

This cross-sectional study investigates the frequency with which participants in the Multi-Ethnic Study of Atherosclerosis (MESA, previously described in detail in Chapter I) consume organic fruit, fruit juice and vegetables ("organic produce"). All participants attending MESA Exam 5 (2010-2012) were asked to complete a Food Frequency Questionnaire (FFQ) that documented eating habits over the previous year and included items about organic produce consumption. Specifically, participants were asked "If you eat fresh fruit or drink fruit juice, how often is that fruit or fruit juice 'organically grown' (fruit or fruit juice with a 'USDA Organic label', purchased locally from an 'organic farm' or grown without pesticides in a home garden)?" and "If you eat fresh vegetables, how often are those vegetables 'organically grown' (vegetables with a 'USDA Organic' label, purchased locally from an 'organic farm', or grown

without pesticides in a home garden)?" Response options were "Seldom or Never", "Sometimes", and "Often or Always". * For this analysis, participants who reported that they sometimes, often or always ate either organic fruit or organic vegetables were categorized as "organic consumers", and those who reported that they seldom or never ate organic fruit and organic vegetables were categorized as non-consumers. A separate, secondary analysis restricted the definition of organic consumers just to those who reported they "often or always" consumed organic fruit and organic vegetables.

Individual-Level Variables

We hypothesized that organic consumption habits were associated with individual-level factors, including sex, age, race/ethnicity, metropolitan area, marital status, per capita income (total household income divided by number of persons living in the household), education, and employment status.

Neighborhood-Level Variables

We also hypothesized a relationship between organic consumption habits and characteristics of the local food environment, after controlling for individual-level variables. Specifically, we hypothesized that organic produce was more likely to be consumed by individuals living in areas with more supermarkets and in neighborhoods where there is a perception of a larger selection of produce in general. These measures were developed by the

*One other option was required by the structure of this form: participants could also answer "I do not eat the food". This was necessary to fit into the existing FFQ table, but is admittedly confusing. Ideally, this would only be checked in the rare case where a participant never eats fruit or fruit juice, or vegetables. However, a number of participants (n=707) who did report eating produce in previous parts of the FFQ did select this option. In this analysis, and in the analysis presented in Chapter III, these participants were grouped with those who said they "rarely or never" ate organic produce, based on the assumption that they meant "I do not eat organic food". However, it does indicate that these participants may not have fully understood the question, and they were later excluded from the primary analysis presented in Chapter IV (but included in a sensitivity analysis).

MESA Neighborhood Study, an ancillary study to MESA that characterized the local food environments of MESA participants.[18,19] Each measure is described here.

The first measure of the local food environment was a GIS-based calculation representing the density of supermarkets within 1 mile of participants' homes. The density of supermarkets was determined using data obtained from the National Establishment Time Series (NETS) database from Walls and Associates.[20] Additional supermarket data was obtained from Nielsen/TDLinx to enhance the identification of supermarkets.[21] Supermarkets were defined as grocery stores (SIC code #5411) with at least $2 million in annual sales or at least 25 employees. Participant addresses were geocoded using TeleAtlas EZ-Locate web-based geocoding software,[22] and simple densities per square mile were created for 1-mile buffers around each address using the point density command in ArcGIS 9.3.

The second measure was each participant's self-report of the selection of fruits and vegetables available in his or her neighborhood, defined as the area within approximately 1 mile of his or her home ("MESA self-reports"). At MESA Exam 5, participants were asked the extent to which they agreed with the statement "A large selection of fresh fruits and vegetables is available in my neighborhood", and responses were coded on a five-point Likert scale (strongly agree; agree; neutral; disagree; and strongly disagree).

The third measure, the Aggregated Neighborhood Survey (ANS), was constructed by aggregating responses of multiple respondents residing in each participant's census tract (as a proxy for neighborhood). Survey respondents used in the calculation of the ANS included other MESA participants living within a given census tract as well as other residents in those census tracts who were included to increase the sample size in areas with few MESA respondents.[23] This supplementary survey was conducted on a random sample of residents in selected tracts

identified through address-based sampling methods. Availability of healthy food was ascertained based on responses to three survey items: "A large selection of fresh fruit and vegetables is available in my neighborhood", "A large selection of low-fat food is available in my neighborhood", and "The fresh fruits and vegetables in my neighborhood are of high quality", with responses coded on five-point Likert scales.

Conditional empirical Bayes estimates, which borrow information across all tracts in order to increase reliability, were derived from three level hierarchical linear models to account for the nested structure of the data.[23] More specifically, these metrics were calculated using a 3-level mixed model, where Level 1 is census tract, Level 2 is person, and Level 3 is question. This model included random effects for census tract and person, adjusted for person-level age and gender (in Level 2) and neighborhood-level study site (in Level 1). This then creates an adjusted mean score for each census tract by taking the overall mean (e.g., the fixed effects intercept from the model) and adds to that the error term for each census tract output from the random census tract effects. While somewhat complicated, this method has several advantages. For census tracts where there are few participants, the crude mean on its own might not be reliable, but this modeling approach adjusts the mean to be more like other census tracts with similar characteristics. In addition, for census tracts in which the respondents are not well-represented by the overall sample, this method adjust the means to account for these differences.

Statistical Analyses

For the analysis of the association between organic food consumption and individual-level demographics and SES, we first conducted bivariate comparisons, using either chi-squared tests or log-binomial regression. We then included the full set of individual-level variables in a log-binomial regression to model the association with organic consumption. Log-binomial

models were used in the primary analysis due to the relatively high prevalence of sometimes, often or always consuming organic produce (40%) and are not rare events. Individual-level variables found to be statistically significant in the full model were included in subsequent analyses of organic consumption and the local food environment. In the secondary analysis, where the outcome was the smaller set of individuals who reported they "often or always" consumed organic food (5%), we employed logistic regression models.

The relationship between each measure of the local food environment and organic consumption was evaluated separately with and without control for individual-level variables. For each of these measures, we also examined the impact of including a random intercept for census tract. In sensitivity analyses, we examined the effect of stratification by education and income category in the individual-level analyses. All analyses were conducted in SAS v9.3 [Cary, NC].

Results

Of the original MESA cohort (n=6,814), 4,466 (66%) participated in Exam 5 and completed the questions related to organic food consumption on the Exam 5 FFQ. Complete individual-level demographic and socioeconomic data were available on 4,064 of these participants. Overall, 204 (5%) reported "often or always" eating both organic fruit and organic vegetables, 1,440 (35%) reported that they "sometimes" ate organic fruit and/or organic vegetables, and 2,420 (60%) "seldom or never" ate organic produce.

Organic Produce Consumption and Individual-Level Variables

Table II.1 shows descriptive individual-level statistics by reported organic consumption habits. In bivariate analyses, organic consumption was significantly more common among

women, younger individuals, and those currently employed. Metropolitan area was also significantly associated with organic consumption, as were higher per capita household income and education.

Table II.2 shows the associations between individual-level variables and organic consumption in a multivariate log-binomial regression model including all variables with statistically significant bivariate associations. Race/ethnicity was also included because of the importance of this variable in the MESA cohort and to diet in general. After accounting for other individual-level factors, women were more likely to be organic consumers than men (prevalence ratio [PR]: 1.21, confidence interval [CI]: 1.12 – 1.30, $p<0.0001$). Chinese participants were less likely than other participants to be organic consumers, though this difference was not large and overall, race/ethnicity did not show a statistically significant effect ($p = 0.23$). Age was highly associated with organic consumption; for every +10-year increment in age, there was a 13% reduction in the likelihood of being an organic consumer.

Metropolitan area was also significantly associated with organic consumption in this cohort; participants living in more populated cities (Chicago, LA and New York) were more likely to be organic consumers compared to those living in Winston-Salem, Baltimore and St. Paul. Education was found to be an important predictor: being in the highest (graduate school) versus the lowest (less than high school) education categories was associated with a 68% greater likelihood of organic consumption.

Being in the highest income category compared to the lowest (per capital household income of <$14,999 versus >$45,000) was associated with a 10% greater likelihood of organic consumption, but the overall relationship between organic food consumption and per capita household income was not statistically significant ($p = 0.06$), and higher income was not always

associated with greater consumption. For example, participants with per capita household income between $15,000 and $25,000 were less likely to consume organic produce than those in the <$15,000 category. Employment status was not associated with organic consumption in multivariable analyses. Results were not sensitive to stratification of the sample; prevalence ratio point estimates were similar when restricted to just those participants in the lower and higher education and income brackets.

Organic Produce Consumption and the Local Food Environment

Of those participants included in the individual-level analyses, 84% (n= 3,428) consented to MESA Neighborhood and had complete data for the neighborhood-level analyses. The distribution of demographic and socioeconomic characteristics between this group and those shown in Table II.1 is nearly identical (data not shown). Table II.3 shows the frequency of organic consumption among these participants by each measure of the local food environment. In bivariate analyses, whether measured by self-report, supermarket density, or ANS score, participants for whom accessibility was greater were more likely to be organic consumers.

This association remained in fully adjusted models as well (Figure II.1). After adjusting for individual-level variables, self-reported produce availability within a participant's neighborhood was positively associated with organic consumption; each unit increase on the Likert scale, was associated with a 7% greater likelihood of eating organic food (PR: 1.07, CI: 1.02 – 1.11, p = 0.002). The ANS score analysis also suggested an effect of local food environment on organic consumption; the likelihood of being an organic consumer was 8% higher per interquartile change in score (0.5 units) (PR: 1.08, CI: 1.00 – 1.17, p = 0.05). The GIS-based supermarket density measure was not significantly associated with organic consumption after control for individual-level variables, though the direction of the effect was

unchanged (PR: 1.02, CI: 0.99 – 1.05, p=0.16). Inclusion of a random intercept for each census tract did not substantially modify estimates or standard errors in any of the three models. All individual factors associated with organic consumption remained significant with the inclusion of the measures of the local food environment.

Frequent Organic Consumers

While the primary analysis aimed to understand the factors associated with the decision to consume organic produce at least occasionally, this secondary analysis explored the question of whether individual and local food environment factors were associated with more frequent organic produce consumption. Here, the definition of organic consumers was restricted to those who reported that the fruit and vegetables they ate were "often or always" organic. In general, the relationships between this more frequent organic produce consumption and individual-level factors were similar to those reported in the primary analyses. In fully adjusted models of individual factors, women, younger individuals, participants in more urban metropolitan areas, and those with higher levels of education were all more likely to "often or always" consume organic produce, as was the case in the primary analysis. Race/ethnicity and marital status were not significantly associated with organic produce consumption. Per capita household income was significantly associated with "often or always" consuming organic produce ($p = 0.04$), but the relationship was not linear. Instead, those in the lowest and highest income groups were more likely to report that they "often or always" consumed organic produce, and those in the middle income groups were significantly less likely to be frequent organic produce consumers.

In contrast to the results of the primary analysis, the local food environment was not associated with the decision to "often or always" consume organic produce. Though density of supermarkets within 1 mile of the residence remained strongly associated with organic produce

consumption in bivariate analyses (p = 0.0002), aggregated neighborhood survey and self-report of accessibility were no longer significantly associated (p = 0.09 and p = 0.17, respectively). Furthermore, once individual-level variables were accounted for in a fully adjusted model, no significant relationship was found between "often or always" consuming organic produce and any of the measures of the local food environment (supermarket density: OR = 1.05, CI= 0.95-1.17; self-report: OR= 1.00, CI= 0.85-1.17; ANS Score: OR = 1.01, CI = 0.52-1.98).

Discussion

To our knowledge, this is the first study to examine the associations of both individual and neighborhood characteristics and organic food consumption. We found that both were associated with this dietary choice. Women, younger individuals, those with higher education, and those living in more urban cities were more likely to consume organic produce. Neither race/ethnicity nor per capita household income was significantly associated with organic produce consumption. We found that characteristics of the local food environment, including both supermarket density and individual and community perceptions of produce availability, were associated with the decision to consume organic produce at least occasionally.

Individual-Level Findings

Organic food consumption is increasing; consistent with our findings, several studies over the past decade have reported that 40 to 50% of individuals and households purchase organic food at least occasionally.[24-28] However, the specific factors associated with organic food consumption have not been well understood, and early studies had contradictory findings regarding the socioeconomic status and demographics of organic food consumers.

Organic food consumption has been found to be associated with higher education,[29,30] lower education,[31] or not associated with education at all.[32] Results have also been mixed for the relationship between income and organic food. Some studies observed consumers with high incomes to have less tolerance for food with blemishes and to be less likely to purchase organic food,[30] while others found people with higher income to be more likely to make organic purchases,[29,31] and others found no association.[32,33] Findings with respect to age and ethnicity have also been inconsistent; in fact, the only demographic attribute to be reliably associated was sex, with women purchasing more organic food than men.[29,31,32] However, all of these studies employed convenience samples, and typically included people who were already shopping at either food cooperatives or at expensive specialty grocers, missing substantial segments of the general population. More recent research has capitalized on Nielsen Consumer Panel studies, in which thousands of American households are provided handheld scanners to scan each item they purchase.[25,28,34] These studies have consistently found higher income and education to be associated with purchasing organic food, but age and race/ethnicity have continued to show varying effects.

Our results are consistent with previous research showing that women purchase organic food more frequently than men, and with the Nielsen Consumer Panel studies' observation that higher education is associated with more organic food purchasing. In MESA, older participants were less likely than younger participants to consume organic food. However, since all participants in this study were aged 45 and older, this result could also be consistent with a "U-shaped" relationship between age and organic consumption, in which middle aged people are more likely to consume organic food than both younger and older individuals, as other researchers have suggested.[35]

The relationship between per capita household income and organic produce consumption was sensitive to adjustment for other individual level variables, and to the categorization of organic consumers. In bivariate analyses, self-report of either "sometimes" or "often or always" consuming organic produce was strongly associated with income category, but the strength of this relationship was attenuated by adjustment for other individual level factors. When restricted to individuals who "often or always" consumed organic produce, the relationship with income was decidedly non-linear; individuals with the lowest and highest per capita household incomes were more likely to report frequent consumption of organic produce.

To our knowledge, this is the first study to examine geographical differences in organic food consumption; we found participants in more populated cities (Los Angeles, Chicago, and New York) to consume more organic food than those in less densely populated regions (St. Paul, Winston-Salem and Baltimore). This difference may also be related to the local food environment and food access; more research is needed to fully understand the relationship between organic food consumption and urbanicity.

Local Food Environment Findings

Over the past decade, the US obesity epidemic – and in particular, disparities in obesity prevalence – has led the public health community to think more broadly about factors influencing diet. No longer are dietary motivations understood only in the framework of individual lifestyle choices. Instead, the food environment has been increasingly recognized as important to diet,[15,19,36-40] and the results of this work are consistent with the idea that this environment influences a variety of dietary choices.

While this is the first study to explicitly investigate the relationship between the local food environment and organic consumption, it is not the first study to look at factors beyond

individual-level demographics and socioeconomics on this dietary choice. Zepeda and colleagues explored the motivations behind organic food consumption in a national survey of nearly 1,000 US adults.[24,41] When variables related to personal beliefs and habits were considered, organic food consumption was not found to be associated with direct economic variables, such as household income or weekly food expenditures. Instead, the important factors in choosing organic food included both perceptions about the healthfulness of organic food and opportunity, where opportunity was defined as shopping at food venues where organic food was more likely to be available. This represents a somewhat different approach to exploring the influence of food accessibility on organic consumption, but the results are consistent with our finding that access may play an important role in the decision to at least occasionally consume organic foods.

The results from our secondary analysis of the characteristics of frequent organic consumers support the notion that additional factors – possibly factors like personal beliefs and perceptions – may drive the decision to often or always consume organic food. This relatively small group of people may be willing to go out of their way to make this dietary choice, even if produce and supermarkets are not readily available in their neighborhoods.

Limitations

A primary limitation of this study was the lack of a direct measure of organic food availability. Instead, we employed supermarket density and both self-report and community perception of availability of produce and healthy food as proxies for organic food availability. The USDA's 2009 report, "Marketing US Organic Foods: Recent Trends from Farms to Consumers" shows that sales of organic food from conventional supermarkets and groceries now account for 46% of the total organic market share, with natural-products retailers and direct markets each accounting for another 44% and 10%, respectively.[42] This report also states that

organic food is now available in more than 80% of all supermarkets. Given the high proportion of supermarkets in which organic food is available, we believe that it is reasonable to assume that areas with more supermarkets (as opposed to, say, convenience stores) are also more likely to provide greater access to organic food. In addition, it follows that organic produce is more likely to be available in areas with a greater selection of produce in general. However, further research in this area, including more specific measures of organic food availability, is warranted.

As recent reports in the literature have shown that subjective and objective measures of the local food environment do not always agree,[29,43] we investigated three complementary measures of the local food environment, each with strengths and weaknesses. Supermarket densities are the most objective of the three but rely on the assumption that supermarkets offer organic foods. Further, the use of supermarket density within a straight-line distance neglects actual travel patterns along road networks and further assumes that people reliably shop at supermarkets near their homes. Recent research by Drewnowski et al. suggests that this assumption may not accurately reflect actual shopping patterns.[44] Self-reports reflect each individual's perceptions but their interpretation is affected by the possibility of same source bias, which may arise if a person's behavior affects their reported perceptions of access to healthy foods. The strength of the aggregate survey measure is that averages of multiple respondents are likely to eliminate the influence of individual subjectivities and eliminate the possibility of same–source bias. However, it may not accurately reflect access for a particular participant. The consistency of associations across the three types of measures increases confidence that the local food environment plays a role in organic produce consumption habits.

