Title: *A Study of Florida Pesticide Applicators*

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16. Abstract (Limit: 200 words) A retrospective cohort analysis was performed of the cancer incidence and general mortality among a cohort of Florida licensed pesticide applicators. Proportional mortality ratio studies and mortality odds ratio were performed. The cohort included 33,669 licensed pesticide applicators. From January 1, 1975 to January 1, 1994 there were 1,874 deaths and 1,266 incident cancer cases in this cohort. The pesticide applicators were consistently and significantly healthier compared to the general Florida population. The risk of cardiovascular disease and of diseases associated with alcohol and tobacco use were significantly decreased. Prostate cancer mortality and incidence and testicular cancer incidence were significantly elevated. No confirmed cases of soft tissue sarcoma were noted and nonHodgkin's lymphoma incidence was not increased. While the number of female pesticide applicators was small, cervical cancer incidence was significantly increased. Breast cancer incidence and mortality were not elevated. The author notes that a possible recommendation from these findings would be to include screening of male pesticide applicators for testicular and prostate cancer, and screening of female pesticide applicators for cervical cancer, as well as providing specific risk avoidance instruction for aerial applicators.

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Significant Findings and Usefulness of Findings

In this cohort of 33,669 Florida licensed pesticide applicators assembled through extensive data linkages, there were a total of 1874 deaths and 1266 incident cancer cases with 320,250 person-years from 1/1/75 to 1/1/94. Using a variety of analysis methodologies, the pesticide applicators are consistently and significantly healthier compared to the general Florida population and the NCI occupational database. As with many occupational cohorts, the risk of cardiovascular disease and of diseases associated with ethanol and tobacco use are significantly decreased, even in the subpopulations (eg. males, females,and license subcategories).

Among male applicators as seen in prior studies, prostate cancer mortality [SMR=2.38 (95% confidence interval=1.83-3.04)] and incidence [1.92 (1.73-2.14)] and testicular cancer incidence [SIR=2.49 (1.58-3.74)] were significantly elevated. There were no confirmed cases of soft tissue sarcoma in this cohort of pesticide applicators, and non Hodgkin's lymphoma was not increased; these findings are at odds with prior literature associating the use of the phenoxy herbicides with an increased risk of both these cancers. The number of female applicators was relatively small, as were the numbers of deaths and incident cancer cases. Nevertheless, cervical cancer incidence [3.71 (1.85-6.64)] was significantly increased; breast cancer incidence and mortality were not elevated.

This study adds to existing knowledge of diseases associated with occupational pesticide exposure, especially issues of incident cancer. Possible recommendations derived from these findings could include screening of male pesticide applicators for testicular and prostate cancer, and screening of female pesticide applicators for cervical cancer, as well as specific risk avoidance instruction for aerial applicators. In addition, further study of this cohort may be warrented concerning the reasons for their relatively low mortality from a variety of causes including cardiovascular disease and breast cancer.

ABSTRACT

A Study of Florida Pesticide Applicators

Lora Elderkin Fleming MD PhD MPH Msc

Pesticides are chemicals used since ancient times to destroy or control pests. Although the primary hazard to humans associated with pesticide exposure is acute poisoning, there has been considerable concern surrounding the possibility of cancer and other chronic health effects in humans. Given the huge volume of pesticides now used throughout the world, as well as environmental and food residue contamination leading to chronic low-level exposure, the study of possible chronic human health effects is important.

This study is a retrospective cohort analysis of the cancer incidence and general mortality among a cohort of Florida licensed pesticide applicators. In addition, proportional mortality ratio (PMR) studies and mortality odds ratio (MOR) studies were performed. Comparison groups consisted of the general Florida population and subgroups from a National Cancer Institute pooled worker cohort.

In this cohort of 33,669 Florida licensed pesticide applicators assembled through extensive data linkages, there were a total of 1874 deaths and 1266 incident cancer cases with 320,250 person-years from 1/1/75 to 1/1/94. Using a variety of analysis methodologies, the pesticide applicators are consistently and significantly healthier compared to the general Florida population and the NCI occupational database. As with many occupational cohorts, the risk of cardiovascular disease and of diseases associated with ethanol and tobacco use are significantly decreased, even in the subpopulations (eg. males, females,and license subcategories).

Among male applicators as seen in prior studies, prostate cancer mortality [SMR=2.38 (95% confidence interval=1.83-3.04)] and incidence [1.92 (1.73-2.14)] and testicular cancer incidence [SIR=2.49 (1.58-3.74)] were significantly elevated. There were no confirmed cases of soft tissue sarcoma in this cohort of pesticide applicators, and non Hodgkin's lymphoma was not increased; these findings are at odds with prior literature associating the use of the phenoxy herbicides with an increased risk of both these cancers. The number of female applicators was relatively small, as were the numbers of deaths and incident cancer cases. Nevertheless, cervical cancer incidence [3.71 (1.85-6.64)] was significantly increased; breast cancer incidence and mortality were not elevated. Additional subcohort and exposure analyses were performed.

Chapter One: Introduction

This chapter presents the rationale and overall plan for a study of a cohort of licensed pesticide applicators in Florida.

1.0. Background

Pesticides are chemicals used since ancient times to destroy or control pests. Although the primary hazard to humans associated with pesticide exposure is acute poisoning, concern surrounding the possibility of pesticide carcinogenicity and other chronic health effects in humans exists. The pesticides which have generated the greatest concern for possible carcinogenicity include the herbicides, heavy metals, non-herbicide organochlorines, and certain fumigation agents. This is important, given the huge volume of pesticides now used throughout the world in agriculture, industry, and homes. In addition, environmental and food residue contamination from pesticides could lead to mass chronic low-level exposure.

Since 1970 under the Environmental Protection Agency (EPA), the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) has required that persons who buy or use restricted-use pesticides must be certified as competent pesticide applicators or must be directly supervised by a certified applicator. The State of Florida has computerized records of over 37,000 certified pesticide applicators with paper records for up to 20 years. As a highly agricultural and tropical state, Florida is a major pesticide user.

2.0. Original Proposed Study

This study proposes to perform retrospective studies of cancer incidence and general mortality, as well as a nested case control study of specific cancer incidences of these licensed Florida Pesticide Applicators. Because the greatest exposures to pesticides occur in the occupational setting, this study adds to the body of knowledge concerned with pesticides and their health effects in humans. Furthermore, results from the study (ie. specific cancer and other mortality rates) can be incorporated into existing mandatory educational programs of the Florida Department of Agriculture Bureau of Pesticides to prevent future illness in this and similar workforces.

The study specifically examines the question of increased lung cancer found in two prior studies of pesticide applicators, but not in agricultural workers. {Barthel 1986, Blair 1983} Other specific cancers reported elevated in studies of pesticide-exposed workers included: leukemia, lymphoma, and testicular cancer. In addition, internal analysis of "pure" pesticide exposed applicators (ie. commercial and public licensees) and agriculture-exposed farmer pesticide applicators (ie. private licensees) are performed to differentiate between the carcinogenic effects of pesticides (such as the arsenicals) as opposed to zoonotic oncogenic viruses and other potential carcinogens associated with agricultural work. This internal comparison analysis is of specific interest for both lung and testicular cancer previously found elevated in "pure pesticide" exposures, and for leukemia elevated among agricultural workers. {Barthel 1986, Blair 1983, Wiklund 1989, Pearce 1990, Blair 1985, Blair 1982, Wiklund 1986, Brown 1991, Burmeister 1990, Burmeister 1983} Other issues, such as female breast cancer associated with organochlorine exposure, are also explored.

2.1. The study hypotheses are:

1. Age-adjusted rate of overall cancer incidence for Florida population is higher than the rate for a cohort of licensed pesticide applicators in Florida (ie. the healthy worker

effect);

2. Adjusted cancer incidence rates for lung cancer, lymphoma, leukemia, multiple myeloma, soft tissue sarcoma, and testicular cancer are higher for this cohort of Florida pesticide applicators than the Florida population rates;
3. Adjusted cancer incidence rates for lung cancer, lymphoma, leukemia, multiple myeloma, soft tissue sarcoma, and testicular cancer increase as time of exposure to pesticides increases (ie. dose response);
4. These increased specific cancer incidence rates are independent of confounding risks (ie. smoking, race/ethnic group, and other possible confounders);
5. Adjusted cancer incidence rates for certain cancers are associated with increased exposure to certain groups of pesticides (ie. lymphoma and herbicides, lung cancer and arsenicals);
6. As with cancer incidence, in general, the age-adjusted cause-specific mortality rates for the cohort as a whole are less than the Florida population rates (ie. healthy worker effect);
7. Adjusted cancer mortality rates for the private (farmers) applicators with agricultural and pesticide exposure differ from the commercial and public applicators with only pesticide exposure. In particular, lung cancer mortality will be increased among the commercial and public applicators, but not the private (farmer) applicators.

3.0. Organizational Outline

The literature concerning the possible human health effects of occupational exposure to pesticides is summarized in the Chapter Two. Included in this chapter is a extensive Bibliography and a tabular summary of all epidemiologic studies of pesticide applicators.

The computerized database of licensed pesticide applicators in Florida since 1970 was obtained from the Florida Dept of Agriculture and Consumer Services. Due to missing information, this database was repeatedly linked with a variety of existing databases to obtain date of birth, mortality and cancer incidence information; in addition, the hardcopies of the license applications have been reviewed by the Investigator. Cancer incidence data since 1980 were obtained by linking the database with the Florida Cancer Data System (FCDS). Using the linkages with the Florida Vital Statistics Death Tapes, the Florida Motor Vehicles Registry, HCFA, and the Florida AHCA, as well as two private data linkage firms (ie. EQUIFAX and Epidemiology Resources Inc.), date of birth and date of death information were added to the database. A Master Database has been constructed which consists of those applicators with date of birth and vital status information, as well as cancer incidence and other information where applicable. The methodology and results of these linkages, as well as summary information from the Master Database, are described in detail in Chapter Three. In addition, the nested case control study of cancer incidence and the subsample general survey were attempted for confounding and exposure information; however, these studies could not be performed due to logistical issues, discussed in detail in the **Appendix**.

The statistical analyses and rationale used in this study are described in Chapter Four. Proportional Mortality Ratio (PMR) studies and Mortality Odds Ratio (MOR) studies comparing the cohort to both the Florida and a National Cancer Institute worker comparison cohort have been performed; the methodology and results are described in Chapter Five. The results of retrospective cohort analyses of both general mortality and cancer incidence among a cohort of Florida licensed pesticide applicators with occupational pesticide exposure are described in Chapters Six and Seven, respectively. Finally, the overall conclusions of the statistical analyses are discussed in Chapter Eight.

Chapter Two: Background

This chapter briefly describes pesticides as a chemical group and presents the evidence for non-cancer associated human health effects. The published literature concerning the possible carcinogenic effects of pesticides, especially with respect to farmers and pesticide applicators, is reviewed in depth.

1.0. Pesticides Background

Since ancient times, humans have attempted to control or destroy a variety of pests for the purposes of agriculture, disease prevention, structural preservation, and even aesthetics.{Smith 1975, Igbedioh 1991, IARC 1991, Maroni 1993} Under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), administered by the US Environmental Protection Agency (EPA), a pesticide is defined as an economic (as opposed to medicinal) poison. Pesticide is a generic term that can include insecticides, herbicides, fungicides, rodenticides, nematocides, ascaracides, molluscides, and avicides, according to the pest target. {Moses 1993}

In 1985, worldwide, the majority of pesticide use was as herbicides (46%), then insecticides (31%) and fungicides (18%).{WHO 1990} In 1988, in the US over 1 billion pounds of pesticides were applied, 80% as agricultural use; 75% of the cropland and 70% of the livestock in the US are treated with pesticides.{EPA 1988, Weisenburger 1993} In agriculture, herbicides are used mainly on corn and soy beans; insecticides are applied on cotton and horticultural crops; fungicides are used for horticultural crops and wheat. The major non-agricultural use of herbicides is for public-way-access, while insecticides are used for public health purposes and fumigants for structural fumigation.{IARC 1991}

Commercial pesticides are rarely used in their pure chemical state. The active ingredients of pesticides and their by-products are composed of a great many different chemical mixtures. In addition, there are a multitude of "inactive" ingredients, such as solvents, surfactants, carriers, and emulsifiers, used to improve the effectiveness of the pesticides. In fact, many of the so-called inert or inactive ingredients may not be active as pesticides, but can be biologically active (e.g. the carcinogens, asbestos, and carbon tetrachloride). Furthermore, there can be undesirable contaminants such as dioxins, nitrosamines, and other toxic compounds. In the United States, there are over 45,000 individual pesticide products incorporating over 1500 active ingredients currently registered with the Federal Government. {Maddy 1983, Moses 1993}

Since 1970, under FIFRA, EPA has required that persons who buy or use restricted-use pesticides must be certified as competent pesticide applicators or must be directly supervised by a certified applicator. However, most of the pesticides used for non-agricultural purposes (such as home pest control, gardening, right of way, public health vector control, etc) and bought "over the counter" without licensure are just different formulations of the same active ingredients used in the restricted agricultural pesticides.

1.1. Pesticide Exposure

Exposure to pesticides can be occupational, accidental, intentional, and environmental. Pesticides are applied through release or propulsion through the air as dusts, granules, or liquid sprays; directly applied to the plant or through injection into the plant or soil; released in irrigation water; or as a fumigation in the air; drift, accidental spills and contaminations can also occur into all environmental media. Direct and indirect occupational exposure involves inhalation, skin absorption, and sometimes oral ingestion, while accidental and intentional exposures are usually through ingestion. Occupational exposures can vary from very high to extremely low, depending on the knowledge and training of the applicator, personal protective equipment, application method, climate, and other factors. Environmental exposures, usually through water, food chain and even soil/dust contamination, are often very low but can be chronic exposures, especially with environmentally persistent chemicals such as the organochlorines.{IARC 1991, WHO 1990, Maddy 1990, Blain 1990}

Occupations associated with pesticide exposure are usually divided into agricultural and non-agricultural. In the US, there are approximately 2.1 million farmers, 3 million hired farm workers, and 6 million farm family members (including children); worldwide, agricultural work is still the most common occupation, often employing more than one third of the population. Other agricultural occupations include pesticide applicators, pesticide manufacturing workers, and veterinarians. Non-agricultural occupations include exterminators and structural fumigators, public health vector control workers, landscape and right-of-way workers, as well as flower distributors, paint manufacturers, and pet groomers.{Moses 1993, Weisenburger 1993, Lang 1993, Cordes 1991}

Discrete accidental mass poisoning episodes, usually through food contamination, and accidental or intentional exposures in individuals, can result in extremely high pesticide exposures.{Levine 1992, Lang 1993, WHO 1990, Ferrer 1989, Blain 1990} However, the majority of non-occupational exposures are low, but often chronic. Indirect exposure through pesticide residues on food, in breast milk, and in lifetime fat storage may play an important role in the exposure of the general population to pesticides.{Forget 1991, Olszyna-Marzys 1978} Household usage of pesticides in both industrialized and developing nations can be considerable, especially in warmer climates. In 1981, more than 500 different pesticide formulations were found in 8,500 households sampled in 25 metropolitan and 25 county areas in the US, with the southeast households using the greatest quantities; in California alone, an estimated 30 million kilograms of pesticides were sold for home and garden use in 1980.{Savage 1981, Weisenburger 1993} In 1988, the US Environmental Protection Agency estimated that one third of US single family households regularly either self-applied or had a commercial application of herbicides to their lawns.{Palackdharry 1994} Furthermore, local environmental conditions (such as "tight buildings") can make application of pesticides in the home or workplace quite persistent over time.{Wright 1978} The NHANES III (1991-1994) data showed that 82% of participants had measurable amounts (mean 4.5 ug/L) of the metabolites of the rapidly metabolized and widely used organophosphate pesticide, Chlorpyrifos, in their urine.{J Davies, verbal communication}

Particular subgroups in the population may be more sensitive to exposure to pesticides. Children, with or without para-occupational exposure through their parents, may be at greater risk than adults both in terms of exposure and health impact, from pesticides; in addition to increased respiratory rate and caloric intake, children have an increased ingestion potential through hand-to-mouth exposure.{NRC 1993, Roberts 1989} In developing nations, extensive malnutrition, concurrent infectious diseases, and environmental pollution can contribute to increased toxicity from pesticide exposure.{Jamall 1991, Igbedioh 1991, El Sebae 1993}

The type of pesticide formulation and the method of pesticide application can determine the type and amount of exposure. Application can range from hand-held sprayers with significant risk of skin and inhalation contact to the significant risk of environmental contamination with application through existing irrigation systems. Pesticides can be applied as liquids, solutions, powders, dusts, granules, emulsifiable concentrates, seed treatments, drenches, and baits. An increasingly used formulation which is potentially very dangerous is the "ultra-low volume" (ULV); it is applied almost undiluted, thus it is particularly dangerous to both the mixer and the applicator.{Moses 1993, WHO 1990, IARC 1991} Interestingly, manufacturing workers often have lower exposures since the processes are often highly automated, at least in the industrialized nations.

Exposure monitoring in the occupational setting was traditionally by ambient sampling during work processes. However, given extensive skin absorption, especially during pesticide application, estimates are now obtained using dermal patch testing with video monitoring, as well as breathing zone air measurements.{Methner 1994a, Fenske 1991} Biological monitoring, which traditionally used the problematic blood cholinesterase levels in the case of organophosphate exposure, is now moving towards the measurement of urine metabolites of particular pesticides.{Woollen 1993, He 1993} In non-occupational settings, fat biopsies, blood and urine levels, and breast milk levels of various pesticides have been used. These somewhat more invasive monitoring methods are particularly suited to the lipophilic and persistent pesticides such as the organochlorines. Environmental monitoring of water, earth and air for particular pesticides is particularly important for the environmentally persistent pesticides and the issue of community exposure. This is especially true in developing nations where inappropriate use of pesticides can add to the substantial levels of existing environmental pollution.{El Sebae 1993} Finally, food residue measurement is especially relevant for the body burden of the general public, as well as prevention of accidental mass poisonings, even if the actual health effects risk of non-occupational chronic low level exposure are unknown.{IARC 1991, Chester 1993}

2.0. Pesticides and Human Health Effects

The types of pesticides applied have changed dramatically over the five decades since World War II. After WWII, environmentally persistent but less acutely toxic chemicals such as the organochlorines were heavily applied. This lasted until the 1970s when many of these chemicals were banned (at least in the more industrialized nations) as the implications of their prolonged environmental effects became manifest. Since then, there has been a rapid expansion of the less environmentally persistent, but more acutely toxic pesticides, such as the organophosphates and carbamates. This shift in toxicity has had implications for human health. At the same time, recent work suggests that the older chemicals, such as the organochlorines, may cause chronic health effects in humans as well as in other animals. {WHO 1990, Moses 1993, IARC 1991}

2.1. Acute Health Effects

WHO (1990) estimates that there are at least 1 million unintentional severe pesticide poisonings annually worldwide, with at least 20,000 deaths. Occupational exposure accounts for over 70% of these severe unintentional poisonings. Jeyaratnam (1985) estimated that there are an additional 2 million cases annually worldwide of intentional pesticide poisoning, resulting in more than 220,000 deaths; in 1990, he expanded this estimate to 25,000,000 unintentional poisonings per year based on a 3% occupational poisoning rate reported in a survey from 4 Asian countries extrapolated to the International Labor Organization estimate of 830 million agricultural workers worldwide. {Jeyaratnam 1990, Levine 1992, Jeyaratnam 1987} Jeyaratnam (1985) stated that only 6% of the pesticide-associated deaths are due to occupational exposure and over 90% related to suicide; however, Wesseling *et al.* (1993) found that only 62% of the pesticide fatalities were related to suicide in Costa Rica. Regardless, both fatal and non-fatal pesticide poisonings are believed to be significantly under-reported, both in industrialized and developing nations. Estimates of reported to unreported cases have ranged from 1:6 to 1:100. Under-reporting issues range from inadequate knowledge about pesticide illness on the part of patients and healthcare providers. to a lack of healthcare facilities and reporting mechanisms. {WHO 1990, Jeyaratnam 1985, Moses 1993, IARC 1991, Maroni 1993, Maddy 1990, Levine 1992}

Since the majority of pesticides are neurotoxins, it is not surprising that the major acute health effects are neurologic. These effects have been extensively described.{McConnell 1994, Schenker 1992, Jeyaratnam 1994, Moses 1989, Hayes 1991, Maroni 1993, Blain 1990} In addition, fatal and non-fatal accidents are increased in many populations working with pesticides, possibly related in some cases to the concomitant exposures to neurotoxic chemicals in dangerous workplaces.{Cantor 1991, Purschwitz 1990} Children are at particular risk for farm-related mortality, especially from machinery; the role of concomitant pesticide exposure is unknown.{Schenker 1995} Additional acute health effects of pesticide exposures include dermatoses, both allergic and irritant contact dermatitis, and respiratory problems such as asthma and upper respiratory irritation.{Cellini 1994, Abrams 1991, Moses 1989, Weisenburger 1993, Moses 1993, Cordes 1991, Lang 1993, Maroni 1993, Scarborough 1989}

2.2. Chronic <u>Non</u> Cancer Health Effects

In general, the relationship between pesticides and chronic disease (both morbidity and mortality), especially non-cancer effects, in humans with chronic exposure has been studied relatively little. As with acute effects, neurologic disease predominates.{Sharp 1986, Blain 1990} The subchronic delayed pesticide intoxication syndrome and the chronic delayed induced axonopathy associated with severe poisoning with certain organophosphate chemicals have been well documented and described.{Davies 1990, Sharp 1986, Richardson 1995, Blain 1990} Neuropsychologic changes have been noted, especially after acute poisoning episodes rather than with well controlled occupational exposures.{Rosenstock 1991, Daniell 1992, Steenland 1994, Rosenstock 1990. Davies 1990} Chronic neurologic diseases, such as Parkinson's, may be elevated in pesticide-exposed populations, especially with chronic low level exposure.{Davies 1990, Moses 1993, Butterfield 1993, Tanner 1990, Schoenberg 1987, Golbe 1993, Rajput 1987, Weschsler 1991, Semchuck 1993, Hubble 1993, Fleming 1994a} The pesticides associated with an increased risk of chronic neurologic diseases are certain organochlorines and the herbicide paraquat, as well as the organophosphates.

Other chronic health effects include lung disease (eg. fatal restrictive fibrosis following paraquat poisoning), possible immunotoxicity (especially associated with the organochlorines), reproductive effects, aplastic anemia, and chronic skin diseases.{Jamall 1991, Cellini 1994, Abrams 1991, Lang 1993, Jeyaratnam 1994, Thrasher 1993, Sharp 1986, Cordes 1991, Moses 1989, Fleming 1993, Lang 1993, Moses 1993, WHO 1990, Maroni 1993, Blain 1990, Betta 1989, Botham 1990, Burrell 1993} Lack of adequate worldwide diagnosis and reporting make it difficult to estimate the magnitude of these chronic health effects, especially in the general population.

Reproductive health has been studied in various pesticide-exposed populations, especially in relation to herbicides. Although misclassification bias with respect to exposure may be a problem with many of the studies, the majority showed no statistically significant increased risks for miscarriages, birth defects, or sex ratio specifically for herbicides in occupationally exposed populations.{Roan 1984, Smith 1982, Pearn 1985} However, both occupational and non-occupational exposure to other pesticides has suggested reproductive outcome risks, including increased spontaneous abortion (maternal and paternal), increased perinatal mortality (maternal), spina bifida (paternal), anencephaly (paternal), hemangiomas (maternal and paternal), and cleft palate (maternal and paternal), as well as various other birth defects (paternal).{Taha 1993, Brender 1990, Restrepo 1990a, Restrepo 1990b, Nurminen 1994, Olshan 1991, Gordon 1981, White 1988, Schwartz 1986, Rita 1987, Weisenburger 1993, Moses 1989, Moses 1993, Maroni 1993} In addition, certain pesticides, such as the organochlorines Dibromochloropropane (DBCP) and chlordecone (Kepone), have been found to adversely affect reproductive health, including causing permanent male infertility.{Whorton 1992, Weisenburger 1993, Moses 1989, Moses 1993} Finally, where it has been studied, laboratory fetal and/or genetic toxicity has been reported with the residuals of many commonly used pesticides.{Kida 1993} Again, a lack of adequate worldwide diagnosis and reporting make it difficult to estimate the magnitude of the reproductive health effects associated with pesticide exposure.

2.3. Non Cancer Mortality in Occupational groups

In studies of the major occupational groups exposed to pesticides (ie. farmers, production workers, and applicators), the most consistent findings have been increased rates of specific cancers and death from injury. In general, cardiovascular disease risk has been lower in these pesticide-exposed groups compared with the general population, and even when compared to other occupational groups. Part of this may be due to lifestyle factors (such as decreased smoking and increased exercise, at least among farmers). On the other hand, the bias of the healthy worker effect, especially the use of inappropriate comparison groups, as well as the dearth of information (especially for migrant farmworkers) are also contributing factors.{Park 1991}

2.3.1. Agricultural Workers

The majority of studies of chronic disease mortality in farmers have focused on cancer; therefore, there is a relative dearth of information on non-cancer mortality in agricultural workers. {Reif 1989, Pearce 1986, Burmeister 1983, Burmeister 1990, Blair 1982, Hoar 1986, Gallagher 1985, Saftlas 1987, Blair 1979, Wiklund 1983, Axelson 1980, Pearce 1990, Gallagher 1984, Zahm1993, Cantor 1992, Ritter

1990, Linet 1995, Morrison 1992a, Viel 1993, Eriksson 1992, Forastiere 1993, Davis 1992, Blair 1993} Overall mortality, and alcohol and tobacco-related causes of death are usually decreased among farmers when compared to the general population and to many other occupational groups. Disabling injuries (from machinery and motor vehicles), suicide, and non-malignant respiratory diseases (including tuberculosis) are the major causes of chronic disease mortality that are increased in farmers.{Cordes 1991, Beaumont 1995, Boxer 1995, Saftlas 1987, Weisenburger 1993, Moses 1993, Maroni 1993, Blair 1993} With relation to the increase in non-malignant respiratory diseases, possible pesticide-related immunologic effects are postulated, given the *in vitro* immunologic effects of many pesticides, and the widespread prevalence of dermatitis and asthma in farming populations.{Gallagher 1984, Weisenburger 1993, Moses 1993, Cordes 1991, Daniel 1995, Wiggle 1990}

Usually, cardiovascular disease mortality, when it is evaluated, is decreased in farmers. {Marx 1990, White 1989, Stubbs 1984, Coye 1985, Purshwitz 1990, Rust 1990, Burmeister 1982, Carlson 1978, Davis 1992, Blair 1993} Of note, Beaumont *et al.* (1995) found a statistically insignificant increase in heart disease mortality (SMR=1.32, CI 0.86-1.94) in a subcohort of California agricultural workers who filed compensation claims for systemic pesticide illness.

2.3.2. Other Non Applicator Pesticide Exposed Occupational Groups

The risk of suicide was elevated among all categories of veterinarians.{Boxer 1995} Mabuchi *et al.* (1979) found a significant increase in anemia mortality in a cohort of 1,393 workers in an inorganic arsenical manufacturing plant in Baltimore. Ditraglia *et al.* (1981) studied the mortality experience of 2100 organochlorine pesticide production workers in 4 manufacturing plants. In the aldrin, dieldrin, eldrin plant, there was a significant increase in non-malignant respiratory mortality and a non-significant increase in suicide. Wong *et al.* (1984) evaluated workers manufacturing a variety of organic and inorganic brominated compounds: only diabetes mortality was significantly elevated compared with national rates.

There have been numerous mortality studies of cohorts of phenoxy herbicide manufacturing workers. although the majority have focused on cancer.{Amoateng-Adjepong 1995, Bueno de Mesquita 1993. Kogevinas 1993, Coggon 1991, Bloemen 1993, Maroni 1993, Saracci 1991, Lynge 1985} In general, there were no significant increases in the overall mortality, the circulatory system, digestive system, and respiratory system mortality rates compared with national rates in these studies.

2.3.3. Pesticide Applicators

Among the relatively few chronic disease studies available on pesticide applicators, there is little information on general causes of mortality. Often, the researchers evaluated only cancer mortality. {Stark 1990, Wiklund 1987, Wiklund 1988, Wiklund 1986, Wiklund 1988, Barthel 1976, Barthel 1981, Barthel 1985, Kay 1974, Luchtrath 1983, Wiklund 1989, Council on Scientific Affairs 1988, IARC 1983, Corrao 1989, Tollestrup 1995, Littorin 1993, Saracci 1991, Alavanja 1988, Alavanja 1989, Swaen 1992, Hansen 1992, Figa-Talamanca 1993a, Figa-Talamanca 1993b, Pesatori 1994, Asp 1994, Notkola 1993, Riihimaki 1982, Stein 1964, Morgan 1980, Alberghini 1991} Again, where there is information, either there is evidence of the healthy worker effect, especially with respect to inappropriate comparison populations, inadequate follow-up, or no significant increases from other causes of mortality are found.{Park 1991} As with farmers, in general overall mortality, alcohol and tobacco-related causes of death are usually decreased among pesticide applicators when compared to the general population and to many other occupational groups.

Coggon *et al.* (1986) evaluated the mortality of 5784 workers who formulated, manufactured, and sprayed the herbicide, 2 methyl 4 chlorophenoxyacetic acid, from 1947-1983. Atherosclerotic, respiratory and digestive diseases were not significantly elevated compared to national rates. Swaen *et al.* (1992) found only a non-significant elevation in death from external causes compared to national rates in a cohort of 1,341 herbicide applicators in the Netherlands from 1980-1988. Mortality from infectious diseases, circulatory, respiratory, or digestive system diseases was not elevated. Asp *et al.* (1994) analyzed 18 years of follow up in the cohort of 1,909 Finnish herbicide applicators first studied by Riihimaki *et al.* (1982, 1983). Compared to national rates, only violent, accidental, nephritis, and nephrosis deaths were elevated, but not with statistical significance. Smoking data were available for some members of the cohort. Saracci *et al.* (1991) studied 18,390 herbicide-exposed workers, of whom 5,898 were sprayers, from 10 countries from 1955-1990. No information is given concerning non cancer mortality among the sprayers; however, for the definitively exposed workers compared to national rates, only benign and unspecified neoplasms were significantly elevated, while diseases of the respiratory and circulatory systems were significantly decreased.

Nelson *et al.* (1973) performed a retrospective mortality study of three groups of persons established in 1935 due to known lead arsenate exposure in Washington state, which included applicators/orchardists, non-exposed women and children, and a group of other workers felt to have only intermediate exposure. The overall mortality, the stroke mortality, and the heart disease mortality for orchardists were not increased compared to the other populations. Tollestrup (1995) followed up on this cohort of 1,225 orchardists. Compared with unexposed consumers, stroke, coronary heart, and other heart diseases were all insignificantly elevated among only the male orchardists.

First, Wang and MacMahon (1979), and then MacMahon *et al*. (1988), followed a cohort of 16,124 male pesticide applicators for a total of 17 years. Atherosclerotic, respiratory, and digestive diseases were not significantly elevated compared to national rates. Blair *et al.* (1983) reviewed the mortality experience of 3827 male Florida pesticide workers from 1965-79. There were no increases in the overall mortality, the circulatory system, digestive system, and respiratory system mortality rates compared with national rates. Follow-up by Pesatori *et al.* (1994) of the same cohort through 1982 found no increases in the overall mortality, the circulatory system, digestive system, and respiratory system mortality rates compared with national rates. Morgan *et al.* (1980) surveyed 70% of a cohort of 2620 pesticide exposed workers. Compared to 43% of control deaths, cardiovascular disease was the cause of 60% of the deaths among pest control-fumigators; compared to 19% of control deaths, trauma caused 40% of the pest control-fumigators' deaths in the study.

Alberghini *et al.* (1991) evaluated 4,580 pesticide licensed farmers in Italy from 1974-1987. All cause mortality was decreased compared to both national and regional population data; only cancer mortality data were presented. Figa-Talamanca *et al.* (1993a) studied 2,310 male pesticide applicators licensed in the province of Rome from 1973 through 1988. In addition, Figa-Talamanca *et al.* (1993b) evaluated the mortality experience of a cohort of 168 pesticide applicators employed for the disinfections service of the city of Rome for an average of 20 years. There was no increase in overall mortality nor in cardiovascular mortality compared to the general population of the province of Rome for either study. Smoking data were not available.

Cantor and Booze (1991) found significant excesses in overall mortality and, in particular, from non-motor vehicle accidents (mostly aircraft crashes) among 9677 aerial pesticide applicators from 1965-1979. Using a comparison of 9727 instructors, arteriosclerotic heart disease and cirrhosis were not elevated; respiratory disease and stroke were non statistically significantly elevated. No smoking data were available.

Alavanja *et al.* (1988, 1989) studied two pesticide applicator cohorts in PMR/MOR studies: 1495 agricultural extension agents, and 1,411 forest and soil conservationists, from 1970-1979. Among the agricultural extension agents, infectious, respiratory, and digestive (including cirrhosis) diseases were significantly decreased, while circulatory, allergic, and endocrine, and external causes of death were not significantly elevated compared to US national rates. In the cohort of conservationists, there were similar results. Green (1986, 1991) studied the mortality experience of 1222 Canadian forestry workers for a public utility from 1950-1982. Compared to local province rates, there was no significant increase in mortality from circulatory, accidents, nervous system and sense organs, respiratory, digestive, or genitourinary system. Suicide was the only cause of death with a significantly increased SMR compared to the general Ontario population, although there was a inverse correlation with length of time worked. Notkola *et al.* (1993) evaluated 2298 forestry and 772 farmer-forestry workers in 1970, 1975 and 1980, with follow up through 1985, in Finland. Compared with all working Finish men, forestry workers had significantly increased risk of all causes of death, circulatory disease, suicide, and other accidents, while farmer-forestry workers had only a non-significant increase of suicide.

Littorin *et al.* (1993) studied market gardeners and orchardists in Sweden between 1965-1982. Compared to regional rates, only mental disorder mortality was elevated, although not significantly; nervous system, cardiovascular, respiratory, and violent deaths were not increased.

2.4. Cancer

Although the primary hazard to humans associated with pesticide exposure is acute poisoning, there has been considerable concern surrounding the possibility of pesticide carcinogenicity in humans. {IARC 1983, Council on Scientific Affairs 1988, Jeyaratnam 1990, WHO 1990, IARC 1991, Vineis

1990. Weisenburger 1993, Davis 1992. Maroni 1993} The pesticides which have generated the greatest concern for possible carcinogenicity include the herbicides (chlorophenoxy acids and chlorophenols), heavy metals (especially arsenicals), petroleum products (polycyclic aromatic hydrocarbons), organochlorines (DDT, Chlordane, Aldrin), and several fumigation agents (EDB. Methyl Bromide). However. many other pesticides and their by-products have proved to be carcinogenic and/or genotoxic in experimental animals and short-term tests. {Borzsonyi 1984, Council on Scientific Affairs 1988, Barthel 1983, Kay 1974, Axelson 1987, Falk 1965, Sharp 1986. Terracini 1967, Innes 1969, Nagao 1978, Durham 1972, Garry 1990, Paldy 1987, Rupa 1989, Rupa 1991a. Rupa 1991b, IARC 1991, Vineis 1990} Furthermore, work has just begun on the effects of pesticide mixtures and the individual "inactive" ingredients, not to mention their synergistic effects with the pesticides and other ingredients.

However, it is difficult to study the carcinogenic effects of pesticides. As has been mentioned, there is a large number of individual pesticides and an even greater number of additives, besides the different formulations and interactions. In addition, there are limitations to typical bioassays (which are only required for registration of <u>new</u> pesticides by EPA under FIFRA unless there is sufficient evidence to justify testing an established pesticide); these bioassays are expensive, there is wide species and strain variability of susceptibility, and ultimately these bioassays are often judged as inconclusive evidence when trying to interpret their relevancy for cancer in humans. Finally, the evaluation of low level chronic exposures seen with environmental contamination is difficult because these low level exposures require large numbers of people and long periods of time to study them properly. Therefore, as with other groups of chemicals, the workplace and workers, where the exposures are highest, become the laboratory for evaluating carcinogenicity and other health effects.{IARC 1983, Council on Scientific Affairs 1988}

2.4.1. Cytogenetic Pesticide Studies

Before discussing formal epidemiologic studies of pesticide-exposed populations, mention should be made of several studies which have examined the mutagenic effects of pesticides. Many of the organochlorine, organophosphate, carbamate, and pyrethroid group of pesticides have been reported to be positive for genetic and cytogenetic effects in mammalian systems.{Rupa 1989, IARC 1991, Maroni 1993, Kida 1993} As with other bioassays for the carcinogenicity of pesticides, there are problems of interpretation with these assays; some of the problems are a lack of confounding information (especially smoking), as well as the lack of background rates and predictive values, and small poorly defined study populations. Still, the evidence is suggestive of mutagenic activity with certain occupational pesticide exposures.{IARC 1991}

The urine of greenhouse workers has been found to be mutagenic using Salmonella testing. {Shane 1988} Sister chromatid exchange (SCE), micronuclei, and chromosome aberrations were found generally to be increased first in cultured lymphocytes exposed to selected fumigants, and then in the lymphocytes of pesticide applicators in various countries after exposure to selected fumigants and organophosphates through their work. In some cases, there was an apparent dose-response effect. Confounding information, especially for tobacco use, was not always available.{Garry 1990, Garry 1989, Paldy 1987, Rupa 1991a, Rupa 1991b, Nehez 1988, Hogstedt 1980, Yoder 1973, Bolognesi 1993a, Kourakis 1992, De Ferrari 1991, Bolognesi 1993b, Desi 1990} However, smoking cotton field pesticide and other agricultural workers had significantly greater SCE compared with unexposed smoker controls.{Rupa 1991a, Rupa 1991b, Carbonell 1990} Dulout *et al.* (1985) evaluated SCE and chromosomal aberrations in a population of floriculturists exposed predominantly to organophosphates with and without the symptoms of chronic pesticide intoxication; the symptomatic group had a statistically significant increase of SCE frequency, but not of chromosomal aberrations. Carbonell *et* *al.* (1993) found similar results in a cross sectional study of agricultural workers and unexposed controls in Spain, even after adjusting for age and cigarette smoking. Linnainmaa (1983) found differences in SCE frequency only between smokers and non-smokers in workers exposed to phenoxy acid herbicides and their unexposed controls; Edwards and Priestly (1994) found no increase in SCE frequency in workers exposed to the organochlorines Aldrin and Dieldrin, consistent with the lack of genotoxicity of these particular compounds.

Fagioli *et al.* (1992) evaluated a variety of cytogenetic and immunologic markers on the bone marrow for patients with acute myeloid leukemia (AML) with and without a history of pesticide or solvent exposure.{Cuneo 1992} A variety of recurring chromosomal aberrations was noted only in the exposed subjects. In addition, conventional chemotherapy was ineffective in achieving complete remission in the majority of the exposed individuals, and they had a decreased mean survival, compared with the unexposed group. In a case control study of acute acute myelogenous leukemia (AML), Ciccone *et al.* (1993) found a statistically significant increase in risk for exposure to pesticide in women (OR=4.4, CI=1.7-11.5); furthermore, these pesticide-associated AMLs were more likely to be in the M4 subcategory. San *et al.* (1989) and See *et al.* (1990) used chromosomal aberrations in Chinese ovary cells as the endpoint to assay the urine of non-smoking orchardists exposed to organophosphates in Canada. Compared to samples collected prior to the spraying season and from non-smoking controls, chromosomal damage activity was elevated. Finally, Garry *et al.* (1992) found chromosomal rearrangements in fumigant appliers consistent with those associated with non Hodgkin's lymphoma compared to unexposed controls.

2.4.2. Organochlorines and Breast Cancer

Environmental factors have long been suspected to play an etiologic role in the development of breast cancer. Recent work by Wolff *et al.* (1993) and others has highlighted the organochlorines. a diverse group of chemicals used extensively in the past as pesticides and insulating fluids, as possible etiologic breast cancer agents. {Kreiger 1994, Falck 1992, Westin 1990, Hunter 1993, Wasserman 1976, Unger 1984} These chemicals are not only environmentally persistent, but they are also highly lipophilic. Thus, persistent levels of the organochlorine pesticide DDTand its metabolites have been measured in adipose tissue and human breast milk for many years, even after the cessation of exposure. {Hayes 1991, Levine 1992, Dewailly 1994} Various investigators have hypothesized that the decrease risk of breast cancer associated with early first birth and breast-feeding may be due to the decreased body burden for the woman of DDT and other organochlorines resulting from breast feeding and the excretion of the vernix caseosa with birth.{Westin 1990, Wolff 1993, Hayes 1991, Dewailly 1994, Olszyna-Marzys 1978, Levine 1992} Several of these chemicals and their metabolites, such as the DDT metabolite DDE, have been shown to be estrogen analogues in mammalian systems.{Wolff 1993, Robison 1982, Robison 1985} Furthermore, as environmentally persistent estrogen analogues, these chemicals may also be related to reported worldwide decreases in mean sperm counts in human males, and other male reproductive effects in animals.{Wright 1996}

One set of observations to be explained if breast cancer and pesticide exposures are associated is that breast cancer rates are not increased among women agricultural workers, although the numbers studied have been small.{McDuffie 1994, Zahm1993, Erickson 1992}

2.5. Pesticides, Cancer and Specific Occupational Groups

In 1991, after reviewing the available literature on occupational exposure to pesticides, IARC concluded that spraying and application of nonarsenical pesticides entail exposures that are *probably* *carcinogenic to humans (Group 2A).*{IARC 1991}

2.5.1. Farmers and other Agricultural workers

Agricultural workers are exposed to a variety of potential carcinogens, in addition to pesticides. These include ultra violet radiation from sunlight, nitrates in fertilizers, chronic antigenic stimulation, and zoonotic oncogenic viruses. {Blair 1985, Blair 1982, King 1986, Borzsonyi 1984, Pearce 1990, Weisenburger 1993} There have been several PMR/MOR studies, numerous case control studies, and several large retrospective cohort mortality studies of farmers in different parts of the world. {Blair 1985, Blair 1982, Burmeister 1990, Reif 1989, Pearce 1990, Saftlas 1987, Burmeister 1983, Wiklund 1986, Sharp 1986, Wiklund 1983, Cordes 1991, Linet 1995, Forastiere 1993, Alberghini 1991, Delzell 1985, Blair 1993} Overall mortality rates among farmers, even total and certain specific cancer mortalities such as lung, colon, and bladder, are less than in the general population and certain other occupational groups. This has been attributed to the healthy worker effect, the active lifestyle associated with farming, and the decreased prevalence among farmers of other carcinogens, especially cigarette smoking and ethanol abuse.

However, consistent increases in several specific cancer types have been found among farmers. Elevated risks have been reported among agricultural workers for leukemia, Hodgkin's Disease, non Hodgkin's lymphoma, multiple myeloma, and cancers of the lip and skin (non-melanotic), stomach, prostate, testicles, ovaries, brain, and connective tissue (soft tissue sarcomas). {Pearce 1990, Blair 1985, Blair 1982, Wiklund 1986, Musicco 1982, Brown 1991, Burmeister 1990, Burmeister 1983, Saftlas 1987, Sharp 1986, Milham 1976, Milham 1983, Cordes 1991, Gallagher 1984, Zahm1993, Cantor 1992, Ritter 1990, Linet 1995, Morrison 1992, Viel 1993, Eriksson 1992, Forastiere 1993, Brown 1993, Weisenburger 1993, Donna 1989, Godon 1991, Alberghini 1991, Smith Rooker 1992, Blair 1993} The increases in lip and skin cancers (both melanoma and non-melanoma) have been attributed to ultraviolet radiation exposure. The increases in stomach cancer have been associated with increased exposures, through fertilizer contamination and natural deposits, to nitrates, as well as dietary factors and socio-economic class. Brain cancer was found to be elevated not only in farmers, but also in children of farmers and in persons living and working in counties with rice, cotton, or wood production; in a study of Italian farmers, an increased risk of glioma was associated with agricultural work for more than 10 years and since 1960. Ovarian cancer risk was elevated with exposure to triazine herbicides. The hematologic, connective tissue, and testicular cancers have been variably associated with exposures to pesticides (especially herbicides) and zoonotic oncogenic viruses. In particular, the elevated risks of multiple myeloma and prostate cancers have had no consistent etiologic association among the farmer cohorts studied.

In various countries, leukemia risk has been found to be highest among farmers born after 1900 and/or dying before the age of 65, which suggests that the increase may parallel the increased use of agricultural chemicals in this century.{Pearce 1990, Blair 1985, Blair 1982, Wiklund 1986, Brown 1991, Burmeister 1990, Burmeister 1983, Saftlas 1987, Sharp 1986, Gallagher 1984, Cordes 1991, Loevinsohn 1987, Viel 1993, Richardson 1992, Steineck 1986} And in certain studies, leukemia risk increased with increased reported pesticide use, especially with animal insecticides. In other studies, leukemia among farmers was also associated with the poultry industry, suggesting a possible link with the zoonotic viruses involved in fowl leukosis; epidemiologic studies attempting to link increased leukemia rates with exposure to another zoonotic oncogenic virus, bovine leukemia virus, have been less successful. Heavy pesticide and fertilizer use have been associated with increased rates of Hodgkin's Disease and non Hodgkin's lymphoma, as well as multiple myeloma. {Brown 1993, Eriksson 1992, Steineck 1986, Viel 1993, Zahm 1992}

There is on-going controversy concerning the relationship between herbicide exposure (specifically the chlorophenoxy acids, chlorophenols, atrazine, and possibly dioxin contaminants) and soft tissue sarcomas, non Hodgkin's lymphoma, and other cancers. {Johnson 1989, Blair 1990a, Sterling 1986a, Michalek 1990, Pearce 1990, Blair 1985, Sharp 1986, Hoar 1986, Hardell 1979, Hardell 1981, Axelson 1974, IARC 1983, Axelson 1980, Sterling 1986b, Saracci 1991, Persson 1993, Asp 1994, Kogevinas 1994, Woods 1989, Zahm 1990, Smith 1992, Zahm1993, Wiggle 1990, Ritter 1990, Davis 1992, Lynge 1985, Garry 1992, Serraino 1992} Due to the extensive use of these herbicides (especially for "rights of way"), as well as their presence in Agent Orange and the apparent increases in the incidence of both soft tissue sarcomas and non Hodgkin's lymphoma in industrialized countries, this controversy has attracted international attention. These associations have been studied not only in agricultural workers, but also forestry workers, manufacturing workers, pesticide applicators, and of course, Vietnam veterans and Vietnamese people.

There are methodologic and other concerns with respect to these studies such as small sample sizes and rare cancers, biases associated with case control studies and variable risk estimates, as well as the variable presence of dose-response relationships, contamination with dioxin, and the lack of reliable exposure measures. In addition, many of the cohorts, such as the agricultural workers, do have other concurrent carcinogenic exposures.{Johnson 1989, Blair 1990, Sterling 1986a, Pearce 1990, Vineis 1992, CJohnson 1990, Kelly 1989, Blair 1990a, Blair 1990b, Zahm 1992, Ibrahaim 1991, Munro 1992, EJohnson 1990, Weisenburger 1993, Morrison 1992b, Maroni 1993, Palackdharry 1994, Doe 1994} Recent international studies pooling cohorts of manufacturing and spraying workers have found significant risk for soft tissue sarcomas with occupational exposure to phenoxy herbicides and possibly their dioxin contaminants; the association for non Hodgkin's lymphoma was generally weaker than those for the soft tissue sarcomas.{Saracci 1991. Kogevinas 1994}

Non Hodgkin's lymphoma has been found to be elevated in agricultural workers with exposure to pesticides other than the phenoxy herbicides, including organophosphates. carbamates. and organochlorines. The risk of cancer seems to be increased with first exposure prior to 1965. when protective clothing and equipment were rarely or inadequately used. {Zahm1993, Cantor 1992, Weisenburger 1990, Wiggle 1990, Weisenburger 1993, Godon 1991} Zahm *et al.* (1993) found the risk of non Hodgkin's lymphoma to be especially high for female agricultural workers.

Finally, childhood brain cancer and leukemia have been associated with parental farming and pesticide exposure. A Finnish case control study of childhood cancer (brain tumors, leukemia, and all other malignancies) and parental occupation found increased risk for all these categories with parental occupation of farming for both mothers and fathers. {Hemminki 1981} In Brazil, the risk for Wilm's tumor was markedly increased for both paternal and maternal agricultural occupations.{Sharpe 1995} In the San Francisco area, Ewing's Sarcoma was associated with paternal occupational exposure to herbicides, pesticides, or fertilizers.{Holly 1992} Of note, in Los Angeles, significantly increased risk for childhood leukemia was found in homes where pesticides were used; in Baltimore and in Missouri, an increased risk for childhood brain cancer was significantly associated with home insecticide application; in Denver, increased odds ratios were found between soft tissue sarcomas and yard herbicide treatment, and between leukemia and use of pest strips, among others. Recall bias, relatively small numbers, and multiple comparisons are unsolved problems in all these case control studies.{Lowengart 1987, Gold 1979, Leiss 1995, Davis 1993, Weisenburger 1993}

2.5.2. Other Non Applicator Pesticide Exposed Occupational Groups

Veterinarians, abattoir workers, grain millers, and pesticide manufacturing workers have all been studied in an effort to evaluate the differential risks for cancer associated with exposure to pesticides and to some of the other potential carcinogens mentioned above with agricultural workers. Veterinarians have exposure to farm animals and pesticides, while abattoir workers are predominantly exposed only to the animals.

Variable increased risks for hematologic malignancies, as well as skin and brain cancers, have been reported among veterinarians; children of veterinarians may also be at increased risk for childhood cancer. {Olsen 1991} Problems of relatively small numbers as well as confounding with socio-economic class are obvious. {Blair 1982} Abattoir workers have been found to have increases in Hodgkin's Disease, specifically associated with slaughtering. {Johnson 1986, Pearce 1988}

Alavanja *et al.* (1990) performed retrospective cohort and nested case control studies on a cohort of the American Federation of Grain Millers with extensive pesticide exposure, both direct and indirect. They found non-statistically significant elevations in leukemia, non-Hodgkin's lymphoma, and pancreatic cancer among workers employed in flour mills; this risk increased with years of employment for Hodgkin's and pancreatic cancer. Lung cancer was not elevated. By prior questionnaire data, 31% of the cohort applied pesticides. In the nested case control study of leukemia, non-Hodgkin's lymphoma, and pancreatic cancer, the risk of developing non Hodgkin's lymphoma was twice (OR=4.2) that for the other cancers; "ever work" in the maintenance and elevator departments was associated with the highest risk of developing lymphoma.

