AN EXAMINATION OF ORGANOCHLORINE INSECTICIDE EXPOSURES AND ASSOCIATED CANCER RISKS AMONG THE AGRICULTURAL HEALTH STUDY (AHS) FARM SPOUSES

By

LYDIA MARIE LOUIS

A dissertation submitted to the

School of Graduate Studies

Rutgers, The State University of New Jersey

In partial fulfillment of the requirements

For the degree of

Doctor of Philosophy

Graduate Program in Public Health

Written under the direction of

Mark Gregory Robson, PhD, MPH, DrPH

And approved by

_____

_____

_____

_____

_____

New Brunswick, New Jersey
May 2019

ABSTRACT OF THE DISSERTATION

An examination of organochlorine insecticide exposures and associated cancer risks among the Agricultural Health Study (AHS) farm spouses

By: LYDIA MARIE LOUIS

Dissertation Director:

Mark Gregory Robson, PhD, MPH, DrPH

Introduction: Organochlorine insecticides (OCs) are a class of pesticides historically used to control for insects in agriculture worldwide and that are still used in developing countries today for the control of vector borne illnesses. OCs were mostly banned in the United States in the 1970s and 1980s, with lindane and endosulfan having only been banned recently in 2006 and 2010, respectively. The strongest epidemiologic evidence for OC insecticide exposures and cancers comes from occupational and population-based studies of lymphohematopoietic cancers, specifically non-Hodgkin lymphoma (NHL). Many population-based studies evaluating OCs have focused on breast cancer, but the majority of these results have been inconsistent. While most epidemiologic studies of OCs have included male pesticide applicators, few analyses have included female spouses of pesticide applicators, warranting further research to examine the impact of OC exposures on the risk of female-specific cancers. Female spouses of pesticide applicators may be

exposed to OC insecticides from their personal use (i.e., mixing/applying of pesticides), and indirect exposure from non-occupational exposure pathways (i.e., agricultural drift, take-home and residential use). The following projects will explore the impact of both personal use and non-occupational exposures to seven OCs (i.e., aldrin, chlordane, dieldrin, DDT, heptachlor, lindane and toxaphene), with risk of cancer among the Agricultural Health Study (AHS) farm spouses (n=32,345).

Methods: My first aim is to conduct an epidemiologic analyses to examine associations between the AHS farm spouses' personal use of each of seven OCs with total and specific cancers. My second aim is to characterize the AHS farm spouses' non-occupational OC exposures to each of the seven OCs by applying an active ingredient-specific exposure algorithm recently developed by AHS researchers. My third aim is to conduct a second epidemiologic analysis examining the associations between the AHS farm spouses' non-occupational exposures on their risk of developing breast cancer. Together, these aims will elucidate the impact of exposures to seven individual OCs, through personal use and multiple non-occupational exposure pathways, on the risk of cancer among the AHS farm spouses.

Results: In the first aim, most cancers were not associated with OC use. Risk of glioma was increased among users of at least one OC and specifically among lindane users. Multiple myeloma was also associated with chlordane. There were also positive associations between pancreatic cancer and lindane, and ER-PR- breast cancer and dieldrin.

The second aim identified an additional 1.2-10.0% of female farm spouses exposed to individual OCs through individual non-occupational pathways. In addition, I captured variability in OC exposure intensities among the AHS spouses, with ratios of the 75th to 25th percentiles ranging from 2.8 to 8.5. The agricultural drift and take-home pathway estimates were highly correlated with each other across all OCs ($r_s \geq 0.98$). The residential use pathway was not correlated with either the agricultural drift nor take-home pathways for chlordane or heptachlor ($r_s < 0.02$), which were the only OCs with residential use. In the third aim, most individual exposure pathways of individual OCs were not associated with breast cancer overall or with ER+PR+ breast cancer. Toxaphene exposure through the take-home pathway was associated with ER+PR+ breast cancer. Aldrin and toxaphene exposures through the agricultural drift pathway were associated with overall and ER+PR+ breast cancers. Chlordane and heptachlor exposures through the residential use pathway were associated with ER+PR+ breast cancer. Finally, overall non-occupational exposures of aldrin, heptachlor and toxaphene were associated with ER+PR+ breast cancer.

Discussion: This dissertation has demonstrated that exposures to OCs through their personal use and through non-occupational pathways may contribute to an increased cancer risk among female farm spouses of pesticide applicators. Prior to this study, few analyses have examined OC insecticide use and cancer risk among female spouses of pesticide applicators. In addition, studies which have evaluated cancer associations with non-occupational pesticide exposures have been limited by surrogate measurements, unavailable questionnaire information, and non-specific biological markers. Furthermore,

the studies presented herein may help to inform future risk analyses of OC exposures and cancer outcomes, as well as future exposure assessments of non-occupational OC exposures among farm women.

DEDICATION

This dissertation is dedicated to my grandmother, Marie Brulotte Michaud, who taught me to foster resilience and value integrity. Even in her passing, the lessons she bestowed continue to guide me through life's challenges as I approach the future with an optimistic and hopeful heart.

"Je t'aime mémère, grand comme le monde !"

IN MEMORIAM

Two dear colleagues, who were lost too soon, taught me important lessons that have helped give me clarity as to what is most important in life. I think about them often and about the legacies they each leave behind: Mrs. Lakshmi Raman and Dr. Dmitry Govorko

ACKNOWLEDGEMENTS

Throughout my graduate education I have been faced with a myriad of hurdles, many of which often felt impossible to overcome. In reflecting back on these challenging moments, as well as on my successes, I am filled with deep gratitude for those who have continued to support me with their advice, belief in my abilities and care for my personal well-being. First and foremost, I would like to acknowledge my fiancée **Dr. Oliver Lontok** whose support continues to be unflappable and who serves as my biggest cheerleader. In addition, I am fortunate to have several incredibly supportive life-long friends whom are akin to family. Their love for me and belief in me have served as a guiding light during my dimmest moments: **Ms. Ping Yeh, Mrs. Shazia Ansari, Mrs. Jessica Pollak, Mr. Ripple Shah, Mrs. Beth Wright** and **Mrs. Stacey Young**.

I would also like to acknowledge several faculty who have played principal roles in my fondest memories in academia. **Dr. Bruce Babiarz** has been a constant reminder of the academician I strive to be. His passion for science, admirable teaching ability and empathy for students are qualities I hope to emulate, and I cherish him dearly. **Dr. Diana Martin** has been a steadfast supporter since my first week as a freshman biology student. I have greatly enjoyed the evolution of our relationship from student and teacher to colleagues, and am incredibly grateful for the many roles she has played in my life. **Dr. Kathleen Scott** taught me to have confidence in the value of my aptitudes for mentoring students and transmitting my scientific passion. Her confidence in me and appreciation for my work gave me many moments to cherish during times of transition.

Along my journey, there are have been many other faculty and staff who have afforded me opportunities to evolve as a scientist. Each individual has provided critical forms of emotional and academic support, and all of whom have helped me reach important milestones. They include:

Dr. Diane Heck
Dr. Martha Haviland
Dr. Shawna Hudson
Dr. Evelyne Erenrich
Dr. Jerome Langer
Dr. Beatrice Haimovich
Dean Rebecca Reynolds
Dr. Jerald Fagliano
Dr. Emanuel DiCicco-Bloom
Dr. Sally Temple
Mrs. Ghada Endick
Dr. Frank and Mrs. Louise Deis
Dr. Elizabeth Vogel
Mrs. Tracey Hasse
Dr. Brian Buckley
Dr. Lauren Aleksunes

I would also like to acknowledge the Rutgers School of Public Health faculty and staff who have persisted with me during my critical final years as a fellow at the National Cancer Institute (NCI). My doctoral committee members have given me constructive feedback while serving to foster my scientific aptitude and have been a source of positivity: **Dr. Michael Gochfeld, Dr. Jun-Yan Hong** and **Dr. Qingyu Meng**. Additionally, **Dr. Bernadette West, Ms. Karen Meenan, Dr. Alan Monheit** and **Dr. George Rhoads** have provided me consistent encouragement and support as I navigated between two institutions. **Dr. Mark Robson** has remained one of my strongest advocates since my first master's degree. As my doctoral committee chair, he has championed my successes and committed himself whole-heartedly to my academic goals. His continued support and care hold a special place.

I am deeply appreciative for my NCI mentors and advocates. **Dr. Debra Silverman** willingly took me on as a fellow in her branch, and has continued to support me in every endeavor I have pursued. **Dr. Jackie Lavigne** has served as a fully dedicated and unyielding support system, and is someone who I admire and enjoy very much. **Dr. Laura Beane Freeman** and **Dr. Melissa Friesen**, my co-mentors, have reignited my passion for scientific research and have cultivated my scientific and professional talents. They are incredible examples of truly great scientists, whose personal investment in me has been an incredible privilege.

Finally, I would like to acknowledge the NCI staff and fellows who have been instrumental in my successes, and who have provided every imaginable level of support. I am utterly grateful to be able to call them my colleagues and friends:

Dr. Gabriella Andreotti
Dr. Bryan Bassig
Dr. Benjamin Booth
Dr. Catherine Callahan
Dr. Pam Dopart
Dr. Jared Fisher
Ms. Pabitra Josse
Dr. Scott Kelly
Dr. Payal Khincha
Dr. Catherine Lerro
Dr. Tracy Layne
Ms. Sarah Locke
Dr. Erikka Loftfield
Dr. Amy Moore
Dr. Deven Patel
Dr. Jessica Petrick
Dr. Jean-François Sauvé
Dr. Joe Shearer
Dr. Ray Troche
Dr. Alison VanDyke
Dr. Emily Vogtmann

TABLE OF CONTENTS

LIST OF TABLES, EQUATIONS AND FIGURE

Aim 1.

Aim 2.

Aim 3.

LIST OF ABBREVIATIONS

OCs	organochlorine insecticides
IARC	International Agency for Research on Cancer
PCP	pentachlorophenol
DDT	dichlorodiphenyltrichloroethane
TCP	2,4,6-trichlorophenol
HCH	hexachlorocylcohexane
HCB	hexachlorobenzene
NHL	non-Hodgkin Lymphoma
AHS	Agricultural Health Study
MM	multiple myeloma
DLBCL	diffuse large B-cell lymphoma
SEER	Surveillance Epidemiology and End Results
ER	estrogen receptor
PR	progesterone receptor
RR	relative risk
CI	confidence interval
PCB	polychlorinated biphenyl
BEEA	Biomarkers of Exposure and Effect in Agriculture
ELEA	Early Life Exposures in Agriculture

DECLARATIONS

Ethics approval and consent to participate: Study procedures and documents were approved in 1993 by the National Cancer Institute Special Studies Institutional Review Board, Westat Institutional Review Board, and the University of Iowa Institutional Review Board-01.

Availability of data and materials: The data sets used and/or analyzed during the current study may be made available through approval by the Agricultural Health Study executive committee.

Funding: This work was supported by the intramural research program of the NIH, the National Cancer Institute (Z01-CP010119) and the National Institute of Environmental Health Sciences (Z01-ES049030) and by the NIEHS sponsored Center Grant P30 ES005022 and the New Jersey Agricultural Experiment Station.

ACKNOWLEDGEMENT OF PREVIOUS PUBLICATION

Aim 1 analyses of this dissertation have been previously published.

Louis, L.M.[1,2], Lerro, C.C. [1], Friesen, M.C. [1], Andreotti, G. [1], D., Koutros, S. [1], Sandler, D.P. [3], Blair, A. [1], Robson, M.G. [4], Beane Freeman, L.E[1]. *A prospective study of cancer risk among Agricultural Health Study farm spouses associated with personal use of organochlorine insecticides*. Environmental Health. 2017 September 6; 16(1):95. PMCID C5585902

Affiliations:

[1]Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.

[2]School of Public Health, Rutgers University, Piscataway, NJ, USA.

[3]Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, Durham, NC, USA.

[4]School of Environmental and Biological Sciences, Rutgers University, New Brunswick, NJ, US

Chapter 1. An examination of organochlorine insecticide exposures and associated cancer risks among the Agricultural Health Study (AHS) farm spouses

INTRODUCTION

Organochlorine (OC) insecticides are a class of cyclic hydrocarbon chlorinated insecticides that have been historically used to control insects in agriculture and residential settings worldwide and that are still used for the control of vector borne illnesses in developing countries [1, 2]. Developed in the late nineteenth century, OCs came to prevalence of use during World War II (WWII) for the prevention of vector borne illnesses including, malaria, typhus, body lice, and the bubonic plaque. OC insecticides were later introduced in the United States during the 1940s and were widely used throughout the 1960s [3], comprising 72% of total U.S. insecticide use [4]. Early studies raised concern over their environmental persistence as well as potential adverse effects on wildlife and human health [5-7]. As a result, most OC insecticides (e.g., aldrin, chlordane, chlordecone, dieldrin, DDT, endrin, heptachlor, hexachlorocylcohexanes (HCH), methoxychlor, mirex, pentachlororphenol (PCP), and toxaphene) were banned in the 1970s and 1980s [6, 8]. Lindane and endosulfan, the last remaining OC active ingredients, were banned for use in the U.S. in 2006 and 2010 respectively [9, 10].

Although OC insecticides are no longer used in the United States, their derivatives can remain in the environment for extended durations of time and have been designated as persistent organic pollutants (POPs) [11]. Soil half-lives of DDT and its byproducts dichlorodiphenyldichloroethylene (e.g., ρ,ρ'-DDE) have been reported as ranging between 2 and 20 years [12], while in an aquatic environment the half-life of DDT is reported at

150 years [13]. Sources of human OC insecticide exposures include ingestion of contaminated groundwater and food sources, past residential and occupational use, drift from treated fields and take-home pathways [14]. OC insecticides are lipid-soluble and have a propensity to biomagnify through the food chain, deposit into tissues of high fat content [6] and have been known to persist in the human body for up to 50 years [12]. Levels of OC insecticides in human tissues generally increase as a person ages due to cumulative environmental exposure [14].

Because of their persistence and bioaccumulation in humans, there is an interest in understanding the impact of OC insecticides on human health and specifically human cancer risk. Currently, the International Agency for Research on Cancer (IARC) classifies fifteen OC insecticides with respect to their human carcinogenicity. Lindane and PCP [15] have been classified as a human carcinogen (Group 1), dichlorodiphenyltrichloroethane (DDT) [16, 17], aldrin and dieldrin[15], have been classified as probably carcinogenic to humans (Group 2A). 2,4,6-trichlorophenol (TCP) [15], chlordane [18], chlordecone [19], heptachlor [18], HCH [19], hexachlorobenzene (HCB) [18], mirex [19], and toxaphene [18] have been classified as possible human carcinogens (Group 2B). Several others, including endrin, and methoxychlor, were not classifiable with respect to carcinogenicity (Group 3) at the time of their reviews [17, 18].

Evidence for associations between OC insecticide active ingredients and cancer has come mainly from cohort and case-control studies of occupational exposures and lymphohematopoietic cancers [20-27]. An occupational-based analysis from Sweden found a significantly increased risk for multiple myeloma among farmers exposed to DDT

[26]. A population-based case-control study among white men from the U.S. Midwest reported use of lindane as having significantly increased the risk of non-Hodgkin Lymphoma (NHL) by 50% [21]. Based on questionnaire and blood plasma data, two separate case-control studies from Canada found a statistically significant increased risk for NHL with exposure to lindane and aldrin [22], as well as mirex [25] and derivatives of lindane, DDT, and chlordane [25]. OCs and lymphohematopoietic cancers have also been evaluated within the Agricultural Health Study (AHS) applicators [20, 24]. The most recent analysis from this prospective cohort study demonstrated statistically significant increased risks for NHL, with significant positive exposure-response trends for lindane and DDT [20]. In further subtype analyses, lindane was also associated with follicular lymphoma, while DDT was also associated with small cell lymphoma/chronic lymphocytic leukemia/marginal cell lymphoma. These findings were among the first to suggest links between DDT and lindane with NHL subtypes. A previous AHS study analysis also found significantly increased relative risks for leukemia with chlordane and heptachlor use [24]. There is strong evidence that some OC insecticides, including lindane and DDT, cause immunosuppressive effects in humans, as well as oxidative stress; these biological effects are thought to possibly play a role in the development of lymphohematopoietic cancers [16, 28].

Potential associations between OCs and hormonally-mediated cancers, particularly female breast cancer, are of interest due to results of *in vitro* and animal studies that suggest OCs are endocrine disrupting compounds that act as estrogen agonists or antagonists [29, 30]. Breast cancer has been the most frequently examined cancer with OC exposure;

however, the majority of findings have been inconclusive [16, 31]. In an early epidemiologic study, *Wolff et al.* found a two to four-fold increased risk of breast cancer among women with the highest serum DDE levels, with a positive trend with increasing serum DDE [32]. However, a follow-up study with greater sample size found no evidence for an association of breast cancer risk with serum DDE levels [33]. While two studies [34, 35] have suggested an association with dieldrin, other epidemiological studies of OC exposures and breast cancer risk have found null or no positive statistically significant associations [31, 36-42].

Similarly, an analysis of endometrial cancer did not observe statistically significant associations with serum DDE, HCH, HCB, oxychlordane and alachlor [43]. No studies to our knowledge thus far have investigated associations with ovarian or uterine cancers. It is possible that a lack of statistical power or specific information on exposure to OC active ingredients has prevented researchers from determining associations between OC insecticide exposures and female-specific cancers. Nevertheless, the relationship between OCs and hormonally-mediated cancers among women remains unclear.

A few other cancer sites have been evaluated for associations with OCs. According to the IARC, the strongest evidence for associations with cancer at other sites comes from case-control studies of liver and testicular cancers [44-48]. Several nested and population-based case-control studies in China reported strong dose-related associations between hepatocellular carcinoma (HCC) and serum DDT, ρ, ρ'-DDE, and β-HCH after adjustment for potential confounders [44-46]. Another case-control analysis found statistically significant associations with testicular germ cell tumors (TGCT) and prediagnostic serum

DDE and chlordane metabolites [48]. A more recent study in Norway found statistically significant associations for metastatic prostate cancer with serum oxychlordane [47]. There is also limited evidence for significant positive associations with OC exposures and cancers of the prostate [49], skin (cutaneous melanoma) [24], lung [24], rectum [24], and pancreas [50-52].

Most epidemiologic studies of OCs have included male pesticide applicators and have had limited power for analyses among women. Female spouses of pesticide applicators are a group with potential intermediate-level OC insecticide exposures due to their personal use (i.e., mixing/applying of pesticides) [53], and indirect exposure from non-occupational exposure pathways [54] (i.e., take-home [55], agricultural drift, [56-58] and residential use [55]). Despite their potential higher exposure to OC insecticides relative to the general population, only few studies have examined OC insecticide use and cancer risk among spouses of pesticide applicators. A case-control study found no association with DDT and alachlor for glioma [59]. Moreover, the authors did not examine additional OC active ingredients or cancer sites, thus limiting this study's scope. Several analyses from the AHS have found positive, though not statistically significant, associations between dieldrin [34] and heptachlor[60] used by pesticide applicators and breast cancer among their female farm spouses. Further research is warranted to help elucidate the impact of active ingredient-specific OC exposures on risks of female-specific cancers among this group.

The following projects outlined below, examine of seven OC active ingredients (i.e., aldrin, chlordane, dieldrin, DDT, heptachlor, lindane and toxaphene) on the risk of

cancer among the Agricultural Health Study (AHS) female farm spouses. The AHS is the largest prospective cohort of agricultural pesticide exposures in the United States and includes farm spouses (n=32,345) who are predominantly female and have been followed for cancer incidence and mortality since initial enrollment in 1993-1997 [61]. Personal use of seven OC active ingredients was collected for each AHS farm spouse using enrollment questionnaires, which covered the time period of OC use in the United States [61]. In the first aim I examine associations between the AHS farm spouses' personal use of each of the seven OC insecticides with total and specific cancers, with a particular emphasis on lymphohematopoietic cancers and female-specific cancers. In the second aim I characterize the AHS farm spouses' non-occupational OC exposure to each of the seven OC insecticides, by applying an active ingredient-specific exposure algorithm recently developed by AHS researchers [62]. This algorithm was developed to assess the contributions of the para-occupational, agricultural drift, and residential use exposure pathways to total non-occupational pesticide exposure among the AHS farm spouses. In the third aim I examine associations between the AHS farm spouses' non-occupational exposure on the risk of developing breast cancer and breast cancer subtypes. The specific objectives of each aim are as follows:

> **Aim1.** To examine the association between self-reported personal use of OC insecticides and risk of developing specific cancers among the AHS female farm spouses.
>
> **Aim 2.** To characterize cumulative non-occupational exposures to OC insecticides from the take-home, agricultural drift, and residential use exposure pathways among the AHS farm spouses.

Sub-aim 2a. To examine the correlation between cumulative OC insecticide exposure estimates in the AHS farm spouses from each non-occupational exposure pathway and the aggregate of these three pathways.

Sub-aim 2b. To examine whether the cumulative exposure estimates from each of the non-occupational pathways, and their aggregate, differs based on the AHS farm spouses' personal use of OC insecticide active ingredients.

Aim 3. To evaluate the impact of exposures to OC insecticides from non-occupational pathways on the risk of developing breast cancer among the AHS farm spouses.

Chapter 2. AIM 1. A prospective study of cancer risk among Agricultural Health Study (AHS) farm spouses associated with personal use of organochlorine insecticides.

ABSTRACT

BACKGROUND: Organochlorine insecticides (OCs) have historically been used worldwide to control insects, although most have now been banned in developed countries. Evidence for an association between OC exposures and cancer predominantly comes from occupational and population based-studies among men. I evaluated the association between the use of specific OCs and cancer among the female spouses of pesticide applicators in the Agricultural Health Study. **METHODS:** At enrollment (1993–1997), spouses of private applicators in the cohort provided information about their own use of pesticides, including seven OCs (aldrin, chlordane, dieldrin, DDT, heptachlor, lindane, and toxaphene), and information on potential confounders. I used Poisson regression to estimate relative risks (RRs) and 95% confidence intervals (CIs) for cancers ($n \geq 3$ exposed cases) reported to state cancer registries from enrollment through 2012 (North Carolina) and 2013 (Iowa), and use of the individual OCs, as well as use of any of the specific OCs. **RESULTS:** Among 28,909 female spouses, 2,191 (7.58%) reported ever use of at least one OC, of whom 287 were diagnosed with cancer. Most cancers were not associated with OC use. Risk of glioma was increased among users of at least one OC ($N_{exposed}$=11, RR=3.52, 95%CI 1.72-7.21) and specifically among lindane users ($N_{exposed}$=3, RR=4.45, 95%CI 1.36-14.55). Multiple myeloma was associated with chlordane ($N_{exposed}$=6, RR=2.71, 95%CI 1.12-6.55). Based on 3 exposed cases each, there were also positive associations between pancreatic cancer and lindane, and ER-PR- breast cancer and dieldrin.

No other associations with breast cancer were found. **CONCLUSIONS:** Overall, there were some associations with OC use and cancer incidence, however I was limited by the small number of exposed cancer cases. Future research should attempt to expand on these findings by assessing environmental sources of OC exposures, to fully evaluate the role of OC exposures on cancer risk in women.

INTRODUCTION

Organochlorine insecticides (OCs) are a class of chlorinated hydrocarbon insecticides historically used worldwide in agriculture. Some are still used in some developing countries [26, 27] for the control of vector borne illnesses [3, 6, 7]. OCs were first introduced in the United States in the 1940s and were used widely in agriculture and pest control through the 1960s. Due to their environmental persistence and ability to bioacccumulate, most OCs were banned for use in the U.S. during the 1970s and 1980s. Lindane and endosulfan were banned more recently in 2006 and 2010, respectively [8-10]. The International Agency for Research on Cancer (IARC) has reviewed the carcinogenicity of fifteen OCs. Of these, lindane [16] and pentachlorophenol (PCP) [15] were classified as Group 1, carcinogenic to humans; dichlorodiphenyltrichloroethane (DDT) [16], aldrin [15] and dieldrin [15] as Group 2A, probably carcinogenic to humans; 2,4,6-trichlorophenol (TCP) [15], chlordane [19], chlordecone [18], heptachlor [19], hexachlorocylcohexanes (HCH) [18], hexachlorobenzene (HCB) [19], mirex [18], and toxaphene [19] as Group 2B, possibly carcinogenic to humans; and endrin [18] and methoxychlor [18] classified as Group 3, not classifiable as to their carcinogenicity to humans.

The strongest epidemiologic evidence for a link between OC exposures and cancer risk comes from occupational and population-based studies of non-Hodgkin lymphoma (NHL) [20, 22, 25-27, 63-65]. Previous analyses of licensed pesticide applicators in the Agricultural Health Study (AHS) found significant positive exposure-response trends for lindane and DDT use with NHL [20], and chlordane and heptachlor use with leukemia [24]. In a pooled analysis of Canadian and U.S. based case-control studies, self-reported

ever use of DDT was significantly associated with multiple myeloma (MM) [66]. The strongest evidence for associations with cancer at other sites comes from case-control studies of liver and testicular cancers [44-46, 48]. DDT, dichlorodiphenyldichloroethylene (ρ, ρ' -DDE), and β-HCH have been associated with hepatocellular carcinoma [44-46], and testicular germ cell tumors have been significantly associated with prediagnostic serum DDE and chlordane metabolites [48]. There is also evidence for significant positive associations with OC exposures and cancers of the prostate [49], skin (cutaneous melanoma) [24], lung [24], rectum [24], and pancreas [50, 51]. An evaluation of pesticides and glioma reported no association with OCs [67].