In this study, we chose to focus on produce rather than other food types. This was intended to be consistent with previous studies evaluating the relationship between consumption

of organic food and organophosphate pesticide exposure,[4] which is the focus of this dissertation. Over 33 million pounds of organophosphates are applied annually in the US – more than any other class of insecticides – and their metabolites are found in the urine of a majority of the US population.[45] These compounds are registered for use on a wide variety of fruits and vegetables, but are not widely used in the production of meat or dairy.[46] We do not expect that this decision to focus on produce had a large impact on our results, as recent USDA research shows that US retail sales of organic fruits and vegetables are larger than all other organic food categories combined.[42] Nonetheless, it is worth noting that there are several other categories of organic food not considered here, such as dairy, meat and grains.

Conclusions

This study demonstrates that both individual- and neighborhood-level characteristics are associated with the decision to consume organic produce at least occasionally, and provides further evidence of the impact of neighborhood and of food accessibility on dietary choices. While previous research has shown that healthy food environments are associated with healthy diets, this is the first study to explore the relationship between the local food environment and organic food consumption. While it remains unclear whether or not there is a health benefit to eating organic food, there is growing evidence that consumption of organic food can reduce pesticide exposure and that, at least for some segments of the population, low levels of pesticide exposure may impact health. There are also other reasons that people may choose to eat organic food, including concerns for farmworker safety and ecological health. Allowing equality in the ability to make this choice may present yet another argument for leveling the playing field of food accessibility.

Beyond the contribution to the literature on health disparities and our knowledge of the influence of place on health behaviors, this study also has additional relevance to the aims of this dissertation. By identifying important individual- and neighborhood-level variables associated with organic produce consumption habits, we were better able to define an appropriate set of potential confounding variables for the epidemiological analyses described subsequently in Chapter IV. As a result of these findings, we included individual-level variables (age, sex, race/ethnicity, metropolitan area, education and income) and neighborhood-level characteristics (supermarket density, self-reported perception of produce availability, and community perception of health food availability) as potential confounders when exploring the relationship between OP exposure and cognition.

Tables and Figures

Table II.1. Demographic and socioeconomic characteristics of the Multi-Ethnic Study of Atherosclerosis cohort at Exam 5 (2010-2012), by organic produce consumption habits.

	Never or rarely consume organic produce		Sometimes, often or always consume organic produce		Bivariate analysis[a]
Total sample (n=4,064)	**2420**	**60%**	**1644**	**40%**	
Gender					
Female	1213	57%	927	43%	**<0.0001**
Male	1207	63%	717	37%	
Race / Ethnicity					
Caucasian	975	58%	710	42%	0.08
Chinese	304	62%	187	38%	
African-American	616	59%	434	41%	
Hispanic	525	63%	313	37%	
Age					
45-54	26	39%	40	61%	**<0.0001[b]**
55-64	750	54%	634	46%	
64-74	764	58%	545	42%	
75-84	690	67%	345	33%	
>85	190	70%	80	30%	
Marital status					
Married	1443	59%	1019	41%	0.13
Not married	977	61%	625	39%	
Metropolitan area					
Chicago, IL	415	53%	361	47%	**<0.0001**
Winston-Salem, NC	414	63%	245	37%	
New York, NY	398	56%	312	44%	
Baltimore, MD	345	62%	215	38%	
St. Paul, MN	464	67%	225	33%	
Los Angeles, CA	384	57%	286	43%	
Per capita household income					
< $14,999	713	65%	382	35%	**<0.0001**
$15,000 - 24,999	533	65%	293	35%	
$25,000 - $34,999	425	60%	287	40%	
$35,000 - $44,999	215	54%	185	46%	
> $45,000	534	52%	497	48%	
Education					
Less than high school	375	71%	151	29%	**<0.0001**
High school degree	490	70%	206	30%	
Some college	681	57%	521	43%	
Bachelor's degree	441	58%	315	42%	
Graduate degree	433	49%	451	51%	
Employment Status					
Unemployed or Retired	1900	60%	1243	40%	**0.03**
Employed	520	56%	401	44%	

[a]p-values derived from either chi-squared (gender, race, marital status, metropolitan area and employment status, per capita income, education) or log-binomial regression (age).
[b]The age distribution is shown in categories for display purposes, but was modeled as a continuous variable in a log-binomial regression.

Table II.2. Prevalence ratios and 95% confidence intervals for the association between organic food consumption and individual-level demographic and socioeconomic characteristics in adjusted models.

	Prevalence ratio	Confidence Interval	p-value
Gender			
Male	Referent		**<0.0001**
Female	1.21	1.12 – 1.30	
Race / Ethnicity			
Caucasian	Referent		0.23
Chinese	0.86	0.75 – 1.00	
African-American	0.96	0.88 – 1.06	
Hispanic	0.98	0.87 – 1.10	
Age			
Continuous, per 10 years	0.87	0.84 – 0.91	**<0.0001**
Metropolitan area			
Chicago, IL	Referent		**<0.0001**
Winston-Salem, NC	0.84	0.74 – 0.95	
New York, NY	1.05	0.94 – 1.19	
Baltimore, MD	0.86	0.75 – 0.97	
St. Paul, MN	0.78	0.67 – 0.89	
Los Angeles, CA	1.13	1.00 – 1.27	
Per capita household income			
< $14,999	Referent		0.06
$15,000 - 24,999	0.94	0.83 – 1.06	
$25,000 - $34,999	1.03	0.91 – 1.16	
$35,000 - $44,999	1.10	0.96 – 1.27	
> $45,000	1.10	0.98 – 1.24	
Education			
Less than high school	Referent		**<0.0001**
High school degree	1.05	0.88 – 1.26	
Some college	1.49	1.27 – 1.75	
Bachelor's degree	1.39	1.16 – 1.65	
Graduate degree	1.68	1.42 – 1.99	
Employment status			
Unemployed or Retired	Referent		0.43
Employed	1.03	0.95 – 1.12	

Table II.3. Frequency of organic food consumption in relationship to measures of the local food environment.

	Never or rarely consume organic produce		Sometimes, often or always consume organic produce		Bivariate analyses[a]
	n	%	n	%	p-value
Total sample (n=3,428)	**2046**	**60%**	**1382**	**40%**	
Density of supermarkets within 1 mile of residence (by quartile)					
Quartile 1 (0 - 0.3 per sq mile)	703	63%	417	37%	**<0.0001**
Quartile 2 (0.3 - 0.6 per sq mile)	456	60%	302	40%	
Quartile 3 (0.6 - 1.6 per sq mile)	363	61%	234	39%	
Quartile 4 (1.6 - 11.8 per sq mile)	524	55%	429	45%	
Self-report: "A large selection of fresh fruits/vegetables is available in my neighborhood"					
Disagree or strongly disagree	390	67%	192	33%	**<0.0001**
Neutral	159	59%	109	41%	
Agree or strongly agree	1497	58%	1081	42%	
Aggregated Neighborhood Survey (by quartile)					
Quartile 1 (2.8-3.5)	553	65%	304	35%	**<0.0001**
Quartile 2 (3.5 - 3.8)	546	64%	310	36%	
Quartile 3 (3.8 – 4.0)	496	58%	361	42%	
Quartile 4 (4.0 - 4.5)	451	53%	407	47%	

[a]p-values derived from log-binomial regression with variables specified as continuous.

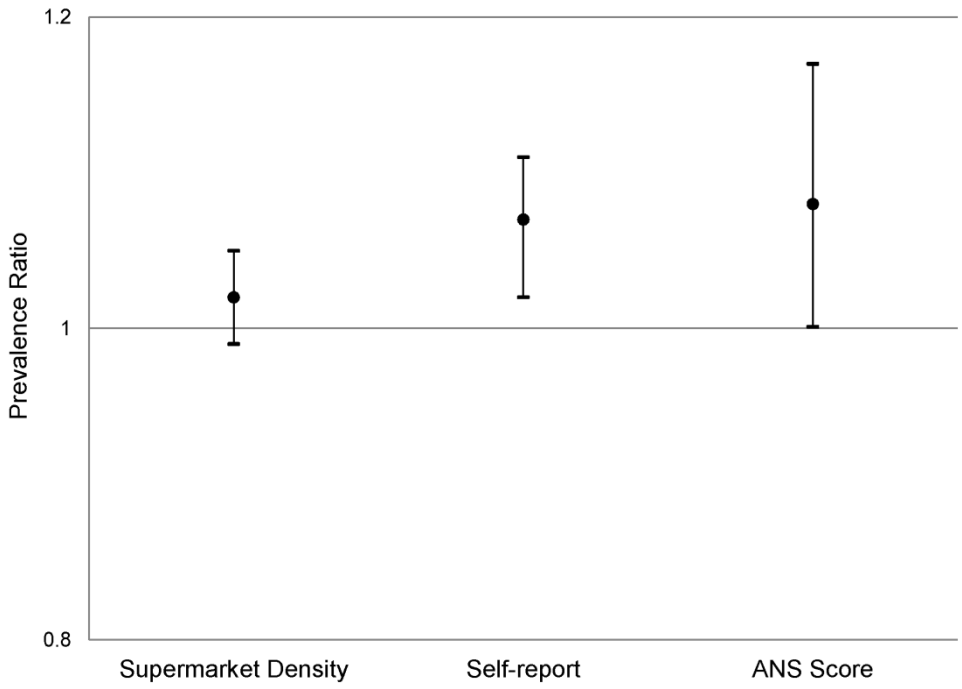

Figure II.1. Associations of organic food consumption with neighborhood food accessibility. Food accessibility is estimated by a) density of supermarkets (per increase in one supermarket per mile); b) self-report of fruit and vegetable selection in a participant's neighborhood (per one point increase on the Likert scale); and c) Aggregated Neighborhood Survey (per interquartile difference, represented by a 0.5 increase on the Likert scale). Models are adjusted for sex, age, education, income, metropolitan area, and race/ethnicity.

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CHAPTER III. Estimating Long-Term Dietary OP Exposure based on Food Frequency Questionnaires and Self-Reported Organic Produce Consumption Habits

Background

Chapter I of this dissertation outlined the widespread agricultural use of OPs, the potential for dietary OP exposure to the general US population, and the uncertainty around the health effects of long-term low-level OP exposure. A critical step in correctly characterizing the relationship between long-term dietary OP exposure and health outcomes is accurate exposure assessment. To understand the relationship between dietary OP intake and health, this exposure assessment must: 1) correctly identify the source of the exposure as specific individual OP pesticides on food and beverage items; 2) account for the wide range of different toxicities among individual OPs; 3) include all OPs to which individuals could be exposed; and 4) represent an appropriate timeframe, which in this case is long-term exposure.

Methods of Exposure Assessment - Biomonitoring

One common method of assessing OP exposure is through biomonitoring, a method in which contaminants or markers of those contaminants (e.g., metabolic products) are measured directly in human biological specimens.[1] These specimens can include media such as blood, urine, saliva, sweat, expired air, hair, and adipose tissue.[2] While there are limitations to biomonitoring, it is often seen as a "gold standard" because it reflects the amount of contaminant that has actually made its way into the body.

Cholinesterase Biomonitoring among Occupational Cohorts

Occupational exposure to OPs has historically been assessed using blood as the medium for biomonitoring.[3-9] Most often in blood, the actual levels of OPs or their metabolites are not measured; instead, acetylcholinesterase (AChE) levels in red blood cells or in plasma are monitored to determine whether or not exposure has occurred. Plasma AChE monitoring is a

common assessment tool for agricultural workers, and is often used to ascertain ability to continue working. The California Department of Health Services, for example, requires medical supervision and cholinesterase testing of all agricultural pesticide applicators.[10]

There are several notable disadvantages of cholinesterase monitoring as a marker of OP exposure. In the general population, the primary disadvantage is that it is an insensitive measure at low exposure levels, as relatively large doses are required for significant cholinesterase inhibition to occur.[11] In addition, cholinesterase monitoring is not specific to OP exposure – other health conditions and exposures to other cholinesterase-inhibiting pesticides can impact measured levels. Furthermore, a baseline measurement is required to account for normal fluctuations in cholinesterase levels.[12]

Measurement of Urinary Metabolites

Urine is another common medium in which to assess OP exposure, through metabolic biomonitoring. While fairly high levels of OP exposure are required to induce cholinesterase inhibition, OP metabolites can be measured in urine samples at much lower exposure levels.[12-14] There are essentially two types of OP metabolites that can be measured in urine: 1) the six dialkylphosphates (DAPs), which are common metabolic products of most OPs, and 2) pesticide-specific metabolites, which are formed from the leaving groups of the central phosphorus atom, and which are, for the most part, unique to individual parent compounds. OPs metabolism typically proceeds through a Phase I oxidation and/or hydrolysis reaction, followed by a Phase II conjugation reaction.[15] Figure III.1 shows the hydrolytic step of chlorpyrifos metabolism, in which the oxon form of the compound is hydrolyzed to yield diethylphosphate (DEP, a DAP metabolite common to many OPs) and 3,5,6-TCPY (the specific metabolite formed from the leaving group of chlorpyrifos), either of which can be measured to assess chlorpyrifos exposure.

Urinary OP biomonitoring is probably the most common method to assess OP exposure in non-occupational studies, and though there are strengths to this method, there are also several important features of these markers that must be considered. First, not all OPs form measurable specific metabolites, and the common DAPs cannot be directly associated with specific parent compounds. In addition, OP metabolites can be found, preformed, in food items, potentially resulting in overestimation of exposure.[16,17] Further, diet is not the only potential route of OP exposure, but biomarkers do not inform the means by which exposure occurs. Finally, OP metabolites have short half-lives, only representing exposures over approximately two days prior to sample collection,[18-20] and within-individual measurements are highly variable.[21-23] Each of these characteristics is discussed in detail below.

Pesticide-Specific Biomarkers Cannot be Measured for Most OPs

As described above, one method of urinary OP biomonitoring is to measure compound-specific metabolites (e.g., 3,5,6-TCPY for chlorpyrifos [Figure III.1]). These compounds originate from an identifiable parent OP, for which toxicity can be determined. However, because of the large number of OPs, the chemical nature of some of the specific OP metabolites, and the lack of availability of the analytic standards, it is not feasible to measure all of the specific metabolites of all OPs at this time.[12] Currently, just nine parent OPs yield pesticide-specific metabolites that can be analyzed: acephate, chlorpyrifos and chlorpyrifos-methyl (which yield the same metabolite), coumaphos, ethyl parathion, malathion, methamidophos, methyl parathion, and pirimiphos-methyl.[12] Of these, two have undergone voluntary cancellation, one is only intended for use on livestock, and another is only registered for use on stored corn, seed and grain. Thus, analyzing specific metabolites it is not a reasonable method for assessing cumulative exposure to all OPs, and measurement of DAPs is much more common.

DAPs Represent Combined Exposure to Many OPs but Cannot Inform Toxicity

DAP metabolites are common byproducts of the metabolism of most OPs, and are probably the most frequently used urinary OP biomarkers. Measurement of the DAPs is appealing, as just six compounds (dimethylphosphate [DMP], dimethylthiophosphate [DMTP], dimethyldithiophosphate [DMDTP], diethylphosphate [DEP], diethylthiophosphate [DETP], and diethyldithiophosphate [DEDTP]) represent combined exposure to more than 30 pesticides. However, as previously discussed, individual OPs can vary in toxicity by as much as 6,000-fold,[24] and this lack of specificity limits the utility of DAPs in risk assessment.

All OPs do not form all DAPs, and some information can be gained by understanding which parent compounds yield which metabolites. The identities of the DAP compounds resulting from metabolism of the individual OPs depends first on whether the two alkyl groups in the parent OP are dimethyl compounds (in which case, DMDTP, DMTP, and DMP are possible metabolites) or diethyl compounds (whereby DEDTP, DETP, and DEP are possible metabolites). The identity of the DAPs generated from a given OP further depends on whether the parent compound is a phosphate or a phosphoro-thionate, and whether the atom connecting the central phosphorus atom to the leaving group is oxygen or sulfur. Only compounds in which there are two sulfur atoms can form a dithiophosphate (DMDTP or DEDTP); at least one must be sulfur to form a thiophosphate (DMTP or DETP); and if neither is sulfur, that OP metabolizes only to the phosphate (DMP or DEP). OPs that can form the more sulfonated compounds can also form the less sulfonated metabolites. While DAPs can therefore provide some limited information on the OPs they represent, given the large number and wide range of toxicities covered by OPs, it is challenging (if not impossible) to assess risk based entirely on DAP metabolite levels.

Further complicating the use of DAPs to assess OP exposure is the fact that not all OPs metabolize to form DAPs. In order to yield one or more of DAPs upon metabolism, two structural criteria must be met by the parent compound. First, the two alkyl groups bonded to the central phosphorus atom must be either both methyl ("dimethyl") or both ethyl ("diethyl") groups. Of the 49 OPs reassessed under the FQPA, 22 are dimethyl compounds, and 17 are diethyl compounds. The other 10 compounds either contain propyl, isopropyl, or butyl groups, or include one methyl and one ethyl compound, and thus do not form DAPs. Second, the connections between the two methyl or two ethyl groups and the central phosphorus atom must be via oxygen bridges. Three compounds do not meet this criterion: in both acephate and methamidophos, one of the methyl groups is connected to the central phosphorus atom via a sulfur atom, and one of the ethyl groups in fonophos is connected to the central phosphorus atom directly. Thus, of the 49 OPs reassessed under the FQPA, just 36 metabolize to form one or more DAPs. Some of the OPs that do not form DAPs are very common in American agriculture (in particular, acephate and methamidophos), but exposure to these compounds is not identified by measurement of urinary DAPs.

DAPs can Represent Exposure to Non-Toxic, Pre-Formed Metabolites

Critics of DAP measurement for assessment of OP exposure further argue that the DAPs measured in urine may reflect exposure to the non-toxic metabolites themselves, preformed on food items, rather than exposure to a toxic OP. This could potentially lead to overestimation of OP exposure. Zhang et al. analyzed 153 previously frozen produce samples for 12 parent OPs and for the six DAPs.[16] The produce samples were selected based on previous analysis during routine monitoring and all were known to contain measurable levels of at least one parent OP. The authors found that 60% of the samples tested contained more moles of DAP residues than

parent OPs, with molar fractions (DAPs/OP+DAPs) ranging from 0.06 to 0.99 with a mean of 0.62 and a geometric mean of 0.55.