Except for the herbicide manufacturing workers, results from studies of pesticide manufacturing workers have been generally unrevealing. {Ditraglia 1981, Wang 1979a, Coggon 1986, IARC 1983, Sharp 1986, Johnson 1989, Ott 1980, Hearn 1984, Amoateng-Adjepong 1995, Bueno de Mesquita 1993, Lynge 1993, Kogevinas 1993, Coggon 1991, Bloemen 1993, Garabrant 1992, Maroni 1993, Wong 1984} One major problem has been the low numbers of available subjects exposed to the manufacture of a particular pesticide or pesticide group, thus limiting the statistical power to detect increased risks of particular cancers. In addition to multiple exposures, there has been a lack of information concerning possible confounding exposures, especially tobacco. This is especially true for rare cancers such as soft tissue sarcomas. In addition, exposures (except in the case of accidents) have been much lower than those experienced by agricultural workers and pesticide applicators. Finally, the majority of the studies have concentrated on herbicide manufacturing workers, as discussed above. Of interest, a retrospective cohort study by Garabrant *et al.* (1992) of chemical manufacturing workers with organochlorine exposure found a statistically significant increase in pancreatic cancer which increased with duration of exposure and latency since first exposure.

One exception to the lack of startling associations between pesticide exposure and cancer in these worker groups has been the establishment of an increased risk of lung cancer with exposure to arsenical pesticides. Although there is no animal model available, arsenic is a known human carcinogen for skin, lung, liver, and possibly other cancers in a variety of occupational groups including copper smelter workers and sheep-dip factory workers. Arsenical pesticide male production workers in two separate studies were found to have a significantly increased risk of lung cancer with a positive dose-response relationship, although tobacco use information was not available. {Mabuchi 1979, Ott 1974, Hill 1948}

2.5.3. Pesticide Applicators

There have been relatively few epidemiologic studies specifically of pesticide applicators (summarized in **Table 1** and the text below). {Axelson 1974, Barthel 1976, Barthel 1981, Barthel 1985, Barthel 1986, Blair 1983, Coggon 1986, Luchtrath 1983, MacMahon 1988, Morgan 1980, Nelson 1973, Riihimaki 1982 & 1983, Wang 1979b, Wiklund 1988a, Wiklund 1988b, Wiklund 1989b, Wiklund 1989a, Wiklund 1986b, Wiklund 1986c, Johnson 1990, Green 1986 & 1991, Wang 1981, Corrao 1989, Moses 1989, Wiklund 1988c, Balarajan 1988, Cantor 1991, Tollestrup 1995, Littorin 1993, Saracci 1991, Alavanja 1988, Alavanja 1989, Swaen 1992, Hansen 1992, Figa-Talamanca 1993a, Figa-Talamanca 1993b, Pesatori 1994, Asp 1994, Notkola 1993, Thomas 1996}. Most of these studies have been retrospective cohort studies of cancer incidence or mortality. These applicator studies have included a variety of job categories, including: forestry workers, licensed agricultural workers, railroad workers, gardeners, horticulturists, orchardists, vineyard workers, termite control operators, and pesticide applicators.

The variety of possible carcinogenic exposures experienced by agricultural workers has already been discussed. In general, agricultural workers are heavy users of herbicides, and more recently, of fumigants. Forestry workers and railroad workers are exposed mainly to herbicides. Vineyard workers and orchardists were heavily exposed to arsenicals until fairly recently; termite control workers were exposed to certain non-herbicide organochlorines, and increasingly to fumigants. Pesticide applicators per se have been exposed to: herbicides (especially the chlorophenoxy acids and the chlorophenols), insecticides (organophosphates and carbamates), non-herbicide organochlorines, heavy metals (arsenicals and mercurials), and fumigants (EDB, Methyl Bromide). As mentioned before, throughout the world, the use of herbicides, fumigants, and organophosphate insecticides has grown over the past 30 years, while the use of organochlorines and the heavy metals has decreased, except for specific purposes (such as mosquito and termite control, vineyards, and wood treatment). {IARC 1983, Council on Scientific Affairs 1988, Maddy 1983, Wiklund 1989a, Personal

Communication Florida Department of Agriculture 1996, WHO 1990, Moses 1993, Maroni 1993, IARC 1991, Dich 1989}

The majority of pesticide applicator studies have had overall cancer rates which are somewhat increased, even when compared to national (rather than worker) populations. Although not usually statistically significant, a variety of different cancers are increased among the pesticide applicators in the above studies, including skin, lung, lymphatic and hematopoietic, bladder, brain, testis and pancreas (see **Table 1**).

A major focus of pesticide applicator research has been the possible association between occupational exposure to several of the widely used herbicides and the rare soft tissue sarcomas and a variety of hematopoietic cancers, especially non Hodgkin's lymphoma. Besides the predominantly herbicide applicator populations (Coggon 1986, Asp 1994, Swaen 1992, Saracci 1991), only Hansen *et al.* (1992) among Danish male gardeners, Littorin *et al.* (1993) in Swedish gardeners and orchardists, and Alavanja *et al.* (1989) with US forest and soil conservationists found increased risks of soft tissue sarcoma and/or non Hodgkin's lymphoma. Interestingly, several of the pure herbicide applicator populations, but only one of the pesticide applicator groups, also have an increased risk of multiple myeloma; this has been seen in farmers as well.{Riihimaki 1983, Swaen 1992, Figa-Talamanca 1993a, Coggon 1986, Steineck 1986} Small numbers and limited exposure information makes it difficult to establish a definitive carcinogenic role from herbicide exposure on the basis of these particular studies alone.

In fact, Hodgkin's lymphoma and leukemia appear to be more common among pesticide applicator, than farmer, populations. US agricultural extension workers (Alavanja 1980), English forestry workers (Balarajan 1988), and Swedish pesticide applicators (Wiklund 1989a) have an increased risk of Hodgkin's lymphoma: Wiklund's cohort, a subpopulation comparison revealed that pesticide applicators had an increased the risk of Hodgkin's lymphoma compared to farmers. Leukemia risk was elevated in US aerial applicators (Cantor 1990), Danish gardeners (Hansen 1992), Florida structural pesticide applicators (Pesatori 1994), and English pest control officers (Thomas 1996). The solvent benzene has been the compound most infamously associated with occupational leukemia risk. A wide variety of solvents, including benzene, have frequently been used as "inert" ingredients in pesticides for many years. In addition, pesticide exposure has been associated with aplastic anemia, as discussed above.{Fleming 1994b}

One of the most interesting cancer increases for the pesticide applicator studies is in lung cancer noted by Axelson *et al.* (1980) in Sweden, Barthel (1981) in Germany (GDR), Blair *et al.* (1983) in Florida, and Green (1991) in Canada. This lung cancer increase does not appear to be associated with smoking, and has been associated with a dose-response by increasing years of exposure, although an increase in lung cancer was noted in the two studies of the same cohort of pesticide applicators cohort by Wang (1979) with follow-up by MacMahon (1988), but without an apparent dose-response.

No smoking data were available for the original Blair *et al.* (1983) study, however no increases in other smoking-related chronic diseases were noted in this cohort; in the Pesatori *et al.* (1994) follow up of this cohort, with a nested case control study of 54 cases of lung cancer, the risk of lung cancer continued with increasing years from first exposure even when controlling for smoking. Only one of the lung cancer cases was a non-smoker and tobacco use was strongly associated with the risk of lung cancer; reported exposure to the carbamates (carbaryl, propoxur), organophosphates (diazinon), the phenoxy acetic herbicides, and DDT was also associated with increased cancer risk. In the Barthel

(1981) cohort, a simple random sample of pesticide applicators compared with non-pesticide exposed men did not have an increased prevalence of cigarette smoking. Wiklund (1989a,b) found low risks for all cancers associated with cigarette smoking among all licensed Swedish pesticide applicators; a mail survey of a sample of her cohort showed that these workers had significantly less smoking prevalence than other occupational groups. Other investigators have found decreased risk from tobacco-associated diseases, including cancer, in pesticide applicator groups, even when actual smoking information was not available (see **Table 1**). Finally, a case control study of occupational risk factors for lung cancer among non-smoking women in Missouri found that a history of occupational pesticide exposure was associated with a significantly elevated risk of lung cancer (OR=2.4, CI=1.1-5.6).{Brownson 1993}

One hypothesis is that the cause of increased lung cancer could be related to exposure to arsenicals, both as pesticides (such as lead arsenate) and in wood treatment. Moselle wine growers with heavy exposure to arsenical pesticides have increases in lung, skin, and internal cancers, at least by case series; in another case series in Egypt, an increased risk for hepatic angiosarcoma was associated with farmers who had sprayed arsenical pesticides. {Luchtrath 1983, El Zayadi 1986} Barthel (1981) attributed at least part of the lung cancer increase found in his cohort of German pesticide applicators to arsenical pesticide exposures. In addition, there are the studies of Mabuchi (1979) and Ott (1974) of arsenical pesticide manufacturing workers with an increased lung cancer risk. In a retrospective study of occupational mortality in Washington State, Milham (1976, 1983) found increased lung cancer in nurserymen and orchardists (there was no separate occupational category for pesticide applicators); lead arsenate had been used heavily in the 1930s by Washington state orchardists. However, when Wiklund looked specifically at orchardists in Washington State with known 30% increase in lung cancer, her case control study did not reveal any increased risk associated with exposure to lead arsenate when controlling for smoking. {1988b} Nor did Tollestrup *et al.* (1995) find any increase in lung cancer in an overlapping cohort of orchardists exposed to lead arsenate. In the Brownson (1993) case control study of non smoking women with lung cancer, occupational arsenic exposure was not associated with an increased risk.

Wiklund (1989a, 1986) pointed out an interesting increase in testicular cancer incidence in her Swedish cohort. Testicular cancer was increased among all Swedish pesticide applicators with a non-significant increasing trend of risk with time from license; using agricultural pesticide applicators as the control group, this testicular cancer risk was even greater among non-agricultural pesticide applicators. Because there was an increase in the cancer incidence with time, Wiklund postulated that the concomitant increased use of pesticides and fertilizers might be responsible. Alberghini *et al.* (1991) in Italy, Coggon *et al.* (1986) in the USA, and Pesatori *et al.* (1994) in the follow-up of the Blair study also found increased testicular cancer risk among pesticide applicators. Increased risk of testicular cancer among agricultural workers has been found in some, but not all, case control studies of testicular cancer.{McDowall 1984, Mills 1984, Sewell 1986} Testicular cancer has also been associated with solvent use, especially dimethylformamide, possibly as a vehicle for other substances through its increased skin absorption.{Ducatman 1988, Ducatman 1989, Fleming 1994b} Again, a wide variety of solvents have frequently been used as "inert" ingredients in pesticides for many years.

Brain and nervous system cancers appear to be increased in several pesticide applicator populations. Multiple studies have found this association including: Figa-Talamanca *et al.* (1993a) and Alberghini et al. (1991) in different pesticide licensed populations in Italy; herbicide applicator cohorts studied by Asp et al. (1994) in Finland, Swaen et al. (1992) in the Netherlands, and Coggan *et al.* (1986) in the US; agricultural extension agents in the US (Alavanja 1988); gardeners and orchardists in

Sweden (Littorin 1993); pesticide applicators in Sweden (Wiklund 1989a); and, structural applicators in Florida (Pesatori 1994). In Wiklund's Swedish cohort, comparing pesticide applicators to farmers increased the risk of brain cancer in the pesticide applicator subcohort. Brain cancer has been associated with a number of occupations, including farming. Farmers who worked before 1960 and with livestock seem to be particularly at risk. {Thomas 1986, Demers 1994, Musicco 1988, Musico 1982, Blair 1985} As mentioned earlier, brain cancer risk may be increased for children whose parents are exposed to pesticides. {Hemminki 1981, Lowengart 1987, Gold 1979, Leiss 1995, Davis 1993, Weisenburger 1993} As discussed earlier, this is especially intriguing given the possible increased risk of chronic neurologic diseases such as Parkinson's with pesticide exposure. The lipophilic and chronically neurotoxic organochlorines are capable of crossing the blood brain barrier and are stored for years in the highly fatty brain tissues.{Butterfield 1993, Tanner 1990, Schoenberg 1987, Golbe 1993, Rajput 1987, Weschsler 1991, Semchuck 1993, Hubble 1993, Fleming 1994a}

In those studies which report it, skin (both melanoma and non-melanoma) cancer is increased in several pesticide applicator populations.{Wiklund 1989a, Coggon 1986, Cantor 1990, Corrao 1989, Morgan 1980, Littorin 1993, MacMahon 1988, Wang 1979, Swaen 1992, Barthel 1986, Thomas 1996) As with the farmer studies, the majority of the authors attribute this increase to unprotected uv light exposure, rather than pesticides. Rosenman *et al.* (1995) interviewed farmers and their families in Michigan concerning their knowledge and reported behaviors towards the use of skin protection. Although over 80% of the population knew about the risk of skin cancer, only 40% of the men and 60% of the women reported protecting their skin when they went outside. Nevertheless, the use of arsenicals in other occupations is associated with an increased risk of skin cancer.{Cordis 1991, Forrester 1994}

Finally, elevated risk of prostate, stomach and pancreatic cancers have all been found in various studies of agricultural workforces, as discussed above. These cancers are also increased in several of the pesticide applicator cohorts: prostate cancer in forest and soil conservationists (Alavanja 1989), aerial applicators (Cantor 1990), and herbicide applicators (Coggon 1986, Riihimaki 1983, Swaen 1992); stomach cancer in railroad workers (Axelson 1980), German pesticide applicators (Barthel 1986), Canadian forestry workers (Green 1991), Swedish gardeners and orchardists (Littorin 1993), and English pest control officers (Thomas 1996); and, pancreatic cancer in aerial applicators (Cantor 1990), Italian pesticide applicators (Figa-Talamanca 1993a), and herbicide applicators (Swaen 1992). As with the farmers, the increases in stomach cancer have been associated with increased exposures, through fertilizer contamination and natural deposits, to nitrates, as well as dietary factors and socio-economic class. Pancreatic cancer may be elevated with pesticide exposure, especially with exposure to the organochlorines. {Fleming 1992, Garabrant 1992} The increase in prostate cancer, also seen in farmers, has no obvious etiologic explanation, and seems at odds with current theories concerning the protective effects of vitamin D.{Hanchette 1992} However, it may be due to the decreased mortality from other causes and increased life span noted with these worker cohorts since prostate cancer is a relatively common chronic disease in elderly men.

3.0. Conclusions

Pesticides have become an ubiquitous exposure for both workers and the general public due to their increasing and extensive applications, and their environmental contamination. The acute health effects of pesticides on humans are well documented, if under-reported. Of these, neurologic and skin diseases are the most important. The chronic health effects are currently being investigated, with considerable interest focused on cancer, and the chronic neurologic and neuropsychological diseases.

Genotoxic and some recent general population studies point to the real possibility of carcinogenic health effects in humans exposed to pesticides. The most obvious groups in which to study the chronic effects of pesticides in humans are those occupational groups who apply pesticides in high doses as part of their daily activities.

However, the majority of the chronic disease studies of various pesticide worker populations have suffered from a gamut of methodologic problems. Small numbers of subjects have made it difficult to generalize or draw etiologic conclusions from individual studies due to lack of power. Use of inappropriate comparison populations (e.g.. the healthy worker effect) and lack of reporting mechanisms have probably lead to an under-estimation of the magnitude of the health effects. A further limit to the studied populations is that the majority of the studies have concerned only white males; there is little information available on women or race-ethnic minority groups with occupational exposure to pesticides. Inadequate information concerning both pesticide and possible confounding exposures is another problem; with both the pesticide and confounding exposure information, there are also issues of recall bias, surrogate information deficiencies (in the case of deceased workers), and even subject information deficiencies due to the large quantities of different pesticides used over the past 40 years. Because most pesticide exposed populations were exposed to multiple different types of pesticides, this raises the specter of mixed pesticides exposures (with synergistic and/or antagonist effects). Furthermore, it makes the possibility of single exposure studies and related etiologic hypotheses highly unlikely. With multiple exposures and small study populations, the statistical issue of multiple comparisons leads to questionable conclusions from individual studies. {Doe 1994, Blondell 1990, IARC 1991, Maroni 1993, Blair 1990a, Blair 1990b, Cordes 1991, Munro 1992, Richardson 1995, Moses 1993, Council 1988} Overall, adequate quantitation of disease risks associated with specific pesticides is not possible from existing studies due to methodologic and logistic problems.

Nevertheless, in spite of the many methodologic issues, some conclusions can be drawn from the plethora of chronic disease studies in pesticide-exposed worker populations. Farmers, manufacturers, and pesticide applicators are the main worker groups that have been studied, with obvious overlap between these groups. As with many other occupational populations, these groups tend to be healthier compared to the general population, especially with respect to cardiovascular disease, and the diseases associated with heavy tobacco and ethanol use. They are at increased risk from accidents, some of this possibly pesticide-related. Farmers are more likely to die from infectious and non-malignant respiratory diseases; to the extent that certain pesticides have immunologic effects, pesticide exposure may contribute towards these risks, although it has not been studied as yet.

With respect to cancer, pesticide applicator groups (as opposed to farmers) have a somewhat increased risk of cancer compared to the general population and other worker groups in most studies. The worker populations exposed to the phenoxy acid and other herbicides may be at increased risk for soft tissue sarcoma and non Hodgkin's lymphoma. Increased skin cancer risk is seen, but may be unrelated to pesticide exposure. Brain cancer appears to be increased not only in these populations, but possibly in their offspring. Farmers have increased risks of leukemia, multiple myeloma and prostate cancer. Pesticide applicators, and arsenic-exposed manufacturing workers, are at risk for lung cancer. Testicular cancer may also be increased in pesticide applicators. Both farmers and pesticide applicators can have elevated risks of prostate and stomach cancers.{Maroni 1993, Moses 1993, IARC 1991, Blair 1990a, McDuffie 1994, Alavanja 1994}

Chapter Three: Data Linkage Methodology and Master Database Description

This chapter describes the databases, the data linkages, and the ultimate criteria used to create a Master Database for the further statistical analyses. First, there is a description of all the different databases used. Then, the discussion focuses on the data linkages and revisions performed, as well as various issues which emerged. Finally, a summary of the demographic and other information of the Master Database is presented.

1.0. Databases

The core database for this study was the list of pesticide applicators licensed in the State of Florida by the Florida Department of Agriculture and Consumer Services (DACS) since 1970. However, in order to locate additional important information (e.g.. date of birth, date of death and/or incident cancer, etc), linkages with other available databases were performed. A description of each database is given below.

1.1. Licensed Pesticide Applicators

Under EPA since 1970, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) requires that persons who buy or use restricted-use pesticides must be certified as competent pesticide applicators or must be directly supervised by a certified applicator. Persons who are not certified pesticide applicators may not purchase or use restricted pesticides unless directly supervised by a certified applicator (up to 15 persons per certified applicator). Certification requires training and written testing for competency in the safe and effective handling and use of these pesticides.

Pesticides are restricted for use under FIFRA if there is a potential for poisoning of humans (in the formulation, use, or place where used) and/or potential for harm to the environment. Of note, specific state restrictions for restricted use pesticides can be more restrictive than the federal.{EPA 1980} There are approximately 123 pesticides registered for restricted use in Florida, with only approximately 50% actually in active use.

Private applicators are persons who use or supervise the use of restricted-use pesticides in agriculture on property owned or rented by themselves or their employer. Examples of private applicators are: farmers, ranchers, floriculturists, and orchardists. **Commercial applicators** are persons who use restricted-use pesticides for hire on property other than their own, and government workers (**Public applicators**) who apply pesticides in their jobs. There is also a **Dealer** license to be able to sell the restricted-use pesticides. Officially, a person can only hold one of these licenses at a given time. The State of Florida, through the Department of Agriculture and Consumer Services Bureau of Pesticides, requires permits for the actual pesticide use. These include Transport Permits, Dealer Permits, and Applicator Certifications.

In addition, until 1995, the Entomology Services in the Florida Department of Health and Rehabilitative Services (HRS) were responsible for licensing all commercial and personal certification for general household pest and rodent control, some structural fumigators, termite control, and lawn and ornamental pest applicators during the study period. Of note, it was this latter group of pesticide applicators from HRS which was studied by Blair et al. (1983) and Pesatori et al. (1994); these are not the pesticide applicators licensed by the Department of Agriculture which are the subjects of this study.

As of October 1990, there were over 10,000 private applicator licenses, 4500 commercial applicator licenses, and 2000 public applicator licenses currently registered in the Department of Agriculture Bureau of Pesticides Program. These licenses must be renewed every 4 years for a minimal fee, after the initial license is gained by passing a written examination; renewal is now dependent on attending continuing education courses, the majority provided by the Agricultural Extension Services. If the license is not renewed within 60 days at the end of the 4 year period, the license is considered no longer valid; however, if the license is subsequently renewed after some period of lapse, the original license number is assigned.

The certification process for the private applicators has been in effect since 1947. Records have been stored on computer since 1980. Although in 1970, FIFRA made the licensure a strict requirement for buying and applying of restricted pesticides, in Florida the first pesticide licenses were distributed in 1976 with the majority of the total licenses in this cohort given out by 1980. It should be noted that members of the licensed cohort could have been exposed to the restricted pesticides prior to the beginning of the licensure process.

The licensure examination is available in English; prior to 1994, it had been available in Spanish, but this was changed when it was realized that all the pesticide labels are in English. The examination consists of a cCore which is taken by all applicants, and then specialty sections, according to which restriction(s) will apply. The Core Examination is taken after 5-6 hours of instruction in courses approved by the Bureau of Pesticides, often given by personnel of the Agricultural Extension Services. Private applicators take the Core Examination, as well as additional certification for aerial spraying; commercial and public applicators take the core examination and can apply for different application categories.

There are 13 separate application categories (e.g.. agricultural pest control [plant or animal], forest pest control, aerial [sub category of both agricultural and forestry], ornamental and turf pest control, seed treatment, wood treatment, aquatic pest control, right-of-way pest control, industrial/institutional/structural pest control, regulatory, and research and demonstration pest control) for specific licensure; the applicator can be licensed in as many categories as s/he is able to pass the specialty examinations. It is illegal to apply a restricted-use pesticide in a category in which the operator does not have specific certification. However, under the present system, all three applicator categories allow the applicator to buy and apply almost any pesticide available.

The hard copy files at the Bureau of Pesticides at DACS contain the following information: name, social security number, date of birth (added as of 1980 to establish that the person is $\geq$ 18 years as required by law), residential address and phone number, license number, date of license issue (first and most recent), date of license expiration, crops/uses, and license certifications. In addition, the names of the people to be supervised by the Licensee and the Purchasing Agent are listed. The computer files contain all of the above information, except for the date of birth, the names of supervisees, and the Purchasing Agent. In addition, the date of issue in the computer files is the most recent date of issue, not the original date of licensure. The copies of the computer files can be obtained from DACS for a fee after review by the Bureau of Pesticides at DACS; the license hardcopies can be viewed in the DACS Bureau of Pesticide Licensure Office in Tallahassee with permission.

Additional information concerning this database is discussed below, at the conclusion of the Data Linkage Section.

1.2. Florida Pesticide Use Survey

Since 1980 the Bureau of Pesticides collects data annually or biannually on specific pesticide use (pesticide names, amounts and number of acres, dates of use, crops sprayed, application method, and county where used) by a random survey of 1000 licensed applicators in Florida using a mailed questionnaire. The most recent response rate has been 50%. There is no follow-up contact of non-respondents.

1.3. Florida Cancer Data System (FCDS)

Under the Florida Department of Health and Rehabilitative Services (HRS), the Florida Cancer Data System (FCDS) has collected all incident cases of cancer diagnosed in Florida Residents since 1980. It is one of the largest statewide, population-based cancer registry systems in the USA, collecting data on over 80,000 cancer patients per year. There are over 250 hospitals reporting all their cancer cases to the FCDS annually.

The FCDS estimates that it presently captures at least 95% of all incident cancer cases in the state of Florida. The pathology laboratories and free-standing clinics are not required to report to the FCDS although some do; discussions with FCDS Staff indicate that the cancers which are not reported to FCDS are melanomas or other skin cancers for which only outpatient radiation or other treatments are prescribed.

For the FCDS purposes, "cancer" is defined as any malignant tumor which arises as a result of abnormal or uncontrolled division of cells and is categorized as invasive or non-invasive (in situ); non-melanoma, basal and squamous cell carcinomas of the skin are not reported to FCDS.{FCDS 1989} There is at most a two year reporting delay for the FCDS.

The data items collected for FCDS are compatible with national standards set by the cancer Surveillance Epidemiology and End Results (SEER) reporting program; data are available on age, gender, race/ethnic group, and cause-specific cancer incidence rates for Florida since 1980. Individual researchers can apply to the FCDS for access to these data using personal identifiers such as social security number and name. With this access, tumor-specific diagnosis and histology, as well as information extracted from the medical records at the time of diagnosis of the cancer cases on race/ethnicity, marital status, and tobacco use, are available on those subjects found in the FCDS files. Data linkage is available for a scheduled fee, after applying to Florida HRS. Association with a state or federal agency is helpful; prior Human Subjects Committee approval and FCDS peer-review are required.

1.4. Florida Motor Vehicles

The Florida Department of Highway Safety (Division of Licensure) has computerized records for over 12 million Florida residents by name, gender, home address, and date of birth. In 1991, the social security number was first required for licensure; an estimated 75-85% of licenses currently have social security numbers. It is estimated that less than 500,000 eligible Florida Residents (ie. at least 15 years of age without certain health restrictions) are unlicensed.

Licenses must be renewed every 6 years and the records are cleaned 15 months after failure to renew; back records are available on microfiche (although not used in this study). Computerized linkage with other data sets is possible, performed by personnel at the Dept of Highway Safety. Data linkage is available for a fee, after application through the Dept of Highway Safety.

1. 5. Florida Vital Statistics (Death Tapes)

The Florida Department of Health and Human Services Office of Vital Statistics records have been computerized, with complete information from 1970 through 1994 (additional years are added after February of the following year). With name and social security number, it is possible to access these records for confirmation of death. Copies of the death certificates for specific individuals can be obtained for a separate fee per death certificate. The death tapes are available for research (after clearance through the State Registrar of Vital Statistics) for a fee. Prior approval by external Human Subjects Committee is required; association with a state or federal agency is helpful.

When the study proposal was first written, the State of Florida Division of Vital Statistics provided a data linkage service to link smaller databases with the Florida Death Tapes. However, due to infrequent use, this service was discontinued. After negotiations, copies of the Florida Death Tapes from 1970 until 1994 were provided to the Investigator for use on this project with a substantial reduction in fee.

Extensive information is available on the death tapes for successfully linked subjects including: date of death, date of birth, gender, race, place of death, parental names, various causes of death (underlying etc), autopsy, injury (at work, place), and marital status; more recently, Hispanic status, education, veteran, and autopsy findings have been added.

1.6. Health Care Financing Administration (HCFA)

HCFA is a federal agency located in Maryland which performs linkages with their files of all persons who are receiving or have received Medicare ($\geq$65 years) or Disability Benefits (any age after 30 months of receiving social security disability benefits), including family members. The name database which includes both active (approximately 38 million) and inactive files has over

80 million records going back to the 1960s. The majority of Americans over the age of 65 are in the HCFA system; exceptions include persons dying before age 65, persons who never apply for Medicare, persons less than 65 who die within 30 months of applying for disability, certain federal employees, and undocumented persons.

Information is available on the gender and race; linkages are made on a regular basis with social security death tapes, so that vital status information is available. Last residence, birth date, death date, and location of death are available, as applicable. Vital statistics linkage is completed using the social security number.

Formal application must be made to HCFA with a scheduled fee payment (waived for the Investigator on this project). Association with a state or federal agency is helpful; external Human Subjects Committee approval is necessary.

1.7. Epidemiology Resources Inc (ERI)

ERI is a private consulting service in Massachusetts which provides data linkages with the social security death tapes. A scheduled fee is required for a variety of matching options (exact social security number, inexact social security number using 7-8 numbers plus parts of the name, and name match). Information available on successful linkages include date of birth, date of death, and state or zip code of last residence. Although not substantiated, ERI claims to have a more informative output than the National Death Index (NDI).

1.8. EQUIFAX

EQUIFAX is a private consulting service in Virginia which provides data linkages using their own program, the Equifax National Death Search (ENDS). ENDS includes the social security death tapes and 127 other contributors including the State Departments of Vital Statistics, the Defense Department, Rail Road Retirement Fund, etc. The database has over 61,000,000 deaths since 1955 and is continuously updated (allegedly more rapidly than the NDI). A scheduled fee is required for a variety of matching options. There are also more expensive options, such as using credit files to determine vital status and location.

Information available on successful linkages with ENDS include date of birth, date of death, and state or zip code of last residence, as well as the validity of social security numbers and the source of the data.

Rich-Edwards et al. (1994) compared the sensitivity and specificity of ENDS with the National Death Index based on data from the Nurses Health Study. The overall sensitivity of NDI was 98% and Equifax was 79%; for women aged 65 and older, the sensitivity was 98% and 94% respectively; for women less than 65, the sensitivities were 94.5% and 60%, respectively. The specificity of both services was approximately 100%. The difference in sensitivity was believed to be partially due to the increased matching criteria in the matching algorithm used by NDI compared with Equifax. The decreased expense, effort (compared with NDI), and the ability to detect inappropriate social security numbers were stated as Equifax advantages. The authors stated that the Equifax ENDS linkage was particularly suited to retrospective cohort studies.

1.9. Florida Agency for Heath Care Administration (AHCA)

The Florida Agency for Health Care Administration has a database with records from all Florida in-hospital discharges. The social security number, and sometimes the hospital record number (if different from the social security number), are the only personal identifiers: there are no names available. 1992 was the first year that detailed data were collected; from 1992-1994, there were 1.3 million discharge records/year.

Date of birth and vital status ("death" if a result of the in patient visit, and "alive" based on the date of hospital or nursing home encounter) are available, as well as gender, ethnicity, payer, referral source, and discharge disposition.

Data linkage is available for a fee after application approval by social security number and other variables, if available. Association with a state or federal agency is helpful; internal review and external Human Subjects Committee approval are necessary.

1.10. National Death Index (NDI)

The National Death Index was recommended by reviewers to obtain death certificates for all persons who are defined as "lost to follow-up" after the other data linkages had been accomplished. NDI provides linkages with deaths from 1979 until 1994 for a scheduled fee. However, due to lack of monies, this was not attempted. Furthermore, existing linkages as detailed above were considered to be equal to or better than the NDI.

1.11. Social Security Death Tapes

Attempts were made to link with the Social Security Death Tapes, including obtaining computer discs (CDS) of the Social Security Death Benefit Records Index from Automated Research Inc. These CDS include records from 1936 containing over 55,000,000 names with social security number, name, death date, birth date, and last place of residence. However, these files are encrypted so that no more than 6 individuals at a time can be linked. Since the Social Security Death Tape information was available through several of the databases detailed above, further attempts were abandoned.

2.0. Data Linkages

All data linkages were performed by the investigators using SAS Version 6.11. The algorithms of linkage are detailed below. Discrepancies (e.g.. not exact matches) were reviewed individually by the Investigator for each data linkage.

2.1. Pesticide Licensure Database

The Florida Dept of Agriculture and Consumer Services (DACS) released a copy of the computer tape of the licensed Florida pesticide applicators from 1976 until 1/1/94. Backfiles from 1988 were also made available, but they did not contribute any new information to the database, and therefore were not used.

This tape included all applicators in 4 licensure categories (private, commercial, public, and dealer). The variables available were:

License Number (by license category)
Social security number
Full name
"First" date of licensure (actually most recent date, if re-licensed)
Mailing address (most recent)
Phone number (most recent)
County
State
Purchasing agents
Crop/Application Certification Category

The tapes had never been cleaned, and were only updated for the purpose of re-licensure (e.g., address, phone number, other people supervised, and application categories). Therefore, the tapes included all individuals ever licensed in the State of Florida until 1/1/94 since licenses were first granted in 1976. Of note, the license number was assigned sequentially at time of licensure, and kept assigned to the same individual, even with renewal. Officially, each individual could only hold one license at a given time.

Date of birth was never included on the computer tapes; it was collected by DACS on the license application hardcopies as of 10/82. Gender and race-ethnic group information was never collected on either the hardcopies or the computer tapes. In addition, some individuals were listed with initials only for first name, as well as various other designations (e.g.. Jr, Sr, Mrs, II, III), nicknames, and numerous DACS codes.

The Pesticide Applicators Database was set up by the Investigators in INFORMIX. An unique numerical code called the "Serial Number" was assigned to each license for the purposes of database linkage. New variables were created for: updated name, designation (Sr, Jr, Mrs, roman numeral), updated address, original date of issue, date of birth, race, ethnic group, gender, original date of issue, record modification date, and data linkage source variables.

Various DACS staff members were questioned concerning the DACS codes, but no one had worked with the database for more than 6 years; therefore, all DACS codes were eliminated from the name fields. All 618 licenses with addresses listed outside Florida were eliminated. The less than 400 Dealer licenses were eliminated since their exposure was believed to be minimal and the numbers trivial. The following Table summarizes the original uncleaned database.

License	All	Florida
Private	26287	26146
Commercial	9620	9156
Public	3801	3788
	39708	39090

Social security number was only missing for 11 persons. These were clearly incorrect social security number (e.g.. 999999999; per DACS staff, these were assigned for missing social security numbers at time of licensure). These individuals were eliminated from the database since effective data linkage would not be possible.

Last names were re-formatted (e.g.. delacorte = de la Corte) to allow for more exact data linkages. Further revisions of the Master Database deriving from data linkages with other databases are detailed below.

2.2. Licensure Hardcopies (DACS)

Three multiple day trips (12/94, 4/95, 8/95), as well as further review in 7/96, were taken by the Investigator to review over 10,000 license application hardcopies, and to talk with the staff at the DACS Pesticide License Bureau facility in Tallahassee. During this time, all available license hardcopies were reviewed for any subjects missing date of birth after initial data linkage with the Florida Motor Vehicles, FCDS, and the Death Tapes (see below). In addition, random initial licensure dates were collected (never greater than one month duration). The hardcopies were also examined for possible clues as to gender for persons with unknown gender (e.g.. names with initials only).

2.3. Florida Cancer Data System (FCDS)

Data linkage of the entire Pesticide Applicator Database was performed twice by the FCDS. Initial linkage used social security number and SOUNDEX of name; subsequent linkage incorporated newly obtained date of birth information in an algorithm with SOUNDEX of last name and 7+ digits of the social security number. Linkage provided date of birth, date of cancer incidence, gender, race, ethnic group, and type of cancer information, as well as other variables.

2.4. Florida Motor Vehicles

Data linkage was performed once by the Florida Department of Motor Vehicles for the entire Pesticide Applicator Database, using social security number and SOUNDEX of name. Positive linkage (e.g., alive at time of motor vehicle licensure) and date of birth information were supplied with the linkage.

2.5. Florida Vital Statistics Death Tapes

Data linkage with the entire Pesticide Applicator Database was performed several times by the Investigators using the Death tapes provided. Before beginning linkage, a Master Death Tape was created which excluded inappropriate social security numbers, persons who died less than 18 years of age, or inadequate vital status information. Initial linkage used social security number and/or SOUNDEX of name to locate dates of birth and death; subsequent linkages for additional dates of birth and death incorporated an algorithm described below. Linkage provided date of birth, date of death, gender, race, and cause of death, as well as other information.

2.6. Health Care Finance Administration (HCFA)

Data linkage was performed once by the Health Care Financing Administration for the entire

Pesticide Applicator Database, using an algorithm of social security number and full name (no soundex). Positive linkage (e.g.. alive in the database), date of death, gender, race, ethnic group, and date of birth information were supplied with the linkage.

2. 7. Initial Lost To Follow-up

After all of the above data linkages, there were over 3800 subjects "Lost to Follow Up", initially defined as:

a) not licensed in the last 4 years as a pesticide applicator;

b) not licensed in the last 6 years by Florida Motor Vehicles;

c) not dead by the Florida Death Tapes or HCFA files;

d) not with incident cancer by the FCDS; and/or,

e) not alive in HCFA files;

as of 1/1/94. Another issue was the lack of date of birth for 1492 of the lost to follow up subjects. This smaller data set consisting of only this subset of persons considered initially lost to follow-up and/or without date of birth was sent for the following data linkages.

2. 8. Epidemiology Resources Inc (ERI)

ERI performed data linkage of those persons considered initially lost to follow-up and/or without date of birth (see above). The linkage used exact social security number, inexact social security number using 7-8 numbers plus first initial of the first name and 4-12 characters of the last name, and a name match. Linkage provided date of birth, date of death, state of last residence, and zip code of last residence.

2.9. Equifax

Equifax performed data linkage of those persons considered initially lost to follow-up and/or without date of birth (see above). The linkage used social security number. Linkage provided date of birth, date of death, state of death, zip code, and whether the social security number was adequate with the year it was issued. The linkage found 203 inadequate social security numbers (ie. they had never been issued by the Social Security Administration).

2.10. Florida Agency for Heath Care Administration (AHCA)

AHCA performed data linkage of those persons considered initially lost to follow-up and/or without date of birth (see above). The linkage used social security number only since no names are available. Positive linkage provided date of birth, and the disposition and year the person was seen in the Florida health care system.

3.0. Creating the Master Database

Prior to beginning the final data linkage to create a Master Database, gender, ethnic, and race group assignments were made for the whole cohort by the Investigator as described below.

3.1. Gender Assignment

All first names were reviewed. Gender (male, female, unknown) was assigned by the Investigator using Kolatch's Dictionary of First Names (1990). Where there were "unisex" names (e.g.. Leslie, Bobbie, etc.), male gender was assigned arbitrarily since the vast majority of the applicators were male. In addition, all names accompanied by a Jr, Sr, or roman numeral (e.g.. II, III) were first assigned male gender, then all names accompanied by "Mrs" were assigned a female gender. Maiden names were included in the updated "first name" field since none of the proposed database linkages listed maiden names as separate last names. Nicknames and abbreviations (e.g., Wm=William) were replaced with full names where available. Initials (without roman numeral, Jr, Sr, or Mrs) were assigned "unknown" gender, until further data linkage.

3.2. Ethnic group and Race Assignment

Ethnic group (Hispanic, non-Hispanic) was assigned by the Investigator based on the 1980 US Census List of Hispanic Last Names (obtained from the Bureau of the Census), as well as a review of common Hispanic first names. Under-reporting of Hispanic ethnicity is a problem when using only last names to determine status, especially with persons who are greater than second generation in the US. {Rosenwaike 1991, Census 1980}

Race (black, white, unknown) was gained through subsequent data linkages. However, there was not a complete accounting of race for the Pesticide Applicators Database since this information is not included in all the databases (as noted in the database descriptions above). Therefore, complete accounting of race is only available for the incident cancer cases and the deaths.

3.3. Issue Date Assignment

The major exposure variables depended on the first and last dates of licensure issue. The most recent date of licensure issue was available on the DACS computer files of licensed pesticide applicators. As described above, original licensure issue date was extracted on approximately a monthly basis from record hardcopies by the Investigator. Since the license numbers are assigned sequentially, original issue date was assigned randomly by the Investigator within each time period to all subjects still missing their original issue date. The number of years exposed was thus based on the DACS computer file year minus the original year of licensure plus 4 years (until 1/1/94) since the licenses are held for 4 years.

3.4. Linkage Dataset Review

Before starting the final data linkage to create a Master Database, all matches which were not perfect by exact social security number and SOUNDEX of last name with first initial were reviewed individually by the Investigator. If confirming information (e.g.. same name but only 7+ digits of the social security number, or same name plus date of birth when available, and/or same social security number and gender and date of birth when available) was not available or inconsistent, then the match was discarded.

3.5. Algorithm

In order to perform the final data linkage to create a Master Database, both a hierarchy and an algorithm were developed. {Newcombe 1988, Neutel 1991}

The algorithm used for the final linkage with the Florida death tapes was similar to that used in the second FCDS linkage. It combined: a) exact social security number, b) exact social security number and SOUNDEX of the last name; c) 7+ digits of the social security number and SOUNDEX of last name; and/or, d) 7+ digits of the social security number, SOUNDEX of last name and first initial. All matches were reviewed by the Investigator as per above.

3.6. Hierarchy

The hierarchy of linking all the different datasets was based on two criteria. The first was to maximize the use of the data with regards to the proximity of the data source to the actual subject; the second criterion was the thoroughness of the data linkage.

The hard copy records culled from Tallahassee were considered the "gold standard" because they were filled out by the subject him/herself and were hard copy records. The FCDS, although collected from medical records, has its own external controls for checking the reliability of the data; in addition, an extensive algorithm as described above, was used to obtain the matches. Motor Vehicles records are filled out by the subject, but the data linkage is very simplistic. The Florida Death Tapes originate from death record extraction, and the latter are not filled out by the subject; however, the algorithm for matching was thorough. HCFA records are derived from state and federal databases, as are the ERI, EQUIFAX and AHCA databases; the matching algorithms varied as described above.

3.7. Hierarchy Linkage

The following hierarchies were used in the crescendo of linkages ultimately required to both gain information (date of birth, date of death/cancer incidence, or vital status) and to establish the Master Database for the purposes of subsequent statistical analyses.

1) Hierarchy and Source for the Date of Birth and the Follow Up Status Information:

a) for the entire cohort:

- Hardcopies (3 trips);
- FCDS;
- Motor Vehicles;
- Florida Death Tapes;
- HCFA;

b) for only the Initial Lost-to-Follow-Up subset:

- ERI;
- Equifax;
- AHCA;

2) Hierarchy and Source for the Gender Information:

a) for the entire cohort:

- FCDS;
- Florida Death Tapes;

- HCFA;
- Assignment by Investigator (as described above);

b) for only the Initial Lost-to-Follow-Up subset:
- Equifax;

c) In addition, matches with the other databases, which gave full first names where only initial first names were available, were used by the Investigator to determine gender in some cases (as detailed above).

3) Hierarchy and Source for the Race Ethnic group Information:
a) for the entire cohort:
- FCDS;
- Florida Death Tapes;
- HCFA;
- Assignment by Investigator (as described above);

b) for only the Initial Lost-to-Follow-Up subset:
- no relevant database available;

4) For Cancer Incidence and Death Information:

Cancer incidence data were only available from the FCDS. Cause-of-death data were only available from the Florida Death Tapes, although limited date-of-death data were available from HCFA, hardcopies, ERI, EQUIFAX, and AHCA.

Cancer incidence and deaths were only included for the study period 1/1/70-1/1/94, because there was incomplete death ascertainment after this period. All cases of cancer found in the death tapes were also found in the FCDS data linkages.

4.0. Final Database Revisions

Ultimately, to be a subject in the Master Database, the individual had to:

1) be aged 18 years or older at the date of first licensure;

2) have a valid social security number;

3) be assigned a gender category;

4) have a designated vital status (including cancer incidence) only during the study period (1/1/70-1/1/94) in Florida; and,

5) have a birth date assigned from one of the database categories (by hierarchy as per above).

Therefore, the Master Database was further revised to address the following issues (**Table 2**).

4.1. Initial Lost to Follow-Up

Any subject initially defined as "lost-to-follow-up" (see above), and not found by the ERI and Equifax or was found by the AHCA linkages, was considered to be alive at the time of study closure (1/1/94). These people were included in the Master Database if a date of birth was available.

4.2. Duplicates

Individuals with multiple licenses in different categories were identified by a merge using same social security number and SOUNDEX on name; if the other available information were the same, then this was considered to be a single individual with multiple licenses. Licenses were also reviewed and cleaned by the Investigator for duplicate names with different social security numbers and vice versa; if address and other available information were the same, then this was considered to be a single individual with multiple licenses. These names were flagged to keep only the earliest license category per individual to avoid duplication in the analysis.

4.3. Unknown Gender

Persons with unknown gender after hierarchy linkage were eliminated from the Master Database.

4.4. Other Database Revisions

Persons who were less than 18 years of age at time of first licensure (ie. inclusion in the cohort) or time of death were also excluded. Death dates and cancer incidence dates-after 1/1/94 were removed because there was incomplete information available for the entire cohort after this date due to reporting lag in the various databases; these individuals were assumed to be alive and without cancer for the duration of the cohort. Persons with inadequate social security numbers (ie. per Equifax match) were eliminated.

4.5. Out of State Deaths

Persons with out-of-state deaths were eliminated from the study because of lack of time and monies to ascertain authenticity and exact cause of death.

4.6. Non Death Tape Dates of Death

128 deaths were found in HCFA, ERI, EQUIFAX, and AHCA which were not readily found in the Death Tapes. Out-of-state deaths were removed as per above. Rematch with the Death Tapes was performed. Unmatched allegedly Florida deaths were sent to HRS Vital Statistics for rematch. Where matches from either source were found, the dates of birth (and other relevant information) were added to the Master Database.

4.7. Date of Birth

After the hierarchy data linkage, there were additional individuals without date of birth due to the tighter matching and "cleaning" (as described above). Rematch with HRS using looser criteria, and individual review was performed. Review of the hard copies for these new individuals was performed by the Investigator; the majority were found to be individuals licensed prior to the collection of date of birth information. Where matches from either source were found, the dates of birth (and other relevant information) were added to the Master Database.

The same subgroup was also sent to Equifax for another ENDS linkage, as described above. There were 75 incorrect social security numbers; there were 75 matches with only 32 records which were confirmed in the Master Database and in state deaths. Out-of-state deaths were removed as per above. Rematch with the Death Tapes was performed. Unmatched allegedly Florida deaths were sent to HRS Vital Statistics for rematch; 18 persons were identified and found to be excluded by initial Death Tape screening due to incomplete data. Where complete matches from either source were found, the dates of birth (and other relevant information) were added to the Master Database.

Ultimately, the 2664 (8%) persons still without date of birth were eliminated from the Master Database. Unfortunately, the majority of these persons (>95%) were from the early license years from 1975 until 1982 since date of birth was not collected at that time by DACS.

5.0. Master Database

As stated above, individuals in the Master Database must meet the following criteria (database sources given in **Table 3**):

1) aged 18 years or older at date of first licensure;

2) have a valid social security number;

3) be assigned a gender category;

4) have designated vital status (including cancer incidence) only during the study period (1/1/70-1/1/94) in Florida; and,

5) have a birth date assigned from one of the database categories (by hierarchy as per above).

By the multiple data linkages described above, the following information was available on all subjects in the Master Database:

Database Serial Number
License Number (indicates License Category)
Name
Social Security Number
Date of Birth
Address*
Phone Number*
Original Date of License Issue
Last Date of License Issue
Gender
Hispanic/Non Hispanic
Race (limited information)
Application Category
Cancer Incidence (etc., where applicable)
Date of Death (etc., where applicable)

*at time of last licensure (although for those individuals with cancer incidence and/or death data, additional data were available)

5.1. Master Database Summary

The following is a summary of the available variables for the final cohort, as well as a similar summary for the subsequent studies including the cancer incident cases, the deaths, and the Proportionate Mortality Ratio (PMR) subpopulations.

5.1.1. Overall:

Out of 39,090 original licenses, there were 37,072 unduplicated licenses by social security number and name. Any license without a date of birth, missing information including gender, date of death or licensure before 18 years of age, or with an out-of-state death was excluded from the final cohort. There were 34,211 (92%) unique individuals for whom there was complete information. Of these, there were 3556 (10%) women and 30,655 (90%) men.

Using last name assignment as described above, only 1392 (4%) of the cohort were Hispanic; the distribution by gender and Ethnic group can be seen in **Table 4**. As seen in **Table 5**, the Hispanics were significantly younger at first licensure (37.05$\pm$11.84) and at death (61.91$\pm$13.67), and were licensed on average less (5.25$\pm$3.45) than non Hispanics. Information on race was only available for 7417 (22%) of the cohort; the majority of these individuals (97%) were white.

The mean age at first licensure issue was 39.26$\pm$13.19 with a range of 18 to 89 years; the mean age at first licensure for the women was significantly younger than for men by ttest (**Table 6**). The mean number of years licensed was 6.93$\pm$4.27 with a range of 1 month to 19.64 years; for the women, the mean number of years licensed was significantly less than the men by two group t-test. Although licenses were issued in all the Florida counties, the greatest number of licenses (29%) were issued in some of the most populous counties: Dade (7.59%), Palm Beach (6.24%), Hillsborough (5.62%), Orange (4.98%), and Polk (4.67%).

Of the different types of licensure, 23,301 (68%) were Private licenses, 7691 (23%) Commercial, and 3219 (9%) Public licenses. As seen in **Table 7**, the Private licenses were significantly older at first licensure (41.43$\pm$13.66) and at death (67.57$\pm$12.52), and were licensed on average significantly longer (7.52$\pm$4.38) than the Commercial and Public licenses; **Table 8** shows the different licensure distributions by gender. There are 15 categories of licensure for which specialty examinations are necessary; there were only 12,517 certifications listed, with multiple certifications for some individuals. Ornamental plant care (40%) and aquatic application (18%) were the most frequent certifications (**Table 9**).

5.1.2. Cancer Incidence:

There were 1266 (4%) cases of incident cancer as of 1/1/94. There were 107 (8.5%) women and 1159 (91.5%) men. Using last name assignment as described above, only 33 (2.5%) of the incident cancer cases were Hispanic; the distribution by gender and Ethnic group can be seen in **Table 4**. Information on race was available for this sub-cohort of persons with incident cancer; the majority of these individuals (97%) were white.

The mean age at first licensure issue was 54.87 ± 11.41 with a range of 19 to 86 years, with the women licensing at a significantly younger age than the men by ttest (**Table 6**). The mean number of years licensed was 8.80 ± 3.67 with a range of 0.80 to 17.99 years; again the women had significantly fewer years of licensure exposure on average than the men by ttest (**Table 6**). Although licenses were issued in all the Florida counties, the greatest number of licenses (30%) were issued in Dade (8.10%), Palm Beach (5.17%), Hillsborough (5.87%), Orange (5.24%), and Polk (5.10%) counties.