In addition, potential associations between OCs and hormonally-mediated cancers, particularly female breast cancer, are of concern due to the endocrine disrupting properties of OCs. [31, 32, 34-40, 68]. While two studies [34, 35] have suggested an association with dieldrin, most studies are null [31, 36-41]. However, several reports provide evidence for an increased risk of breast cancer in adulthood with early life exposure to OCs [69-72]. The one study of endometrial cancer found no associations with OCs overall [43]. No studies to our knowledge have investigated associations with ovarian cancer. Although i*n vitro* and *in vivo* studies suggest OCs may act as estrogen agonists or antagonists [29, 30, 73, 74], the relationship between OCs and hormonally-mediated cancers among women remains unclear. The specific objectives of this analysis were as follows:

> **Aim1.** To examine the association between self-reported personal use of OC insecticides and risk of developing specific cancers among the AHS female farm spouses.

METHODS

Study population and follow-up

The AHS is a prospective cohort that includes licensed private pesticide applicators (mostly farmers), and the spouses of private pesticide applicators residing in Iowa and North Carolina. The AHS has been previously described in detail [61]. Pesticide applicators were recruited from 1993-1997 when obtaining a license to apply restricted-use pesticides. Private pesticide applicators who reported being married at the time of enrollment were given questionnaires to be completed by their spouses. The spouses (n=32,345) of these private pesticide applicators are the focus of this study. The Spouse Enrollment questionnaire elicited information on demographic and lifestyle factors, family and personal medical histories, farm exposures, and agricultural activities, including the application or mixing of specific pesticides. In addition, 60.0% of the spouses in this analysis also completed the Female and Family Health questionnaire which focused on reproductive health histories. The study protocol was approved by all relevant institutional review boards. Study questionnaires are publicly available: https://aghealth.nih.gov/collaboration/questionnaires.html.

Cancer incidence was assessed regularly via linkage with the North Carolina and Iowa state cancer registries. Mortality incidence was assessed through regular linkage with state mortality registries and The National Death Index. Cancer sites were classified according to the *International Classification of Diseases for Oncology, 3rd revision* (World Health Organization). For NHL, I followed the Surveillance Epidemiology and End Results (SEER) lymphoma coding scheme [75].

Exposure Assessment and Questionnaires

Spouses of private pesticide applicators were enrolled in the AHS from 1993-1997, during which time they reported their lifetime never/ever personal use of fifty pesticides including past use of seven OCs (aldrin, chlordane, dieldrin, DDT, heptachlor, lindane and toxaphene). For each pesticide, they were asked 'During your lifetime, have you ever personally mixed or applied [pesticide]? (Includes pesticides used for farm use, commercial application and personal use in your home or garden)'. Participants who indicated ever use of at least one of these seven OCs were classified as having personally used 'any OC', whereas those who indicated never use of any of these OCs were classified as never having personally used 'any OC'. Otherwise, participants were considered to be missing as to their 'any OC' use. In the following analysis, the term 'any OC' will be used to refer to the ever personal use of at least one of these seven OCs.

Statistical Analysis

For this analysis I excluded, the 219 male spouses, women who were diagnosed with cancer prior to study enrollment (n=905), those with zero or missing person years of follow-up (n=161), and those missing information on use for all seven OCs (n=2,146), leaving 28,909 female spouses in our analytic cohort. Relative risks (RR) and 95% confidence intervals (95% CI) were calculated for risk of cancer among ever users, compared to never users, using multivariable *Poisson* regression in SAS version 9.3 (SAS Institute, Inc., Cary, N.C.). I evaluated all cancer sites with at least three exposed cases for associations with each of the seven individual OCs and for the use of any OC as defined previously. Person-time accrued from the date of study enrollment until date of death,

cancer diagnosis, movement out of state or last study-follow-up (December 31, 2012 and December 31, 2013 for North Carolina and Iowa respectively), whichever was earliest. For the evaluation of uterine and ovarian cancers, person-time was censored at the time of hysterectomy or oophorectomy, where applicable.

All models were adjusted for age at enrollment (≤ 44 years, 45-54 years, 55-64 years, ≥ 65 years), educational attainment (high school degree or less, some college or college graduate, one or more years of graduate school), alcohol use (never, less than 1 drink per month, ≥ 1-3 per month), cigarette pack-years smoked as reported at enrollment (pack-year quartiles: Never, ≤ 6.75, 6.751-16.75, ≥ 16.751), and state of residence (Iowa or North Carolina). I considered the following additional confounders: BMI, race, family history of cancer, and ever use of any pesticide, but did not include them in our final models as they did not appreciably alter our results by ≥ 10%. For all cancer sites, mutually adjusting for individual non-OC and OC pesticides that were correlated at $\rho \geq 0.4$ (i.e. aldrin and dieldrin ($\rho=0.43$), aldrin and heptachlor ($\rho=0.42$)) did not appreciably change our results and these adjustments were not included in our final models. Moreover, because dieldrin is also a biological metabolite of aldrin, I performed sensitivity analyses where 'dieldrin metabolite' (i.e. those farm spouses who personally used either aldrin or dieldrin) was modeled as the exposure. However, these analyses did not significantly alter our existing aldrin and dieldrin results and were not included in our final analyses.

Additionally, I examined potential confounders known to be associated with specific cancer sites, such as total meat consumption (colon, rectum, stomach), sun sensitivity (melanoma), asbestos exposure (lung), autoimmune disorders, exposure to

livestock and poultry, and benzene exposure (lymphohematopoietic cancers); adjusting for these specific cancer-related covariates did not alter our results and were not included in our final models. All OC-exposed brain cancer cases were glioma subtypes; thus, I report associations here for glioma only. Breast cancers were examined overall, as well as by estrogen receptor (ER) and progesterone receptor (PR) status, where available. Female health and reproductive covariates at enrollment were also examined, with respect to breast, ovarian and uterine cancer, and included the following: menopausal status, ever use of oral contraceptives, ever use of estrogen-based hormone replacement therapy, ever use of progestin-based hormone replacement therapy, age at menarche, and parity. These female reproductive covariates did not appear to significantly alter our results and thus were not included in our final models. Due to a lack of questionnaire information availability, I was unable to assess age at first live birth as a potential covariate. I conducted stratified analyses by several female health covariates, including menopausal status at enrollment (yes/no), ever use of oral contraceptives at enrollment (yes/no), ever use of hormone replacement therapy at enrollment (yes/no) and age at first menarche ($\leq$ 12 years or below, > 12 years). Due to the small number of nulliparous women (n=294), I was unable to evaluate risks among nulliparous women.

RESULTS

From enrollment through 2012/2013, the 28,909 female spouses contributed a total of 502,895 person-years of follow-up (Mean=16.19 standard deviation +/- 3.8). Overall, 15,112 (52.3%) reported ever using any pesticide (data not shown), and 2,191 (7.6%) reported ever use of any of the seven OCs included in the enrollment questionnaire. The most commonly reported OCs were chlordane (4.1%), DDT (3.55%) and lindane (1.5%), with less than 1% of participants reporting ever use of aldrin, heptachlor, toxaphene and dieldrin (Table 1). Among women who reported using any OC, 718 (32.8%) reported use of more than one OC. Ever OC users tended to be older, have higher BMIs, be from Iowa, and have a higher educational level than OC non-users. They were also more likely to have reported a family history of cancer, grown up on a farm, used oral contraceptives, and have an earlier onset of menarche. Additionally, 77.5% of OC users completed the Female and Family Health Questionnaire versus 60.5% of never OC users.

Table 1. Select characteristics of AHS farm spouses at enrollment with OC insecticide personal use information (n=28,909).*

	Any OC Use[1]				
	NEVER		EVER		
	N=26,718	%	N=2,191	%	p Value±
Age at enrollment					
≤ 44	13,153	49.23	447	20.40	<.0001
45-54	6,677	24.99	771	35.19	
55-64	4,823	18.05	731	33.36	
≥ 65	2,065	7.73	242	11.05	
Race					
White	26,164	97.93	2178	99.4	<.0001
Other	510	1.91	8	0.37	
Missing	44	0.16	5	0.23	
State of Residence					
North Carolina	8,739	32.71	632	28.85	0.0002
Iowa	17,979	67.29	1,559	71.15	
Educational Attainment					
High School or less	13,905	52.04	1102	50.3	0.0015
Some College or College Graduate	8,662	32.42	679	30.99	
1 or more years of Graduate School	3,833	14.35	378	17.25	
Missing	318	1.19	32	1.46	
Body Mass Index					
0-24.99	11,756	40.67	902	41.17	<.0001
25.00-29.99	7,448	25.76	717	32.72	
≥ 30.00	4,298	14.87	440	20.08	
Missing	3,216	11.12	132	6.02	

Table 1 Continued. Select characteristics of AHS farm spouses at enrollment with OC insecticide personal use information (n=28,909).*

Alcohol					
Never	12,042	45.07	939	42.86	0.2371
less than once/month	7,099	26.57	603	27.52	
≥ 1-3 times per month	7,277	27.24	621	28.34	
Missing	300	1.12	28	1.28	
Cigarette Smoking (Pack-years)					
Never Smoker	18,820	70.44	1,493	68.14	0.0003
≤ 6.75	3,544	13.26	294	13.42	
6.751-16.75	1,752	6.56	127	5.80	
≥16.751	1,700	6.36	186	8.49	
Missing	902	3.38	91	4.15	
Family History of Cancer					
No / Missing	13,949	52.21	949	43.31	<.0001
Yes	12,769	47.79	1242	56.69	
Grew up on a farm					
No	10,913	40.85	534	24.37	<.0001
Yes	15,579	58.30	1,643	74.99	
Missing§	226	0.85	14	0.64	

Table 1 Continued. Select characteristics of AHS farm spouses at enrollment with OC insecticide personal use information (n=28,909).*

Menopause at Enrollment					
No	8,922	33.39	534	24.37	<.0001
Yes	6,777	25.36	1,127	51.44	
Unsure	245	0.92	22	1.00	
Missing§	10,774	40.32	508	23.19	
Number of Live Births					
0	235	0.88	29	1.32	<.0001
1 or 2	7,216	27.01	688	31.40	
> 2	7,526	28.17	887	40.48	
Missing§	11,741	43.94	587	26.79	
Oral Contraceptive Use					
Never	4,236	15.85	576	26.29	<.0001
Ever	11,722	43.87	1,106	50.48	
Missing§	10,760	40.27	509	23.23	
Age of first menarche					
12 years or less	7,099	26.57	788	35.97	<.0001
13 years	4,851	18.16	493	22.5	
14 years or greater	3,855	14.43	398	18.17	
Missing§	10,913	40.85	512	23.37	
OC Insecticides					
Overall OC (Any OC)	-	-	2,191	7.58	-
Chlordane	-	-	1,196	4.13	-
DDT	-	-	1,028	3.55	-
Lindane	-	-	430	1.47	-
Aldrin	-	-	235	0.81	-
Heptachlor	-	-	222	0.77	-
Toxaphene	-	-	203	0.70	-
Dieldrin	-	-	105	0.36	-

* Excluded: n=2,146 with missing information for personal use of all OCs; n=905 female spouses diagnosed with cancer prior to enrollment; n=219 male spouses; n=161 with missing or 0 person-years of follow-up leaving a total n=28,909 female farm spouses

[1] Ever use of any of the seven OC insecticides

± Chi Square test for homogeneity

§ From Female & Family Health Questionnaire responses

AHS, Agricultural Health Study; RR, relative risks; OC, organochlorines.

Any OC use was significantly associated with an increased risk of glioma ($N_{exposed}$=11; RR=3.52, 95% CI 1.72 to 7.21) (Table 2). Lindane use was significantly associated with an increased risk of glioma ($N_{exposed}$=3, RR=4.45 95% CI 1.36 to 14.55) and pancreatic cancer ($N_{exposed}$=3, RR=3.70 95% CI 1.15 to 12.0). Use of any OC was also associated with non-significantly elevated risks of stomach cancer ($N_{exposed}$=5, RR=2.61, 95% CI 0.96 to 7.11), and colon cancer ($N_{exposed}$= 28, RR=1.19, 95% CI 0.80 to 1.75).

Although chlordane use ($N_{exposed}$=6, RR=2.71, 95% CI 1.12 to 6.55) was significantly associated with an increased risk for MM, any OC use ($N_{exposed}$=8, RR=2.01, 95% CI 0.91 to 4.42) and DDT use ($N_{exposed}$=4, RR=1.75, 95% CI 0.61 to 5.01) were non-significantly associated with an increased risk of MM (Table 2). There were also several suggestive associations for lymphohematopoietic malignancies. Any OC use was non-significantly associated with an increased risk for NHL overall ($N_{exposed}$=28, RR=1.23, 95% CI 0.82 to 1.83). Similarly, use of chlordane ($N_{exposed}$=17, RR=1.30, 95% CI 0.82 to 2.22), DDT ($N_{exposed}$=17, RR=1.35, 95% CI 0.81 to 2.22), and lindane ($N_{exposed}$=6, RR=1.60, 95% CI 0.71 to 3.60) were also non-significantly associated with increased risks in NHL. I had limited power for NHL subtype analyses. However, all 28 OC exposed cases were B-cell lymphomas. Among women who reported any OC use, there were eight MM cases and six diffuse large B-cell lymphoma (DLBCL); no other B-cell subtype had more than four exposed cases.

I also evaluated hormone-mediated cancers including ovarian, uterine, and breast (see Table 2). No significant associations were found for any OC use or for use of the seven individual OCs and uterine or ovarian cancers. Similarly, I found no association between

any OC use or for use of the seven individual OCs and breast cancer. In analyses of breast cancer subtype, there was a statistically significant elevated association between dieldrin use and ER-PR- breast cancer ($N_{exposed}$=3, RR=3.55, 95% CI 1.12 to 11.18).

Table 2. RR and CIs* for ever versus never use of OC insecticides, for all cancer sites.±

		Any OC[1]			Chlordane			DDT			Lindane		
	N_{total}	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI
All Cancer Sites§	3,204	287	0.96	0.85-1.08	160	0.99	0.84-1.16	158	0.98	0.83-1.15	46	0.91	0.68-1.22
SOLID TUMORS													
Bladder	103	4	0.64	0.23-1.77	1	_	_	3	0.83	0.26-2.67	1	_	_
Colon	236	28	1.19	0.80-1.75	18	1.42	0.87-2.32	16	1.17	0.70-1.95	3	0.79	0.25-2.49
Glioma	44	**11**	**3.52**	**1.72-7.21**	4	1.81	0.64-5.12	2	_	_	**3**	**4.45**	**1.36-14.55**
Kidney	71	6	0.89	0.38-2.08	3	0.85	0.26-2.72	5	1.41	0.56-3.57	0	_	_
Lung	203	15	0.70	0.41-1.20	10	0.90	0.47-1.71	10	0.84	0.44-1.59	2	_	_
Melanoma (cutaneous)	145	12	1.08	0.59-1.97	4	0.63	0.23-1.72	5	0.88	0.36-2.18	2	_	_
Pancreas	55	7	1.33	0.59-2.97	3	1.03	0.32-3.34	1	_	_	**3**	**3.70**	**1.15-12.0**
Rectum	69	8	1.27	0.60-2.70	6	1.80	0.77-4.21	6	1.79	0.76-4.22	0	_	_
Stomach	26	5	2.61	0.96-7.11	1	_	_	3	2.64	0.76-9.15	1	_	_
Thyroid	54	5	0.66	0.26-1.63	4	0.97	0.36-2.67	1	_	_	0	_	_
LYMPHOHEMATOPOIETIC MALIGNANCIES													
NHL±	233	28	1.23	0.82-1.83	17	1.35	0.82-2.22	17	1.35	0.81-2.22	6	1.60	0.71-3.60
Multiple Myeloma	42	8	2.01	0.91-4.42	**6**	**2.71**	**1.12-6.55**	4	1.75	0.61-5.01	1	_	_
DLBCL[2]	56	6	1.09	0.46-2.58	4	1.38	0.49-3.85	4	1.31	0.47-3.67	2	_	_
Follicular Lymphoma	49	4	0.86	0.3-2.43	2	0.74	0.18-3.09	2	0.78	0.19-3.24	0	_	_
CLL/SLL[3]	39	4	1.29	0.86-1.93	1	_	_	4	1.42	0.86-2.34	2	_	_
Myeloid Leukemia	34	4	1.26	0.44-3.65	3	1.82	0.55-6.09	3	1.66	0.49-5.56	0	_	_
FEMALE SPECIFIC SITES													
Breast	1,214	99	0.89	0.72-1.09	56	0.93	0.71-1.22	52	0.89	0.67-1.18	17	0.88	0.54-1.42
ER+PR+	736	64	0.94	0.73-1.23	36	0.98	0.70-1.37	33	0.93	0.65-1.33	9	0.75	0.39-1.45
ER-PR-	202	15	0.82	0.48-1.40	9	0.90	0.46-1.76	7	0.76	0.36-1.63	4	1.22	0.45-3.30
ER+PR-	125	8	0.65	0.32-1.35	5	0.78	0.32-1.92	4	0.61	0.22-1.67	2	_	_
Ovarian	106	9	0.65	0.30-1.61	7	1.05	0.40-2.89	5	0.77	0.20-2.46	2	_	_
Uterine	276	20	0.83	0.50-1.32	10	0.80	0.40-1.50	10	0.82	0.42-1.56	2	_	_

Table 2 Continued. RR and CIs* for ever versus never use of OC insecticides, for all cancer sites.±

		Aldrin			Heptachlor			Toxaphene			Dieldrin		
	N_{total}	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI	$N_{exposed}$	RR	95% CI
All Cancer Sites§	3,204	41	1.12	0.82-1.53	36	1.06	0.76-1.48	29	1.05	0.73-1.52	17	1.02	0.63-1.65
SOLID TUMORS													
Bladder	103	0	_	_	0	_	_	1	_	_	0	_	_
Colon	236	6	1.73	0.76-3.91	4	1.24	0.46-3.36	3	1.31	0.42-4.12	4	2.41	0.89-6.53
Glioma	44	1	_	_	2	_	_	2	_	_	0	_	_
Kidney	71	1	_	_	0	_	_	2	_	_	0	_	_
Lung	203	2	_	_	1	_	_	5	2.13	0.87-5.21	2	_	_
Melanoma (cutaneous)	145	3	2.20	0.69-7.02	3	2.40	0.75-7.64	1	_	_	1	_	_
Pancreas	55	1	_	_	1	_	_	0	_	_	0	_	_
Rectum	69	1	_	_	1	_	_	1	_	_	0	_	_
Stomach	26	1	_	_	0	_	_	0	_	_	0	_	_
Thyroid	54	1	_	_	1	_	_	0	_	_	0	_	_
LYMPHOHEMATOPOIETIC MALIGNANCIES													
NHL±	233	1	_	_	3	1.03	0.33-3.24	3	1.49	0.48-4.68	0	_	_
Multiple Myeloma	42	0	_	_	1	_	_	1	_	_	0	_	_
DLBCL[2]	56	0	_	_	1	_	_	1	_	_	0	_	_
Follicular Lymphoma	49	0	_	_	1	_	_	0	_	_	0	_	_
CLL/SLL[3]	39	1	_	_	0	_	_	1	_	_	0	_	_
Myeloid Leukemia	34	0	_	_	1	_	_	0	_	_	0	_	_
FEMALE SPECIFIC SITES													
Breast	1,214	11	0.88	0.48-1.59	11	0.93	0.51-1.68	5	0.49	0.20-1.18	6	1.06	0.48-2.38
ER+PR+	736	8	1.00	0.50-2.02	8	1.05	0.52-2.11	2	_	_	3	0.83	0.27-2.60
ER-PR-	202	2	_	_	2	_	_	1	_	_	**3**	**3.55**	**1.12-11.18**
ER+PR-	125	0	_	_	0	_	_	1	_	_	0	_	_
Ovarian	106	2	_	_	2	_	_	1	_	_	1	_	_
Uterine	276	4	1.50	0.60-4.06	3	1.12	0.40-3.51	2	_	_	1	_	_

± n ≥ 3 exposed cases

[1] Ever use of any of the seven OC insecticides

[2] DLBCL: diffuse large B-cell lymphoma

[3] CLL/SLL: chronic lymphocytic leukemia/small lymphocytic lymphoma

Abbreviations: AHS, Agricultural Health Study; RR, relative risks; OC, organochlorines; ER, estrogen receptor; PR, progesterone receptor.

Significant Findings are listed in **boldface**

± All NHL subtypes consisted of B-cell Lymphomas

§ Inclusive of all reported cancer sites

* Adjusted for age, education, state of residence, pack-years smoked, and alcohol consumption

DISCUSSION

In this study, I prospectively evaluated associations between the reported personal use of individual OCs and incident cancers in a population of female farm spouses. Although the numbers of exposed cases were small, I observed statistically significant increased risks for use of individual OCs insecticides and several cancers, including any OC use and glioma, lindane use and glioma and pancreatic cancer, chlordane use and MM, and dieldrin use and ER-/PR- breast cancer.

In addition to chlordane, MM was non-significantly associated with any OC use and with DDT specifically. These associations are consistent with previous findings [20, 22, 23, 25, 26, 66]. The definition of NHL used in our study is based on the most recent lymphoma classification system, which includes MM as a subtype of NHL [75], whereas most previous studies relied on earlier classifications which considered MM separately. A previous population-based case-control study found non-significant positive associations of ever handling (mixing or applying) aldrin, DDT, or lindane with MM [76]. A pooled analysis of U.S. and Canadian case-controls studies found that DDT use was significantly associated with MM [66]; cumulative exposure to DDT, as measured by lifetime-days of use, was also significantly associated with an increasing risk trend for MM. Although not significant, in the current study, chlordane use was also positively associated with NHL and myeloid leukemia, DDT use was positively associated with NHL and myeloid leukemia, and lindane use was positively associated with NHL. There is evidence that some OCs, including lindane and DDT, cause oxidative stress and immunosuppressive effects,

and that these mechanisms possibly play a role in the development of lymphohematopoietic cancers [16, 28, 77-79]

I observed no significant association with Any OC use and breast cancer overall. Although some studies have reported an increased risk of breast cancer among women exposed to OCs during critical developmental windows in early life [70-72], our findings are consistent with most other studies that also did not evaluate timing of exposure [16, 31, 32, 34-41]. Although I did not have information on timing of exposure, I conducted sensitivity analyses using year of birth as a surrogate for the potential for exposure during critical developmental periods. OCs were first registered in 1948, therefore I assumed women born before 1936 would not have any OC exposures prior to menarche. When I restricted analyses to women born after 1936, the RR for breast cancer and any OC use was 1.22 (0.94-1.59) (n=61 exposed cases) although the interaction was not significant compared to 0.84 (0.60-1.18) (n=38 exposed cases) among women who were born prior to 1936. An early study by Wolff et al. found a two- to four-fold increased risk of breast cancer among women with the highest serum DDE levels, with a positive trend with increasing serum DDE [32]. However, a follow-up study with a larger sample size found no evidence for an association of breast cancer risk with serum DDE levels [33]. Additional studies of breast cancer and OC exposures have examined associations with mirex, HCB, and chlordane; most of these studies also reflected null or inconclusive findings [36, 39, 42, 80, 81].

I did however see an association between dieldrin use and ER-/PR- breast cancer based on only 3 exposed cases. Two previous studies reported positive associations with

dieldrin use and breast cancer overall. The first, a Danish case-control study found a significant dose-related increased risk of breast cancer among women and increasing serum concentrations of dieldrin [35]. Additionally, a previous study of AHS farm spouses found evidence for a significant increased risk of breast cancer overall among women who never personally used dieldrin, but whose husbands did personally apply the pesticide [34]. This study was unable to assess associations between the wives' personal use of dieldrin and breast cancer due to the low number of dieldrin exposed breast cancer cases. Our current analysis includes 60 more OC exposed cases and thirteen additional years of follow-up than this previous analysis [34], and was sufficiently powered to examine breast cancer subtypes. Few epidemiologic studies have examined associations between OC exposures and breast cancer subtypes [71, 82-84], and most have not found positive associations with ER-negative breast cancers. *In vitro* and animal studies have suggested that dieldrin, DDT, endosulfan, HCH, and toxaphene have the potential to elicit tumor promoting effects mediated through the induction of ER, androgen receptor and aromatase activities [30, 73, 74, 85, 86]. Given this body of literature and the small number of dieldrin exposed ER-PR- breast cancer cases, our positive finding warrants further investigation. Overall, I do not see strong evidence of an association between use of an individual OC and breast cancer, consistent with the existing epidemiologic literature.

Aldrin use was associated with a non-statistically significant elevated risk for uterine cancer based on four exposed cases. Only one case-control study has examined OC exposures and endometrial cancer; no statistically significant associations were observed with several OC derivatives including DDE, oxychlordane, HCH, and HCB [43]. Very few

occupational studies have examined the relationship between endometrial cancer and exposure to other OC compounds, including polychlorinated biphenyls (PCBs) [87-89] and the majority of these studies' findings were null. To our knowledge, this is the first prospective study to examine the relationship between personal use of specific OC insecticides and uterine cancer.