Preformed DAPs have also been found to form in fresh fruit juices. Lu et al. measured DAP levels in organic and conventional apple and orange juice purchased from grocery stores.[17] Preformed DAPs were found in both types of juices regardless of whether they were organically or conventionally produced, though the levels were significantly lower in the organic samples. After initial measurement of DAP levels, the authors then spiked the juices with known amounts of three parent OPs and stored the juices for 72 hours at 4°C. They found that 12% of the azinphosmethyl and 36% of the chlorpyrifos and diazinon were degraded to their DAP metabolites during this time. The authors concluded that urinary DAPs have many critical limitations when being used as biomarkers for OP exposure.

OP Biomarkers Cannot Be Used to Attribute Exposure to Specific Routes

One characteristic of biomonitoring, which is typically seen as an advantage, is that this method integrates all possible exposure routes and sources. Regardless of whether OP exposure occurs through dermal absorption of OPs from residential surfaces, inhalation of agricultural spray drift, or consumption of OP-treated produce, urinary biomarker measurements – in theory – represent an individual's total integrated exposure. However, several comprehensive studies of OP exposure and metabolic excretion have failed to successfully explain all of the urinary metabolite output with environmental measurements.

As part of the Children's Total Exposure to Persistent Pesticides and Other Persistent Environmental Pollutants (CTEPP) study, researchers investigated exposures of preschool children to the OP chlorpyrifos and its specific metabolite, 3,5,6-TCPY in everyday environments.[25,26] These studies involved comprehensive environmental sampling, including

duplicate diets, indoor and outdoor air samples, indoor floor dust samples, play area soil samples, and transferable residue and surface wipe samples from hands, food preparation surfaces and hard floor surfaces homes and day care centers in North Carolina[25] and Ohio[26]. The researchers also measured urinary 3,5,6-TCPY concentrations in children residing in these homes and attending these day cares. The goal of this work was to reconstruct the total dose of chlorpyrifos to which these children were exposed and to attribute that does to each exposure route. While the researchers found that the primary exposure to chlorpyrifos was through diet, they were not able to explain more than 27% of the excreted 3,5,6-TCPY. The authors concluded that measurement of urinary 3,5,6-TCPY did not reliability allow quantitative estimation of the children's environmental exposures to chlorpyrifos.[26]

Given all of these possible ways in which people could theoretically be exposed to OPs, it is also clear that urinary biomarkers are not ideal tools if one is interested in identifying exposure from one specific route (as in this study, with diet). While for most people, we might expect dietary exposure to dominate total exposure, urinary biomonitoring cannot rule out exposures from other routes, and the CTEPP data described above suggests that we do not necessarily understand all potential routes of exposure reflected in urinary biomonitoring measurements.

DAPs Have Short Half-Lives, and thus Represent Acute Exposure

The last feature of urinary biomonitoring that warrants mention is the timeframe of exposure which it represents. Controlled human experimental studies have shown that, when orally administered, more than 90% of an OP dose is excreted in the urine as DAPs over the course of at most 2-3 days, with most excretion occurring in the first 24 hours.[18-20,27] While this timeframe could be useful in an occupational setting, as it could potentially reflect exposure over a particular work shift, spot measurements of DAP levels do not reflect long-term exposure.

Only if there is evidence that the exposure period preceding the urine sample is typical, and that DAP excretion is relatively constant, should these measurements to be extrapolated to estimate long-term exposure.

Unfortunately, evidence suggests that there is large intra-individual variability in DAP levels over time. Our research group evaluated the within- and between-individual variability in urinary DAP levels in a longitudinal study of pre-school children living in an agricultural community.[21] For this analysis, between 10 and 26 bi-weekly urine samples were collected from 44 children aged 2-5 years over a 21-month period; this period included both times of the year with active pesticide spraying in these communities and non-spray periods. We found the within-child component of variability to be much larger than the between-child component, regardless of whether pesticides actively were being sprayed in the community at the time of sample collection. The within-child geometric standard deviation (GSD) of DMTP (the DAP found in the highest levels in the urine samples) was 5.04, while the between-child GSD was 1.51.

This longitudinal study evaluated intra-individual DAP levels at the bi-weekly scale; we have also investigated changes in urinary DAP levels across a single day. In 2005, we published a study comparing DAP levels from 13 children who provided up to 4 samples within a single 24-hr period.[22] Samples were collected at specific time points: before bed, first morning void, after lunch, and before dinner. We found significant differences in DAP concentrations collected at each of the time points, and as found in the agricultural cohort described previously, the intra-individual variability was large compared to the inter-individual variability.

Assessing Long-Term Dietary OP Exposure Based on Intake Data

For all of these reasons, the commonly used urinary biomarkers do not actually provide a gold standard for assessing long-term dietary OP exposure, and blood markers will not be useful

for the low levels of exposures anticipated from diet. Another potential method of exposure assessment is to pair contaminant measurements in a given medium or environment with relevant intake rates. In the case of the current exposure of interest (OPs in diet), this approach involves combining information on parent OP residue levels in food with typical food ingestion rates, through what is termed a "food consumption-chemical residue" approach (FCCR).[28] While this method does not reflect internal dose in the same way as biomonitoring, it has several key advantages. The FCCR approach can be used to quantify exposure to specific parent compounds of known toxicity, can represent any and all parent compounds for which residue data is available, can definitively identify dietary exposures, and can be used to inform typical, rather than acute, exposures. The purpose of this current study, and the primary aim of this dissertation, was to develop an FCCR approach to assessing long-term dietary OP exposure that avoids the aforementioned limitations of biomonitoring.

Methods

This study combines dietary intake data collected in the Multi-Ethnic Study of Atherosclerosis (MESA, previously described in Chapter I) with pesticide residue data from the USDA's Pesticide Data Program (PDP, also described in Chapter I) to estimate dietary OP exposure. We then assessed the face validity of this new method by evaluating its comparability with urinary DAP biomonitoring in a subset of participants, while recognizing the weakness of those urinary biomarkers. Finally, we explored the association between self-reported organic food consumption and OP exposure.

Dietary Intake Data

All participants attending MESA Exam 5 (2010-2012) were asked to complete a modified Block-style 120-item FFQ,[29] in which they were queried about their "usual" consumption frequency and serving size of specific foods and beverages "over the past year". Characteristic of the Block FFQ designs, serving sizes were quantified as small, medium or large.

The MESA FFQ was based on an FFQ originally designed for the Insulin Resistance and Atherosclerosis Study, the validity of which was previously studied in a sample of non-Hispanic whites, African Americans and Hispanics.[30] Because Chinese participants were also included in MESA, modifications were made to accommodate unique features of their diets. Specifically, questions were included to determine consumption frequency of various types of stir-fried dishes, fried rice, Chinese dumplings, spring rolls, dim sum, miso soup, and others. FFQs were translated from English into both Spanish and Mandarin, and were provided to each participant in their self-selected primary language. All FFQs were interviewer-administered in the clinic during MESA Exam 5. Specific studies have been conducted within MESA to assess the validity of this tool in the cohort; an analysis of the relationship between macronutrient intake and plasma lipid levels showed significant and consistent associations.[31]

The MESA FFQ includes 20 line items pertaining specifically to fruit and vegetable consumption. A given fruit or vegetable line item refers to between one and six individual foods, and a total of 47 unique fruits and vegetables are included in the MESA FFQ (e.g., Item #40: "Carrots"; Item #41: "Broccoli, cabbage, cauliflower, brussel sprouts, sauerkraut, kimchee"). The current study incorporated information on intake of any fruit or vegetable for which there was intake data available from any line item on the MESA FFQ and for which pesticide residue data was also available from the USDA PDP from years 2008-2010 (see section below).

Ultimately, the following foods were included in this analysis: apples, apple juice, asparagus, blueberries, broccoli, cantaloupe, grapes, green beans, collard greens, lettuce, mangoes, nectarines, oranges, peaches, pears, spinach, strawberries, summer squash, sweet potatoes, and tomatoes.

In order to determine each participant's typical daily intake of a given food, the relative contribution of individual foods to each line item of the FFQ was calculated according to weighted "recipes" using the Nutrition Data System for Research (NDS-R database, Nutrition Coordinating Center, Minneapolis, MN, USA). This database uses national consumption data to estimate the relative frequency of consumption of each food in a line item. For example, if a participant reports eating one medium serving per day of "Apples, applesauce and pears", they are assumed to consume 0.86 servings of apples, 0.08 servings of applesauce, and 0.06 servings of pears. Corresponding weight in grams was imputed according to survey data from the National Health and Nutrition Examination Survey (NHANES).[32]

The United States Department of Agriculture (USDA) Pesticide Data Program (PDP)

As described previously in Chapter I, comprehensive information on pesticide residues in food at "point-of-sale" locations (e.g., grocery stores) is provided by USDA through their Pesticide Data Program.[33] Since 1991, the PDP has repeatedly tested over 95 commodities, including fruits, vegetables and juices, for residues of more than 450 pesticides, including all OPs registered in the US or for which there are import tolerances. Not all commodities are or pesticides monitored in every year. To capture a more complete set of food items to which OPs are applied, we combined PDP data from 2008-2010, which were the most recent years available at the time of this analysis.

During each of these years, a total of between 1.8 and 1.9 million analyses were conducted through the PDP, predominantly on fruit and vegetable items (~85%). In a given year, residues of approximately 300 pesticides and pesticide metabolites were measured. This study included all OP pesticides analyzed between 2008-2010 that were detected at least once in a fruit or vegetable sample for which the MESA FFQ provides intake information. These criteria therefore exclude the following compounds: 1) herbicides, fungicides, aracacides, molluscicides, and plant and insect growth regulators; 2) insecticides other than OPs (e.g., permethrins, pyrethroids, and carbamates); 3) pesticide metabolites; 4) OPs that were never detected in any samples; and 5) OPs that were only detected on a fruit or vegetable item for which we do not have any available information on consumption from the MESA FFQ (e.g., hot peppers). This resulted in inclusion of the following 14 OPs: azinphosmethyl, chlorpyrifos, diazinon, dichlorovos, dimethoate, malathion, methidathion, omethoate, oxydemeton methyl, phosmet, acephate, bensulide, ethoprop and methamidophos.

After identifying the specific pesticides and food items to be included in this analysis, we calculated the average concentration of each OP measured in each food item. PDP samples with values below detection limits were set to zero.

Long-Term Dietary Exposure Assessment: FCCR Approach

Individual-level exposures were calculated in two ways, both using the Food Consumption-Chemical Residue approach. First, we calculated exposure in units of methamidophos equivalents. As shown below, we multiplied each individual's typical intake of each food item (g food/day) by the average residue of each pesticide measured on that food (mg OP/g food). The resulting amount of each OP consumed by each individual on each food item was then multiplied by the relative toxicity (unitless) of that particular OP as compared to an index chemical

(methamidophos), using a Relative Potency Factor approach,[24] which was previously described in Chapter I. Although the methamidophos registration was cancelled in December of 2009, this does not impact its ability to be used as an index chemical to evaluate toxicity. This exposure was divided by each participant's body weight to yield an exposure estimate in units of ng/kg-day, which can be compared to the reference dose for methamidophos and other benchmarks of toxicity to assess risk.

$$Exposure\left(\frac{ng\ methamidophos\ equivalents}{kg\ body\ weight * day}\right) = \frac{\left\{average\ daily\ intake\left(\frac{g\ food}{day}\right) * concentration\left(\frac{ng\ OP}{g\ food}\right) * toxicity\ (unitless)\right\}}{body\ weight\ (kg)}$$

The resulting exposures were then summed across all 14 pesticides and 20 food items, to yield an estimate of total daily exposure for each participant.

These "methamidophos-equivalent" exposures are most useful for understanding toxicity and predicting risk, but are not directly comparable to results from urinary biomarker analyses, where moles, rather than mass, of exposure is the relevant quantity. For comparison with measurements of urinary DAPs, we calculated individual-level exposure in units of nmols/day. In this calculation, shown below, we converted average OP residue levels in each food item to their molar equivalents, and multiplied that quantity by each individual's reported typical intake of each food item:

$$Exposure\left(\frac{nmols\ OPs}{day}\right) = \left\{average\ daily\ intake\left(\frac{g\ food}{day}\right) * concentration\left(\frac{ng\ OP}{g\ food}\right) * molecular\ weight\left(\frac{nmol\ OP}{ng\ OP}\right)\right\}$$

We then summed across food items and OPs to yield a total number of nmol of OPs consumed per day by each individual. For this analysis, we excluded four OPs that do not metabolize to form DAPs: acephate, bensulide, ethoprop and methamidophos.

Evaluating the Relationship between FCCR Predictions and DAPs

We did not hypothesize a strong correlation at the individual level between the FCCR-based exposure estimates and urinary biomarker measurements, due to the temporal mismatch between the exposures these measures represent (acute vs long-term). Instead, we hypothesized that individuals with higher estimated long-term OP exposures would, in aggregate, have higher DAP concentrations in any given spot urine sample than those with lower estimated exposures. Testing this hypothesis evaluates the inter-method comparability of the FCCR-based exposure estimates and the DAP measurements, and thus provides a check on the face validity of our estimates. Because consumption of organic food has been shown to reduce OP exposure, we evaluated the relationship between the FCCR-based exposure estimates (in units of nmol OPs/day) and urinary DAP concentrations exclusively in those participants who reported that they "rarely or never" consumed organic produce, termed "conventional consumers."

After calculating FCCR-based exposure estimates for all MESA participants, we evaluated the range of estimated exposures among the conventional consumers. We then determined the boundaries of three tertiles of exposure – high, medium and low – each designed to include an equal number of conventional consumers. Each of these participants was then assigned to the appropriate tertile based on their estimated exposure. We then analyzed urinary DAP concentrations two independent subsets of conventional consumers, each of which included 240 participants:

1) Random sample. This comparison included three groups of 80 participants who were randomly selected from among each of the three tertiles of exposure.

2) Demographically-matched sample. This comparison included three groups of 80 participants who were selected from each tertile of exposure estimates. These groups were

intentionally selected have similar distributions of gender, race/ethnicity, age, income and education.

Urinary DAP concentrations were compared across groups using generalized linear regression models (SAS 9.3, Cary, NC).

Evaluation of the Impact of Organic Consumption Habits on DAPs

We were also interested in understanding the influence of self-reported organic produce consumption habits on urinary DAP levels. As described in Chapter II, participants were asked "If you eat fresh fruit or drink fruit juice, how often is that fruit or fruit juice 'organically grown' (fruit or fruit juice with a 'USDA Organic label', purchased locally from an 'organic farm' or grown without pesticides in a home garden)?" and "If you eat fresh vegetables, how often are those vegetables 'organically grown' (vegetables with a 'USDA Organic' label, purchased locally from an 'organic farm', or grown without pesticides in a home garden)?" Response options were "Seldom or Never", "Sometimes", and "Often or Always". [†]

For this analysis, we again selected 80 sets of three participants. Each set contained one participant each from three categories of organic produce consumption: "rarely or never"; "sometimes"; or "often or always". These sets were matched on estimated exposure, such that the standard deviation of the exposure estimates was less than 0.5 nmol OP/day within a given set. By matching on estimated exposure (which is a weighted metric of produce intake), we ensure that any differences in DAP concentrations are based exclusively on differences in

[†]One other option was required by the structure of this form: participants could also answer "I do not eat the food". This was necessary to fit into the existing FFQ table, but is admittedly confusing. Ideally, this would only be checked in the rare case where a participant never eats fruit or fruit juice, or vegetables. However, a number of participants (n=707) who did report eating produce in previous parts of the FFQ did select this option. In this analysis, and in the analysis presented previously in Chapter II, these participants were grouped with those who said they "rarely or never" ate organic produce, based on the assumption that they meant "I do not eat organic food". However, it does indicate that these participants may not have fully understood the question, and they were later excluded from the primary analysis presented in Chapter IV (but included in a sensitivity analysis).

organic consumption habits rather than differences in produce intake. We then compared urinary DAP levels across the resulting three groups of 80 individuals. As above, urinary DAP concentrations were compared across groups using generalized linear regression. Note the selected sets were constructed separately from the subsets of 240 participants described in the previous section.

Urinary Biomarker Analysis

Spot urine samples were collected from all MESA participants attending Exam 5 upon arrival at the clinic. Samples were frozen in multiple aliquots at -80°C, shipped frozen and stored at -80°C at a central laboratory at the University of Vermont. Creatinine concentration was measured at the central lab upon receipt.

Aliquots (1.0 mL) of selected samples were shipped frozen to the Exposure Biology Laboratory at Harvard School of Public Health. These samples were analyzed for four DAP metabolites (DMP, DMTP, DEP, and DETP), using the method described by DeAlwis et al. (2009), which involves automated solid phase extraction, on-support derivatization and isotope dilution-GC/MS. Two DAPs (DMDTP and DEDTP) were not measured, due to analytical expense and the fact that these compounds are typically found in relatively low concentrations compared to the other DAPs.[34] Quality control was assessed with standards, blanks, and spiked samples. Average matrix spike recoveries ranged from 92% (DMP) to 105% (DETP).

Analysis occurred in two batches, and detection limits varied between batches. The detection limits were as follows: DMP, 0.5 and 1.0 ng/mL; DEP, 0.5 ng/mL in both sets; DMTP, 2.0 and 0.5 ng/mL; and DETP, 0.5 and 1.0 ng/mL. To avoid batch-related biases, samples of a given metabolite were censored at the higher of the two batch's detection limit. All results below the higher detection limits were assigned a value of that detection limit divided by the square

root of two. Urinary metabolite concentrations were creatinine adjusted to account for hydration, divided by their molecular weights to yield molar equivalents, and summed to yield total creatinine-adjusted molar equivalents (nmol DAPs/g creatinine).