Of the different types of licensure, 1060 (84%) were Private licenses, 128 (10%) Commercial, and 78 (6%) Public licenses; **Table 8** shows the different licensure distributions by gender. There are 15 categories of licensure for which specialty examinations are necessary; there were only 312 certifications listed, with multiple certifications for some individuals. Ornamental plant care

(34%), aquatic application (16%), and row control (14%) were the most frequent certifications.

518 (41%) of those with incident cancer had died by 1/1/94; all cases of cancer death found in the death tapes were present through the FCDS data linkage.

5.1.3. All Deaths:

There were 1875 (5%) deaths in this cohort as of 1/1/94. The mean age at death was 65.92±13.65 with a range from 21 to 99 years. There were 97 (5%) women with a mean age at death of 62.61±15.43 with a range from 22 to 99 years; 95% of the deaths were in men, with a mean age at death of 66.14±13.54 with a range from 21 to 99 years. The women died at a significantly younger age than the men by two group t-test (**Table 6**).

Using last name assignment as described above, only 44 (2%) of the cohort were Hispanic; the distribution by gender and Ethnic group can be seen in **Table 4**. Information on race was available for 1873 (99%) of the cohort; the majority of these individuals (96%) were white.

The mean age at first licensure issue was 56.38±12.42 with a range from 18 to 99 years; the women licensed at a significantly younger age than the men by two group t-test (**Table 6**). The mean number of years licensed was 8.18±2.98 with a range of 1.83 to 17.90 years; the women had significantly less licensure years exposure than the men (**Table 6**). Although licenses were issued in all the Florida counties, the greatest number of licenses (28%) were issued in Dade (7.47%), Palm Beach (5.07%), Hillsborough (7.31%), Orange (3.89%), and Polk (4.80%) counties.

Of the different types of licensure, 1613 (86%) were Private licenses, 172 (9%) Commercial, and 90 (5%) Public licenses; **Table 8** shows the different licensure distributions by gender. There are 15 categories of licensure for which specialty examinations are necessary; there were only 305 certifications listed, with multiple certifications for some individuals. Ornamental plant care (32%), aquatic application (18%), and institution/industry/structure (16%) were the most frequent certifications.

5.1.4. PMR/MOR Subcohort:

The PMR/MOR subcohort by definition contained only the 1696 white males whose date of death was 18 years or greater. There were 43 (3%) Hispanics in this group (**Table 4**). The mean age at death was 66.17±13.58 with a range of 21 to 99 years. The mean age at licensure issue was 56.59±12.39 with a range of 18 to 88 years; the average number of years licensed was 8.24±3.00 (range 1.83-17.90) (**Table 6**).

Of the different types of licensure, 1457 (86%) were Private licenses, 158 (9%) Commercial, and 81 (5%) Public licenses (**Table 8**). Although licenses were issued in all the Florida Counties, the greatest number of licenses (29%) were issued in Dade County (7.78%), Palm Beach (5.13%), Hillsborough (7.43%), Orange (3.60%), and Polk (4.89%) Counties. There are 15 categories of licensure for which specialty examinations are necessary; there were only 208 certifications listed, with multiple certifications for some individuals. Ornamental plant care (31%), aquatic application (18%), and institution/industry/structure (17%) were the most frequent certifications.

5.1.4. Exposure Information:

Checkoway *et al* (1989) recommends the use of the following measures of exposure when individual exposure data for occupational cohorts are limited: the number of years of exposure, the first calendar year of exposure (ie. year of entrance into the cohort), and the age at first calendar year of exposure. In the case of this cohort, these exposure measures can be translated as: the number of years of licensure, the first calendar year of licensure, and the age at first licensure. The frequency distributions for the entire cohort, the deaths, and the incident cases of cancer for number of years licensed by first calendar year of licensure can be seen in **Table 10**. For the overall cohort, the numbers of individuals entering the cohort in 5 year intervals is relatively evenly distributed throughout the cohort time period from 1975-1994. As seen above with the mean number of years of exposure and the mean age at first licensure (**Table 6**), this cohort has relatively little exposure based on the licensure information available.

Examination of the distribution of the exposure measures for the various calendar year subcohorts (ie. 1975-79, 1980-84, etc) showed similar distributions of the exposure measures (**Table 10**). As would be expected, the majority of the deaths (72%) and the cases of incident cancer (68%) occurred among those persons in the earliest subcohort from 1975-1979.

Examination of the exposure measures for correlation (**Table 11**) reveals that for all three groups (ie. Entire Cohort, Deaths, and Incident Cancers), the number of years licensed and the first calendar year of licensure are highly correlated with a Pearson Correlation Coefficient=0.78 for the entire cohort; the other exposure measures were not highly correlated. Similar correlation relationships are seen for the subcohorts (eg. 1975-1979).

6.0. Conclusions

A computerized database of licensed Florida pesticide applicators was obtained from the State of Florida DACS. Through multiple data linkages and hard copy review described in detail above, vital statistics information was obtained for the 34,211 (92%) unduplicated licenses with age 18 years or older, a social security number, and an assigned gender. Ultimately, the 2664 (8%) persons still without date of birth were eliminated from the Master Database. The majority of these persons (>95%) were from the early license years from 1975 until 1982 since date of birth was not collected at that time by DACS.

Of the 34,211 subjects in the Master Database, there were 3556 (10%) women and 30,655 (90%) men; additional demographic information has been summarized above. There were 1875 (5%) deaths in this cohort as of 1/1/94. There were 1266 (4%) cases of incident cancer as of 1/1/94; 518 (41%) of those with incident cancer had died by 1/1/94. Additional analyses are described in subsequent chapters.

Chapter Four: Statistical Methodology

This chapter discusses the methodology and results of four separate but related analyses of the cohort of licensed pesticide applicators in Florida. Three of these analyses are mortality studies: a Proportionate Mortality Ratio (PMR) study, a Mortality Odds Ratio (MOR) study, and a retrospective cohort study of general mortality (including a standardized mortality study (SMR) and Cox proportional hazard analysis). The fourth study is a retrospective cohort study of cancer incidence (including a standardized incidence study (SIR) and Cox proportional hazard analysis). In addition to the specific statistical analyses, the comparison populations are described: the general Florida population, and PMR and SMR subpopulations from the National Cancer Institute (NCI) and National Institute of Occupational Safety and Health (NIOSH) Computerized Occupational Referent Population System (CORPS).

1.0. Methodology

PMR and MOR studies have been used in occupational epidemiology. {Checkoway 1989, Monson 1990, Steenland 1993, Breslow 1987} They are performed as a preliminary analysis, "hypothesis generating", to seek disease-exposure associations when cause of death information (e.g.. Death Certificate) is available, but little else. SMRs and SIRs have been used extensively in occupational epidemiology in the analysis of retrospective cohort studies. More recently, Cox proportional hazard analysis has been utilized to fit regression models to cohort data.{Checkoway 1989, Monson 1990, Breslow 1987, Kleinbaum 1988}

1.1. Proportionate Mortality Ratio (PMR) Studies

PMR studies are conducted because they are relatively easy and inexpensive to perform, compared with a full cohort study. The proportion of a specific disease mortality to all other causes of death mortality for the population of interest to the same proportion for the referent or comparison population. As opposed to SMR studies, PMR studies are interested in counts of deaths, not person time. Furthermore, information concerning the survivors is not necessary, only the deaths.

	Study Population	Comparison Population
Specific Disease	a	b
Other Causes	c	d
	a+c	b+d

$$PMR = \frac{a/a+c}{b/b+d}$$

PMRs can also be thought of as observed over expected where "a" is the number of observed deaths.

$$PMR = \frac{a}{(a+c)(b/b+d)} = \frac{\text{Observed}}{\text{Expected}}$$

To the extent that age and calendar year-specific information are also available, the PMR can be standardized as follows {Miettinen 1972}:

$$\text{Standardized PMR} = \frac{\sum a_i}{\sum b_i\ (a_i+c_i)/(b_i+d_i)}$$

The confidence interval is calculated similar to the confidence interval for the Standardized Mortality Ratio study (SMR), as discussed below, using a Poisson distribution when the observed observations (ie. "a") are less than 50; otherwise, the 95% confidence interval is calculated as {Anders 1993, Kyle Steenland PhD (NIOSH) personal communication, Wiklund 1983, Ahlbom 1993}:

$$PMR \pm 1.96\ (PMR/Expected)^{1/2}$$

The PMR is attractive because under certain circumstances, it can approximate an SMR, especially when the cause of death of interest is rare. In general, if the all cause mortality of the SMR is approximately equal to one, then the PMR is approximately equal to the SMR.{Decloufle 1980, Wong & Decoufle 1982, Wong 1985} A further discussion of this issue is given below in the SMR/SIR section.

However, PMR studies can be highly biased by a number of factors. If the ascertainment of death is incomplete, a bias could be over-reporting of a particular cause of death. For example, as Checkoway *et al* (1989) point out, this can happen with worker groups when a particular disease is compensable or of particular concern. Therefore, a fairly complete or at least representative sample of deaths for the cohort needs to exist. In addition, the PMR assumes that the exposure of interest does not affect the "other causes" of death. More worrisome is the arbitrary effect noticed by Miettinen and Wang (1981) of the dependence on the size of the "other causes" of death. Unless the disease of interest is a relatively rare disease, an undue increase in a particular disease can in turn significantly decrease the number of "other causes" of death. For example, if a large number of workers die of cancer, then there are fewer workers to die of "other causes" which unduly increases the proportion of cancer deaths in the worker population compared to the referent population. The reverse situation may occur when comparing a young relatively healthy working population to the older generally less healthy referent group of the general population (a.k.a. a form of the healthy worker effect). One approach to this problem is to perform a PMR within a disease grouping, for example cancer (ie. The proportionate cancer mortality ratio (PCMR)), since cancer is believed to be generally less affected by the healthy worker effect than cardiovascular disease.{Checkoway 1989, Steenland 1993, Breslow 1987}

1.2. Mortality Odds Ratio (MOR) Studies

Another approach proposed by Miettinen and Wang (1981) is the calculation of the mortality (or morbidity) odds ratio (MOR). {Checkoway 1989, Monson 1990, Steenland 1993}

The MOR specifically addresses the criticism of the biased proportion of "other causes" in the PMR. Instead of comparing a specific disease to all "other causes", for the MOR a specific disease is selected which is believed to be unaffected by the exposures of interest and equally biased by the healthy worker effect. For example, atherosclerotic heart disease (AHD) has not been found to be increased in pesticide exposed populations, as discussed previously; in fact, AHD is usually less in pesticide working populations, probably due to the effects of the healthy worker effect. The logic of Miettinen and Wang (1981) is to treat the MOR as a type of modified case control study in which the cases are the exposed population and the controls are the comparison population. The point of the MOR is to evaluate the ratio of the "exposure odds" for the disease of interest compared to the other unrelated disease.

	Exposed	Non Exposed	Total
Specific Disease	a	b	m_1
Chosen Other Cause	c	d	m_0
Total	n_1	n_0	T

$$MOR = \frac{a/c}{b/d} = \frac{ad}{bc}$$

To the extent that age and calendar year specific information are also available, the MOR can be standardized as follows {Spiegelman 1983}:

$$\text{Standardized MOR} = \frac{\sum a_i}{\sum b_i c_i / d_i}$$

The 95% confidence interval of the standardized MOR is calculated as:

$$UL = \text{Standardized MOR}^{(1+1.96/X)}$$

$$LL = \text{Standardized MOR}^{(1-1.96/X)}$$

where the Mantel Haenszel X is calculated as:

$$X = \frac{\sum a_i - \sum m_{1i} n_{1i} / T_i}{[\sum n_{1i} n_{oi} m_{1i} m_{oi} / T^2_i (T_i - 1)]^{1/2}}$$

In the MOR study, described below and in Chapter Five, ASHD (atherosclerotic heart disease including congestive heart disease(CHD)) rather than AHD (atherosclerotic heart disease without CHD) was used as the comparison disease because this category existed for both comparison populations (ie. the general Florida population and the National Cancer Institute (NCI) Computerized Occupational Referent Population System (CORPS) database) using the ICD diagnosis codes (see **Tables 12 and 13**) as per the National Institute of Cancer (NCI) classification. The PMR for this disease category was also approximately equal to one.

1.3. Standardized Mortality Ratio (SMR) and Standardized Cancer Incidence Ratio (SIR)

The SMR and SIR studies are used in occupational epidemiology when a suitable unexposed comparison group is not easily available or is inadequate due to small population size. Therefore, these studies often use comparison rates from the general population. The advantage of the general population rates is that they are usually relatively easy to obtain, and these rates are stable due to the large population size. The disadvantage of using general population rates is obviously the bias of the healthy worker effect, as well as other biases such as significant group differences in socio-economic class, smoking, diet, and other confounding variables.{Checkoway 1985, Fox 1976, Gilbert 1982, Monson 1986, Wickramaratne 1987}

SMR is a ratio of the rate for a particular cause of mortality in the exposed population divided by the rate for the same cause in the comparison population; the SIR is a similar ratio but only of cancer incidence. Thus, the following discussion will refer only to SMRs but apply equally to SIRs, unless specifically noted. SMRs are usually indirectly standardized, often for gender, age and calendar year. Breslow and Day (1987) define age-adjusted SMRs as a weighted average of the age-specific rate ratios where the weights are the expected number of deaths for the i^{th} age group. SMRs are calculated as the ratio of the observed over expected, where a_i is the number of persons with a specific cause of death in the i^{th} stratum of age and time, and $E(a_i)$ is the expected number of people based on age and calendar year-specific general population rates for that specific cause of death.

$$SMR = \frac{\sum a_i}{\sum E(a_i)} \times 100 = \frac{\text{Observed}}{\text{Expected}} \times 100$$

Obviously, the SIR would consist of a similar formula except that a_i is the number of persons with a specific cause of cancer incidence in the i^{th} stratum of age and time, and $E(a_i)$ is the expected number of people based on age and calendar year-specific general population rates for that specific cause of cancer incidence.

It can be argued that SMRs are similar to the proportionate mortality ratio (PMR) studies since they are the percentages of disease in the exposed compared with the comparison population. However, the computation of the SMR involves considerable more information to develop. In addition to the disease-specific cause of death, the SMR requires the minimal knowledge of individual dates of birth, dates of death, and most important, the individual years of exposure. Using this information, person-year exposure data are assembled for each individual in the cohort and then summarized by age and calendar year groupings (usually by 5 year intervals) for each disease-specific cause of mortality. Separate tables are created with the same stratum groupings for the actual numbers of deaths (ie. a_i), as well as similar tables for the rates of the comparison population. Then, the person-years in each stratum are multiplied by the comparison population rates in each stratum to create the expected number of deaths (ie. $E(a_i)$). After summing the observed and expected, the ratio is created, by convention multiplied by 100.

As described in Chapter Three, all persons included in this cohort analysis had a date of birth, dates of first and most recent licensure, one licensure category assignment, and gender information; they were considered to be alive at the end of the study period, unless data linkage with the Florida HRS Death Tapes had revealed a date and cause of death. For the SMR study, person-years started upon the first calendar year and month of licensure, and ended with the date of death or at 1/1/94, the end of the study period; for the SIR study, person-years started upon the first calendar year and month of licensure, and ended with the date of cancer diagnosis, the date of death or at 1/1/94, or the end of the study period. The age and calendar year groupings are in 5 year groups, starting with age 20 in 1975.

As discussed above, the PMR is considered to be an approximation of the SMR, especially when the cause of death of interest is rare. In general, if the all cause mortality of the SMR is approximately equal to one, then the PMR is approximately equal to the SMR.{Decloufle 1980, Wong & Decoufle 1982, Wong *et al* 1985} However, these assumptions, especially with the general population as the comparison population for a working study population, are not always met. Furthermore, the incorporation of individual person-year data, not found in the PMR, renders the SMR a more detailed and stable risk measure. As a weighted average of the ratios, the weights minimize the variance of the weighted average; the standard error of the SMR depends on the fluctuations of the total number of deaths ($\sum a_i$), rather than the age-specific numbers of deaths. Breslow and Day (1987) point out that this quality makes the SMR less sensitive to small population sizes and unstable rates in particular age and calendar year strata .

The 95% confidence interval were calculated for the SMR in the following way, assuming a constant denominator {Rothman 1979, Checkoway 1989, Kelsey 1996}:

$$LL = \frac{Obs\ [1-1/9(obs)-(Z/3)(1/obs)^{1/2}]^3}{Exp}$$

$$UL = \frac{(Obs+1)\ [1-1/9(obs+1)-(Z/3)(1/obs+1)^{1/2}]^3}{Exp}$$

in which Obs is the observed number of deaths (the SMR numerator), Exp is the expected number of deaths (the denominator of the SMR) and Z is the standard normal deviate specifying the width of the confidence interval (ie. Z=1.96 for the 95% confidence interval).

SMRs cannot be compared between subpopulations of the same cohort, due to differing distributions of confounder variables and the process of indirect standardization inherent in the SMR. Therefore, the different subpopulations (by gender and/or licensing category) are presented without comparison in tables (see below). In the Cox proportional hazard analysis, these subpopulations are included in the analysis as covariables.{Checkoway 1989, Breslow 1987}

1.4. Cox Proportional Hazard Analysis

Rather than perform multiple "stratified" SMR (or SIR) analyses for the exposure measures and other variables, Cox proportional hazard analysis allows the simultaneous incorporation of multiple variables (using only internal subpopulations as comparison groups), as well as the incorporation of time.{Checkoway 1989, Monson 1990, Breslow 1987, Kleinbaum 1988, Clayton 1993, Kelsey 1996, Cox 1975} In particular, age is a major confounding variable when examining mortality or cancer incidence rates in working populations since these rates rise rapidly with age. In addition, in this study (as well many occupational studies),the inexact measures of duration of exposure (ie. number of years licensed and calendar year of licensure) are heavily correlated with time in the study. Therefore, as recommended by Breslow *et al* (1983), Checkoway *et al* (1989), and Kelsey *et al* (1996), in performing the Cox proportional hazard analysis for this mortality study, age is made the outcome or "time" variable, rather than the traditional variable of follow-up or survival time. In this way, confounding by age is tightly controlled due to the extensive stratification on age implicit in the Cox proportional hazard analysis: the model creates a stratum for each case. In other words, each person who dies is compared to all other persons at risk who are the same age in the same calendar period, regardless of exposure duration. In the model, 10-year birth cohorts are entered as a stratum-specific covariable starting in 1900. Other variables of interest (such as calendar year of cohort entry, years of exposure, gender,and licensure type) can be controlled as covariables in the model.

The general form of the Cox proportional hazard analysis in which age is the outcome variable can be written as:{Checkoway 1989, Monson 1990, Breslow 1987, Kleinbaum 1988, Clayton 1993, Kelsey 1996, Cox 1975}

$$\frac{\lambda(t)}{\lambda_o(t)} = \exp(b_1X_1 + b_2X_2 + \ldots\ldots\ldots\ldots + b_jX_j)$$

where t is age, $\lambda(t)$ is the incidence rate at age t in persons with specified values of X_1, X_2, ..., X_j; and $\lambda_o(t)$ is the unknown incidence rate at baseline at age t. Of note, according to Checkoway *et al*

(1989). the Cox proportional hazard model is very similar to Poisson regression except that Poisson involves only a few strata.

It should be noted that there is no external comparison group for the Cox proportional hazard analyses: the cohort is its own comparison group.

1.5. Other Issues

SAS Version 6.11 was used to perform all the database manipulations and the statistical analyses, including macros developed to perform the PMR, MOR, SMR, SIR, standardizations, and statistical significance calculations, including Proc LIFETEST and Proc PHREG..

The ICD diagnosis codes were standardized to the 8th Revision (see **Tables 12** and **13**) as per the National Institute of Cancer (NCI) classification to ease comparison when using the NCI CORPS data (see below). Of note, this did restrict the examination of some subgroupings of diseases; for example, for infectious diseases, only tuberculosis was available as a subgrouping for all three studies, while soft tissue sarcoma did not exist as a category. In addition, review of this classification system by FCDS personnel revealed that there are some rather undesirable groupings, in particular, liver and biliary tree cancer, and penile with testicular cancer. However, due to the use of the CORPS comparison data (described below), this ICD classification grouping list was used in all the studies (ie. PMR, MOR, and the two cohort studies). For the cancer incidence study, the ICD groups were assigned C Code (cancer incidence location codes) equivalents with assistance of the FCDS experts (**Table 13**). {Anon 1992, verbal communication FCDS personnel}

The "Primary Cause of Death" as listed on the Florida Vital Statistics Death Tapes (or given by the NCI CORPS PMR data) was used in these analyses as the Cause of Death. Only the first cancer incidence event from the FCDS match was included.

2.0. Populations

The study population for all the analyses consisted of all deaths and incident cancer cases found by the previously described extensive data linkages among Florida licensed applicators between 1/1/76 and 1/1/94. The only exclusions were out-of-state deaths, inadequate death and birth dates and/or social security number, and persons less than 20 years of age.

Information is available on each death from the HRS death tapes, including date of death, causes of death (primary cause was used for the analysis), gender, race, ethnic group, etc.; similar data are available for each incident cancer case. In addition, from the Department of Agriculture and Consumer Services (DACS), information concerning type of licensure, application categories, year of first licensure, and number of years licensed is available for the pesticide applicators. Some subcohort analyses (ie. Private vs Commercial and Public Applicators) were possible.

2.1. Comparison Population I: Florida General Population

The major comparison population for all these studies was the Florida population.

For the PMR and the MOR studies, expected proportions of death were constructed using the Florida Death Tapes provided by the Florida Department of Health and Rehabilitative Services (HRS). The expected proportions were calculated for the overall PMRs and MORs, and then for 5-year age and calendar year categories for age- and calendar year-adjusted PMRs and MORs, as per above. Only white male expected proportions for Florida were generated as a comparison. Additional modifications are described in the CORPS section below.

For the SMR studies, the following modifications were made. Florida population denominator data were based on the entire population. In addition, the HRS Death Tape data of Florida deaths were incomplete for 1993; therefore only 1990-1992 deaths and population were used to calculate the rates from 1990-1994. Additional modifications are described in the CORPS section below. For the SIR studies only, the FCDS database began in 198; therefore, there are no incident cases of cancer prior to 1980, even though the earliest date of exposure (ie. Licensure) for the cohort was 1/1/75.

2.2. Comparison Population II: Computerized Occupational Referent Population System: The CORPS data system was developed by the National Cancer Institute (NCI) and the National Institute of Occupational Safety and Health (NIOSH) to provide cohort and proportionate mortality comparison ratios for use in studies of worker populations. It represents a pooling of data from 19 PMR studies and 39 SMR studies of different occupational cohorts throughout the US. Obviously, all these occupational cohorts were studied due to interest in the possible health effects of their exposures; nevertheless, they are fairly representative of working populations in the US and represent a welcome alternative to the sole use of national or state comparison populations. These worker comparison populations are particularly needed to deal with the issue of the healthy worker effect, as well as other biases such as socio-economic class, smoking, and diet.{Checkoway 1985, Fox 1976, Gilbert 1982, Monson 1986, Wickramaratne 1987} In addition, the pooling of populations allows for increased numbers of subjects, since small populations have been another issue for many occupational studies.{Thomas 1986, CORPS Documentation 1992}

2.2.1. PMR CORPS

In addition to overall PMR ratios, the PMR ratios can be generated for single race/gender groups (e.g.. white men and women, non white men and women). They can vary by particular study population grouping, geographic region, ever blue collar vs always white collar, employment duration (for SMR studies), and last employment status. For the PMR studies, the job of longest employment was selected. The ratios can also be generated for any of the specific worker cohorts only. The ratios are age and calendar year-specific by 5 year periods.

For the PMR ratios, there are 19 distinct study populations of which 5 are known pesticide-exposed. Therefore, for the PMR study, 13 populations were used to include only all white male workers without known pesticide exposures for the comparison ratios. These 13 populations include: artists, boot and shoe workers, embalmers, shoe manufacturers, metal polishers and platers, oil and petroleum refinery workers, pharmaceutical workers, press photographers, plumbers and pipefitters, and potters; excluded were corn and grain millers, Department of Agriculture employees, tobacco workers, and veterinarians, as well as a cohort of female chemists.

The CORPS database used for this PMR study contained a total of 26,053 white male deaths from throughout the US (only 106 from Florida). The ICD diagnosis codes are standardized to the 8th Revision (see **Tables 12** and **13**).

2.2.2. SMR CORPS

For the SMR rates, there are 39 distinct study populations of which 4 are known pesticide exposed. Therefore, for the SMR study, 35 populations were used to include workers without known pesticide exposures for the comparison ratios. These 35 populations include: air force mechanics, anatomists, attapulgite (asbestos) and talc workers, aromatic amine dye workers, lead smelter workers, rubber workers, cadmium workers, coast guard, chromium workers, metal machinists, dry cleaners, copper smelters, fragrance plant, formaldehyde workers, fur dyers, furniture workers, leather workers, grain miller, gold miners, boiler makers, mineral wool workers, PCB workers, phosphate miners, pulp and paper workers, pottery workers, plywood workers, leather workers, styrene and butadiene workers, petrochemical workers, naval shipyard workers, and uranium millers; excluded were pesticide applicators, pesticide manufacturing workers, corn and grain millers, and aerial applicators.

The CORPS database used for this SMR study contained a total of 149,292 white males with 38,544 deaths and a total of 3,337,545 person-years; there were 19,448 white female with 3136 deaths and 441,524 person-years. There were 2418 (1.6%) white males and 200 (1%) white females from Florida. The ICD diagnosis codes are standardized to the 8th Revision (see **Tables 12** and **13**).

2.2.3. General CORPS Issues

Unfortunately, the CORPS data have not been updated recently so that there are no data after 1984, and the data from 1980-1984 are considered incomplete. {T Helde, CORPS NCI/Information Management Services Inc. Programmer, personal communication} Therefore, after discussions with NCI and their CORPS data consultants, 1975-1980 PMR ratios were used for all subsequent calendar year comparisons (ie. 1980-1984, 1985-1989, 1990-1994). For the purposes of this study, only white male workers were requested for the CORPS expected proportions for the PMR.

Of note, these comparison ratios can be produced in OCMAP, MONSON, O/E and NIOSH LIFE-

TABLE format; O/E (ie. b_i/b_i+c_i) and Monson formats were used for this study.

3.0. Summary

The retrospective cohort of general mortality and cancer incidence of licensed Florida pesticide applicators was analyzed in a variety of ways. There are two PMR studies (one using the general Florida population; the other study a subpopulation of NCI CORPS PMR comparison dataset without obvious pesticide exposure) and an MOR study with the general Florida population as a comparison group; all three analyses only examined white male applicators.

The retrospective cohort study of general mortality was performed first as an SMR study with a variety of comparison populations and subpopulation analyses: all applicators compared to the general Florida population; male and female applicators separately compared to the gender-specific Florida population; male and female applicators separately compared to a gender-subpopulation of the NCI CORPS SMR dataset without obvious pesticide exposure; and private and public male applicators separately compared to the Florida population. Then, Cox proportional hazard analysis of mortality was performed without external comparison groups.

The retrospective cohort study of cancer incidence was performed first as an SIR study with a variety of comparison populations and subpopulation analyses: all applicators compared to the general Florida population; male and female applicators separately compared to gender-specific Florida population, and private and public male applicators separately compared to the Florida population. Finally, Cox proportional hazard analysis of cancer incidence was performed without external comparison groups. The subsequent chapters describe the results of these analyses in considerable detail.

Chapter Five: Proportionate Mortality Ratio (PMR) and Mortality Odds Ratio (MOR) Studies

This chapter discusses the results of three separate but related analyses of the cohort of licensed pesticide applicators in Florida. The first study is a Proportionate Mortality Study (PMR) using Florida deaths as the comparison population; the second is a Mortality Odds Ratio (MOR) study using the same comparison population. The third study is a PMR which uses subpopulations from the National Cancer Institute (NCI) and National Institute of Occupational Safety and Health (NIOSH) Computerized Occupational Referent Population System (CORPS) as the comparison populations These studies were performed to be hypothesis-generating and to compare with previous PMR studies of pesticide applicators, as well as take advantage of the CORPS comparison data.

1. 0. Results

As mentioned above, all results presented are for white males only. All data are adjusted for age and calendar year in 5 year increments. In the MOR study, atherosclerotic heart disease with congestive heart disease (ASHD) rather than atherosclerotic heart disease without congestive heart diseaese (AHD) was used as the comparison disease because this category existed for both comparison populations (ie. the general Florida population and the National Cancer Institute (NCI) Computerized Occupational Referent Population System (CORPS) database) using the ICD diagnosis codes (see **Tables 12** and **13**) as per the National Institute of Cancer (NCI) classification; the PMR for this disease category was also approximately equal to one.

There were 1696 deaths evaluated in the study population of White Male Florida Licensed Pesticide Applicators. The results of the three studies (ie. the Florida Population PMR, the Florida

Population MOR and the NCI CORPS data PMR) are presented in **Tables 14-19**, with separate tables for Non Cancer Mortality and Cancer Mortality. Rather than describe each study separately, the results will be discussed comparing the three different studies (e.g.. Florida PMR, Florida MOR and CORPS PMR); unless otherwise specified, the data are presented in this order: Florida PMR, Florida MOR and CORPS PMR. A comparison is made between Private (Farmer) applicators and Public and Commercial applicators, again across the three studies.

1.1. All White Male Applicators

In general, with only two exceptions, the Florida PMR and the Florida MOR had very similar results: the numerical value of the cause-specific MORs were consistently less than the corresponding PMR. The two exceptions in terms of the direction of risk are for Hodgkin's Disease and External Causes of Death. For Hodgkin's Disease, the risk was insignificantly elevated in the PMR [1.32 (0.13-4.74)], but was not in the MOR [0.94 (0.12-7.41)]. In the case of External Causes of Death (as well as the subgroupings of All Accidents, Motor Vehicle Accidents, and Suicide), the PMR was significantly elevated [1.24 (1.05-1.43)] while the MOR was significantly decreased [0.69 (0.59-0.91)].

1.1.1. Non Cancer Mortality (**Table 14**):

Overall mortality was insignificantly decreased in the Florida MOR [0.91 (0.87-2.61)] and significantly increased in the CORPS PMR [1.19 (1.14-1.24)]. For non cancer causes of mortality, there was no cause of death with an Observed/Expected ratio greater than 2 across all three studies. All three studies found increased risks of Nervous System disease, with the highest risks found in the CORPS PMR.

All three studies had significantly decreased risks for the following non cancer causes of mortality related to tobacco and ethanol use: Respiratory Diseases, Pneumonia, Emphysema. and Cirrhosis. Bone and Joint Diseases, and Skin Diseases were decreased for all three studies, although not significantly. There were no cases of death from Chronic Nephritis or Senility.

The direction of risk for non cancer causes of mortality differed between the Florida and CORPS studies in several areas. Infectious Diseases (although not Tuberculosis, the only ICD subcategory available for all three studies) were significantly elevated in the CORPS PMR [8.12 (5.59-11.40)], yet a decreased risk was found in the two Florida studies. Similar elevations for the CORPS PMR but not the Florida studies were seen for: Mental Diseases, Allergic and Endocrine (including Diabetes), Genito Urinary, and Digestive Diseases. Finally, as alluded to above, there was significant disagreement in risk direction across the three studies for External Causes of Death and its subcategories; in general, the risks were significantly increased in the Florida PMR, significantly decreased in the Florida MOR, and equal to the risk of the comparison populations in the CORPS PMR.

1.1.2. Cancer Mortality (**Table 15**):

There were 479 deaths from Cancer in the study population. As with overall mortality, overall mortality from cancer was significantly elevated in the CORPS PMR [1.29 (1.18-1.40)], but not in the two Florida studies [1.03 (0.94-1.12); 0.99 (0.88-1.11)]. There was only one cancer with ratios greater than 2 across all three studies: the risk for Eye Cancer; this was based on only 3 total cases. Both Prostate and Brain/Central Nervous System cancers were also elevated, in the case of Prostate Cancer significantly. Liver cancer, Leukemia/Aleukemia, and Skin had increased risks in all three studies.

Decreased risks of specific cancer mortality, often significantly, were found for Stomach cancer and Lymphosarcoma. Although the risk for the tobacco-associated cancers of Buccal/Pharyngeal. Larynx, and Bladder were decreased in all three studies, in both All Respiratory Cancers and the subcategory of Lung Cancers, there were slightly elevated but insignificant risks for the CORPS PMR comparison only. There were no cases of Thyroid cancer death.

The direction of risk for cancer causes of mortality differed between the Florida and CORPS studies in several areas. Although based on only 3 cases of cancer, Bone Cancer risk was elevated in the two Florida studies but not in the CORPS PMR. As mentioned above, Hodgkin's Disease risk was elevated in the Florida PMR, but was decreased in both the Florida MOR and the CORPS PMR. Finally, risk for Other Lymphatic Cancer was decreased in the two Florida Studies but the risk was elevated in the CORPS PMR.

1.2. Private (Farmers) vs Commercial and Public Applicators

A possible exposure variable, in addition to years of licensure, is the licensure category: Private, Commercial, and Public. As described elsewhere, the Private Applicators are primarily farmers with a variety of occupational exposures in addition to pesticides, while the Commercial and Public Applicators work as full-time pesticide applicators. Therefore, the three studies were repeated for the two different subpopulations; the results are seen in **Tables 16** and **17** for Private (Farmer) applicators, and **Tables 18** and **19** for Commercial and Public applicators. There were 1457 deaths among Private Applicators and 239 deaths among the Commercial and Public Applicators. Interpretation of the Commercial and Public Applicator group is somewhat hampered by the small sample size; for several causes of mortality, no cases occurred.

1.2.1. Private (Farmers) Non Cancer Mortality (**Table 16**):

Overall Mortality, as with the Overall Analysis, was significantly but not dramatically increased for the CORPS PMR [1.19 (1.13-1.25)]. There was no single disease entity with a ratio greater than 2 across all three studies. Nervous System Disease, and to a lesser extent, CNS Vascular Lesions and Diseases of the Blood, were increased across all three studies for the Private applicators. The risks for Skin, and Bone and Joint were uniformly decreased among the Private applicators. The tobacco- and ethanol-associated diseases were decreased, including Respiratory Diseases, Pneumonia, Emphysema, and Cirrhosis.

The direction of risk for non cancer causes of mortality differed between the Florida and CORPS studies in several areas. As with the overall cohort, Infectious Diseases, Mental, Endocrine and Allergic (including Diabetes), Genito-Urinary, and Digestive Diseases had elevated risks for the CORPS PMR, but not the two Florida studies. External Causes of Death (including All Accidents) were increased in the Florida PMR, but not in the other two studies; Motor Vehicle Accident risk was increased in the CORPS PMR, not in the Florida for Private (Farmer) applicators.

1.2.2. Commercial and Public Applicators Non Cancer Mortality (**Table 18**):

The Overall Mortality was decreased among the Commercial and Public Applicators in the MOR and, significantly, in the CORPS PMR. There was no disease entity with ratios greater than 2 across all three studies. Only Nervous System Disease risk was uniformly increased across all three studies.

The risks of Mental Diseases and Digestive Diseases were decreased for all three studies. The tobacco- and ethanol-associated diseases of Respiratory Diseases, Pneumonia, and Cirrhosis were all decreased; there were no cases of emphysema among the Commercial and Public Applicators. There were also no cases of Tuberculosis, Diseases of the Blood, Asthma, Skin, and Bone and Joint Diseases deaths.

The direction of risk for non cancer causes of mortality differed between the Florida and CORPS studies in several areas. The CORPS PMR Infectious Disease risk was significantly elevated [10.26 (5.19-17.56)], but not in the two Florida studies. Allergic and Endocrine, Genito Urinary, CNS Vascular, and Ulcers were increased in the Florida Studies but not the CORPS PMR. With regards to the risks from External Accidents and its various subcategories, the Florida PMR was increased, the Florida MOR was uniformly and significantly decreased, and the CORPS PMR was decreased except for Motor Vehicle Accidents.

1.2.3. Private (Farmers) Cancer Mortality (**Table 17**):

There were 402 total deaths from cancer among the Private (Farmer) applicators. The Overall Cancer mortality risk was significantly increased in the CORPS PMR and decreased in the MOR. Only for Eye cancer was the mortality risk significantly elevated at ratios greater than 2 across all three studies, although again there were only 3 cases. Cancer of the Brain/CNS, Prostate, Leukemia/Aleukemia, Skin, and Liver were elevated for all three studies, with variable degrees of statistical significance.

Cancers of the Esophagus, Stomach, and Lymphosarcoma were uniformly decreased. Cancers associated with tobacco use were decreased in general, including All Respiratory, Larynx, Buccal/Pharyngeal, Lung, Kidney, and Bladder. There were no deaths from Testicular Cancer.

The direction of risk for cancer causes of mortality differed between the Florida and CORPS studies in several areas. Other Lymphatic and Large Intestine cancers had increased risks in the CORPS PMR, but not the two Florida Studies. Bone Cancer and Hodgkin's Disease were elevated in the Florida studies but not the PMR; there were only 2 deaths for each type of cancer.

1.2.4. Commercial and Public Applicators Cancer Mortality (**Table 19**):

There were 80 total cancer deaths among the Commercial and Public applicators. The Overall Cancer mortality was increased in the Florida studies but not the CORPS PMR. Bone and Testicular cancers were the only cancers with ratios greater than 2 across all three studies, although there was only 1 case of cancer each. Other cancers with increased risk for this group of applicators were Kidney, Skin, Digestive, Stomach, Esophageal, and Brain/CNS. Although Buccal/Pharyngeal, Renal, and Bladder cancers, all tobacco-associated cancers were decreased, both All Respiratory and Lung Cancers had elevated risks, primarily in the two Florida studies.

All Lymphopoietic, Other Lymphatic, Prostate, Buccal/Pharyngeal, and Pancreatic Cancers had no or decreased risks. There were no cases of death from Cancer of the Bladder, Lymphosarcoma, or Hodgkin's lymphoma.

The direction of risk for cancer causes of mortality differed between the Florida and CORPS studies most dramatically for Leukemia/Aleukemia, with an elevated risk in the two Florida studies and decreased risk in the CORPS PMR.

Chapter Six: Retrospective Cohort Study of General Mortality

This chapter describes the rationale and the results of a retrospective cohort study of general mortality in a cohort of the Florida licensed pesticide applicators. This includes a standardized mortality study (SMR) and Cox proportional hazard regression modeling. The latter allows for control and modeling of multiple variables, while the former allows for external comparison populations (both the general Florida and the CORPS populations) and evaluation of stratified data.

1.0. Results

The retrospective cohort study of general mortality was performed first as a SMR study with a variety of comparison populations and subpopulation analyses: all applicators compared to the general Florida population; male applicators separately compared to the male Florida population and separately compared to a male subpopulation of the NCI CORPS SMR dataset without obvious pesticide exposure; similar analyses for the female applicator; and private and public male applicators separately compared to the Florida population. In addition, exposure analyses are presented. Then, Cox proportional hazard analysis of mortality is performed without external comparison groups.

1.1. Florida SMR Results

As described above, all data are adjusted for age and calendar year in 5-year increments, unless otherwise specified.

1.1.1. All Applicators:

In the total cohort of 33,669 age 20 years and older, there were a total of 1874 deaths. Of the 1874 deaths, 1855 had an ICD code allowing cause of death subgroup analysis. The majority of these deaths (55%) had taken place by 1989. The total number of person-years for the entire cohort was 320,250 from 1/1/75 to 1/1/94. The SMR results for non cancer and cancer causes of mortality for all applicators compared to the Florida population are presented in **Tables 20 and 21**. Of the 341 applicators who had an aerial spraying licensure category, 64 (19%) died by 1/1/94; of the 2174 persons with an aquatic licensure category, 190 (9%) had died. Additional demographic information has already been given in Chapter Three, as well as described below.

The age- and calendar year-adjusted non cancer mortality for all applicators was statistically significantly decreased compared to the general Florida populations [0.69 (0.67-0.73)]. Other non cancer causes of death were all decreased or equal to that of the Florida population. In particular, causes of death associated with exposure to ethanol were significantly decreased, such as Cirrhosis [0.45 (0.29-0.66)], and with exposure to tobacco such as Emphysema [0.65 (0.35-1.12)]. The greatest single cause of death was from Circulatory diseases (42%); the SMR was also significantly decreased for all the Circulatory System Diseases. There were no cases of death from Senility or Chronic Nephritis. Of interest, certain causes of death, which were elevated in the Florida PMR study of male applicators described in the previous chapter, were decreased in the SMR study, in particular External Causes [0.88 (0.76-1.02)] and Nervous System Diseases [1.08 (0.75-1.50)].

The age- and calendar year-adjusted SMR for all malignancies was significantly decreased compared to the general Florida population [0.76 (0.70-0.84)]. In general, most cancer mortalities were decreased for the pesticide applicators compared to the Florida population. There were no cases of Thyroid cancer death. Cancers associated with tobacco exposure were significantly decreased, such as Respiratory [0.83 (0.72-0.96)] and Lung [0.85 (0.74-0.99)]. The exceptions to this, but consistent with the Florida PMR of male applicators, were increased cancer mortalities for Eye [4.27 (0.86-

12.49)]. Bone [2.47 (0.50-7.23)]. Leukemia [1.30 (0.81-1.99)], and Brain/CNS [1.28 (0.81-1.92)]: none were significantly elevated, and both Eye and Bone consisted of only 3 cases each. The gender-specific cancers (ie. Prostate, Testicular, Breast and Cervix) are described below in the gender subpopulation analyses.

Of note, there was only 1 case of soft tissue cancer (ICD 171.9), but review of the morphology revealed that it was not a sarcoma. Therefore, there were no cases of Soft Tissue Sarcoma death in this cohort.

1.1.2. Male Applicators:

There were 30,160 male subjects in the cohort with 1776 male deaths (1758 with ICD code). The total number of person-years for the males was 290,791. The SMR results for non cancer and cancer causes of mortality for all male applicators compared to the Florida population are presented in **Tables 22** and **23**.

1.1.2.a. Florida Comparison

The age- and calendar year-adjusted non cancer mortality for all male applicators was statistically significantly decreased compared to the general Florida populations [0.72 (0.69-0.75)]. Other non cancer causes of death were all decreased or equal to that of the Florida population. In particular, causes of death associated with exposure to ethanol were significantly decreased, such as Cirrhosis [0.49 (0.32-0.72)] and with exposure to tobacco such as Emphysema [0.71 (0.38-1.22)]. The greatest single cause of death was from Circulatory diseases (44%); the SMR was also significantly decreased for all the Circulatory System Diseases. There were no cases of death from Senility or Chronic Nephritis. Of interest, causes of death which were elevated in the Florida PMR study of male applicators, were decreased in the SMR study of male applicators, in particular External Causes [0.90 (0.77-1.04)].

The age- and calendar year-adjusted SMR for all malignancies was significantly decreased compared to the general Florida population [0.78 (0.72-0.86)]. In general, most cancer mortalities were decreased for the male pesticide applicators compared to the Florida population. Cancers associated with tobacco exposure were decreased, such as Respiratory [0.87 (0.75-1.01)] and Lung [0.89 (0.76-1.03)]. The exceptions to this, but consistent with the Florida PMR of male applicators, were increased cancer mortalities for Eye [4.67 (0.94-13.66)], Bone [2.72 (0.55-7.96)], Prostate [2.38 (1.83-3.04)], Brain/CNS [1.34 (0.84-2.03)], Leukemia [1.29 (0.78-2.02)], and Liver [1.23 (0.71-2.01)]; only Prostate was significantly elevated, and both Eye and Bone consisted of only 3 cases each.

1.1.2.b. CORPS Comparison

In general, the mortality rates for men using the CORPS dataset as the comparison group were remarkably similar to the Florida general population comparison described above. All of the rates for the CORPS comparison are presented in **Tables 24** and **25**.

The age- and calendar year-adjusted non cancer mortality for all male applicators was statistically significantly decreased compared to the CORPS population [0.45 (0.43-0.47)]. The majority of the other non cancer causes of death were all decreased or equal to that of the CORPS population. In particular, causes of death associated with exposure to ethanol were significantly decreased, such as Cirrhosis [0.26 (0.17-0.39)] and with exposure to tobacco such as Emphysema [0.26 (0.14-0.44)]. The SMR was also significantly decreased for all the Circulatory System Diseases. As with the CORPS PMR, the risk of death from Infectious Diseases was significantly increased [2.07 (1.44-

2.88)]; diseases of the Nervous System [1.45 (1.00-2.02)] and Diseases of the Skin [1.55 (0.02-8.36)] were also elevated, although not significantly and the latter was based on only one case. Of interest, causes of death which were elevated in the Florida PMR but not the CORPS PMR studies of male applicators, were significantly decreased in the SMR study of male applicators, in particular External Causes [0.64 (0.54-0.74)].

The age- and calendar year-adjusted SMR for all malignancies was significantly decreased compared to the CORPS population [0.67 (0.61-0.73)]. In general, most cancer mortalities were decreased for the male pesticide applicators compared to the CORPS population. Cancers associated with tobacco exposure were significantly decreased, such as Respiratory [0.68 (0.58-0.78)] and Lung [0.70 (0.60-0.81)]. The exceptions to this, but consistent with the CORPS PMR of male applicators, were increased cancer mortalities for Eye [1.86 (0.37-5.44)]], Skin [1.44 (0.80-1.48)], Brain/CNS [1.36 (0.85-2.06)], and Liver [1.39 (0.80-2.26)]; none were significantly elevated, and Bone consisted of only 3 cases. Prostate cancer was only minimally and insignificantly elevated [1.16 (0.89-1.48)]. Also similar to the CORPS PMR, Leukemia [0.77 (0.46-1.21)] and Bone [1.07 (0.22-3.13)] were not elevated.

1.1.3. Female Applicators:

There were 3,503 female subjects in the cohort with 98 female deaths (97 with ICD code). The total number of person-years for the females was 29,459. The SMR results for non cancer and cancer causes of mortality for all female applicators compared to all the Florida population are presented in **Tables 26** and **27**.

1.1.3.a. Florida Comparison

The age- and calendar year-adjusted non cancer mortality for female applicators was statistically significantly decreased compared to the general Florida populations [0.44 (0.36-0.54)]. With the exception of Pneumonia and Ulcers, the other non cancer causes of death were all decreased or equal to that of the Florida population. In particular, causes of death associated with exposure to tobacco and ethanol were decreased or not present; there were no cases of Cirrhosis or Emphysema. The greatest single cause of death was from Circulatory diseases (27%), although substantially less than among the male applicators; the SMR was also significantly decreased for all the Circulatory System Diseases. There were no cases of death from Senility, Chronic Nephritis, Tuberculosis, Diabetes, Diseases of the Blood, Mental Diseases, Rheumatic Heart Disease, Asthma, Skin Diseases, nor Bone Diseases. Causes of death which were elevated in the Florida PMR study of male applicators, were also decreased in the female SMR study, in particular External Causes [0.74 (0.41-1.22)] and Nervous System Diseases [0.35 (0.01-1.94)].

The age- and calendar year-adjusted SMR for all malignancies was significantly decreased compared to the general Florida population [0.58 (0.40-0.81)]. In general, most cancer mortalities were decreased for the female pesticide applicators compared to the Florida population. Given the 3503 female applicators with only 98 deaths, it is not surprising that there were no cases of Esophagus, Stomach, Liver, Larynx, Bone, Skin, Bladder, Eye, Thyroid, non Hodgkin's Lymphoma, nor Hodgkin's Lymphoma cancer death. Cancers associated with tobacco exposure were decreased, such as Respiratory [0.47 (0.22-0.90)] and Lung [0.49 (0.22-0.93)], both significantly. Female cancers were decreased, including Breast [0.76 (0.20-1.94)] and All Genital [0.75 (0.08-2.72)], despite the small number of female cancers in this cohort; only Cervical cancer was elevated [1.32 (0.02-7.34)], but this was based on 1 case. The exceptions to this, but statistically insignificant and based on very low numbers, were increased cancer mortalities for Kidney [1.80 (0.20-6.49)], Large Intestine [1.44

(0.58-2.97)]. and Leukemia [1.42 (0.16-5.12)].

1.1.3.b. CORPS Comparison

In general, the mortality rates for women using the CORPS dataset as the comparison group were remarkably similar to the Florida general population comparison described above. All of the rates for the CORPS comparison are presented in **Tables 28** and **29**.

The age- and calendar year-adjusted non cancer mortality for female applicators was statistically significantly decreased compared to the CORPS population [0.49 (0.40-0.60)]. With the exception of Pneumonia and Ulcers, the other non cancer causes of death were all decreased or equal to that of the CORPS population. In particular, causes of death associated with exposure to tobacco and ethanol were decreased or not present. The SMR was also significantly decreased for all the Circulatory System Diseases; the SMRs were insignificantly increased for External Causes [0.83 (0.46-1.36)] and Nervous System Diseases [0.37 (0.01-2.04)].

The age- and calendar year-adjusted SMR for all malignancies was significantly decreased compared to the CORPS population [0.70 (0.48-0.98)]. In general, most cancer mortalities were decreased for the female pesticide applicators compared to the CORPS population. Most female cancers were decreased, despite the small number of female cancers in this cohort; All Genital [0.24 (0.03-0.87)] was significantly decreased, but this was based on 2 cases. Breast [0.44 (0.12-1.14)] was minimally and insignificantly increased. However, similar to Florida population comparison, but statistically insignificant and based on very low numbers, there were increased cancer mortalities for Kidney [3.17 (0.36-11.43)], Rectum [2.78 (0.04-15.47)], Leukemia [1.65 (0.19-5.95)], and Large Intestine [1.43 (0.04-15.47)]. Interestingly, based on 9 cases, Respiratory [1.20 (0.55-2.28)] and Lung [1.25 (0.57-

2.37)] cancers were insignificantly elevated.