Any OC use and lindane specifically were associated with risk of glioma. While I lacked sufficient power for further subtype analyses, the OC-exposed glioma cases consisted of glioblastomas (n=7), an astrocytoma (n=1), an oligodendroma (n=1), and mixed gliomas (n=2). Previous studies of male farming populations have found some evidence for an increased risk of glioma with associated pesticide use [90-92]. However, studies examining associations between glioma and pesticide exposures among women, in agricultural populations, have provided inconsistent results. In an earlier case-control study of central nervous system cancers among women across twenty-four U.S. states, increased risks were found for women generally exposed to herbicides, insecticides, or fungicides [93]. An analysis of occupational risk factors for glioma found significantly increased risks among women involved in occupations in agricultural services and farming, though this analysis did not examine exposures to specific pesticides [94]**.** However, a case-control analysis of women in Nebraska found no association between individually evaluated OCs (i.e. aldrin, chlordane, DDT, dieldrin, heptachlor and lindane) and brain cancer [90]. Similarly, in a case-control analysis of women in the Midwest, no association was found for gliomas and the personal application of pesticides including OCs [59]**.** Mechanisms of action for OC-induced gliomas have not been proposed; however, i*n vitro* studies have

found that neurotoxic effects induced by the interaction of OCs with ER-mediated signaling pathways may play a role [95].

The increased risk of pancreatic cancer associated with lindane use in our study was based on only three exposed cases. Some studies have shown significant increased risks for pancreatic cancer with occupational DDT exposure [50, 51] and significantly higher levels of DDT exposure among pancreatic cancer cases versus controls [51]. However, a previous AHS study found no evidence for an increased risk of pancreatic cancer with the OCs aldrin, DDT, heptachlor or toxaphene [52]. The aforementioned study did not evaluate risk estimates among the spouses only, but examined combined risk estimates among the applicators and their spouses. Furthermore, a lack of exposed cases prohibited the insecticide-specific evaluation of chlordane, dieldrin and lindane. To our knowledge, no other studies have evaluated OC use and pancreatic cancers among women.

Strengths of our study include the prospective longitudinal design with little loss-to-follow-up, questionnaire information on the use of specific OCs, and regular assessment of cancer incidence and mortality via linkage with state registries. The AHS also has detailed information on many possible confounders. Most previous studies of OC exposures and cancer, except for studies of DDT and breast cancer [16, 31, 32, 36, 37, 40, 68, 96] have primarily focused on occupationally-exposed men [20, 21, 23-26, 44, 48, 65, 76]. Our study examined the personal use of DDT, and other specific OCs, in a population of farm women. Few studies have evaluated personal use of specific OCs. While breast cancer has been the most widely studied cancer with respect to OCs, in particular DDT, no studies thus far have prospectively studied OCs and other hormone-mediated cancers.

Limitations of this analysis include the small number of cases exposed to specific OCs and lack of information on duration, time period, and intensity of OC use. While I had a low response rate of the female and family health questionnaire, our reported results and final models were based solely on information collected from the spousal enrollment questionnaire. Questionnaire information was collected at study enrollment (1993-1997), thus changes in individual characteristics (i.e. menopausal status, smoking) since enrollment were not captured in this analysis. In addition, most OCs examined in this analysis have been banned for use in the United States since the 1970s. Because OCs have long half-lives and are known to persist in the environment and human body for long periods of time [3, 6, 7], exposure to OCs through environmental exposure pathways may also contribute to lifetime cumulative exposure. This could be particularly important in farm situations where OCs may have been used in the past.

CONCLUSIONS

I observed significant increased risks for some cancers associated with individual OC insecticides. Despite the large size of the cohort, the numbers of exposed women and cancer cases were small for most cancer sites of interest. While some of our findings are consistent with previous findings, results need replication with longer follow-up time in other studies. Due to the environmental persistence of OCs, future research should attempt to expand on these findings by assessing environmental sources of OC exposures in order to fully evaluate the role of OC exposures on cancer risk in women.

Chapter 3. Aim 2. A characterization of non-occupational OC exposures among the Agricultural Health Study female farm spouses

ABSTRACT

BACKGROUND: Women living in agricultural areas may be exposed to pesticides via multiple pathways including occupational exposures from personal use of pesticides on the farm, as well as non-occupational exposures, such as from their husband's pesticide activities and from living in close proximity to treated fields. For the first time, I applied a newly developed quantitative active ingredient-specific algorithm to capture cumulative non-occupational OC exposures for female farm spouses of pesticide applicators enrolled in Agricultural Health Study (AHS) prospective cohort. **METHODS:** This previously developed algorithm calculates exposure for three non-occupational pathways of exposure: take-home, agricultural drift and residential pesticide use. Each equation incorporates subject-specific questionnaire information and data-driven quantitative weights derived from published pesticide dust concentrations. In the present analyses, these equations were applied to the study population to obtain exposures estimates for the three pathways for 7 OCs. The residential use pathway was applied to chlordane and heptachlor only. The pathway estimates were then summed together for an overall non-occupational exposure estimate for each OC. Median and IQRs of non-zero OC exposure estimates were calculated overall and stratified by the spouses' personal use of seven individual OCs (aldrin, chlordane, dieldrin, DDT, heptachlor, lindane and toxaphene). Spearmen rank correlations were calculated between the exposure estimates for the three non-occupational pathways and their sum. **RESULTS:** I identified an additional 1.2 - 10.0% (379 - 2,776)

female farm spouses exposed to individual OCs through non-occupational pathways than when compared to exposure through their personal use alone. In addition, I captured variability in OC exposure intensities among the AHS spouses, with ratios of the 75^{th} to 25^{th} percentiles ranging from 2.8 to 8.5. The take-home and agricultural drift pathways were highly correlated with each other across all OCs ($r_s \geq 0.98$), while the residential use pathway was not correlated with either the agricultural drift nor take-home pathways for chlordane or heptachlor ($r_s < 0.02$). **CONCLUSIONS:** I identified an increase in prevalence of OC exposures through non-occupational paths, compared to exposure through the spouse's personal use alone. In addition, I captured variability in OC exposure intensities among the spouses. This exposure characterization represents an improvement of previous studies of pesticide exposure estimates, which relied solely on direct pesticide use or surrogate metrics to estimate non-occupational exposures. Furthermore, this first application of the algorithm allows us to better characterize relative OC exposure differences among the spouses thereby reducing exposure misclassification in future etiologic analyses of the AHS spouses.

INTRODUCTION

In the previous chapter, the impact of OC insecticides on cancer risk was examined among farm spouses of the Agricultural Health Study (AHS). However, this analysis only considered the spouses' personal use of seven OCs (i.e. aldrin, chlordane, dieldrin, DDT, heptachlor, lindane and toxaphene) and did not consider their potential exposures from non-occupational exposures arising from their husband's pesticide application activities. According to a recent literature review [1], non-occupational exposures including take-home exposures, agricultural drift and residential use have been found to increase pesticide concentrations of house dust of residences in North American agricultural areas. In this review, take-home exposure pathways were defined as the introduction of pesticides into the home from the skin, clothes and shoes of applicators who use or have contact with pesticides at work. Agricultural drift was defined as the transport of pesticides to non-treatment sites at the time of application (i.e. primary drift), and the volatilization and movement of pesticide residues from soil and plants or the movement of pesticide-laden dust or soil by wind after the time of application (i.e. secondary drift). Residential use of pesticides was defined as the application of pesticides to the home, lawn, or garden or pets for insects and weeds.

While occupational use of pesticides is expected to be the largest contributory pathway to pesticide exposures among applicator populations [54], farm spouses are exposed to pesticides primarily through their personal use or from non-occupational pathways [54]. A failure to account for non-occupational pathways of exposure for these women may increase exposure misclassification and reduce power to detect associations if

they exist. It is therefore important to consider pesticide exposures from both occupational and non-occupational sources of OC exposures among the farm spouses, to fully evaluate the role of OC exposures on cancer risk among women.

Within the AHS, systematically classifying non-occupational exposures was recently made possible with the development of an exposure algorithm that accounts for the contributions of these three non-occupational pesticide exposure pathways for the AHS farm spouses [97, 98]. This deterministic model provides for the first time, active ingredient-specific, quantitative estimates of cumulative lifetime pesticide exposures that capture daily exposure across the adult life of the AHS farm spouses from the time of their marriage to their pesticide applicator-husbands [98]. Each pathway equation in this algorithm incorporates participants' questionnaire responses on farm and home activities and measurement-based weights from a meta-regression analysis of published pesticide concentrations in house dust of homes in agricultural areas ($k_{take\text{-}home}$, k_{drift}, k_{res}) [2]. These equations are described in more detail in the following methods section.

The first application of this algorithm, to quantify these exposure routes for OCs for this unique population, represents an essential improvement over previous approaches which focused solely on direct pesticide use or were based on surrogate metrics to estimate non-occupational pesticide exposures among farm women. The specific objectives of this analysis were as follows:

> **Aim 2.** To characterize cumulative non-occupational exposures to OC insecticides from the take-home, agricultural drift, and residential use exposure pathways among the AHS farm spouses.
>
> > **Sub-aim 2a.** To examine the correlation between cumulative OC insecticide exposure estimates in the AHS farm spouses from each non-occupational exposure pathway and the aggregate of these three pathways.
> >
> > **Sub-aim 2b.** To examine whether the cumulative exposure estimates from each of the non-occupational pathways, and their aggregate, differs based on the AHS farm spouses' personal use of OC insecticide active ingredients.

METHODS

Algorithm Overview

The recently developed non-occupational exposure pathway algorithm was created by AHS researchers to quantify the contributions of the take-home, agricultural drift, and residential use exposure pathways to total non-occupational pesticide exposure among the AHS farm spouses [62]. In this algorithm, cumulative pesticide exposures were separately estimated for each of the three exposure pathways ($E_{take\text{-}home,ai}$, $E_{drift,ai}$, $E_{res,ai,}$) and then aggregated together for an overall estimated exposure intensity weighted value ($E_{non\text{-}occ,ai}$) (Figure 1). Subject-specific differences in pesticide exposures were identified from detailed questionnaire responses of the AHS farm spouses and their respective applicator-husbands, and included information on their pesticide use, farming characteristics and other activities performed. Meta-regression mixed-effects models of published pesticide dust concentrations were used to derive data-driven quantitative weights for the relative contribution of each of the three pathways ($k_{take\text{-}home,}$ $k_{drift,}$ k_{res}) [97].

In the non-occupational algorithm, the take-home exposure estimate ($E_{take\text{-}home,ai}$) was estimated to be a function of the farm spouses' time at home and the number of days and years of pesticide use by their respective applicator-husband while cohabitating (Equation 1). The agricultural drift exposure estimate ($E_{drift,ai}$) was estimated to be a function of the distance between the spouses' homes and treated fields, and the days and years the applicator-husband applied that active ingredient while cohabitating (Equation 2). Lastly, the residential use exposure estimate ($E_{res,ai}$) was estimated to be a function of the combined contributions of multiple home pest treatments, while cohabitating, and the

probability that the active ingredient was used in the treatment (Equation 3). Each equation included data-driven quantitative weights for the relative contribution of each of the three pathways ($k_{take\text{-}home}$, k_{drift}, k_{res}). These weights were derived from previous meta-regression mixed-effects models of published pesticide dust concentrations. Each exposure pathway was then additively combined for an aggregate estimate of total non-occupational exposures for each OC active ingredient ($E_{non\text{-}occ,ai}$) (Equation 4).

$$E_{take\text{-}home,ai} = k_{take\text{-}home} \times [\text{Hours per Day Spouse at Home}/24\ \text{Hours per Day}] \times [\text{Days Applicator Applied}_{ai}/\text{Median Application Days}] \times \text{Years Applied While Together} \quad [1]$$

$$E_{drift,ai} = k_{drift} \times (\text{Days Applicator Applied}_{ai}/\ \text{Median Application Days}) \times \text{Years Applied While Together}_{ai} \quad [2]$$

$$E_{res,ai} = (k_{termites,ai} \times Treated_{termites} + k_{insects,ai} \times Treated_{insects} + k_{fleas\ home,ai} \times Treated_{fleas\ home} + k_{fleas\ pets,ai} \times \text{Treated}_{fleas\ pets} + k_{weeds,ai} \times \text{Treated}_{\text{weeds}}) \times \text{Years Together} \quad [3]$$

$$E_{non\text{-}occ,ai} = E_{take\text{-}home,ai} + E_{drift,ai} + E_{res,ai} \quad [4]$$

Study Population

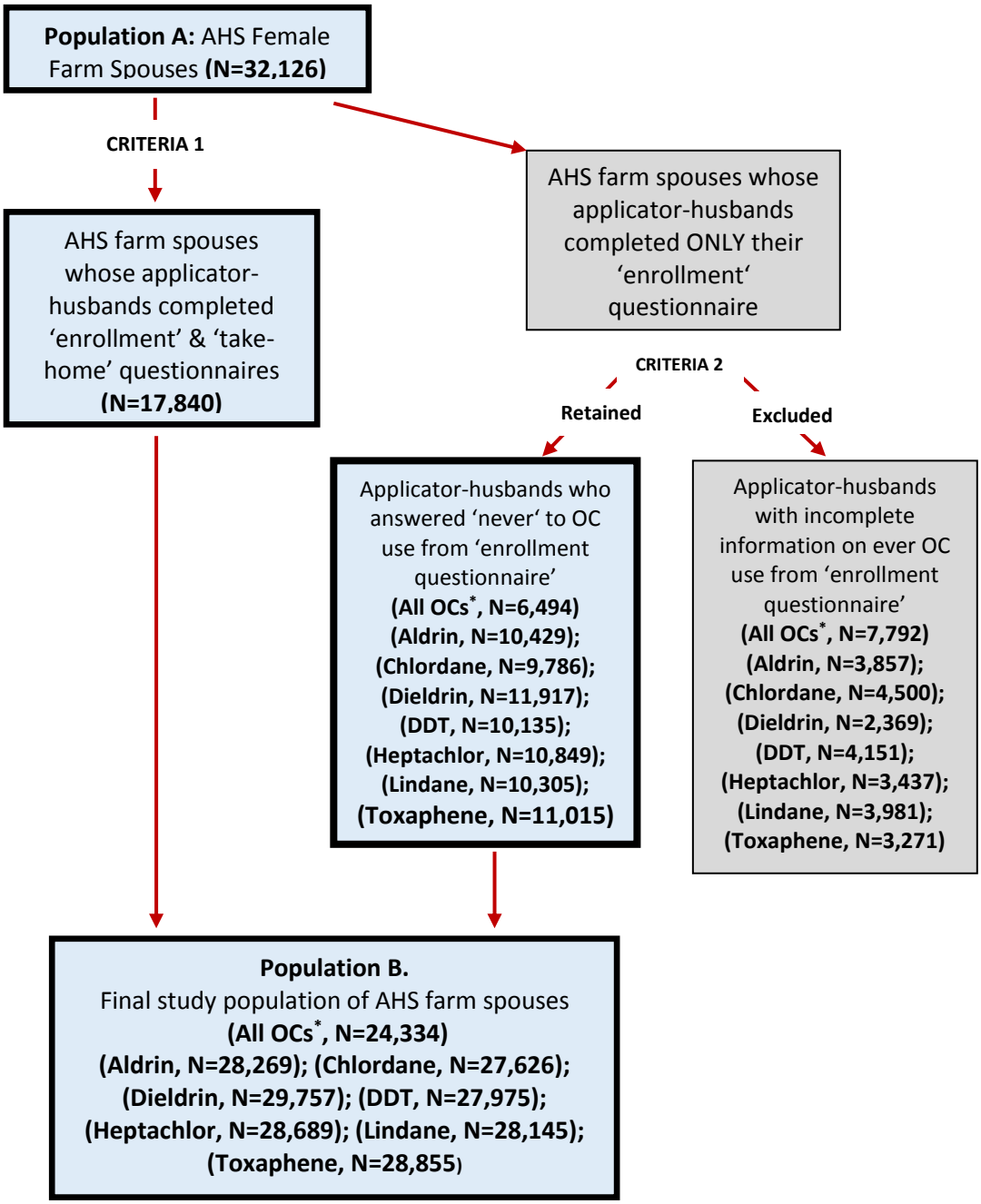
As described in the previous chapter, the AHS is a prospective cohort that includes licensed private pesticide applicators (mostly farmers), and their spouses (n=32,345), residing in Iowa and North Carolina. Briefly, pesticide applicators were recruited from 1993-1997 when applying for their license to apply restricted-use pesticides. Applicator level information was gathered from the applicators' AHS enrollment questionnaires and included active ingredient-specific information on agricultural use of each active

ingredient, including the seven OCs, as well as information on livestock raised, personal protective equipment used, smoking and alcohol consumption, and demographic information. Furthermore, a subset of pesticide applicators completed a 'take-home' questionnaire, which contained additional information on active ingredient-specific pesticide use, frequency and duration. Concurrently, 32,345 spouses of these pesticide applicators were enrolled by completing a questionnaire' reporting information on their demographics, lifestyle factors, family and personal medical histories, farm exposures, and agricultural activities, including the 'ever' applying or mixing of specific active ingredients including seven OCs.

Figure 1 illustrates the criteria used to determine the study population for which non-occupational pesticide estimates could be obtained. In following, the term 'farm spouse' will be used to indicate an enrolled AHS female farm spouse, the term 'applicator-husband' will be used to indicate an enrolled AHS male applicator who is married to an enrolled female spouse, and the term 'wife-husband pair' will be used to indicate enrolled female farm spouses and their respective enrolled applicator-husbands. Our initial study population in Aim 1 was restricted to the female farm spouses of these wife-husband pairs (n=32,126, excludes 219 male spouses) (Population A). To apply the spousal non-occupational pesticide algorithm, information on the frequency and duration of OC use by the enrolled applicator-husband was necessary. Thus, I restricted our initial study population (Population A) to those spouses who met one of two criteria that enabled the application of the non-occupational algorithm and retained these individuals in the final study population (Population B). Criteria 1 included those spouses whose applicator-

husbands completed both the ‘enrollment’ and ‘take-home questionnaires’ (n=17,840). Criteria 2 included those spouses whose applicator-husbands completed the ‘enrollment’ but not the ‘take-home’ questionnaire, and who indicated ‘never’ use for each of the individual OC pesticides on their enrollment questionnaires. The size of Population B varied by active ingredient due to the second criterion and includes those female spouses whose husbands provided sufficient use information for each individual OC active-ingredient. For example, our study population for the evaluation of chlordane comprised 27,626 farm spouses. Of these, 17,840 wife-husband pairs had a completed applicator take-home questionnaire and 9,786 wife-husband pairs did not have an applicator take-home questionnaire, but the applicator-husband indicated having ‘never” used chlordane on his ‘enrollment questionnaire’. 4,500 spouses were excluded because of the applicator-husband indicated ‘yes’ to chlordane use on the enrollment questionnaire but no information on frequency of chlordane use was available because the take-home questionnaire was not completed. The following subsequent descriptive analyses have been restricted to those spouse-applicator pairs in Population B.

Figure 1. Flowchart defining AHS farm spouse study population.



** ALL OCs: inclusion of all seven OC active-ingredients, referenced on the AHS applicator enrollment questionnaire*

Application of non-occupational algorithm to AHS spouses

The non-occupational active ingredient specific exposure algorithm was applied to the spouses (Figure 1. Population B) and assigned subject-specific exposure estimates for each pathway ($E_{take\text{-}home,ai}$, $E_{drift,ai}$ and $E_{res,ai}$), and their aggregate ($E_{non\text{-}occ,ai}$) for each individual OC insecticide. Responses from the spouse enrollment questionnaires were used in the derivation of the algorithm for each spouse as described in *Appendix A: Derivation of algorithm inputs from AHS questionnaires*. Pathway exposure estimates were determined for each OC active ingredient for the take-home and agricultural drift exposure pathways. Since estimates for the take-home and agricultural drift pathways were calculated using similar metrics, statistical results for the common components of these pathways are reported as "take-home/drift" where applicable (e.g., days of OC use). The historical residential use of OCs in the United States was evaluated, and I determined that of the OC active-ingredients, only chlordane and heptachlor were used in residential settings specifically for the treatment of termites from approximately 1945 through 1988 for chlordane and 1953 through 1974 for heptachlor. Therefore, the residential use pathway exposure estimate was only applied to chlordane and heptachlor, and only included the variable component representing OC applications for the treatment of termites. The following amended equation reflecting the application of the residential use pathway for chlordane and heptachlor was used:

$$E_{res,ai} = (k_{termites,ai} \times Treated_{termites}) \times Years\ Together \quad [5]$$

At the time of this analysis I further restricted this population to only include those 'wife-husband' pairs whose wives had completed the phase III questionnaire (2005 through

2010). The phase III questionnaire included information on the time periods that the wife has lived with the applicator-husband, which was necessary for calculating the 'years together' variables necessary for all three algorithm pathways. Additional efforts are currently underway by Agricultural Health Study researchers to characterize these time periods from other information sources for farm spouses without phase III information, for application to the full Population B study population shown in Figure 1, but this information was not available at the time of these analyses.

Statistical Analyses

To characterize the prevalence and distribution of OC exposures, descriptive statistics were calculated for the take-home, agricultural drift and residential use exposure estimates for each OC active ingredient. Exposure to an OC through a non-occupational pathway was defined as a non-zero estimate of exposure for that pathway. Median and interquartile ranges (IQRs) of the non-zero estimates were calculated overall and stratified by the spouses' personal use of each OC active ingredient. Descriptive statistics were calculated overall for each OC active ingredient for each non-occupational pathway, as well as stratified by the spouses' personal use (Yes, No). Kappa statistics were calculated to compare the spouses' personal use of OC active ingredients (yes vs. no) to exposure to each of the non-occupational exposure pathways (Yes, No), where "Yes" was defined as any non-zero exposure estimate for that pathway.

To evaluate the relationship between the active ingredient-specific non-occupational exposure estimates for each pathway and their sum, Spearman rank

correlations were calculated between the exposure estimates for the take-home ($E_{take\text{-}home,ai}$) and agricultural drift ($E_{drift,ai}$) pathways, as well as between each of these pathways and the summed estimate of non-occupational OC exposures ($E_{non\text{-}occ,ai}$). For chlordane and heptachlor, Spearman correlation statistics were also calculated between the residential use exposure estimates ($E_{res,ai}$) and exposure estimates for the take-home, agricultural drift and aggregate non-occupational pathways.

RESULTS

Algorithm Inputs

Distributions of pathway-specific components were calculated based on the spouses' questionnaire responses for the farm spouses that have completed phase III questionnaire. The take-home pathway used off-farm job as a surrogate of potential pesticide exposure: most AHS spouses reported having full-time off-farm jobs (72.9%), while 16.7% reported having part-time off-farm jobs and 10.4% reported having no off-farm jobs (Table 1). The agricultural drift pathway used distance between house and field as a surrogate: 47.3% of AHS spouses reported living between 150 and 449 feet from treated fields and 26.4% reported living ≥ 1,350 feet from treated fields. The residential use pathway incorporated residential pest treatments, which were common in this population, with 50.3% reporting treatment for non-termite insects being the most prevalent, 38.1% reporting treatments for pet fleas, 36.0% reporting treatment for weeds, 15.7% reporting treatment for termites, and 3.2% reporting treatment for fleas at home.

Table 1. Distributions of algorithm components obtained from the spouse's questionnaire responses (N=30,552).[a.,b.]

	N [%]
Pathway Components	
Take-home	
Hours per Day Spouse at Home	
Full-time off-farm job (15.6 hr)	22,282 [72.9]
Part-time off-farm job (17.8 hr)	5,100 [16.7]
No off-farm job (21.0 hr)	3,170 [10.4]
Drift	
Distance (ft) between house and fields	
150 - 449	14,437 [47.3]
450 - 749	6,009 [19.7]
750 - 1349	2,028 [6.6]
1350	8,078 [26.4]
Residential Treatments	
Termites: Yes	4,789 [15.7]
Non-termite insects: Yes	15,381 [50.3]
Fleas: Yes	988 [3.2]
Pet fleas: Yes	11,639 [38.1]
Weeds: Yes	10,992 [36.0]

a. Those spouses with complete questionnaire information needed to apply the non-occupational algorithm for at least one OC

b. Calculations based on the spouses' questionnaire responses for those farm spouses that completed phase III questionnaire

The estimated proportion of spouses who experienced exposures to OC active ingredients through the take-home and agricultural drift pathways due to the applicators' use ranged from 2.2% for dieldrin to 15.0% for DDT (Table 2). The duration of OC use among those who reported applying pesticides was a median of 3.5 years for all OCs except chlordane, which had a median duration of use of 1.0 year. A narrower IQR for duration was observed for aldrin, dieldrin, and heptachlor (IQR: 3.5-3.5) than for DDT, lindane and toxaphene (IQR: 3.5-8.0). Median application frequency among OC users was 2.5 day/year for all OC active ingredients, with a narrower IQR observed for chlordane (0.0-2.5) than for all other OCs (2.5-7.0).

Table 2. Distributions of algorithm components obtained from the questionnaire responses of the spouse's applicator-husband.[a.,c.]

	Aldrin (N= 28,269)	**Chlordane (N= 27,626)**	**Dieldrin (N= 29,757)**	**DDT (N= 27,975)**
	N [%]	**N [%]**	**N [%]**	**N [%]**
Applicator-husband applied active ingredient				
No	24,727 [87.5]	23,790 [86.1]	28,783 [96.7]	23,377 [83.6]
Yes	3,187 [11.2]	3,464 [12.5]	665 [2.2]	4,201 [15.0]
Missing	355 [1.3]	372 [1.4]	309 [1.0]	397 [1.4]
	Median (25th-75th%)	**Median (25th-75th%)**	**Median (25th-75th%)**	**Median (25th-75th%)**
Duration Metrics, exposed subjects [b.]				
Years Applicator Applied While Together$_{ai}$ (yr)	3.5 (3.5-3.5)	1.0 (0.0-1.0)	3.5 (3.5-3.5)	3.5 (3.5-8.0)
Days Applicator Applied$_{ai}$ (d/yr)	2.5 (2.5-7.0)	2.5 (0.0-2.5)	2.5 (2.5-7.0)	2.5 (2.5-7.0)
Years Applicator Applied While Together$_{ai}$ * Days Applicator Applied$_{ai}$ (yr/day)	20.0 (8.8-24.5)	2.5 (0.0-8.8)	8.8 (8.8-24.5)	20.0 (8.8-56.0)

a. OC-specific populations defined based on whether there was complete information on days and years the husband applied an OC active ingredient (Ai)

b. Applied active ingredient = Yes

c. calculations based on the spouses' questionnaire responses for those farm spouses that completed phase III questionnaire

Table 2 Continued. Distributions of algorithm components obtained from the questionnaire responses of the spouse's applicator-husband.[a.,c.]