Results

Of the original MESA cohort (n=6,814), 4,466 (66%) participated in Exam 5 and completed the questions related to organic food consumption on the Exam 5 FFQ (Table III.1). Consistent with the MESA study design, this is a diverse group; 41% of these participants were Caucasian, 12% were Chinese, 26% were African-American, and 22% were Hispanic. The gender ratio was fairly equal, with slightly more women (53%) than men (47%). MESA is a cohort of older adults, with just over a third of this group aged 55-64, another third aged 65-74 and the remainder over 75 years of age.

Evaluation of FCCR-Based Exposure Estimates

We estimated FCCR-based exposure estimates in units of ng methamidophos equivalents per kg body weight per day (ng/kg-day) for all of these participants (Table III.2). These values were lognormally-distributed, with a median exposure of 2.8 ng/kg-day and an interquartile range of 1.4 to 5.2 ng/kg-day. Participants who reported more frequent consumption of organic food also reported eating more fruits and vegetables, which is reflected in the higher exposure estimates for those participants who report that they "often or always" eat organic food.

In the analysis of the relationship between FCCR-based exposure estimates and urinary metabolite levels, we considered only those participants who reported that they rarely or never ate either organic fruit or organic vegetables (n=2670, 60%). We refer to this group as "conventional consumers". For these conventional consumers, we also calculated FCCR-based

exposure estimates in units of nmol/day. The range of estimated exposures was 0 – 49.3 nmol OPs/day. As shown in Figure III.2, the lowest tertile of exposure estimates ranged from 0 – 1.9 nmol OPs/day ("low predicted exposure); the middle tertile ranged from 1.9 – 4.8 nmol OPs/day ("medium predicted exposure"); and the highest tertile ranged from 4.8– 49.3 ("high predicted exposure").

The first comparison of the FCCR-based exposure estimates and urinary DAP levels included three groups of 80 conventional consumers who were randomly selected from each tertile of estimated exposure to OPs. One individual who was randomly selected from Tertile 2 was excluded from all analyses, due to an implausibly high DAP result (33,145 nmol DAPs/g creatinine). The demographic and socioeconomic status (SES) distributions of participants were not similar across tertiles (Table III.3). More men, African-American and Hispanic participants, younger individuals, and those with less education were in the lowest tertile of estimated exposure, indicating that these participants ate fruits and vegetables less frequently. Table III.4 shows the distributions of exposure predictions (nmol OPs/day) in each group included in the urinary DAP comparisons. By design, the three groups compared in the random sample have distinctly different magnitudes of estimated exposure to OPs, and urinary DAP concentrations were found to be significantly different across the three groups (medians: 56, 79, and 104 nmol DAP/g creatinine, $p<0.04$; Table III.5 and Figure III.3a) within these conventional consumers.

The second analysis included three different groups of 80 conventional consumers who were selected from each tertile of exposure estimates in order to provide each group with similar frequency distributions of gender, race/ethnicity, age, income and education. The resulting groups were all 55-56% women, 55-56% Caucasian, 15-16% Chinese, 14% African-American, 14-15% Hispanic, and similarly matched in age group, income and education (Table III.3). This

demographically-matched analysis yielded the same result as the random selection analysis: urinary DAP concentrations were found to be significantly different across the three tertiles of estimated OP exposure in conventional consumers (medians: 63, 70 and 110 nmol DAP/g creatinine, $p<0.03$; Table III.5 and Figure III.3b).

Comparison of Organic Produce Consumption and DAPs

We also conducted a separate analysis of the association between urinary DAP concentration and organic consumption habits among three groups matched on FCCR-based exposure estimates but differing by self-reported frequency of organic produce consumption ("rarely or never", "sometimes", and "often or always"). Among participants included in this analysis, the median FCCR-based exposure estimate was 9.0 nmol OPs/day (interquartile range 7.0 – 11.4 nmol OPs/day, Table III.4). Because participants in each group were constrained to essentially match on fruit and vegetable intake (which is notably high among individuals who choose to consume organic food), the characteristics of each group in this analysis are more similar than might otherwise be expected. Participants in this comparison were nearly two-thirds women, and were more educated, younger, of slightly higher income, and were somewhat more likely to be Caucasian than the cohort as a whole (Table III.3).

We observed significant differences in urinary DAP concentrations based on self-reported frequency of organic produce consumption ($p<0.02$; Table III.5 and Figure III.4). The median DAP concentrations among individuals who rarely or never consumed organic produce was 163 nmol DAP/g creatinine. Among those who sometimes consumed organic produce, the median DAP level was 121 nmol DAP/g creatinine, and among individuals who often or always ate organic produce, the median was 106 nmol DAP/g creatinine.

Discussion

This is the first study to estimate individual-level long-term dietary OP exposure using dietary intake data alongside information on organic food consumption habits. The consistency between the FCCR estimates and urinary DAP levels among conventional consumers increases our confidence in this methodology, and is consistent with previous research showing that higher DAP levels are associated with increased produce intake.[35,36] We also observed a significant relationship between increasing consumption of organic produce and lower DAP levels among individuals who were matched on FCCR-based exposure. Since the FCCR-based exposure estimates are essentially weighted metrics of produce intake, this finding is consistent with previous studies showing that consumption of organic food measurably reduces OP exposure compared to consuming conventional food.[37,38] Given the relatively high prevalence of at least occasional consumption of organic food in this cohort (40%), we conclude that organic food consumption may be an important modifier of the potential relationship between OP intake as estimated based on food consumption patterns and adverse health effects.

DAP biomarkers are imperfect measures of long-term OP exposure, due to their short half-lives, lack of specificity to parent compounds, and potential to represent exposure to preformed metabolites.[39] Despite these limitations, numerous studies have successfully used DAPs to identify risk factors for OP exposure, including proximity to farmland,[40] agricultural season and timing of pesticide applications,[41] living with pesticide applicators,[42] and consuming conventional diets.[37] In this study, we used these DAP biomarkers in a novel way: to assess the face validity of our proposed exposure assessment method, which suffers from none of the aforementioned limitations of the DAPs. These urinary measures of acute exposure substantiated our long-term estimates.

While this is the first study of its kind to include information on organic food consumption habits, it is not the first to use a "food consumption – chemical residue" approach to estimate dietary exposure. Macintosh and colleagues estimated exposures to 11 contaminants – including three OPs – in a population of 120,000 US adults enrolled in the Nurses' Health Study and the Health Professionals' Follow Up Study.[43] In subsequent analyses, the researchers analyzed arsenic and mercury concentrations in toenail samples collected from a subset of these participants.[28] Using the FCCR approach, estimated arsenic and mercury exposures were compared to measured levels in the toenails, and the authors found significant, though somewhat weak, correlations (Spearman correlation coefficients of 0.15 and 0.35). These coefficients are within the range found for similarly-estimated dietary intake of chlorpyrifos and urinary 3,4,5-TCPY concentrations[44] and chlordecone from diet and in blood.[45] They are also similar to coefficients observed between FFQ-based estimates of intake and biomarkers of dietary carotene[46] and polyunsaturated fat.[47]

In this study, we chose not to focus on correlation coefficients between the FCCR-based OP exposure estimates and the urinary DAP metabolites. From the outset, we did not hypothesize a strong direct correlation between individual results from these assessment methods, due to the temporal mismatch between the biological markers and the dietary information captured in the FFQ. The short half-lives of OP metabolites, and their correspondingly high intra-individual variability, are well established[21,22] and the purpose of this work was to develop a metric for long-term dietary OP exposure – which the DAP biomarkers simply cannot do. Therefore, we focused the DAP analysis on providing a check of the face validity of our exposure estimates, rather than evaluating the direct agreement between the two

assessment techniques. The results of this study suggest that this approach was successful and informative.

We estimated long-term dietary OP exposure for the MESA population in units of methamidophos equivalents per kg body weight per day. Unlike urinary biomarkers, these estimates can be used to inform risk. Within the MESA cohort, the 95th percentile of exposure was 0.000011 mg/kg-day. This is the same order of magnitude as the 95th percentile of single day dietary exposure predicted in the EPA's 2006 OP Cumulative Risk Assessment for adults over the age of 50 years.[24] That value, 0.000092 mg/kg-day, is approximately 8-fold higher than the 95th percentile in the MESA population. This difference may reflect both the earlier data used in that risk assessment (prior to the more recent reductions in OP use) and the fact that the EPA was predicting a single-day maximum, whereas we are predicting typical exposure over the course of a year. Given that the EPA determined that those estimates were protective of health within a 870-fold margin of error, our results do not suggest unacceptable risk using current risk benchmarks, which are based on thresholds of cholinesterase inhibition.

While these levels are below current risk thresholds, those thresholds may not reflect important mechanisms of low-level toxicity, which are only beginning to be understood. The importance of understanding long-term, low-level exposures to OPs is underscored by the results of several studies of the effects of low levels of OP exposure to infants and children, outlined in detail in Chapter I. As described, these mother-child cohort studies have found prenatal maternal urinary DAP levels to be significantly associated with attention problems and ADHD in children at 5 years of age,[48] poorer intellectual development at 7 years of age,[49] and decreased cognitive development in children at one year of age and at 6-9 years.[50] Mothers in these studies were thought to have either agricultural or residential OP exposure, in addition to dietary exposure.

Interestingly, a more recent study in a fourth cohort of mother/infant pairs found that higher prenatal urinary DAP levels were associated with improved neurobehavioral outcomes among infants at five weeks of age.[51] This population was not suspected to have agricultural or residential exposures. As might be expected in such a cohort, the mothers with higher OP exposure also reported more frequent consumption of fruits and vegetables than those with lower OP exposure, suggesting that produce intake (and other correlated residual confounders associated with SES) might have influenced these results. This finding emphasizes the potential value in an analysis that incorporates information on organic food consumption habits.

Consistent with previous studies of the relationship between organic food and DAP levels,[37,38] we found that—when matched on produce intake — individuals who reported eating organic produce more frequently had lower urinary DAP levels than those who ate it less often or not at all. It is worth noting that even individuals who reported that they "often or always" consumed organic produce had measurable urinary DAP levels, and that the median DAP level in these individuals was above the median of the conventional consumer group as a whole. These findings are explained by the fact that individuals with organic diets ate significantly more fruits and vegetables than those who reported eating only conventional produce.

While this work provides a method for assessing long-term dietary OP exposure and supports that method with the results of urinary biomonitoring, there are several limitations. Notably, we were only able to compare our proposed estimates to the very biomarkers we find lacking. Unfortunately, this is the state of the science, as no gold standard is available. Another limitation is that these FCCR-based estimates are based on data acquired from FFQs, which can be limited by recall bias. However, among all dietary assessment tools, FFQs are best suited to provide information for studies where typical, long-term diet is the conceptually important

exposure, rather than intake on a few specific days.[52] Moreover, individuals are known to do a better job of recalling their diets in "generic" rather than "episodic" ways,[52] which makes FFQ data well suited for the purposes of this study.

An additional limitation is that, while the PDP provides the most comprehensive OP residue data available, it is a national database, and does not reflect the specific residues to which individuals are exposed. We also did not include every food item to which OPs are applied. Some items were excluded because no OPs were detected on any samples of that type, which is unlikely to affect the results of this study. Others were excluded because there was no available intake information regarding that item on the MESA FFQ; however, the MESA FFQ does include the most commonly eaten food item, and so any potential effect would also be small.

A final limitation of this study is that we did not allow produce consumption frequency and organic produce choice to vary freely within the analytic datasets. Because of the costs associated with determining the DAP concentration, we made some statistical selections to maximize efficiency while avoiding confounding. Among conventional consumers, we evaluated the relationship between FCCR-based exposure predictions and urinary DAP concentrations using two different sampling strategies and found strikingly consistent results. The first comparison included individuals who were randomly selected from across the spectrum of estimated exposure, removing the possibility of selection bias. However, the FCCR-based estimates are strongly related to frequency of produce consumption, which is in turn related to demographic and SES factors. Therefore, distributions of demographics and SES were notably different across the randomly selected groups. By evaluating DAP concentrations among groups matched on demographics and SES, as in our second comparison, we can be fairly confident that the observed differences in DAPs were not related to these factors.

While there were limitations to this study, it also had several notable strengths. We employed a large and well-characterized cohort, for which data was collected using standardized methods. The exposure estimation approach we employed allows identification of parent compounds, which in turn allows evaluation of risk. Compared to urinary metabolite analysis, the FCCR-based assessment approach is non-invasive, inexpensive, and can be easily implemented in cohorts in which FFQ data are already available (though information on organic food consumption habits may still need to be acquired). Further, this methodology provides estimates of long-term exposure, which cannot be obtained from existing biomarker methods.

Conclusions

This food composition – chemical residue method may prove useful in future epidemiological studies of long-term dietary OP exposure, particularly if paired with information on organic food consumption, which may modify the observed exposure-response relationship. As concern grows regarding potential effects of low-level OP exposures, the need increases for more sophisticated exposure assessment methods. These methods must consider the relevant time frame of exposure and be able to define the parent compounds to which individuals are exposed, in order to truly assess risk.

In the context of this dissertation work, this exposure assessment methodology provided a set of long-term dietary OP exposure predictions for all members of the MESA cohort who completed an FFQ at Exam 5. These exposure predictions, in conjunction with information on organic produce consumption habits, were used to assess the relationship between OP exposure and results of a battery of cognitive tests reflecting different cognitive domains in the MESA cohort (Chapter IV).

Tables and Figures

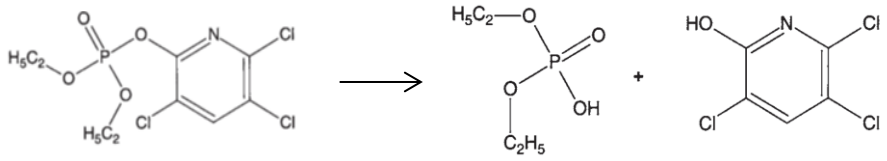

Figure III.1. Paraoxonase-mediated hydrolysis of chlorpyrifos oxon.
The reaction products are the leaving group (3,5,6 trichloro-2-pyridinol, 3,5,6-TCPY) and a dialkyl phosphate (diethyl phosphate, DEP).

Table III.1. Demographic distributions of all MESA participants who attended Exam 5 and completed the organic food consumption questions on the Exam 5 FFQ (n=4,466).

		Gender		Race/Ethnicity				Age			Annual Household Income[a]			Education[b]		
	N	Female	Male	White	Chinese	Black	Hispanic	<65 yrs	65-74 yrs	>75 yrs	<$30K	$30K-$75K	>$75K	High school or less	Some college	Bachelors or higher
Full cohort	*4466*	53%	47%	41%	12%	26%	22%	35%	32%	33%	33%	39%	28%	31%	29%	39%
Self-reported frequency of organic produce consumption																
"Rarely or never"	*2670*	51%	49%	40%	12%	26%	23%	31%	31%	38%	37%	40%	23%	37%	28%	35%
"Sometimes"	*1574*	55%	45%	43%	11%	27%	19%	39%	33%	27%	27%	38%	35%	23%	32%	45%
"Often or always"	*222*	65%	35%	39%	10%	23%	27%	44%	34%	23%	34%	35%	32%	23%	29%	48%

[a]147 participants were missing information on income.
[b]7 participants were missing information on education.

Table III.2. Percentiles of FCCR-based exposure estimates (ng/kg-day) for all participants completing the Exam 5 FFQ, and for subgroups based on self-report of organic produce consumption habits.

		Percentile of FCCR-Based Exposure Estimates[a] (ng methamidophos equivalents/kg body weight-day)				
	n	**10%**	**25%**	**50%**	**75%**	**90%**
Full cohort	*4464*	0.69	1.4	2.8	5.2	8.6
Self-reported frequency of organic produce consumption						
"Rarely or never"	*2670*	0.57	1.2	2.4	4.6	7.8
"Sometimes"	*1574*	0.93	1.8	3.4	5.7	9.4
"Often or always"	*222*	1.5	2.3	4.0	6.8	11.0

[a]These exposure estimates do not incorporate information on organic consumption habits; they are based exclusively on self-reported produce intake and residue levels in foods. The higher exposure estimates among individuals reporting that they more frequently consume organic food is reflective of the fact that these participants eat more produce than those who exclusively consume conventionally grown food.

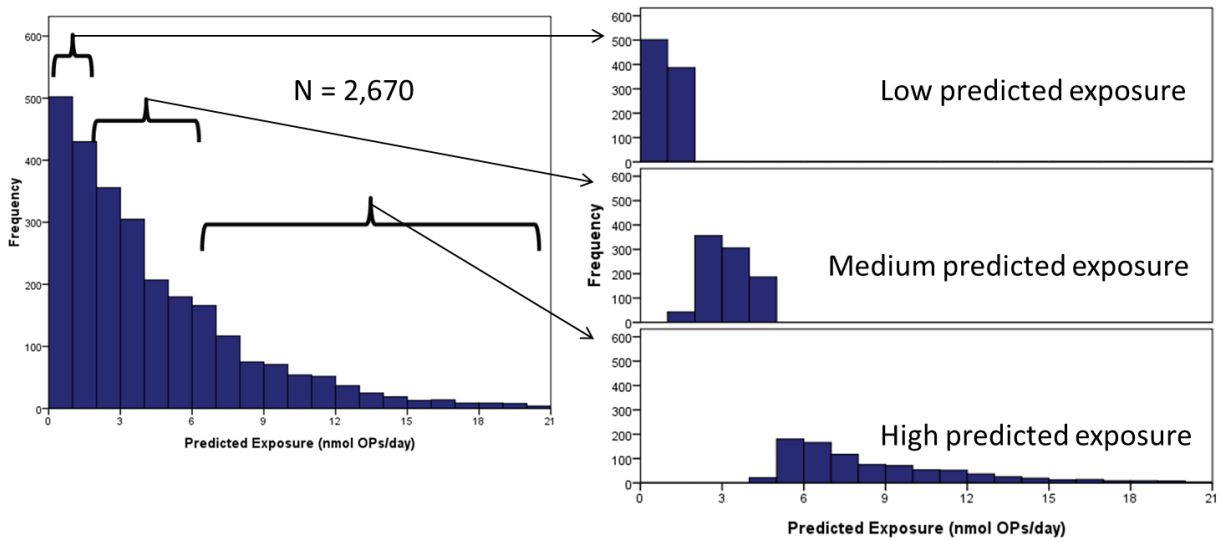

Figure III.2. Distribution of predicted OP exposure, in units of nmols/day.
This figure shows the three tertiles of predicted exposure from which urinary DAP samples were selected. Note that the maximum predicted exposure was 49.3 nmol/day but these figures are truncated at 21 to preserve scale.