.1.1.4. Exposure:

As described in Chapter Three, the majority of the cohort (54%) had obtained their pesticide license by 1984 with 39±13.19 as the mean age of licensure; the mean number of years licensed for the whole cohort was 6.93±4.27 years, ranging from 1 month to 19.64 years. The total number of person-years for the cohort was 320,250 from 1/1/75 to 1/1/94. The SMR results for the following Overall, Prostate Cancer, and External Causes mortality results for all, male, and female applicators compared to all the Florida population using various measures of exposure are presented in **Tables 30, 31** and **32**.

The age-adjusted SMRs for overall mortality by the calendar year of first licensure in 5 year groupings are consistently and significantly less than that of the Florida population (**Table 30**). However, there is a trend of decreasing mortality from the earliest years of licensure [1975-79: 0.70 (0.66-0.74)] to the most recent [1990-94: 0.39 (0.34-0.54)], despite age adjustment; a similar pattern was seen for Prostate cancer and External Causes of Mortality. Similar results and trends are found by gender subgroups.

However, for the Overall Mortality by numbers of years licensed in 4-year groupings (**Table 31**), there is an inverse dose-response relationship in which the trend is of decreasing risk with increasing years of licensure, from the fewest years of licensure [0-4: 0.64 (0.49-0.82)] to the greatest number [16-20: 0.15 (0.10-0.21)]. Similar results and trends are seen by gender subgroup for Overall Mortality. Although similar results are present for Prostate Cancer for the entire cohort, when analysis is performed for the earliest subcohort from 1975-1979, there is a suggestion of a positive dose-response with increasing risk of Prostate cancer with increasing years of exposure. For External Causes of

Death. there is an inverse dose-response relationship (ie. increasing years of licensure are associated with a decreased risk of death from external causes).

There is no obvious dose-response for age at first licensure for overall mortality in either the entire group, nor by gender subgroup (**Table 32**). In fact there appears to be an inverse dose-response relationship for both the number of years licensed and the first age of licensure with overall mortality. A similar situation exists for both Prostate cancer and for External Causes of Death.

1.1.5. Private (Farmers) Male Applicators:

Only male applicators were included in these subpopulation analyses due to the relatively small numbers of female applicators in each licensure subpopulation. There were 20,755 Private (Farmer) male applicators with 1527 (81%) of the entire cohort deaths. The SMR results for non cancer and cancer causes of mortality for all Private (Farmer) male applicators compared to all the Florida population are presented in **Tables 33** and **34**.

Similar to the entire cohort, the age- and calendar year-adjusted overall mortality for the Private male applicators was significantly decreased compared to the Florida population [0.71 (0.68-0.75)]. In addition, the vast majority of the mortality rates were decreased, often significantly, compared to the Florida population. This includes diseases associated with ethanol such as Cirrhosis [0.53 (0.33-0.80)] and tobacco exposure such as Emphysema [0.81 (0.43-1.39)], as well as Circulatory System Diseases [0.87 (0.81-0.94)] and its subgroups. In contrast to the Florida PMR analysis for Private male applicators, External Causes [0.91 (0.76-1.09)] was slightly decreased while Nervous System Diseases was only minimally and insignificantly elevated [1.20 (0.81-1.71)].

Age- and calendar year-adjusted Cancer mortality for the Private male applicators was significantly decreased compared with the Florida population [0.77 (0.70-0.85)]. The majority of cancer mortalities were decreased compared to the Florida population, including tobacco-related Respiratory [0.84 (0.71-0.99)] and Lung [0.86 (0.73-1.01). Despite the low number of cases, Eye was significantly increased [5.52 (1.11-16.12)]. Prostate cancer was significantly increased [2.56 (1.96-3.29).]: there were no cases of Testicular cancer death. In addition, similar to the Florida PMR for Private male applicators, Bone [2.29 (0.26-8.27)], Leukemia [1.31 (0.75-2.12)], and Brain/CNS [1.28 (0.74-2.04)] were all increased, but not significantly.

1.1.6. Commercial and Public Male Applicators:

There were 9,900 Commercial and Public male applicators with 250 (13%) of the cohort deaths. Of these combined male applicators, 7086 were Commercial (72%) and 2814 were Public (28%). The SMR results for non cancer and cancer causes of mortality for all Commercial and Public male applicators compared to all the Florida population are presented in **Tables 35** and **36**.

Similar to the entire cohort, the age- and calendar year-adjusted overall mortality for the Commercial and Public male applicators was significantly decreased compared to the Florida population [0.70 (0.62-0.79)]. In addition, the vast majority of the mortality rates were decreased compared to the Florida population. This includes diseases associated with ethanol such as Cirrhosis [0.31 (0.06-0.89)] and tobacco exposure such as Emphysema [no cases], as well as Circulatory System Diseases [0.74 (0.59-0.93)] and its subgroups. There were no deaths from Tuberculosis, Diseases of the Blood, Asthma, and Skin Diseases. In contrast to the Florida PMR analysis for Commercial and Public male applicators, External Causes [0.84 (0.61-1.14)] and Nervous System Diseases [0.86 (0.23-2.20)] were not elevated. Similar to the Florida PMR analysis, Genito Urinary [1.48 (0.40-3.79)] and Ulcers [1.37

(0.02-7.64)] were elevated. but not significantly.

Age- and calendar year-adjusted Cancer mortality for the Commercial and Public male applicators was decreased compared with the Florida population [0.83 (0.69-1.03)]. The majority of cancer mortalities were the same or decreased compared to the Florida population, including tobacco-related Respiratory [1.03 (0.71-1.44)] and Lung [1.04 (0.72-1.46). There were no cases of Bladder, Eye, or Hodgkin's Disease cancer death. Although there were very few cases, Bone [4.38 (0.06-24.35)], Brain/CNS [1.62 (0.52-3.79)], and Leukemia [1.23 (0.25-3.61)] were elevated, similar to the Private male applicators. Testicular cancer was insignificantly elevated with 1 case [4.32 (0.06-24.02)], while Prostate cancer mortality was not increased [0.73 (0.08-2.65)]. As opposed to the Private male applicators but similar to the Florida PMR for Commercial and Public male applicators, Esophagus, LymphoSarcoma, Kidney, Liver, and Stomach cancer mortality were elevated, although not significantly.

1.2. Cox Proportional Hazards Results

With age as the dependent variable and 10-year birth cohorts as a stratum-specific covariable (starting in 1990), the following variables were considered in modeling overall mortality:

Gender (dichotomous): females are compared to males
Hispanic (dichotomous): Hispanics are compared to non Hispanics
Incident cancer (dichotomous): Incident Cancer compared to non cases
Year of first licensure (categorical): 1975-1979, 1980-1984 compared to 1985+
Age at first licensure (continuous)
Number of years licensed (continuous)
Number of years licensed (categorical): 4-8, 8-12, 12-16, 16-20 compared to 0-4
Licensure type (dichotomous):all Private (Farmers) compared to all Commercial and Public
Aerial licensure (dichotomous): Aerial sprayers are compared to non
Aquatic licensure (dichotomous): Aquatic applicators are compared to non

The majority of these variables have already been explored above in the SMR analysis, although not as continuous variables or in the same model. The analyses were modeled with single covariables, and then with an exposure model (described below). There is no external comparison group. The results of the analyses are presented in **Tables 37** to **39**.

In the single covariable modeling of Overall Mortality, not surprisingly the most dramatic risk for death is with a history of incident cancer (RR=3.01; $p<0.0001$). Female gender is significantly protective (RR=0.62; $p<0.0001$); Hispanic by last name is insignificantly protective. As with the SMR, there is a positive and significant dose-response with year of first licensure; however, the number of years licensed as either a continuous or categorical variable shows significantly increased risk of death with less exposure. However, different from the SMR analysis, there is a significantly decreased risk of death with increasing age at first licensure although it is trivially protective (RR=0.94; $p<0.0001$). Private applicators are at a statistically significant but trivially protective risk of death compared to Commercial and Public applicators (RR=0.99; $p<0.01$). Aerial and Aquatic licensure categories were not associated with any significant increased risk of Overall Mortality.

An exposure model was devised using only the continuous variables of numbers of years licensed and age at first licensure (since there was a high correlation between years of licensure and first calendar year of licensure as seen in **Table 11**). {Checkoway 1989} As with the single covariable analysis, neither variable was an increased risk for overall mortality, either for the entire cohort or for the earliest subcohort which licensed from 1975-1979. In other words, increasing number of years of exposure and increasing age at entry into the cohort were both significantly protective for overall mortality.

Modeling of External Causes of death was performed (**Table 38**), because this is often the only elevated risk found when comparing worker cohorts to the general population: it was an elevated risk in the Florida PMR, although not in any of the SMR studies described above. The most remarkable finding was the significantly increased risk associated with Aerial licensure category (RR=4.38; p<0.001). Fewer years of licensure as either a categorical or continuous variable (for example, 4-8 years of licensure RR=2.38; p<0.01 compared to 16 to 20 years RR=0.51; p<0.51)) was also associated with a significantly increased risk. As with the Cox regression of overall mortality, but different from the SMR, increasing age at first licensure was associated with a significantly protective effect (RR=0.91; p<0.0001). The Exposure models were negative, echoing the results of the single variable analyses.

Finally, modeling of the risk of Prostate cancer death was undertaken (**Table 39**) since this was significantly and consistently elevated among the male applicators in the SMR, as described above. In the case of Prostate cancer, a lack of cases made modeling impossible to perform for several covariables (for example, with only 64 cases of Prostate cancer, the use of the categorical covariables of either number of years of exposure or year of first exposure is not possible). The only significant relationship was an expected significant and markedly increased risk for Prostate cancer mortality for individuals with a prior history of incident cancer (RR=18.36; p<0.0001). No other risks were significant; however, the insignificantly increased risk for Private applicators (RR=2.69; p<0.18) and the increased risk with earlier calendar year of licensure are expected based on the SMR analyses described earlier. The Exposure models had significantly protective risks associated with both increasing age at first licensure and increasing number of years licensed. Further modeling was not attempted.

Chapter Seven: Retrospective Cohort Study of Cancer Incidence

This chapter describes the results of a retrospective cohort study of cancer incidence in a cohort of the Florida licensed pesticide applicators. This includes a standardized cancer incidence study (SIR) and Cox proportional hazard regression modeling. The latter allows for the control and modeling of multiple variables, while the former involves the use of an external comparison group and forces close stratified evaluation of the data.

1..0. Results

The retrospective cohort study of cancer incidence was performed first as an SIR study with a variety of comparison populations and subpopulation analyses: all applicators compared to the general Florida population; male and female applicators separately compared to gender-specific Florida population; and private and public male applicators separately compared to the Florida population. In addition, exposure analyses are presented. Finally, Cox proportional hazard analyses of cancer incidence are performed without external comparison groups.

1.1. SIR Results

As described above, all data are adjusted for age and calendar year in 5-year increments, unless otherwise specified.

1.1.1. All Applicators:

In the total cohort of 33,663 age 20 years and older, there were a total of 1266 cases of cancer. The majority of these cancer cases (54%), had been diagnosed by 1988. Of these 1266 incident cancer cases, 518 (41%) had died by 1/1/94. The total number of person-years for the entire cohort was

316.226 from 1/1/75 to 1/1/94. The SIR results for cancer incidence for all applicators compared to the Florida population are presented in **Table 40**. Additional demographic data are described below, as well as previously in Chapter Three.

The age- and calendar year-adjusted cancer incidence for all applicators was statistically significantly decreased compared to the general Florida populations [0.72 (0.68-0.76)]. In general, most cancer incidences were decreased for the pesticide applicators compared to the Florida population. Cancers associated with tobacco exposure were significantly decreased, such as Respiratory [0.76 (0.66-0.86)] and Lung [0.79 (0.69-0.90)]. The exceptions to this, but consistent with the Florida PMR and SMR of male applicators, were increased cancer incidences for Eye [1.65 (0.53-3.84)], and Bone [1.42 (0.46-3.32)]; both Eye and Bone consisted of only 5 cases and were not significantly elevated. The incidence rates for the gender-specific cancers (ie. Prostate, Testicular, Breast, and Cervical) are described below in the gender subpopulation analyses.

Of note, there was one sarcoma reported by morphology; however, the location was not in the soft connective tissues. Therefore, there were no incident cases of Soft Tissue Sarcoma in the cohort.

1.1.2. Male Applicators:

There were 30,160 male subjects in the cohort with 1159 male incident cancers. The total number of person-years for the males was 287,151. As described in Chapter Three, the mean age of first licensure was 55.91 ± 10.81, the mean age at death was 57.96 ± 10.41, and the mean number of years licensed was 9.12 ± 3.94 for the male incident cases of cancer; these were all significantly greater than the overall means for the entire cohort by t-test. The SIR results for cancer incidence for all male applicators compared to all the Florida population are presented in **Table 41**.

The age- and calendar year-adjusted SIR for all malignancies was significantly decreased compared to the general Florida population [0.72 (0.68-0.76)]. In general, most cause-specific cancer incidences were decreased for the male pesticide applicators compared to the Florida population. Cancers associated with tobacco exposure were significantly decreased, such as Respiratory [0.77 (0.68-0.88)] and Lung [0.81 (0.70-0.92)]. The exceptions to this, but consistent with the Florida PMR and SMR of male applicators, were increased cancer incidences for Testicular [2.49 (1.58-3.74)] and Prostate [1.92 (1.73-2.14)], Eye [1.80 (0.53-3.84)], and Bone [1.57 (0.51-3.66)]; Prostate and Testicular cancers were significantly elevated, while both Eye and Bone consisted of only 5 cases each.

1.1.3. Female Applicators:

There were 3,503 female subjects in the cohort with 107 female incident cancers. The total number of person-years for the females was 29,075. The female applicators with cancer diagnosis were significantly younger (with a mean age at first licensure 49.58±12.71), were significantly younger at cancer death (mean age 54.47±9.34), and had significantly less exposure (mean number of years licensed 7.38±3.31) than their male colleagues with cancer. The SIR results for cancer incidence for all female applicators compared to all the Florida population are presented in **Table 42**.

The age- and calendar year-adjusted SIR for all malignancies was significantly decreased compared to the general Florida population [0.73 (0.59-0.88)]. In general, most cause-specific cancer incidences were decreased for the female pesticide applicators compared to the Florida population. There were no cases of Esophagus, Stomach, Liver, Larynx, Bone, Skin, Eye, nor Hodgkin's Lymphoma cancer. Cancers associated with tobacco exposure were decreased, such as Respiratory [0.56 (0.31-0.93)] and Lung [0.62 (0.35-1.03)], the latter significantly. Female Genital cancers were significantly increased, including All Genital [2.08 (1.32-3.12)] and Cervical [3.71 (1.85-6.64)]; Breast cancer was not significantly elevated [1.14 (0.74-1.67)]. In addition, Thyroid cancer was slightly elevated [1.33 (0.15-4.79)], but this was statistically insignificant and based on very low numbers.

1.1.4. Exposure:

As described in Chapter Three, the majority of the cohort (54%) had obtained their pesticide license by 1984 with 39±13.19 as the mean age of; the mean age of licensure for the whole cohort was 6.93±4.27 years, ranging from 1 month to 19.64 years. The total number of person-years for the cohort was 320,250 from 1/1/75 to 1/1/94. The SIR results for the following overall cancer incidence results for all applicators compared to all the Florida population using various measures of exposure are presented in **Table 43, 44** and **45**.

The age-adjusted SIRs for overall cancer incidence by the calendar year of first licensure in 5 year groupings are consistently and significantly less than that of the Florida population **(Table 43)**. However, there is a trend of decreasing cancer incidence from the earliest years of licensure [1975-79: 0.76 (0.71-0.82)] to the most recent [1990-94: 0.34 (0.20-0.54)], despite age adjustment. Similar results and trends are seen by gender subgroup and for Testicular and Prostate cancer. The only exception is Cervical cancer, which had a significant increase in the 1985-89 subcohort [8.54 (3.68-16.82)].

However, for the overall cancer incidence by numbers of years licensed in 4-year groupings **(Table 44)**, there is an inverse dose-response relationship in which the trend is of decreasing risk with increasing years of licensure, from the fewest years of licensure [0-4: 0.84 (0.65-1.06)] to the greatest number [16-20: 0.42 (0.33-0.53)]. Similar results and trends are seen by gender subgroup and with Cervical cancer, although there is some suggestion of a positive dose-response relationship in the analysis of Cervical cancer risk for the earliest 1975-79 subcohort. Testicular cancer [12-16: 4.98 (1.60-11.61)] showed a suggestion of a trend of increasing risk with increasing number of years exposed, especially in the calendar year subpopulations. Prostate cancer had an uniformly elevated risk despite increasing years of exposure, although again for the earliest 1975-79 subcohort, there is a suggestion of a positive dose-response.

There is no obvious dose-response for age at first licensure for overall cancer incidence in either the entire group, nor by gender subgroup (**Table 45**). In fact there appears to be an inverse dose-response relationship for both the number of years licensed and the first age of licensure with overall cancer incidence; this is also seen in the males (including for Testicular and Prostate cancer), but not for the females (including Cervical cancer at 20-24 [14.03 (2.82-41.00)]).

1.1.5. Private (Farmers) Male Applicators:

Only male applicators were included in these subpopulation analyses due to the relatively small numbers of female applicators in each licensure subpopulation. There were 20,755 Private (Farmer) male applicators with 966 (76%) of the entire cohort incident cancers. The SIR results for causes of cancer incidence for all Private (Farmer) male applicators compared to all the Florida population are presented in **Table 46.**

Age-and calendar year-adjusted cancer incidence for the Private male applicators was significantly decreased compared with the Florida population [0.72 (0.68-0.77)]. The majority of cause-specific cancer incidences was decreased compared to the Florida population, including tobacco-related Respiratory [0.76 (0.65-0.87)] and Lung [0.78 (0.67-0.91). As opposed to the Florida SMR and PMR, both Testicular [2.38 (1.33-3.92)] and Prostate cancer [1.98 (1.77-2.12)] were both significantly elevated. Hodgkin's [1.51 (0.65-2.97)] and Eye [1.34 (0.27-3.91)] were somewhat elevated, but not significantly.

1.1.6. Commercial and Public Male Applicators:

There were 9,900 Commercial and Public male applicators with 193 (15%) of the cohort incident cancers. Of these combined male applicators, 7086 were Commercial (72%) and 2814 were Public (28%). The SIR results for cancer incidence for all Commercial and Public male applicators compared to all the Florida population are presented in **Table 47**.

Age- and calendar year-adjusted cancer incidence for the Public and Commercial male applicators was significantly decreased compared with the Florida population [0.69 (0.60-0.80)]. The majority of cause-specific cancer incidences were decreased compared to the Florida population, including tobacco-related Respiratory [0.86 (0.62-1.16)] and Lung [0.92 (0.66-1.25). As opposed to the Florida SMR and PMR, both Testicular [2.37 (1.18-5.39)] and Prostate cancer [1.55 (1.09-2.14)] were significantly elevated. Eye [3.77 (0.42-13.60)], Bone [2.68 (0.30-9.69)], Stomach [1.34 (0.49-2.91)], and Large Intestine [1.29 (0.84-1.89)] were elevated, but not significantly; there were only 2 cases each for Eye and Bone cancers.

1.2. Cox Proportional Hazards Results

With age as the dependent variable and 10 year birth cohorts as a stratum-specific covariable (starting in 1990), the following variables were entered into a model for overall cancer incidence:

Gender (dichotomous): females are compared to males
Hispanic (dichotomous): Hispanics are compared to non Hispanics
Year of first licensure (categorical): 1975-1979, 1980-1984 compared to 1985+
Age at first licensure (continuous)

Number of years licensed (continuous)
Number of years licensed (categorical): 4-8, 8-12, 12-16, 16-20 compared to 0-4
Licensure type (dichotomous): all Private (Farmers) compared to all Commercial and Public
Aerial licensure (dichotomous): Aerial sprayers are compared to non
Aquatic licensure (dichotomous): Aquatic applicators are compared to non

The majority of these variables has already been explored above in the SIR analysis, although not as continuous variables or in the same model. The analyses were modeled with single covariables, and then with an exposure model. There is no external control group. The results of the analyses are presented in **Tables 48** to **51**.

In the single covariable modeling of Overall Cancer risk, as with the SIR, there is a positive and significant dose-response with year of first licensure (for 1975-79, RR=1.46; 0.0002; for 1980-84, RR=1.35; p<0.0006). The number of years licensed (as either a continuous or categorical variable) showed no significant risk of cancer incidence with increasing exposure. Different from the SIR analyses, there was a significantly decreased risk of cancer with increasing age at first licensure (RR=0.94; p<0.00). Gender and ethnic group, licensure and category types were not significantly associated with an increased risk for incident cancer.

An exposure model was devised using only the continuous variables of numbers of years licensed and age at first licensure (since there was a high correlation between years of licensure and first calendar year of licensure as seen in **Table 11**). {Checkoway 1989} Neither variable had an elevated relative risk for cancer incidence, neither for the entire cohort nor for the subcohort which licensed from 1975-1979. In other words, increasing number of years of exposure and increasing age at entry into the cohort were both significantly protective for cancer incidence.

Modeling of Testicular cancer diagnosis was performed **(Table 49)** because an elevated risk was found for male applicators, including both licensure subpopulations. The only significantly increased risk was associated with the increasing number of years of exposure as a continuous variable (RR=1.15; p< 0.04); the categorical analysis, although not significant, suggests a positive dose-response for testicular cancer risk and increasing years of exposure. Again different from the SIR, increasing age at first licensure was associated with a significantly decreased risk of cancer incidence (RR=0.85; p<0.0008). Exposure modeling was negative, although there were relatively few cases (n=23); the number of years of exposure as a continuous variable was not associated with an increased risk for testicular cancer for either the entire cohort or for the 1975-79 subcohort.

Modeling of the risk of Prostate cancer incidence was undertaken (**Table 50**) since this was significantly and consistently elevated among the male applicators in both subpopulations in the SIR, as described above. There were no significantly elevated risk factors for Prostate cancer, including no effect of earlier calendar year of licensure nor increasing years of exposure. There was a significantly decreased risk was for increasing age at first licensure, although not a markedly decreased risk ratio (RR=0.96; p<0.008). Exposure modeling showed a significantly protective effect of increasing years of licensure and increasing age at first licensure in both the entire cohort and the subcohort for prostate cancer.

Finally, modeling of the risk of Cervical cancer diagnosis was undertaken (**Table 51**) since this was significantly and consistently elevated among the female applicators, in both subgroups, in the SIR, as described above. Of note, in the case of Cervical cancer, a lack of cases made modeling impossible to perform for several covariables, such as Aerial licensure. The only significant relationship was a significant and increased risk with earlier calendar year of licensure (for example, 1975-79, RR=1.46; p<0.0002); of note, there was an obvious but insignificant trend of increasing risk of Cervical cancer diagnosis with increasing years of exposure. Unlike the SIR, there was a significantly decreased risk for increasing age at licensure (RR=0.86; p<0.04). No other risks were significant, although there were relatively few cases (n=11). Of note, exposure modeling showed a significantly decreased risk for increasing years of licensure, an insignificant protective effect of increasing age at licensure was negative. Further modeling was not attempted.

Chapter Eight : Conclusions

This chapter discusses the conclusions of the studies presented in the previous chapters, considering the findings in previous investigations. After a discussion of data limitations, the overall conclusions of this series of studies are given.

1.0. Background

Exposure to pesticides has become ubiquitous to workers and the general public due to increasing and extensive applications, and environmental contamination. The acute health effects of pesticides in humans are well documented, if under-reported under current surveillance; chronic health effects are currently being investigated. The most obvious groups in which to study the chronic effects of pesticides in humans are those occupational groups who apply pesticides in high doses as part of their daily activities (at least seasonally). Genotoxicity studies and some recent epidemiologic studies in the occupationally exposed populations point to the real possibility of carcinogenic health effects in humans exposed to pesticides.

However, the majority of these studies of various pesticide worker populations have suffered from a gamut of methodologic problems. Small numbers of subjects have made it difficult to generalize or draw etiologic conclusions from individual studies due to lack of power in several studies. Use of inappropriate comparison populations (eg. the healthy worker effect) and lack of reporting mechanisms have probably led to an under-estimation of the magnitude of the health effects. A further limitation is that the majority of the studies have concerned only white males; thus little information is available on women or race-ethnic minority groups with occupational exposure to pesticides. Inadequate data on both pesticide and possible confounding exposures are another problem. In addition, there are also issues of recall bias, surrogate information deficiencies (in the case of deceased workers), and even subject information deficiencies due to the large quantities of different pesticides used over the past 40 years. Since most pesticide-exposed populations were exposed to multiple different types of pesticides, this raises the specter of mixed pesticides exposures (with synergistic and/or antagonist effects). Furthermore, it makes single exposure studies and related etiologic hypotheses highly unlikely. With multiple exposures and small study populations, many studies involve the statistical issue of multiple comparisons. All these factors lead to questionable conclusions from individual studies. {Doe 1994, Blondell 1990, IARC 1991, Maroni 1993, Blair 1990a, Blair 1990b, Cordes 1991, Munro 1992, Richardson 1995, Moses 1989, Council 1988} Overall, adequate quantitation of disease risks associated with specific pesticides is not possible from individual existing studies due to methodologic and logistic problems.

Nevertheless, in spite of the many methodologic issues, conclusions can be drawn from the aggregate of available chronic disease studies in pesticide exposed worker populations. Farmers, manufacturers, and pesticide applicators, the main worker groups that have been studied (with obvious overlap between them), tend to be healthier compared to the general population, especially with respect to cardiovascular disease and the diseases associated with heavy tobacco and ethanol use. They are at increased risk from accidents, some of this possibly pesticide-related (e.g. aerial sprayers). Farmers are more likely to die from infectious and non-malignant respiratory diseases; to the extent that certain pesticides have immunologic effects, pesticide exposure may contribute towards these risks, although it has not been studied as yet.

With respect to cancer, pesticide applicator groups (as opposed to farmers) have a somewhat increased risk of cancer compared to the general population and other worker groups in most studies. The worker populations exposed to the phenoxy acids and other herbicides may be at increased risk for soft tissue sarcoma and non Hodgkin's lymphoma. Increased skin cancer risk is seen. but may be unrelated to pesticide exposure (ie. uv exposure). Brain cancer appears to be increased. not only in these populations, but possibly in their offspring. Farmers have increased risks of leukemia. multiple myeloma, and prostate cancer. Pesticide applicators and arsenic-exposed manufacturing workers are at risk for lung cancer. Testicular cancer may also be increased in pesticide applicators. Both farmers and pesticide applicators can have elevated risks of stomach cancers.{Maroni 1993, Moses 1989, IARC 1991, Blair 1990a, McDuffie 1994, Alavanja 1994}

2.0. Summary of the Results

Out of the 37,072 original licenses, complete information was obtained for 34,211 (92%) individual pesticide applicators. Of these, 10% were women and 90% men. Only 1392 (4%) of the cohort were Hispanic by last name; information on race was only available for 7417 (22%) of the cohort, predominantly through the death tapes and cancer incidence; the vast majority (97%) was white.

The overall mean age at first licensure issue was 39.26 ± 13.19 with a range of 18 to 89 years; the mean age at first licensure for the women was significantly younger than for men by 2 years ($p<0.0001$). The mean number of years licensed was 6.93 ± 4.27; for the women, the mean number of years licensed was significantly less than the men by 1.5 years ($p<0.0001$). Of the different types of licensure, 23,301 (68%) were Private licenses, 7691 (23%) Commercial, and 3219 (9%) Public licenses. The Private license holders were significantly older at first licensure and at death, and were licensed on average longer than the Commercial and Public licenses.

2.1. Overall

The PMR and MOR studies were useful in providing a contrast between the general Florida population (PMR and MOR) and the NCI CORPS dataset (PMR) as comparison populations. In particular, Prostate, Eye and Brain cancers were elevated across all three studies (although the numbers of cancers were very small for Eye and Brain), while cardiovascular diseases and those associated with tobacco and ethanol use were decreased.

In the Florida PMR, as seen in many studies comparing a relatively healthy occupational group to the general population, external causes of death are significantly elevated. However, for the Florida MOR using the proportion of deaths from ASHD as a relatively unbiased denominator, the risk of death from all external causes is significantly less than the risk for the general Florida population; for the CORPS PMR, using a more appropriate control group of other workers, there is no difference between the risk of death from this cause for the study population and the other working populations. Similar results were seen in the Florida and CORPS SMR study. Therefore, external causes of death would not appear to be truly elevated for the study population. Of note, there was an appropriately inverse dose-response effect for the SMR for external causes of death with increasing years of exposure, especially with the Cox proportional hazard analysis (**Table 38**), since less experienced workers are at greatest risk of "accidental" death. In addition, the significantly increased risk of external causes mortality associated with Aerial licensure in the same analysis has been described in previous studies; it is thought to be associated with the acute and chronic neurotoxic effects of many pesticides on a highly skilled dangerous job.{Cantor 1990}

For both the general mortality SMR and the cancer incident SIR studies, these licensed Florida pesticide applicators have significantly decreased cancer incidence and overall mortality compared with the general Florida population. As with many occupational cohorts, the risks for chronic diseases, such as cancer, were significantly decreased, even in the subpopulations by gender and license type. Furthermore, as seen with similar worker cohorts, this cohort has a decreased risk of cancer and other causes of mortality from etiologies associated with the use of tobacco products and ethanol. Different from the CORPS PMR, the CORPS SMR is markedly similar in its mortality profile to the general Florida population.

2.2. Males

With regards to cancer among male applicators, the most consistently elevated cancer incidence and mortality were Testicular and Prostate. However, different from the literature, the incidence rates of these cancers were elevated in both the licensure type subcohorts (Private vs Commercial and Public) which suggests the possibility that previous mortality studies may have underestimated the risks of these cancers. {Blair 1985, Burmeister 1990, Council 1988, Maroni 1993, McDowall 1984, Pearce 1990} It is also interesting the CORPS SMR comparison did not show an increase in Prostate cancer mortality; this was the only major difference between the CORPS SMR and the Florida general population comparisons. It is possible that these relatively healthy working populations are more likely to die from prostate cancer exactly because they do not die of other causes so common in the general population.

Eye and Bone were also elevated among the male applicators, more dramatically in the mortality than the incidence study; the small number of cases makes definitive interpretation difficult although similar elevations have been seen in other studies. Compared to other studies, the risks of leukemia and brain cancer were not elevated in the incidence study, and only somewhat elevated in the mortality study.{Blair 1985, Burmeister 1990, Brown 1991, Maroni 1993, Morrison 1992, Figa-Talamanca

1993a, Figa-Talamanca 1993b}

There were no confirmed cases of soft tissue sarcoma in this cohort of pesticide applicators, and non Hodgkin's lymphoma was not increased in any of the subpopulations examined. These findings are at odds with previously published literature associating the use of the phenoxy herbicides with an increased risk of both non Hodgkin's lymphoma and soft tissue sarcoma.{Cantor 1992, Johnson ES 1990, Palackdharry 1994, Zahm 1992}

2.3. Females

The number of female applicators was relatively small, as were the numbers of deaths and incident cases of cancer in this subpopulation. They were also significantly younger and had significantly decreased exposure time compared to their male counterparts. Although comparisons cannot be made across SMRs or SIRs, as described above, nevertheless as a whole the female applicators appear to be healthier than the male applicators which is confirmed in the overall mortality Cox modeling; this may be due to their decreased exposure, as well as the unstable risk measurements due to the small number of female applicators. Breast cancer was not significantly elevated in any of the subpopulations, despite the presence of multiple organochlorine pesticides on the Restricted Pesticide List. Very few studies exist of occupational exposure to organochlorines in women with which to test current hypotheses concerning the possible etiologic relationship between exposure to organochlorines (as estrogen analogues) and the increased risk of breast cancer.{Krieger 1994, Wolff 1993}

Cervical cancer incidence was significantly increased in all women and in both subpopulations; in the SMR study, Cervical cancer was insignificantly increased compared to the Florida population but not the CORPS population. The fact that Cervical cancer was only increased in the cancer incidence and not the mortality study is consistent with existing excellent screening and treatment availability. A significantly increased risk of Cervical cancer with increased number of years of exposure was seen. Very little has been published on female pesticide applicators in general; therefore, although a small subpopulation, these findings are of interest and deserve to be studied further.{Alavanja 1994, Hoar Zahm 1993, McDuffie 1994}

2.4. Private (Farmers) vs Commercial and Public Applicators

With regards to the comparison of licensure category, both licensure subcategories have a significantly elevated risk for both Prostate and Testicular cancer incidence but not mortality. As discussed in Chapter Two, Prostate cancer has been found to be elevated in farmers in multiple studies, while the elevation for incident testicular cancer was seen in Swedish pesticide applicators by Wiklund as well as limited elevated mortality in other groups. {Wiklund 1986, McDowall 1984, Blair 1983, Alberghini 1991, Alavanja 1989, Coggon 1986, Cantor 1990, Swaen 1992} As reviewed in Chapter Two, many of the pesticide applicator studies have been cancer mortality rather than cancer incidence studies. This is important since both Testicular and Prostate cancers have much higher incidence rates than mortality rates due to excellent treatment available for the former and the general indolence of the latter. This does not explain why the subpopulations would have different mortality rates but similar incidence rates, unless the cancers are more aggressive in the licensure subcategories, or there are access to care issues, possibly a diagnostic bias, or relative lack of competing causes of death.

As opposed to the mortality study, Eye and Bone cancers were elevated in both licensure subcategories, more strongly among the Commercial and Public applicators. Again, the small numbers of cancer cases make interpretation difficult. Insignificant but elevated risks for Hodgkin's Disease was only seen in the Private applications. Insignificant but elevated risks for Bone, Brain, and

Leukemia death, but not cancer incidence, were shared by both licensure subpopulations.

Finally, as opposed to the increased risk for lung cancer seen among several cohorts of pesticide applicators (including a separate cohort in Florida), lung cancer incidence was insignificantly decreased among the Commercial and Public pesticide applicators.{Barthel 1986, Blair 1983, Pesatori 1994, Wang 1979}

2.6. Exposure

The most difficult findings to interpret in these analyses concern the cumulative occupational pesticide exposure as measured by: calendar year of first exposure, number of years of exposure, and age at first exposure. As per Checkoway *et al* (1989) and others, if a positive dose-response relationship exists between pesticide exposure and various causes of mortality or cancer incidence, then there should be: decreasing risk with more recent calendar year of licensure; increasing risk with increased years of licensure; and an increased risk with earlier age at licensure. Obviously, age is the most important confounder in these dose-response analyses; however, in the SMR, SIR and the Cox proportional hazard analyses, age is very tightly controlled.

For overall mortality and cancer incidence, as well as several other specific causes of mortality and cancer incidence including Prostate cancer, an increased risk for earlier calendar year of licensure was found consistently in the analyses, suggesting a positive dose-response with exposure. However, an inverse dose-response relationship (ie. the risk for death decreased with increasing number of years of exposure) was found for the number of years exposed in all the analyses. This suggests a paradoxical dose-response relationship, inconsistent with the possibility of associating occupational pesticide exposure with risk of disease.

One possible explanation for the apparently contradictory dose-response measurements is that this cohort is relatively young and has not yet had time to develop its cancer incidence and mortality profile. As possible supporting evidence (**Table 10**), is the concentration of the vast majority of the deaths (72%) and the incident cases of cancer (68%) in the earliest subcohort (32% of the people) licensed from 1975-1979. Subsequent subcohorts are younger with less exposure time, ie. an inadequate latency period for the risk profile to have developed..

Another contributing factor may be relatively recent changes in cancer survival. Although there is no strong dose-response relationship for mortality (**Table 31**) with the number of years licensed, there is some suggestion of a dose-response relationship for Prostate, Testicular and Cervical cancer incidence (**Table 44**) with increasing years of exposure, especially for the earliest subcohort from 1975-1979. As noted above, it is possible that screening and treatment advances over the past 20 years may have caused the increased incidence without a concomitant increase in mortality, especially for these three cancer types. In other words, people are now more likely to be diagnosed and treated for these particular cancers, but die of other causes of death.

Another issue which should be raised is the possibility of exposure misclassification. The licensure system (and the cohort) began artificially in 1975 with the EPA-mandated program, although many of the Restricted List Pesticides had been used for years, presumably by many of the same people who subsequently licensed. Therefore, the earliest subcohorts of the licensed applicators probably represents a mixture of people, some with significant past pesticide exposure and some with none. In the earliest subcohort (**Table 10**), 89% of the people who died officially had 8 or less years of exposure, but they could have been exposed for many years prior to initiation of the licensure system. Subpopulation analyses looking at the 1980-84 subcohort do not indicate any significantly increased risks; however, the numbers of cases of death and incident cancer are still small. Given the younger age and decreased exposure of this subcohort, it will probably be at least a decade before appropriate latency is reached. Furthermore, over the past 20 years, occupational pesticide exposures have probably decreased due to increasing enforcement and use of personal protective equipment and more selective use of pesticides.

With regards to the third exposure variable, age at first licensure is the least precise of the three exposure variables since it inherently assumes that persons who enter a cohort at an early age are more likely to stay in the cohort for a longer period of time and thus be exposed longer. The correlation coefficients for this cohort showed very little correlation between age at first licensure and the other two exposure variables (**Table 11**); therefore, these basic assumptions are questionable. For the SMR and the SIR (**Tables 32 and 45**), there was a consistently increasing risk with increasing age of first licensure, despite controlling for age, a paradoxical dose-response relationship. It should be noted that the risk of cancer incidence or mortality in the analyses stratified by age at first entry into the cohort was less in general than the Florida population comparison group.

On the other hand, in the Cox proportional hazard model (**Tables 37-37 and 48-51**), increasing age at first licensure was associated with a significantly decreased risk of either mortality or cancer incidence for the diseases examined. As opposed to the SMR and the SIR analyses, the Cox proportional hazard model does not use an outside comparison group. As seen in **Table 10**, this particular cohort has two important populations which can affect this variable: a large number of relatively young people with very little exposure (the majority concentrated in the more recent subcohorts), and an older group of heavily exposed apparently healthy survivors group (20% of the earliest cohort survived with 16+ years of exposure). The impact of this latter group is probably the reason for the paradoxical association of decreasing risk with increasing years of exposure, as well as the decreasing risk with increasing age at first exposure, found in all the Cox analyses.

Therefore, given the lack of correlation with the other exposure variables, and the skewed age and exposure distributions of the cohort, as well as possible over-controlling for age in the Cox proportional hazard model when age is the outcome variable, it is probable that age at first licensure is not an appropriate measure of exposure in the analysis of this cohort. As discussed above, the issues of exposure misclassification (especially the probable inclusion of previously exposed people), as well as the predominantly young age of the cohort, can be postulated to explain the apparently paradoxical dose-response relationship of the other two exposure variables.

3.0. Data Limitations

As discussed above, these analyses suffer from many of the data limitations seen in previous epidemiologic studies of pesticide exposed workers. As with many previous studies, individual and cohort-specific confounding (such as smoking), and detailed pesticide exposure information were not obtained for this cohort. Additional limitations include issues of the healthy worker effect, exposure measures, and loss to follow-up.

The use of the Florida population as the major comparison population is appropriate for geographic and logistic considerations. However, in occupational studies, the use of a general population as a comparison population must inherently raise the issue of the previously discussed healthy worker effect, even for chronic diseases such as cancer.{Checkoway 1989, Monson 1990, Breslow 1987, Kleinbaum 1988} The use of comparison worker populations (such as the National Cancer Institute

(NCI)-National Institute of Occupational Safety and Health (NIOSH) CORPS) when they are available is always preferable. However, there are also inherent limitations with the CORPS dataset, including the fact that these are pooled data from studies of worker populations with known carcinogenic exposures which have not been updated since the mid 1980s. Thus, these comparison worker populations can introduce their own biases. Furthermore, especially in the case of the CORPS SMR data, it would appear that these are not particularly healthy working populations given the similarity of the results to the general Florida SMRs.

As discussed above, the exposure measures are relatively crude and non-specific, based on the licensure calendar year and years of exposure, as well as licensure subgroup and certification subcategory. Therefore, licensure serves as a surrogate measure for exposure; this assumes that the applicator uses the restricted chemicals throughout the 4-year licensure period; that in the case of older persons, the applicator did not apply prior to the beginning of the licensure program (ie. prior to the beginning of the cohort); that the applicator is actually applying the restricted use pesticides rather than acting in a purely supervisory role since each licensed applicator may oversee up to 15 other individuals. Furthermore, licensure allows the acquisition and use of over 125 different restricted use pesticides; there are no individual pesticide exposure data, beyond certain certification categories (such as "aquatic" certification). There are also no individual or even group measures of important confounding exposure variables, such as tobacco use or even non-occupational pesticide exposure. The lack of these data is an important limitations on the conclusions which can be drawn from these analyses.

As discussed in Chapter Three, date of birth information was not available for 2600 individuals in the cohort; this information was not collected by the State nor was it found through the multiple data linkages performed. The majority of these 2600 individuals (>95%) were licensed prior to 1980, had minimal exposure, and are assumed to be alive since they were not located by multiple data linkages. Nevertheless, these persons were ultimately excluded from the Master Database cohort because date of birth information is essential for the statistical analyses performed. If these persons are predominantly alive, this would decrease the paradoxical dose-response effects seen in the SIR and SMR analyses when evaluating number of years licensed and age at first licensure; if these persons are predominantly dead, then the paradoxical effects would be even greater. Regardless, the loss of these persons to the cohort is an important limitation to these analyses and conclusions.

4.0. Conclusions

In general, this is a healthy cohort of men and women who have been relatively recently exposed to restricted-use pesticides through their occupation. Compared to the general Florida population and to a worker comparison group, these pesticide applicators are less likely to develop incident cancer, or to die from variety of cause-specific chronic diseases, including the cardiovascular diseases. In particular, these workers are less likely to develop or die from the tobacco- and ethanol use-associated chronic diseases. With the exception of certified aerial applicators, these pesticide applicators are also less likely to die from external causes of death.

The most interesting findings among the male applicators are the increased Testicular and Prostate cancer incidence and mortality rates. These increases have been reported in the past, but with the emphasis on mortality studies, Prostate cancer has been seen only with farmers and Testicular cancer only with pesticide applicators. This study raises the issue that both Testicular and Prostate cancers are increased among both farmers and pesticide applicators if cancer incidence rather than mortality is examined, suggesting that shared exposures are involved. The differences in mortality rates across licensure category need to be examined further, including issues of differential tumor aggressivity and access to care.

Previously reported elevations in Soft Tissue Sarcoma and non Hodgkin's Lymphoma reported in herbicide exposed workers were not seen in this cohort. The relatively short exposure period and the rarity of Soft Tissue Sarcomas, as well as the lack of exact exposure data, may be important issues in this finding. Elevations in Leukemia and Brain cancer reported in other pesticide-exposed worker groups were found only in the mortality study, not the incidence study; this suggests possible increased tumor aggressivity or access-to-care issues. Finally, increases in Lung cancer reported in other pesticide applicator groups, including a separate Florida cohort, were not observed in this cohort.

Only a relatively small number of female applicators were present in the cohort, with even less exposure than their male colleagues. Nevertheless, the lack of Breast cancer risk in these possibly organochlorine-exposed individuals and the significant increase in Cervical cancer incidence are important findings which deserve further exploration.

Finally, although the exposure information did not consistently show an association with disease and pesticide exposure, the data limitation issues discussed above should be taken into account in the interpretation of these data. Follow up of this cohort in 10 or more years would be recommended to adequately evaluate the effects of exposure.

References

Ahlbom A. Biostatistics for Epidemiologists. Boca Raton: Lewis Publishers. 1993.

Alavanja MCR, Blair A, Master MN. Cancer mortality in the US flour industry. J Nat Cancer Inst. 1990;82:840-848.

Alavanja MCR, Blair A, Merkle S, Teske J, Eaton B, Reed B. Mortality among forest and soil conservationists. Arch Env Health. 1989;44:94-101.

Alavanja MCR, Akland G, Baird , *et al.* Cancer and non cancer risk to women in agriculture and pest control: the Agricultural Health Study. J Occ Med. 1994;36:1247-1250.

Alavanja MCR, Blair A, Merkle S, Teske J, Eaton B. Mortality among agricultural extension agents. Am J Ind Med. 1988;14:167-176.

Alberghini V, Luberto F, Gobba F, Morelli C, Gori E, Tomesani N. Mortality among male farmers licensed to use pesticides. Med Lav. 1991;82:18-24.

Amoateng-Adjepong Y, Sathiakumar N, Delzell E, Cole P. Mortality among workers at a pesticide manufacturing plant. J Occ Med. 1995;37:471-478.

Anon. Computerized Occupational Referent Population System (CORPS) Documentation. Rockville, MD: National Cancer Institute, National Institute of Occupational Safety and Health, April 1992.

Asp S, Riihimaki V, Hernberg S, Pukkala E. Mortality and cancer morbidity of Finish Chlorophenoxy herbicide applicators: an 18 year prospective follow up. Am J Ind Med. 1994;26:243-253.

Axelson O, Sundell L, Andersson K, Edling C, Hogstedt C, Kling H. Herbicide exposure and tumor mortality. Scand J Work Environ Health. 1980;6:73-9.

Axelson O, Sundell L. Herbicide exposure, mortality, and tumor incidence: an epidemiologic investigation of Swedish railroad workers. Scand J Work Env Health. 1974;11:21-8.

Axelson O. Pesticides and cancer risks in agriculture. Med Oncol Tumor Pharmacother. 1987;4:207-17.

Balarajan R. Malignant lymphomas in agricultural and forestry workers in England and Wales. Public Health. 1988; 102:585-592.

Barthel E. Cancer risk in pesticide exposed agricultural workers. Arch Geschwulstforsch 1981;51:579-585.

Barthel E. High incidence of lung cancer in persons with chronic professional exposure to pesticides in agriculture. Z Erkrank Atm Org. 1976;46:266-74.

Barthel E. Increased risk of lung cancer in pesticide-exposed male agricultural workers. J Tox Env Health. 1981;8:1027-40.

Barthel E. Erhohte Mortalitat an Osophaguskrebs, Magenkrebs, und Hautmelanom bei Pestizid exponierten Schadlingsbekampfern in der DDR. Arch Geschwulstforsch. 1985;55:481-8.

Barthel E. Pesticides and cancer risk. Z Erkrank Atm Org. 1983;161:257-65.

Barthel E. Retrospective cohort study on cancer frequency in pesticide exposed male pest control workers. Z Erkrank Amt Org. 1986;166:62-8.

Beaumont JJ, Goldsmith DF, Morrin LA, Schenker MB. Mortality in agricultural workers after compensation claims for respiratory disease, pesticide illness, and injury. J Occ Med. 1995;37:160-169.

Betta A, Maranelli G. Dal Ri C. Pesticide Immunotoxicity. Med Lavoro. 1989;80:381-389.

Blain PG. Aspects of pesticide toxicology. Adv Drug React Acute Poison Rev. 1990;9:37-68.

Blair A, Grauman DJ, Lubin JH, Fraumeni JF. Lung cancer and other causes of death among licensed pesticide applicators. J Nat Cancer Inst 1983;71:31-37.

Blair A, Malker H, Cantor KP, Burmeister L, Wiklund k. Cancer among farmers. Scand J Work Env Health. 1985;11:397-407.

Blair A, Grauman DJ, Lubin JH, Fraumeni JF. Lung cancer and other causes of death among licensed pesticide applicators. J Nat Cancer Inst. 1983;71:31-37.

Blair A. Cancer risks associated with agriculture: epidemiologic evidence. Basic Life Sciences. 1982;21:93-111.

Blair A, Hoar Zahm S. Methodologic issues in exposure assessment for case control studies of cancer and herbicides. Am J Ind Med. 1990a;18:285-93.

Blair A, Hoar Zahm S. Herbicides and cancer: a review and discussion of methodologic issues. Recent Results Cancer Res. 1990b;120:132-145.

Blair A, Hayes HM. Mortality patterns among US veterinarians: 1947-77. Int J Epi. 1982;11:391-7.

Blair A, Dosemeci M, Heineman E. Cancer and other causes of death among male and female farmers from 23 states. Am J Ind Med. 1993;23:729-742.

Bloemen LJ, Mandel JS, Bond GG, Pollock AF, Vitek RP, Cook RR. An update of mortality among chemical workers potentially exposed to the herbicide 2,4-dichlorophenoxyacetic acid and its derivatives. J Occ Med. 1993;35:1208-1032.

Blondell JM. Problems encountered in the design of epidemiologic studies of cancer in pesticide users. Med Lavoro. 1990;81:524-529.

Bolognesi C, Parrini M, Bonassi S, Ianello G, Salanitto A. Cytogenetic analysis of a human population occupationally exposed to pesticides. Mutat Res. 1993a;285:239-249.

Bolognesi C, Parrini M, Merlo F, Bonassi S. Frequency of micronuclei in lymphocytes in a group of floriculturists exposed to pesticides. J Tox Env Health. 1993b;40:405-411.

Bond P, ed. Occupational Cancer Epidemiology (Recent Results in Cancer Research 120). Berlin: Springer-Verlag, 1990.

Borzsonyi M, Torok G, Pinter A, Surjan A. Agriculturally related carcinogenic risk. IARC Scientific Publications. 1984;56:465-86.

Botham PA. Are pesticides immunotoxic? Adv Drug React Acute Poison Rev. 1990;9:91-101.

Boxer PA, Burnett C, Swanson N. Suicide and occupation: a review of the literature. J Occ Med. 1995;37:441-452.

Brender JD, Suarez L. Paternal occupation and anencephaly. Am J Epid. 1990;131:517-521.

Breslow NE, Day NE. Statistical Methods in Cancer Research Volume II: the Design and Analysis of Cohort Studies. Lyon: International Agency for Research on Cancer, 1987.

Breslow NE, Day NE. Statistical Methods in Cancer Research Volume I: The Analysis of Case Control Studies. Lyon: International Agency for Research in Cancer, 1980.

Breslow NE, Lubin JH, Marek P *et al*. Multiplicative models and cohort analysis. J Am Stat Assoc 1983;78:1-12.

Brown, LM, Blair A, Gibson R, *et al.* Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. Cancer Res. 1991;50:6585-91.

Brown LM, Burmeister LF, Everett GD, Blair A. Pesticide exposures and multiple myeloma in Iowa men. Cancer Causes Control. 1993;4:153-156.