	Heptachlor (N= 28,689)	**Lindane (N= 28,145)**	**Toxaphene (N= 28,855)**
	N [%]	**N [%]**	**N [%]**
Applicator-husband applied active ingredient			
No	26,107 [91.0]	25,437 [90.4]	26,443 [91.6]
Yes	2,268 [7.9]	2,386 [8.5]	2,095 [7.3]
Missing	314 [1.1]	322 [1.1]	317 [1.1]
	Median (25th-75th%)	**Median (25th-75th%)**	**Median (25th-75th%)**
Duration Metrics, exposed subjects [b.]			
Years Applicator Applied While Together$_{ai}$ (yr)	3.5 (3.5-3.5)	3.5 (3.5-8.0)	3.5 (3.5-8.0)
Days Applicator Applied$_{ai}$ (d/yr)	2.5 (2.5-7.0)	2.5 (2.5-7.0)	2.5 (2.5-7.0)
Years Applicator Applied While Together$_{ai}$ * Days Applicator Applied$_{ai}$ (yr/day)	2.5 (0.0-14.5)	20.0 (8.8-56.0)	14.4 (8.8-50.8)

a. OC-specific populations defined based on whether there was complete information on days and years the husband applied an OC active ingredient (Ai)

b. Applied active ingredient = Yes

c. calculations based on the spouses' questionnaire responses for those farm spouses that completed phase III questionnaire

Take-Home and Agricultural Drift Algorithm Pathways

The proportion of individuals exposed to an OC active ingredient through the take-home/agricultural drift exposure pathways ranged from 1.3% for dieldrin to 9.3% for DDT (Table 3). Prevalence was highest for DDT and chlordane at 9.3% and 8.0%, respectively. Exposure prevalence for dieldrin, toxaphene and heptachlor were at or below 5.0%, at 1.3%, 4.6% and 5.0%, respectively. The majority of those spouses exposed through the take-home/agricultural drift pathways reported no personal use of OC active ingredients. For example, among the 2,647 spouses with non-zero DDT exposure through the take-home/agricultural drift pathways, 2,165 (81.8%) reported having "No" personal use of DDT. Similarly, among the 428 spouses exposed to dieldrin via the take-home/agricultural drift pathway, 379 (88.6%) spouses reported having "No" personal use of dieldrin. Similar patterns were observed for the remaining 5 OC active ingredients.

The median, maximum, and IQR cumulative active ingredient-specific intensity weighted exposure estimates for spouses with non-zero take-home and agricultural drift exposure are shown in Table 3. Overall, median estimates were higher for the agricultural drift pathway than for the take-home pathway for all OCs except DDT and aldrin. For the take-home pathway, overall median (IQR) cumulative exposure intensity estimates of OC active ingredients ranged from 0.9 (0.4-2.5) for chlordane to 2.6 (0.9-3.4) for aldrin, representing ratios of the 75^{th} to 25^{th} percentiles of 7.2 and 3.8, respectively. Maximum take-home intensity estimates among the OC active ingredients ranged from 144 (dieldrin and heptachlor) to 587 (DDT). The ratio of the 75^{th} to 25^{th} percentile take-home exposure estimates ranged from 2.8 for dieldrin to 7.2 for chlordane. Maximum agricultural drift

intensity estimates among the OC active ingredients ranged from 116 (dieldrin) to 1,035 (DDT). The ratio of the 75^{th} to 25^{th} percentile agricultural drift exposure estimates ranged from 4.4 for aldrin and heptachlor to 8.5 for DDT. The sum of the take-home and agricultural drift exposure estimates resulted in medians ranging from 2.7 for chlordane and dieldrin to 4.6 for aldrin, DDT, and lindane. Similarly, the ratio of the 75^{th} to 25^{th} percentiles of the two pathways summed together ranged from 3.7 for heptachlor to 6.7 for chlordane. The agreement between exposure from personal use (Yes, No) and exposure from take-home/agricultural drift pathways (>0 vs. 0) was very low for all OCs, with kappa values ranging from 0.06 for aldrin to 0.16 for DDT (data not shown).

Table 3. Descriptive statistics of take-home and drift non-occupational exposure estimates stratified by personal use of OCs.[a.]

		Take-Home/Drift >0 [%]	Take-Home/Drift = 0 [%]	Take-Home/Drift = Missing [%]	$E_{TAKEHOME}$ among those > 0			
Active Ingredient	**Personal Use**	**Exposed**	**Unexposed**		**Median**	**25th-75th percentile**	**Ratio of 75th/25th percentile**	**Maximum**
Aldrin	**Yes**	72 [0.2]	87 [0.3]	54 [0.2]	2.5	0.9-5.8	6.4	47
N=28,269	**No**	1,883 [6.5]	22,125 [78.3]	2,123 [7.5]	2.4	0.9-3.4	3.8	188
	Missing	133 [0.4]	1,618 [5.7]	174 [0.6]	2.1	0.9-3.4	3.8	54
	Overall	**2,088 [7.1]**	**23,830 [84.3]**	**2,351 [8.3]**	**2.4**	**0.9-3.4**	**3.8**	**188**
Chlordane	**Yes**	319 [1.1]	591 [2.1]	172 [0.6]	1.0	0.9-2.5	2.8	222
N=27,626	**No**	1,831 [6.5]	20,581 [74.5]	2,327 [8.4]	0.9	0.4-2.4	6.7	515
	Missing	114 [0.4]	1,491 [5.4]	200 [0.7]	0.9	0.9-2.8	3.1	24
	Overall	**2,264 [8.0]**	**22,663 [82.0]**	**2,699 [9.8]**	**0.9**	**0.4-2.5**	**7.2**	**515**
Dieldrin	**Yes**	13 [0.0]	72 [0.2]	16 [0.1]	1.0	0.9-4.0	4.4	47
N=29,757	**No**	379 [1.2]	25,841 [86.8]	1,369 [4.6]	1.0	0.9-2.5	2.8	144
	Missing	36 [0.1]	1,908 [6.4]	123 [0.4]	0.9	0.9-2.5	2.8	37
	Overall	**428 [1.3]**	**27,821 [93.5]**	**1,508 [5.1]**	**1.0**	**0.9-2.5**	**2.8**	**144**
DDT	**Yes**	317 [1.1]	426 [1.5]	188 [0.7]	2.9	1.0-12.0	11.6	587
N=27,975	**No**	2,165 [7.7]	20,597 [73.6]	2,424 [8.7]	2.1	0.9-5.8	6.4	515
	Missing	165 [0.5]	1,482 [5.3]	211 [0.78]	2.5	0.9-5.8	6.4	116
	Overall	**2,647 [9.3]**	**22,505 [80.4]**	**2,823 [10.1]**	**2.1**	**0.9-5.8**	**6.4**	**587**
Heptachlor	**Yes**	57 [0.2]	97 [0.3]	45 [0.2]	2.4	0.9-4.6	5.1	37
N=28,689	**No**	1,333 [4.6]	23,255 [81.1]	1,918 [6.7]	1.2	0.9-2.9	3.2	144
	Missing	82 [0.3]	1,747 [6.1]	155 [0.5]	2.5	0.9-5.2	5.8	33
	Overall	**1,472 [5.0]**	**25,099 [87.5]**	**2,118 [7.4]**	**1.2**	**0.9-2.9**	**3.2**	**144**
Lindane	**Yes**	97 [0.3]	263 [0.9]	39 [0.1]	2.3	0.9-5.8	6.4	127
N=28,145	**No**	1,464 [5.1]	22,701 [80.7]	1,918 [6.8]	2.1	0.9-5.3	5.9	282
	Missing	80 [0.2]	1,448 [5.1]	135 [0.5]	2.5	1.0-5.8	6.0	37
	Overall	**1,641 [5.6]**	**24,412 [86.8]**	**2,092 [7.4]**	**2.1**	**0.9-5.8**	**6.4**	**282**
Toxaphene	**Yes**	68 [0.2]	79 [0.3]	34 [0.1]	2.5	1.1-9.2	8.2	47
N=28,855	**No**	1,220 [4.1]	23,718 [82.2]	1,753 [6.1]	1.2	0.9-4.2	4.6	168
	Missing	86 [0.3]	1,733 [6.0]	164 [0.6]	1.8	0.9-4.0	4.4	43
	Overall	**1,374 [4.6]**	**25,530 [88.5]**	**1,951 [6.8]**	**1.2**	**0.9-5.2**	**5.8**	**168**

a. Calculations based on the spouses' questionnaire responses for those farm spouses that completed phase III questionnaire

Table 3 Continued. Descriptive statistics of take-home and drift non-occupational exposure estimates stratified by personal use of OCs.[a.]

		E_{DRIFT} among those >0				$E_{TAKEHOME} + E_{DRIFT}$ among those >0			
Active Ingredient	**Personal Use**	**Median**	**25th-75th percentile**	**Ratio of 75th/25th percentile**	**Maximum**	**Median**	**25th-75th percentile**	**Ratio of 75th/25th percentile**	**Maximum**
Aldrin	**Yes**	2.9	1.7-6.6	4.0	95	5.6	2.6-12.0	4.6	142
N=28,269	**No**	2.0	1.2-5.1	4.4	210	4.6	2.1-4.6	2.2	398
	Missing	2.0	1.2-4.2	3.7	95	4.4	2.2-7.6	3.5	148
	Overall	**2.0**	**1.2-5.1**	**4.4**	**210**	**4.6**	**2.1-8.5**	**4.1**	**398**
Chlordane	**Yes**	1.8	0.9-4.1	4.5	331	2.7	1.8-6.3	3.4	553
N=27,626	**No**	1.5	0.5-2.6	5.0	518	2.4	0.8-5.1	6.3	1032
	Missing	1.8	0.7-4.1	5.8	36	2.7	1.6-7.2	4.4	60
	Overall	**1.8**	**0.5-3.1**	**6.0**	**218**	**2.7**	**0.9-5.7**	**6.7**	**1032**
Dieldrin	**Yes**	1.8	0.7-5.1	7.1	60	2.8	1.8-9.1	5.2	107
N=29,757	**No**	1.8	0.7-3.6	4.9	116	2.7	1.6-6.2	3.8	260
	Missing	1.8	0.7-2.9	4.0	75	2.7	1.7-5.4	3.2	112
	Overall	**1.8**	**0.7-3.8**	**5.3**	**116**	**2.7**	**1.6-6.2**	**3.8**	**260**
DDT	**Yes**	4.6	1.8-18.1	10.0	1,035	7.6	2.7-32.0	11.8	1,622
N=27,975	**No**	2.0	0.9-7.3	8.1	414	17.4	1.9-12.9	6.7	928
	Missing	2.0	1.6-9.0	7.8	174	4.6	2.2-15.7	7.2	290
	Overall	**2.0**	**0.9-8.0**	**8.5**	**1,035**	**4.6**	**2.1-14.7**	**7.2**	**1,622**
Heptachlor	**Yes**	2.6	1.8-5.8	3.2	75	5.7	2.7-11.6	4.3	112
N=28,689	**No**	1.8	1.2-5.1	4.4	256	3.0	2.1-7.6	3.7	384
	Missing	3.2	1.2-7.3	6.4	49	5.9	2.2-13.1	6.0	73
	Overall	**1.8**	**1.2-5.1**	**4.4**	**256**	**3.0**	**2.1-7.6**	**3.7**	**384**
Lindane	**Yes**	3.2	1.5-8.1	5.5	256	6.2	1.6-13.8	8.5	384
N=28,145	**No**	2.0	1.2-7.3	6.4	478	4.4	2.1-12.3	6.0	750
	Missing	4.1	1.8-11.2	6.2	55	6.3	2.7-17.4	6.4	82
	Overall	**2.1**	**1.2-7.3**	**6.4**	**478**	**4.6**	**2.1-12.6**	**6.2**	**750**
Toxaphene	**Yes**	1.9	0.7-5.1	7.0	75	6.2	2.8-20.5	7.4	142
N=28,855	**No**	1.8	0.7-5.1	7.0	337	2.8	1.8-9.4	5.4	504
	Missing	1.9	0.7-5.1	7.0	75	4.1	1.6-8.6	5.3	118
	Overall	**1.8**	**0.7-5.1**	**7.0**	**337**	**3.0**	**1.8-9.6**	**5.3**	**504**

a. Calculations based on the spouses' questionnaire responses for those farm spouses that completed phase III questionnaire

Residential Use Pathway

The proportion of individuals exposed to chlordane and heptachlor for the residential use pathway was 10.9% and 6.72% respectively (Table 4). When stratified by personal use, a majority of spouses exposed through the residential use pathway also reported no personal use of chlordane and heptachlor. For example, of the 3,085 spouses with non-zero chlordane exposures through the residential use pathway, 2,776 (90.0%) reported having "No" personal use of chlordane. Similarly, of the 1,928 spouses with heptachlor exposure through the residential use pathway, 1,830 (94.9%) reported having "No" personal use of heptachlor.

Median, maximum and IQR for the residential use intensity weighted exposure estimates for chlordane and heptachlor are shown in Table 4. Overall median (IQR) cumulative exposure intensity estimates for chlordane and heptachlor were 31.2 (16.5-49.5) and 16.9 (7.8-25.6), respectively, representing a threefold ratio between the 75^{th} and 25^{th} percentiles. Maximum residential use intensity estimates among chlordane and heptachlor were 107 and 27 respectively. The sum of the take-home, agricultural drift and residential use exposure estimates resulted in median values of 18.9 for chlordane and 22.1 for heptachlor. The ratio of the 75^{th} to 25^{th} percentiles of the three pathways summed together were 10.1 for chlordane and 6.8 for heptachlor. The agreement between the personal use (Yes, No) and the residential use pathway (>0 vs. 0) was very low, with kappa values of 0.02 for chlordane and 0.03 for heptachlor (data not shown).

Table 4. Descriptive statistics of residential use non-occupational exposure estimates stratified by personal use of chlordane and heptachlor.[a.]

					N_{RES} among those>0				$E_{TAKEHOME} + E_{DRIFT} + E_{RES}$ among those >0			
Active Ingredient	**Personal Use**	**$N_{RES>0}$ [%] Exposed**	**$N_{RES=0}$ [%] Unexposed**	**$N_{RES=MISSING}$ [%]**	**Median**	**25th-75th percentile**	**Ratio of 75th/25th percentile**	**Maximum**	**Median**	**25th-75th percentile**	**Ratio of 75th/25th percentile**	**Maximum**
Chlordane	**Yes**	186 [0.6]	591 [2.1]	305 [1.1]	36.0	23.4-51.0	2.2	107	12.0	2.7-37.5	14	553
N=27,626	**No**	2,776 [10.0]	12,412 [44.9]	9,551 [34.6]	34.5	15.6-48.6	3.1	107	19.5	4.5-41.0	9	1100
	Missing	123 [0.4]	936 [3.4]	746 [2.7]	40.3	16.9-58.5	3.5	107	16.1	2.7-48.5	18	107
	Overall	**3,085 [10.9]**	**13,939 [50.4]**	**10,602 [38.4]**	**31.2**	**16.5-49.5**	**3.0**	**107**	**18.9**	**4.0-40.5**	**10**	**1,100**
Heptachlor	**Yes**	13 [0.1]	120 [0.4]	66 [0.2]	13.0	10.4-20.8	2.0	27	7.59	2.7-38.5	14	112
N=28,689	**No**	1,830 [6.4]	14,458 [50.4]	10,218 [35.6]	16.9	7.80-24.7	3.2	27	22.1	6.45-42.0	6	447
	Missing	85 [0.3]	1,070 [3.7]	829 [2.9]	24.7	14.3-27.3	1.9	27	23.4	7.5-52.5	7	125
	Overall	**1,928** [6.7]	**15,648** [54.5]	**11,113** [38.7]	**16.9**	**7.8-25.6**	**3.3**	**27**	**22.1**	**6.2-42.0**	**7**	**447**

a. Calculations based on the spouses' questionnaire responses for those farm spouses that completed phase III questionnaire

Spearman Correlation and Proportion Statistics

Take-home and Agricultural Drift Pathways

Spearman rank correlation statistics comparing the exposure estimates for the take-home pathway, the agricultural drift pathway, and the sum of the two pathway's estimates for each OC active ingredient, are listed in Table 5. OC exposure estimates for the take-home and agricultural drift pathways were highly correlated, with a range of 0.92 for toxaphene to 0.96 for chlordane. Exposure estimates for the take-home pathway and the sum of take-home and agricultural drift pathways and between the agricultural drift pathway and the sum of the two pathways were very highly correlated across all OCs ($r_s \geq 0.97$). The agricultural drift pathway contributed between 45% (aldrin, DDT and lindane) to 67% (chlordane and dieldrin) of the summed take-home and agricultural drift pathway estimates.

Table 5. Correlation and proportion statistics between active ingredient-specific take-home and agricultural drift exposure pathway estimates.[a.]

	Spearman Correlations*			Proportion (%)
	$E_{DRIFT} : E_{TAKEHOME}$	$E_{TAKEHOME} : E_{TAKEHOME} + E_{DRIFT}$	$E_{DRIFT} : E_{TAKEHOME} + E_{DRIFT}$	$E_{DRIFT} / E_{TAKEHOME} + E_{DRIFT}$
Aldrin	**0.93**	**0.98**	**0.99**	**45**
Chlordane	**0.96**	**0.99**	**0.99**	**67**
Dieldrin	**0.93**	**0.98**	**0.98**	**67**
DDT	**0.94**	**0.98**	**0.99**	**45**
Heptachlor	**0.93**	**0.98**	**0.99**	**60**
Lindane	**0.93**	**0.98**	**0.99**	**45**
Toxaphene	**0.92**	**0.97**	**0.99**	**60**

* All p-values < 0.0001

a. Calculations based on the spouses' questionnaire responses for those farm spouses that completed phase III questionnaire

Residential Use Pathway

Spearman rank correlation statistics comparing the exposure estimates for the residential use, agricultural drift, and take-home pathway and the sum of the three pathway estimates for chlordane and heptachlor are listed in Table 6. Chlordane and heptachlor exposure estimates, for the agricultural drift and residential use pathways and for the take-home and residential use pathways were not correlated (r_s <0.05). However, exposures estimates for the residential use pathway and the sum of the three pathways were highly correlated for chlordane and heptachlor ($r_s \geq 0.74$). The residential use pathway contributed to 67% (chlordane) and 76% (heptachlor) of the summed residential use, agricultural drift and take-home pathway estimates.

Table 6. Correlation and proportion statistics between active ingredient-specific residential use exposure pathway estimates.[a.]

	Spearman Correlations*			Proportion (%)
	$E_{DRIFT} : E_{RES}$	$E_{TAKEHOME} : E_{RES}$	$E_{RES} : E_{TAKEHOME} + E_{DRIFT} + E_{RES}$	$E_{RES} / E_{TAKEHOME} + E_{DRIFT} + E_{RES}$
Chlordane	**0.023**	**0.022**	**0.740**	**67**
Heptachlor	**0.010**	**0.003**	**0.860**	**76**

* All p-values < 0.0001

a. Calculations based on the spouses' questionnaire responses for those farm spouses that completed phase III questionnaire

DISCUSSION

I applied the non-occupational spousal algorithm for the first time to quantify the cumulative exposures of OC active ingredients for the take-home, agricultural drift and residential use pathways. Consequently, I identified an additional 1.2-10.0% (379-2,776) farm spouses exposed to individual OC active ingredients through non-occupational pathways than when basing exposure solely on their personal use. In addition, I captured variability in OC non-occupational exposure intensities among the AHS spouses, with pesticide-specific ratios of the 75^{th} to 25^{th} percentiles ranging from 2.8 to 8.5. This OC exposure characterization represents an improvement over previous studies of the AHS spouses, which relied solely on personal pesticide use or used their husband's pesticide use as a surrogate metric [3]. Compared to classification of pesticide exposures through the AHS spouses' personal use alone, by capturing non-occupational exposures of the spouses' pesticide exposure misclassification can be reduced.

The application of the algorithm suggested that the prevalence of OC exposure in the AHS spouses was substantially higher than when estimated through reported personal use alone. There were few reported farm spouses who reported 'Yes' to OC personal use and were classified as having "No" non-occupational OC exposures, suggesting that relying on the personal use alone would provide an underestimate of exposure. For example, the take-home/agricultural drift pathways identified 2.6 times more DDT exposed farm spouses than compared to exposure through the farm spouses' personal use alone. Comparable patterns of exposure prevalence were observed for the other OC active ingredients and the take-home/agricultural drift pathways. Similarly, the residential use

pathway identified for chlordane 2.6 times more exposed spouses and for heptachlor 8.7 times more exposed spouses than compared to metrics based solely on the exposure through the spouses' personal use alone.

Greater variability in exposure estimates were observed among those exposed through the agricultural drift pathway than through the take-home pathway. A source of this pathway-specific variability difference may be due to differences in distribution patterns observed in pathway-specific components (Table 1). For example, there was greater variation in the 'distance between house and treated fields' variable (i.e. 150-449 ft., 450-749 ft., 750-1349 ft., 1350 ft.), which was used in the agricultural drift pathway, than in the off-farm work variable (i.e. 'full-time job', 'part-time job' and 'no job') used in the take-home pathway. An additional source of exposure variability in common to both pathways was the distribution of 'years applied while together * days applicator applied' derived from the spouses' applicator-husbands' reported pesticide use. For example, in Table 2 the IQRs for OC specific duration metrics 'years applied while together * days applicator applied' demonstrate the widest spread for DDT (8.8-56.0), and lindane (8.8-56.0). This pattern of variability is consistent with the variability observed in the exposure estimates for the take-home and agricultural drift pathways, where ratios for the 75^{th} to 25^{th} percentile of DDT and lindane were, 7.2 and 6.2 respectively. Identifying the OC-specific variability in exposure estimates between the agricultural drift and take-home pathways will allow for a greater understanding of non-occupational OC exposure characterization among the AHS farm spouses and improve our ability to evaluate exposure-response associations.

Exposure variability for the residential use pathway compared to the other two pathways differed for the two OCs evaluated. Residential use estimates for chlordane were approximately half of the observed exposure variability from the agricultural drift and take-home pathways. For example, ratios for the 75^{th} to 25^{th} percentile of chlordane were 3.0 for the residential pathway (Table 4), compared to 7.2 and 6.0 for the agricultural drift and take-home pathways, respectively. In contrast, for heptachlor exposure variability from the residential use pathway was similar to the exposure variability observed from the agricultural drift and take-home pathways. The variability differences captured by the residential use pathways were predominantly due to differences in the duration of time the farm spouse lived with the applicator-husband (Table 2) and partly due to differences in who applied the pesticide (i.e., spouse, house resident, or commercial applicator).

Correlations between pathway-specific OC exposure estimates revealed variations in the contributions of the take-home, agricultural drift and residential use pathways to total non-occupational OC exposures. The take-home and agricultural drift pathways were highly correlated with each other for all OCs ($r_s \geq 0.98$) due to their common equation components of days and years of applicator-husbands' use. These results are similar to those from a recent application of the algorithm for atrazine and chlorpyrifos, which also found these pathways to be highly correlated ($r_s \geq 0.98$) [98]. These high correlations suggest that likely only one of these two pathways may be necessary in the estimation of non-occupational OC exposures, which will be examined in future sensitivity analyses. In contrast, the residential use pathway was not correlated with either the agricultural drift or take-home pathways for chlordane or heptachlor ($r_s < 0.02$), indicating an independence of

the residential use pathway. Moreover, the residential use pathway contributed more than half (>65%) of the aggregate non-occupational exposures for both OC active-ingredients. Taken together, these results suggest the residential use pathway may be a very important contributor to total non-occupational exposures for chlordane and heptachlor.

Strengths of this study include the ability to better quantitatively discriminate exposures derived from multiple non-occupational pathways and an improvement on previous analyses that examined OC exposures among spouses based on their husband's application of OCs [62, 99-101]. Previous studies of pesticide exposures among the AHS spouses have relied either on the spouses' reported personal use or were based on surrogate measurements to estimate non-occupational pesticide exposures among the farm women. For the first time, quantitative, subject-level specific non-occupational exposures were obtained for the AHS spouses. This application of this algorithm allows for better characterization of cumulative OC exposures among the spouses, thereby reducing exposure misclassification.

As previously described [62], limitations of the application of this non-occupational spousal algorithm analysis include the potential underestimation of exposures due to an inability to characterize windows of time prior to the spouses' marriage to their applicator-husbands, and an inability to assess other pathways of non-occupational exposures. The algorithm does not include the exposure time window prior to the spouses' marriages to their applicator husband's as this was not included in the AHS questionnaires. Since the peak use of OCs occurred in the prior to study enrollment, this may serve as a particular source of OC exposure underestimation. Moreover, due to a lack of relevant and available

data, the dietary and bystander exposure pathways were omitted from the algorithm and may also contribute to exposure underestimation. Additionally, exposures derived from the spouses' off-farm jobs and neighbors' use of pesticides were not included in the AHS questionnaires and therefore not assessed in the algorithm. Another limitation of this analysis is that the quantitative non-occupational exposure estimates do not reflect doses of exposure among the spouses. The pathway weights were based on an assumption that measurements of pesticide concentrations in house dust serve as a reasonable proxy for adult exposures and therefore do not reflect actual doses of exposure among the spouses. Rather the use of these weights allows for a comparative analysis of relative exposure contrast between pathways.