Table III.3. Demographic distributions of participants who were selected for urinary metabolite analysis.

		Gender		Race/Ethnicity				Age			Annual Household Income			Education		
	n	**Female**	**Male**	**White**	**Chinese**	**Black**	**Hispanic**	**<65 yrs**	**65-74 yrs**	**>75 yrs**	**<$30K**	**$30K-$75K**	**>$75K**	**High school or less**	**Some college**	**Bachelors or higher**
Subgroups Selected for Urinary Metabolite Comparison – Conventional Consumers[a]																
Random Sample[b]																
Tertile 1	*80*	38%	63%	45%	9%	26%	20%	35%	38%	28%	28%	38%	35%	35%	28%	38%
Tertile 2	*79[c]*	48%	52%	51%	18%	16%	15%	25%	37%	38%	41%	30%	29%	29%	32%	39%
Tertile 3	*80*	59%	41%	56%	8%	20%	16%	28%	30%	43%	26%	43%	31%	21%	28%	51%
Demographically-Matched Sample[d]																
Tertile 1	*80*	55%	45%	56%	15%	14%	15%	31%	41%	28%	39%	34%	28%	30%	28%	43%
Tertile 2	*80*	56%	44%	55%	16%	14%	15%	31%	41%	28%	39%	34%	28%	30%	28%	43%
Tertile 3	*80*	56%	44%	56%	16%	14%	14%	31%	43%	27%	38%	35%	28%	30%	28%	43%
Subgroups Selected for Urinary Metabolite Comparison – by Organic Produce Consumption Habits																
"Rarely or never"	*80*	60%	40%	53%	9%	26%	13%	31%	36%	33%	21%	46%	33%	24%	25%	51%
"Sometimes"	*80*	66%	34%	43%	9%	21%	28%	40%	35%	25%	26%	48%	26%	25%	33%	43%
"Often or always"	*80*	66%	34%	45%	13%	20%	23%	43%	34%	24%	29%	38%	34%	20%	26%	54%

[a]Comparisons among conventional consumers are across tertiles of estimated dietary exposure to OPs. The lowest tertile (Tertile 1) includes individuals with estimated exposures of less than 1.8 nmol/day; the middle tertile (Tertile 2) includes individuals with estimated exposures ranging from 1.8-4.7 nmol/day; and the highest tertile (Tertile 3) includes individuals with estimated exposures greater than 4.7 nmol/day. These exposure estimates are not adjusted for potency, but represent total molar intake.
[b]80 participants were randomly selected from each tertile of predicted exposure.
[c]One participant was excluded due to an implausibly high urinary DAP measurement (>30,000 nmol DAP/g creatinine).
[d]Participants in this analysis were selected to provide three groups of 80 participants with similar frequencies of each demographic characteristic shown.

Table III.4. Percentiles of FCCR-based exposure estimates (nmol OPs/day) for of participants who were selected for urinary metabolite analysis.

		Percentile of FCCR-Based Exposure Estimates (nmol OPs/day)				
	n	**10%**	**25%**	**50%**	**75%**	**90%**
Subgroups Selected for Urinary Metabolite Comparison – Conventional Consumers[a]						
Random Sample[b]						
Tertile 1	*80*	0.3	0.5	1.0	1.5	1.7
Tertile 2	*79*[c]	2.1	2.4	3.2	3.9	4.6
Tertile 3	*80*	5.2	6.0	7.5	10.7	13.0
Frequency-Matched Sample[d]						
Tertile 1	*80*	0.5	0.9	1.1	1.6	1.7
Tertile 2	*80*	2.3	2.5	3.2	4.0	4.6
Tertile 3	*80*	5.5	5.9	7.2	9.4	12.3
Subgroups Selected for Urinary Metabolite Comparison – by Organic Produce Consumption Habits[e]						
"Rarely or never"	*80*	5.9	6.9	9.1	11.3	13.8
"Sometimes"	*80*	6.0	7.0	9.0	11.4	13.8
"Often or always"	*80*	6.1	6.9	8.9	11.6	13.8

[a]Comparisons among conventional consumers are across tertiles of estimated dietary exposure to OPs. The lowest tertile (Tertile 1) includes individuals with estimated exposures of less than 1.9 nmol/day; the middle tertile (Tertile 2) includes individuals with estimated exposures ranging from 1.9-4.8 nmol/day; and the highest tertile (Tertile 3) includes individuals with estimated exposures greater than 4.8 nmol/day. These exposure estimates are not adjusted for potency, but represent total molar intake.
[b]80 participants were randomly selected from each tertile of predicted exposure.
[c]One participant was excluded due to an implausibly high urinary DAP measurement (>30,000 nmol DAP/g creatinine).
[d]Participants in this analysis were selected to provide three groups of 80 participants with similar frequencies of relevant demographic characteristics.
[e]Participants in this analysis were selected to provide three groups who were intentionally matched on FCCR-based exposure estimate (a metric of produce intake weighted by frequency and magnitude of OP residues detected in each food item). This is reflected in the similar values across the percentiles of exposure.

Table III.5. Percentiles of urinary DAP concentrations (nmol DAPs/g creatinine) by tertile of FCCR-based exposure estimates among conventional consumers and by self-report of organic produce consumption frequency.

		Percentile of urinary DAP concentration (nmol DAPs/g creatinine)				
	n	**10%**	**25%**	**50%**	**75%**	**90%**
Subgroups Selected for Urinary Metabolite Comparison – Conventional Consumers						
Random Sample						
Tertile 1	*80*	24	33	56	115	228
Tertile 2	*79*[a]	33	48	79	158	275
Tertile 3	*80*	36	67	104	241	489
Frequency-Matched Sample						
Tertile 1	*80*	29	42	63	115	197
Tertile 2	*80*	31	47	70	137	225
Tertile 3	*80*	40	63	110	217	414
Subgroups Selected for Urinary Metabolite Comparison – by Organic Produce Consumption Habits						
"Rarely or never"	*80*	48	80	163	365	638
"Sometimes"	*80*	39	58	121	237	474
"Often or always"	*80*	36	54	106	204	321

[a]One participant was excluded due to an implausibly high urinary DAP measurement (>30,000 nmol DAP/g creatinine).

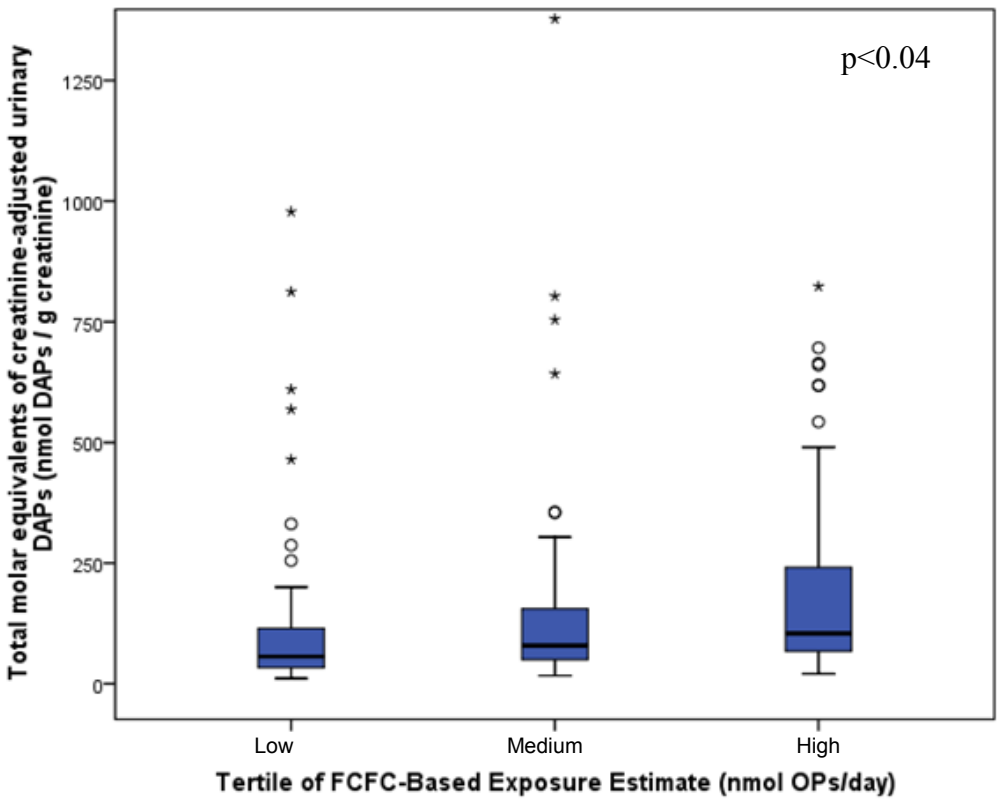

Figure III.3. Urinary dialkylphosphate concentrations (nmol DAPs / g creatinine) by tertile of FCCR-based exposure estimates (nmol OPs / day): Random sample.
This "random sample" comparison includes 80 participants randomly selected from each tertile of FCCR-based exposure estimates. Urinary DAPs were significantly different across the three groups ($p<0.04$).

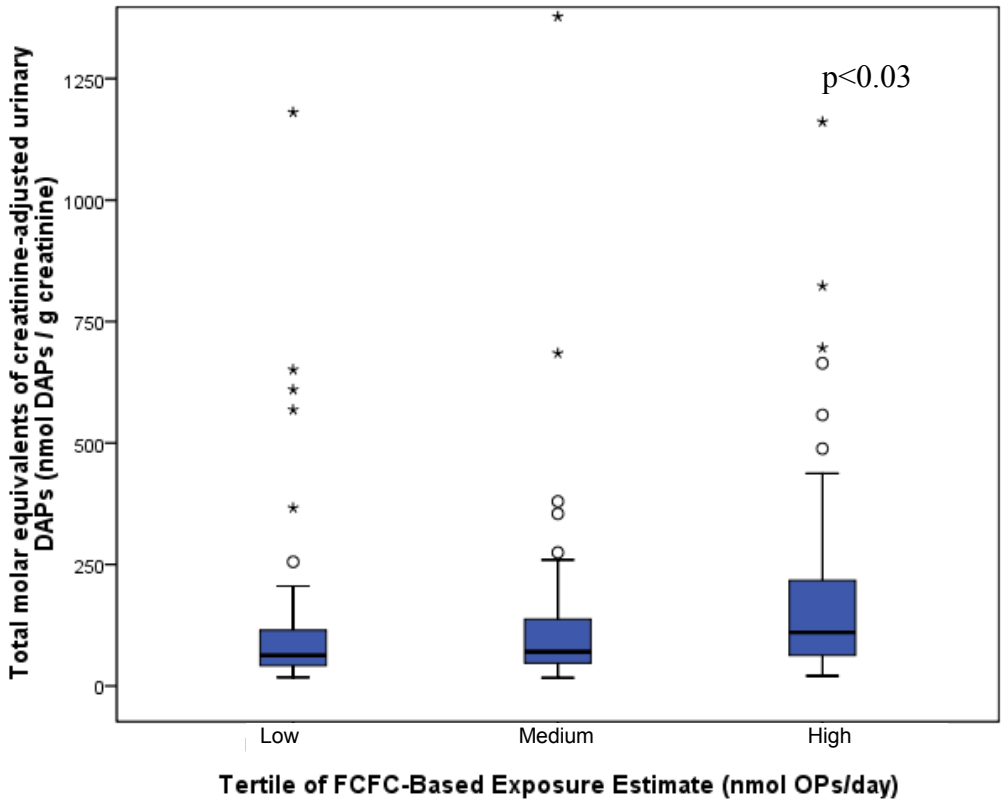

Figure III.4. Urinary dialkylphosphate concentrations (nmol DAPs / g creatinine) by tertile of FCCR-based exposure estimates (nmol OPs / day): Frequency-matched sample.
This "frequency-matched" comparison includes 80 participants from each tertile, which were selected to be frequency-matched on age, gender, race/ethnicity, income and education. Urinary DAPs were significantly different across the three groups ($p<0.03$). One outlier, which was in the "High estimated exposure" group, was not shown to preserve scale (value of 2017 nmol DAPs/g creatinine).

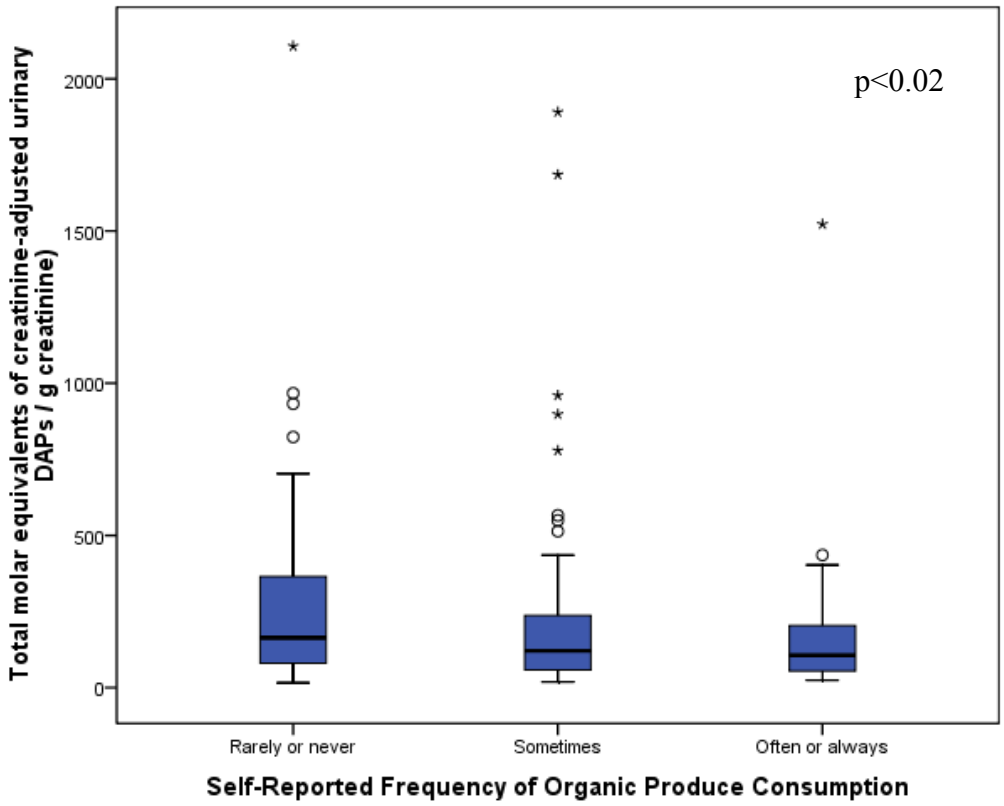

Figure III.5. Urinary DAP concentrations (nmol DAPs / g creatinine) by self-reported frequency of organic produce consumption.
Urinary DAP concentrations were significantly different across groups ($p<0.02$). Two outliers, both of which were in the "rarely or never" group, were not shown to preserve scale (values of 3187 and 3707 nmol DAPs/g creatinine).

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CHAPTER IV. Association between Dietary Exposure to Organophosphate Pesticides and Cognition: The Multi-Ethnic Study of Atherosclerosis

Background

Over 33 million pounds of organophosphate pesticides (OPs) are applied annually in the US, constituting the primary form of insect control in American agriculture.[1] Individual OPs are registered for use on approximately 50 different crop types, and OP residues are commonly found on food items at point-of-sale locations (e.g., grocery stores).[2] While residential uses of OPs were fairly common in the 1980s and 1990s, these uses have been phased out over the last decade, through a combination of regulatory and voluntary cancellations.[3] Thus, for non-occupationally exposed individuals – and particularly those who do not live in agricultural communities – the primary route of OP exposure is believed to be through diet, via ingestion of foods to which these compounds have been applied. National data suggest that low-level exposure to OPs is widespread: OP metabolites are found in the urine of more than half of the US population, with metabolites of some OPs found in as many as 96% of samples tested.[4]

We have previously shown that individual-level food frequency questionnaire (FFQ) data can be combined with average levels of pesticide residues on food items to generate reliable estimates of long-term dietary exposure to OPs (see Chapter III). This work demonstrated that individuals who reported greater consumption of OP-containing fruits, fruit juice and vegetables had significantly higher levels of OP metabolites in their urine than individuals who reported eating less such produce. In addition, individuals who reported that they "sometimes, often or always" consumed organically grown produce had lower levels of OP metabolites in their urine than people who reported "rarely or never" consuming organic food, with the lowest exposures see in the most frequent consumers.