Brownson RC, Alavanja MCR, Chang JC. Occupational risk factors for lung cancer among non smoking women: a case control study in Missouri (United States). Cancer Causes Cont. 1993:4:449-454.

Bueno de Mesquita HB, Doornbos G, van der Kuip D, Kogevinas M, Winkelman R. Occupational exposure to phenoxy herbicides and chlorophenols and cancer mortality in the Netherlands. Am J Ind Med. 1993;23:289-300.

Burmeister LF. Cancer in Iowa Farmers: recent results. Am J Ind Med. 1990;18:295-301.

Burmeister LF, Morgan DP. Mortality in Iowa farmers and farm laborers, 1971-1978. JOM. 1982;24:898-900.

Burmeister LF, Everett GD, Van Lier SF, Isacson P. Selected mortality and farm practices in Iowa. Am J Epi. 1983;118:72-7.

Burrell R. Human Immune Toxicity. Molec Aspects Med. 1993;14:1-81.

Butterfield PG, Valanis, BG, Spencer PS, Lindeman CA, Nutt JG. Environmental antecedents of young-onset Parkinson's disease. Neurology. 1993;43:1150-1158.

Cantor KP, Blair A, Everett G, *et al.* Pesticides and other agricultural risk factors for Non Hodgkins lymphoma among men in Iowa and Minnesota. Cancer Res. 1992;52:2447-2455.

Cantor KP, Booze CF. Mortality among aerial pesticide applicators and flight instructors. Arch Envir Health. (article originally printed in 1990;45:295-302) 1991;46:10-116.

Carbonell E, Puig M, Xamena N, Creus A, Marcos R. Sister chromatid exchange in lymphocytes of agricultural workers exposed to pesticides. Mutagen. 1990;5:403-405.

Carbonell E, Xamena N, Creus A. Cytogenetic monitoring in a Spanish group of agricultural workers exposed to pesticides. Mutagen. 1993;8:511-517.

Carlson ML, Petersen GR. Mortality of California agricultural workers. JOM. 1978;20:30-32.

Cellini A, Offidani A. An epidemiologic study on cutaneous diseases of agricultural workers authorized to use pesticides. Dermatol. 1994;189:129-132.

Checkoway H, Pearce NE, Crawford-Brown DJ. Research Methods in Occupational Epidemiology. New York: Oxford University Press, 1989.

Clayton D, Hills M. Statistical Models in Epidemiology. Oxford: Oxford University Press, 1993.

Checkoway H, Waldman GT. Assessing the possible extent of confounding in occupational case-referent studies. Scand J Work Environ Health 1985;11:131-3.

Chester G. Evaluation of agricultural worker exposure to, and absorption of, pesticides. Ann Occ Hyg. 1993;37:509-523.

Ciccone G, Mirabelli D, Levis A, *et al.* Myeloid Leukemias and myelodysplastic syndromes: chemical exposure, histologic subtype and cytogenetics in a case control study. Cancer Genet Cytogenet. 1993;68:135-139.

Coggon D, Pannett B, Winter PD, Acheson D, Bonsall J. Mortality of workers exposed to 2 methyl 4 chlorophenoxyacetic acid. Scand J Work Env Health. 1986;12:488-54.

Coggon D, Pannett B, Winter P. Mortality and incidence of cancer at four factories making phenoxy herbicides. Brit J Ind Med. 1991;48:173-178.

Cordes DH, Foster Rea D, eds. Health Hazards of Farming. Occupational Medicine: State of the Art Reviews. 1991;6:327-550.

Corrao G, Calleri M, Carle F, Russo R, Bosia S, Piccioni P. Cancer risk in a cohort of licensed pesticide users. Scand J Work Env Health. 1989;15:203-209.

Council on Scientific Affairs. Cancer risk of pesticides in agricultural workers. JAMA. 1988;260 (7):959-66.

Cox DR. Partial likelihood. Biometrika 1975;62:269-276.

Coye MJ. The health effects of agricultural production. J Pub Health Policy. 1985;6:349-368.

Cuneo A, Fagioli F, Pazzi I, *et al.* Morphologic, immunologic and cytogenetic studies in acute myeloid leukemia following occupational exposure to pesticides and organic solvents. Leukemia Res. 1992;16:789-796.

Daniel V, Huber W, Bauer K, Opelz G. Impaired in vitro lymphocyte responses in patients with elevated pentachlorophenol blood levels. Arch Env Health. 1995;50:287-292.

Daniell W, Barnhart S, Demers P, Costa LG, Eaton DL, Miller M, Rosenstock L. Neuropsychological performance among agricultural pesticide applicators. Env Res. 1992;59:217-228.

Davies JE. Neurotoxic concerns of human pesticide exposures. Am J Ind Med. 1990;18:327-331.

Davis JR, Brownson RC, Garcia R, Bentz BJ, Turner A. Family pesticide use and childhood brain cancer. Env Contam Tox. 1993;24:87-92.

Davis DL, Blair A, Hoel DG. Agricultural exposures and cancer trends in developed countries. Env Health Persp. 1992;100:39-44.

De Ferrari M, Artuso M, Bonassi S, *et al.* Cytogenetic biomonitoring of an Italian population exposed to pesticides. Mutat Res. 1991;260:105-113.

Decoufle P, Thomas TL, Pickle LW. Comparison of the proportionate mortality ratio and standardized mortality ratio risk measures. Am J Epi 1980;111:263-269.

Delzell W, Grufferman S. Mortality among white and nonwhite farmers in North Carolina, 1976-1978. Am J Epid. 1985;121:391-402.

Demers PA. Brain neoplasms. In: Textbook of Clinical Occupational and Environmental Medicine. 1st Ed. Rosenstock L, Cullen M, eds. Orlando: Saunders, 1994. pg. 599-603.

Desi I, Nehez M, Palotas M, Tempfli A, Hogye A, Vetro G. Experience of health status surveillance of pesticide workers in Hungary. Med Lavoro. 1990;81:517-523.

Dewailly E, Ayotte P, Brisson J. Protective effect of breast feeding on breast cancer and body burden of carcinogenic organochlorines [Letter]. J Nat Cancer Inst. 1994;86:1255.

Dich H, Wiklund K. The use of phenoxy acid herbicides in Sweden. Chemosphere. 1989;18:391-394.

Ditraglia D, Brown DP, Namekata T, Iverson N. Mortality study of workers employed at organochlorine pesticide manufacturing plants. Scand J Work Env Health. 1981;7:140-6.

Doe JE, Paddle GM. The evaluation of carcinogenic risk to humans: occupational exposures in the spraying and application of insecticides. Regul Toxicol Pharmacol. 1994;19:297-308.

Donna A, Crosignani P, Robutti F, *et al.* Triazine herbicides and ovarian epithelial neoplasms. Scand

J Work Env Health. 1989;15:47-53.

Ducatman AM. Dimethylformamide, metal dyes and testicular cancer. Lancet. 1989;i:911.

Ducatman AM, Crawl JR, Conwill DE. Cancer clusters, causation and common sense. Chemtech. 1988;18:204-210.

Dulout FN, Pastori MC, Olivero OA, *et al.* SCE and chromosomal aberrations in a population exposed to pesticides. Mutat Res. 1985;143:237-244.

Durham WF, Williams CH. Mutagenic, teratogenic and carcinogenic properties of pesticides. An Rev Entomology. 1972;17:123-48.

Edwards JW, Priestly BG. Effect of occupational exposure to Aldrin on urinary d-glucaric acid, plasma dieldrin and lymphocyte SCE. Int Arch Occ Env Health. 1994;66:229-234.

El Zayadi A, Khalil A, El Samny N, Hamza MR, Selim O. Hepatic angiosarcoma among Egyptian farmers exposed to pesticides. Hepato-gastroenterol. 1986;33:148-50.

El Sebae AH. Special problems experienced with pesticide use in developing countries. Regul Toxicol Pharmacol. 1993;17:287-291.

EPA & US Dept of Agriculture. Applying Pesticides Correctly: a Guide for Private and Commercial Applicators. Gainesville, FL: Cooperative Extension Service, University of Florida, Institute of Food and Agricultural Sciences. 1980.

Eriksson M, Karlsson M. Occupational and other environmental factors and multiple myeloma: a population based case control study. Brit J Ind Med. 1992;49:95-103.

Fagioli F, Cuneo A, Piva N, *et al.* Distinct cytogenetic and clinicopathologic features in acute myeloid leukemia after occupational exposure to pesticides and organic solvents. Cancer. 1992:70:77-85.

Falck F, Ricci A, Wolff MS, Godbold J, Deckers P. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relationship to breast cancer. Arch Environ Health. 1992;47:143-46.

Falk JHL, Thompson SJ, Kotin P. Carcinogenic potential of pesticides. Arch Env Health. 1965;10:847-58.

Fenske RA, Curry PB, Wandelmaier F, Ritter L. Development of dermal and respiratory sampling procedures for human exposure to pesticides in indoor environments. J Exp Anal Env Epid. 1991;1:11-30.

Ferrer A, Cabral JPR. Epidemics due to pesticide contamination of food. Food Additives Contaminants. 1989;6 Suppl 1:S95-S98.

Figa-Talamanca I, Mearelli I, Valente P, Bascherini S. Cancer mortality in a cohort of rural licensed pesticide users in a province of Rome. Int J Epid. 1993a;22:579-583.

Figa-Talamanca I, Mearelli I, Valente P. Mortality in a cohort of pesticide applicators in an Urban setting. Int J Epid. 1993b;22:674-676.

Fleiss JL. Statistical Methods for Rates and Proportions. New York: John Wiley and Sons, 1981.

Fleming LE, Timmeny W. Aplastic Anemia and Pesticide Exposure: An Etiologic Association?. J Occupational Med. 1993;35:1106-1116

Fleming LE, Beckett W. Occupational Gastrointestinal Disease. In: Environmental and Occupational Medicine, 2nd Ed., Rom WN, ed. Boston: Little and Brown, 1992.

Fleming LE, Mann JB, Bean JA, Briggle T, Sanchez Ramos J. Organochlorine Pesticides and Parkinsons Disease. Ann Neurology. 1994a;36:100-103.

Fleming LE. Cancers of the reproductive organs. In: Textbook of Clinical Occupational and Environmental Medicine, 1st Ed. Rosenstock L, Cullen M, eds. Orlando: Saunders, 1994. pg. 591-599.

Forastiere F, Quercia A, Micelli M, *et al.* Cancer among farmers in central Italy. Scand J Work Env Health. 1993;19:382-389.

Forget G. Pesticides and the third world. J Tox Env Health. 1991;32:11-31.

Forrester BG, Nethercott J. Skin Cancers. In: Textbook of Clinical Occupational and Environmental

Medicine. 1st Ed. Rosenstock L. Cullen M. eds. Orlando: Saunders. 1994. pg. 603-615.

Fox AJ. Collier PF. Low mortality rates in industrial cohort studies due to selection of work and survival in the industry. Br J Prev Soc Med 1976;30:225-30.

Gallagher RP, Threlfall WJ, Jefferies E, Band PR, Spinell J, Coldman AJ. Cancer and aplastic anemia in British Colombia Farmers. JNCI. 1984;72:1311-15.

Garabrant DH, Held J, Langholz B, Peters JM, Mack TM. DDT and related compounds and the risk of pancreatic cancer. J Nat Cancer Inst. 1992;84:764-771.

Garry VF, Griffith J, Danzl TJ, *et al.* Human genotoxicity: pesticide applicators and phosphine. Science. 1989;246:251-55.

Garry VF, Nelson RL, Griffith J, Harkins M. Preparation for human study of pesticide applicators: sister chromatid exchanges and chromosomal aberrations in cultured human lymphocytes exposed to selected fumigants. Terat Carcinog Mutagen. 1990;10:21-9.

Garry VF, Danzl TJ, Tarone R, *et al.* Chromosome rearrangements in fumigant appliers: possible relationship to non Hodgkins lymphoma risk. Cancer Epid Biomark Preven. 1992;1:287-291.

Gilbert ES. Some confounding factors in the study of mortality and occupational exposures. Am J Epi 1982;116:177-88.

Godon D, La Joie P, Thouez J-P. Morality due to cancers of the brain, lymphatics and leukemia with the use of pesticides, in agriculture, in Quebec (1976-1985). Canad J Pub Health. 1991;82:174-180.

Golbe LI. Risk factors in young-onset Parkinson's Disease. Neurology. 1993; 43:1641-1643

Gold E, Gordis L, Tonascia J, Szklo M. Risk factors for brain tumors in children. Am J Epidemiology. 1979;109:309-18.

Gordon JE, Shy CM. Agricultural chemical use and congenital cleft lip and/or palate. Arch Env Health.1981;36:213-221.

Green LM. A cohort mortality study of forestry workers exposed to phenoxy acid herbicides. Br J Ind Med. 1991;48:234-238.

Green LM. Mortality Analysis of Ontario Hydro Forestry Tradesmen Cohort. Toronto, Ontario: Ontario Hydro Health & Safety Division, 1986.

Hanchette CL, Schwartz GG. Geographic patterns of prostate cancer mortality: evidence for a protective effect of ultraviolet radiation. Cancer. 1992;70:2861-2869.

Hansen ES, Hasle H, Lander F. A cohort study on cancer incidence among Danish gardeners. Am J Ind Med. 1992;21:651-660.

Hardell L. Relation of soft-tissue sarcoma, malignant lymphoma and colon cancer to phenoxy acids, chlorophenols and other agents. Scand J Work Environ Health. 1981;7:119-30.

Hardell L, Sandstrom A. Case control study: soft tissue sarcomas and exposure to phenoxyacetic acids or chlorphenols. Br J Cancer. 1979;39:711-7.

Hayes WJ, Laws ER, eds. Handbook of Pesticide Toxicology. San Diego: Academic Press. 1991.

He F. Biological monitoring of occupational pesticide exposure. Int Arch Occ Env Health. 1993;65:S69-S76.

Hearn S, Ott MG, Kolesar RC, Cook RR. Mortality experience of employees with occupational exposure to DBCP. Arch Env Health. 1984;39:49-55.

Hemminki K, Saloniemi I, Salonen T, Partanen T, Vainio H. Childhood cancer and parental occupation in Finland. J Epid Comm Health. 1981;35:11-15.

Hill AB, Faning EL, Perry K, *et al.* Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic. Brit J Ind Med. 1948;5:1-6.

Hoar Zahm S, Weisenburger DD, Saal RC, Vaught JB, Babbitt PA, Blair A. The role of agricultural pesticide use in the development of Non Hodgkins lymphoma in women. Arch Env Health. 1993;48:353-358.

Hoar SK, Blair A, Holmes FF, *et al.* Agricultural herbicide use and risk of lymphoma and soft tissue sarcoma. JAMA. 1986;256:1141-7.

Hogstedt B, Kolnig A-M, Mitelman F, Skerfving S. Cytogenetic study of pesticides in agricultural work. Hereditas. 1980;92:177-178.

Holly EA, Aston DA, Ahn DK, Kristiansen JJ. Ewings Bone Sarcoma, paternal occupational exposure, and other factors. Am J Epid. 1992;135:122-129.

Hubble JP, Cao T, Hassanein RES, Neuberger JS, Koller WC. Risk factors for Parkinson's Disease. Neurology. 1993;43:1693-1697

Hunter DJ, Kelsey KT. Pesticide Residues and breast cancer: the harvest of a silent spring? J Nat Cancer Inst. 1993;85:598-599.

IARC. Occupational exposure in insecticide application and some pesticides. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. 1991;53:1-587.

IARC. Cancer epidemiology of pesticide manufacturers, formulators and users. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. 1983;30:37-56.

Ibrahaim MA, Bond GG, Burke TA, *et al.* Weight of the evidence on the human carcinogenicity of 2,4 D. Env Health Persp. 1991;96:213-222.

Igbedioh SO. Effects of agricultural pesticides on humans, animals and higher plants in developing countries. Arch Env Health. 1991;46:218-224.

Innes JRM, Ulland BM, Valerio MG et al. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. J Nat Cancer Inst. 1969;42:1101-14.

Jamall IS, Davis D. Chemicals and environmentally caused diseases in developing countries. Inf Dis Clinic N Am. 1991;5:365-375.

Jeyaratnam J. Health problems of pesticide usage in the Third World. Br J Ind Med. 1985;42:505-506.

Jeyaratnam J, Maroni M. Organophosphorus Compounds. Tox. 1994;91:15-27.

Jeyaratnam J. Acute pesticide poisoning: a major global health problem. Wld Hlth Statist Quart. 1990;43:139-44.

Jeyaratnam J, Lun KC, Phoon WO. Survey of acute pesticide poisoning among agricultural workers in four Asian Countries. Bull WHO. 1987;65:521-527.

Johnson ES. Association between soft tissue sarcomas, malignant lymphomas, phenoxy herbicides/chlorophenols: evidence from occupational cohort studies. Fund Appl Tox. 1990;14:219-234.

Johnson ES. Association between soft tissue sarcomas, malignant lymphomas and phenoxy herbicides/chlorophenols: evidence from occupational cohort studies. J Fund & Appl Tox. 1989;14:219-34.

Johnson ES, Fischman HR, Matanoski GM, Diamond E. Cancer mortality among white males in the meat industry. JOM. 1986;28:23-32.

Johnson CC, Feingold M, Tilley B. A meta-analysis of exposure to phenoxy acid herbicides and chlorophenols in relation to risk of soft tissue sarcoma. Arch Occup Env Health. 1990;62:513-520.

Kahn HA, Sempos CT. Statistical Methods in Epidemiology. New York: Oxford University Press, 1989.

Kay K. Occupational cancer risks for pesticide workers. Env Res. 1974;7:243-71.

Kelly SJ, Guidotti TL. Phenoxyacetic acid herbicides and chlorophenols and the etiology of lymphoma and soft tissue neoplasms. Pub Health Rev. 1989;17:1-37.

Kelsey JL, Whittemore AS, Evans AS, Thompson WD. Methods in Observational Epidemiology. New York: Oxford University Press, 1996.

Kida M, Yoshimura K. Mutagenicity and teratogenicity on the residual agricultural chemicals [Abstract]. Jap Teratol Soc Abstract. 1993;48:511.

King WE. Farming and Cancer. Ontario, Canada: Canadian Centre for Occupational Health and

Safety, 1986.

Kleinbaum DG, Kupper LL, Muller KE. Applied Regression Analysis and Other Multivariable Methods. Boston: PWS-KENT Publishing, 1988.

Kogevinas M, Saracci R, Winkelmann R, *et al.* Cancer incidence and mortality in women occupationally exposed to chlorophenoxy herbicides, chlorophenols, and dioxins. Cancer Causes Control. 1993;4:547-553.

Kogevinas M, Kauppinen T, Winkelman R, *et al.* Soft tissue sarcomas and Non Hodgkins lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: two nested case control studies. Epid. 1995;6:396-402.

Kolatch AJ. Dictionary of First Names. NY: Pedigree Books, 1990.

Kourakis A, Mouratidou M, Kokkinos G, *et al.* Frequencies of chromosomal aberrations in pesticide sprayers working in plastic greenhouses. Mutat Res. 1992;279:145-148.

Kreiger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, Orentreich N. Breast cancer and serum organochlorines: a prospective study among white, black and Asian women. J Nat Cancer Inst. 1994;86:589-599.

Maroni M, Fait A. Health effects in man from long term exposure to pesticides. Tox. 1993;78:1-180.

Lang L. Are pesticides a problem? Env Health Persp. 1993;101:578-583.

Leiss JK, Savitz DA. Home pesticide use and childhood cancer: a case control study. Am J Pub Health. 1995;85:249-252.

Levine RS, Dolin P. Pregnancy and breast cancer: a possible explanation for the negative association. Med Hypotheses. 1992;38:276-283.

Levine RS, Doull J. Global estimates of acute pesticide morbidity and mortality. Rev Environ Contam Toxicol. 1992;129:29-50.

Linet MS, Malker HSR, Chow W-H, *et al.* Occupational risks for cutaneous melanoma among men in Sweden. J Occ Med. 1995;37:1127-1135.

Linnainmaa K. SCE among workers occupationally exposed to phenoxy acid herbicides 2,4 D and MCPA. Terat Carcin Mutagen. 1983;3:269-279.

Littorin M, Attewell R, Skerfving S, Horstmann V, Moller T. Mortality and tumour morbidity among Swedish market gardeners and orchardists. Int Arch Occ Env Health. 1993;65:163-169.

Loevinsohn ME. Insecticide use and increased mortality in rural central Luzon, Philippines. Lancet. 1987;i:1359-1362.

Lowengart RA, Peters JM, Cicioni C, *et al.* Childhood leukemia and parents' occupational and home exposures. JNCI 1987;79:39-46.

Luchtrath H. The consequences of chronic arsenic poisoning among Moselle wine growers. J Cancer Res Clin Oncol 1983;105:173-82.

Lynge E. A follow up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. Br J Cancer. 1985;52:259-270.

Lynge E. Cancer in phenoxy herbicide manufacturing workers in Denmark, 1947-87 -- an Update. Cancer Causes Control. 1993;4:261-272.

Mabuchi K, Lilienfeld AM, Snell LM. Lung cancer among pesticide workers exposed to inorganic arsenicals. Arch Env Health. 1979;34:312-320.

MacMahon B, Monson RR, Wang HH, Zheng T. A second follow-up of mortality in a cohort of pesticide applicators. JOM. 1988;30 (5):429-32.

Maddy KT. Pesticide usage in California and the United States. Agriculture, Ecosystems & Env. 1983;9:159-72.

Maddy KT, Edmiston S, Richmond D. Illness, injuries and deaths from pesticide exposures in California 1949-1988. Rev Env Contam Tox. 1990;114:57-123.

Maroni M, Fait A. Health effects in man from long term exposure to pesticides. Tox. 1993;78:1-180.

Marx JJ, Guernsey J, Emanuel DA, Merchant JA, Morgan DP, Kryda M. Cohort studies of immunologic lung disease among Wisconsin dairy farmers. Am J Ind Med. 1990;18:263-268.

McConnell R. Pesticides and related compounds. In: Textbook of Clinical Occupational and Environmental Medicine, 1st Ed. Rosenstock L, Cullen M, eds. Orlando: Saunders, 1994. pg. 847-865.

McDowall M, Balarajan R. Testicular cancer and employment in agriculture. Lancet. 1984;i:510-511.

McDuffie HH. Women at work: agriculture and pesticides. J Occ Med. 1994;36:1240-1246.

Methner MM, Fenske RA. Pesticide exposure during greenhouse application, Part II. Appl Occ Env Hyg. 1994b;9:567-574.

Methner MM, Fenske RA. Pesticide exposure during greenhouse application, Part I. Appl Occ Env Hyg. 1994a;9:560-566.

Michalek JE, Wolfe WH, Miner JC. Health status of air force veterans occupationally exposed to herbicides in Vietnam. JAMA. 1990;264 (14):1832-36.

Miettinen OS, Wan J-D. An alternative to the PMR. Am J Epi 1981;114:144-148.

Miettinen OS. Standardization of risk ratios. Am J Epi. 1972;96:383-388.

Milham S. Occupational Mortality in Washington State, 1950-1979. Cincinnati, OH: NIOSH, #210-80-0088, October 1983.

Milham S. Occupational Mortality in Washington State 1950-71. Cincinnati: NIOSH, Dept of Health, Education and Welfare, 1976. (HEW Pub # [NIOSH] 76-175-A)

Mills PK, Newell GR, Johnson DE. Testicular cancer associated with employment in agriculture and oil and natural gas extraction. Lancet. 1984;i:207-210.

Monson RR. Occupational Epidemiology. Boca Raton: CRC Press, 1990, second edition.

Monson RR. Observations on the healthy worker effect. JOM 1986;28:425-33.

Morgan DP, Lin LI, Saikaly HH. Morbidity and mortality in workers exposed occupationally to pesticides. Arch Env Contam Tox. 1980;9:349-82.

Morrison HI, Semenciw RM, Morrison D, Magwood S, Mao Y. Brain cancer and farming in western Canada. Neuroepid. 1992;11:267-276.

Morrison HI, Wilkins K, Semenciw R, Mao Y, Wigle D. Herbicides and cancer. J Nat Cancer Inst. 1992;84:1866-1874.

Morrison HI, Wilkins K, Semenciw R, Mao Y, Wigle D. Herbicides and cancer. J Nat Cancer Inst. 1992b;84:1866-1874.

Morrison HI, Semenciw RM, Morrison D, Magwood S, Mao Y. Brain cancer and farming in western Canada. Neuroepid. 1992;11:267-276.

Moses M. Cancer in humans and potential occupational and environmental exposure to pesticides. AAOHN J. 1989;37(3):131-136.

Moses M, Johnson ES, Anger WK, *et al.* Environmental Equity and pesticide exposure. Tox Ind Health. 1993;9:914-959.

Munro IC, Carlo GL, Orr JC, *et al.* A comprehensive, integrated review and evaluation of the scientific evidence relating to the safety of the herbicide 2.4 D. J Am Coll Tox. 1992;11:561-661.

Musicco M, Filippini G, Bordo BM, Melotto A, Morello G, Berrino F. Gliomas and agricultural exposure to carcinogens: a case control study. Am J Epid. 1982;116:782-90.

Musicco M, Sant M, Molinari, *et al.* A case control study of brain gliomas and occupational exposure to chemical carcinogens: the risk to farmers. Am J Epid. 1988;128:778-785.

Nagao M, Sugimura T. Environmental mutagens and carcinogens. Ann Rev Genet. 1978;12:117-59.

National Research Council (NRC). Pesticides in the Diets of Infants and Children. Washington DC: National Academy Press, 1993.

Nehez M, Boros P, Ferke A, *et al.* Cytogenetic examination of people working with agrochemicals in the southern region of Hungary. Reg Tox Pharm. 1988;8:37-44.

Nelson WC, Lykins, MH, Makey J, Newill VA, Finklea JF, Hammer DI. Mortality among orchard workers exposed to lead arsenate spray: a cohort study. J Chron Dis. 1973;26:105-18.

Neutel CI, Johansen HL, Walop W. New data from old: epidemiology and record linkage. Prog Food Nutrit Sci. 1991;15:85-116.

Newcombe HB. Handbook of Record Linkage: Methods for Health and Statistical Studies, Administration, and Business. Oxford: Oxford University Press, 1988.

Notkola VJ, Martikainen P, Leino PI. Time trends in mortality in forestry and construction workers in Finland 1970-85 and impact of adjustment for socioeconomic variables. J Epid Commun Health. 1993;47:186-191.

Nurminen T, Rantala K, Kurppa K, Holmberg PC. Agricultural work during pregnancy and selected structural malformations in Finland. Epid. 1995;6:23-30.

Olsen JH, de Nully Brown P, Schulgen G, Jensen OM. Parental employment at time of conception and risk of cancer in offspring. Eur J Cancer. 1991;27:958-965.

Olshan AF, Teschke K, Baird PA. Paternal occupation and congenital anomalies in offspring. Am J Ind Med. 1991;20:447-475.

Olszyna-Marzys AE. Contaminants in human milk. Acta Ped Scand. 1978;67:571-576.

Ott MG, Holder BB, Olson RD. A mortality analysis of employees engaged in the manufacture of 2,4,5 trichlorophenoxyacetic acid. JOM. 1980;22:47-50.

Ott MG, Holder BB, Gordon HL. Respiratory cancer and occupational exposure to arsenicals. Arch Env Health. 1974;29:250-5.

Palackdharry CS. The epidemiology of non Hodgkins lymphoma: why the increased incidence? Oncol. 1994;8:67-73.

Paldy A, Puskas N, Vincze K, Hadhazi M. Cytogenetic studies on rural populations exposed to pesticides. Mutat Res. 1987;187:127-32.

Park RM, Maizlish NA, Punnett L, Moure-Eraso R, Silverstein MA. A comparison of PMRs and SMRs as estimators of occupational mortality. Epid. 1991;2:49-59.

Pearce N, Reif JS. Epidemiologic studies of cancer in agricultural workers. Am J Ind Med.1990;18:133-48.

Pearce NE, Smith AH, Reif JS. Increased risk of soft tissue sarcoma, malignant lymphoma and acute myeloid leukemia in abattoir workers. Am J Ind Med. 1988;14:63-72.

Pearn JH. Herbicides and congenital malformations: a review for the paediatrician. Aust Paedit J.

1985;21:237-242.

Persson B, Fredriksson M, Olsen K, Boeryd B, Axelson O. Some occupational exposures as risk factors for malignant lymphomas. Cancer. 1993;72:1773-1778.

Pesatori AC, Sontag JM, Lubin JH, Consonni D, Blair A. Cohort mortality and nested case control study of lung cancer among structural pesticide control workers in Florida (United States). Cancer Causes Control. 1994;5:310-318.

Prentice RL. On the design of synthetic case-control studies. Biometrics 1986;42:301-310.

Purschwitz MA, Field WE. Scope and magnitude of injuries in the agricultural workplace. AM J Ind Med. 1990;18:172-192.

Rajput AH, Uitti RJ, Stern W, *et al.* Geography, drinking water chemistry, pesticides and herbicides and the etiology of Parkinson's Disease. Can J Neuro Sci. 1987;14:414-418.

Reif J, Pearce N, Fraser J. Cancer risks in New Zealand farmers. Int J Epi. 1989:18:768-74.

Restrepo M, Munoz N, Day NE, Parra JE, de Romero L, Nguyen-Dinh X. Prevalence of adverse reproductive outcomes in a population occupationally exposed to pesticides in Colombia. Scand J Work Env Health. 1990a:16:232-238.

Restrepo M, Munoz N, Day NE, Parra JE, Hernandez C, Blettner M, Giraldo A. Birth defects among children born to a population occupationally exposed to pesticides in Colombia. Scand J Work Env Health. 1990b:16:239-246.

Rich-Edwards JW, Corsano KA, Stampfar MJ. Test of the National Death Index and Equifax Nationwide Death Search. Am J Epid 1994;140:1016-1019.

Richardson RJ. Assessment of the neurotoxic potential of Chlorpyrifos relative to other organophosphorus compounds: a critical review of the literature. J Tox Env Health. 1995;44:135-165.

Richardson S, Zittoun R, Bastuji-Garin S, *et al.* Occupational risk factors for acute leukemia: a case control study. Int J Epid. 1992;21:1063-1073.

Riihimaki V, Asp S, Pukkala E, Hernberg S. Mortality and cancer morbidity among chlorinated phenoxyacid applicators in Finland. Chemosphere. 1983;12:779-84.

Riihimaki V, Asp S, Hernberg S. Mortality of 2,4 dichlorophenoxyacetic acid and 2,4,5 trichlorophenoxyacetic acid herbicide applicators in Finland. Scand J Work Env Health. 1982;8:37-42.

Rita P, Reddy PP, Vankatram Reddy S. Monitoring workers occupationally exposed to pesticides in grape gardens of Andhra Pradesh. Env Res. 1987;44:1-5.

Ritter L, Wigle T, Semenciw RM, Wilkins K, Riedel D, Mao Y. Mortality study of Canadian male farm operators: cancer mortality and agricultural practices in Saskatchewan. Med Lav. 1990;81:499-505.

Roan CC, Matanoski GE, McIlnay CQ, Olds KL, Pylant F, Trout JR, Wheeler P, Morgan DP. Spontaneous abortions, stillbirths, and birth defects in families of agricultural pilots. Arch Env Health. 1984;39:56-60.

Roberts L. Pesticides and kids. News. 1989;243:1280-1281.

Robins JM, Gail MH, Lubin JH. More on "biased selection of controls for case-control analyses of cohort studies." Biometrics 1986;42:273-299.

Robins JM, Prentice RL, Blevins D. Designs for synthetic case-control studies in open cohorts. Biometrics 1989;45:1103-1116.

Robison AK, Stancel GM. The estrogenic activity of DDT: correlation of estrogenic effect with nuclear level of estrogen receptor. Life Sci. 1982;31:2479-2484.

Robison A, Sirbasku DA, Stancel GM. DDT supports the growth of an estrogen-responsive tumor. Tox Letters. 1985;27:109-113.

Rosenman KD, Gardiner J, Swanson GM, Mullan P, Zhu Z. Use of skin cancer prevention strategies among farmers and their spouses. Am J Prev Med. 1995;11:342-347.

Rosenstock L, Daniell W, Barnhard S, Schwartz D, Demers PA. Chronic neuropsychological sequelae of occupational exposure to organophosphate insecticides. Am J Ind Med. 1990;18:321-325.

Rosenstock L, Keifer M, Daniell WE, McConnell R, Claypoole K, *et al.* Chronic central nervous system effects of acute organophosphate pesticide intoxication. Lancet. 1991;338:223-227.

Rosenwaike I, Hempstead K, Rogers RG. Using surname data in US Puerto Rican mortality analysis. Demography 1991;28:175-180.

Rothman KJ, Boice JD. Epidemiologic Analyses with a Programmable Calculator. Washington DC: US Dept of Health, NIH Publication #79-1649, 1979.

Rupa DA, Reddy PP, Reddi OS. Clastogenic effect of pesticides in peripheral lymphocytes of cotton-field workers. Mutat Res. 1991a;261:177-180.

Rupa DS, Reddy PP, Sreemannarayana K, Reddi OS. Frequency of SCE in peripheral lymphocytes of male pesticide applicators. Env Molecular Mutagen. 1991b;18:136-138.

Rupa DS, Reddy PP, Reddi OS. Analysis of sister-chromatid exchanges, cell kinetics and mitotic index in lymphocytes of smoking pesticide sprayers. Mutat Res. 1989;223:253-258.

Rust GS. Health status of migrant farmworkers: a literature review and commentary. Am J Pub Health. 1990;80:1213-1217.

Saftlas AF, Blair A, Cantor KP, Hanrahan L, Anderson HA. Cancer and other causes of death among Wisconsin farmers. Am J Ind Med. 1987;11:119-22.

San RHC, Rosin MP, See RH, Dunn BP, Stich HF. Use of urine for monitoring human exposure to genotoxic agents. In: Biological Monitoring for Pesticide Exposure, Measurement, Estimation, and Risk Reduction. (ACS Symposium Series 382), Wang RGM, *et al.* , Eds. Washington, DC: American Chemical Society, 1989, pg 98-106.

Saracci R, Kogevinas M, Bertazzi P-A, *et al.* Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. Lancet. 1991;338:1027-1032.

Savage EP, Keefe TJ, Wheeler HW, *et al.* Household pesticide usage in the US. Arch Env Health. 1981;36:304-309.

Scarborough ME, Ames RG, Lipsett MJ, Jackson RJ. Acute health effects of community exposure to cotton defoliants. Arch Env Health. 1989;44:355-360.

Schenker M, Albertson TE, Saiki CL. Pesticides. In: Environmental and Occupational Medicine, 2nd Ed., Rom WN, ed. Boston: Little and Brown, 1992. pg. 887-902.

Schenker M, Lopez R, Wintemute G. Farm-related fatalities among children in California, 1980 to 1989. Am J Pub Health. 1995;85:89-92.

Schlesselman JJ. Case Control Studies: Design, Conduct, Analysis. New York: Oxford University Press, 1982.

Schoenberg BS. Environmental risk factors for Parkinson's Disease: the epidemiologic evidence. Can

J Neuro Sci. 1987;14:407-413.

Schwartz DA, Newsum LA, Heifetz RM. Parental occupation and birth outcome in an agricultural community. Scand J Work Env Health. 1986;12:51-54.

See RH, Dunn BP, San RHC. Clastogenic activity in urine of workers occupationally exposed to pesticides. Mutat Res. 1990;241:251-259.

Semchuck KM, Love EJ, Lee RG. Parkinson's Disease: a test of the multifactorial etiologic hypothesis. Neurology. 1993;43:1173-1180.

Serraino D, Franceschi S, La Vecchia C, Carbone A. Occupation and soft tissue sarcoma in northeastern Italy. Cancer Causes Cont. 1992;3:25-30.

Sewell CM, Castle SP, Hull HR. Testicular cancer and employment in agricluture and oil and natural gas extraction. Lancet. 1984;i:553.

Shane BS, Scarlett-Kranz JM, Reid WS, Lisk DJ. Mutagenicity of urine from greenhouse workers. J Tox Env Health. 1988;24:429-37.

Sharp DS, Eskenazi B, Harrison R, Callas P, Smith AH. Delayed health hazards of pesticide exposure. Ann Rev Public Health. 1986;7:441-71.

Sharpe CR, Franco EL, de Camargo B, *et al.* Parental exposure to pesticides and the risk of Wilms tumor in Brazil. Am J Epid. 1995;141:210-217.

Sims J. Tobacco use in Florida: consequences and costs. Cancer Causes Control 1994;1(5):441-445.

Smith A, Secoy D. Forerunners of pesticides in classical Greece and Rome. J Agric Food Chem. 1975;23:1051-5.

Smith Rooker JL, Garrett A, Hodges LC, Shue V. Prevalence of glioblastoma multiforme subjects with prior herbicide exposure. J Neurosci Nursing. 1992;24:260-265.

Smith AH, Fisher DO, Pearce N, Chapman CJ. Congenital defects and miscarriages among New Zealand 2,4,5-T sprayers. Arch Env Health. 1982;37:197-200.

Smith JG, Christophers AJ. Phenoxy herbicides and chlorophenols: a case control study on soft tissue sarcoma and malignant lymphoma. Br J Cancer. 1992;65:442-448.

Spiegelman D, Wand J-D, Wegman D. Interactive electronic computing of the mortality odds ratio. Am J Epi. 1983;118:599-607.

Steenland K, Jenkins B, Ames RG, O'Malley M, Chrislip D, Russo J. Chronic neurologic sequelae to organophosphate pesticide poisoning. Am J Pub Health. 1994;84:731-736.

Steenland K. Case Studies in Occupational Epidemiology. New York: Oxford University Press, 1993.

Stein W, Hayes WJ. Health survey of pesticide control operators. Ind Med Surg. 1964:33:549-553.

Steineck G, Wiklund G. Multiple myeloma in Swedish agricultural workers. Int J Epid. 1986:15:321-325.

Sterling TD, Arundel AV. Review of recent Vietnamese studies on the carcinogenic and teratogenic effects of phenoxy herbicide exposure. Int J Health Serv. 1986b;16:265-78.

Sterling TD, Arundel AV. Health effects of phenoxy herbicides. Scand J Work Env Health. 1986a;12:161-73.

Sterling TD, Weinkam JJ. Smoking patterns by occupation, industry, sex and race. Arch Env Health 1978;33:313-317.

Stubbs HA, Harris J, Spear RC. A proportionate mortality analysis of California agricultural workers, 1978-79. Am J Ind Med. 1984;6:305-320.

Swaen GMH, van Vliet C, Slangen JJM, Sturmans F. Cancer mortality among licensed herbicide applicators. Scand J Work Env Health. 1992;18:201-204.

Taha TE, Gray RH. Agricultural pesticide exposure and perinatal mortality in central Sudan. Bull WHO. 1993;71:317-321.

Tanner C M, Langston JW. Do environmental toxins cause Parkinson's disease? Neurology.

1990;40(suppl 3):17-31

Terracini B. Evaluation of carcinogenicity of the chlorinated hydrocarbons used as pesticides. Tumori. 1967;53:601-18.

Thomas TL, Waxweiler RJ. Brain tumors and occupational risk factors: a review. Scand J Work Env Health. 1986;12;1-15.

Thomas HF, Winter PD, Donaldson LJ. Cancer mortality among local authority pest control officers in England and Wales. Occ Env Med. 1996;53:787-790.

Thomas TL, Mason TJ, Ramsbottom R, White DW *et al.* Development of a computerized occupational referent population system (CORPS) for epidemiologic studies. Am J Epi. 1986;123:918-919.

Thrasher JD, Madison R, Broughton A. Immunologic abnormalities in humans exposed to Chlorpyrifos: preliminary observations. Arch Env Health. 1993;48:89-93.

Tollestrup K, Daling JR, Allard J. Mortality in a cohort of orchard workers exposed to lead arsenate pesticide spray. Arch Env Health. 1995;50:221-229.

Unger M, Klaer H, Blichert-Toft M, Olsen J, Clausen J. Organochlorine compounds in human breast fat from deceased with and without breast cancer and in biopsy material from newly diagnosed patients undergoing breast surgery. Environ Res. 1984;34:24-28.

US General Accounting Office (GAO). Pesticides on the Farms: Limited Capacity Exists to Monitor Occupational Illnesses and Injuries. Washington, DC: US Government Printing Office,#GAO/PEMD-94-6, December 1993.

US Environmental Protection Agency (EPA). Pesticide Industry Sales and Usage, 1987: Market Estimates. Washington, DC: US EPA, 1988.

US Census. 1980 US Census List of Hispanic Last Names (obtained from the Bureau of the Census).

Viel J-F, Richardson ST. Lymphoma, multiple myeloma and leukemia among French farmers in relation to pesticide exposure. Soc Sci Med. 1993;37:771-777.

Vineis, D'Amore F, Working Group. The role of occupational exposure and immunodeficiency in B cell malignancies. Epid. 1992;3:266-270.

Vineis P, Settimi L, Seniori Costantini A. Exposure to agrichemicals and cancer risk. Med Lav. 1990;81:363-372.

Wang HH, MacMahon B. Mortality of workers employed in the manufacture of chlordane and heptachlor. JOM. 1979a;21:745-8.

Wang HH, MacMahon B. Mortality of pesticide applicators. JOM. 1979b;21 (11):741-4.

Wasserman M, Nogueira DP, Tomatis L, *et al.* Organochlorine compounds in neoplastic and adjacent apparently normal breast tissue. Bull Env Contam Tox. 1976:15:478-84.

Weisenburger DD. Human health and agricultural use. Human Path. 1993;24:571-576.

Weisenburger DD. Environmental epidemiology of Non Hodgkins lymphoma in eastern Nebraska. Am J Ind Med. 1990;18:303-305.

Weschsler LS, Checkoway H, Franklin GM, Costa LG. Pilot study of occupational and environmental risk factors for Parkinson's disease. Neurotoxicology. 1991;12:3876-392

Wesseling C, Castillo L, Elinder C-G. Pesticide poisonings in Costa Rica. Scand J Work Env Health. 1993;19:227-35.

Westin JB, Richter E. The Israeli breast cancer anomaly. Ann NY Acad Sci. 1990:609;269-279.

White G, Cessna A. Occupational hazards of farming. Can Fam Physician. 1989;35:2331-2336.

White FMM, Cohen FG, Sherman G, McCurdy R. Chemicals, birth defects and stillbirths in New Brunswick: associations with agricultural activities. CMAJ. 1988;138:117-124.

Whorton MD. Health effects of dibromochloropropane. In: Environmental and Occupational Medicine, 2nd Ed., Rom WN, ed. Boston: Little and Brown, 1992. pg. 903-910.

Wickramaratne PJ, Holford TR. Confounding in epidemiologic studies: the adequacy of the control group as a measure of confounding. Biometrics 1987;43:751-65.

Wigle DT, Semenciw RM, Wilkins K, *et al.* Mortality study of Canadian male farm operators: Non Hodgkins lymphoma mortality and agricultural practices in Saskatchewan. J Nat Cancer Inst. 1990;82:575-582.

Wiklund K, Lidefors B-M, Holm L-E. Risk of malignant lymphoma in Swedish agricultural and forestry workers. Brit J Ind Med. 1988c;45:19-24.

Wiklund K, Dich J, Holm L-E. Testicular Cancer among agricultural workers and licensed pesticide applicators in Sweden. Scand J Work Env Health. 1986b;12:630-1.

Wiklund K, Holm L-E, Dich J. Soft tissue sarcoma risk among agricultural and forestry workers in Sweden. Chemosphere. 1987b;16:2107-2110.

Wiklund K, Dich J, Holm LE. Soft tissue sarcoma risk in Swedish licensed pesticide applicators. JOM. 1988a;30 (10):801-4.

Wiklund K, Dich J, Holm L-E. Risk of malignant lymphoma in Swedish pesticide applicators. Br J Cancer. 1987a;56:505-8.

Wiklund K, Dich J, Holm L-E, Eklund G. Risk of cancer in pesticide applicators in Swedish agriculture. Brit J Ind Med. 1989b;46:809-14.

Wiklund K, Holm L-E. Trends in cancer risks among Swedish agricultural workers. JNCI. 1986a;77:657-664.

Wiklund K. Swedish Agricultural workers: a groups with a decreased risk of cancer. Cancer. 1983;51:566-8.

Wiklund K, Dich J, Holm L-E. Risk of soft tissue sarcoma, Hodgkin's disease and non Hodgkin's lymphoma among Swedish licensed pesticide applicators. Chemosphere. 1989a;18:395-400.

Wiklund K, Holm L-E. Soft tissue sarcoma risk in Swedish agricultural and forestry workers. JNCI. 1986c;76:229-234.

Wiklund K, Daling JR, Allard J, Weiss NS. Respiratory cancer among orchardists in Washington State, 1968 to 1980. JOM. 1988b;30 (7):561-4.

Wiklund K, Steineck G. Cancer in the respiratory organs of Swedish farmers. Cancer. 1988d;61:1055-1058.

Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. Blood levels of organochlorine residues and risk of breast cancer. J Nat Cancer Inst. 1993;85:648-52.

Wong O, Morgan RW, Kheifets L, Larson SR. Comparison of SMR, PMR and PCMR in a cohort of union members potentially exposed to diesel exhaust emissions. Br J Ind Med 1985;42:449-460.

Wong O, Decoufle P. Methodologic issues involving SMR and PMR in occupational studies. JOM 1982;24:299-304.

Woods JS, Polissar L. Non Hodgkins lymphoma among phenoxy herbicide exposed farm workers in western Washington state. Chemosphere. 1989;18:401-406.

Woollen H. Biological monitoring for pesticide absorption. Ann Occ Hyg. 1993;37:525-540.

World Health Organization (WHO). Public Health Impact of Pesticides Used in Agriculture. Geneva: World Health Organization, 1990.

Wright L. Silent Sperm. New Yorker. January 15, 1996:42-55.

Wright CG, Leidy RB. Chlorpyrifos residues in air after application to crevices in rooms. Bull Env Contam Tox. 1978;19:340-344.

Yoder J, Watson M, Benson WW. Lymphocyte chromosome analysis of agricultural workers during extensive occupational exposure to pesticides. Mutat Res. 1973;21:335-340.

Zahm SH, Blair A. Pesticides and Non Hodgkins lymphoma. Cancer Res. 1992;52 (suppl):5485s-5488s.

Zahm S, Weisenburger DD, Saal RC, Vaught JB, Babbitt PA, Blair A. The role of agricultural pesticide use in the development of Non Hodgkins lymphoma in women. Arch Env Health.

1993:48:353-358.

Zahm SH, Weisenburger D, Babbitt PA, *et al.* A case control study of Non Hodgkins lymphoma and the herbicide 2,4 Dichlorophenoxyactic Acid (2,4 D) in eastern Nebraska. Epid. 1990:1:349-356.