There were also two limitations specific to the application of the algorithm to the OCs. First, comparisons were made on only those farm spouses with Phase III questionnaires due to incomplete information to apply the algorithm to the remaining farm spouses at the time of these analyses. It is unlikely that the patterns observed here in exposure variability and relationship between pathways will differ for the full population, but these evaluations will need to be reexamined once the algorithm is applied to the full population. Second, I had to exclude farm spouses whose applicator-husbands did not provide information on the frequency and time periods of OC use that was asked in more detail on the take-home questionnaire. This restriction is not necessary for analyses of ever/never use by either the farm spouses (Aim 1) or their applicator-husbands or for the 50 pesticide active ingredients that were the focus of the enrollment questionnaire.

CONCLUSIONS

In summary, I applied for the first time the recently developed non-occupational exposure algorithm to quantitatively asses OC active-ingredient exposures among the AHS female farm spouses and reduce OC exposure misclassification. This application of the algorithm allowed me to classify an increased proportion of spouses as having OC exposure, independent of those who were classified as exposed based on personal use alone. These findings have the potential to improve subsequent etiologic analyses through the reduction of exposure measurement error, and an increased ability to examine exposure-response associations in cancer risk associated with OC exposures among women.

APPENDIX A: Derivation of algorithm inputs from AHS questionnaires

Below I describe the time duration variables and questionnaire variables used to compute each exposure estimate. In following, each questionnaire variable is ascribed the following notation, <*QUESTION VARIABLE*>.

Time Duration Variables

- ***Days Applicator Applied***

Duration metrics were used in all pathway estimates to account for cumulative active-ingredient specific exposures during adult married life. Both the take-home (*Etakehome,ai*) and agricultural drift (*Edrift,ai)* pathway estimates included the applicator's number of days (*Days Applicator Applied*$_{ai}$) per year and years of active ingredient use while living with their spouse (*Years Applicator Applied While Together ai*). *Days Applicator Applied*$_{ai}$ was derived from the applicator husbands' responses to the following question *<a_ active ingredient name _day1> In an average year when you personally used this pesticide, how many days did you use it? (Less than 5 days, 5-9 days, 10-19 days, 20-39 days, 40-59 days, 60-150 days, More than 150 days).* Responses to this question was standardized by dividing by the median number of days per year of any pesticide application reported across all applicators with at least one day of use at Phase 1 (*Median Application Days*=14.5). This standardization ensured consistency with the pathway-specific weights ($k_{take\text{-}home,}$ $k_{drift,}$ k_{res}), which represented the average contribution aggregated over a long-time span rather than the contribution per pesticide application day.

Years Applicator Applied While Together$_{ai}$ was derived from the applicator's responses to the following two questions: *<a_active ingredient name_fu1> When did you*

first personally use this pesticide (Before 1960, In the 1960s, In the 1970s, In the 1980s, In the 1990s, Last year) **and** *<ayrsmix> How many years did you personally mix or apply pesticides? (1 year or less, 2-5 years, 6-10 years, 11-20 years, 21-30 years, More than 30 years)*. From these responses, the applicator's reported start and stop years of active ingredient use. This information was adjusted based on the start and stop years of marriage and cohabitation between the applicator and spouse, and was used to tabulate a final value for *Years Applicator Applied While Together*.

The residential pesticide use exposure pathway (*Eres,ai*) incorporated the number of years the spouse and applicator lived in the same home (*Years Together*).

Take-Home Exposure Pathway

Hours per Day Spouse at Home was based on the spouses' responses to three questions. 1) <*SJOBOFF*> *Did you ever have a job off a farm? (No/Yes),* 2) <*SWHNWORK*> *When did you usually work at this job? (Year round/Off season only),* **and** 3) <*SWRKTIME*> *How much time did you work at this job? (Half-time or less/More than half-time).* From these responses three categories were developed and spouses were assigned an average proportion of hours per day spent at home based on the 2003 American Time Use Survey (Bureau of Labor Statistics 2003).

- **21.0 hours** was assigned if the spouse answered "No" to <*SJOBOFF* >.
- **17.8 hours** was assigned if the spouses' answers corresponded to any of the following combinations:
    - "Yes" to <*SJOBOFF*> **and** "Half-time or less" to <*SWRKTIME*>
    - "Yes" to <*SJOBOFF*>, "Off season only" to <*SWHNWORK*> **and** either "More than half-time".
    - no answer to <*SWRKTIME*>.
- **15.6 hours** was assigned if the spouses' answers corresponded to any of the following combinations:
    - "Missing" = <*SJOBOFF*>, Any Response <*SWHNWORK*>, **and** Any Response <*SWRKTIME*>.
    - "Yes" = <*SJOBOFF*>, "Year Round" = <*SWHNWORK*>, "Missing" **or** "More than half-time" <*SWRKTIME*>.
    - "Yes" = <*SJOBOFF*>, "Missing" <*SWHNWORK*>, **and** "Missing" **or** 'More than half-time' <*SWRKTIME*>.

Agricultural Drift

Proximity Ratio was based on the spouses' responses to <*SLIVF10A*> Were you living on a farm 10 years ago? (No/Yes). If a spouse responded "No" **or** "Missing", responses to the following question was used to derive the proximity ratio, <*SNPAPDIS*> *How far is your home from the nearest field or orchard where pesticides are applied (Now in the past 12 months)? (Less than 100=1 yards, 100-199 yards=2, 200-299 yards=3, 300 yards or more=4, "Don't know"=5)*. If a spouse responded **either** "300 yards or more", "Don't know" **or** "Missing" the proximity ratio was assigned the baseline value of 1.2. If a spouse responded, "200-299 yards" the proximity ratio was given a value of 1.5. If a spouse responded, "100-199 yards" the proximity ratio was assigned a value of 1.9. If a spouse responded, "Less than 100 yards" the proximity ratio was assigned value of 3.0.

If a spouse responded "Yes" to <*SLIVF10A*>, combinations of responses to <*SNPAPDIS*> and <*SAPAPDIS*> were used to determine the proximity ratio, where <*SAPAPDIS*> represented responses to *How far is your home from the nearest field or orchard where pesticides are applied (10 years ago)? (Less than 100=1 yards, 100-199 yards=2, 200-299 yards=3, 300 yards or more=4, "Don't know"=5)*. If the responses to <*SNPAPDIS*> and <*SAPAPDIS*> were discordant, the proximity ratio was assigned the average of the proximity ratios of the two response values. If there was a response value for one of these variables while the second was marked as "Missing", then the known value was assigned as the proximity ratio.

Residential Use

House ever treated for termites was based on a combination of responses to the following two questions: *<SLSTPCID> When was the last time pesticides or chemical were used to prevent or control termites in this house? (Never use pesticides or chemicals to prevent/control termites problem, Less than 1 year ago, 1 year or more ago, "Don't know")* **and** *<SNUMPCID> How many times has this house been treated for termites? (Never, Once, Twice, Three times, Four times, Five times, More than five times, "Don't know").* If *<SLSTPCID>* and *<SNUMPCID>* were both given a value of either "Don't know" **and/or** "Missing" then the variable for representing whether a house was ever treated for termites was marked as "No=0". Any other combination of responses for *<SLSTPCID>* and *<SNUMPCID>* resulted in an assignment for the variable, representing whether a house was ever treated for termites, as "Yes=1".

Chapter 4. Aim 3. Non-occupational OC exposures and risk of breast cancer among the Agricultural Health Study (AHS) female farm spouses

ABSTRACT

BACKGROUND: Organochlorine (OC) insecticides are a class of pesticides historically used worldwide in agriculture, with some still in use in some developing countries for the control of vector-borne illnesses. Breast cancer has been the most frequently examined hormonally mediated cancer with respect to OC exposures, however most findings have been inconclusive. Recent analyses of the Agricultural Health Study (AHS) female farm spouses have found a positive association with dieldrin use and ER-PR- breast cancer. However, these analyses have only been able to assess the spouses' personal use of OCs or non-occupational sources of OC exposures through surrogate measurements, which may not accurately reflect specific exposure pathways. Due to the environmental persistence of OCs, it is important to assess cancer risk with non-occupational sources of OC exposures to fully evaluate their role on breast cancer risk in women. Here I have evaluated the association between non-occupational OC exposures and risk of breast cancer among the AHS female farm spouses. **METHODS:** The recently published AHS non-occupational spousal algorithm was used to derive quantitative exposure estimates for OC exposures from the take-home, agricultural drift and residential use non-occupational exposure pathways. I used Poisson regression to estimate relative risks (RRs) and 95% confidence intervals (CIs) for overall breast cancer and breast cancer subtypes ($n \geq 3$ exposed cases) with OC exposures from each of the three non-occupational pathways as well as overall non-occupational exposure. OC exposures were evaluated by quartiles and median

categories of exposure based on a sufficient number of exposed cases (n≥3 exposed cases). Incident cancers were reported to state cancer registries from study enrollment through 2014 (North Carolina) and 2015 (Iowa). **RESULTS:** Among the 31,114 female farm spouses, there were 1,214 number of overall breast cancer cases, including 736 number of ER+/PR+ breast cancer. Most individual exposure pathways of individual OCs were not associated with breast cancer overall or with ER+PR+ breast cancer. Toxaphene exposure through the take-home pathway was associated with ER+PR+ breast cancer ($N_{exposed}$ = 31, RR_{Q1} = 1.66, 95% CI 1.16 to 2.39, p_{trend}= 0.03). Aldrin and toxaphene exposures through the agricultural drift pathway were associated with overall ($N_{exposed}$ = 43, RR_{Q1} = 1.38, 95% CI 1.01 to 1.88, p_{trend}= 0.77; toxaphene: $N_{exposed}$ = 25, RR_{Q1} = 1.59, 95% CI 1.07 to 2.37, p_{trend}= 0.42) and ER+PR+ breast cancers (aldrin: $N_{exposed}$ = 31, RR_{Q1} = 1.59, 95% CI 1.10 to 2.31, p_{trend}= 0.26; toxaphene: $N_{exposed}$ = 19, RR_{Q1} = 2.09, 95% CI 1.32 to 3.31, p_{trend}=0.03). Chlordane and heptachlor exposures through the residential use pathway were associated with ER+PR+ breast cancer (chlordane: $N_{exposed}$ = 35, RR_{Q3} = 1.58, 95% CI 1.09 to 2.28, p_{trend}= 0.26; heptachlor: $N_{exposed}$ = 24, RR_{Q3}= 1.84, 95% CI 1.19 to 2.84, p-trend=0.30). Finally, overall non-occupational exposures of aldrin ($N_{exposed}$ = 27, RR_{Q1}= 1.58, 95% CI 1.07 to 2.35, p_{trend}= 0.22) , heptachlor ($N_{exposed}$ = 42, RR_{Q3}= 1.86, 95% CI 1.33 to 2.59, p_{trend}= 0.94), and toxaphene ($N_{exposed}$ = 18, RR_{Q1}= 1.93, 95% CI 1.20 to 3.09; $N_{exposed}$ = 15, RR_{Q4}= 1.80, 95% CI 1.07 to 3.02 ; p_{trend} = 0.02) were associated with ER+PR+ breast cancer. **CONCLUSIONS:** This study is the first etiologic analysis to use the AHS non-occupational spousal algorithm to assess the impact of individual non-occupational pathways of exposure by specific pesticides, on the risk of breast cancer among the AHS

female farm spouses. While I observed some significant associations, in general my findings did not demonstrate strong evidence for an elevated risk of breast cancer with non-occupational OC exposures.

INTRODUCTION

Breast cancer has been the most frequently examined hormonally mediated cancer with respect to OC exposures; however, most findings have been inconclusive [16, 31, 32, 34-41, 80, 81, 102-104]. Recent analyses from the AHS have found some positive associations between OCs and breast cancer among the female farm spouses of applicator-husbands [34, 105]. A study examining the association between pesticide use with breast cancer among the AHS farm spouses found a significant increased risk for breast cancer among women who had never used heptachlor or dieldrin, but whose applicator-husbands had [34]. In addition, this same analysis found no association of breast cancer risk with farm size or washing of clothes worn during pesticide application; however, risk of breast cancer was non-significantly increased among farm women whose homes were closest in proximity to areas of pesticide application. A later study by the same researchers found use of heptachlor by the farm spouses' husbands was associated with a significant increased risk of breast cancer [60]. As a follow-up to this study I evaluated the personal use of OCs and cancer risk among the AHS farm spouses with more accrued person-time and an increased number of exposed cases [105]. I found that ER-PR- breast cancer was significantly associated with the spouses' personal use of dieldrin.

Pesticide exposures among farm women are the result of exposure from both personal use and from indirect exposure through non-occupational pathways [62, 97]. As previously described in Aim 2, non-occupational pathways include take-home exposures, agricultural drift and the residential use of pesticides for the treatment of insects around the home [62, 97]. The evaluation of non-occupational pathways of pesticide exposures is

particularly important to assess for family members of agricultural workers, including female farm spouses, who may not otherwise experience direct exposures to pesticides or exposures that are as high in concentration or duration [62]. Previous epidemiology analyses examining non-occupational pesticide exposures have been limited by surrogate exposure measurements based on self-reported questionnaire data [62, 67, 99-101] or by biological markers of exposure which may not have accurately reflected relevant time windows of exposure [62, 106-109]. Thus, these analyses have generally been unable to determine associations for cancer or other chronic diseases[62] with multiple pathways of pesticide exposures among female farm spouses of pesticide applicators living in agricultural areas [110-112].

To improve upon the exposure assessment of non-occupational pathways of pesticide exposures, AHS researchers created the quantitative non-occupational pesticide algorithm for the AHS female farm spouses [62]. This algorithm assigns quantitative exposure estimates for each of the three non-occupational pathways and for overall non-occupational exposure based on the addition of estimates for the three pathways. [62, 97]. In the previous chapter, I used this algorithm to characterize quantitative estimates of active-ingredient specific OC exposures (i.e. aldrin, chlordane, dieldrin, DDT, heptachlor, lindane and toxaphene) for each pathway for the AHS female farm spouses. In the following analysis, I will use these quantitative exposure estimates to examine the relationship between non-occupational OC exposures and risk of breast cancer among the AHS female farm spouses. Specifically, the objectives of Aim 3 are as follows:

Aim 3. To evaluate the impact of exposures to OC insecticides from non-occupational pathways on the risk of developing breast cancer among the AHS farm spouses.

METHODS

Study Population and Follow-Up

Briefly, the AHS is a prospective cohort that includes licensed private pesticide applicators (mostly farmers), and their spouses (n=32,345), residing in Iowa and North Carolina, and has been previously described in Aims 1 and 2. Pesticide applicators were recruited from 1993-1997 and during this time they completed an 'enrollment' questionnaires containing active ingredient-specific information on the agricultural use of pesticides including seven OCs (i.e., aldrin, chlordane, dieldrin, DDT, heptachlor, lindane and toxaphene) and demographic factors. A further subset of applicators completed a 'take-home' questionnaire, which contained additional information on active ingredient-specific pesticide use, frequency and duration. Concurrently, the spouses of these applicators were also enrolled and completed a questionnaire with information on demographic factors, family and personal medical histories, farm exposures, and agricultural activities, including their 'ever' personal use (i.e. mixing or applying) of specific active ingredients including the seven OCs. Some of these spouses also completed the Female and Family Health Questionnaire, which focused on reproductive health histories.

The study was approved by all relevant Institutional Review Boards and study questionnaires are publicly available (https://aghealth.nih.gov/collaboration/questionnaires.html). Cancer incidence was assessed regularly via linkage with the North Carolina and Iowa state cancer registries. Mortality incidence was assessed through regular linkage with state mortality registries and The National Death Index. Cancer sites were classified

according to the *International Classification of Diseases for Oncology, 3rd revision* (World Health Organization).

Non-Occupational Algorithm and Exposure Assessment

The study population for this analysis included those AHS female spouses whose husbands provided sufficient information for each individual OC-active ingredient, as defined by the criteria used to determine Population B in Aim 2 (Figure 1). Briefly, I excluded male spouses (n=219), to those spouses who were diagnosed with cancer prior to study enrollment (n=905), and those with zero or missing person years of follow-up (n=107), leaving 31,114 female spouses in the analytic cohort. For my analyses of individual OCs, spouses were included if they met one of two criteria: (1) those whose applicator-husbands completed both the 'enrollment' and 'take-home questionnaires' (n=17,840), or (2) those spouses whose applicator-husbands completed the 'enrollment' but not the 'take-home' questionnaire, and who indicated 'never' use for each of the individual OC active ingredients on their enrollment questionnaires. Therefore, my study population varied by individual OC active ingredient. At the time of this analysis my final study population was further restricted to only include those 'wife-husband' pairs whose wives had completed the phase III questionnaire, which was necessary for calculating the 'years together' variables in the take-home and agricultural drift pathway equations. Consequently, my final study population for each individual OC active ingredient were as follows: aldrin n=27,418; chlordane n=26,783; dieldrin n=28,839; DDT n=27,151; lindane n=27,272; heptachlor n=27,810; toxaphene n=27,972. Additional efforts are currently

underway by AHS researchers to characterize this missing information for farm spouses without phase III information, but this information was not available at the time of these analyses.

Spouses were assigned subject-specific exposure estimates for each pathway of the non-occupational algorithm, $E_{take\text{-}home,ai}$, $E_{drift,ai}$ and $E_{res,ai}$. and their summation ($E_{non\text{-}occ,ai}$) for each individual OC active ingredient. For the residential use pathway, it was determined that of the OCs only chlordane and heptachlor were used in residential settings, from approximately 1945 through 1988 for chlordane, and 1953 through 1974 for heptachlor. Therefore, the residential use pathway exposure estimates were only developed for chlordane and heptachlor.

'Ever' exposure to an OC, through an individual non-occupational pathway or total non-occupational exposure, was defined as a non-zero exposure estimate for that individual pathway, as detailed previously in Aim 2. Due to the high correlation of exposure estimates derived for the take-home and agricultural drift pathways (r_s 0.92-0.96), 'ever' exposure to individual OCs via these pathways were analyzed as a single exposure, and herein referred to as the combined 'take-home/agricultural drift exposure'. Continuous exposure estimates from the three non-occupational exposure pathways (i.e. take-home, agricultural drift, and residential use) and their summed non-occupational exposures were categorized into median or quartile categories, based on percentiles of the active ingredient-specific exposure distributions for exposed AHS farm spouses. Exposure estimates for total non-occupational exposures ($E_{non\text{-}occ,ai}$) were determined by the addition of exposure estimates for the agricultural drift and take-home pathways (i.e. $E_{take\text{-}home,ai} + E_{drift,ai}$) for all individual

OC active ingredients, with the exception of chlordane and heptachlor. For these two individual OCs, non-occupational exposures were the result of the addition of exposure estimates of all three individual exposure pathways (i.e. $E_{take\text{-}home,ai} + E_{drift,ai} + E_{res,ai}$). In the following analysis, the term 'overall non-occupational exposure' will be used to refer to the specific aforementioned total non-occupational exposure estimate, for each individual OC active ingredient.

Statistical Analysis

Using multivariable *Poisson* regression in SAS version 9.3 (SAS Institute, Inc., Cary, N.C.), relative risks (RR) and 95% confidence intervals (95% CI) were calculated for overall and subtype breast cancers among my previously mentioned final study population for each individual OC active-ingredient. Each non-occupational pathway-specific exposure metric (i.e. take-home, agricultural drift and residential use) and the overall non-occupational exposure metric were examined in separate regression models to assess their individual impact on cancer risk. Person-time was accrued from the date of study enrollment until date of death, cancer diagnosis, movement out of state or last study-follow-up (December 31, 2014 and December 31, 2015 for North Carolina and Iowa respectively), whichever was earliest.

RRs for breast cancer overall and subtypes (i.e. ER+PR+, ER-PR-, ER+PR-, ER-PR+) were calculated comparing the 'ever' to 'never' exposed, of each individual OC (i.e. aldrin, chlordane, dieldrin, DDT, heptachlor, lindane and toxaphene) through the take-home/agricultural drift pathway, residential use pathway and overall non-occupational

exposure. RRs were also calculated comparing median or quartile categories of each OC through each of the three individual non-occupational exposure pathways and overall non-occupational exposure. The continuous exposure estimates from the three non-occupational exposure pathways (i.e. take-home, agricultural drift, and residential use) and overall non-occupational exposure were categorized into median or quartile categories of exposure, depending on whether a sufficient number of exposed cases ($N \geq 3$) existed for each level. Each category of exposure was based on percentiles of the active ingredient-specific exposure distributions among the spouses. Due to the small number of exposed cases, these analyses were restricted to the evaluation of overall breast cancer and ER+PR+ breast cancer.

All models were adjusted for age at enrollment ($\leq$ 44 years, 45-54 years, 55-64 years, $\geq$ 65 years), educational attainment (high school degree or less, some college or college graduate, one or more years of graduate school), alcohol use (never, less than 1 drink per month, $\geq$ 1-3 per month), cigarette pack-years smoked as reported at enrollment (pack-year quartiles: Never, $\leq$ 6.75, 6.751-16.75, $\geq$ 16.751), and state of residence (Iowa or North Carolina). I considered the following additional confounders: BMI, race, family history of cancer, and ever use of any pesticide, but did not include them in my final models as they did not alter my results by $\geq$ 10%.

Female health and reproductive covariates at enrollment were also examined with respect to breast, ovarian and uterine cancer, and included the following: menopausal status at enrollment (yes/no), ever use of oral contraceptives at enrollment (yes/no), ever use of hormone replacement therapy at enrollment (yes/no) and age at first menarche ($\leq$ 12 years

or below, > 12 years). These female reproductive covariates did not appear to significantly alter my results and thus were not included in my final models. I did not have adequate power to determine whether parity may have affected my results. Moreover, I attempted to conduct sensitivity analyses to examine the possible influence of early life exposures, using the farm spouses' year of birth as a surrogate for the potential for exposure during critical developmental periods. However, due to an insufficient number of exposed cases, I was unable complete these analyses.

Additionally, because dieldrin is also a biological metabolite of aldrin, I performed sensitivity analyses where 'dieldrin metabolite' (i.e. those farm spouses were exposed to either aldrin or dieldrin) was modeled as the exposure. However, these analyses did not significantly alter my existing aldrin and dieldrin results and were not included in my final analyses. Also, many chlordane pesticide formulations are reported as commonly being a mixture of many related chemicals, including heptachlor [113]. Thus, I conducted sensitivity analyses where 'chlordane or heptachlor' (i.e. those farm spouses who were exposed to chlordane or heptachlor) was modeled as the exposure; however, these results did not alter my existing results for chlordane and were not included in my final analysis.

Since OC exposure among the AHS farm spouses may occur from their personal use of OC active-ingredients and from multiple non-occupational pathways, it is necessary to evaluate whether this personal use modifies the association between non-occupational OC exposures and individual cancers of specific sites. However, due to an insufficient number of exposed cases, I was unable to conduct stratified analyses by personal use (never/ever) status of each individual OC.

RESULTS

From enrollment through 2014/2015 the 31,114 female spouses contributed a total of 547,575 person-years of follow-up (Mean=17.59 standard deviation +/- 5.2) (Table 1). Among the female farm spouses in this study cohort, 16,676 had husbands who reported 'ever' personal use of at least one OC active-ingredient (53.6%) (data not shown). Additionally, 60.9% (n=18,941) of spouses in this study population completed the Female and Family Health Questionnaire.

In general, female farm spouses in this study population tended to be young at their age of enrollment, where 46.8% of the population was 44 years or younger. Those farm spouses whose husbands reported 'ever' personally using at least one OC active-ingredient tended to be slightly older at enrollment than those farm spouses whose husbands reported 'never' using any OC (husbands reporting 'ever' vs 'never' OC use: 8.4% vs 6.7% 55-64 years of age; 3.8% vs 2.8% $\geq$ 65 years of age). Among all other demographic variable categories, there was no apparent difference in the proportion between spouses whose husbands reported 'ever' versus 'never' personal use of at least one OC active ingredient. Among farm spouses in this study population, most were white (96.7%), residents of the state of Iowa (67.2%), were less educated (50.2% with their highest reported level of education obtained as 'high school or less'), and had a lower BMI between 0 and 24.9 (43.2%). The farm spouses also tended to be never smokers (68.2%) and never consumers of alcohol (43.3%). Most farm spouses had a family history of cancer (52.2%), and most reported having grown up on a farm (58.0%). In addition, 32.0% of the farm spouses had gone through menopause at the time of enrollment, as well as having had at least one child

in their lifetime (55.9%). Most also reported having ever used oral contraceptives in their lifetime (43.6%), and the most common age of first menarche was 12 years or less (26.9%).

Among the farm spouses, personal use of chlordane (3.9%) was used most frequently, followed by DDT (3.3%), lindane (1.4%), aldrin (0.8%), heptachlor (0.7%), toxaphene (0.7%) and dieldrin (0.3%) (Table 2). However, among their applicator-husbands, DDT (15.2%) was the most frequently used OC, followed by chlordane (12.7%), aldrin (11.2%), lindane (8.6%), heptachlor (7.9%), toxaphene (7.4%) and dieldrin (2.2%). In addition, the farm spouses 'ever' personal use of individual OCs was not correlated with their corresponding applicator-husbands' 'ever' use of individual OCs, with kappa values ranging from 0.05 for dieldrin to 0.14 for chlordane and DDT.