The acute toxicity of OPs, and thus their effectiveness as pesticides, stems from their ability to affect neurotoxicity by inhibiting acetylcholinesterase activity.[5] OP exposure has been

consistently associated with acute neurotoxicity and cognitive dysfunction in occupationally exposed adults.[6-11] At lower exposure levels, more subtle biological mechanisms are suspected to be affected by OP exposure[12,13] (see Chapter I). Notably, agricultural workers with subacute exposure to OPs have shown significantly poorer performance on tests of working memory, mental processing, sustained attention, concentration and motor skills – including the digit symbol coding and digit span tests – than unexposed controls.[14-22] More recently, researchers have demonstrated associations between OP exposure and neurological, cognitive, and behavioral endpoints in children who have much lower exposures than occupationally exposed adults. These effects have been seen both in children living in agricultural regions and in the general population.[23-27] To date, no studies have explored the relationship between low-level OP exposure and neurocognition in non-occupationally exposed adults.

The primary aim of this chapter of this dissertation is to investigate the relationship between long-term dietary OP exposure and results of a battery of tests reflecting different cognitive domains within the Multi-Ethnic Study of Atherosclerosis (MESA, previously described in detail in Chapter I).

Methods

This cross-sectional study aimed to assess the relationship between estimates of long-term dietary exposure to OPs, developed based on a combination of dietary intake data from FFQs and food item-specific OP residue data (see Chapter III), with the following outcomes: 1) the phonological loop component of working memory, as measured by performance on the Forward Digit Span Test;[28] 2) the visuospatial component of working memory, as measured by performance on the Backwards Digit Span Test;[28] 3) mental processing speed, as measured by performance on the Digit Symbol Coding Test;[28] and 4) global cognitive function, as measured

by the Cognitive Abilities Screening Instrument.[29] These analyses will consider potential confounders defined at both the individual- and neighborhood-level (see Chapter II), and will further consider organic food consumption habits as a potential modifier of the exposure-response relationship (see Chapter III).

Population

All MESA participants who completed the Exam 5 FFQ (including questions regarding organic food consumption), provided all relevant individual-level demographic data, and completed any of the four Exam 5 cognitive tests were eligible for inclusion in this analysis. For the primary analyses, we excluded participants who responded to the questions on organic produce consumption with the selection "I do not eat the food",[‡] but these participants were included in a sensitivity analysis. A number of participants were not a part of MESA Neighborhood, and therefore, the neighborhood-scale variables (supermarket density; self-report of neighborhood produce availability; aggregated neighborhood survey regarding produce availability; see Chapter II) were not available for these participants. These participants were excluded from models containing these variables, but are included in less fully specified models.

[‡]As described previously in Chapter II, participants had four options to answer the questions: "If you eat fresh fruit or drink fruit juice, how often is that fruit or fruit juice 'organically grown' (fruit or fruit juice with a 'USDA Organic' label, purchased locally from an 'organic farm', or grown without pesticides in a home garden)?" and "If you eat fresh vegetables, how often are those vegetables 'organically grown' (vegetables with a 'USDA Organic' label, purchased locally from an 'organic farm', or grown without pesticides in a home garden)?". The choices were: "I do not eat the food", "Seldom or Never", "Sometimes", and "Often or Always", required to fit into a pre-existing table in the MESA FFQ. Ideally, the response "I do not eat the food" would only be selected in the rare case where a participant never ate fruit or fruit juice, or vegetables. However, a significant number of participants who reported eating produce in previous parts of the FFQ selected this option (n=707). In previous chapters (Chapters II and III), these individuals were categorized with those who selected "seldom or never", based on the assumption that they meant "I do not eat organic food." However, since the epidemiologic analysis presented in this chapter is focused around issues of cognition (including correctly understanding and answering questions), and since organic food consumption is such a critical factor in OP exposure, we chose not to make this assumption here. Therefore, in the primary analysis described here, individuals who did not answer this question "correctly" (e.g., answered "I do not eat the food" despite reporting consumption of produce previous) were excluded. These participants were included in a sensitivity analysis.

Long-Term Dietary OP Exposure

This analysis takes advantage of the Food Consumption-Chemical Residue (FCCR) approach to exposure assessment described in Chapter III. Briefly, this assessment combines dietary intake data of 20 different fruit, fruit juice and vegetable items from the MESA Exam 5 FFQ (representing "typical" consumption habits "over the past year", administered between 2010-2012) with information on average residue levels of 14 different OPs on those food items from the United States Department of Agriculture's (USDA) Pesticide Data Program (PDP) database from the years 2008-2010. Exposure to each of the 14 OPs is standardized to units of "methamidophos equivalents" to reflect the unique toxicities of each compound relative to this index chemical. Average daily exposure is expressed in units of ng methamidophos equivalents per kg of body weight per day (ng/kg-day).

Cognitive Assessment

MESA Exam 5 included four cognitive tests, the Forward Digit Span Test, the Backward Digit Span Test, the Digit Symbol Coding Test, and the Cognitive Abilities Screening Instrument. Procedures across the six MESA cities were standardized, with careful attention to interviewer training.[30] The tests were administered in the participant's native language (Spanish or Mandarin) if requested, and are described in detail below.

Forward Digit Span Test (FDST)

This test was designed to evaluate the phonological loop, one component of auditory working memory. [31] Working memory refers to a brain system that provides temporary storage and maintenance of information,[32] and the phonological loop temporarily handles languages and

processes information that is received verbally. For example, the short-term process used to remember a phone number utilizes the phonological loop.

In the FDST, the interviewer provides a list of numbers with an increasing quantity of digits and asks the participant to say them back in the same order ("forwards"). Digits are said at a rate of 1 digit per second, and each quantity of digits is attempted twice. The test ends when both sets of the same number of digits are failed. For the forward direction, the list has a maximum of 8 digits (score range: 0-16). The FDST is a sub-test of the Wechsler Adult Intelligence Scale-III,[28] and translations were provided by the publisher (The Psychological Corporation, New York, NY).

Backwards Digit Span Test (BDST)

The Backwards Digit Span Test (BDST) was designed to evaluate a different component of working memory – the visuospatial sketchpad.[31] This is the component of mental faculty that provides a virtual environment for manipulation and optical memory recall. Like the FDST, in the BDST, the interviewer provides a list of numbers with increasing quantity of digits, but this time asks the participant to say them back in the reverse order ("backwards"). In contrast to the FDST, this test requires not just auditory recall but also includes spatial and transformative elements,[33] which can be imagined as "picturing" the digits in opposite order. This test is also more closely related to IQ than is the FDST.[34] Digits are said at the same rate and frequency as the FDST (1 digit per second, each number of digits is repeated twice). The BDST test has a maximum of 7 digits (score range: 0-14). The BDST is also a sub-test of the Wechsler Adult Intelligence Scale-III.[28]

Digit Symbol Coding Test (DSCT)

The Digit Symbol Coding Test (DCST) is a composite test of graphomotor speed (the speed with which one can write down thoughts), perceptual speed (the ability to compare numbers, objects or patterns), and visual-scanning efficiency (the ability to locate targets on a page), and is highly sensitive to neuropsychologial dysfunction.[35] This test consists of a series of digit-symbol pairs, followed by a list of symbols (e.g., +, >). The participant is asked to match the corresponding number to each symbol as quickly as possible, over a maximum period of 120 seconds. There are 133 symbols listed; this is the highest score a participant can achieve on this test. Like the FDST and BDST tests, the DCST is also a subset of the Wechsler Adult Intelligence Scale-III.[28]

Cognitive Abilities Screening Instrument (CASI)

The Cognitive Abilities Screening Instrument (CASI) is a longer and more complex test than the previous three. This tool measures global function, and was developed in 1994 explicitly for cross-national studies to screen for dementia.[29] The CASI combines aspects of the most common dementia screening tests in the US (the Mini-Mental State Exam) and Japan (the Hasegawa Dementia Rating Scale), and has been previously translated and employed in both Spanish and Chinese.[36,37] The CASI has a 100-point scale and was developed to include the following domains: attention, concentration, orientation, short-term memory, long-term memory, language abilities, visual construction, list-generating fluency, and abstraction/judgment. Strengths of the CASI include its short administration time relative to other dementia screening tests (the CASI can typically be administered in 15-20 minutes) and its cultural adaptability.[29] The CASI is often used to screen for cognitive impairment, and as such may be more appropriate

for identifying persons requiring greater evaluation for conditions such as dementia and Alzheimer's disease than subtle neurological dysfunction.[38-40]

Training and Administration

A centralized training of the cognitive evaluations was held prior to MESA Exam 5, during which clinic staff were trained and certified in the administration of each of the four tests.[30] Certification included a taped session of the full battery of tests reviewed by senior faculty with expertise in neuropsychological testing, and conference calls were held throughout the exam period to reinforce the protocol and answer staff questions. Responses on the CASI were collected using an electronic tablet system with total scores automatically calculated. The FDST, BDST and DSCT were administered on paper and electronically entered at a later date.[30]

Statistical Analysis

For the primary analysis, the hypothesized associations were examined for cross-sectional associations according to:

$$Y = \beta_0 + \beta_1 X + \beta_2 Z + \beta_3 (XZ) + \beta_4 S + \varepsilon$$

where:

Y = score on FDST, BDST, DSCT, or CASI;
X = predicted dietary OP exposure
Z = frequency of reported consumption of organic produce
S = adjustment variables, such as age, gender, race/ethnicity, income, education, supermarket density, etc.

This hierarchical analysis included three models, with increasing control for potential confounders and effect modifiers, which we approached in a staged manner. Model 1 was the base model, including individual-level age, gender, race/ethnicity, site, education and income. Model 2 further included frequency of organic produce consumption as a potential modifier of

the relationship between predicted dietary OP exposure and cognition. Model 3 added to Model 2 the neighborhood-level variables that were associated with organic food consumption habits in Chapter II (supermarket density; self-report of neighborhood produce availability; and aggregated neighborhood survey regarding produce availability).

Model 2 was considered the primary model, since Model 3 included more than 700 MESA participants for whom these neighborhood-level variables are not available (individuals who did not participate in MESA Neighborhood, the ancillary study to MESA in which these variables were generated). A sensitivity analysis included a variable to indicate the presence of apolipoprotein E (APOE) ε4 allele, the only recognized genetic risk factor for the sporadic form of Alzheimer's disease.[41] A second sensitivity analysis included participants who responded "I do not eat the food" to the Exam 5 FFQ questions regarding organic food consumption; in this sensitivity analysis, these participants were assumed to "rarely or never" consume organic produce. All analyses employed generalized linear regression methods (proc glm, SAS v9.3, Cary, NC).

Results

A total of 4,505 participants completed the Exam 5 FFQ, and 4,466 answered the questions related to organic food consumption. Of these, 707 responded to these questions by saying "I do not eat the food" and were thus excluded from the primary analyses. Of the remaining 3,759, a total of 124 failed to provide data on household income and 7 failed to provide information on education level; these individuals were also excluded from this analysis, leaving a total of 3,628. All but 15 of these participants completed at least one of the four cognitive tests, so 3,613 individuals were included in the primary analyses described here. Neighborhood-level data were not available on 721 participants who were not a part of MESA

Neighborhood and therefore analyses that employed these variables (e.g., Model 3) included a sample size of 2,892.

Bivariate Comparisons

Individual-level demographic and SES characteristics of this cohort, as well as the neighborhood-level measures of produce availability, the frequency of organic produce consumption, and summary scores from each of the cognitive tests, are shown in Table IV.1. These descriptive statistics are provided both for the cohort as a whole and separately by tertile of predicted dietary OP exposure. Exposure tertiles are as follows: the lowest tertile represents predicted dietary OP exposures less than 1.95 ng/kg-day; the middle tertile includes exposures between 1.95 and 4.29 ng/kg-day; and the highest tertile includes exposures greater than 4.29 ng/kg-day.

This table shows some interesting and, from a health behaviors perspective, contradictory information. As described earlier in Chapter III, participants in the highest tertile of predicted dietary OP exposure also have diets higher in fruits and vegetables. Other – likely related – characteristics of participants with the highest dietary OP exposure include somewhat higher incomes and strikingly greater education levels. For example, nearly half (48%) of the individuals in the highest tertile of predicted OP exposure have a college degree or greater, compared to just a third (33%) of individuals in the lowest tertile of predicted OP exposure. Thirty-one percent (31%) of those in the highest tertile of predicted exposure have a total household income greater than $75,000 per year, compared to 26% of those in the lowest tertile. Individuals in the highest tertile of exposure also tend to have more supermarkets around their homes, and there is slightly greater perception of neighborhood produce availability (both by self-report and by other members of the community).

On the other hand, in addition to having higher OP exposure, individuals in the highest tertile of predicted exposure are also more likely to eat organic food at least occasionally than are those individuals in the lowest tertile of exposure (54% compared to 37%). Participants in the highest tertile of predicted exposure are also a bit older than those in the lowest tertile – 34% of those in the highest tertile are over the age of 75, compared to 28% of those in the lowest tertile.

In the unadjusted totals shown in Table IV.1, scores on all four of the cognitive tests increase slightly across tertiles of exposure, an increase that may not be surprising given the higher levels of produce intake and higher individual-level socioeconomic characteristics, observed across tertiles. This speaks to the critical importance of appropriate control for confounding in this study.

Association between dietary OP exposure and cognition

As described in the Methods section, this evaluation of the relationship between long-term dietary OP exposure and the results of the cognition testing in MESA incorporated three staged epidemiological models with increasing control for potential confounding and modification. Model 1 included individual-level demographic and SES variables: age, sex, race/ethnicity, metropolitan area, education and income. In Model 2, we added organic food consumption habits as a potential modifier between the exposure-response relationship, and Model 3 further added neighborhood-level characteristics related to produce availability. The results of these analyses are shown in Figures IV.1 through IV.4 for the FDST, the BDST, the DSCT and the CASI, respectively. The difference in score shown is per one ng methamidophos equivalents per kg body weight per day.

These figures show that for three of the four tests of cognition, there was no relationship between dietary OP exposure and cognition, regardless of model staging. However, as shown in

Figure IV.1, increasing long-term dietary OP exposure was associated with decreasing FDST score. For each additional 1 ng/kg-day of dietary OP exposure, there was a 0.04 decrement in FDST score. The interquartile range for dietary OP exposure in the MESA cohort (see Chapter III) was approximately equal to 4 ng/kg-day. Therefore, an interquartile difference in dietary OP exposure was associated with a decrement in 0.16 units (or digits) on the FDST test, which is approximately the same scale of effect as 5 years of age in this cohort, based on the same model. These results were not sensitive to inclusion of an indicator for the presence of the APOE ε4 allele.

These results also did not differ substantially by treatment of the individuals who responded to the questions regarding organic produce consumption by selecting "I do not eat the food". In a sensitivity analysis including these individuals, there was no relationship observed between dietary OP exposure and outcome on the BDST, the DSCT, and the CASI. For the FDST, Models 1 and 2 showed similar, but slightly attenuated, associations between dietary OP exposure and FDST score (Model 1: -0.02 FDST units per 1 ng/kg-day, CI: -0.04 to -0.0004; Model 2: -0.03 FDST units per 1 ng/kg-day, CI: -0.06 to -0.0006). The results for Model 3, which included the neighborhood-level variables and therefore included fewer participants, were similar but no longer statistically significant (Model 3: -0.02 FDST units per 1 ng/kg-day, CI: -0.05 to 0.01).

Discussion

To our knowledge, this study was the first to explore the relationship between dietary OP exposure and neurocognition in a large cohort of non-occupationally exposed adults. This unique analysis employed a novel exposure assessment method and the results of a battery of tests reflecting different cognitive domains to evaluate this potential association in a multi-city,

multi-ethnic population. We did not find OP exposure to be associated with the visuospatial component of working memory, with speed of mental processing or with global cognitive health. We did, however, observe a relationship between increasing dietary OP exposure and decrements in the phonological loop component of working memory, as measured by the Forwards Digit Span Test.

An important strength of this study was the inclusion of all four cognitive tests, which provide complementary, but not necessarily overlapping, information regarding cognitive function. When this study was originally proposed,[42] it was anticipated that OP exposure would be most likely to lead to effects that would be observed by the Forwards and Backwards Digit Span Tests, rather than the Digit Symbol or CASI tests. This hypothesis was primarily based on a study of OP exposure and neurocognition among Hispanic farmworkers, conducted by Rothlein and colleagues in 2006.[21] That study involved a comprehensive exposure assessment, including measurement of urinary biomarkers and of OP residues in environmental samples, in addition to occupational class. The researchers evaluated neurobehavioral performance on a battery of 16 tests, including the FDST, the BDST, and the DSCT. The most marked differences across all 16 tests were observed for the digit span tests, with agricultural workers performing more poorly on both the FDST ($p = 0.10$) and the BDST ($p = 0.01$). Though agricultural workers also performed more poorly on the DSCT, this test did not reach significance ($p = 0.38$).

To our knowledge, no studies of OP exposure have employed the CASI to measure potential adverse health effects. Several of the domains of the CASI have not previously been studied in conjunction with OP exposure, including language abilities and list-generating fluency. Others, such as long-term memory, have been evaluated in the context of OP exposure, but no significant effects have been reported. Some of the other domains in CASI overlap with

the other test included here; for example, concentration is measured using a modification of the backwards digit span test.[29] While interesting as a comprehensive measure of global cognitive health relevant to a cross-cultural population, we did not have the *a priori* expectation that OP exposure should lead to large decrements on the CASI, primarily due to the global nature of the test.[42] We were concerned that the multitude of functional assessments included could dilute results in domains we anticipated to be more susceptible to OP exposure.

Our finding that dietary OP exposure was associated with score on the FDST is suggestive of a potential health effect, but the lack of a comparable finding on the BDST makes interpretation of these results more difficult. While it is true that these two tests capture distinct neurological functions,[33,34] it is possible that very low level OP exposure has more impact on the phonological loop component of working memory than on other domains. As discussed in more detail previously in Table I.1, it is not uncommon for studies of occupational OP exposure to find significant differences on some, but not all of these tests.