Table 1. A Summary of Pesticide Applicator Cancer Studies

Citation	Total Subjects	Total Cancer (Obs/Exp)	Risk Estimates	Comments
Alavanja (USA 1988) 1970-79	1,495 (PMR/MOR)	323/306 O/E=1.06	Hodgkins O/E=2.72; NHL O/E=2.32; Brain O/E=2.08; Bladder O/E=2.00; MM O/E=1.97; Leukemia O/E=1.8; Colon O/E=1.46;	Agricultural Extension Agents; + dose response; no smoking data
Alavanja (USA 1989) 1970-79	1,411 (PMR/MOR)	342/310.9 O/E=1.1	NHL O/E=2.40; Kidney O/E=2.10; Prostate O/E=1.60; Colon O/E=1.50	Forest & Soil Conservation; increased risk NHL first employed before 1960; no smoking data
Alberghini (Italy 1991) 1974-87	4,580	305 SMR=0.68	Brain SMR=1.69; Testis SMR=1.63; Peritoneum MR=1.24	licensed farmers; + dose response; no smoking data
Asp (Finland 1994) f/u Riihimaki 1955-71	1,909	77/93.2 SMR=0.82	Thyroid SMR=3.81; MM SMR=2.63; Esophagus SMR=1.31; Eye, Brain SMR=1.22	Herbicide Applicators; no new NHL or STS deaths; no smoking data
Axelson (Sweden, 1974, 1980) 1957-72,'78	735 (348 f/u)	11/5 O/E= 2.2	Lung 0/E=2/0.2; Stomach O/E=3/0.7	Railroad workers; increased total & cancer mortality; + latency effect; no smoking data
Balarajan (England, Wales, 1988)	8,222 (matched controls)		Lymphomas RR=1.23; Lymphosarcoma RR=1.48; Hodgkins RR=1.42	Farmers, Forestry Workers; No Smoking data
Barthel (GDR 1976, 1981) 1948-72	1,658	169	Lung SMR=2.00	+ smoking data; + dose reponse
Barthel (GDR 1986)	1,214	65/48.5 SIR=1.33	Stomach SMR=1.80; Esophagus SMR=4.30; Melanoma SMR=5.88	+dose response
Blair (USA 1983) 1965-66	3,827	84/73.7 SMR=1.14	Lung SMR=1.35; Brain SMR=2.00	+ dose response; no smoking data

Citation	Total Subjects	Total Cancer (Obs/Exp)	Risk Estimates	Comments
Cantor (USA 1990) 1965-79	9,677	85 SMR=0.74 (RR=1.16)	Leukemia SMR=1.71; Larynx SMR=1.76; Prostate SMR=1.36; Skin SMR=1.32 Pancreas SMR=1.34; Kidney SMR=1.26;	Aerial Applicators vs Instructors: no smoking data; no dose response
Coggon (USA 1986) 1947-83	5754 (4,078 herbicide exposed)	297/276.3 SMR=1.07	Nasal SMR=4.93*; Skin SMR=3.06*; Testis SMR=2.23; Leukemia SMR=1.75; Thyroid SMR=1.70; Mult Myel SMR=1.62; Small Intestine SMR=1.54; Larynx SMR=1.34; Prostate SMR=1.32; Brain SMR=1.27	Manufacturers, Applicators phenoxy acids; no smoking data; + dose response
Corrao (Italy 1989) 1970-1983	25,945	631/877.81 SIR=0.70	Lymphatic SIR=1.40; Skin SIR=1.40; (Nervous SIR=2.1 before 1913)	licensed Male farmers; + dose response; + risk forest tree plantation; no smoking data
Green (Canada 1986, 1991) 1950-1982	1,222	18/16.39 SMR=1.09	Lung O/E=5/4.57; Stomach O/E=2/1.05	Forestry workers public Utility; + smoking data
Figa-Talamanca (Italy 1993a) 1973-1988	2,310	86/120.1 SMR=0.72	Brain SMR=2.60*; Mult Myel SMR=1.78; Pancreas SMR=1.45; Kidney SMR=1.20	Licensed pesticide applicators; + dose response; no smoking data
Figa-Talamanca (Italy 1993b) 1973-1982	168	15/12.2 SMR=1.23	NHL SMR=10.00; Liver SMR=5.71*; Leukemia SMR=2.50; Stomach SMR=2.31; Lung SMR=1.22	licensed pesticide applicators; no dose response; no smoking data
Hansen (Denmark 1992) 1975-1984	4,015	217/207.7 SIR=1.04	CLL SIR=2.51; NHL SIR=2.00; STS SIR=4.55	Gardeners; STS in males only; no smoking data
Littorin (Sweden 1993) 1965-1982	2,370	133/156.7 SMR=0.90	STS SMR=1.70; Nervous SMR=1.50; Stomach SMR=1.40; Skin SMR=1.40 Lymphomas 1.20	Market gardeners & Orchardists; + dose response; no smoking data

Citation	Total Subjects	Total Cancer (Obs/Exp)	Risk Estimates	Comments
Luchtrath (FDR 1983)	417 (Case series)		Lung SMR=1.69 (66% of cancers); Skin & Internal Organs [no statistical analysis]	Wine growers: chronic arsenic: no smoking data
MacMahon (USA 1988; follow up of Wang) 1967-84	16,126	232/227.4 SMR=1.11	Lung SMR=1.35*; Bladder SMR=1.23; Skin SMR=1.26	Termite workers no - lung ca (chlordane); No dose response; no smoking data
Morgan (USA 1980) 1971-73	2,620	10/26.7	Skin RR=5.70* [limited statistical analysis]	3,669 (2,620 exposed) volunteers from 13 states; 70% follow-up; no smoking data
Notkola (Finland, 1993) 1970, 1975, 1980 with f/u 1985	2298 forestry 772 farm/forestry	RR=1.17 Forest RR=0.74 Farm/Forest		Forestry, Farm/Forestry, Construction workers; decreasing mortality (30%) with time; no smoking data
Pesatori (USA 1994) f/u Blair 1977-1982	4,411 (54 lung Ca nested case control; 4 matched controls)	130 SMR=1.20	Testis SMR=2.90; Larynx SMR=2.40; Brain SMR=2.20; Buccal/Pharynx SMR=1.40; Lung SMR=1.40; Leukemia SMR=1.20	Structural applicators; + dose response; + latency; +smoking data
Riihimaki (Finland 1982, 1983) 1955-71,'80	1,926	20/24.3 5/11.3	Mult Myel O/E=1/0.20; Prostate O/E 2/1.1	Herbicide applicators; no smoking data
Saracci (10 countries 1991) 1955-1990	18,390 (5,898 sprayers)	262/249.94 SMR=1.05	STS SMR=6.06, SMR=8.82 for sprayers; Thyroid SMR=3.67; Endocrine SMR=4.54; Nose/Nasal Cavity SMR=2.83	Manufacturers & sprayers herbicides; STS excess 10-19 yr latency; + dose response; no smoking data
Stein (USA 1964) 1964	799	17 RR=1.28	(no statistical analysis)	National Pest Control Association pilot survey; no smoking data

Citation	Total Subjects	Total Cancer (Obs/Exp)	Risk Estimates	Comments
Swaen (Netherlands 1992) 1980-1988	1341	31 SMR=1.14	Mult Myel SMR=8.15*; Skin SMR=4.83; Hodgkin SMR=3.34; Brain SMR=3.18; Large Intest SMR=2.55; Pancreas SMR=2.18; Prostate SMR=1.31	Herbicide applicators
Thomas (1996 England) 1980-1994	1,485	65/81.88 SMR=0.79	Connective SMR=3.18; Bladder SMR=2.40; Leukemia SMR=2.14; Rectum SMR=1.95; Melanoma SMR=1.52; Stomach SMR=1.29	Pesticide Applicators in 296 locations; 74/110 participate in random survey; + smoking data
Tollestrup (USA 1995) 1938-1990	1,225	RR=1.20 for males RR=1.31 for females	Males: Digestive RR=2.23; Pancreatic RR=1.42 Females: Digestive RR=3.09	Orchardists w/ lead arsenate exposure; 1938 asssembled Neal Study Cohort mean urine arsenic 140 ug/l (males), 118.1 ug/l (females); no smoking data
Wang (USA 1979b) 1967-76	16,126	47/65.2 SMR=0.83	Bladder SMR=2.77; Lung SMR=1.55; Skin SMR=1.73	3 pesticide applicator companies; no smoking data
Wiklund (Sweden 1986, 1987, 1988a, 1989) 1965-82	20,245	558/649.8 SIR=0.86	Testis SIR=1.55; CNS SIR=1.20; Hodgkins SIR=1.20; Endocrine SIR=1.20	Farmers & Pesticide applicators; + smoking data; +dose response
Wiklund (USA 1988b)	155 cases (155 controls)		Respiratory cancer 30%>state comparison in cohort	Orchardists; lead arsenate; + smoking data; no relation to exposure
el Zayadi (Egypt 1986)	14 cases			Farmers spraying arsenicals; no smoking data

Table 2. Master Database Eliminations

Category	# Records Eliminated
Duplicates	2028
Unknown gender	196
<18 years of age	21
Inadequate Social Security #	286
Inadequate Dates	100
No Date of Birth	2664
Out of state deaths	51

[there is overlap among the categories]

Table 3. Complete listing of Record Source for the Master Database

Source	Number of Records
Hard Copy	7538
Motor Vehicles	24198
FCDS	1432
Death Tapes	1881
HCFA	6243
ERI	26
EQUIFAX	26
AHCA	302

[there is overlap among the categories]

Table 4. Hispanic and Gender distributions

	Female	**Male**	**Total**
Entire Cohort:			
Hispanic	121	1265	1386
Non	3435	29390	32825
Total	3556	30655	34211
Cancer Incidence Cases:			
Hispanic	1	31	32
Non	106	1128	1234
Total	107	1159	1266
All Deaths:			
Hispanic	1	43	44
Non	97	1734	1831
Total	98	1777	1875

Table 5. Mean Age at First Licensure, Length of Time Licensed, Mean Age at Death by **Ethnic Group**

	Hispanic mean±SD	**NonHispanic** mean±SD	**Total** mean±SD	**ttest** p value
Entire Cohort:				
Mean Age First Licensure	37.05±11.84	39.77±13.05	39.26±13.19	0.0001
Mean Years Licensed	5.26±3.45	7.00±4.29	6.93±4.27	0.0001
Mean Age at Death	61.91±13.67	65.93±13.19	65.92±13.65	0.06

Table 6. Mean Age at First Licensure, Length of Time Licensed, Mean Age at Death by **Gender**

	Female mean±SD	**Male** mean±SD	**Total** mean±SD	**ttest** p value
Entire Cohort:				
Mean Age First Licensure	37.68±12.32	39.45±13.27	39.26±13.19	0.0001
Mean Years Licensed	5.47±3.04	7.09±4.36	6.93±4.27	0.0001
Mean Age at Death	62.43±15.45	66.12±13.52	65.92±13.65	0.02
Cancer Incidence Cases:				
Mean Age First Licensure	49.58±12.71	55.91±10.81	54.87±11.41	0.0001
Mean Years Licensed	7.25±3.11	8.94±3.68	8.80±3.67	0.0001
Mean Age at Death	54.47±9.34	57.96±10.41	56.85±11.47	0.05

Table 6. Mean Age at First Licensure, Length of Time Licensed, Mean Age at Death by **Gender** (continued)

	Female mean±SD	**Male** mean±SD	**Total** mean±SD	**ttest** p value
All Deaths:				
Mean Age First Licensure	53.37±13.26	56.55±12.35	56.38±12.42	0.02
Mean Years Licensed	7.27±2.73	8.23±2.99	8.18±2.98	0.001
Mean Age at Death	62.43±15.45	66.12±13.52	65.92±13.65	0.02
PMR Study:				
Mean Age First Licensure	N/A	56.59±12.39	56.59±12.39	
Mean Years Licensed	N/A	8.24±3.00	8.24±3.00	
Mean Age at Death	N/A	66.17±13.58	66.17±13.58	

Table 7. Mean Age at First Licensure, Length of Time Licensed, Mean Age at Death by **LicenseCategory**

	Private mean±SD	**Com/Public** mean±SD	**Total** mean±SD	**ttest** p value
Entire Cohort:				
Mean Age First Licensure	41.42±13.65	35.91±10.59	39.26±13.19	0.0001
Mean Years Licensed	7.52±4.38	5.68±3.74	6.93±4.27	0.0001
Mean Age at Death	67.55±12.52	55.31±12.59	65.92±13.65	0.0001

Table 8. Licensure Type and Gender Distribution

	Female	Male	Total
Entire Cohort:			
Private	2546	20755	23301
Commercial	605	7086	7691
Public	405	2814	3219
Total	3556	30655	34211
Cancer Incidence Cases:			
Private	94	966	1060
Commercial	8	120	128
Public	5	73	78
Total	107	1159	1266
All Deaths:			
Private	86	1527	1613
Commercial	7	165	172
Public	5	85	90
Total	98	1777	1875
PMR Study:			
Private	0	1457	1457
Commercial	0	158	158
Public	0	81	81
Total	0	1696	1696

Table 9. License Certification Categories for the Entire Cohort

Certification Category	Numbers (%)
Ornamental	4994 (40%)
Aquatic	2268 (18%)
Row Control	1565 (13%)
Institution/Industry/Structure	1228 (10%)
Organic Paint	614 (5%)
Demonstration & Research	510 (4%)
Aerial	342 (3%)
Regulatory	280 (2%)
Plant	193 (2%)
Forest	171 (1%)
Animal	111 (1%)
Public Health	86 (<1%)
Wood Treatment	69 (<1%)
County Trainer	58 (<1%)
Seed Treatment	28 (<1%)
Total	12517

Table 10. Number of Years Licensed by Calendar Year of Cohort Entrance

	Year of Cohort Entrance				
	1975- (N Horizontal % Vertical %)	**1980-**	**1985-**	**1990-**	**Total**
Number of Years Licensed					
Entire Cohort:					
00-	**0**	**809**	**1620**	**4933**	**7362** (22%)
	0	11	22	67	
	0	11	18	73	
04-	**1740**	**4206**	**6671**	**1885**	**14502** (42%)
	12	29	46	13	
	16	56	74	27	
08-	**5288**	**2083**	**721**	**0**	**8012** (23%)
	66	26	9	0	
	48	27	8	0	
12-	**1644**	**491**	**0**	**0**	**2135** (6%)
	77	23	0	0	
	15	6	0	0	
16-	**2200**	**0**	**0**	**0**	**2200** (6%)
	100	0	0	0	
	20	0	0	0	
Total	**10848** (32%)	**7636** (22%)	**8978** (26%)	**6749** (20%)	**34211**

Table 10. Number of Years Licensed by Calendar Year of Cohort Entrance (continued)

	Year of Cohort Entrance				
	1975- (N Horizontal % Vertical %)	**1980-**	**1985-**	**1990-**	**Total**
Number of Years Licensed					
Deaths:					
00-	**0**	**39**	**19**	**11**	**69** (4%)
	0	57	28	15	
	0	11	13	46	
04-	**323**	**293**	**120**	**15**	**751** (40%)
	43	39	16	2	
	24	80	84	55	
08-	**875**	**36**	**10**	**0**	**911** (49%)
	96	4	1	0	
	65	9	3	0	
12-	**109**	**2**	**0**	**0**	**111** (6%)
	98	2	0	0	
	8	1	0	0	
16-	**33**	**0**	**0**	**0**	**33** (2%)
	100	0	0	0	
	3	0	0	0	
Total	**1342** (72%)	**368** (20%)	**143** (8%)	**22** (1%)	**1875**

Table 10. Number of Years Licensed by Calendar Year of Cohort Entrance (continued)

	Year of Cohort Entrance				
	1975- (N Horizontal % Vertical %)	1980-	1985-	1990-	Total
Number of Years Licensed					
Cancer:					
00-	**0**	**29**	**33**	**13**	**73** (6%)
	0	39	44	17	
	0	11	27	72	
04-	**167**	**178**	**80**	**5**	**430** (34%)
	39	41	19	1	
	19	69	65	28	
08-	**507**	**38**	**11**	**0**	**556** (44%)
	91	7	2	0	
	59	15	9	0	
12-	**117**	**14**	**0**	**0**	**131** (10%)
	89	11	0	0	
	14	5	0	0	
16-	**74**	**0**	**0**	**0**	**74** (6%)
	100	0	0	0	
	9	0	0	0	
Total	**865** (68%)	**259** (21%)	**124** (10%)	**18** (1%)	**1266**

Table 11. Correlation of Exposure Measures

Exposure Measure	**Correlation** (Pearson Correlation Coefficient)
Entire Cohort (N=34,211):	
Years Licensed - Calendar Year Enter	0.78 (0.0001)
Years Licensed - Age at First Issue	-0.11 (0.0001)
Age at First Issue - Calendar Year Enter	0.25 (0.001)
Deaths (N=1875):	
Years Licensed - Calendar Year Enter	0.72 (0.0001)
Years Licensed - Age at First Issue	-0.03 (0.0001)
Age at First Issue - Calendar Year Enter	0.23 (0.001)
Incident Cancers (N=1266):	
Years Licensed - Calendar Year Enter	0.66 (0.0001)
Years Licensed - Age at First Issue	-0.11 (0.0001)
Age at First Issue - Calendar Year Enter	0.09 (0.001)

Table 12. Non Cancer Mortality ICD Codes used in Study (from NCI CORPS Data System)

Disease	ICD Code*
Overall	000-999
Infectious Diseases	000-136
Tuberculosis	010-019
Allergic Endocrine	240-246, 250-279
Diabetes Mellitus 250	
Diseases of Blood	280-289
Mental	290-315
Nervous System	320-389
Circulatory System	390-398, 400-416, 420-438, 440-458
Rheumatic HD	393-398
ASHD (w/CHD)	410-416
AHD	410.0-414.9, 429.2
CNS Vascular	430-438
Respiratory diseases	460-486, 490-493, 500-519
Pneumonia	480-486
Emphysema	492
Asthma	493
Digestive Diseases	520-577
Ulcers	531-533
Cirrhosis	571
Genito Urinary	580-629
Chronic Nephritis	582
Skin Diseases	680-709
Bones and Joints	710-738
Senility	780-796
External Causes	800-998.0
Accidents	800-949
Motor Vehicle	810-827
Suicide	950-959

* ICD 8th Revision Codes from CORPS data set (NCI, NIOSH)

Table 13. Primesite C Codes and Morphology corresponding to the Cancer incidence ICD Codes used in Study (the latter from NCI CORPS Data System)

Disease	ICD Code*	Primesite C	Morphology
Malignant Neoplasms	140-163, 170 -209	000-349, 400-809	
Buccal/Pharynx	140-149	000-149	-
Digestive	150-159	150-260	
Esophagus	150	150-159	
Stomach	151	160-169	
Large Intestine	153	180-189	
Rectum	154	190-219	
Liver	155-156	220-249	
Pancreas	157	250-259	
Respiratory	160-163	300-349	
Larynx	161	320-329	
Lung	162-163	330-349	
Bone	170	400-419	
Skin	172-173	440-449	
Bladder	188	670-679	
Kidney	189	640-659, 680-689	
Eye	190	690-699	
Brain/CNS	191-192	700-729	
Thyroid	193	730-739	
All Lymphopoietic	200-209	024, 098, 111, 142,	9590-9595, 9670-9714
		170-179, 370-379,	9650-9667, 9800-9941
		420-424, 770-779	9720-9741
Lymphosarcoma	200	same	9590-9595, 9670-9714
Hodgkins	201	same	9650-9667
Leukemia	204-207	420-424	9800-9941
Other Lymphatic	202-203, 208-209	same	9720-9741
Soft Tissue Sarcoma	171	Check location	8800-8804
Male Cancers only:			
Prostate	185	610-619	
Testis	186-187	600-609, 620-639	
Female Cancers only:			
Breast	174	500-509	
All Genital	179-184	510-579	
Cervix	180	530-539	
Uterus	180-182	550-559	
Other Genital	183-184	560-569	

* ICD 8th Revision Codes from CORPS data set (NCI, NIOSH)

Table 14. **All** White Male Applicators: **Non Cancer Mortality PMR and MOR**

Mortality Cause	**Observed Number**	**Florida PMR (95% CI)**	**Florida MOR (95% CI)**	**CORPS PMR (95% CI)**
Overall	1696	1.00 (0.95-1.05)	0.91 (0.31-2.61)	**1.19 (1.14-1.24)***
Infectious Diseases	33	0.72 (0.49-1.01)	**0.48 (0.25-0.89)***	**8.12 (5.59-11.40)***
Tuberculosis	2	1.14 (0.11-4.11)	1.06 (0.27-4.19)	0.89 (0.09-3.20)
Allergic Endocrine	29	0.74 (0.49-1.06)	0.65 (0.42-1.01)	**2.11 (1.41-3.03)***
Diabetes	23	0.79 (0.50-1.18)	0.74 (0.48-1.15)	**1.99 (1.26-2.98)***
Diseases of Blood	6	1.07 (0.39-2.34)	1.01 (0.69-1.49)	1.65 (0.60-3.59)
Mental	10	0.66 (0.31-1.22)	0.63 (0.34-1.15)	**2.76 (1.29-5.08)***
Nervous System	34	1.43 (0.99-1.99)	1.36 (0.99-1.81)	**3.15 (2.18-4.40)***
Circulatory System	740	1.03 (0.96-1.10)	1.01 (0.93-1.11)	**1.09 (1.01-1.17)***
Rheumatic HD	5	1.33 (0.43-3.11)	1.27 (0.54-3.07)	**0.20 (0.06-0.47)***
ASHD (w/CHD)	484	1.05 (0.96-1.14)	1.04 (0.92-1.18)	0.92 (0.83-1.01)
AHD	510	1.01 (0.92-1.10)	1.00 (0.96-1.04)	no ICD Code available
CNS Vascular	88	1.16 (0.92-1.40)	1.16 (0.93-1.45)	1.18 (0.93-1.43)
Respiratory Diseases	52	**0.72 (0.54-0.94)***	**0.73 (0.55-0.97)***	**0.66 (0.48-0.84)***
Pneumonia	18	**0.59 (0.35-0.93)***	**0.59 (0.37-0.94)***	0.78 (0.46-1.23)
Emphysema	13	0.78 (0.41-1.34)	0.77 (0.45-1.33)	**0.37 (0.20-0.63)***
Asthma	1	0.59 (0.06-3.31)	0.52 (0.07-3.80)	1.39 (0.14-7.78)
Digestive Diseases	53	0.81 (0.59-1.03)	0.78 (0.57-1.07)	**1.38 (1.01-1.75)***
Ulcers	6	1.29 (0.47-2.82)	1.26 (0.57-2.79)	0.66 (0.24-1.44)
Cirrhosis	25	**0.66 (0.43-0.97)***	**0.63 (0.42-0.96)***	**0.67 (0.43-0.97)***

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted; the MOR comparison disease = ASHD]

Table 14. **All** White Male Applicators: **Non Cancer Mortality PMR and MOR** (continued)

Mortality Cause	**Observed Number**	**Florida PMR (95% CI)**	**Florida MOR (95% CI)**	**CORPS PMR (95% CI)**
Genito Urinary	16	0.94 (0.55-1.53)	0.96 (0.58-1.58)	**1.96 (1.15-3.19)***
Chronic Nephriti	0			
Skin Diseases	1	0.74 (0.07-4.15)	0.73 (0.10-5.25)	0.51 (0.05-2.86)
Bones and Joints	2	0.67 (0.07-2.41)	0.63 (0.16-2.54)	0.46 (0.05-1.66)
Senility	0			
External Causes	170	**1.24 (1.05-1.43)***	**0.69 (0.52-0.91)***	1.03 (0.87-1.18)
Accidents	106	**1.42 (1.15-1.69)***	**0.76 (0.64-0.90)***	1.12 (0.91-1.33)
Motor Vehicle	46	1.10 (0.82-1.50)	0.53 (0.00-5.63)	1.35 (0.99-1.80)
Suicide	47	1.05 (0.77-1.39)	0.64 (0.01-90.19)	0.81 (0.59-1.08)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted; the MOR comparison disease = ASHD]

Table 15. All White Male Applicators: **Cancer Mortality PMR and MOR**

Mortality Cause	**Observed Number**	**Florida PMR (95% CI)**	**Florida MOR (95% CI)**	**CORPS PMR (95% CI)**
Malignant Neoplasms	482	1.03 (0.94-1.12)	0.99 (0.88-1.11)	**1.29 (1.18-1.40)***
Buccal/Pharynx	7	0.57 (0.23-1.17)	0.54 (0.22-1.12)	0.54 (0.22-1.11)
Digestive	111	1.01 (0.82-1.20)	0.98 (0.73-1.32)	**1.65 (1.34-1.96)***
Esophagus	11	0.95 (0.47-1.70)	0.91 (0.49-1.67)	1.12 (0.55-2.01)
Stomach	11	0.82 (0.40-1.47)	0.91 (0.45-1.55)	**0.36 (0.18-0.65)***
Large Intestine	42	1.01 (0.73-1.37)	0.98 (0.65-1.49)	**2.52 (1.82-3.41)***
Rectum	7	0.95 (0.38-1.95)	0.91 (0.43-1.92)	1.05 (0.42-2.16)
Liver	16	1.49 (0.88-2.42)	1.46 (0.86-2.37)	**1.98 (1.16-13.13)***
Pancreas	22	0.99 (0.62-1.49)	0.96 (0.59-1.56)	1.03 (0.65-1.55)
Respiratory	176	0.95 (0.81-1.09)	0.91 (0.76-1.09)	1.11 (0.95-1.27)
Larynx	2	0.34 (0.03-1.22)	0.32 (0.09-1.20)	**0.25 (0.03-0.90)***
Lung	174	0.97 (0.82-1.11)	0.94 (0.78-1.13)	1.14 (0.97-1.30)
Bone	3	3.58 (0.71-10.48)	2.52 (0.92-6.89)	0.88 (0.18-2.58)
Skin	15	1.24 (0.69-2.05)	1.12 (0.77-1.61)	1.42 (0.79-2.45)
Prostate	59	**1.43 (1.07-1.79)***	**1.45 (1.11-1.91)***	**2.69 (2.00-3.38)***
Testis	1	1.02 (0.10-5.70)	0.61 (0.04-9.08)	0.80 (0.08-4.48)
Bladder	7	0.56 (0.22-1.15)	0.55 (0.26-1.15)	0.53 (0.22-1.09)
Kidney	13	1.16 (0.62-1.99)	1.11 (0.63-1.95)	0.60 (0.32-1.03)
Eye	3	**5.51 (1.11-16.30)***	**5.46 (1.11-16.00)***	4.94 (0.98-14.43)
Brain/CNS	21	**1.75 (1.08-2.67)***	1.49 (0.91-2.29)	**1.76 (1.09-2.68)***

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted; the MOR comparison disease = ASHD]

Table 15. All White Male Applicators: **Cancer Mortality PMR and MOR** (continued)

Mortality Cause	**Observed Number**	**Florida PMR (95% CI)**	**Florida MOR (95% CI)**	**CORPS PMR (95% CI)**
Thyroid	0			
All Lymphopoietic	40	0.99 (0.71-1.35)	0.90 (0.44-1.85)	1.03 (0.74-1.40)
LymphoSarcoma	1	0.38 (0.04-2.13)	0.33 (0.05-2.24)	**0.08 (0.01-0.45)***
Hodgkins	2	1.32 (0.13-4.74)	0.94 (0.12-7.41)	0.64 (0.06-2.30)
Leukemia	19	1.57 (0.95-2.45)	1.43 (0.93-2.19)	1.31 (0.79-2.04)
Other Lymphatic	18	0.75 (0.45-1.19)	0.69 (0.41-1.16)	1.18 (0.70-1.86)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted; the MOR comparison disease = ASHD]

Table 16. White Male **Private Applicators (Farmers)**: Non Cancer Mortality PMR and MOR

Mortality Cause	**Observed Number**	**Florida PMR (95% CI)**	**Florida MOR (95% CI)**	**CORPS PMR (95% CI)**
Overall	1457	1.00 (0.95-1.05)	0.93 (0.64-1.34)	**1.19 (1.13-1.25)***
Infectious Diseases	20	**0.59 (0.01-0.91)***	**0.39 (0.20-0.79)***	**6.68 (4.08-10.30)***
Tuberculosis	2	1.38 (0.14-4.97)	1.28 (0.32-5.14)	1.12 (0.11-4.02)
Allergic Endocrine	25	0.75 (0.49-1.10)	0.69 (0.47-1.05)	**2.42 (1.57-3.56)***
Diabetes	20	0.79 (0.48-1.22)	0.75 (0.47-1.19)	**2.33 (1.42-3.59)***
Diseases of Blood	6	1.20 (0.44-2.62)	1.16 (0.54-2.50)	1.84 (0.67-4.02)
Mental	9	0.71 (0.32-1.35)	0.68 (0.37-1.24)	**3.86 (1.72-7.34)***
Nervous System	30	1.43 (0.96-2.04)	1.38 (0.99-1.94)	**2.53 (1.70-3.61)***
Circulatory System	663	1.04 (0.96-1.12)	1.02 (0.91-1.13)	**1.12 (1.03-1.21)***
Rheumatic HD	3	0.93 (0.19-2.72)	0.89 (0.27-2.87)	**0.13 (0.01-0.18)***
ASHD (w/CHD)	433	1.06 (0.96-1.16)	1.04 (0.92-1.19)	0.95 (0.86-1.04)
AHD	466	1.02 (0.93-1.11)	1.00 (0.95-1.05)	no ICD Code available
CNS Vascular	78	1.13 (0.88-1.38)	1.14 (0.89-1.46)	1.19 (0.93-1.45)
Respiratory Diseases	48	0.76 (0.56-1.01)	0.75 (0.55-1.02)	**0.63 (0.46-0.84)***
Pneumonia	16	**0.58 (0.34-0.94)***	**0.58 (0.35-0.96)***	0.92 (0.54-1.50)
Emphysema	13	0.87 (0.46-1.49)	0.85 (0.50-1.47)	**0.45 (0.24-0.77)***
Asthma	1	0.72 (0.07-4.03)	0.66 (0.09-4.80)	1.57 (0.16-8.75)
Digestive Diseases	48	0.88 (0.65-1.17)	0.83 (0.58-1.19)	1.36 (1.00-1.80)
Ulcers	5	1.22 (0.39-2.86)	1.17 (0.49-2.77)	0.57 (0.18-1.33)
Cirrhosis	22	0.72 (0.45-1.09)	0.67 (0.43-1.04)	0.69 (0.43-1.04)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted; the MOR comparison disease = ASHD]

Table 16. White Male **Private Applicators (Farmers)**: Non Cancer Mortality PMR and MOR (continued)

Mortality Cause	**Observed Number**	**Florida PMR (95% CI)**	**Florida MOR (95% CI)**	**CORPS PMR (95% CI)**
Genito Urinary	12	0.78 (0.40-1.36)	0.78 (0.44-1.38)	1.83 (0.95-3.96)
Chronic Nephriti	0			
Skin Diseases	1	0.82 (0.08-4.59)	0.81 (0.11-5.85)	0.64 (0.06-3.59)
Bones and Joints	2	0.78 (0.08-2.81)	0.72 (0.18-2.95)	0.59 (0.06-2.12)
Senility	0			
External Causes	129	**1.29 (1.07-1.51)***	**0.86 (0.76-0.97)***	1.05 (0.83-1.27)
Accidents	78	**1.43 (1.11-1.75)***	**0.94 (0.89-0.98)***	1.17 (0.91-1.43)
Motor Vehicle	32	1.08 (0.74-1.52)	0.64 (0.06-6.54)	**1.51 (1.03-2.13)***
Suicide	36	1.08 (0.75-1.49)	0.75 (0.52-1.04)	**0.71 (0.50- 0.98)***

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted; the MOR comparison disease = ASHD]

Table 17. White Male **Private Applicators (Farmers)**: Cancer Mortality PMR and MOR

Mortality Cause	**Observed Number**	**Florida PMR (95% CI)**	**Florida MOR (95% CI)**	**CORPS PMR (95% CI)**
Malignant Neoplasms	402	0.99 (0.89-1.09)	0.95 (0.74-1.21)	**1.22 (1.10-1.34)***
Buccal/Pharynx	5	0.49 (0.16-1.15)	0.45 (0.19-1.07)	0.44 (0.14-1.03)
Digestive	90	0.95 (0.75-1.16)	0.91 (0.71-1.15)	**1.53 (1.21-1.85)***
Esophagus	7	0.72 (0.29-1.48)	0.67 (0.32-1.41)	0.84 (0.30-1.73)
Stomach	8	0.69 (0.29-1.36)	0.66 (0.33-1.33)	**0.26 (0.11-0.51)***
Large Intestine	36	0.99 (0.69-1.37)	0.95 (0.66-1.38)	**2.59 (1.81-3.58)***
Rectum	6	0.94 (0.35-2.05)	0.90 (0.40-2.01)	1.13 (0.34-2.47)
Liver	13	1.39 (0.74-2.39)	1.33 (0.77-2.30)	1.87 (0.99-3.21)
Pancreas	19	0.99 (0.59-1.55)	0.95 (0.57-1.57)	1.00 (0.59-1.56)
Respiratory	143	0.91 (0.76-1.08)	0.85 (0.70-1.04)	1.09 (0.91-1.27)
Larynx	1	0.20 (0.02-1.12)	0.19 (0.03-1.08)	0.18 (0.56-1.01)
Lung	142	0.93 (0.77-1.09)	0.88 (0.72-1.07)	1.12 (0.94-1.30)
Bone	2	2.94 (0.29-10.59)	2.27 (0.65-7.87)	0.39 (0.04-1.40)
Skin	12	1.22 (0.63-2.24)	1.12 (0.70-1.80)	1.15 (0.59-2.01)
Prostate	57	**1.49 (1.13-1.88)***	**1.52 (1.15-2.00)***	**2.77 (2.05-3.49)***
Testis	0			
Bladder	7	0.62 (0.24-1.28)	0.61 (0.29-1.29)	0.58 (0.23-1.19)
Kidney	10	1.04 (0.49-1.91)	0.98 (0.55-1.76)	**0.54 (0.25-0.99)***
Eye	3	**6.46 (1.33-19.13)***	**6.19 (2.28-16.81)***	**6.46 (1.13-16.60)***
Brain/CNS	16	1.63 (0.96-2.65)	1.45 (0.91-2.32)	1.48 (0.87-2.41)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted; the MOR comparison disease = ASHD]

Table 17. White Male **Private Applicators (Farmers)**: Cancer Mortality PMR and MOR (continued)

Mortality Cause	**Observed Number**	**Florida PMR (95% CI)**	**Florida MOR (95% CI)**	**CORPS PMR (95% CI)**
Thyroid	0			
All Lymphopoietic	36	1.04 (0.73-1.44)	0.97 (0.27-3.47)	1.04 (0.73-1.44)
LymphoSarcoma	1	0.45 (0.05-2.52)	0.42 (0.06-2.84)	**0.09 (0.01-0.50)***
Hodgkins	2	1.69 (0.17-6.10)	1.44 (0.43-4.87)	0.69 (0.07-1.94)
Leukemia	16	1.54 (0.91-2.52)	1.44 (0.91-2.29)	1.13 (0.66-1.84)
Other Lymphatic	17	0.82 (0.48-1.31)	0.76 (0.45-1.30)	1.46 (0.85-2.34)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted; the MOR comparison disease = ASHD]

Table 18. White Male **Commercial & Public Applicators**: Non Cancer Mortality PMR and MOR

Mortality Cause	**Observed Number**	**Florida PMR (95% CI)**	**Florida MOR (95% CI)**	**CORPS PMR (95% CI)**
Overall	239	1.00 (0.87-1.13)	0.79 (0.35-1.79)	**0.81 (0.71-0.91)***
Infectious Diseases	13	1.05 (0.56-1.80)	0.69 (0.01-5.13)	**10.26 (5.19-17.56)***
Tuberculosis	0			
Allergic Endocrine	4	0.67 (0.17-1.71)	0.47 (0.09-2.57)	1.51 (0.38-3.85)
Diabetes	3	0.74 (0.15-2.17)	0.70 (0.20-2.54)	0.71 (0.14-2.08)
Diseases of Blood	0			
Mental	1	0.40 (0.04-2.24)	0.37 (0.04-3.02)	0.33 (0.03-1.85)
Nervous System	4	1.47 (0.37-3.75)	1.13 (0.72-1.76)	2.12 (0.53-5.39)
Circulatory System	77	0.93 (0.72-1.14)	0.99 (0.01-4.13)	**0.52 (0.40-0.64)***
Rheumatic HD	2	3.77 (0.38-13.58)	**3.68 (1.01-13.42)***	0.31 (0.03-1.12)
ASHD (w/CHD)	51	0.96 (0.70-1.22)	1.05 (0.72-1.53)	**0.45 (0.33-0.57)***
AHD	55	0.91 (0.67-1.15)	1.00 (0.74-1.26)	no ICD Code available
CNS Vascular	10	1.38 (0.55-2.54)	1.42 (0.76-2.67)	**0.36 (0.17-0.66)***
Respiratory Diseases	4	0.56 (0.14-1.43)	0.53 (0.20-1.38)	0.91 (0.23-2.32)
Pneumonia	2	0.69 (0.07-2.49)	0.63 (0.13-3.17)	**0.22 (0.02-0.79)***
Emphysema	0			
Asthma	0			
Digestive Diseases	5	0.46 (0.15-1.08)	0.49 (0.21-1.17)	**0.39 (0.12-0.91)***
Ulcers	1	1.89 (0.05-10.57)	2.03 (0.29-14.17)	0.57 (0.06-3.20)
Cirrhosis	3	0.41 (0.08-1.20)	0.46 (0.15-1.41)	0.35 (0.07-1.03)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted; the MOR comparison disease = ASHD]

Table 18. White Male **Commercial & Public Applicators**: Non Cancer Mortality PMR and MOR (continued)

Mortality Cause	**Observed Number**	**Florida PMR (95% CI)**	**Florida MOR (95% CI)**	**CORPS PMR (95% CI)**
Genito Urinary	4	2.69 (0.67-6.85)	**2.79 (1.07-7.28)***	0.87 (0.22-2.22)
Chronic Nephriti	0			
Skin Diseases	0			
Bones and Joints	0			
Senility	0			
External Causes	41	1.11 (0.79-1.51)	0.42 (0.07-2.55)	0.92 (0.66-1.25)
Accidents	28	1.39 (0.92-2.01)	**0.50 (0.25-0.99)***	1.05 (0.70-1.52)
Motor Vehicle	14	1.16 (0.64-1.95)	0.38 (0.04-3.94)	1.23 (0.68-2.07)
Suicide	11	0.97 (0.48-1.74)	0.44 (0.04-5.58)	0.77 (0.38-1.38)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted; the MOR comparison disease = ASHD]

Table 19. White Male **Commercial & Public Applicators**: Cancer Mortality PMR and MOR

Mortality Cause	Observed Number	Florida PMR (95% CI)	Florida MOR (95% CI)	CORPS PMR (95% CI)
Malignant Neoplasms	80	1.24 (0.97-1.51)	1.25 (0.96-1.63)	0.99 (0.77-1.21)
Buccal/Pharynx	2	0.96 (0.10-3.46)	1.05 (0.17-6.36)	0.67 (0.07-2.41)
Digestive	21	1.44 (0.89-2.19)	1.52 (0.94-2.47)	1.04 (0.64-1.59)
Esophagus	4	2.25 (0.56-5.73)	2.41 (0.91-6.39)	1.59 (0.40-4.05)
Stomach	3	1.67 (0.34-4.92)	1.76 (0.57-5.43)	1.04 (0.21-3.05)
Large Intestine	6	1.18 (0.43-2.58)	1.25 (0.55-2.86)	0.54 (0.20-1.18)
Rectum	1	0.97 (0.09-5.44)	0.95 (0.09-10.12)	0.26 (0.03-1.46)
Liver	3	2.09 (0.42-6.11)	2.16 (0.70-6.67)	1.71 (0.34-5.03)
Pancreas	3	0.99 (0.20-2.90)	1.07 (0.34-3.41)	0.73 (0.15-2.14)
Respiratory	33	1.22 (0.84-1.71)	1.31 (0.86-2.01)	1.05 (0.72-1.47)
Larynx	1	1.05 (0.11-5.89)	1.14 (0.13-7.33)	1.22 (0.12-4.59)
Lung	32	1.23 (0.84-1.73)	1.33 (0.86-2.04)	1.05 (0.72-1.48)
Bone	1	6.26 (0.63-35.0)	3.26 (0.62-17.16)	1.45 (0.15-8.12)
Skin	3	1.37 (0.27-4.02)	1.10 (0.69-1.75)	1.75 (0.35-5.15)
Prostate	2	0.63 (0.06-2.27)	0.67 (0.16-2.76)	0.20 (0.05-1.76)
Testis	1	4.11 (0.42-23.33)	2.01 (0.46-8.71)	2.68 (0.27-15.14)
Bladder	0			
Kidney	3	1.81 (0.97-11.61)	1.97 (0.63-6.15)	2.01 (0.40-4.83)
Eye	0			
Brain/CNS	5	2.31 (0.74-5.42)	1.95 (0.89-4.31)	1.44 (0.46-3.37)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted; the MOR comparison disease = ASHD]

Table 19. White Male **Commercial & Public Applicators**: Cancer Mortality PMR and MOR (continued)

Mortality Cause	**Observed Number**	**Florida PMR (95% CI)**	**Florida MOR (95% CI)**	**CORPS PMR (95% CI)**
Thyroid	0			
All Lymphopoietic	4	0.69 (0.17-1.76)	0.56 (0.16-1.89)	**0.35 (0.09-0.89)***
LymphoSarcoma	0			
Hodgkins	0			
Leukemia	3	1.71 (0.34-5.03)	1.37 (0.47-4.03)	0.65 (0.13-1.91)
Other Lymphatic	1	0.29 (0.03-1.62)	0.27 (0.04-1.87)	**0.16 (0.02-0.89)***

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted; the MOR comparison disease = ASHD]

Table 20. **All Applicators: Non Cancer Mortality SMR**

Mortality Cause	**Observed Number**	**Florida SMR (95% CI)**
Overall	1875	**0.69 (0.67-0.73)***
Infectious Diseases	37	**0.49 (0.34-0.68)***
Tuberculosis	2	0.58 (0.06-2.10)
Allergic Endocrine	34	**0.53 (0.37-0.75)***
Diabetes	26	**0.56 (0.36-0.81)***
Diseases of Blood	6	0.71 (0.26-1.55)
Mental	10	**0.46 (0.21-0.80)***
Nervous System	35	1.08 (0.75-1.50)
Circulatory System	791	**0.81 (0.76-0.87)***
Rheumatic HD	5	0.55 (0.16-1.27)
ASHD (w/CHD)	510	**0.91 (0.84-0.99)***
AHD	551	**0.88 (0.81-0.96)***
CNS Vascular	96	**0.79 (0.64-0.97)***
Respiratory Diseases	58	**0.63 (0.48-0.82)***
Pneumonia	24	**0.63 (0.40-0.93)***
Emphysema	13	0.65 (0.35-1.12)
Asthma	1	0.21 (0.01-1.16)
Digestive Diseases	56	**0.57 (0.43-0.74)***
Ulcers	7	1.16 (0.46-2.38)
Cirrhosis	25	**0.45 (0.29-0.66)***
Genito Urinary	18	0.74 (0.44-1.17)
Chronic Nephriti	0	
Skin Diseases	1	0.37 (0.39-1.06)
Bones and Joints	4	0.48 (0.13-1.25)
Senility	0	
External Causes	188	0.88 (0.76-1.02)
Accidents	117	1.01 (0.83-1.22)
Motor Vehicle	54	0.82 (0.62-1.07)
Suicide	52	0.90 (0.67-1.19)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 21. **All** Applicators: **Cancer Mortality SMR**

Mortality Cause	**Observed Number**	**Florida SMR (95% CI)**
Malignant Neoplasms	532	**0.76 (0.70-0.84)***
Buccal/Pharynx	8	**0.49 (0.21-0.97)***
Digestive	124	**0.83 (0.69-0.99)***
Esophagus	11	0.75 (0.38-1.35)
Stomach	11	0.63 (0.32-1.13)
Large Intestine	49	0.86 (0.64-1.15)
Rectum	8	0.81 (0.35-1.60)
Liver	16	1.12 (0.64-1.83)
Pancreas	26	0.82 (0.54-1.21)
Respiratory	191	**0.83 (0.72-0.96)***
Larynx	2	0.30 (0.03-1.08)
Lung	189	**0.85 (0.74-0.99)***
Bone	3	2.47 (0.50- 7.23)
Skin	15	1.07 (0.60-1.77)
Bladder	7	0.59 (0.24-1.22)
Kidney	15	1.15 (0.64-1.89)
Eye	3	4.27 (0.86-12.49)
Brain/CNS	23	1.28 (0.81-1.92)
Thyroid	0	
All Lymphopoietic	44	0.79 (0.57-1.07)
LymphoSarcoma	2	0.49 (0.06-1.77)
Hodgkins	2	0.79 (0.09-2.89)
Leukemia	21	1.30 (0.81-1.99)
Other Lymphatic	19	**0.58 (0.35-0.91)***
Soft Tissue Sarcoma	0	

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 22. **Male** Applicators: **Non Cancer Mortality SMR**. Florida Comparison

Mortality Cause	**Observed Number**	**Florida SMR (95% CI)**
Overall	1776	**0.72 (0.69-0.75)***
Infectious Diseases	35	**0.52 (0.36-0.73)***
Tuberculosis	2	0.64 (0.07-2.30)
Allergic Endocrine	32	**0.56 (0.38-0.78)***
Diabetes	26	**0.61 (0.40-0.89)***
Diseases of Blood	6	0.78 (0.29-1.71)
Mental	10	**0.48 (0.23-0.88)***
Nervous System	34	1.15 (0.80-1.61)
Circulatory System	765	**0.85 (0.80-0.92)***
Rheumatic HD	5	0.60 (0.19-1.39)
ASHD (w/CHD)	498	0.97 (0.89-1.06)
AHD	536	0.94 (0.86-1.02)
CNS Vascula	90	0.81 (0.65-1.00)
Respiratory Diseases	53	**0.63 (0.47-0.83)***
Pneumonia	19	**0.54 (0.33-0.85)***
Emphysema	13	0.71 (0.38-1.22)
Asthma	1	0.23 (0.01-1.27)
Digestive Diseases	55	**0.61 (0.46-0.80)***
Ulcers	6	1.09 (0.40-2.36)
Cirrhosis	25	**0.49 (0.32-0.72)***
Genito Urinary	17	0.77 (0.45-1.22)
Chronic Nephriti	0	
Skin Diseases	1	0.41 (0.01-2.28)
Bones and Joints	4	0.53 (0.14-1.37)
Senility	0	
External Causes	173	0.90 (0.77-1.04)
Accidents	110	1.05 (0.87-1.27)
Motor Vehicle	48	0.81 (0.59-1.07)
Suicide	46	0.88 (0.65-1.18)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 23. **Male** Applicators: **Cancer Mortality SMR**: Florida Comparison

Mortality Cause	**Observed Number**	**Florida SMR (95% CI)**
Malignant Neoplasms	498	**0.78 (0.72-0.86)***
Buccal/Pharynx	7	**0.47 (0.19-0.97)***
Digestive	113	0.83 (0.68-1.00)
Esophagus	11	0.82 (0.41-1.47)
Stomach	11	0.69 (0.35-1.24)
Large Intestine	42	0.81 (0.59-1.10)
Rectum	7	0.78 (0.31-1.60)
Liver	16	1.23 (0.71-2.01)
Pancreas	24	0.83 (0.53-1.24)
Respiratory	182	0.87 (0.75-1.01)
Larynx	2	0.33 (0.04-1.18)
Lung	180	0.89 (0.76-1.03)
Bone	3	2.72 (0.55- 7.96)
Skin	15	1.18 (0.66-1.94)
Bladder	7	0.65 (0.26-1.33)
Kidney	13	1.09 (0.58-1.86)
Eye	3	4.67 (0.94-13.66)
Brain/CNS	22	1.34 (0.84-2.03)
Thyroid	0	
All Lymphopoietic	41	0.81 (0.58-1.10)
LymphoSarcoma	2	0.54 (0.06-1.94)
Hodgkin's	2	0.88 (0.10-3.17)
Leukemia	19	1.29 (0.78-2.02)
Other Lymphatic	18	**0.61 (0.36-0.96)***
Soft Tissue Sarcoma	0	
Male Cancers only:		
Prostate	64	**2.38 (1.83-3.04)***
Testis	1	1.05 (0.01-5.81)

[*= statistically significant 95% Confidence Interval; all ratios are age- and calendar year-adjusted]

Table 24. Male Applicators: **Non Cancer Mortality SMR**: CORPS Comparison

Mortality Cause	**Observed Number**	**CORPS SMR (95% CI)**
Overall	1776	**0.45 (0.43-0.47)***
Infectious Diseases	35	**2.07 (1.44-2.88)***
Tuberculosis	2	0.34 (0.04-1.24)
Allergic Endocrine	32	**0.68 (0.46-0.95)***
Diabetes	26	**0.66 (0.43-0.96)***
Diseases of Blood	6	1.08 (0.39-2.35)
Mental	10	0.55 (0.27-1.02)
Nervous System	34	1.45 (1.00-2.02)
Circulatory System	765	**0.44 (0.41-0.47)***
Rheumatic HD	5	**0.27 (0.09-0.63)***
ASHD (w/CHD)	498	**0.41 (0.38-0.45)***
AHD	536	No ICD Code Available
CNS Vascular	90	**0.49 (0.40-0.60)***
Respiratory Diseases	53	**0.24 (0.18-0.31)***
Pneumonia	19	**0.29 (0.17-0.45)***
Emphysema	13	**0.26 (0.14-0.44)***
Asthma	1	0.30 (0.00-1.67)
Digestive Diseases	55	**0.37 (0.28-0.48)***
Ulcers	6	**0.42 (0.15-0.91)***
Cirrhosis	25	**0.26 (0.17-0.39)***
Genito Urinary	17	0.72 (0.42-1.16)
Chronic Nephriti	0	
Skin Diseases	1	1.55 (0.02-8.63)
Bones and Joints	4	0.66 (0.18-1.68)
Senility	0	
External Causes	173	**0.64 (0.54-0.74)***
Accidents	110	**0.67 (0.55-0.81)***
Motor Vehicle	48	**0.63 (0.46-0.84)***
Suicide	46	**0.62 (0.45-0.82) ***

[*= statistically significant 95% Confidence Interval; all ratios are age- and calendar year-adjusted]

Table 25. Male Applicators: **Cancer Mortality SMR**: CORPS Comparison

Mortality Cause	**Observed Number**	**CORPS SMR (95% CI)**
Malignant Neoplasms	498	**0.67 (0.61-0.73)***
Buccal/Pharynx	7	**0.45 (0.18-0.93)***
Digestive	113	**0.63 (0.52-0.75)***
Esophagus	11	0.94 (0.47-1.69)
Stomach	11	**0.37 (0.19-0.67)***
Large Intestine	42	**0.63 (0.46-0.86)***
Rectum	7	0.63 (0.25-1.29)
Liver	16	1.39 (0.80-2.26)
Pancreas	24	0.83 (0.53-1.24)
Respiratory	182	**0.68 (0.58-0.78)***
Larynx	2	**0.20 (0.02-0.71)***
Lung	180	**0.70 (0.60-0.81)***
Bone	3	1.07 (0.22- 3.13)
Skin	15	1.44 (0.80-2.37)
Bladder	7	**0.37 (0.15-0.76)***
Kidney	13	0.69 (0.37-1.19)
Eye	3	1.86 (0.37-5.44)
Brain/CNS	22	1.36 (0.85-2.06)
Thyroid	0	
All Lymphopoietic	41	**0.60 (0.43-0.82)***
LymphoSarcoma	2	0.28 (0.03-1.00)
Hodgkin's	2	0.32 (0.04-1.14)
Leukemia	19	0.77 (0.46-1.21)
Other Lymphatic	18	0.67 (0.40-1.06)
Soft Tissue Sarcoma	0	
Male Cancers only:		
Prostate	64	1.16 (0.89-1.48)
Testis	1	0.34 (0.01-1.91)

[*= statistically significant 95% Confidence Interval; all ratios are age- and calendar year-adjusted]

Table 26. **Female** Applicators: **Non Cancer Mortality** SMR: Florida Comparison

Mortality Cause	**Observed Number**	**Florida SMR (95% CI)**
Overall	98	**0.44 (0.36-0.54)***
Infectious Disease	2	0.64 (0.07-2.30)
Tuberculosis	0	
Allergic Endocrine	2	0.36 (0.04-1.30)
Diabetes	0	
Diseases of Blood	0	
Mental	0	
Nervous System	1	0.35 (0.01-1.94)
Circulatory System	26	**0.33 (0.21-0.48)***
Rheumatic HD	0	
ASHD (w/CHD)	12	**0.26 (0.14-0.46)***
AHD	15	**0.29 (0.16-0.48)***
CNS Vascular	6	0.57 (0.21-1.24)
Respiratory Diseases	5	0.62 (0.20-1.46)
Pneumonia	5	1.46 (0.47-3.42)
Emphysema	0	
Asthma	0	
Digestive Diseases	1	**0.12 (0.01-0.67)***
Ulcers	1	1.91 (0.03-10.64)
Cirrhosis	0	
Genito Urinary	1	0.47 (0.01-2.61)
Chronic Nephriti	0	
Skin Diseases	0	
Bones and Joints	0	
Senility	0	
External Causes	15	0.74 (0.41-1.22)
Accidents	7	0.64 (0.26-1.31)
Motor Vehicle	6	0.94 (0.34-2.04)
Suicide	6	1.11 (0.41-2.42)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 27. **Female** Applicators: **Cancer Mortality SMR**: Florida Comparison