Table 1. Select characteristics of the AHS female farm spouses at enrollment by their applicator-husbands' OC personal use (N=31,114).*

	Among all farm spouses		Any OC use by applicator-husbands						
			Never		Ever		Missing		p-Value ±
	N	%±±	N	%±±	N	%±±	N	%±±	
Age at enrollment									< 0.001
≤ 44	14,579	46.9	10,088	32.4	2,056	6.6	2,435	7.8	
45-54	7,999	25.7	3,535	11.4	2,447	7.9	2,017	6.5	
55-64	5,995	19.3	2,079	6.7	2,608	8.4	1,308	4.2	
≥ 65	2,541	8.2	874	2.8	1,174	3.8	493	1.6	
Race									< 0.001
White	29,736	95.6	15,708	50.5	8,108	26.1	5,920	19.0	
Other	535	1.7	367	1.2	71	0.2	97	0.3	
Missing	843	2.7	501	1.6	106	0.3	236	0.8	
State of Residence									< 0.001
North Carolina	10,197	32.8	5,098	16.4	3,032	9.7	2,067	6.6	
Iowa	20,917	67.2	11,478	36.9	5,253	16.9	4,186	13.5	
Highest Educational Attainment									< 0.001
High School or Less	15,626	50.2	8,155	26.2	4,631	14.9	2,840	9.1	
Some College or College Graduate	9,743	31.3	5,386	17.3	2,415	7.8	1,942	6.2	
1 or more years of Graduate School	4,437	14.3	2,312	7.4	964	3.1	1,161	3.7	
Missing	1,308	4.2	723	2.3	275	0.9	310	1.0	
Body Mass Index									< 0.001
0-24.99	13,437	43.2	7,416	23.8	3,663	11.8	2,358	7.6	
25.00-29.99	8,717	28.0	4,280	13.8	2,722	8.7	1,715	5.5	
≥ 30.00	5,064	16.3	2,576	8.3	1,563	5.0	925	3.0	
Missing	3,896	12.5	2,304	7.4	337	1.1	1,255	4.0	
Alcohol									< 0.001
Never	13,484	43.3	6,611	21.2	4,184	13.4	2,689	8.6	
Less than once/month	8,024	25.8	4,508	14.5	1,961	6.3	1,555	5.0	
≥ 1-3 times per month	8,305	26.7	4,724	15.2	1,910	6.1	1,671	5.4	
Missing	1,301	4.2	733	2.4	230	0.7	338	1.1	
Cigarette Smoking (Pack-years)									< 0.001
Never Smoker	21,214	68.2	11,212	36.0	5,739	18.4	4,263	13.7	
≤ 6.75	4,005	12.9	2,270	7.3	954	3.1	781	2.5	
6.751-16.75	1,954	6.3	1,095	3.5	479	1.5	380	1.2	
≥16.751	1,969	6.3	926	3.0	647	2.1	396	1.3	
Missing	1,972	6.3	1,073	3.4	466	1.5	433	1.4	

Table 1 Continued. Select characteristics of the AHS female farm spouses at enrollment by their applicator-husbands' OC personal use (N=31,114).[*]

Family History of Cancer									< 0.001
No/Missing	16,468	52.9	9,383	30.2	3,867	12.4	3,218	10.3	
Yes	14,646	47.1	7,193	23.1	4,418	14.2	3,035	9.8	
Grew up on a farm									< 0.001
No	11,875	38.2	6,610	21.2	2,889	9.3	2,376	7.6	
Yes	18,036	58.0	9,291	29.9	5,213	16.8	3,532	11.4	
Missing	1,203	3.9	675	2.2	183	0.6	345	1.1	
Menopause at Enrollment [¥]									< 0.001
No	9,947	32.0	6,379	20.5	2,519	8.1	1,049	3.4	
Yes	8,534	27.4	3,189	10.2	4,377	14.1	968	3.1	
Unsure	286	0.9	136	0.4	114	0.4	36	0.1	
Missing[§]	12,347	39.7	6,872	22.1	1,275	4.1	4,200	13.5	
Number of Live Births [¥]									< 0.001
0	275	0.9	180	0.6	72	0.2	23	0.1	
1 or 2	8,386	27.0	4,533	14.6	3,004	9.7	849	2.7	
> 2	9,001	28.9	4,318	13.9	3,592	11.5	1,091	3.5	
Missing[§]	13,452	43.2	7,545	24.2	1,617	5.2	4,290	13.8	
Oral Contraceptive [¥]									< 0.001
Never	5,206	16.7	2,146	6.9	2,516	8.1	544	1.7	
Ever	13,572	43.6	7,568	24.3	4,495	14.4	1,509	4.8	
Missing[§]	12,336	39.7	6,862	22.1	1,274	4.1	4,200	13.5	
Age of first menarche [¥]									0.0205
12 years or less	8,358	26.9	4,263	13.7	3,223	10.4	872	2.8	
13 years	5,677	18.3	2,928	9.4	2,112	6.8	637	2.0	
14 years or greater	4,570	14.7	2,411	7.7	1,633	5.2	526	1.7	
Missing[§]	12,509	40.2	6,974	22.4	1,317	4.2	4,218	13.6	

[*]Post exclusion of: male spouses (N=219), those with missing or 0 person-years (N=107), those female spouses with history of cancer prior to study enrollment (N=905)

[‡‡]% of full study cohort (N=31,114)

[‡]Chi square test for homogeneity

[¥] From Female and Family Health Questionnaire

[§] Did not complete Female and Family Health Questionnaire

DDT, dichlorodiphenyltrichloroethane

Table 2. Frequency of 'ever' OC personal use and agreement between the AHS female farm spouses and their applicator husbands (N=31,114).*£

OC Active Ingredients	Spouses		Applicator-Husbands		Kappa Statistics Farm Spouse : Applicator
	N	%	N	%	
Aldrin	235	0.8	3,068	11.2	0.06
Chlordane	1,197	3.9	3,389	12.7	0.14
Dieldrin	105	0.3	647	2.2	0.05
DDT	1,029	3.3	4,115	15.2	0.14
Hepatchlor	222	0.7	2,185	7.9	0.06
Lindane	433	1.4	2,341	8.6	0.07
Toxaphene	203	0.7	2,059	7.4	0.08

** All p-values < 0.0001

*Post exclusion of: male spouses (N=219), those with missing or 0 person-years (N=107), those female spouses with history of cancer prior to study enrollment (N=905)

£ Among spouses whose applicator-husbands had complete information on use of OC active-ingredient use based on responses to Take-Home and Enrollment Questionnaires

Among those wife-husband pairs with "complete" information: Aldrin n=27,418; Chlordane n=26,783; Dieldrin n=28,839; DDT n=27,151; Lindane n=27,272; Heptachlor n=27,810; Toxaphene n=27,972

DDT, dichlorodiphenyltrichloroethane

‘Ever’ non-occupational exposures

Overall among the AHS female farm spouses, my results did not suggest associations between individual non-occupational pathways of OC exposures with breast cancer overall or with the ER+PR+ subtype subtypes. My only significant finding for ‘ever’ exposure through the combined take-home/agricultural drift exposure, was for toxaphene and ER+PR+ breast cancer ($N_{exposed}$ = 57; RR=1.57, 95% CI 1.19 to 2.07) (Table 3). There was a suggested elevated risk for take-home/agricultural drift ‘ever’ exposures of toxaphene with breast cancer overall ($N_{exposed}$ = 79; RR=1.24, 95% CI 0.98 to 1.57), as well as for aldrin ($N_{exposed}$ = 84; RR=1.26, 95% CI 0.99 to 1.61) and DDT ($N_{exposed}$ = 103; RR=1.20, 95% CI 0.96 to 1.52) ‘ever’ exposure with ER+PR+ breast cancer. There was also suggested evidence for an increased risk of breast cancer overall with residential use ‘ever’ exposures to chlordane ($N_{exposed}$ =156, RR 1.17, 95% CI 0.97 to 1.41) and heptachlor ($N_{exposed}$ =114, RR 1.18, 95% CI 0.94 to 1.49) through the residential use pathway.

Risk of overall breast cancer was not significantly associated with overall non-occupational OC exposures (Table 4). However, there was suggestive evidence for an increased risk of breast cancer with overall non-occupational exposure to heptachlor ($N_{exposed}$ = 186, RR 1.16, 95% CI 0.98 to 1.37) and toxaphene ($N_{exposed}$ = 79, RR 1.24, 95% CI 0.98 to 1.57). Overall non-occupational exposures to heptachlor ($N_{exposed}$ = 120, RR 1.32, 95% CI 1.07 to 1.62) and toxaphene ($N_{exposed}$ = 57, RR 1.57, 95% CI 1.19 to 2.07) were also associated with a significant increased risk of ER+PR+ breast cancer. While overall non-occupational exposures to aldrin ($N_{exposed}$ = 84, RR 1.26, 95% CI 0.99 to 1.61)

and DDT ($N_{exposed}$ = 103, RR 1.20, 95% CI 0.96 to 1.52) were suggestive of an increased risk with ER+PR+ breast cancer.

Table 3. RR and CIs for ever versus never OC exposures by take-home/agricultural drift and residential use pathways, for breast cancer and breast cancer subtypes.*

Take-Home/Agricultural Drift																
		Aldrin				Chlordane				Dieldrin				DDT			
		$N_{unexposed}$	$N_{exposed}$	RR	95% CI	$N_{unexposed}$	$N_{exposed}$	RR	95% CI	$N_{unexposed}$	$N_{exposed}$	RR	95% CI	$N_{unexposed}$	$N_{exposed}$	RR	95% CI
Breast		818	115	1.07	0.87-1.31	814	106	0.95	0.78-1.17	1,025	25	1.04	0.69-1.55	770	153	1.06	0.88-1.28
	ER+PR+	489	84	1.26	0.99-1.61	501	69	1.05	0.81-1.36	628	18	1.17	0.73-1.89	479	103	1.20	0.96-1.52
	ER-PR-	140	15	0.81	0.47-1.41	135	14	0.85	0.48-1.48	172	4	1.06	0.39-2.90	138	15	0.65	0.37-1.13
	ER+PR-	81	9	0.83	0.41-1.70	80	9	0.71	0.35-1.43	101	1	—	—	73	14	0.83	0.46-1.52
	ER-PR+	10	0	—	—	11	0	—	—	14	0	—	—	9	1	—	—
		Lindane				Heptachlor				Toxaphene							
		$N_{unexposed}$	$N_{exposed}$	RR	95% CI	$N_{unexposed}$	$N_{exposed}$	RR	95% CI	$N_{unexposed}$	$N_{exposed}$	RR	95% CI				
Breast		910	70	0.97	0.76-1.23	890	76	1.00	0.79-1.28	925	79	1.24	0.98-1.57				
	ER+PR+	557	48	1.05	0.78-1.42	534	57	1.19	0.90-1.58	561	57	1.57	1.19-2.07				
	ER-PR-	150	11	0.94	0.51-1.74	154	10	0.77	0.40-1.49	163	2	—	—				
	ER+PR-	86	7	1.01	0.46-2.19	88	4	0.51	0.19-1.43	91	11	1.59	0.84-3.01				
	ER-PR+	11	0	—	—	13	0	—	—	11	2	—	—				
Residential Use																	
		Chlordane				Heptachlor											
		$N_{unexposed}$	$N_{exposed}$	RR	95% CI	$N_{unexposed}$	$N_{exposed}$	RR	95% CI								
Breast		781	156	1.17	0.97-1.41	588	114	1.18	0.94-1.49								
	ER+PR+	494	85	1.14	0.89-1.47	387	64	1.21	0.89-1.64								
	ER-PR-	131	21	1.08	0.66-1.78	91	16	1.25	0.67-2.33								
	ER+PR-	75	18	1.14	0.64-2.02	55	13	0.90	0.45-1.79								
	ER-PR+	9	3	2.53	0.58-11.0	6	1	—	—								

* Among spouses whose applicator-husbands had complete information on use of OC active-ingredient use based on responses to Take-Home and Enrollment Questionnaires

Those farm spouses with "complete" information: Aldrin n=27,418; Chlordane n=26,783; Dieldrin n=28,839; DDT n=27,151; Lindane n=27,272; Heptachlor n=27,810; Toxaphene n=27,972

N = farm spouse cases exposed to individual OC active ingredient via the Take-Home/Agricultural Drift, or Residential Use pathways

All Models Adjusted for: age at enrollment, state of residence, education, alcohol use, and smoking (pack-years)

DDT, dichlorodiphenyltrichloroethane

Table 4. RR and CIs for ever versus never OC active ingredient exposures by overall non-occupational exposures, for breast cancer and breast cancer subtypes.*

	Aldrin				Chlordane				Dieldrin				DDT			
	$N_{unexposed}$	$N_{exposed}$	RR	95% CI	$N_{unexposed}$	$N_{exposed}$	RR	95% CI	$N_{unexposed}$	$N_{exposed}$	RR	95% CI	$N_{unexposed}$	$N_{exposed}$	RR	95% CI
Breast	818	115	1.07	0.87-1.31	715	222	1.08	0.92-1.27	1,025	25	1.04	0.69-1.55	770	153	1.06	0.88-1.28
ER+PR+	489	84	1.26	0.99-1.61	453	126	1.05	0.85-1.29	628	18	1.17	0.73-1.89	479	103	1.20	0.96-1.52
ER-PR-	140	15	0.81	0.47-1.41	121	31	1.01	0.66-1.53	172	4	1.06	0.39-2.90	138	15	0.65	0.37-1.13
ER+PR-	81	9	0.83	0.41-1.70	69	24	1.00	0.61-1.64	101	1.00	0.38	0.05-2.76	73	14	0.83	0.46-1.52
ER-PR+	10	0	–	–	9	3	1.24	0.31-4.99	14	0	–	–	9	1	–	–
	Lindane				**Heptachlor**				**Toxaphene**							
	$N_{unexposed}$	$N_{exposed}$	RR	95% CI	$N_{unexposed}$	$N_{exposed}$	RR	95% CI	$N_{unexposed}$	$N_{exposed}$	RR	95% CI				
Breast	910	70	0.97	0.76-1.23	794	186	1.16	0.98-1.37	925	79	1.24	0.98-1.57				
ER+PR+	557	48	1.05	0.78-1.42	482	120	1.32	1.07-1.62	561	57	1.57	1.19-2.07				
ER-PR-	150	11	0.94	0.51-1.74	141	25	0.94	0.61-1.47	163	2	–	–				
ER+PR-	86	7	1.01	0.46-2.19	77	16	0.88	0.50-1.54	91	11	1.59	0.84-3.01				
ER-PR+	11	0	–	–	12	1	–	–	11	2	–	–				

* Among spouses whose applicator-husbands had complete information on use of OC active-ingredient use based on responses to Take-Home and Enrollment Questionnaires

Those farm spouses with "complete" information: Aldrin n=27,418; Chlordane n=26,783; Dieldrin n=28,839; DDT n=27,151; Lindane n=27,272; Heptachlor n=27,810; Toxaphene n=27,972

N = farm spouse cases exposed to individual OC active ingredient via total Non-Occupational exposures

All Models Adjusted for: age at enrollment, state of residence, education, alcohol use, and smoking (pack-years)

DDT, dichlorodiphenyltrichloroethane

Categories of non-occupational exposures

In general, most analyses examining categories of individual pathway OC exposures, were not significantly associated with a risk of breast cancer overall or with ER+PR+ breast cancer. With respect to categories of take-home pathway exposures, only the lowest categories of toxaphene were significantly associated with an increased risk for ER+PR+ breast cancer ($N_{exposed}$ = 31, RR_{low} = 1.66, 95% CI 1.16 to 2.39, p_{trend}=0.03), with suggested evidence for a positive exposure-response trend (Table 5). Agricultural drift pathway exposures did not generally present any consistent risk associations or exposure response trends for breast cancer overall or for ER+PR+ breast cancer (Table 6). Additionally, there was no evidence for an increased risk of breast cancer overall or for ER+PR+ breast cancer, with the highest categories of OC agricultural drift exposures. The only significant risk associations for breast cancer were observed at the lowest quartile categories of exposure for aldrin ($N_{exposed}$ = 43, RR_{Q1} = 1.38, 95% CI 1.01 to 1.88, p_{trend}= 0.77) and toxaphene **(**$N_{exposed}$ = 25, RR_{Q1} = 1.59, 95% CI 1.07 to 2.37, p_{trend}=0.42) for breast cancer overall. Similarly, there was also a significant increased risk of ER+PR+ breast cancer with the lowest categories of exposure for aldrin ($N_{exposed}$ = 31, RR_{Q1} = 1.59, 95% CI 1.10 to 2.31, p_{trend}=0.26) and toxaphene. ($N_{exposed}$ = 19, RR_{Q1} = 2.09, 95% CI 1.32 to 3.31, p_{trend}=0.03) with evidence for a positive-exposure response trend for toxaphene only. Finally, there was suggestive evidence for an increased risk of ER+PR+ breast cancer and the second quartile category of chlordane exposure ($N_{exposed}$ = 25, RR_{Q2} = 1.49, 95% CI 0.99 to 2.23, p_{trend}=0.71).

Residential use pathway exposures for chlordane and heptachlor did not present consistent significant risk elevations or any evidence for exposure-response trends (Table 7). The only significant increased risks were observed for the third quartile categories of exposure to chlordane ($N_{exposed}$ = 35, RR_{Q3} = 1.58, 95% CI 1.09 to 2.28, p_{trend}= 0.26) and heptachlor ($N_{exposed}$ = 24, RR_{Q3} = 1.84, 95% CI 1.19 to 2.84, p_{trend}= 0.30) with ER+PR+ breast cancer. Chlordane exposure at the third quartile level, provided suggestive evidence for an increased risk of breast cancer overall ($N_{exposed}$ = 53, RR_{Q3} = 1.30, 95% CI 0.97 to 1.75, p_{trend}= 0.14). Heptachlor exposures at the first quartile category provided suggestive evidence for an elevated risk in overall breast cancer ($N_{exposed}$ = 25, RR_{Q1} = 1.48, 95% CI 0.99 to 2.23, $p_{trend=}$0.21), while exposures at the second quartile category provided suggestive evidence for an elevated risk of ER+PR+ breast cancer ($N_{exposed}$ = 20, RR_{Q2} = 1.57, 95% 0.99 to 2.51, $p_{trend=}$0.30) respectively.

Overall non-occupational exposures presented few significant findings of elevated breast cancer risks with OC exposures, all with no observed positive exposure-response trends. Toxaphene exposures at the lowest and highest quartile categories presented significant increased risks for ER+PR+ cancer with evidence for a positive-exposure response trend ($N_{exposed}$ = 18, RR_{Q1}= 1.93, 95% CI 1.20 to 3.09; $N_{exposed}$ = 15, RR_{Q4}= 1.80, 95% CI 1.07 to 3.02 ; p_{trend} = 0.02). Heptachlor exposure at the third quartile category of exposure presented significant increased risks for breast cancer overall ($N_{exposed}$ = 59, RR_{Q3}= 1.39, 95% CI 1.06 to 1.83, p_{trend}= 0.22) and ER+PR+ breast cancer ($N_{exposed}$ = 42, RR_{Q3}= 1.86, 95% CI 1.33 to 2.59, p_{trend}= 0.94). Aldrin exposure at the first quartile category presented a significant increased risk for ER+PR+ breast cancer ($N_{exposed}$ = 27, RR_{Q1}= 1.58,

95% CI 1.07 to 2.35, p_{trend}=0.22). Although non-significant, chlordane ($N_{exposed}$ = 77, RR_{Q4} 1.25, 95% CI 0.97 to 1.63, p_{trend} = 0.06) was the only OC to demonstrate suggestive evidence for an elevated risk of breast cancer overall with a positive exposure response trend. Aldrin ($N_{exposed}$ = 38, RR_{Q1}= 1.39, 95% CI 0.99 to 1.93, p_{trend}= 0.88) and toxaphene ($N_{exposed}$ = 24, RR_{Q1}= 1.48, 95% CI 0.99 to 2.22, p_{trend}=0.33) exposures also demonstrated suggestive evidence for an elevated risk for breast cancer overall.

Table 5. RR and CIs for quartiles of OC exposures by take-home, for breast cancer and breast cancer subtypes.*

Active-Ingredient	Exposure	Breast			ER+ PR+		
		N	RR	95% CI	N	RR	95% CI
Aldrin	0	818	REF	—	489	REF	—
	> 0 - 0.90	46	1.24	0.91-1.67	31	1.35	0.93-1.95
	0.91 - 2.35	14	0.79	0.46-1.34	11	1.00	0.54-1.82
	2.36 - 3.40	30	1.15	0.79-1.66	22	1.36	0.88-2.11
	> 3.40	25	0.95	0.63-1.42	20	1.23	0.78-1.93
				p-trend = 0.97			*p trend = 0.19*
Chlordane	0	814	REF	—	501	REF	—
	> 0 - 0.35	23	0.81	0.54-1.24	15	0.93	0.55-1.56
	0.35 - 0.90	35	1.05	0.75-1.48	22	1.11	0.72-1.71
	0.91 - 2.52	32	1.13	0.79-1.62	21	1.23	0.79-1.91
	> 2.52	16	0.75	0.45-1.23	11	0.86	0.47-1.57
				p-trend = 0.39			*p-trend = 0.89*
Dieldrin	0	1,025	REF	—	628	REF	—
	> 0 - 1.03	17	1.24	0.76-2.01	12	1.37	0.77-2.44
	> 1.03	8	0.77	0.38-1.55	6	0.92	0.41-2.05
				p-trend = 0.72			*p-trend= 0.85*
DDT	0	770	REF	—	479	REF	—
	> 0 - 0.90	47	0.96	0.71-1.29	32	1.10	0.76-1.59
	0.91 - 2.06	26	1.12	0.75-1.67	14	1.00	0.58-1.72
	2.06 - 5.77	47	1.25	0.92-1.69	34	1.54	1.08-2.20
	> 5.77	33	0.96	0.67-1.37	23	1.13	0.74-1.73
				p-trend = 0.99			*p-trend = 0.40*
Lindane	0	910	REF	—	557	REF	—
	> 0 - 2.06	41	1.30	0.74-1.39	27	1.07	0.73-1.58
	> 2.07	29	0.90	0.62-1.30	21	1.03	0.66-1.59
				p-trend = 0.59			*p-trend = 0.87*
Hepatchlor	0	890	REF	—	534	REF	—
	> 0 - 1.21	35	0.93	0.66-1.31	26	1.10	0.74-1.64
	> 1.21	41	1.08	0.78-1.48	31	1.28	0.88-1.85
				p-trend = 0.73			*p-trend = 0.18*
Toxaphene	0	925	REF	—	561	REF	—
	> 0 - 1.21	42	1.32	0.97-1.80	31	1.66	1.16-2.39
	> 1.21	37	1.16	0.83-1.62	26	1.47	0.99-2.20
				p-trend = 0.28			*p-trend = 0.03*

* Among spouses whose applicator-husbands had complete information on use of OC active-ingredient use based on responses to Take-Home and Enrollment Questionnaires

Those farm spouses with "complete" information: Aldrin n=27,418; Chlordane n=26,783; Dieldrin n=28,839; DDT n=27,151; Lindane n=27,272; Heptachlor n=27,810; Toxaphene n=27,972

N = farm spouse cases exposed to individual OC active ingredient via the Take-Home pathway

All Models Adjusted for: age at enrollment, state of residence, education, alcohol use, and smoking (pack-years)

p < 0.05 compared with no exposure

DDT, dichlorodiphenyltrichloroethane

Table 6. RR and CIs for quartiles of OC exposures by agricultural drift, for breast cancer and breast cancer subtypes.*

Active-Ingredient	Exposure	Breast			ER+ PR+		
		N	RR	95% CI	N	RR	95% CI
Aldrin	0	818	REF	—	489	REF	—
	> 0 - 1.15	43	1.38	1.01-1.88	31	1.59	1.10-2.31
	1.16 - 2.03	22	0.86	0.56-1.32	13	0.82	0.47-1.44
	2.04 - 5.07	28	1.03	0.71-1.51	22	1.31	0.85-2.03
	> 5.07	22	0.94	0.61-1.45	18	1.25	0.77-2.01
				p-trend = 0.77			*p-trend= 0.26*
Chlordane	0	814	REF	—	501	REF	—
	> 0 - 0.52	23	0.81	0.53-1.23	15	0.93	0.55-1.56
	0.52 - 1.70	34	1.21	0.86-1.71	25	1.49	0.99-2.23
	1.71 - 3.21	27	0.97	0.66-1.43	15	0.90	0.54-1.51
	> 3.21	22	0.81	0.53-1.25	14	0.87	0.51-1.48
				p- trend = 0.43			*p-trend= 0.71*
Dieldrin	0	1,025	REF	—	625	REF	—
	> 0 - 1.81	20	1.28	0.82-2.00	15	1.51	0.90-2.54
	> 1.81	5	0.59	0.24-1.42	3	0.56	0.18-1.73
				p-trend = 0.38			*p-trend= 0.55*
DDT	0	770	REF	—	479	REF	—
	> 0 - 0.94	31	0.88	0.61-1.27	21	1.02	0.65 - 1.59
	0.95 - 2.03	48	1.22	0.91-1.65	29	1.24	0.85 - 1.83
	2.03 - 8.19	39	1.14	0.82-1.58	26	1.27	0.85 - 1.91
	> 8.19	35	0.98	0.70-1.39	27	1.28	0.86 - 1.91
				p-trend = 0.97			*p-trend= 0.18*
Lindane	0	910	REF	—	557	REF	—
	> 0 - 2.07	38	1.00	0.72-1.39	27	1.14	0.77-1.67
	> 2.07	32	0.93	0.65-1.32	21	0.96	0.62-1.49
				p-trend= 0.64			*p-trend= 0.57*
Hepatchlor	0	890	REF	—	534	REF	—
	> 0 - 1.15	23	0.99	0.65-1.51	20	1.37	0.87 - 2.15
	1.16 - 1.81	14	0.88	0.52-1.51	8	0.81	0.40 - 1.63
	1.81 - 5.07	23	1.06	0.70-1.62	16	1.17	0.70 - 1.93
	> 5.07	16	1.06	0.64-1.75	13	1.34	0.77 - 2.34
				p-trend = 0.80			*p-trend= 0.29*
Toxaphene	0	925	REF	—	561	REF	—
	> 0 - 0.72	25	1.59	1.07-2.37	19	2.09	1.32 - 3.31
	0.73 - 1.81	20	1.15	0.74-1.79	13	1.26	0.73 - 2.19
	1.81 - 5.07	16	1.04	0.63-1.71	11	1.28	0.70 -2.34
	> 5.07	18	1.18	0.74-1.90	14	1.68	0.98 - 2.88
				p-trend = 0.42			*p-trend= 0.03*