While significant results of a single test must be interpreted with caution, the magnitude of effect suggested may have some health relevance. We observed a decrement of 0.16 digits in FDST associated with an increase in exposure of 4 ng/kg-day, an amount approximately equal to the interquartile range of exposure among the MESA population. This statistically significant difference is similar to the effect of approximately 5 years of age in this cohort, derived from the same model.

We previously measured urinary OP metabolites in 698 MESA participants at Exam 5 as part of the urinary biomonitoring work described in Chapter III. While not a random sample of the MESA population, it is interesting to note that measurable levels of urinary OP metabolites were detected in 93% of these samples. This is consistent with previous findings from the

National Health and Nutrition Examination Survey, in which detectable OP metabolites were observed in 96% of the US population.[4] Other studies in the NHANES dataset have previously shown that some of the highest levels of OPs are found in older adults in similar age brackets as those in this study.[43] Therefore, while this effect size might be considered small at the individual level, the prevalence of the exposure suggests that there could be significant implications at a population level.

In addition to the comprehensive battery of cognitive tests available in MESA, this study is also strengthened by the novel exposure assessment method it employs. As described in detail in Chapter III, OP exposure is typically measured using urinary biomonitoring, an approach with many significant limitations for assessment of long-term dietary exposure.[44] In contrast to urinary biomonitoring, the FCCR approach employed here allowed us to account for varying toxicity across OPs to which individuals are exposed, representing a chronic scale of exposure and exposure to parent compounds rather than to preformed metabolites (see Chapter III for further discussion).

A further strength of this analysis was the incorporation of information on organic food consumption habits. Previous studies have shown that consumption of an organic diet can lead to marked and immediate reductions in OP exposure,[45-47] and yet to date, most studies of OP exposure have not considered this potentially important variable. In our current analysis, we incorporated organic food consumption as a potential modifier of the relationship between predicted OP exposure (based on dietary intake) and health outcome. This approach seemed appropriate given that the effect of food intake choices on cognition should be different based on whether or not that food is grown with the use of OP pesticides. As shown in Figure IV.1, the effect estimate resulting from Model 2 (which includes organic food consumption) was about

40% greater than the effect estimate resulting from the model without this variable (-0.041 vs -0.025), although the confidence intervals were also wider.

This analysis was also able to take advantage of careful consideration of potential confounders at both the individual- and neighborhood-level, particularly with respect to understanding factors associated with organic food consumption. As we continue to increase our understanding of the influence of location on health,[48] these types of analyses are likely to become more frequent.

Though this study had important strengths, it also had several notable limitations. First, this was a cross-sectional analysis, and so despite the observation of a significant relationship between dietary OP exposure and working memory, we cannot draw causal inference from this analysis. This study was also complicated by the fact that estimation of OP exposure is intrinsically tied to produce consumption, a behavior with known health benefits. To address this issue directly, we analyzed the direct association between total produce intake and scores on the cognitive tests. After accounting for socioeconomic and demographic factors, no relationship was observed between produce intake and cognitive test scores, increasing our confidence that dietary OP exposure was responsible for the effects observed.

While organic food consumption clearly has the potential to play a critical role in dietary OP exposure, very few (6%) MESA participants reported that they "often or always" consumed organic food. If a larger number of MESA participants were habitual organic food consumers, we could have made more direct comparisons of cognitive outcomes in groups of individuals with and without organic diets. It is worth noting that even among the subset of individuals who reported that they "often or always" consumed organic food, we observed OP exposure based on urinary biomonitoring (Chapter III, Figure III.5). We assumed that this is due to the fact that

"often" does not mean "always" and that individuals who ate organic food most frequently also ate the largest quantity of produce in general. The intermediate category of organic food consumption frequency, "sometimes", is also difficult to quantify. It is likely that this category represented a broad range of organic consumption habits within the MESA cohort. This study would be improved by a more comprehensive characterization of organic food consumption habits and ideally would occur in a population with a larger proportion of regular organic consumers. However, MESA is an observational study of older adults, reflecting a multi-ethnic population, and the reported frequency of organic food consumption is consistent with what we would have expected from previous studies.[49,50]

To our knowledge, this is the first study to investigate non-occupational OP exposure in a population of older adults. This study therefore provides a valuable addition to the existing literature, but there is a reason that previous research has focused on pregnant women and children. Compared to the general adult population, children have higher rates of metabolism, less mature immune systems, and unique diets, all of which may lead to higher risks from pesticide exposures.[51] It is therefore possible that low-level exposures to OPs may lead to effects in children not observed in other populations. On the other hand, older adults also have some of these same unique characteristics – they too have dietary differences compared to the general public, and are perhaps more susceptible to neurotoxins given that conditions like Parkinson's and Alzheimer's are diseases of the elderly. National data shows that older Americans experience some of the highest OP exposures,[43] and therefore it is critical that we fully understand the potential for health effects from these exposures in this population.

Conclusions

This study demonstrates a statistically significant decrement in the phonological loop component of working memory associated with increased dietary exposure to organophosphate pesticides. OP exposure was not associated with three other measures of cognition, including the visuospatial component of working memory, speed of mental processing, or a more global measure of cognitive health. This finding suggests that there may be a health benefit to reducing dietary OP exposure, although this effect is only reflected in one cognitive domain. It is worth noting that a staggering number of studies have demonstrated clear health benefits from consumption of a healthy diet including fruits and vegetables. While not the focus of this research, we believe that the health benefits of consuming a diet rich in fruits and vegetables significantly outweigh the potential adverse health effects of low levels of dietary OP exposure. However, OP exposure can also be reduced by consuming an organic diet, or by preferentially consuming organic versions of those fruits and vegetables known to contain higher levels of pesticide residues.

In addition to contributing to the literature regarding the potential for health effects of low-level dietary OP exposure, this study also provided us an opportunity to use the novel exposure assessment methodology developed in Chapter III in an epidemiological context. This exposure assessment methodology is relatively inexpensive and non-invasive, and can easily be transferred to other populations – particularly those populations in which dietary intake data is already available. Future research to understand the effects of low-level dietary OP exposure in multiple populations will further inform the extent to which dietary choices, such as the decision to consume organic food, can improve cognitive health.

Tables and Figures

Table IV.1 Characteristics of MESA participants who provided demographic data, completed the Exam 5 FFQ and completed at least one of the four cognitive tests.
Distributions are presented both for the full cohort and by tertile of predicted dietary OP exposure. Values are counts unless otherwise indicated; totals add down rows within a category.

		Tertile of Predicted Dietary OP Exposure		
	Full cohort	<1.95 ng/kg-day	1.95 – 4.29 ng/kg-day	>4.29 ng/kg-day
N	3613	1204	1204	1205
Gender				
Female	1929 (53%)	497 (41%)	665 (55%)	767 (64%)
Male	1684 (47%)	707 (59%)	539 (45%)	438 (36%)
Race/ethnicity				
White	1484 (41%)	397 (33%)	517 (43%)	570 (47%)
Chinese	426 (12%)	170 (14%)	141 (12%)	115 (10%)
Black	960 (27%)	334 (27%)	327 (27%)	299 (25%)
Hispanic	743 (21%)	303 (25%)	219 (18%)	221 (18%)
Site				
Winston-Salem, NC	571 (16%)	167 (14%)	205 (17%)	199 (17%)
New York, NY	524 (17%)	199 (17%)	189 (16%)	236 (20%)
Baltimore, MD	504 (14%)	161 (13%)	169 (14%)	174 (14%)
St. Paul, MN	586 (16%)	258 (21%)	178 (15%)	150 (12%)
Chicago, IL	655 (18%)	173 (14%)	234 (19%)	248 (21%)
Los Angeles, CA	673 (19%)	246 (20%)	229 (19%)	198 (16%)
Age				
45 – 54	61 (2%)	21 (2%)	25 (2%)	19 (2%)
55 – 64	1274 (35%)	430 (36%)	435 (36%)	409 (34%)
65 – 74	1167 (32%)	411 (34%)	378 (31%)	378 (31%)
75 – 84	886 (25%)	278 (23%)	295 (25%)	313 (26%)
85 or older	221 (6%)	64 (5%)	71 (6%)	86 (7%)
Total household income				
<$30,000	1150 (32%)	419 (35%)	374 (31%)	357 (30%)
$30,000 - $75,000	1412 (39%)	470 (39%)	473 (39%)	469 (39%)
> $75,000	1051 (29%)	315 (26%)	357 (30%)	379 (31%)
Education				
High school or less	1045 (29%)	403 (33%)	349 (29%)	293 (24%)
Some college	1088 (30%)	401 (33%)	353 (29%)	334 (28%)
College degree or more	1480 (41%)	400 (33%)	502 (42%)	578 (48%)
Organic consumption habits				
Rarely or never	1959 (54%)	763 (63%)	643 (53%)	553 (46%)
Sometimes	1438 (40%)	404 (34%)	480 (40%)	554 (46%)
Often or Always	216 (6%)	37 (3%)	81 (7%)	98 (8%)
Cognitive Score: Mean (standard deviation)				
FDST (n=3603)	9.8 (2.8)	9.8 (2.9)	9.7 (2.7)	9.8 (2.8)
BDST (n=3603)	5.7 (2.4)	5.5 (2.4)	5.7 (2.3)	5.9 (2.5)
DSCT (n=3295)	51.8 (18.3)	50.6 (17.9)	52.4 (18.0)	52.4 (18.9)
CASI (n=3555)	87.8 (10.7)	86.8 (10.8)	88.1 (10.7)	88.4 (10.5)
Neighborhood characteristics (n = 2892): Mean (standard deviation)				
Supermarket density (w/in 1 mile)	1.6 (2.1)	1.5 (2.1)	1.6 (2.1)	1.7 (2.3)
Self-report of produce availability	3.9 (1.1)	3.7 (1.1)	3.9 (1.1)	3.9 (1.1)
Aggregated neighborhood survey	3.8 (0.3)	3.7 (0.3)	3.8 (0.4)	3.8 (0.3)

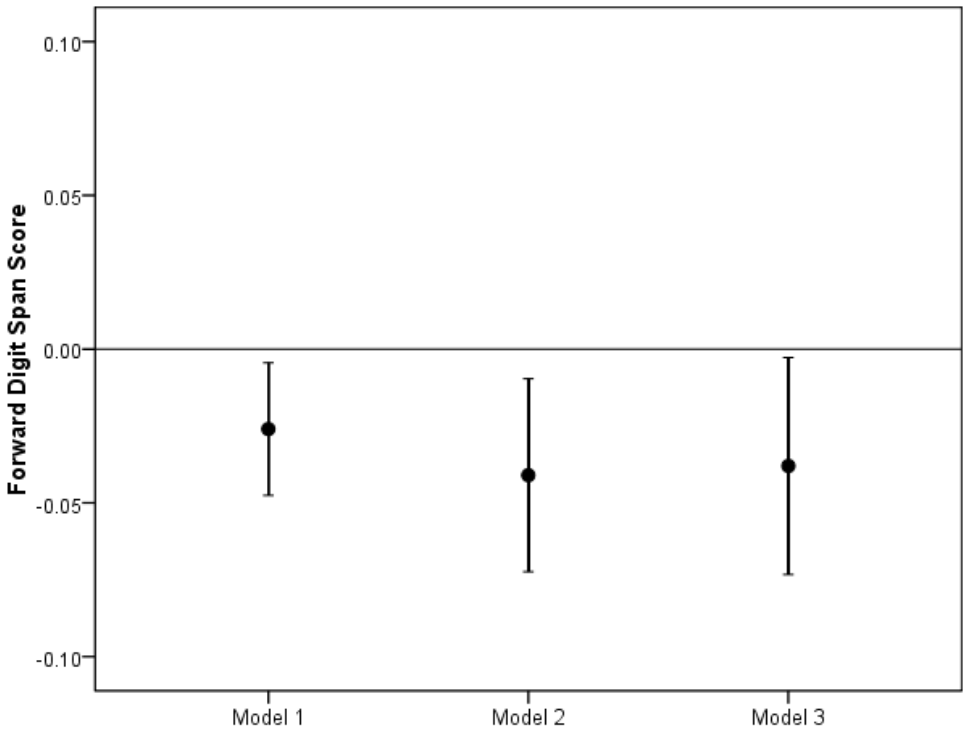

Figure IV.1. Change in FDST score per 1 ng/kg-day increase in dietary OP exposure.
Model 1 included adjustment for individual-level demographic and SES factors: age, sex, race/ethnicity, metropolitan area, education and income.
Model 2 added to Model 1 organic food consumption as an interaction term with dietary OP exposure.
Model 3 added to Model 2 factors associated with neighborhood-level produce availability.

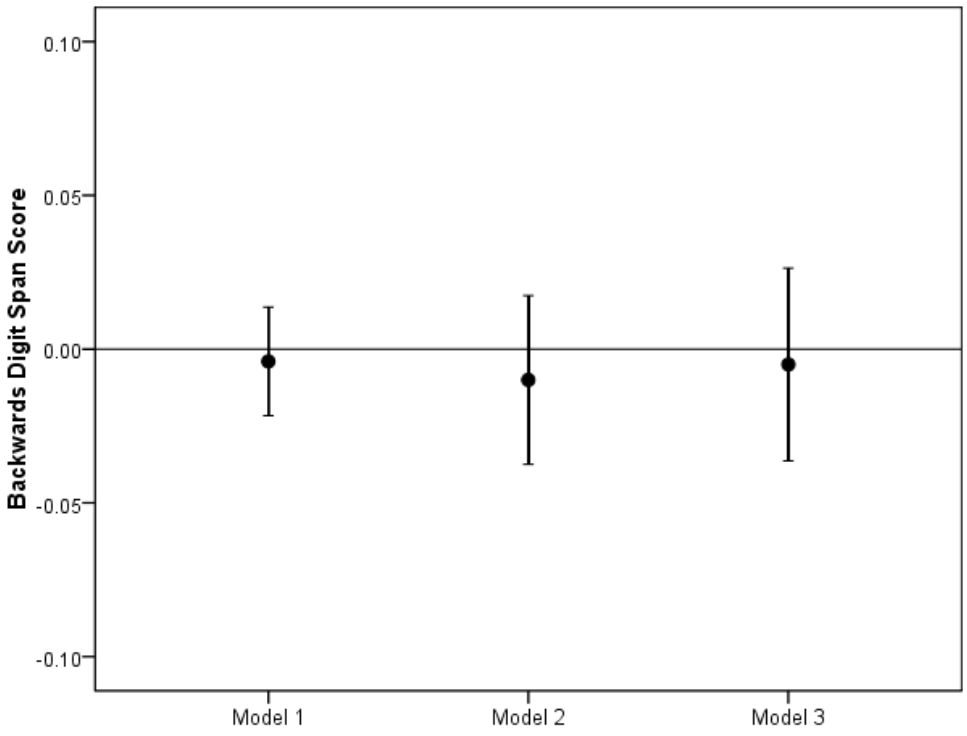

Figure IV.2. Change in BDST score per 1 ng/kg-day increase in dietary OP exposure.
Model 1 included adjustment for individual-level demographic and SES factors: age, sex, race/ethnicity, metropolitan area, education and income.
Model 2 added to Model 1 organic food consumption as an interaction term with dietary OP exposure.
Model 3 added to Model 2 factors associated with neighborhood-level produce availability.

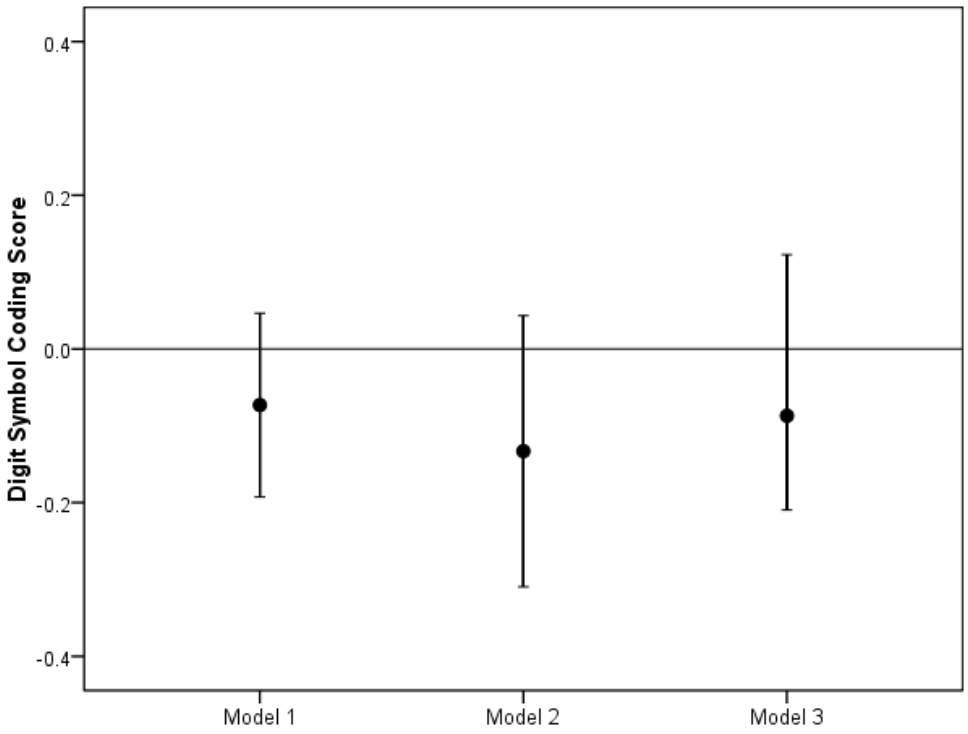

Figure IV.3. Change in DSCT score per 1 ng/kg-day increase in dietary OP exposure.
Model 1 included adjustment for individual-level demographic and SES factors: age, sex, race/ethnicity, metropolitan area, education and income.
Model 2 added to Model 1 organic food consumption as an interaction term with dietary OP exposure.
Model 3 added to Model 2 factors associated with neighborhood-level produce availability.