Mortality Cause	**Observed Number**	**Florida SMR (95% CI)**
Malignant Neoplasms	34	**0.58 (0.40-0.81)***
Buccal/Pharynx	1	0.74 (0.01-4.11)
Digestive	11	0.86 (0.43-1.54)
Esophagus	0	
Stomach	0	
Large Intestine	7	1.44 (0.58-2.97)
Rectum	1	1.19 (0.02-6.63)
Liver	0	
Pancreas	2	0.74 (0.08-2.69)
Respiratory	9	0.47 (0.22-0.90)
Larynx	0	
Lung	9	**0.49 (0.22-0.93)***
Bone	0	
Skin	0	
Bladder	0	
Kidney	2	1.80 (0.20-6.49)
Eye	0	
Brain/CNS	1	0.65 (0.01-3.60)
Thyroid	0	
All Lymphopoietic	3	0.62 (0.12-1.80)
LymphoSarcoma	0	
Hodgkins	0	
Leukemia	2	1.42 (0.16-5.12)
Other Lymphatic	1	0.35 (0.01-1.95)
Soft Tissue Sarcoma	0	
Female Cancers only:		
Breast	4	0.76 (0.20-1.94)
All Genital	2	0.75 (0.08-2.72)
Cervix	1	1.32 (0.02-7.34)
Uterus	1	0.94 (0.01-5.22)
Other Genital	1	0.63 (0.01-3.49)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 28. **Female** Applicators: **Non Cancer Mortality SMR**: CORPS Comparison

Mortality Cause	**Observed Number**	**CORPS SMR (95% CI)**
Overall	98	**0.49 (0.40-0.60)***
Infectious Diseases	2	2.04 (0.23-7.38)
Tuberculosis	0	
Allergic Endocrine	2	0.43 (0.05-1.56)
Diabetes	0	
Diseases of Blood	0	
Mental	0	
Nervous System	1	0.37 (0.01-2.04)
Circulatory System	26	**0.32 (0.21-0.47)***
Rheumatic HD	0	
ASHD (w/CHD)	12	**0.24 (0.12-0.41)***
AHD	15	No ICD Code available
CNS Vascular	6	**0.37 (0.14-0.81)***
Respiratory Diseases	5	0.71 (0.23-1.66)
Pneumonia	5	1.83 (0.59-4.26)
Emphysema	0	
Asthma	0	
Digestive Diseases	1	**0.14 (0.01-0.76)***
Ulcers	1	4.97 (0.06-27.63)
Cirrhosis	0	
Genito Urinary	1	0.38 (0.01-2.10)
Chronic Nephriti	0	
Skin Diseases	0	
Bones and Joints	0	
Senility	0	
External Causes	15	0.83 (0.46-1.36)
Accidents	7	1.07 (0.43-2.21)
Motor Vehicle	6	2.33 (0.85-5.07)
Suicide	6	0.54 (0.20-1.17)

[*= statistically significant 95% Confidence Interval; all ratios are age- and calendar year-adjusted]

Table 29. **Female** Applicators: **Cancer Mortality SMR**: CORPS Comparison

Mortality Cause	**Observed Number**	**CORPS SMR (95% CI)**
Malignant Neoplasms	34	**0.70 (0.48-0.98)***
Buccal/Pharynx	1	4.57 (0.06-25.41)
Digestive	11	0.94 (0.47-1.69)
Esophagus	0	
Stomach	0	
Large Intestine	7	1.43 (0.57-2.94)
Rectum	1	2.78 (0.04-15.47)
Liver	0	
Pancreas	2	0.67 (0.08-2.42)
Respiratory	9	1.20 (0.55-2.28)
Larynx	0	
Lung	9	1.25 (0.57-2.37)
Bone	0	
Skin	0	
Bladder	0	
Kidney	2	3.17 (0.36-11.43)
Eye	0	
Brain/CNS	1	2.48 (0.03-13.78)
Thyroid	0	
All Lymphopoietic	3	0.76 (0.15-2.22)
LymphoSarcoma	0	
Hodgkins	0	
Leukemia	2	1.65 (0.19-5.95)
Other Lymphatic	1	0.47 (0.01-2.63)
Soft Tissue Sarcoma	0	
Female Cancers only:		
Breast	4	0.44 (0.12-1.14)
All Genital	2	**0.24 (0.03-0.87)***
Cervix	1	0.31 (0.01-1.74)
Uterus	1	0.20 (0.01-1.09)
Other Genital	1	0.31 (0.01-1.73)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 30. **All, Male and Female** Applicators: **SMR by Calendar Year of First Licensure**

Licensure Year	**Observed Number**	**Florida SMR (95% CI)**
Overall Mortality		
All Applicators:		
1975-1979	1327	**0.70 (0.66-0.74)***
1980-1984	364	**0.73 (0.66-0.81)***
1985-1989	142	**0.59 (0.50-0.69)***
1990-1994	22	**0.39 (0.34-0.54)***
All Males:		
1975-1979	1270	**0.72 (0.68-0.76)***
1980-1984	341	**0.77 (0.79-0.85)***
1985-1989	127	**0.60 (0.50-0.72)***
1990-1994	20	**0.39 (0.24-0.60)***
All Females:		
1975-1979	57	**0.43 (0.32-0.55)***
1980-1984	23	**0.45 (0.29-0.68)***
1985-1989	15	**0.50 (0.28-0.82)***
1990-1994	2	0.42 (0.05-1.51)

[*= statistically significant 95% Confidence Interval; all ratios are age adjusted]

Table 30. **All, Male and Female** Applicators: **SMR by Calendar Year of First Licensure** (continued)

Licensure Year	**Observed Number**	**Florida SMR (95% CI)**
Prostate Cancer Mortality		
All Males:		
1975-1979	51	**2.51 (1.87-3.30)***
1980-1984	11	**2.39 (1.19-4.27)***
1985-1989	2	1.15 (0.13-4.15)
1990-1994	0	
External Causes of Mortality		
All Applicators:		
1975-1979	93	0.86 (0.70-1.06)
1980-1984	58	1.04 (0.79-1.34)
1985-1989	36	0.91 (0.63-1.25)
1990-1994	1	**0.10 (0.01-0.54)***
All Males:		
1975-1979	90	0.89 (0.72-1.10)
1980-1984	53	1.07 (0.80-1.40)
1985-1989	29	0.86 (0.58-1.23)
1990-1994	1	**0.11 (0.01-0.60)***
All Females:		
1975-1979	3	0.44 (0.09-1.27)
1980-1984	5	0.78 (0.25-1.82)
1985-1989	7	1.16 (0.47-2.40)
1990-1994	0	

[*= statistically significant 95% Confidence Interval; all ratios are age adjusted]

Table 31. **All, Male and Female** Applicators: **SMR by years of Licensure**

Years of Licensure	Observed Number	Florida SMR (95% CI)
<u>Overall Mortality</u>		
All Applicators:		
0≤4	63	**0.64 (0.49-0.82)***
4≤8	743	**0.86 (0.80-0.93)***
8≤12	900	**0.74 (0.69-0.79)***
12≤16	115	**0.42 (0.35-0.51)***
16≤20	33	**0.15 (0.10-0.21)***
All Males:		
0≤4	57	**0.66 (0.50-0.85)***
4≤8	696	**0.91 (0.84-0.98)***
8≤12	859	**0.77 (0.72-0.82)***
12≤16	113	**0.44 (0.36-0.53)***
16≤20	32	**0.15 (0.10-0.21)***
All Females:		
0≤4	6	0.51 (0.19-1.11)
4≤8	47	**0.50 (0.36-0.66)***
8≤12	41	**0.44 (0.32-0.60)***
12≤16	2	**0.15 (0.02-0.53)***
16≤20	1	**0.17 (0.01-0.93)***
<u>Prostate Cancer Mortality</u>		
All Males:		
0≤4	21	**2.59 (1.60-3.96)***
4≤8	37	**2.78 (1.95-3.83)***
8≤12	5	1.83 (0.59-4.28)
12≤16	1	0.49 (0.01-2.74)
16≤20	0	
1975-79 Male Applicators:		
0≤4	9	**2.58 (1.18-4.89)***
4≤8	36	**2.90 (2.03-4.01)***
8≤12	5	2.15 (0.67-4.88)
12≤16	1	0.48 (0.02-2.69)
16≤20	0	
1980-84 Male Applicators:		
0≤4	10	**3.20 (1.53-5.89)***
4≤8	1	1.08 (0.01-6.00)
8≤12	0	
12≤16	0	
16≤20	0	

[*= statistically significant 95% Confidence Interval; all ratios are age & calenar year adjusted]

Table 31. **All, Male and Female** Applicators: **SMR by years of Licensure** (continued)

Years of Licensure	Observed Number	Florida SMR (95% CI)
External Causes of Mortality		
All Applicators:		
0≤4	8	0.52 (0.23-1.03)
4≤8	104	**1.30 (1.06-1.57)***
8≤12	63	0.95 (0.73-1.21)
12≤16	9	**0.36 (0.16-0.69)***
16≤20	4	**0.16 (0.04-0.41)***
All Males:		
0≤4	8	0.60 (0.26-1.19)
4≤8	93	1.35 (1.09-1.66)
8≤12	60	0.98 (0.75-1.26)
12≤16	9	**0.38 (0.17-0.72)***
16≤20	3	**0.12 (0.02-0.36)***
All Females:		
0≤4	0	
4≤8	11	0.97 (0.49-1.74)
8≤12	3	0.57 (0.11-1.67)
12≤16	0	
16≤20	1	1.77 (0.02-9.87)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 32. **All, Male and Female** Applicators: **SMR by Age at Licensure Issue**

Age Group	Observed Number	Florida SMR (95% CI)
Overall Mortality		
All Applicators:		
20-24	18	**0.37 (0.22-0.59)***
25-29	46	**0.54 (0.39-0.72)***
30-34	52	**0.49 (0.37-0.65)***
35-39	67	**0.54 (0.42-0.69)***
40-44	115	**0.71 (0.59-0.85)***
45-49	171	**0.67 (0.58-0.79)***
50-54	257	**0.70 (0.62-0.79)***
55-59	322	**0.78 (0.69-0.87)***
60-64	312	**0.73 (0.65-0.81)***
65-69	258	**0.74 (0.65-0.84)***
70-74	144	**0.67 (0.56-0.78)***
75-79	60	**0.64 (0.49-0.83)***
80-84	28	0.74 (0.49-1.07)
85+	5	0.96 (0.31-2.23)
All Males:		
20-24	14	**0.33 (0.18-0.55)***
25-29	45	**0.59 (0.43-0.79)***
30-34	49	**0.52 (0.38-0.69)***
35-39	60	**0.53 (0.40-0.68)***
40-44	102	**0.68 (0.56-0.83)***
45-49	165	**0.71 (0.60-0.82)***
50-54	248	**0.74 (0.65-0.83)***
55-59	302	**0.79 (0.70-0.89)***
60-64	298	**0.76 (0.67-0.85)***
65-69	248	**0.77 (0.68-0.87)***
70-74	137	**0.70 (0.58-0.82)***
75-79	58	**0.68 (0.51-0.88)***
80-84	27	0.73 (0.48-1.06)
85+	5	0.96 (0.31-2.23)

[*= statistically significant 95% Confidence Interval; calendar year adjusted]

Table 32. **All, Male and Female** Applicators: **SMR by Age at Licensure Issue** (Continued)

Age Group	**Observed Number**	**Florida SMR (95% CI)**
Overall Mortality		
All Females:		
20-24	4	0.79 (0.21-2.02)
25-29	1	**0.12 (0.01-0.64)***
30-34	3	**0.30 (0.06-0.89)***
35-39	7	0.65 (0.26-1.34)
40-44	13	1.01 (0.54-1.73)
45-49	6	**0.33 (0.12-0.72)***
50-54	9	**0.30 (0.14-0.57)***
55-59	20	**0.63 (0.39-0.98)***
60-64	14	**0.37 (0.20-0.62)***
65-69	10	**0.38 (0.18-0.70)***
70-74	7	**0.36 (0.14-0.74)***
75-79	2	**0.27 (0.03-0.97)***
80-84	1	1.39 (0.02-7.75)
85+	0	
Prostate Cancer Mortality		
All Males:		
40-44	3	**5.63 (1.13-16.45)***
45-49	1	0.63 (0.01-3.49)
50-54	5	1.36 (0.59-2.68)
55-59	8	1.47 (0.63-2.90)
60-64	14	**2.18 (1.19-3.66)***
65-69	21	**3.88 (2.40-5.93)***
70-74	6	2.11 (0.77-4.59)
75-79	4	**4.88 (1.31-12.49)***
80-84	1	4.51 (0.06-25.10)
85+	1	33.18 (0.43-184.61)

[*= statistically significant 95% Confidence Interval; calendar year adjusted]

Table 32. **All, Male and Female** Applicators: **SMR by Age at Licensure Issue** (Continued)

Age Group	**Observed Number**	**Florida SMR (95% CI)**
External Causes of Mortality		
All Applicators:		
20-24	14	**0.53 (0.29-0.89)***
25-29	24	**0.66 (0.42-0.98)***
30-34	24	0.74 (0.47-1.10)
35-39	16	0.62 (0.35-1.01)
40-44	25	1.20 (0.77-1.77)
45-49	17	0.86 (0.50-1.38)
50-54	17	0.94 (0.55-1.50)
55-59	13	0.96 (0.51-1.64)
60-64	13	1.31 (0.70-2.24)
65-69	13	**2.09 (1.11-3.59)***
70-74	7	**2.21 (0.88-4.55)***
75-79	4	**3.95 (1.06-10.12)***
80-84	1	3.77 (0.05-20.97)
85+	8	0.52 (0.23-1.03)

[*= statistically significant 95% Confidence Interval; calendar year adjusted]

Table 32. **All, Male and Female** Applicators: **SMR by Age at Licensure Issue** (Continued)

Age Group	**Observed Number**	**Florida SMR (95% CI)**
External Causes of Mortality		
All Males:		
20-24	11	**0.47 (0.23-0.84)***
25-29	23	0.71 (0.45-1.06)
30-34	22	0.75 (0.47-1.14)
35-39	15	0.64 (0.36-1.06)
40-44	24	1.26 (0.81-1.87)
45-49	15	0.83 (0.46-1.35)
50-54	16	0.97 (0.55-1.57)
55-59	12	0.96 (0.50-1.69)
60-64	12	1.34 (0.69-2.33)
65-69	12	**2.11 (1.09-3.69)***
70-74	6	2.12 (0.77-4.62)
75-79	4	**4.44 (1.19-11.36)***
80-84	1	3.77 (0.05-20.97)
85+	0	
All Females:		
20-24	3	1.06 (0.21-3.10)
25-29	1	0.26 (0.01-1.45)
30-34	2	0.62 (0.07-2.22)
35-39	1	0.41 (0.01-2.30)
40-44	1	0.55 (0.01-3.07)
45-49	2	1.27 (0.14-4.58)
50-54	1	0.62 (0.01-3.48)
55-59	1	0.92 (0.01-5.14)
60-64	1	1.04 (0.01-5.80)
65-69	1	1.88 (0.02-10.48)
70-74	1	2.91 (0.04-16.20)
75-79	0	
80-84	0	
85+	0	

[*= statistically significant 95% Confidence Interval; calendar year adjusted]

Table 33. Male **Private (Farmer)** Applicators: **Non Cancer Mortality SMR**

Mortality Cause	**Observed Number**	**Florida SMR (95% CI)**
Overall	1527	**0.71 (0.68-0.75)***
Infectious Diseases	22	**0.47 (0.30-0.72)***
Tuberculosis	2	0.79 (0.09-2.85)
Allergic Endocrine	28	**0.58 (0.39-0.84)***
Diabetes	23	**0.64 (0.40-0.96)***
Diseases of Blood	6	0.94 (0.34-2.04)
Mental	9	0.53 (0.24-1.00)
Nervous System	30	1.20 (0.81-1.71)
Circulatory System	686	**0.87 (0.81-0.94)***
Rheumatic HD	3	0.38 (0.08-1.11)
ASHD (w/CHD)	446	0.99 (0.90-1.09)
AHD	480	0.95 (0.87-1.04)
CNS Vascular	79	0.81 (0.64-1.01)
Respiratory Diseases	49	**0.67 (0.50-0.89)***
Pneumonia	17	**0.56 (0.33-0.90)***
Emphysema	13	0.81 (0.43-1.39)
Asthma	1	0.28 (0.01-1.57)
Digestive Diseases	50	**0.67 (0.50-0.89)***
Ulcers	5	1.04 (0.34-2.43)
Cirrhosis	22	**0.53 (0.33-0.80)***
Genito Urinary	13	0.67 (0.35-1.14)
Chronic Nephriti	0	
Skin Diseases	1	0.47 (0.01-2.62)
Bones and Joints	3	0.49 (0.10-1.42)
Senility	0	
External Causes	130	0.91 (0.76-1.09)
Accidents	81	1.05 (0.83-1.30)
Motor Vehicle	34	0.79 (0.54-1.10)
Suicide	35	0.90 (0.63-1.26)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 34. Male **Private (Farmer)**Applicators: **Cancer Mortality SMR**

Mortality Cause	**Observed Number**	**Florida SMR (95% CI)**
Malignant Neoplasms	416	**0.77 (0.70-0.85)***
Buccal/Pharynx	5	**0.41 (0.13-0.95)***
Digestive	92	**0.79 (0.64-0.97)***
Esophagus	7	0.63 (0.25-1.29)
Stomach	8	0.59 (0.26-1.17)
Large Intestine	36	0.81 (0.57-1.12)
Rectum	6	0.78 (0.29-1.71)
Liver	13	1.18 (0.63-2.02)
Pancreas	21	0.85 (0.53-1.30)
Respiratory	148	**0.84 (0.71-0.99)***
Larynx	1	0.20 (0.01-1.09)
Lung	147	0.86 (0.73-1.01)
Bone	2	2.29 (0.26- 8.27)
Skin	12	1.17 (0.61-2.05)
Bladder	7	0.74 (0.30-1.52)
Kidney	10	0.99 (0.48-1.83)
Eye	3	**5.52 (1.11-16.12)***
Brain/CNS	17	1.28 (0.74-2.04)
Thyroid	0	
All Lymphopoietic	36	0.85 (0.60-1.18)
LymphoSarcoma	1	0.32 (0.01-1.76)
Hodgkins	2	1.13 (0.13-4.09)
Leukemia	16	1.31 (0.75-2.12)
Other Lymphatic	17	0.68 (0.40-1.09)
Soft Tissue Sarcoma	0	
Male Cancers only:		
Prostate	62	**2.56 (1.96-3.29)***
Testis	0	

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 35. Male **Commercial and Public** Applicators: **Non Cancer Mortality SMR**

Mortality Cause	**Observed Number**	**Florida SMR (95% CI)**
Overall	250	**0.70 (0.62-0.79)***
Infectious Diseases	13	0.64 (0.34-1.09)
Tuberculosis	0	
Allergic Endocrine	4	0.41 (0.11-1.06)
Diabetes	3	0.45 (0.09-1.31)
Diseases of Blood	0	
Mental	1	0.26 (0.01-1.46)
Nervous System	4	0.91 (0.24-2.33)
Circulatory System	79	**0.74 (0.59-0.93)***
Rheumatic HD	2	1.62 (0.18-5.84)
ASHD (w/CHD)	52	0.86 (0.64-1.13)
AHD	56	0.83 (0.63-1.07)
CNS Vascular	11	0.82 (0.41-1.47)
Respiratory Diseases	4	**0.36 (0.10-0.93)***
Pneumonia	2	0.44 (0.05-1.59)
Emphysema	0	
Asthma	0	
Digestive Diseases	5	**0.32 (0.10-0.75)***
Ulcers	1	1.37 (0.02-7.64)
Cirrhosis	3	**0.31 (0.06-0.89)***
Genito Urinary	4	1.48 (0.40-3.79)
Chronic Nephriti	0	
Skin Diseases	0	
Bones and Joints	1	0.76 (0.01-4.23)
Senility	0	
External Causes	43	0.84 (0.61-1.14)
Accidents	29	1.08 (0.72-1.55)
Motor Vehicle	14	0.86 (0.47-1.44)
Suicide	11	0.82 (0.41-1.47)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 35. Male **Commercial and Public** Applicators: **Non Cancer Mortality SMR**

Mortality Cause	**Observed Number**	**Florida SMR (95% CI)**
Overall	250	**0.70 (0.62-0.79)***
Infectious Diseases	13	0.64 (0.34-1.09)
Tuberculosis	0	
Allergic Endocrine	4	0.41 (0.11-1.06)
Diabetes	3	0.45 (0.09-1.31)
Diseases of Blood	0	
Mental	1	0.26 (0.01-1.46)
Nervous System	4	0.91 (0.24-2.33)
Circulatory System	79	**0.74 (0.59-0.93)***
Rheumatic HD	2	1.62 (0.18-5.84)
ASHD (w/CHD)	52	0.86 (0.64-1.13)
AHD	56	0.83 (0.63-1.07)
CNS Vascular	11	0.82 (0.41-1.47)
Respiratory Diseases	4	**0.36 (0.10-0.93)***
Pneumonia	2	0.44 (0.05-1.59)
Emphysema	0	
Asthma	0	
Digestive Diseases	5	**0.32 (0.10-0.75)***
Ulcers	1	1.37 (0.02-7.64)
Cirrhosis	3	**0.31 (0.06-0.89)***
Genito Urinary	4	1.48 (0.40-3.79)
Chronic Nephriti	0	
Skin Diseases	0	
Bones and Joints	1	0.76 (0.01-4.23)
Senility	0	
External Causes	43	0.84 (0.61-1.14)
Accidents	29	1.08 (0.72-1.55)
Motor Vehicle	14	0.86 (0.47-1.44)
Suicide	11	0.82 (0.41-1.47)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 36. Male **Commercial and Public** Applicators: **Cancer Mortality SMR**

Mortality Cause	Observed Number	Florida SMR (95% CI)
Malignant Neoplasms	82	0.83 (0.66-1.03)
Buccal/Pharynx	2	0.78 (0.09-2.83)
Digestive	21	1.06 (0.65-1.61)
Esophagus	4	1.83 (0.49-4.69)
Stomach	3	1.26 (0.25-3.69)
Large Intestine	6	0.84 (0.31-1.82)
Rectum	1	0.74 (0.01-4.11)
Liver	3	1.52 (0.31-4.43)
Pancreas	3	0.72 (0.15-2.11)
Respiratory	34	1.03 (0.71-1.44)
Larynx	1	0.98 (0.01-5.46)
Lung	33	1.04 (0.72-1.46)
Bone	1	4.38 (0.06-24.35)
Skin	3	1.19 (0.24-3.49)
Bladder	0	
Kidney	3	1.59 (0.32-4.65)
Eye	0	
Brain/CNS	5	1.62 (0.52-3.79)
Thyroid	0	
All Lymphopoietic	5	0.61 (0.20-1.42)
LymphoSarcoma	1	1.80 (0.02-10.04)
Hodgkins	0	
Leukemia	3	1.23 (0.25-3.61)
Other Lymphatic	1	0.21 (0.01-1.18)
Soft Tissue Sarcoma	0	
Male Cancers only:		
Prostate	2	0.73 (0.08-2.65)
Testis	1	4.32 (0.06-24.02)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 37. All Applicators Cox Proportional Hazard Analyses for **Overall Mortality**

Covariable	**Parameter Estimate**	**Standard Error**	**Risk Ratio**	**p value**
<u>Single Covariable Regression</u>:				
Gender (D) [females=1]	-0.4848	0.1043	0.62	**0.0001**
Hispanic (D) [Hispanic=1]	-0.0661	0.1529	0.94	0.19
Incident cancer (D) [Cancer=1]	1.1018	0.0544	3.01	**0.0001**
Year of first licensure (C)				
1975-79	0.6526	0.0939	1.92	**0.0001**
1980-84	0.5175	0.1005	1.68	**0.0001**
Age at first licensure (CO)	-0.0672	0.0058	0.94	**0.0001**
Number of years licensed (CO)	-0.0397	0.0068	0.96	**0.0001**
Number of years licensed (C)				
4-8	0.4782	0.1319	1.61	**0.0003**
8-12	0.5557	0.1328	1.74	**0.0001**
12-16	0.0084	0.1577	1.01	0.96
16-20	-0.9887	0.2134	0.37	**0.0001**
Licensure type (D) [Private=1]	-0.0074	0.0708	0.99	**0.01**
Aerial licensure (D) [Aerial=1]	0.0505	0.2599	1.05	0.85
Aquatic licensure (D) [Aquatic=1]	0.1166	0.1374	1.12	0.39
<u>Exposure Model</u> (Entire Cohort):				
Age at first licensure (CO)	-0.1309	0.0090	0.88	**0.0001**
Number of years licensed (CO)	-0.1312	0.0072	0.88	**0.0001**
<u>Exposure Model</u> (1975-1979)				
Age at first licensure (CO)	-0.0593	0.0108	0.94	**0.0001**
Number of years licensed (CO)	-0.1495	0.0119	0.86	**0.0001**

[D= Dichotomous; C=Categorical; CO=Continuous]

Table 38. All Applicators Cox Proportional Hazard Analyses for **External Causes** Mortality

Covariable	Parameter Estimate	Standard Error	Risk Ratio	p value
Single Covariable Regression:				
Gender (D) [females=1]	-0.2144	0.2698	0.81	0.43
Hispanic (D) [Hispanic=1]	-0.2629	0.4541	0.77	0.56
Incident cancer (D) [Cancer=1]	-0.3622	0.3522	0.69	0.31
Year of first licensure (C)				
1975-79	0.4059	0.2228	1.50	0.07
1980-84	0.5441	0.2148	1.72	**0.01**
Age at first licensure (CO)	-0.0958	0.0167	0.91	**0.0001**
Number of years licensed (CO)	-0.0579	0.0212	0.94	**0.006**
Number of years licensed (C)				
4-8	0.8687	0.3483	2.38	**0.01**
8-12	0.7534	0.3651	2.12	**0.04**
12-16	0.0191	0.4745	1.02	0.96
16-20	-0.6689	0.6042	0.51	0.27
Licensure type (D) [Private=1]	0.0043	0.1765	1.00	0.98
Aerial licensure (D) [Aerial=1]	1.4767	0.3636	4.38	**0.001**
Aquatic licensure (D) [Aquatic=1]	0.3841	0.2813	1.47	0.17
Exposure Model (Entire Cohort)				
Age at first licensure (CO)	-0.2064	0.0265	0.81	**0.0001**
Number of years licensed (CO)	-0.1845	0.0349	0.83	**0.0001**
Exposure Model (1975-1979)				
Age at first licensure (CO)	-0.2842	0.0495	0.75	**0.0001**
Number of years licensed (CO)	-0.1133	0.0457	0.89	**0.01**

[D= Dichotomous; C=Categorical; CO=Continuous]

Table 39. All Male Applicators Cox Proportional Hazard Analyses for **Prostate Cancer** Mortality

Covariable	**Parameter Estimate**	**Standard Error**	**Risk Ratio**	**p value**
<u>Single Covariable Regression</u>:				
Gender (D) [females=1]				
Hispanic (D) [Hispanic=1]				
Incident cancer (D) [Cancer=1]	2.9099	0.3032	18.36	**0.0001**
Year of first licensure (C)				
1975-79	0.8095	0.7291	2.25	0.27
1980-84	0.8159	0.7715	2.26	0.29
Age at first licensure (CO)	-0.0481	0.0339	0.95	0.16
Number of years licensed (CO)	-0.0247	0.0400	0.98	0.54
Number of years licensed (C)				
4-8				
8-12				
12-16				
16-20				
Licensure type (D) [Private=1]	0.9900	0.7296	2.69	0.18
Aerial licensure (D) [Aerial=1]				
Aquatic licensure (D) [Aquatic=1]	0.1087	1.0162	1.12	0.92
<u>Exposure Model</u> (Entire Cohort)				
Age at first licensure (CO)	-0.2635	0.05662	0.77	**0.0001**
Number of years licensed (CO)	-0.1956	0.0652	0.82	**0.003**
<u>Exposure Model</u> (1975-1979)				
Age at first licensure (CO)	-0.3021	0.0739	0.74	**0.0001**
Number of years licensed (CO)	-0.1104	0.0848	0.89	0.19

[D= Dichotomous; C=Categorical; CO=Continuous]

Table 40. All Applicators: **Cancer incidence SIR**

Cancer Cause	**Observed Number**	**Florida SIR (95% CI)**
Malignant Neoplasms	1266	**0.72 (0.68-0.76)***
Buccal/Pharynx	40	**0.70 (0.50-0.95)***
Digestive	242	**0.75 (0.66-0.85)***
Esophagus	14	0.78 (0.42-1.30)
Stomach	15	**0.49 (0.28-0.81)***
Large Intestine	108	**0.71 (0.58-0.86)***
Rectum	55	0.86 (0.65-1.12)
Liver	18	1.12 (0.64-1.83)
Pancreas	27	0.82 (0.54-1.19)
Respiratory	245	**0.76 (0.66-0.86)***
Larynx	12	**0.44 (0.23-0.76)***
Lung	231	**0.79 (0.69-0.90)***
Bone	5	1.42 (0.46- 3.32)
Skin	53	0.94 (0.70-1.23)
Kidney	27	0.70 (0.46-1.02)
Eye	5	1.65 (0.53-3.84)
Brain/CNS	26	1.08 (0.70-1.58)
Thyroid	8	0.51 (0.22-1.01)
All Lymphopoietic	82	0.89 (0.71-1.11)
LymphoSarcoma	34	0.88 (0.61-1.23)
Hodgkins	8	0.96 (0.41-1.89)
Leukemia	28	0.96 (0.64-1.38)
Other Lymphatic	12	0.78 (0.40-1.36)
Soft Tissue Sarcoma	0	

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 41. **Male** Applicators: **Cancer incidence SIR**

Cancer Cause	**Observed Number**	**Florida SIR (95% CI)**
Malignant Neoplasms	1159	**0.72 (0.68-0.76)***
Buccal/Pharynx	35	**0.67 (0.47-0.93)***
Digestive	227	**0.76 (0.67-0.87)***
Esophagus	14	0.85 (0.46-1.42)
Stomach	15	**0.54 (0.30-0.89)***
Large Intestine	98	**0.70 (0.57-0.86)***
Rectum	52	0.89 (0.66-1.16)
Liver	18	1.13 (0.67-1.79)
Pancreas	26	0.86 (0.56-1.26)
Respiratory	230	**0.77 (0.68-0.88)***
Larynx	12	**0.48 (0.25-0.83)***
Lung	216	**0.81 (0.70-0.92)***
Bone	5	1.57 (0.51- 3.66)
Skin	48	0.94 (0.69-1.24)
Prostate	353	**1.92 (1.73-2.14)***
Testis	23	**2.49 (1.58-3.74)***
Bladder	59	0.94 (0.74-1.25)
Kidney	26	0.74 (0.48-1.08)
Eye	5	1.80 (0.58-4.21)
Brain/CNS	24	1.09 (0.70-1.63)
Thyroid	6	**0.43 (0.16-0.93)***
All Lymphopoietic	76	0.91 (0.71-1.14)
LymphoSarcoma	32	0.91 (0.62-1.28)
Hodgkins	8	1.07 (0.46-2.11)
Leukemia	25	0.94 (0.61-1.38)
Other Lymphatic	11	0.78 (0.39-1.40)
Soft Tissue Sarcoma	0	

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 42. **Female** Applicators: **Cancer incidence SIR**

Cancer Cause	**Observed Number**	**Florida SIR (95% CI)**
Malignant Neoplasms	107	**0.73 (0.59-0.88)***
Buccal/Pharynx	5	1.04 (0.33-2.42)
Digestive	15	**0.56 (0.31-0.92)***
Esophagus	0	
Stomach	0	
Large Intestine	10	0.79 (0.38-1.45)
Rectum	3	0.56 (0.11-1.64)
Liver	0	
Pancreas	1	0.36 (0.01-2.02)
Respiratory	15	**0.56 (0.31-0.93)***
Larynx	0	
Lung	15	0.62 (0.35-1.03)
Bone	0	
Skin	5	0.94 (0.30-2.18)
Bladder	3	0.55 (0.11-1.59)
Kidney	1	0.31 (0.01-1.72)
Eye	0	
Brain/CNS	2	0.92 (0.10-3.33)
Thyroid	2	1.33 (0.15-4.79)
All Lymphopoietic	6	0.74 (0.27-1.61)
LymphoSarcoma	2	0.59 (0.07-2.12)
Hodgkins	0	
Leukemia	3	1.18 (0.24-3.44)
Other Lymphatic	1	0.78 (0.01-4.33)
Soft Tissue Sarcoma	0	
Female Cancers only:		
Breast	26	1.14 (0.74-1.67)
All Genital	23	**2.08 (1.32-3.12)***
Cervix	11	**3.71 (1.85-6.64)***
Uterus	11	1.45 (0.72-2.59)
Other Genital	3	0.90 (0.18-2.63)

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 43. **All, Male and Female** Applicators:**Cancer incidence SIR by Calendar Year of First Licensure**

Licensure Year	**Observed Number**	**Florida SIR (95% CI)**
Overall Cancer Incidence		
All Applicators:		
1975-1979	865	**0.76 (0.71-0.82)***
1980-1984	259	**0.69 (0.61-0.78)***
1985-1989	124	**0.61 (0.50-0.72)***
1990-1994	18	**0.34 (0.20-0.54)***
All Males:		
1975-1979	807	**0.77 (0.71-0.82)***
1980-1984	232	**0.69 (0.60-0.78)***
1985-1989	104	**0.58 (0.47-0.70)***
1990-1994	16	**0.33 (0.19-0.54)***
All Females:		
1975-1979	58	**0.73 (0.56-0.95)***
1980-1984	27	0.70 (0.46-1.02)
1985-1989	20	0.78 (0.48-1.21)
1990-1994	2	0.46 (0.05-1.66)
Testicular Cancer Incidence		
All Males:		
1975-1979	11	**3.15 (1.57-5.64)***
1980-1984	8	**2.98 (1.28-5.86)***
1985-1989	4	1.73 (0.47-4.44)
1990-1994	0	
Prostate Cancer Incidence		
All Males:		
1975-1979	265	**1.99 (1.75-2.25)***
1980-1984	65	**1.89 (1.45-2.40)***
1985-1989	29	**1.79 (1.20-2.57)***
1990-1994	3	0.67 (0.14-2.07)
Cervical Cancer		
All Females:		
1975-1979	2	2.19 (0.25-7.89)
1980-1984	1	1.08 (0.01-6.00)
1985-1989	8	**8.54 (3.68-16.82)***
1990-1994	0	

[*= statistically significant 95% Confidence Interval; all ratios are age adjusted]

Table 44. **All, Male and Female** Applicators: **Cancer incidence SIR by years of Licensure**

Years of Licensure	**Observed Number**	**Florida SIR (95% CI)**
Overall Cancer Incidence		
All Applicators:		
0≤4	69	0.84 (0.65-1.06)
4≤8	431	**0.71 (0.65-0.78)***
8≤12	552	**0.77 (0.71-0.84)***
12≤16	136	**0.72 (0.60-0.85)***
16≤20	69	**0.42 (0.33-0.53)***
All Males:		
0≤4	60	0.83 (0.63-1.07)
4≤8	373	**0.70 (0.63-0.77)***
8≤12	520	**0.79 (0.72-0.86)***
12≤16	131	**0.73 (0.61-0.86)***
16≤20	66	**0.41 (0.32-0.52)***
All Females:		
0≤4	9	0.91 (0.41-1.72)
4≤8	58	0.85 (0.65-1.10)
8≤12	32	**0.58 (0.39-0.82)***
12≤16	5	0.51 (0.16-1.19)
16≤20	3	0.71 (0.14-2.06)
Testicular Cancer Incidence		
All Males:		
0≤4	2	2.28 (0.26-8.22)
4≤8	6	1.52 (0.55-3.30)
8≤12	7	**2.86 (1.15-5.90)***
12≤16	4	**4.98 (1.60-11.61)***
16≤20	3	2.24 (0.25-8.10)
1975-79 Male Applicators:		
0≤4	1	3.25 (0.08-15.09)
4≤8	1	1.96 (0.03-10.90)
8≤12	6	**3.85 (1.41-8.38)***
12≤16	1	1.68 (0.02-9.33)
16≤20	3	3.54 (0.71-10.35)
1980-84 Male Applicators:		
0≤4	1	3.60 (0.05-20.01)
4≤8	3	2.12 (0.43-6.19)
8≤12	1	1.28 (0.02-7.15)
12≤16	3	**14.00 (2.81-40.89)***
16≤20	0	

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 44. **All, Male and Female** Applicators: **Cancer incidence SIR by years of Licensure** (continued)

Years of Licensure	**Observed Number**	**Florida SIR (95% CI)**
Prostate Cancer Mortality		
All Males:		
0≤4	13	**2.00 (1.06-3.42)***
4≤8	109	**1.83 (1.50-2.21)***
8≤12	165	**2.01 (1.71-2.34)***
12≤16	40	**2.11 (1.51-2.88)***
16≤20	24	1.55 (0.99-2.31)
1975-79 Male Applicators:		
0≤4	8	**1.80 (1.05-3.50)***
4≤8	44	**1.97 (1.43-2.64)***
8≤12	152	**2.03 (1.72-2.38)***
12≤16	36	**2.23 (1.56-3.09)***
16≤20	24	**1.58 (1.01-2.34)***
1980-84 Male Applicators:		
0≤4	5	1.70 (0.55-3.96)
4≤8	45	**2.00 (1.46-2.68)***
8≤12	12	1.61 (0.83-2.82)
12≤16	3	1.87 (0.38-5.47)
16≤20	0	

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 44. **All, Male and Female** Applicators: **Cancer incidence SIR by years of Licensure** (continued)

Years of Licensure	**Observed Number**	**Florida SIR (95% CI)**
Cervical Cancer Incidence		
All Females:		
0≤4	4	**12.86 (3.46-32.93)***
4≤8	4	2.41 (0.65-6.16)
8≤12	2	2.72 (0.31-9.81)
12≤16	1	5.55 (0.07-30.90)
16≤20	0	
1975-79 Female Applicators:		
0≤4	2	1.98 (0.65-6.16)
4≤8	0	
8≤12	1	2.04 (0.03-11.35)
12≤16	1	10.88 (0.14-60.53)
16≤20	0	
1980-84 Female Applicators:		
0≤4	0	
4≤8	1	1.73 (0.02-9.63)
8≤12	0	
12≤16	0	
16≤20	0	

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 45. **All, Male and Female** Applicators: **Cancer incidence SIR by Age at Licensure Issue**

Age Group	Observed Number	Florida SIR (95% CI)
Overall Cancer Incidence		
All Applicators:		
20-24	14	0.64 (0.35-1.07)
25-29	23	**0.46 (0.29-0.69)***
30-34	29	**0.38 (0.25-0.54)***
35-39	45	**0.43 (0.32-0.58)***
40-44	77	**0.55 (0.43-0.69)***
45-49	146	**0.69 (0.58-0.81)***
50-54	221	**0.74 (0.64-0.84)***
55-59	226	**0.71 (0.62-0.81)***
60-64	225	**0.82 (0.71-0.93)***
65-69	163	0.98 (0.84-1.14)
70-74	66	0.88 (0.68-1.12)
75-79	23	1.16 (0.74-1.74)
80-84	7	1.33 (0.53-2.75)
85+	1	1.89 (0.03-10.50)
All Males:		
20-24	10	**0.51 (0.24-0.94)***
25-29	17	**0.38 (0.22-0.60)***
30-34	22	**0.32 (0.20-0.48)***
35-39	34	**0.36 (0.25-0.50)***
40-44	71	**0.55 (0.43-0.70)***
45-49	135	**0.69 (0.58-0.82)***
50-54	205	**0.75 (0.65-0.85)***
55-59	206	**0.71 (0.61-0.81)***
60-64	210	**0.84 (0.73-0.96)***
65-69	155	1.02 (0.86-1.19)
70-74	63	0.93 (0.72-1.19)
75-79	23	1.27 (0.81-1.91)
80-84	7	1.36 (0.55-2.80)
85+	1	1.89 (0.02-10.50)

[*= statistically significant 95% Confidence Interval]

Table 45. **All, Male and Female** Applicators: **Cancer incidence SIR by Age at Licensure Issue** (Continued)

Age Group	**Observed Number**	**Florida SIR (95% CI)**
Overall Cancer Incidence		
All Females:		
20-24	4	1.75 (0.47-4.47)
25-29	6	1.20 (0.44-2.61)
30-34	7	1.00 (0.40-2.05)
35-39	11	1.21 (0.60-2.17)
40-44	6	0.52 (0.19-1.14)
45-49	11	0.70 (0.35-1.25)
50-54	16	0.63 (0.36-1.02)
55-59	20	0.82 (0.50-1.26)
60-64	15	0.62 (0.34-1.02)
65-69	8	0.59 (0.25-1.16)
70-74	3	0.42 (0.08-1.22)
75-79	0	
80-84	0	
85+	0	
Testicular Cancer Incidence		
All Males:		
20-24	4	2.68 (0.72-6.85)
25-29	8	**3.63 (1.56-7.16)***
30-35	4	2.26 (0.61-5.79)
35-39	1	0.96 (0.01-5.33)
40-44	2	3.14 (0.35-11.33)
45-49	1	1.87 (0.02-10.40)
50-54	0	
55-59	0	
60-64	1	3.16 (0.04-17.57)
65-69	1	5.17 (0.07-28.78)
70-74	1	11.43 (0.15-63.57)
75-79	0	
80-84	0	
85+	0	

[*= statistically significant 95% Confidence Interval]

Table 45. **All, Male and Female** Applicators: **Cancer incidence SIR by Age at Licensure Issue** (Continued)

Age Group	**Observed Number**	**Florida SIR (95% CI)**
Prostate Cancer Incidence		
All Males:		
35-39	2	1.03 (0.12-3.73)
40-44	12	**2.00 (1.03-3.50)***
45-49	20	1.24 (0.76-1.92)
50-54	59	**1.78 (1.35-2.29)***
55-59	70	**1.59 (1.24-2.01)***
60-64	81	**1.95 (1.55-2.42)***
65-69	68	**2.68 (2.08-3.40)***
70-74	29	**2.58 (1.73-3.70)***
75-79	8	**2.93 (1.26-5.76)***
80-84	3	4.00 (0.80-11.70)
85+	1	11.49 (0.15-63.92)
Cervical Cancer Incidence		
All Females:		
20-24	3	**14.03 (2.82-41.00)***
25-29	2	4.38 (0.49-15.80)
30-34	3	**5.81 (1.17-16.97)***
35-39	2	4.56 (0.51-16.46)
40-44	0	
45-49	0	
50-54	0	
55-59	0	
60-64	1	6.93 (0.09-38.57)
65-69	0	
70-74	0	
75-79	0	
80-84	0	
85+	0	

[*= statistically significant 95% Confidence Interval]

Table 46. Male **Private (Farmer)**Applicators: **Cancer incidence SIR**

Cancer Cause	Observed Number	Florida SIR (95% CI)
Malignant Neoplasms	966	**0.72 (0.68-0.77)***
Buccal/Pharynx	26	**0.62 (0.40-0.90)***
Digestive	181	**0.72 (0.62-0.83)***
Esophagus	11	0.80 (0.40-1.44)
Stomach	9	**0.38 (0.18-0.73)***
Large Intestine	72	**0.61 (0.47-0.76)***
Rectum	48	0.98 (0.72-1.30)
Liver	16	1.21 (0.69-1.96)
Pancreas	22	0.86 (0.54-1.30)
Respiratory	187	**0.76 (0.65-0.87)***
Larynx	10	**0.48 (0.23-0.89)***
Lung	175	**0.78 (0.67-0.91)***
Bone	3	1.23 (0.25-3.58)
Skin	37	0.96 (0.67-1.32)
Bladder	53	1.02 (0.76-1.33)
Kidney	22	0.76 (0.48-1.15)
Eye	3	1.34 (0.27-3.91)
Brain/CNS	20	1.17 (0.72-1.81)
Thyroid	4	**0.39 (0.10-0.99)***
All Lymphopoietic	65	0.96 (0.74-1.22)
LymphoSarcoma	26	0.91 (0.60-1.34)
Hodgkins	8	1.51 (0.65-2.97)
Leukemia	22	1.00 (0.63-1.52)
Other Lymphatic	9	0.76 (0.35-1.44)
Soft Tissue Sarcoma	0	
Male Cancers only:		
Prostate	316	**1.98 (1.77-2.12)***
Testis	15	**2.38 (1.33-3.92)***

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 47. Male **Commercial and Public** Applicators: **Cancer incidence SIR**

Cancer Cause	**Observed Number**	**Florida SIR (95% CI)**
Malignant Neoplasms	193	**0.69 (0.60-0.80)***
Buccal/Pharynx	9	0.89 (0.41-1.69)
Digestive	46	1.01 (0.74-1.34)
Esophagus	3	1.05 (0.21-3.07)
Stomach	6	1.34 (0.49-2.91)
Large Intestine	26	1.29 (0.84-1.89)
Rectum	4	0.42 (0.11-1.06)
Liver	2	0.76 (0.09-2.74)
Pancreas	4	0.87 (0.23-2.22)
Respiratory	43	0.86 (0.62-1.16)
Larynx	2	0.44 (0.05-1.58)
Lung	41	0.92 (0.66-1.25)
Bone	2	2.68 (0.30- 9.69)
Skin	11	0.87 (0.44-1.56)
Bladder	6	0.69 (0.25-1.51)
Kidney	4	0.64 (0.17-1.65)
Eye	2	3.77 (0.42-13.60)
Brain/CNS	4	0.82 (0.22-2.10)
Thyroid	2	0.53 (0.06-1.91)
All Lymphopoietic	11	0.69 (0.34-1.23)
LymphoSarcoma	6	0.88 (0.32-1.92)
Hodgkins	0	
Leukemia	3	0.63 (0.13-1.84)
Other Lymphatic	2	0.90 (0.10-3.24)
Soft Tissue Sarcoma	0	
Male Cancers only:		
Prostate	37	**1.55 (1.09-2.14)***
Testis	8	**2.73 (1.18-5.39)***

[*= statistically significant 95% Confidence Interval; all ratios are age & calendar year adjusted]

Table 48. All Applicators Cox Proportional Hazard Analyses for **Overall Cancer Incidence**

Covariable	**Parameter Estimate**	**Standard Error**	**Risk Ratio**	**p value**
Single Covariable Regression:				
Gender (D) [females=1]	0.0301	0.1011	1.03	0.77
Hispanic (D) [Hispanic=1]	-0.0263	0.1793	0.97	0.88
Year of first licensure (C)				
1975-79	0.3780	0.1013	1.46	**0.0002**
1980-84	0.3024	0.1106	1.35	**0.006**
Age at first licensure (CO)	-0.0606	0.0068	0.94	**0.0001**
Number of years licensed (CO)	0.0088	0.0077	1.01	0.25
Number of years licensed (C)				
4-8	-0.1319	0.1305	0.88	0.31
8-12	0.0214	0.1308	1.02	0.87
12-16	0.0739	0.1489	1.08	0.62
16-20	-0.3022	0.1661	0.74	0.06
Licensure type (D) [Private=1]	-0.1173	0.0797	0.89	0.14
Aerial licensure (D) [Aerial=1]	-0.1765	0.3350	0.88	0.59
Aquatic licensure (D) [Aquatic=1]	-0.0077	0.1706	0.99	0.96
Exposure Model (Entire Cohort):				
Age at first licensure (CO)	-0.0849	0.0083	0.92	**0.0001**
Number of years licensed (CO)	-0.0473	0.0096	0.95	**0.0001**
Exposure Model (1975-1979)				
Age at first licensure (CO)	-0.0643	0.0135	0.94	**0.0001**
Number of years licensed (CO)	-0.0388	0.0118	0.96	**0.001**

[D= Dichotomous; C=Categorical; CO=Continuous]

Table 49. All Applicators Cox Proportional Hazard Analyses for **Testicular Cancer** Incidence

Covariable	Parameter Estimate	Standard Error	Risk Ratio	p value
<u>Single Covariable Regression</u>:				
Gender (D) [females=1]				
Hispanic (D) [Hispanic=1]				
Year of first licensure (C)				
1975-79	1.1869	0.6447	3.28	0.06
1980-84	0.8785	0.6173	2.41	0.16
Age at first licensure (CO)	-0.1688	0.0502	0.85	**0.0008**
Number of years licensed (CO)	0.1385	0.0479	1.15	**0.04**
Number of years licensed (C)				
4-8	-0.2963	0.8176	0.74	0.74
8-12	0.6835	0.8242	1.98	0.41
12-16	1.3291	0.8456	3.78	0.11
16-20	0.9770	0.9332	2.67	0.29
Licensure type (D) [Private=1]	-0.0556	0.4555	0.95	0.90
Aerial licensure (D) [Aerial=1]	1.4181	1.0287	4.13	0.17
Aquatic licensure (D) [Aquatic=1]				
<u>Exposure Model</u> (Entire Cohort):				
Age at first licensure (CO)	-0.0426	0.0582	0.96	0.47
Number of years licensed (CO)	-0.0967	0.0379	0.91	**0.01**
<u>Exposure Model</u> (1975-1979)				
Age at first licensure (CO)	0.0694	0.1036	1.072	0.50
Number of years licensed (CO)	-0.1581	0.0970	0.85	0.10

[D= Dichotomous; C=Categorical; CO=Continuous]

Table 50. All Male Applicators Cox Proportional Hazard Analyses for **Prostate Cancer** Incidence

Covariable	**Parameter Estimate**	**Standard Error**	**Risk Ratio**	**p value**
Single Covariable Regression:				
Gender (D) [females=1]				
Hispanic (D) [Hispanic=1]	0.1585	0.3213	1.17	0.62
Year of first licensure (C)				
1975-79	0.0568	0.1997	1.06	0.78
1980-84	0.0838	0.2243	1.09	0.71
Age at first licensure (CO)	-0.0534	0.0136	0.96	**0.008**
Number of years licensed (CO)	0.0146	0.0152	1.02	0.34
Number of years licensed (C)				
4-8	-0.1259	0.2947	0.88	0.67
8-12	-0.0242	0.2911	0.98	0.93
12-16	0.1420	0.3200	1.15	0.66
16-20	-0.0239	0.3398	0.98	0.94
Licensure type (D) [Private=1]	0.0534	0.1782	1.06	0.76
Aerial licensure (D) [Aerial=1]	0.1677	0.5812	1.18	0.77
Aquatic licensure (D) [Aquatic=1]	-0.1770	0.4138	0.84	0.67
Exposure Model (Entire Cohort):				
Age at first licensure (CO)	-0.1711	0.0108	0.84	**0.0001**
Number of years licensed (CO)	-0.0801	0.0118	0.92	**0.0001**
Exposure Model (1975-1979):				
Age at first licensure (CO)	-0.3238	0.0177	0.72	**0.0001**
Number of years licensed (CO)	-0.0129	0.0132	0.99	0.33

[D= Dichotomous; C=Categorical; CO=Continuous]

Table 51. All Applicators Cox Proportional Hazard Analyses for **Cervical Cancer** Incidence

Covariable	Parameter Estimate	Standard Error	Risk Ratio	p value
Single Covariable Regression:				
Gender (D) [females=1]				
Hispanic (D) [Hispanic=1]				
Year of first licensure (C)				
1975-79	0.3780	0.1013	1.46	**0.002**
1980-84	0.3024	0.1106	1.35	**0.006**
Age at first licensure (CO)	-0.1457	0.0711	0.86	**0.04**
Number of years licensed (CO)	0.0177	0.1162	1.02	0.88
Number of years licensed (C)				
4-8	-1.5258	0.7096	0.22	**0.03**
8-12	-0.6509	0.9347	0.52	0.49
12-16	0.2844	1.1407	1.33	0.80
16-20				
Licensure type (D) [Private=1]	-0.0074	0.0708	0.99	**0.01**
Aerial licensure (D) [Aerial=1]				
Aquatic licensure (D) [Aquatic=1]	0.6465	1.0549	1.91	0.54
Exposure Model (Entire Cohort):				
Age at first licensure (CO)	-0.1691	0.0607	0.84	**0.005**
Number of years licensed (CO)	-0.0613	0.0950	0.94	0.52
Exposure Model (1975-1979):				
Age at first licensure (CO)				
Number of years licensed (CO)				

[D= Dichotomous; C=Categorical; CO=Continuous]

Acknowledgments

This study would never have been performed without the intellectual contribution and encouragement of my mentor and the study biostatistican, Judy A. Bean PhD. Nor would it have been possible without the hard work, humor and creativity of Mark Rudolph BS and Kara Hamilton MPH, as well as their colleagues Robert Tamer, Deede Stephens BS and Sheila Matthews. The uncompromising and supportive prodding and encouragement of Ronald Prineas MD PhD have acted as an inspiration throughout this study.