* Among spouses whose applicator-husbands had complete information on use of OC active-ingredient use based on responses to Take-Home and Enrollment Questionnaires
Those farm spouses with "complete" information: Aldrin n=27,418; Chlordane n=26,783; Dieldrin n=28,839; DDT n=27,151; Lindane n=27,272; Heptachlor n=27,810; Toxaphene n=27,972
N = farm spouse cases exposed to individual OC active ingredient via the Agricultural Drift pathway
All Models Adjusted for: age at enrollment, state of residence, education, alcohol use, and smoking (pack-years)
p < 0.05 compared with no exposure
DDT, dichlorodiphenyltrichloroethane

Table 7. RR and CIs for quartiles of chlordane and heptachlor exposures by residential use, for breast cancer and breast cancer subtypes.*

Active-Ingredient	Exposure	Breast			ER+ PR+		
		N	RR	95% CI	N	RR	95% CI
Chlordane	0	781	REF	—	494	REF	—
	> 0 - 16.5	25	1.09	0.73-1.63	11	0.80	0.44-1.47
	16.6 - 31.2	31	1.12	0.78-1.61	17	1.07	0.65-1.74
	31.3 - 49.5	53	1.30	0.97-1.75	35	1.58	1.09-2.28
	> 49.5	47	1.13	0.82-1.55	22	1.01	0.64-1.59
				p-trend = 0.14			*p-trend = 0.26*
Hepatchlor	0	866	REF	—	538	REF	—
	> 0 - 7.8	25	1.48	0.99-2.23	12	1.35	0.75-2.43
	7.9 - 16.9	29	1.17	0.80-1.72	20	1.57	0.99-2.51
	17.0 - 24.7	34	1.41	0.98-2.02	24	1.84	1.19-2.84
	> 24.7	26	1.00	0.66-1.51	8	0.59	0.29-1.21
				p-trend = 0.21			*p-trend = 0.30*

* Among spouses whose applicator-husbands had complete information on use of OC active-ingredient use based on responses to Take-Home and Enrollment Questionnaires
Those farm spouses with "complete" information: Aldrin n=27,418; Chlordane n=26,783; Dieldrin n=28,839; DDT n=27,151; Lindane n=27,272; Heptachlor n=27,810; Toxaphene n=27,972
N = farm spouse cases exposed to individual OC active ingredient via the Residential Use pathway
All Models Adjusted for: age at enrollment, state of residence, education, alcohol use, and smoking (pack-years)
p < 0.05 compared with no exposure
DDT, dichlorodiphenyltrichloroethane

Table 8. RR and CIs for quartiles of OC exposures for overall non-occupational exposure, for breast cancer and breast cancer subtypes.*

Active-Ingredient	Exposure	Breast			ER+ PR+		
		N	RR	95% CI	N	RR	95% CI
Aldrin	0	818	REF	—	489	REF	—
	> 0 - 2.05	38	1.39	0.99-1.93	27	1.58	1.07-2.35
	2.06 - 4.55	25	0.90	0.60-1.35	15	0.88	0.52-1.48
	4.56 - 8.47	27	1.03	0.70-1.52	22	1.36	0.88-2.10
	> 8.47	25	0.96	0.64-1.43	20	1.24	0.79-1.95
				p-trend= 0.88			*p-trend= 0.22*
Chlordane	0	715	REF	—	453	REF	—
	> 0 - 4.50	48	0.94	0.70-1.26	29	0.90	0.62-1.31
	4.60 - 19.50	40	0.97	0.70-1.33	21	0.84	0.54-1.30
	19.60 - 42.00	57	1.16	0.88-1.54	33	1.20	0.83-1.74
	> 42.00	77	1.25	0.97-1.63	43	1.30	0.92-1.85
				p-trend= 0.06			*p-trend= 0.10*
Dieldrin	0	1,025	REF	—	628	REF	—
	> 0 - 2.71	19	1.35	0.85-2.13	15	1.68	1.00-2.82
	> 2.71	6	0.60	0.27-1.34	3	0.47	0.15-1.46
				p-trend = 0.48			*p-trend = 0.48*
DDT	0	770	REF	—	479	REF	—
	> 0 - 2.05	39	0.98	0.70-1.36	27	1.14	0.77-1.70
	2.06 - 4.55	35	1.06	0.75-1.50	21	1.08	0.69-1.68
	4.56 - 15.34	44	1.23	0.90-1.69	28	1.32	0.89-1.96
	> 15.34	35	0.98	0.69-1.38	27	1.27	0.86-1.90
				p-trend=0.96			*p-trend= 0.19*
Lindane	0	910	REF	—	557	REF	—
	> 0 - 4.55	37	0.99	0.71-1.37	26	1.11	0.75-1.64
	> 4.55	33	0.94	0.67-1.34	22	0.99	0.65-1.52
				p-trend= 0.42			*p-trend= 0.54*
Hepatchlor	0	794	REF	—	482	REF	—
	> 0 - 2.84	40	1.07	0.78-1.48	26	1.12	0.75-1.66
	2.85 - 10.40	45	1.13	0.83-1.53	31	1.34	0.93-1.93
	10.41 - 22.10	59	1.39	1.06-1.83	42	1.86	1.33-2.59
	> 22.10	42	1.02	0.73-1.41	21	0.95	0.61-1.51
				p-trend=0.22			*p-trend= 0.94*
Toxaphene	0	925	REF	—	561	REF	—
	> 0 - 1.81	24	1.48	0.99-2.22	18	1.93	1.20-3.09
	1.82 - 3.02	19	1.21	0.77-1.91	13	1.40	0.81-2.43
	3.03 - 10.40	17	1.03	0.63-1.67	11	1.18	0.65-2.16
	> 10.40	19	1.24	0.78-1.96	15	1.80	1.07-3.02
				p-trend= 0.33			*p-trend= 0.02*

* Among spouses whose applicator-husbands had complete information on use of OC active-ingredient use based on responses to Take-Home and Enrollment Questionnaires

Those farm spouses with "complete" information: Aldrin n=27,418; Chlordane n=26,783; Dieldrin n=28,839; DDT n=27,151; Lindane n=27,272; Heptachlor n=27,810; Toxaphene n=27,972

N = farm spouse cases exposed to individual OC active ingredient via total Non-Occupational exposures

All Models Adjusted for: age at enrollment, state of residence, education, alcohol use, and smoking (pack-years)

p < 0.05 compared with no exposure

DDT, dichlorodiphenyltrichloroethane

DISCUSSION

This study was the first etiologic analysis to assess the impact of individual non-occupational pathways of exposure by specific pesticides on the risk of cancer among the AHS female farm spouses. I evaluated associations between incident breast cancer and the ER+PR+ subtype, with individual OC insecticide exposures through the agricultural drift, take-home, and residential use pathways as well as with overall non-occupational exposure. While I observed some significant associations, in general my findings did not demonstrate strong evidence for an elevated risk of breast cancer with non-occupational OC exposures. Among my significant findings, a majority were observed at the lowest categories of OC exposures for each non-occupational pathway and for overall non-occupational exposures. Specifically, I observed significant associations for take-home exposures of toxaphene and DDT with ER+PR+ breast cancer, agricultural drift exposures of toxaphene and aldrin with breast cancer overall and ER+PR+ breast cancer, residential use exposures of heptachlor and chlordane with ER+PR+ breast cancer, and overall non-occupational exposures of toxaphene, heptachlor, aldrin, and dieldrin with ER+PR+ breast cancer.

Aldrin and toxaphene both demonstrated significant associations with breast cancer overall and ER+PR+ breast cancer; however, most etiologic studies of toxaphene and aldrin exposures among farm women report no associations with breast cancer [34, 60, 105]. My current analysis demonstrated significant associations for several pathways of toxaphene and aldrin exposures with ER+PR+ breast cancer, most of which were reported at the lowest categories of individual pathway exposures including the take-home (toxaphene), agricultural drift pathways (toxaphene and aldrin), as well as overall non-

occupational exposures (toxaphene and aldrin). Contrary to my findings, two studies examining breast cancer and 'ever' use of pesticides by the AHS farm spouses and their applicator-husbands showed no association with use of toxaphene or aldrin [34, 60]. In my recent analysis of OC personal use among the farm spouses, I found no association for 'ever' use of toxaphene or aldrin with breast cancer overall or any breast cancer subtype [105]. Despite these previous findings, *in vitro* and *in vivo* analyses of toxaphene and aldrin have shown estrogenic and antiestrogenic effects suggesting that these OCs may give rise to breast cancer through endocrine disrupting pathways [18, 29, 73, 114-116]. Since my current significant findings were mostly reported at the lowest exposure categories of aldrin and toxaphene, it is possible that these findings may be due to exposure misclassification or statistical anomaly. Thus, my analysis warrants additional studies to further examine associations with OC exposures among women with breast cancer.

Chlordane and heptachlor exposures by the residential use pathway were each associated with significant increased risks for ER+PR+ breast cancer at the third quartile categories of exposure. While these findings are consistent with one earlier study of the AHS farm spouses [34], they are inconsistent with findings of more recent analyses among the AHS farm spouses [60, 105] as well as most analyses examining chlordane and heptachlor exposures and breast cancer [39, 80, 81, 102, 104, 117], which have found mostly null or inconclusive findings. A recent analysis among the AHS farm spouses revealed no association and a non-significant increased risk for breast cancer with 'ever' use of chlordane and heptachlor by the spouses' applicator-husbands[60]. Similarly, in my previous analysis of OC personal use among the AHS farm spouses, neither chlordane nor

heptachlor were associated with breast cancer. In addition to my significant findings for heptachlor residential use exposure, I also reported significant associations for breast cancer overall and ER+PR+ breast cancer at the third quartile category of exposure. Overall non-occupational exposure estimates for heptachlor were derived from all three individual non-occupational pathways. Moreover, estimates from the residential use pathway of heptachlor exposure were found to contribute between 63% and 100% of the overall non-occupational heptachlor exposures among cases of breast cancer and breast cancer subtypes (data not shown). Few prior studies have been able to evaluate specific residential use exposures to heptachlor; it is therefore possible that my significant findings are due to the added exposure contributed by the estimates representing the residential use pathway.

Overall non-occupational dieldrin exposures were significantly associated with an increased risk for ER+PR+ breast cancer among 15 exposed cases. Dieldrin was recently reclassified by IARC as a 2A carcinogen [15], based on limited evidence for breast cancer among humans [34, 35, 102] and sufficient evidence for carcinogenicity in animal studies [118-120]. However, few epidemiology studies have examined associations with OCs and breast cancer subtypes, and most have not found positive associations [82-84, 121]. An earlier study of AHS farm spouses found evidence for a significant increased risk of breast cancer among women who never personally used dieldrin, but whose husbands did personally apply the pesticide [34]. However, this study was unable to assess associations between the wives' personal use of dieldrin and breast cancer due to the low number of dieldrin exposed breast cancer cases. In my follow-up analysis of OC personal use among the AHS farm spouses and cancer risk, dieldrin was significantly associated with an

increased risk of ER-PR- breast cancer based on 3 exposed cases [105]. Similar to other OCs, i*n vitro* and animal studies have suggested that dieldrin also has the potential to elicit tumor promoting effects through the induction of ER androgen receptor and aromatase activities [30, 73, 74, 85, 86]. However, given the existing literature and the lower number of exposed cases in my two most recent analyses, I do not see strong evidence for an association between dieldrin and breast cancer.

There was a significant increased risk for ER+PR+ breast cancer and DDT exposure through the take-home pathway at the third quartile level, with no evidence for a positive exposure-response trend. Most epidemiology studies examining breast cancer and OCs have focused largely on exposures to DDT and have demonstrated null or no associations [31, 35, 37, 40, 68, 102, 122]. An early epidemiologic study found a two to four-fold increased risk of breast cancer among women with the highest serum DDE categories, with a positive trend with increasing serum DDE [32]. However, a follow-up study with greater sample size found no evidence for an association of breast cancer risk with serum DDE categories [33]. In addition several studies among the AHS farm spouses have found no evidence for an association with DDT and breast cancer [34, 60], including my most recent analysis of OC personal use and cancer incidence among the AHS farm spouses [105]. Given my results here and the existing body of literature, I do not see strong evidence for a suggestion between active-ingredient specific OC exposures and breast cancer.

Strengths of this study include the ability to assess associations between cancer outcomes and quantitative subject-specific estimates of individual OC active-ingredients through multiple non-occupational pathways of exposure. This study is an improvement

over previous etiologic analyses that relied on either the spouses' personal use of OCs [105], or were based on surrogate measurements to estimates non-occupational pesticide exposures [34, 60]. In addition, most OCs examined in this analysis have been banned for use in the United States since the 1970s. Since OCs have long half-lives and are persistent in the environment and the human body [3, 6, 7], it is important to assess OC exposures through non-occupational pathways, particularly among farm populations where OCs may have been used in the past. Moreover, kappa values between the 'ever' personal use of individual OC active-ingredients among the female farm spouses and their applicator-husbands revealed little to no agreement. The driving force behind the non-occupational spousal algorithm relied on the applicators' 'ever' pesticide usage. Thus, these correlations suggest that the results of this study capture previously unassessed OC exposures compared to my previous analysis of OC personal use and cancer risk among the AHS spouses. Furthermore, the inclusion of these pathway exposures allows for additional power to detect associations with OC exposures and cancer outcomes while reducing exposure misclassification. Other strengths of this study include the prospective longitudinal design of the AHS with little loss-to-follow-up, subject-specific questionnaire information on the use of specific OCs, available information on many possible confounders, and regular assessment of cancer incidence and mortality via linkage with state registries.

Limitations of this study include exposure misclassification, which underestimated OC exposures. The non-occupational spousal algorithm is not able to account for the impact of OC exposures prior to the spouses' marriage to their applicator-husbands. Since the non-occupational spousal algorithm is limited by the AHS questionnaire information,

it does not include an exposure time-window prior to the spouses' marriages to their applicator-husbands. Given that the time-period of peak OC use occurred prior to study enrollment, it is possible that the risk estimates are based on underestimated exposures to individual OCs. In addition, the algorithm does not account for alternative pathways of non-occupational exposures including dietary and bystander exposure pathways. Because OCs are a historically used group of insecticides, with an ability bioaccumulate in the environment [3, 6, 7], it has been reported that dietary routes may contribute most significantly to OC exposures in human populations [3, 14]. The inability to account for the dietary pathway in particular, may also contribute to an underestimation of OC exposures.

An additional limitation of this study is the restriction of my study population to those farm spouses with complete Phase III questionnaires. The 'years together while applied' variable was a critical component to both the take-home pathway and agricultural drift pathway equations. However, this variable was based on information provided by the Phase III questionnaire. At the time of this analysis, this variable had not been determined for those spouses without a complete Phase III questionnaire, and they were subsequently excluded from this study analysis. Overall, this excluded group was on average 7.8 years older than the current study population (data not shown). Since OCs were historically used it is likely that this excluded spouse subset had higher exposures to the aforementioned OCs, than the current study population. Therefore, the reintroduction of this spouse population into the study analysis should increase the number of exposed cases for each of these OCs, and thus contribute more power to risk analyses.

Another limitation in this analysis includes the inability to disentangle associated cancer risks of OC exposures between the take-home and agricultural drift pathways, due to their common equation components of days and years of applicator-husbands' use. From my Aim 2 analyses it was found that across all OCs, exposures between the take-home and agricultural drift pathways were highly correlated ($r_s \geq 0.98$). Additionally, exposures for the take-home pathway and the sum of take-home and agricultural drift pathways and between the agricultural drift pathway and the sum of the two pathways were also highly correlated across all OCs ($r_s \geq 0.97$). These correlations help to explain the inability to analyze separately the 'ever' vs 'never' OC exposures by the take-home and agricultural drift pathways (Table3). In addition, this also helps to explain the similarities between risk estimates of breast cancer with each individual category of OC exposures for each of the take-home and agricultural drift pathways. As more published exposure data becomes readily available, future analyses may want to consider reexamining and amending the predictor variables which make up the individual pathway equations of the non-occupational spousal algorithm.

Other limitations include the small number of exposed cases to specific OCs across categories of exposure. In addition, individual pathway specific OC exposure estimates were partly based on pathway weights which were derived from measurements of pesticide concentrations in house dust (Aim 2), and do not reflect doses of OC exposures among the spouses. The exposure estimates calculated only allow for comparisons between relative categories of exposure among OCs and between individual pathways and cannot be interpreted as doses of exposure.

CONCLUSIONS

While most of the results of this analysis did not demonstrate consistent significant associations, this study represents the first evaluation of cancer risk with quantitative estimates of non-occupational pesticide exposures among the AHS female farm spouses. Future AHS studies should look to include the formerly excluded AHS female farm spouses from this study population in order to increase study power. While a few of my findings were consistent with previous results, most were not and thus warrant replication in future analyses with additional exposed cases and longer follow-up time. Finally, to fully evaluate the role of non-occupational OC exposures on cancer risk in women, future studies should look to examine all possible cancer sites, including uterine and ovarian cancers.

Chapter 5. DISCUSSION

This dissertation sought to better understand OC exposures and associated cancer risks among the AHS farm women. Prior to this study, few analyses had examined personal OC insecticide use or pathway specific sources of non-occupational OC exposures with cancer risk among female spouses of pesticide applicators. In addition, studies which had evaluated cancer associations with non-occupational pesticide exposures, had been limited by surrogate measurements, unavailable questionnaire information, or non-specific biological markers. The analyses of this dissertation help to inform both future evaluations of OC exposures with risk of cancer, as well as future exposure characterizations of non-occupational OC exposures among farm women.

Summary of Aims

My first aim prospectively evaluated associations between the self-reported personal use of seven individual OCs (i.e. aldrin, chlordane, dieldrin, DDT, heptachlor, lindane and toxaphene) and incident cancers among the AHS female farm spouses [105]. Although the numbers of exposed cases were small, I observed statistically significant increased risks for use of individual OCs insecticides and several cancers, including any OC use and glioma, lindane use and glioma and pancreatic cancer, chlordane use and MM, and dieldrin use and ER-/PR- breast cancer. Most previous studies of OC exposures and cancer, with the exception of DDT and breast cancer [16, 31-33, 35-37, 39, 40, 68, 96], have been conducted among occupationally exposed men [20, 21, 23-26, 44, 48, 65, 66, 76]. In addition, few studies have examined the personal use of specific OCs, and no studies

had previously prospectively evaluated OCs and other hormone-mediated cancers among women. Farm women may be exposed to pesticides via personal use and non-occupational OC exposures, such as from their husband's pesticide activities and from living in close proximity to treated fields. Due to this, my second aim sought to better understand and quantify OC exposures via non-occupational pathways among the AHS female farm spouses.

In my second aim, I applied for the first time a newly developed quantitative active ingredient-specific algorithm [62] to characterize cumulative non-occupational OC exposures for the AHS female farm spouses of pesticide applicators. I calculated median and IQRs of non-zero OC exposure estimates stratified by the spouses' personal use of the seven individual OCs (aldrin, chlordane, dieldrin, DDT, heptachlor, lindane and toxaphene). I identified an increase in prevalence of OC exposures through non-occupational pathways, compared to exposure through the spouse's personal use alone. In addition, I captured variability in OC exposure intensities among the spouses. This exposure characterization allowed for an improvement of previous studies of pesticide exposure estimates, which relied solely on direct pesticide use or surrogate metrics to estimate non-occupational exposures. Furthermore, this first application of this algorithm allowed for an improved characterization of OC exposure differences among the spouses, thereby reducing exposure misclassification in future etiologic analyses of the AHS farm spouses.

Finally, my third aim used the OC exposure estimates derived from my second aim analyses to examine risk associations between OC non-occupational exposures and breast

cancer risk among the AHS female farm spouses. This etiologic analysis represented the first risk analysis to examine associations of cancer risk with quantitative estimates of non-occupational pathways of pesticide-specific exposures among the AHS female farm spouses. While I observed some significant associations, in general my findings did not demonstrate strong evidence for an elevated risk of breast cancer. Among my significant findings, most were observed at the lowest category of OC exposures. Take-home exposures of toxaphene and DDT were associated with ER+PR+ breast cancer. Agricultural drift exposures of toxaphene and aldrin were associated with breast cancer overall and ER+PR+ breast cancer. Residential use exposures of heptachlor and chlordane were associated with ER+PR+ breast cancer, and overall non-occupational exposures of toxaphene, heptachlor, aldrin, and dieldrin were associated with ER+PR+ breast cancer. Taken together, my dissertation showed that exposures to OCs through their personal use and through non-occupational pathways, may contribute to increased cancer risk among female farm spouses of pesticide applicators

My three dissertation analyses represent a unique characterization of OC exposures and evaluation of cancer risks associated with multiple pathways of non-occupational exposures among the AHS female farm spouses. The results of my studies may help to inform both future risk analyses of OC exposures and cancer outcomes, as well as future characterizations of non-occupational OC exposures among farm women.

Future Directions

The studies presented in this dissertation have helped to identify opportunities for future research. Firstly, the AHS non-occupational spousal algorithm [62] may be applied to other populations outside of the spouses of pesticide applicators including other family members of pesticide applicators living and working on farms, as well as to general populations living near or around agricultural areas. However, the intensity weighted exposure estimates calculated using the algorithm would need to be validated in order for the algorithm to be extrapolated to other populations. AHS researchers are currently using house dust samples among a subset of AHS applicators enrolled in the Biomarkers of Exposure and Effect in Agriculture (BEEA) study [123] to determine if the algorithm calculated pathway specific pesticide exposure estimates are associated with pesticide dust concentrations. A similar approach was used in the validation of the formerly created AHS applicator's occupational exposure algorithm [124-126].

Another area of future research should include addressing the underestimation of algorithm derived non-occupational OC exposures estimates among the AHS farm spouses. As previously mentioned, the non-occupational spousal algorithm does not capture the time-window of exposure prior to when the spouses were married to their applicator husbands. This is particularly limiting for the evaluation of OCs and is a source of possible exposure underestimation, given the OCs peak use in the U.S. (1940s-1960s) relative to the enrollment time period of the AHS spouse-applicator pairs (1990s). Since OCs are a highly persistent class of pesticides, their detection in blood serum has been used as an indication for past exposures in previous studies [14, 31, 37, 127]. For example,

previous biomonitoring studies have found detectable categories of DDT derivatives in blood serum among general populations as well as those occupationally exposed through the production of DDT, many years following past exposures. Similar biomonitoring studies among farming populations may serve to capture previous exposures to OCs and reduce OC misclassification, while increasing power to detect associations with cancer in future etiologic analyses.

Early life exposures to OCs during critical developmental windows have been suggested to play a role in the onset of breast cancer in adulthood [69-72] and should also be explored in future studies. OCs have been reported as having endocrine disrupting properties with an ability to bioaccumulate in human adipose tissues [29, 31]. It is therefore possible that early life exposures to OCs may contribute to cumulative OC exposures in the human body and the onset of hormone-mediated cancers later in life. Limitations with respect to questionnaire information make it difficult to assess early life exposures to OCs and their impact on incident cancers within the AHS farm spouse cohort. Currently, AHS researchers are developing a cohort comprised of the offspring of AHS pesticide applicators called the study of Early Life Exposures in Agriculture (ELEA). This study may serve to help better characterize exposures to OCs in childhood and elucidate their relationship to cancer outcomes in adulthood. Future studies of farm women should also look to address these questionnaire gaps while developing surrogate measurements of early life exposures to improve upon current exposure characterizations of OCs in etiologic analyses.

Subsequent analyses among the AHS farm spouses should look to address additional limitations of the AHS non-occupational spousal algorithm, including the inability to assess bystander exposures and dietary routes. A better characterization of OC exposures by these pathways may help in the application of the algorithm to general populations and to those living in or around farming communities, which may experience pesticide exposures through these indirect paths. Due to the ban of OCs in western countries and their environmental persistence, general populations are most likely to experience exposures through dietary routes as well as through runoff from manufacturing plants that previously produced OC containing products [14]. At the time of publication of the non-occupational algorithm, there was limited data available to quantify bystander and dietary routes of exposures to OCs and these paths were thereby removed from the final algorithm. However, as more data becomes available it is possible that surrogate measurements of exposure for these paths may be developed in order to better capture cumulative OC exposures.