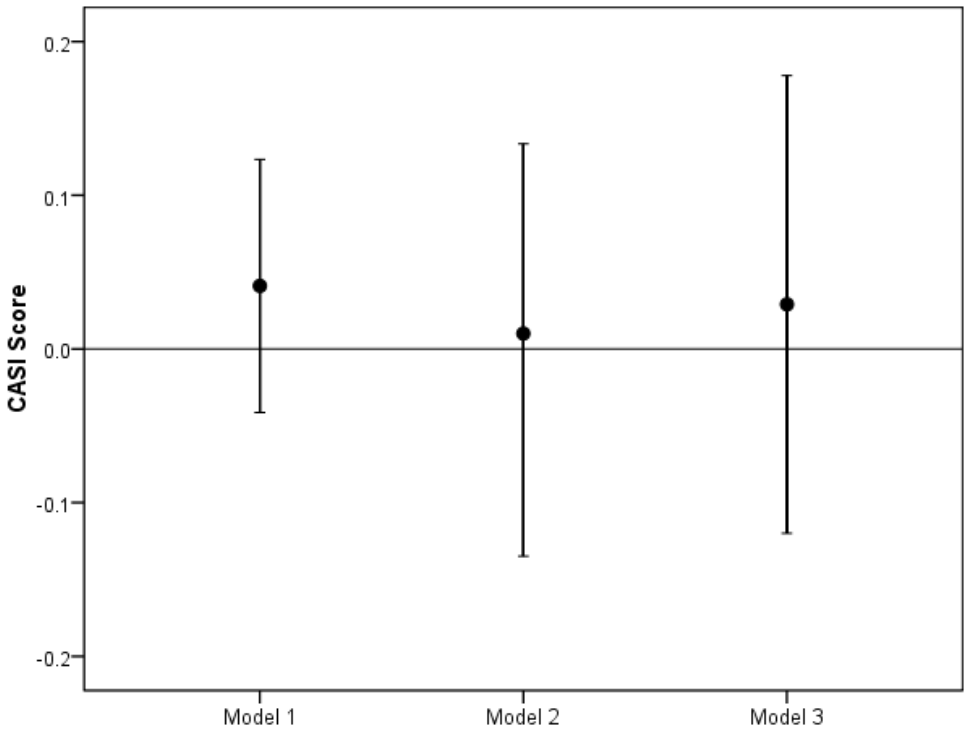

Figure IV.4. Change in CASI score per 1 ng/kg-day increase in dietary OP exposure.
Model 1 included adjustment for individual-level demographic and SES factors: age, sex, race/ethnicity, metropolitan area, education and income.
Model 2 added to Model 1 organic food consumption as an interaction term with dietary OP exposure.
Model 3 added to Model 2 factors associated with neighborhood-level produce availability.

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CHAPTER V. Conclusions

Study Context

As a discipline, environmental health seeks to understand the ways in which the natural and built environment may affect human health, and the central goal of an environmental health scientist is promote public health. One of the ways that we do this is by trying to understand whether people are coming into contact with contaminants that are causing them harm. From there, we borrow from translational science as we try to make this information useful to the public. We develop appropriate interventions at either the community level, by enacting legislation that will reduce exposure (e.g., air quality regulations), or at the individual level, by providing people with information about risks and effective risk reduction techniques (e.g., lead paint abatement).

In the case of organic food, an intervention has been developed for a risk that has not yet been characterized. And unlike many environmental health issues, which may only affect people living in certain places or who partake in certain activities, the question of whether to choose organic food is one faced by almost anyone who enters a grocery store. Organic food is sold in more than 80% of American groceries,[1] and it is sold at a premium, requiring that individuals, on an almost daily basis, make a choice about whether to spend more money on foods which may or may not provide a health benefit to them or their families.

It is certainly worth noting that there are other reasons that someone might choose to purchase organic food, some of which are less ambiguous than the question of whether organic food is healthier for the consumer than conventional food. Organic growing practices clearly promote ecological health in comparison to conventional practices.[2] Organic farming uses less synthetic fertilizers and pesticides, which reduces runoff to streams and other waterways; it encourages soil quality and biodiversity through crop rotation practices; and it uses less energy

and produces less waste.[3] Organic farming practices also reduce the frequency of farmworker poisonings, by reducing the opportunity for workers to come into contact with toxic chemicals.

However, for many in the general public, these are not the aspects of organic food that are most important. There is tremendous public interest in understanding whether organic food is healthier than conventional food, either due to improved nutrient content or to reduced contamination. Truly, the public's interest in this topic cannot be overstated, perhaps because this choice is both ubiquitous and personal, but also because information on the potential health benefit of organic food is scarce and, when available, often contradictory.[4-8]

Most researchers do agree that consumption of organic food can reduce dietary exposure to pesticides. This conclusion is drawn both from studies of pesticide residue levels on food items[9] and of biological levels of pesticide metabolites in consumers of organic and conventional food.[10-12] Unfortunately, no one has been able to conclude whether reductions in dietary exposure to pesticides actually lead to a difference in health. This is a classic environmental health problem: Are people coming into contact with pesticides in their diets that are causing them harm? We have a responsibility as public health practitioners to provide better guidance on this topic, particularly given that an intervention already exists, and that we are currently asking people to make this decision without adequate information.

Summary of Results

In the first study presented in this dissertation, we examined characteristics associated with the decision to consume organic food (Chapter II). Ours is not the first study to address this question. Several previous researchers have explored the demographic and socioeconomic status (SES) variables most likely to be associated with organic consumers.[13-28] These studies showed some consistencies (all found women more likely to buy organic food than men) and some

contradictions (most notably with respect to the relationship between income and organic food consumption). Perhaps the most compelling finding of these studies was that the factors most associated with the decision to consume organic food were personal values, perceptions and beliefs about the healthfulness of organic food.[15,27,28] This finding further speaks to the need to provide the public with concrete information about the true costs and benefits of this dietary choice, given that this is perhaps the primary basis on which this choice is made.

Our investigation of the factors associated with organic food consumption did not incorporate information on food beliefs, but did expand the existing work in this area to a large, multi-city cohort, the Multi-Ethnic Study of Atherosclerosis. We examined the factors associated with organic food consumption within a broad framework, including a variety of individual-level demographic and SES variables, as well as features of the neighborhoods in which people live. We found several individual-level variables to be associated with organic food consumption: women, younger individuals, those with higher education, and those living in more urban regions consumed organic food more frequently than the rest of the cohort.

We also found that people who live in neighborhoods with more supermarkets and a perception of greater produce availability were more likely to be at least occasional consumers of organic food, even after control for individual-level variables. This may cautiously be interpreted to mean that, all other things being equal, if a person lives in a neighborhood where supermarkets and produce options are more available, they are more likely to eat organic food. A similar association has been well established with respect to healthy food environments. A number of studies over the past decade have shown that better access to healthy foods is associated with better diets,[29-34] but to our knowledge, ours is the first study to show a relationship between neighborhood food environment and the decision to consume organic food.

There is at least one obvious difference in researching the relationships between the local food environment and consumption of organic diets as compared to healthy diets: we know that healthy diets improve health but the same cannot be said about organic diets. Therefore, while we can speak about the environmental justice issues related to food deserts in the context of dietary quality, we do not know if improved access to organic food provides people with a healthier option, or just a more expensive one.

One reason that we do not have a better understanding of the potential health benefits of eating organic food is that accurately assessing long-term dietary pesticide exposure is extremely difficult. This dissertation focuses on understanding dietary exposure to one class of pesticides, organophosphates, which are the most widely-used insecticides in American agriculture. Currently, the most common method for measuring low-level exposure to OPs is through urinary biomonitoring. As discussed in Chapter III, this is far from a gold standard for measuring long-term dietary OP exposure. OP metabolites have short half-lives, only representing exposures over approximately two days prior to sample collection,[35-37] and within-individual measurements are highly variable.[38-40] Further, OP metabolites can be found – preformed – in food items, potentially resulting in overestimation of exposure.[41,42] For these and other reasons, we aimed to develop a new method for assessing long-term dietary OP exposure. This method was intended to accurately quantify exposure to specific parent compounds of known toxicity and to reflect typical, rather than acute, exposures.

Chapter III of this dissertation described our proposed method, in which we combined information on typical intake of specific food items from food frequency questionnaires (FFQ) with average OP residue levels on those items from national databases. We successfully employed this method to estimate long-term dietary OP exposure to more than 4,000 participants

in MESA, thereby maximizing existing FFQ data to provide inexpensive, non-invasive estimates of exposure.

We further assessed the relationship between the estimates we generated and measurements of urinary metabolite concentrations in a subset of participants with conventional diets, in an attempt to provide a check of the face validity of our estimates. We hypothesized that individuals with higher estimated OP exposures would, in aggregate, have higher metabolite concentrations in any given spot urine sample than those with lower estimated exposures. As hypothesized, individuals within groups defined by higher predicted exposures also had higher concentrations of OP metabolites in their urine than individuals within groups defined by lower predicted exposures. The results of these urinary analyses increased our confidence in this new methodology.

We were also interested in understanding the influence of self-reported organic produce consumption habits on OP exposure, as we hypothesized that this might be another dietary characteristic that we would need to understand in order to adequately estimate exposure. We measured OP biomarker levels in three subsets of MESA participants with similar produce intake but differing frequency of organic food consumption. We found that biomarker levels were significantly lower in groups reporting more frequent consumption of organic produce. This finding adds to the existing literature showing that consumption of an organic diet can lead to measurable reductions in pesticide exposure, and suggests that methods that employ self-reported dietary intake data to estimate pesticide exposures should also consider organic food consumption habits.

The basic framework of this method – combining dietary intake data with pesticide residue data – can be applied to any population in which food frequency questionnaire data is

available and any class of chemicals for which there is residue data. By varying the length of dietary recall (e.g., asking about consumption patterns over the past week, during the current season, or over the past year), this method could be used to explore acute, sub-chronic, and chronic timeframes of exposure. In addition to being flexible in terms of timescale and contaminant, this method further ensures specificity to parent compounds. This latter characteristic is crucial, as it allows quantification of toxicity-based risk and removes the possibility of inadvertently assessing exposure to preformed metabolites, both of which are potential pitfalls of urinary biomonitoring. While there are important limitations to this method (outlined in Chapter III), its strengths – including its flexibility, inexpensiveness, and non-invasiveness – suggest that this methodology has the potential to be broadly useful.

The exposure assessment presented here focused on organophosphate pesticides both because of their widespread use and because of their well-recognized toxicity. The third section of this dissertation investigated whether this toxicity was sufficient to lead to health effects in a non-occupationally exposed cohort of older adults. OPs are neurotoxins, with known health effects at high exposure levels and suspected effects at lower exposure levels. Several recent cohort studies of mother-child pairs have shown significant associations between low-level prenatal and childhood exposure to OPs and a number of neurological and cognitive health effects, including increased attention deficit-hyperactivity disorder, decreased memory and decreased IQ.[43-46]

There have been also several studies of neurological and cognitive health in adults with occupational exposure, and these studies have not been limited to investigations of acute exposures. On the contrary, a body of literature has investigated the long-term effects of occupational exposure among individuals who have not experienced an acute poisoning.[47-54]

These studies have generally been limited by small sample sizes and imperfect exposure assessment, and do not always demonstrate consistent findings with respect to the specific health effects of OP exposure. Collectively, however, the majority of this research has indicated that occupational OP exposure is associated with neurological and cognitive deficits, and these deficits have most consistently been observed in the results of Digit Span Tests[49,52-54] and Digit Span Coding Tests,[47,48,52] which evaluate working memory and speed of mental processing, respectively. Other studies have shown differences in functions like reaction times and motor steadiness.[50,51]

In the final section of this dissertation (Chapter IV), we examined the relationship between estimated long-term dietary OP exposure and results of a battery of tests reflecting different cognitive domains in the MESA cohort, representing: 1) the phonological loop component of working memory, as measured by performance on the Forward Digit Span Test; 2) the visuospatial component of working memory, as measured by performance on the Backwards Digit Span Test; 3) mental processing speed, as measured by performance on the Digit Symbol Coding Test; and 4) global cognitive function, as measured by the Cognitive Abilities Screening Instrument. This analysis incorporated self-reported organic food consumption habits as a potential modifier of the relationship between predicted dietary OP exposure and cognition. We considered this aspect of the study to be particularly important, given that our exposure assessment methodology incorporates frequency of consumption of given food items but does not explicitly include information on whether that food is organically grown.

We did not find dietary OP exposure to be associated with the visuospatial component of working memory, with speed of mental processing, or with global cognitive health. We did observe a relationship between increasing dietary OP exposure and decrements in the

phonological loop component of working memory, as measured by the Forwards Digit Span Test (FDST). Specifically, we found a 0.04 decrement in FDST score associated with each additional 1 ng/kg-day of dietary OP exposure. As described previously in Chapter III, the interquartile range for dietary OP exposure in the MESA cohort is approximately 4 ng/kg-day. Therefore, we found an interquartile difference in dietary OP exposure to be associated with a decrement of 0.16 units on the FDST test. This is approximately the same scale of effect as 5 years of age in this cohort. This result adds to the growing body of literature indicating a potential health benefit to reducing exposure to OPs. This finding is, however, tempered by the lack of consistency with the other three tests, where no such result was observed.

Extensions of the Current Analyses and Additional Questions

This work advances our understanding of who eats organic food, of the quantity of OP pesticides to which people are exposed through their diets, and of the potential for those exposures to lead to subtle cognitive effects. It also presents a number of opportunities for additional research. It would be extremely valuable to employ this proposed exposure assessment methodology in other cohorts, and to evaluate the results of those assessments with additional biological samples. Ideally, a future analysis would incorporate multiple, repeated biological samples over the course of a longer time period (e.g., bi-weekly, for a year) to provide a better metric of long-term exposure as a comparison.

It would also be useful to conduct this exposure assessment in another cohort in which more participants had consistently organic diets. While 35% of the MESA cohort reported that they "sometimes" ate organic food, only 5% "often or always" did so, and even this category does not necessarily represent individuals with a fully organic diet. We believe that including organic food consumption habits as an effect modifier in our epidemiological analysis was a

critical part of this study. However, organic food consumption habits on their own were not significantly related to cognitive endpoints. We suspect that this was due to the low prevalence of frequent organic consumers and ambiguity around the meaning of "sometimes" consuming organic food. This relationship is further complicated by the fact that people who eat organic food at least occasionally tend to eat more fruits and vegetables than people who primarily eat conventional food. Therefore, occasional organic food consumption may actually be associated with higher absolute OP exposure, due to an increased intake in volume of foods to which OPs are applied.

In MESA, we were limited to adding a small number of questions regarding organic food consumption to an already very long exam. It would be useful for future research to include a more thorough investigation of organic food consumption habits, including differences by individual produce types and times of year, and greater specificity with regards to consumption frequency (e.g., more resolved categories than just "rarely or never", "sometimes" and "often or always").

In some ways, MESA represents a potentially sensitive subpopulation with respect to OP exposure. Older adults are at great risk for neurological and cognitive diseases and national data has shown that older adults also tend to have higher biological levels of pesticide metabolites than younger adults.[55] However, most previous research on OP exposure has focused on pregnant women and children, reflecting important concerns about developing immune systems, unique diets, and small size.[56] Studies of the chronic effects of OP exposure in adult populations have been somewhat variable, even in occupationally exposed populations, whereas the results of studies of low-level exposure in childhood and in utero have been more consistent. We could learn a great deal about the health effects of dietary OP exposure and about the potential benefits

of organic food consumption by conducting a study similar to this one in a cohort of pregnant women or young children. It would be especially valuable to do so in a cohort that included participants with a broad range of organic food consumption habits, intentionally including individuals with consistently organic diets.

Conclusions

This dissertation presents a new methodology to assess exposure to OP pesticides and employs estimates generated from this new method to understand the relationship between dietary OP exposure and the results of tests of several cognitive domains. In this analysis, we incorporated a sophisticated set of confounding variables, which were carefully selected as part of a unique investigation of the individual- and neighborhood-level factors associated with organic food consumption within the MESA cohort. This work adds to the mounting evidence that diet is an important route of OP exposure for the general population and that low-level dietary OP exposure may result in health effects unlikely to be caused by established mechanisms like cholinesterase inhibition.

The results of this analysis suggest that reduced OP exposure may lead to improved performance in at least one cognitive domain, the phonological loop component of working memory. This study is not able to more specifically address the potential for a health benefit from organic food consumption, as the MESA population was not specifically recruited to facilitate that comparison, and the exposure of interest in this study was OP exposure and not necessarily exposure to conventional food. However, given what we know from this study and others about the ability of organic food consumption to reduce dietary OP exposure, it is likely that if our results are correct, consumption of an organic diet may lead to small but measurable improvements in cognitive function in older adults.

End Notes

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VITA

Cynnie Curl was born in Nassawadox, Virginia and grew up on the Eastern Shore of Virginia, a tiny sandbar of a peninsula between the Chesapeake Bay and the Atlantic Ocean. She earned a Bachelor's Degree in Chemistry from Swarthmore College in 1998 and a Master's Degree in Environmental and Occupational Health Sciences from the University of Washington in 2000. After graduation, Cynnie worked as a research scientist with the Pacific Northwest Agricultural Safety and Health Center at the University of Washington, where she studied pesticide exposures to a variety of populations in Washington State. She then spent time studying the school nutrition environment as a scientist with the non-profit Environment and Human Health in New Haven, CT. After a brief stint in environmental consulting, Cynnie returned to academia in 2006, as the project manager of the Multi-Ethnic Study of Atherosclerosis and Air Pollution. In parallel with this position, Cynnie began working towards her Doctor of Philosophy in Environmental and Occupational Health Sciences at the University of Washington in 2008, earning this degree in 2014. Cynnie currently resides in Seattle, Washington, where she and her husband Adam are expecting their first child in the spring of 2014.