Conclusions

The studies presented here demonstrate that the personal use of OCs as well as non-occupational OC exposures may be related to an increased risk of some cancers among the AHS farm women. In addition, the characterization of non-occupational OC exposures among the AHS farm spouses, as well as the subsequent risk analysis, represent the first application of the newly published AHS non-occupational spousal algorithm [62]. Few prior studies have been able to examine active-ingredient specific personal use of pesticides and cancer risk among a population of farm women, or characterize and analyze the

relationship between quantitative estimates of non-occupational pathway specific pesticide exposures and cancer. The analyses of this dissertation may help to serve as a starting point for future exposure characterization studies of non-occupational pesticide exposures and subsequent cancer etiologic analyses, among populations living near or around agricultural areas.

Bibliography

1. Chang, J.-H.K.a.Y.-S., *Organochlorine Pesticides in Human Serum, Pesticides - Strategies for Pesticides Analysis*. 2011, Rijeka, Croatia: InTech.
2. Ritter, L., Solomon, K.R. , Forget, J. , *PERSISTENT ORGANIC POLLUTANTS An Assessment Report on: DDT-Aldrin-Dieldrin-Endrin-Chlordane, Heptachlor-Hexachlorobenzene,Mirex-Toxaphene,Polychlorinated Biphenyls, Dioxins and Furans*. 1995, For: The International Programme on Chemical Safety (IPCS) within the frame work of the Inter-Organization Programme for the Sound Management of Chemicals (IOMC).
3. Gorman S, T.E., *Persistent organic pollutants-a legacy of environmental harm and threats to health.* Environ Strategy Notes, 2003. **6**: p. 1-4.
4. Zhang W.J., Jiang F.B., and O. J.F., *Global pesticide consumption and pollution: with China as a focus.* Proceedings of the International Academy of Ecology and Environmental Sciences, 2011(1): p. 125-44.
5. Carson, R., *Silent spring*. 2002, Houghton: Mifflin Harcourt.
6. *Persistent Organic Pollutants: A Global Issue, A Global Response*. 2009; Available from: http://www2.epa.gov/international-cooperation/persistent-organic-pollutants-global-issue-global-response.
7. *DDT: a review of scientific and economic aspects on the decision to ban its use as a pesticide,* U.S. Environmental Protection Agency, Editor. 1975: Washington D.C. 20460.

8. *Draft PBT National Action Plan for the Level 1 Pesticides*, The U.S. EPA Persistent Bioaccumulative and Toxic Pollutants (PBT) Pesticides Work Group, Editor. 2000, U.S. Environmental Protection Agency,.

9. *Endosulfan Phase-out*, U.S. Environmental Protection Agency, Editor. 2010.

10. *Pesticide News Story: Remaining Lindane Registrations Cancelled*, U.S. Environmental Protection Agency, Editor. 2006.

11. United Nations Industrial Development Organization. *Stockholm Convention*. 2015; Available from: http://www.unido.org/en/what-we-do/environment/capacity-building-for-the-implementation-of-multilateral-environmental-agreements/the-stockholm-convention.html.

12. WHO, *JointWHO/ConventionTask Force on the HealthAspects ofAir Pollution. Health Risks of Persistent Organic Pollutants from Long Range Transboundary Air Pollution*. 2003: Copenhagen, Denmark.

13. National Institutes of Health Department of Health and Human Services, *The Hazardous Substances Data Bank (HSDB) [CD-ROM]*. 1998, U.S. National Library of Medicine: Bethesda, MD.

14. Centers for Disease Control, *Fourth National Report on Human Exposure to Environmental Chemicals*. 2009, Department of Health and Human Services and the Centers for Disease Control and Prevention,.

15. Guyton, K., Loomis D., Grosse, Y., El Ghissassi, F., Bouvard, V., Benbrahim-Tallaa, L., Guha, N., Mattock, H., Straif, K., *Carcinogenicity of pentachlorophenol and some related compounds.* Lancet Oncology, 2016. **117**.

16. Loomis, D., Guyton, K., Grosse,Y., El Ghissasi,F., Bouvard,V., Benbrahim-Tallaa,L., Guha,N., Mattock,H., Straif,K., *Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid.* Lancet Oncology, 2015. **16** (8): p. 891-892.

17. *IARC Monographs on the Evaluation of Carcinogenic Risk in Humans: Agents Classified by the IARC Monographs, Volumes 1–113*. [cited 2015 October 2, 2015]; Available from: http://monographs.iarc.fr/ENG/Classification/latest_classif.php.

18. *Overall evaluations of carcinogenicity: an updating of IARC monographs*, in *Monographs on the Evaluation of Carcinogenic Risk to Humans*, International Agency for Research on Cancer, Editor. 1987, IARC: Lyon.

19. *Some thyrotropic agents*, in *Monographs on the Evaluation of Carcinogenic Risk to Humans*, International Agency for Research on Cancer, Editor. 2001, IARC: Lyon.

20. Alavanja, M.C., et al., *Non-hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the agricultural health study.* PLoS One, 2014. **9**(10): p. e109332.

21. Blair, A., Cantor, K.P.,Zahm, S.H., *Non-hodgkin's lymphoma and agricultural use of the insecticide lindane.* American Journal of Industrial Medicine, 1998. **33**: p. 82-87.

22. McDuffie H.H., P., P., McLaughlin, J.R., et al., *Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health.* Cancer Epidemiology, Biomarkers and Prevention, 2001. **10**: p. 115-63.

23. Cocco, P., et al., *Cancer mortality among men occupationally exposed to dichlorodiphenyltrichloroethane.* Cancer Res, 2005. **65**(20): p. 9588-94.

24. Purdue, M.P., et al., *Occupational exposure to organochlorine insecticides and cancer incidence in the Agricultural Health Study.* Int J Cancer, 2007. **120**(3): p. 642-9.

25. Spinelli JJ, N.C., Weber JP, et al., *Organochlorines and risk of non-Hodgkin lymphoma.* International Journal of Cancer, 2007. **121**: p. 2767-75.

26. Eriksson M, K.M., *Occupational and other environmental factors and multiple myeloma: a population based case-control study.* British Journal of Industrial Medicine, 1992. **49**: p. 95-103.

27. Pahwa, M., et al., *Pesticide use, immunologic conditions, and risk of non-Hodgkin lymphoma in Canadian men in six provinces.* Int J Cancer, 2012. **131**(11): p. 2650-9.

28. Hong, H.L. and G.A. Boorman, *Residual myelotoxicity of lindane in mice.* Fundam Appl Toxicol, 1993. **21**(4): p. 500-7.

29. Mrema, E.J., et al., *Persistent organochlorinated pesticides and mechanisms of their toxicity.* Toxicology, 2013. **307**: p. 74-88.

30. Silva, E., A. Kabil, and A. Kortenkamp, *Cross-talk between non-genomic and genomic signalling pathways--distinct effect profiles of environmental estrogens.* Toxicol Appl Pharmacol, 2010. **245**(2): p. 160-70.

31. Calle, E.E., et al., *Organochlorines and breast cancer risk.* CA Cancer J Clin, 2002. **52**(5): p. 301-9.

32. Wolff, M.S., et al., *Blood levels of organochlorine residues and risk of breast cancer.* J Natl Cancer Inst, 1993. **85**(8): p. 648-52.

33. Wolff, M.S., et al., *Risk of breast cancer and organochlorine exposure.* Cancer Epidemiol Biomarkers Prev, 2000. **9**(3): p. 271-7.

34. Engel, L.S., et al., *Pesticide use and breast cancer risk among farmers' wives in the agricultural health study.* Am J Epidemiol, 2005. **161**(2): p. 121-35.

35. Hoyer, A.P., et al., *Organochlorine exposure and risk of breast cancer.* Lancet, 1998. **352**(9143): p. 1816-20.

36. Ahlborg, U.G., et al., *Organochlorine compounds in relation to breast cancer, endometrial cancer, and endometriosis: an assessment of the biological and epidemiological evidence.* Crit Rev Toxicol, 1995. **25**(6): p. 463-531.

37. Snedeker, S.M., *Pesticides and breast cancer risk: a review of DDT, DDE, and dieldrin.* Environ Health Perspect, 2001. **109 Suppl 1**: p. 35-47.

38. Gatto, N.M., et al., *Serum organochlorines and breast cancer: a case-control study among African-American women.* Cancer Causes Control, 2007. **18**(1): p. 29-39.

39. Itoh, H., et al., *Serum organochlorines and breast cancer risk in Japanese women: a case-control study.* Cancer Causes Control, 2009. **20**(5): p. 567-80.

40. Salehi, F., et al., *Review of the etiology of breast cancer with special attention to organochlorines as potential endocrine disruptors.* J Toxicol Environ Health B Crit Rev, 2008. **11**(3-4): p. 276-300.

41. Wolff, M.S. and A. Weston, *Breast cancer risk and environmental exposures.* Environ Health Perspect, 1997. **105 Suppl 4**: p. 891-6.

42. Pavuk, M., et al., *Case-control study of PCBs, other organochlorines and breast cancer in Eastern Slovakia.* J Expo Anal Environ Epidemiol, 2003. **13**(4): p. 267-75.

43. Weiderpass, E., et al., *Organochlorines and endometrial cancer risk.* Cancer Epidemiol Biomarkers Prev, 2000. **9**(5): p. 487-93.

44. Persson EC, G.B., Evans AA, et al. , *Dichlorodiphenyltrichloroethane and risk of hepatocellular carcinoma.* International Journal of Cancer, 2012. **131**: p. 2078-84.

45. Zhao, B., Shen, H., Liu, F., Sheng, L., Jianjun, N., Fei, G. and Xueli, S., *Exposure to organochlorine pesticides is an independent risk factor of hepatocellular carcinoma: a case-control study.* . Journal of Exposure Science and Environment Epidemiology, 2012. **22**(541-48).

46. McGlynn KA, A.C., Zhang M, et al. , *Serum concentrations of 1,1,1-trichloro-2,2-bis(pchlorophenyl)ethane (DDT) and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) and risk of primary liver cancer.* Journal of the National Cancer Institute, 2006. **98**: p. 1005-10.

47. Koutros, S., et al., *Prediagnostic Serum Organochlorine Concentrations and Metastatic Prostate Cancer: A Nested Case-Control Study in the Norwegian Janus Serum Bank Cohort.* Environ Health Perspect, 2015. **123**(9): p. 867-72.

48. McGlynn KA, Q.S., Graubard BI, Weber JP, Rubertone MV, Erickson RL, *Persistent organochlorine pesticides and risk of testicular germ cell tumors.* Journal of the National Cancer Institute Monograph, 2008. **100**(9): p. 663-71.

49. Koutros, S., et al., *Risk of total and aggressive prostate cancer and pesticide use in the Agricultural Health Study.* Am J Epidemiol, 2013. **177**(1): p. 59-74.

50. Garabrant, D.H., et al., *DDT and related compounds and risk of pancreatic cancer.* J Natl Cancer Inst, 1992. **84**(10): p. 764-71.

51. Hoppin, J.A., et al., *Pancreatic cancer and serum organochlorine levels.* Cancer Epidemiol Biomarkers Prev, 2000. **9**(2): p. 199-205.

52. Andreotti, G., et al., *Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort.* Int J Cancer, 2009. **124**(10): p. 2495-500.

53. Kirrane EF, H.J., Umbach DM, Samanic C, Sandler DP, *Patterns of pesticide use and their determinants among wives of farmer pesticide applicators in the Agricultural Health Study.* Journal of Occupational Environmental Medicine, 2004. **46**(8): p. 856-865.

54. Deziel, N.C., et al., *A review of nonoccupational pathways for pesticide exposure in women living in agricultural areas.* Environ Health Perspect, 2015. **123**(6): p. 515-24.

55. Curwin, B.D., et al., *Pesticide contamination inside farm and nonfarm homes.* J Occup Environ Hyg, 2005. **2**(7): p. 357-67.

56. Arbuckle, T.E., et al., *Indirect sources of herbicide exposure for families on Ontario farms.* J Expo Sci Environ Epidemiol, 2006. **16**(1): p. 98-104.

57. Curl, C.L., et al., *Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children.* Environ Health Perspect, 2002. **110**(12): p. A787-92.

58. Lu, C., et al., *Pesticide exposure of children in an agricultural community: evidence of household proximity to farmland and take home exposure pathways.* Environ Res, 2000. **84**(3): p. 290-302.

59. Carreon, T., et al., *Gliomas and farm pesticide exposure in women: the Upper Midwest Health Study.* Environ Health Perspect, 2005. **113**(5): p. 546-51.

60. Engel, L.S., et al., *Insecticide Use and Breast Cancer Risk among Farmers' Wives in the Agricultural Health Study.* Environ Health Perspect, 2017. **125**(9): p. 097002.

61. Alavanja MC, S.D., McMaster SB, Zahm SH, McDonnell CJ,Lynch CF, Pennybacker M, Rothman N, Dosemeci M, Bond AE,Blair A. , *The Agricultural Health Study.* Environ Health Perspect, 1996. **104**: p. 362-69.

62. Deziel, N.C., et al., *An algorithm for quantitatively estimating non-occupational pesticide exposure intensity for spouses in the Agricultural Health Study.* J Expo Sci Environ Epidemiol, 2018.

63. De Roos, A.J., et al., *Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men.* Occup Environ Med, 2003. **60**(9): p. E11.

64. Cocco P, F.D., Billai B, D'Atri M, Melis M, Blair A., *Cancer mortality among menoccupationally exposed to dichlorodiphenyltrichloroethane.* Cancer Research, 2005. **65**: p. 9588-94.

65. Orsi, L., et al., *Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study.* Occup Environ Med, 2009. **66**(5): p. 291-8.

66. Presutti, R., et al., *Pesticide exposures and the risk of multiple myeloma in men: An analysis of the North American Pooled Project.* Int J Cancer, 2016. **139**(8): p. 1703-14.

67. Ruder, A.M., et al., *Gliomas and farm pesticide exposure in men: the upper midwest health study.* Arch Environ Health, 2004. **59**(12): p. 650-7.

68. Wolff, M.S., et al., *Organochlorine exposures and breast cancer risk in New York City women.* Environ Res, 2000. **84**(2): p. 151-61.

69. Cohn, B.A., et al., *DDT and breast cancer in young women: new data on the significance of age at exposure.* Environ Health Perspect, 2007. **115**(10): p. 1406-14.

70. Cohn, B.A., *Developmental and environmental origins of breast cancer: DDT as a case study.* Reprod Toxicol, 2011. **31**(3): p. 302-11.

71. Niehoff, N.M., et al., *Childhood and Adolescent Pesticide Exposure and Breast Cancer Risk.* Epidemiology, 2016. **27**(3): p. 326-33.

72. White, A.J., et al., *Exposure to fogger trucks and breast cancer incidence in the Long Island Breast Cancer Study Project: a case-control study.* Environ Health, 2013. **12**: p. 24.

73. Soto, A.M., K.L. Chung, and C. Sonnenschein, *The pesticides endosulfan, toxaphene, and dieldrin have estrogenic effects on human estrogen-sensitive cells.* Environ Health Perspect, 1994. **102**(4): p. 380-3.

74. Soto, A.M., et al., *The E-SCREEN assay as a tool to identify estrogens: an update on estrogenic environmental pollutants.* Environ Health Perspect, 1995. **103 Suppl 7**: p. 113-22.

75. SEER Program, N.C.I., *Lymphoma Subtype Recodes.* Accessed: August 18, 2016.

76. Brown, L.M., et al., *Pesticide exposures and multiple myeloma in Iowa men.* Cancer Causes Control, 1993. **4**(2): p. 153-6.

77. Daniel, V., et al., *Associations of dichlorodiphenyltrichloroethane (DDT) 4.4 and dichlorodiphenyldichloroethylene (DDE) 4.4 blood levels with plasma IL-4.* Arch Environ Health, 2002. **57**(6): p. 541-7.

78. Reed, A., et al., *Immunomodulation of human natural killer cell cytotoxic function by organochlorine pesticides.* Hum Exp Toxicol, 2004. **23**(10): p. 463-71.

79. Thomas, P.T., *Pesticide-induced immunotoxicity: are Great Lakes residents at risk?* Environ Health Perspect, 1995. **103 Suppl 9**: p. 55-61.

80. Zheng, T., et al., *Environmental exposure to hexachlorobenzene (HCB) and risk of female breast cancer in Connecticut.* Cancer Epidemiol Biomarkers Prev, 1999. **8**(5): p. 407-11.

81. Zheng, T., et al., *Oxychlordane and trans-nonachlor in breast adipose tissue and risk of female breast cancer.* J Epidemiol Biostat, 2000. **5**(3): p. 153-60.

82. Dewailly, E., et al., *High organochlorine body burden in women with estrogen receptor-positive breast cancer.* J Natl Cancer Inst, 1994. **86**(3): p. 232-4.

83. Woolcott, C.G., et al., *Organochlorines and breast cancer risk by receptor status, tumor size, and grade (Canada).* Cancer Causes Control, 2001. **12**(5): p. 395-404.

84. Hoyer, A.P., et al., *Organochlorine exposures influence on breast cancer risk and survival according to estrogen receptor status: a Danish cohort-nested case-control study.* BMC Cancer, 2001. **1**: p. 8.

85. Andersen, H.R., et al., *Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity in vitro.* Toxicol Appl Pharmacol, 2002. **179**(1): p. 1-12.

86. Kelce, W.R., et al., *Persistent DDT metabolite p,p'-DDE is a potent androgen receptor antagonist.* Nature, 1995. **375**(6532): p. 581-5.

87. Lynge, E., *A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark.* Br J Cancer, 1985. **52**(2): p. 259-70.

88. Brown, D.P., *Mortality of workers exposed to polychlorinated biphenyls--an update.* Arch Environ Health, 1987. **42**(6): p. 333-9.

89. Kogevinas, M., et al., *Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: two nested case-control studies.* Epidemiology, 1995. **6**(4): p. 396-402.

90. Lee, W., Colt, JS, Heineman, E F, McComb, R, Weisenburger, D D, Lijinsky, W, Ward, MH, *Agricultural pesticide use and risk of glioma in Nebraska, United States.* Occupational Environmental Medicine, 2005. **62**: p. 786-792.

91. Musicco, M., et al., *Gliomas and occupational exposure to carcinogens: case-control study.* Am J Epidemiol, 1982. **116**(5): p. 782-90.

92. Brownson, R.C., et al., *An analysis of occupational risks for brain cancer.* Am J Public Health, 1990. **80**(2): p. 169-72.

93. Cocco, P., E.F. Heineman, and M. Dosemeci, *Occupational risk factors for cancer of the central nervous system (CNS) among US women.* Am J Ind Med, 1999. **36**(1): p. 70-4.

94. Zheng, T., et al., *Occupational risk factors for brain cancer: a population-based case-control study in Iowa.* J Occup Environ Med, 2001. **43**(4): p. 317-24.

95. Briz, V., et al., *Differential estrogenic effects of the persistent organochlorine pesticides dieldrin, endosulfan, and lindane in primary neuronal cultures.* Toxicol Sci, 2011. **120**(2): p. 413-27.

96. Lopez-Cervantes, M., et al., *Dichlorodiphenyldichloroethane burden and breast cancer risk: a meta-analysis of the epidemiologic evidence.* Environ Health Perspect, 2004. **112**(2): p. 207-14.

97. Deziel, N.C., Beane Freeman, L.E., Graubard, B.I., Jones, R.A., Hoppin, J.A., Thomas, K., Hines, C.J., Blair, A., Sandler, D., Chen, H., Lubin, J., Andreotti, G., Alavanja, M.C., Friesen, M.C., *Quantifying relative contributions of environmental sources of pesticide house dust concentrations in agricultural*

populations using meta-regression models of published data. In preparation, 2015.

98. Deziel, N.C., Beane Freeman, L.E., Graubard, B.I., Jones, R.A., Hoppin, J.A., Thomas, K., Hines, C.J., Blair, A., Sandler, D., Chen, H., Lubin, J., Andreotti, G., Alavanja, M.C., Friesen, M.C., *A quantitative algorithm for estimating non-occupational pesticide exposure for farm women in the Agricultural Health Study.* In preparation, 2015.

99. Folsom, A.R., et al., *Cancer incidence among women living on farms: findings from the Iowa Women's Health Study.* J Occup Environ Med, 1996. **38**(11): p. 1171-6.

100. Aschengrau, A., et al., *Cancer risk and residential proximity to cranberry cultivation in Massachusetts.* Am J Public Health, 1996. **86**(9): p. 1289-96.

101. Duell, E.J., et al., *A population-based case-control study of farming and breast cancer in North Carolina.* Epidemiology, 2000. **11**(5): p. 523-31.

102. Gammon, M.D., et al., *Environmental toxins and breast cancer on Long Island. II. Organochlorine compound levels in blood.* Cancer Epidemiol Biomarkers Prev, 2002. **11**(8): p. 686-97.

103. Zheng, T., et al., *DDE and DDT in breast adipose tissue and risk of female breast cancer.* Am J Epidemiol, 1999. **150**(5): p. 453-8.

104. Ward, E.M., et al., *Serum organochlorine levels and breast cancer: a nested case-control study of Norwegian women.* Cancer Epidemiol Biomarkers Prev, 2000. **9**(12): p. 1357-67.

105. Louis, L.M., et al., *A prospective study of cancer risk among Agricultural Health Study farm spouses associated with personal use of organochlorine insecticides.* Environ Health, 2017. **16**(1): p. 95.

106. Curwin, B.D., et al., *Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in iowa.* Ann Occup Hyg, 2007. **51**(1): p. 53-65.

107. Alexander, B.H., et al., *Chlorpyrifos exposure in farm families: results from the farm family exposure study.* J Expo Sci Environ Epidemiol, 2006. **16**(5): p. 447-56.

108. Alexander, B.H., et al., *Biomonitoring of 2,4-dichlorophenoxyacetic acid exposure and dose in farm families.* Environ Health Perspect, 2007. **115**(3): p. 370-6.

109. Arbuckle, T.E. and L. Ritter, *Phenoxyacetic acid herbicide exposure for women on Ontario farms.* J Toxicol Environ Health A, 2005. **68**(15): p. 1359-70.

110. Blair, A., et al., *Methodological issues regarding confounding and exposure misclassification in epidemiological studies of occupational exposures.* Am J Ind Med, 2007. **50**(3): p. 199-207.

111. Hoppin, J.A., et al., *Environmental exposure assessment of pesticides in farmworker homes.* Environ Health Perspect, 2006. **114**(6): p. 929-35.

112. Barr, D.B., et al., *Biomonitoring of exposure in farmworker studies.* Environ Health Perspect, 2006. **114**(6): p. 936-42.

113. Centers for Disease Control, A.f.T.S.a.D.R., *Toxicological Profile for Chlordane.* 2018.

114. Wolff, M.S. and P.G. Toniolo, *Environmental organochlorine exposure as a potential etiologic factor in breast cancer.* Environ Health Perspect, 1995. **103 Suppl 7**: p. 141-5.

115. *Bioassay of Endrin for Possible Carcinogenicity (CAS No. 72-20-8).* Natl Cancer Inst Carcinog Tech Rep Ser, 1979. **12**: p. 1-110.

116. Romero, M.L., J.G. Dorea, and A.C. Granja, *Concentrations of organochlorine pesticides in milk of Nicaraguan mothers.* Arch Environ Health, 2000. **55**(4): p. 274-8.

117. Demers, A., et al., *Risk and aggressiveness of breast cancer in relation to plasma organochlorine concentrations.* Cancer Epidemiol Biomarkers Prev, 2000. **9**(2): p. 161-6.

118. Davis, K.J. and O.G. Fitzhugh, *Tumorigenic potential of aldrin and dieldrin for mice.* Toxicol Appl Pharmacol, 1962. **4**: p. 187-9.

119. Epstein, S.S., *The carcinogenicity of dieldrin. Part I.* Sci Total Environ, 1975. **4**(1): p. 1-52.

120. National Toxicology, P., *Bioassays of aldrin and dieldrin for possible carcinogenicity.* Natl Cancer Inst Carcinog Tech Rep Ser, 1978. **21**: p. 1-184.

121. Anderson, K.A. and E. Johnson, *Bioavailable organochlorine pesticides in a semi-arid region of eastern Oregon, USA, as determined by gas chromatography with electron-capture detection.* J AOAC Int, 2001. **84**(5): p. 1371-82.

122. Krieger, N., et al., *Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women.* J Natl Cancer Inst, 1994. **86**(8): p. 589-99.

123. Hofmann, J.N., et al., *The Biomarkers of Exposure and Effect in Agriculture (BEEA) Study: Rationale, Design, Methods, and Participant Characteristics.* J Toxicol Environ Health A, 2015. **78**(21-22): p. 1338-47.

124. Coble, J., et al., *The validation of a pesticide exposure algorithm using biological monitoring results.* J Occup Environ Hyg, 2005. **2**(3): p. 194-201.

125. Thomas, K.W., et al., *Assessment of a pesticide exposure intensity algorithm in the agricultural health study.* J Expo Sci Environ Epidemiol, 2010. **20**(6): p. 559-69.

126. Hines, C.J., et al., *Captan exposure and evaluation of a pesticide exposure algorithm among orchard pesticide applicators in the Agricultural Health Study.* Ann Occup Hyg, 2008. **52**(3): p. 153-66.

127. Glynn, A., et al., *Determinants of serum concentrations of organochlorine compounds in Swedish pregnant women: a cross-sectional study.* Environ Health, 2007. **6**: p. 2.