At Yale, I would like to thank the other members of my Dissertation Committee, Jan Stolwijk PhD and Stan Kasl PhD, as well as Rob Dubrow PhD. I also thank Vera Wardlow, the School of Public Health Registrar, for not forgetting about me. Stuart Shalat PhD and Mark Cullen MD MPH share responsibility (and my thanks) for starting me on this road, as do Rick Letz PhD and Fred Gerr MD MPH.

During the course of this study, I have been helped by many generous people. In particular, Shelia Hoar Zahm PhD and her colleagues at the National Cancer Institute (NCI) have been consistently helpful, despite an endless flow of questions and requests. Kirsten Wiklund PhD at the Karolinska Institute in Sweden was encouraging and generous from the very beginning of this study. In addition to Drs. Zahm and Wiklund, Caroline Tanner PhD, Dave Otto MD, Bonnie Levin PhD, Gary Schwartz PhD, Sheri Porcelein PhD, and Matt Keifer MD MPH, generously allowed me to utilize their questionnaires.

This study has given me an opportunity to interact with a remarkable group of people in the state of Florida. This study began with the licensed pesticide applicators database at the Florida Department of Agriculture and Consumer Services (DACS). It has been a great pleasure to work with Pam Houmere and her wonderful staff, Marlene Czerniak, Marion Fuller PhD, and Cheryl Spencer, as well as Liz Braxton, Bob Wells, and Ashok Shanhane PhD. From the Florida Agricultural Extension Services, Mary Lamberts PhD and Norm Nesheim PhD have been very helpful and informative. Of course, I would like to thank all those licensed Florida pesticide applicators who participated at various stages in this study.

It has been my pleasure to work with people from the Florida Department of Health (formerly the Department of Health and Rehabilitative Services). In particular, Richard Hopkins MD MPH, the Florida State Epidemiologist, has been a continuous source of information, concrete resources, and encouragement. Jill McKinnon and her Staff at the Florida Cancer Data System (FCDS), as well as Doug Palin, always treated me with humor, information, and creativity, even when I kept coming back. The same can be said of Gary Sammet of the State of Florida Vital Statistics. I also received help from Jackie Seabrooks at the Florida Agency for Health Care Administration (AHCA), as well as Iris Shephard at the Florida Department of Motor Vehicles. Although not a Florida institution, Lois Schein and Wayne Collier at the Health Care Financing Administration (HCFA) were remarkably enthusiastic and generous of their time.

At the Department of Epidemiology and Public Health of the University of Miami School of Medicine, in addition to those already mentioned, I am grateful to Dick Donahue PhD, Peggy O'Hara PhD, and Ed Trapido ScD for their collegial input and encouragement. At the National

Institute of Occupational Health and Safety (NIOSH), Kyle Steenland PhD, Karen Davis-King MPH, Avima Ruder PhD, Dave Chrislip, and John Russo gave me considerable helpful advice. Thanks also to the people at Equifax and Epidemiology Resources Inc.

This study has been funded by (and would not have been completed without) a Career Development Award (#1-KO1-OHOO125) from the National Institute of Occupational Safety and Health (NIOSH), as well as with considerable institutional support from the University of Miami School of Medicine, the State of Florida (in particular, Vital Statistics and the Florida Cancer Data System), the Health Care Finance Administration, and the Fleming Foundation.

I want to give my deepest thanks to my daughter Alejandra (Aleja) Campbell Ortiz and my husband Mauricio Ortiz MS. Many thanks and apologies to all my friends and family for all the time I did not spend with them while working on this study. This study is dedicated with thanks, love and admiration to my parents, Cynthia Dunn Fleming MA and T Corwin Fleming MD.

Appendix

Appendix: Nested Case Control and General Survey

Attachment 1: Human Subjects

a) Human Subjects Approval (University of Miami School of Medicine IRB)

b) Original Approved Consent Form

c) Modified Approved Consent Form

Attachment 2: Questionnaires:

a) Original Questionnaire

b) Revised Shortened Questionaire

Attachment 3: Letters

a) Original Case Control Mailing Letter

b) Follow up Case Control Mailing Letter

Attachment 4: Questionnaire Protocol Manual

Appendix: Nested Case Control Study and General Survey

This Appendix describes the rationale and the attempts of the Investigator to perform first a nested Case Control of selected incident cancers, and then a General Survey to obtain exposure and confounding information in a subsample of the Florida licensed pesticide applicators cohort.

1.0. Human Subjects

At the beginning of the study (6/92), an application was approved (IRB #91/303) by the University of Miami School of Medicine Human Subjects Committee for performing the nested case control study (see **Attachment 1a and 1b**). This approval was later amended to incorporate the changes detailed below with regards to contacting participants and using a questionnaire (see **Attachment 1c**). The IRB approval was renewed yearly during the time period of the study.

2.0. Questionnaire

A questionnaire was developed, originally for the purposes of the proposed nested case control study, and ultimately used for the General Survey after modification (see **Attachment 2a and 2b**).

To the extent possible, questionnaires were used from previous studies of pesticide applicators and farmers, or from previously piloted studies. The initial Questionnaire was 19 pages long, based on the following sources: Wiklund (Sweden), Zahm (NCI), Otto (UNC), Tanner (Parkinson's Institute), Schwartz (UM), Porcelein (UM), and the State of Florida Pesticide Survey. Drs. Kirsten Wiklund and Shiela Hoar Zahm both shared actual questionnaires from similar studies of licensed pesticide applicators (Sweden) and farmers (Iowa); the majority of the questionnaire content was extracted from their survey instruments. Dr. Dave Otto provided a copy of neuropsychological questions used in a study of Egyptian pesticide applicators; these were reviewed and selected by a collaborating Neuropsychologist, Dr. Bonnie Levin. The pesticide exposure questions were extracted primarily from the Florida Department of Agriculture and Consumer Services (DACS) "Florida Pesticide Use Survey" since the format would be familiar to some of the study population through the yearly DACS survey in Florida. Dr. Carolyn Tanner sent 12 validated questions for determining the possible diagnosis of Parkinson's Disease which were included. Dr. Gary Schwartz supplied questions on vitamin D exposure from his prior prostate cancer work and Ms. Sheri Procelein provided questions on sun exposure (knowledge, attitude and behavior) used in previous skin cancer studies in South Florida.

The Questionnaire (see **Attachment 2a**) was piloted using licensed pesticide applicators in South Florida recommended by Dr. Mary Lamberts of the Florida Agricultural Extension (Dade County Division). Fourteen (14) individuals (9 men, 5 women) were approached by mail, and 9 participated (6 men, 3 women); 4 people never replied, and 1 person had never actively used pesticides. The education level ranged from high school to doctoral degrees. The participants noted that it was a long questionnaire, but easy to fill out; the average time taken to fill it out was reportedly between 15 to 20 minutes. Suggestions were made about ambiguous wording of specific questions, and appropriate changes were made.

After it became apparent from the mailing of the original Questionnaire that the nested case control study needed to be modified (see below), a significantly shortened version of the Questionnaire was prepared (see **Attachment 2b**). The shortened version was only 3 pages long. It included brief demographic information, a modified version of the exposure questions, and brief confounding information (cigarettes and ethanol). Since this revised Questionnaire was primarily developed from the original lengthier instrument, a separate pilot study was not performed.

As described below, the shortened Questionnaire was used in the telephone approach in Phase II for the nested case control study. When the decision was made to perform a General Survey of a subsample of the cohort, rather than a nested case control, the same shortened version of the Questionnaire was used.

3.0. Nested Case Control

A nested case control study of incident cases of certain cancers was planned. The primary reason for the nested case control was to obtain more detailed exposure and confounding information from a subsample of the cohort (ie. the controls) which could be applied proportionally to the entire cohort. The further advantage and goal of the nested case control was to obtain incident based estimates of risk for a variety of cancer, since this case control study would be based on the larger cohort studies. {Breslow 1980, Breslow 1987, Schlessman 1982, Prentice 1986}

The following cancers were chosen due to prior associations in the literature (as discussed in a detail in Chapter Two) for either farmers and/or pesticide applicators: lung, prostate, skin (including nose), breast (female), testis, brain, bone marrow, lymph nodes, and soft tissue sarcoma. There were a total of 517 cases of these types of cancer obtained from initial linkage with the Florida Cancer Data System (FCDS), as discussed in Chapter Three.

The controls were to be selected according to the methodology of Prentice (1986), Robins (1986, 1989), and others. This methodology involves the creation of risk cohorts for each case based on age $\pm$ 5 years and same gender; controls would be randomly selected without replacement. Controls would be culled for the risk sets from the entire cohort, including cases. Although, this means that theoretically, especially with a small study population, a control could go on to become a case, this methodology avoids the biases introduced by exclusion of subsequent cases.

The main goals of this nested case control study were to obtain individual exposure and confounding information for the cancer cases and their matched controls. In addition, the information from the controls could be generalized to the entire cohort, to the extent that they still represented the entire cohort after performing the matching procedures described above. However, given the matching criteria and the formation of risk cohorts, it is not clear that the exposure and confounder exposure information of these controls would have ultimately been generalizable to the whole cohort.

The Nested Case Control study was attempted in two phases.

3.1. Phase I. Mailing

The most recent address and phone number of each case were obtained from the Master Database of Florida licensed pesticide applicators.

Each case was sent a packet with: a letter, 2 consent forms (1 to return; 1 to keep), the Initial Questionnaire, and a stamped addressed envelope. The letter (**Attachment 3a**) invited participation in the study, briefly described the general purpose of the study, and gave instructions concerning participation. There was space on the letter for an explanation of refusal of participation. Participants were offered $10 if they returned a completed questionnaire.

One month after sending out the questionnaires, a modified letter (see **Attachment 3b**) was sent out to the 245 persons who had not yet returned anything. Returned addresses were also checked for forwarding addresses and the FCDS files were examined for more recent addresses; if additional addresses were found, the packet was re-sent.

The following accounts for all of the 517 cases in Phase I of the nested case control study:

517 Cases:

- 31 yes
- 7 refusal
- 124 "soft" refusals:
  - - 64 dead
  - - 28 "no use pesticides in long time ± retired"
  - - 13 "too elderly ± too sick"
  - - 16 "never used pesticides"
  - - 2 no reply but sent back forms
  - - 1 out of town
- 150 Address Problems
  - - 46 Forwarding Order Expired (FOE)
  - - 104 bad
- 205 No Reply (after 2 letters)

After extensive discussions with the Dissertation Committee and National Institute of Occupational Safety and Health (NIOSH) personnel, a Phase II nested case control study was attempted.

3. 2. Phase II. Telephone

First, the Questionnaire was revised by drastic shortening (from over 19 pages to 3 pages) as described above. All the questions were kept the same so that data from Phases I and II could be pooled. Questions concerning pesticide exposure and confounding variable exposure, as well as brief demographic and health information were retained. A brief study explanation and telephone consent statement were included as part of the Revised Questionnaire (see **Attachment 2b**). Participants were no longer offered any monetary compensation; they were offered the opportunity to receive a copy of the Final Report, as before. The modification of the Questionnaire, as well as the issue of a telephone informed consent were submitted as an Amendment to the University of Miami Human Subjects Committee approved protocol (see above); approval of the Amendment was given.

An experienced Interviewer was trained in telephone administration of the Revised Questionnaire. A Questionnaire Administration Manual was developed by the Investigator (see **Attachment 4**), and reviewed by the Interviewer and the Biostatistician, Dr. Bean. Differing approaches for subjects, as opposed to surrogate relatives, were discussed. A phone contact protocol was established: at least twice in each 3 separate time periods (day, evening, and weekends) for each phone number, with a total of 3 different phone numbers if necessary. No messages were left on answering machines of subjects to avoid ambiguous contact information. Hard copy records were obtained for all completed contacts.

It was decided to concentrate on those 205 people from the mail case control who apparently had good addresses (since nothing had been returned by mail), but who had not responded to the 2 mailings. First, if there was a phone number available from the Pesticide Applicator Database, this number was tried as per above. If the phone number was incorrect (eg. disconnected, incorrect, etc) or there was no phone number available, the Interviewer checked for accuracy, and for the most current phone number and address in Florida using CD Rom software entitled "88 Million

Households Phonebook" and a World Wide Web (WWW) site called "Switchboard" (http//www.switchboard.com). This search was further broadened by using name and town only; if the name was unusual, all Florida telephone numbers were searched through the WWW and the software. In addition, where applicable, the other study databases were also searched for additional phone numbers and addresses (ie. FCDS and the Dept of Motor Vehicles). Of note, all phone numbers available through any source were tried by the Interviewer even if not confirmed on the WWW or software.

The above work and the following activities (in bold) were performed by the Interviewer over the period of 4 weeks. The actual interviews took approximately 15 minutes, sometimes longer with surrogates.

517 Cases
- 31 yes
- 7 refusals
- 124 "soft" refusals: **20 no phone available; 104 + phone**
    - 64 dead
    - 28 "no use pesticides in long time $\pm$ retired"
    - 13 "too elderly $\pm$ too sick"
    - 16 "never used pesticides"
    - 2 no reply but sent back forms
    - 1 out of town
- 150 Address Problems
    - 46 Forwarding Order Expired (FOE)
    - 104 bad address
- **205** No Reply (x 2 letters)
    - **161 had phone number**
        - **35 completed contact**
            - **23 yes**
            - **12 refusals**
        - **80 $\geq$ 1 phone call**
        - **46 no contact attempted**
    - **44 problem phone**
        - **32 no phone**
        - **12 disconnected**

Summary of Phase I and Phase II:

- 54 Yes (Responders)
- 19 No
- 104 "Soft No" with a Phone number
- 150 Bad Address
- 64 Bad phone
- 126 Pending

Entire Case Group vs Responders

Of the 54 persons who responded, there were 2 women (4%). For a distribution by decade of birth and gender, see **Table 1**. The mean age at cancer diagnosis for the responders was 56.97 ± 13.19 compared to the mean age of 63.67 ± 12.89 for the entire case group. The mean number of years licensed was 8.64 ± 4.44 years for the responders compared to 8.46 ± 3.93 years for the entire case group. Given the small number (10%) of responders and their lack of representation for either the entire case group or the entire cohort, further analyses were not attempted.

4. 0. General Survey

After further extensive discussions with the Dissertation Committee, it was realized that the nested case control study of incident cancers was not feasible. There were logistic issues in terms of participation and loss to follow up. Furthermore, lack of significant participation would render the interpretation of any results from the nested case control of any particular cancer unintelligible. Finally, due to proposed matching procedures for the nested case control, the generalizability of the control information was in serious doubt.

Therefore, a General Survey of a subsample of the entire cohort was proposed. A target number of successful participants was based on the expected frequency of cigarette smoking (the most important confounding variable) in the entire cohort.

There exist no estimates for cigarette smoking in this cohort. There is the frequently quoted statement that farmers in general smoke less than the general population. As reviewed in the Chapter Two, in general in both pesticide exposed and farming populations, the risk of the tobacco-related diseases is decreased compared to the general population and to other working populations, with the possible exception of lung cancer in some pesticide applicator studies. Initial results from the PMR/MOR studies of this entire cohort did not reveal any increase in deaths due to tobacco-related diseases. As discussed in Chapter Two, Barthel (1981) in his study of German pesticide applicators mentions that their rate of smoking was similar to the general population; he found an increased risk of lung cancer which he associated with occupational arsenical exposures. Blair *et al* (1983) studied a separate group of Florida pesticide applicators and also found an increased risk of lung cancer, but had no information available on tobacco use. Pesatori *et al* (1994) performed a follow up study and a nested case control of the 78 lung cancers in the white males of the same pesticide applicator group; she found that all but one of the cases of lung cancer was a tobacco user. Wiklund *et al* (1989) reported on a 1963 survey of smoking habits in Sweden that 34% of workers in farming, forestry or fish industry smoked tobacco daily compared with 54% in other occupations; in 1981, an updated Swedish survey found 21% and 38% respectively. In addition, as part of Wiklund's study of pesticide exposed workers in Sweden, in 1984 she found that 21% of pesticide applicators smoked daily, 33% were ex smokers and 46% were never smokers.{J Dich unpublished data, quoted by Wiklund 1989} Sterling and Weinkam (1978) evaluated smoking patterns by occupation, industry, gender and race using the 1970 Health Interview Survey found for white males the age adjusted percentages for Farmers and Farm Managers, and for Farm Laborers and Foremen (see **Table 2**). Finally, Sims (1994) reported that in 1992, 22% of all adult Floridians were smokers

(24.4% of the men and 20% of the women).

To obtain an approximate sample size for the subsample in the General Survey, it was assumed that the true proportion of pesticide applicators who are current and former smokers would be 55%. For an estimated proportion (E) to be within 10% of the true Prevalence (P), the sample size (n) can be calculated as {Fleiss 1981}:

$$n \geq \frac{Z^2(1-P_y)}{E^2 P_y} = \frac{(2)^2 (1-0.55)}{(0.10)^2(0.55)} = 327$$

In addition, the subsample was stratified based on decade of birth and gender distribution of the entire cohort for appropriate age and gender frequency selection using proportional allocation with random selection within each stratum (see **Table 3**); SAS procedure called "RANUNI" was used to generate the random number.

As with the nested case control study above, using the same Revised Questionnaire, Manual and trained Interviewer, this subsample of the entire population were approached by the Trained Interviewer by phone using the same protocol as above in Phase II of the nested Case Control study. All phone numbers were checked with the phone software and World Wide Web database prior to use; hard copy records were kept of all completed contacts. Participants were not offered any monetary compensation; they were offered the opportunity to receive a copy of the Final Report, as before.

After 2 months of full-time work (including weekend and evening hours), the Trained Interviewer was able to determine the following from the subsample of 328 age and gender frequency distributed randomly selected Subjects.

328 Subjects
- 23 NO phone number available ever
- 305 some phone number
    - 119 with $\geq$ 1 bad phone number
    - 16 completed interviews (Responders)
    - 14 refusals
    - 45 "lost to follow up" (ie. 6 calls but no contact made)
    - 107 $\geq$ 3 calls but no contact made

4.1. Entire Cohort vs Responders

Of the 16 (5%) persons who responded, there was 1 woman (6%); all the responders were alive at the time of the interview. For a distribution by decade of birth and gender, see **Table 4**. The mean age at the time of the interview for the responders was 52.40$\pm$ 14.30 compared to the mean age of 50.30$\pm$14.56 for all alive persons for the entire cohort group. The mean number of years licensed was 7.08$\pm$5.13 years for the responders compared to 7.48$\pm$4.38 years for the entire cohort.

In addition, from the 16 people who consented to complete the shortened Questionnaire, the following was reported. With regards to completed level of education, 1/16 reported Elementary school, 6/16 High School, 2/16 Jr College, 6/16 College, and 1/16 College+.

Fifteen out of 16 (94%) reported ever having used pesticides, including 5 (32%) currently using pesticides; the average duration of self-reported pesticide use was 13$\pm$7 years. With regards to herbicides, 14 (88%) reported having used herbicides with 4 (25%) currently using; the average duration of self-reported herbicide use was 13$\pm$6 years. Eight (50%) used pesticides at home for an average duration of 25$\pm$21 years. Finally, 13 (81%) had lived on a farm for an average duration of 24$\pm$25 years.

Eleven (69)% were "ever smokers" with a mean start age of 17±5 years of age; 4 (25%) were current smokers. Eight (50%) were "regular" ethanol users with a mean duration 28±12 years of use.

Only 2 (13%) reported no symptoms. The other subjects reported: arthritis (7), asthma or breathing problems (6), skin problems (5), cancer (3) including 2 skin cancer and 1 with leukemia and prostate, heart problems (2), and "other" (4).

Of note, there were 18 (6%) refusals to participate, with only one woman (6%). The mean age of the 12 (67%) people alive at the time of the request to participate was 68.8±15.5; the mean age at death of the 6 (33%) people who were not alive was 61±20.3.

Further analyses were not preformed given the small sample size.

5.0. Conclusion

Both a nested case control of cancer incidence and a general survey of a frequency selected subsample were attempted in this cohort of licensed pesticide applicators. The major purpose was to gain confounding and exposure information which could be generalizable to the entire cohort.

However, a variety of logistical issues interfered with the successful completion of both of these studies. There was a poor response rate to either mail or phone approaches, despite the use of a trained interviewer, shortened questionnaire, monetary incentives, and a varied interview schedule. Furthermore, a lack of current phone numbers and accurate addresses were also issues.

Of interest, there were respondents who did not use pesticides ever, yet had a pesticide license. On the other hand, there were other respondents who had used pesticides longer than the time they were licensed. Both these issues have implications for the use of "years licensed" as the major exposure variable.

Ultimately, the small numbers and lack representativeness rendered these efforts valiant, but essentially meaningless for their purposes.

Table 1. Nested Case Control by Decade and Gender

Birth Decade	Entire Case Group: Females	Males	Case Respondents: Females	Males
1890-1900	0	6	0	0
1901-1910	1	50	0	4
1911-1920	7	156	1	17
1921-1930	13	162	0	20
1931-1940	4	63	0	8
1941-1950	7	21	1	2
1951-1960	7	21	0	1
1961-1970	3	18	0	0
1971-1975	0	6	0	0
Total	35	482	2	52

Table 2. Age Adjusted Smoking Percentages among 31,803 White Males

	%Never Smoked	%Current Smokers	%Former Smokers
Farmers, Farm Managers	43.4	31.9	24.7
Farm Laborers, Foremen	41.7	45.5	12.9

[Sterling and Weinkam, 1978]

Table 3. Sampling Scheme for General Survey

Birth Decade	**Females**	n_h	**Males**	n_h
1890-1900	$1xC^*=0.01$	0	$61xC^*=0.6$	1
1901-1910	$33xC^*=0.3$	0	$483xC^*=4.7$	5
1911-1920	$179xC^*=1.7$	2	$1958xC^*=18.9$	19
1921-1930	$317xC^*=3.1$	3	$3969xC^*=38.3$	38
1931-1940	$423xC^*=4.1$	4	$4637xC^*=44.8$	45
1941-1950	$749xC^*=7.2$	7	$6522xC^*=63$	63
1951-1960	$1242xC^*=12.0$	12	$8251xC^*=79.7$	80
1961-1970	$557xC^*=5.6$	6	$4218xC^*=40.7$	41
1971-1975	$19xC^*=0.2$	0	$217xC^*=2.1$	2
Total	3540	34	30,316	294

C^* = constant equal to the sample size divided by the confirmed number in the cohort at the time of the general Survey

= 327/33856

for each stratum, $n_h=N_h(n/N)$

where n_h= number of persons sampled in the h^{th} stratum

N_h= number of persons sampled in the h^{th} stratum

n = calculated sample size (in this case, 327)

N = number in the Cohort (in this case, 33856)

Table 4. General Survey by Decade and Gender

Birth Decade	Entire Cohort: Females	Males	Survey Sample: Females	Males	Survey Responders: Females	Males
1890-1900	2	64	0	1	0	0
1901-1910	36	546	0	5	0	0
1911-1920	184	2085	2	19	0	1
1921-1930	319	4061	3	38	0	3
1931-1940	424	4654	4	45	0	2
1941-1950	749	6536	7	63	0	5
1951-1960	1246	8269	12	80	1	3
1961-1970	577	4223	6	41	0	1
1971-1975	19	217	0	2	0	0
Total	3556	30655	34	294	1	15

Attachment A: Human Subjects

a) Human Subjects Approval (University of Miami School of Medicine IRB)

b) Original Approved Consent Form

c) Modified Approved Consent Form

UNIVERSITY OF MIAMI
SCHOOL OF MEDICINE

MEMORANDUM

TO: Lora E. Fleming, M.D., MPH., Epidemilogy & Public Health

FROM: Jay M. Sosenko, M.D., Chairman Jay M. Sosenko

DATE: July 22, 1992

PROTOCOL NUMBER: 91/303

TITLE OF PROTOCOL: "Cancer Incidence in a Cohort of Florida Pesticide Applicators"

DATE OF ANNUAL APPROVAL: July 20, 1992

The Medical Sciences Subcommittee for the Protection of Human Subjects in Research has reviewed and approved the annual report for the above titled protocol.

In the consent form Maria Arnold's phone number should be updated to 547-3327.

If you have any questions, please contact Maria Arnold at 547-3327.

Medical Sciences Subcommittee
for the Protection of Human Subjects
Research and Graduate Studies (M809)
P.O. Box 016960 Tel (305) 547-3327
Miami, Florida 33101
Fax (305) 547-3328

UNIVERSITY OF
Miami
SCHOOL OF MEDICINE

MEMORANDUM

TO: Lora E. Fleming, M.D., MPH

FROM: Maria J. Arnold, IB. Administrator *Maria J Arnold/MT*

DATE: April 9, 1996

SUBJECT: Protocol 91/303
"Cancer Incidence in a cohort of Florida Pesticide Applicators"

The Chairman of the Medical Sciences Subcommittee for the Protection of Human Subjects in Research has approved Amendment to the protocol and revised consent form.

You must use the approved (IRB stamp) consent form, for your subjects.

If you have any questions, please contact our office at 243-3327.

Human Subjects Office (M-809)
PO Box 016960 Tel 305-243-3327
Miami, Florida 33101
Fax 305-243-3328

STANDARD CONSENT FORM: University of Miami School of Medicine

Health Effects in a Cohort of Florida Pesticide Applicators

PURPOSE:

You are invited to participate in a research Study of Florida Pesticide Applicators by investigators from the University of Miami School of Medicine. You have been selected to participate in this Study from the complete list of licensed Pesticide Applicators provided by the Florida Department of Agriculture Bureau of Pesticides or because you are on this same list of Pesticide Applicators. This Study will examine the connection between work-related pesticide exposure and health effects. This is a Study of the University of Miami School of Medicine, not the Florida Department of Agriculture Bureau of Pesticides.

PROCEDURE:

To participate in this Study, you are asked to fill out and return the enclosed Questionnaire and 1 signed copy of the Consent Form. This Questionnaire asks for information concerning the types and amounts of pesticides you use, as well as the equipment for application and protection. It also asks for information concerning other health risks such as cigarette smoking, and for demographic information.

When the Study is completed, you will receive a copy of the Final Summary of Results if you indicate that you wish to receive this Final Summary at the end of this Consent Form.

RISKS:

There should be no risks to participating in this study.

BENEFITS:

No other benefit can be promised to you by your participation in this study.

ALTERNATIVES:

You have the alternative not to participate in this study.

COMPENSATION:

You will receive $10.00 by mail when the completed Questionnaire and 1 copy of the signed Consent Form have been returned to the Principal Investigator in the enclosed stamped addressed envelope.

CONFIDENTIALITY:

The individual results of the Questionnaire will be known by a numbered code; your name and this code will be known only by the Principal Investigator at the University of Miami. The Florida Department of Agriculture Bureau of Pesticides will receive only the Final Summary of Results, never any individual information.

The Principal Investigator and her assistants will consider your records confidential to the extent permitted by law. Your records and results will not be identified as pertaining to you in any publication without your expressed permission. In rare circumstances, the US Food and Drug Administration (FDA) or the US Department of Health and Human Services (DHHS) may request copies of your records. If this happens, the FDA or DHHS request will be granted.

RIGHT TO WITHDRAW:

Your participation in this study is voluntary and you have the right to withdraw at any time by informing the Principal Investigator. If you decide to withdraw at any time from this study, your future care will not be prejudiced by your withdrawal or lack of participation. In addition, the Principal Investigator can remove you from the study at any time without your consent either because of failure to follow the study schedule or if she feels that it is in the best interests for you medically.

The Investigators will answer any questions that you may have regarding the investigation, including specific questions concerning the Questionnaire.

If you have any questions about your rights as a research subject, you may contact Ms. Marie Arnold at: 305-243-3327.

______________________ ____________

Signature of Subject (or Relative) Date

______________________ ______________________

Printed Name of Subject (or Relative) Social Security Number of Subject (or Relative)

______________________ ____________

Signature of Witness Date

Name, Address, and day/night Phone Numbers of the Principal Investigator:

Lora E. Fleming MD MPH
c/o Dept of Epidemiology & Public Health (R-669)
University of Miami School of Medicine
PO Box 016069
Miami, Florida
33101

tel: 305-243-5912 (work day)
tel: 305-939-9943 (digital beeper)

Please return one signed copy of this Consent Form and the filled out Questionnaire in the enclosed stamped, addressed envelope to the Principal Investigator:

Lora E. Fleming MD MPH
c/o Dept of Epidemiology & Public Health (R-669)
University of Miami School of Medicine
PO Box 016069
Miami, Florida
33101

Final Summary of Results

I ________________ (name) wish to receive a copy of the Final Summary of Results of this study when the study of Florida Pesticide Applicators is completed. Please send a copy of this Final Summary to:

____

(number, Street)

____

____

(City, State)

____

(Zip Code)

Please return this Form with the Consent Form and Questionnaire in the enclosed stamped, addressed envelope to the Principal Investigator:

Lora E. Fleming MD MPH
c/o Dept of Epidemiology & Public Health (R-669)
University of Miami School of Medicine
PO Box 016069
Miami, Florida
33101

Pesticide Applicator's Questionnaire Consent

University of Miami School of Medicine
Department of Epidemiology & Public Health (R-669)
Lora E. Fleming, MD, MPH (Principal Investigator)

Status of Pesticide Applicator ₁☐ Alive

₂☐ Dead Year Died 19____

Phone contact	__/__/__	9 -5 wkday	__/__/__	5 -9 wkday	__/__/__	wkend
1st #	__/__/__	9 -5 wkday	__/__/__	5 -9 wkday	__/__/__	wkend
Phone contact	__/__/__	9 -5 wkday	__/__/__	5 -9 wkday	__/__/__	wkend
2nd #	__/__/__	9 -5 wkday	__/__/__	5 -9 wkday	__/__/__	wkend
Phone contact	__/__/__	9 -5 wkday	__/__/__	5 -9 wkday	__/__/__	wkend
3rd #	__/__/__	9 -5 wkday	__/__/__	5 -9 wkday	__/__/__	wkend

Date of actual contact ___/___/___

Consent Information Paragraph

You are invited to participate in a research study of Florida Pesticide Applicators by investigators from the University of Miami School of Medicine. You were selected from the complete list of licensed Pesticide Applicators provided by the Florida Department of Agriculture. This Study is examining the possible connection between work-related pesticide exposure and health effects. This is a Study of the University of Miami, not the Florida Department of Agriculture.

You will be asked 5 to 10 minutes of questions concerning your work and possible health risks such as cigarette smoking. There are no risks or benefits to participating in this study. Participation is voluntary, and you can withdraw at any time.

Your information is confidential. Your records and results will not be identified individually in any publication. The Florida Department of Agriculture will receive only the Final Summary of Results, never any individual information.

Dr. Fleming, the Principal Investigator, can answer any questions that you may have regarding the investigation at (305)243-5912. If you have any questions about your rights as a research subject, you may contact Ms. Marie Arnold, administrator of University of Miami Human Subjects, at (305)243-3327.

Spoke to:

Name:______________________________ Relationship:____________________

Does the subject (or proxy) consent to phone interview?

₀☐ No
₁☐ Yes
₂☐ Unable to contact

If No, may I ask you why? ____________________________

Attachment B: Questionnaires

a) Original Questionnaire

b) Revised Shortened Questionnaire

PESTICIDE APPLICATORS QUESTIONNAIRE

In general, this questionnaire has answers which are in the following forms:

CHOICES where you check the ***one*** appropriate choice.

Example:

Do you work with Pesticides?

- ☐ No
- ☐ Don't Know
- ☐ Yes
- ☐ Not Applicable (N/A)

TABLES where you fill out or check the appropriate space for each line.

Example:

When working with pesticides, how often did you use a mask (respirator)?

	Always	Sometimes	Seldom	Never	N/A	Don't Know
1960 - 1969	☐	☐	☐	☐	☐	☐
1970 - 1979	☐	☐	☐	☐	☐	☐
1980 - 1989	☐	☐	☐	☐	☐	☐
1990 - present	☐	☐	☐	☐	☐	☐

WRITE IN with a specific format; you write the information in a particular format:

Example:

What is your Date of Birth (Month - Day - Year)? ____ — ____ — ____

If there is any question you do not wish to answer, just circle or write "N/A" for "Not Applicable."

Please do not hesitate to telephone (305)243-5912 if any particular question or other aspect of this questionnaire is confusing. You should also feel free to write any questions you have in the margins or on the back of the questionnaire, and you will be contacted by the Principal Investigator.

Your accurate answers are very important to us. We realize that filling out this questionnaire is somewhat time-consuming. However, please take the time to thoughtfully complete the questionnaire. The answers provided by you and your colleagues will hopefully prevent health effects from pesticides in pesticide applicators and other groups in the future.

ID# ____

Pesticide Applicator's Questionnaire

University of Miami School of Medicine

Department of Epidemiology & Public Health
Lora E. Fleming, MD, MPH
Phone: (305) 243-5912
FAX: (305) 243-5544

If this Questionnaire is completed by someone other than the Pesticide Applicator, please write your **NAME** (First, Middle, Last), and your **relationship** to the Pesticide Applicator.

Name:______________________ Relationship:______________

Please write today's **DATE** (mm-dd-yy): ____—____—____

Please write your **NAME**

FIRST NAME ____________ MIDDLE ______ LAST NAME ____________

What is your **age**? ______ years

What is your **date of birth** (mm-dd-yy) ____—____—____

Please indicate your **sex**?
1 ☐ Male
2 ☐ Female

What is your **home address**?

STREET______________________ APT#________

CITY________________ STATE______ ZIP__________

What is your **Home Telephone number**? (______) ______—________

Please indicate the **Place of Birth** for each of the following persons:

	You	Mother	Father
United States	11 ☐	21 ☐	31 ☐
Caribbean	12 ☐	22 ☐	32 ☐
Latin America	13 ☐	23 ☐	33 ☐
Europe	14 ☐	24 ☐	34 ☐
Other	15 ☐	25 ☐	35 ☐
Don't Know	16 ☐	26 ☐	36 ☐

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How would you describe your **Race/Ethnic Group**?

- 1 ☐ White -Non Hispanic
- 2 ☐ Black Non Hispanic
- 3 ☐ White Hispanic
- 4 ☐ Black Hispanic
- 5 ☐ Asian
- 6 ☐ Polynesian
- 7 ☐ Native American
- 8 ☐ Other ________________
- 9 ☐ Don't Know

What is your **Primary Language** (i.e. the one you use the most)?

- 1 ☐ English
- 2 ☐ Spanish
- 3 ☐ Other ________________
- 4 ☐ Don't Know

How many years of **school** have you completed?

- 1 ☐ Elementary (Grades 1-6)
- 2 ☐ Junior High School (Grades 7-9)
- 3 ☐ High School (Grades 10-12)
- 4 ☐ Junior College or Technical School
- 5 ☐ College
- 6 ☐ College (4 years +)
- 7 ☐ Other ________________
- 8 ☐ Don't Know

What is your present average **yearly family income** before taxes?

- 1 ☐ Less than $15,000
- 2 ☐ $15,000 - 30,000
- 3 ☐ $30,000 - 45,000
- 4 ☐ $45,000 - 60,000
- 5 ☐ $60,000 and above
- 6 ☐ Don't Know

Please indicate your **present Marital Status** (check only one)

- 1 ☐ Married
- 2 ☐ Single
- 3 ☐ Widowed
- 4 ☐ Divorced
- 5 ☐ Separated
- 6 ☐ Living with someone
- 7 ☐ Don't Know

How many **living children** do you presently have?

- 0 ☐ None
- 1 ☐ One
- 2 ☐ Two
- 3 ☐ Three
- 4 ☐ Four or more
- 5 ☐ Don't Know

Have you ever lived on a **Farm or Agricultural Enterprise**?

- 0 ☐ No
- 9 ☐ Don't Know
- 1 ☐ Yes

If Yes, for how many years did you live on a farm? ________years.

If Yes, what type of farm did you live on (check all that apply)?

- 1 ☐ Dairy
- 2 ☐ Chicken or other fowl
- 3 ☐ Grain
- 4 ☐ Citrus
- 5 ☐ Fruits and vegetables
- 6 ☐ Other________________

How many **years** have you **lived in Florida**? ________years

For all the jobs you have worked for 6 months or more, including the Armed Forces, please list the following:

Job title

Name of company (or self)

Actual years worked (ex. 1965 - 1967)

Known hazards to which you were exposed (ex. pesticides, asbestos, solvents, metals, radiation, etc.)

Please use the back of this page is more space is needed.

1960 - 1969

JOB TITLE	COMPANY	YEARS WORKED	KNOWN HAZARDS

1970 - 1979

JOB TITLE	COMPANY	YEARS WORKED	KNOWN HAZARDS

1980 - 1989

JOB TITLE	COMPANY	YEARS WORKED	KNOWN HAZARDS

1990 - present

JOB TITLE	COMPANY	YEARS WORKED	KNOWN HAZARDS

How would you describe your **Present Job Title**? (Check all that apply).

1 ☐ Pesticide Applicator
2 ☐ Farmer
3 ☐ Agricultural Worker
4 ☐ Other____________________
5 ☐ Don't Know

In what year did you **start working** at your present job? 19_____

How would you describe the present **job of your spouse**?

1 ☐ Not Applicable
2 ☐ Pesticide Applicator
3 ☐ Farmer
4 ☐ Agricultural Worker
5 ☐ Other____________________
6 ☐ Don't Know

The following questions concern the Pesticide Applicators License which you obtained through the Bureau of Pesticides, Florida Department of Agriculture.

In what year did you get your first license? 19_____

Are you presently licensed?

- 0 ☐ No
- 1 ☐ Yes
- 9 ☐ Don't Know

Have you renewed the License consistently every 4 years since you were first licensed?

- 0 ☐ No
- 1 ☐ Yes
- 9 ☐ Don't Know

In what year was your most recent License issued? 19_____

What type(s) of License do you presently have (check all that apply)?

- 1 ☐ Public
  - 11 ☐ County Trainer (public only)
- 2 ☐ Commercial
  - 21 ☐ Aerial
  - 22 ☐ Agricultural Animal
  - 23 ☐ Agricultural Plant
  - 24 ☐ Aquatic
  - 25 ☐ Demonstration & Research
  - 26 ☐ Forest
  - 27 ☐ Industrial, Institutional, Structural & Health
  - 28 ☐ Ornamental & Turf
  - 29 ☐ Public Health
  - 30 ☐ Regulatory
  - 31 ☐ Right of Way Control
  - 32 ☐ Seed Treatment
  - 33 ☐ Organotin Anti-fouling Paint
- 4 ☐ Private
- 5 ☐ Not Applicable
- 6 ☐ Don't Know

How many persons are listed by name on your Present License under your supervision?

- 0 ☐ None
- 1 ☐ 1 - 5
- 2 ☐ 6 - 10
- 3 ☐ 11 - 15
- 4 ☐ Not Applicable
- 5 ☐ Don't Know

Did you apply pesticides for others before getting your license?

- 0 ☐ No
- 9 ☐ Don't Know
- 1 ☐ Yes

If Yes, for how many years? _______ years.

If Yes, exactly which years did you apply pesticides others: 19_____ to 19_____

PESTICIDE USE — INSTRUCTIONS

We are interested in knowing the four (4) major **Restricted Use Pesticides** you commonly work with presently, and the four (4) major restricted use pesticides you have worked with in each of the past decades. In addition, we are interested in their approximate amounts, number of days per year, the actual years you applied them, and the application technique used.

Please read the following explanations for each column before filling out the **Pesticide Use Chart** on the following page.

If you use or have used a Pesticide commonly which you do not find on the Restricted Pesticide list enclosed, then just enter it in the chart by name only; fill out the rest of the chart as with the other pesticides.

1. Types of Pesticides Applied:
   Use the Restricted Use Pesticide List enclosed to find the code for the four (4) Restricted Use Pesticide you have used most during the particular time period; write the **names and the codes** in these columns.

2. Amounts in pounds or gallons per year:
   Please estimate the **total number of gallons or pounds per year** of the particular Restricted Use Pesticide during the particular time period.

3. Number of days/year applied:
   Please estimate the **total number of days/year** that you have applied the particular Restricted Use Pesticide during the particular decade.

4. Number of years applied:
   Please estimate the **total number of years** you have applied the particular Restricted Use Pesticide during the particular decade.

5. Application Technique:
   Please record the **method of application** used for the particular Restricted Use Pesticide. Use the following codes:
   - 1= ***Aerial***. Defined as applying pesticides in the air using aircraft, both fixed wing and rotary wing.
   - 2= ***Surface***. Defined as ground application using surface equipment, such as foliar spray equipment, structural or storage fumigation, wick application, etc., or surface aquatic application.
   - 3= ***Sub-surface application***. Defined as applying pesticides directly into the ground, below the soil surface, such as drenching, ground insertion, or disking in broadcast-applied granular material, etc., or aquatic application the surface of the water.

We realize that this is very detailed information to provide, but it is important information in order to determine the possible health effects of pesticide exposure. Please provide as thoughtful and as accurate information as possible. Again, please contact us if this form is confusing, or if you have any questions. Telephone: (305)243-5912

Pesticide Use Chart (see enclosed *Restricted Pesticide Codes* on next page)

1960 - 1969

Code	Pesticide Applied	Amount/ year	Unit (circle)	Number of days/year	Number of years	Technique (1-3)
			lbs. / gal.			
			lbs. / gal.			
			lbs. / gal.			
			lbs. / gal.			

1970 - 1979

Code	Pesticide Applied	Amount/ year	Unit (circle)	Number of days/year	Number of years	Technique (1-3)
			lbs. / gal.			
			lbs. / gal.			
			lbs. / gal.			
			lbs. / gal.			

1980 - 1989

Code	Pesticide Applied	Amount/ year	Unit (circle)	Number of days/year	Number of years	Technique (1-3)
			lbs. / gal.			
			lbs. / gal.			
			lbs. / gal.			
			lbs. / gal.			

1990 - present

Code	Pesticide Applied	Amount/ year	Unit (circle)	Number of days/year	Number of years	Technique (1-3)
			lbs. / gal.			
			lbs. / gal.			
			lbs. / gal.			
			lbs. / gal.			

Restricted Pesticide Codes

25= AC 3422
71= Acaraben
01= acrolein
02= acrylonitrile
101= Agri-Mek
91= Agrimet
100= alachlor
03= aldicarb
58= aldrin
04= allyl alcohol
05= aluminum phosphide
90= Ambush
06= amitraz
59= amitrole
62= 4-aminopyridine
15= Ammo
15= Arrivo
60= arsenic acid
07= arsenic pentoxide
61= arsenic trioxide
112= Asana
101= avermectin
62= avitrol
08= azinphos-methyl
37= Azodrin
102= bendiocarb
107= bifenthrin
25= Bladan
75= Bladex
63= brodifacoum
64= bromodiolone
65= calcium arsenate
09= calcium cyanide
107= Capture 2 EC
66= captafol
10= carbofuran
67= carbon tetrachloride
68= carbophenothion
109= CCA
69= chlordane
70= chlordimeform
11= chlorfenvinphos
71= chlorobenzilate
72= chlorophacinone
12= chloropicrin
109= chromated copper arsenate
13= clonitralid
73= coal tar
54= Counter
74= creosote
75= cyanazine
117= Cycle
14= cycloheximide
06= Cyhalothrin
15= Cymbush
15= cypermethrin
76= DBCP
16= demeton
77= diallate
109= 1,3 dichloropropene
17= diclofop methyl
18= dicrotophos
19= diflubenzuron
78= dinocap
20= dioxathion
110= diphacinone
111= disodium methanearsonate
21= disulfoton
21= Di-syston
79= dodemorph
90= Dragnet
111= DSMA
36= Duraphos
122= dylox
22= endrin
118= Epibloc
23= EPN
112= esfenvalerate
113= etephon
114= ethofumesate
24= ethoprop
25= ethyl parathion
26= fenamiphos
27= fensulfothion
81= fenvalerate
102= Ficam
82= flucythrinate
28= fluoroacetamide 1081
103= fluvalinate
25= Folidol
35= Folidol M
29= fonofos
120= Force 1.5G
05= Fumitoxin
70= Fundal
10= Furadan
70= Galecron
05= Gastoxin
69= Gold Crest
40= Gramoxone
72= Ground force
08= Guthion
84= Gypsine
83= heptachlor
30= hydrocyanic acid
104= isazophos
105= isofenphos
106= Karate
45= Kerb
33= Lannate
100= Lasso
84= lead arsenate
85= lindane
31= magnesium phosphide
103= Mavrik 2E
86= Mesurol
35= Metacide
88= Metasystox-R
32= methamidophos
87= methidathion
86= methiocarb
33= methomyl
34= methyl bromide
35= methyl parathion
36= mevinphos
24= Mocap
32= Monitor
37= monocrotophos
37= Monodrin
26= Nemacur 3
38= nocotine (alkaloid)
33= Nudrin
39= oxamyl
115= oxadiazon
88= oxydemeton
89= PCP
40= paraquat
35= Penncap-M
89= pentachlorophenol
89= Pentacon
90= permethrin
116= phenylmercury
91= phorate
41= phosacetim
36= Phosdrin
25= Phoskil
42= phosphamidon
05= Phostoxin
57= Phosvin
43= picloram
116= PMAS
92= potassium pentachlorophenate
93= potassium tetrachlorophenate
90= Pounce
113= Prep
117= procyazine
44= profenofos
114= Prograss
45= pronamide
118= propanediol
46= propetamphos
105= Pryfon 6
81= Pydrin
57= Ratol
64= ratimus
57= Ridall-zinc
66= Sanspor
119= simazine
94= sodium arsenate
47= sodium cyanide
48= sodium fluoroacetate
95= sodium pentachlorophenate
84= Soprabel
96= starlicide
49= strychnine
50= sulfotep
51= sulfuryl fluoride
52= sulprofos
97= sumithion
87= Supracide
84= Talbot
63= Talon
121= Tedion
120= tefluthrin
109= Telone
03= Temik
53= TEPP
54= terbufos
98= terbutryn
121= tetradiphon
91= Thimet
90= Torpedo
99= toxaphene
55= tralomethrin
122= trichlorion
56= triphenyltin hydroxide
68= trithion
104= Triumph
51= Vikane
39= Vydate
57= zinc phosphide

How often have you been responsible for **mixing** the pesticides which you apply?

	Always	Sometimes	Seldom	Never	N/A	Don't Know
1960 - 1969	11 ☐	21 ☐	31 ☐	41 ☐	51 ☐	61 ☐
1970 - 1979	12 ☐	22 ☐	32 ☐	42 ☐	52 ☐	62 ☐
1980 - 1989	13 ☐	23 ☐	33 ☐	43 ☐	53 ☐	63 ☐
1990 - present	14 ☐	24 ☐	34 ☐	44 ☐	54 ☐	64 ☐

Have you had any **part-time or periodic jobs, in addition to your regular** job?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

If Yes, have any of these jobs involved **applying Pesticides**?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

Have you regularly applied **pesticides at home**?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

Have you regularly applied **pesticides for friends** and acquaintances?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

PROTECTIVE EQUIPMENT

When working with pesticides, how often did you use a **mask (respirator)**?

	Always	Sometimes	Seldom	Never	N/A	Don't Know
1960 - 1969	11 ☐	21 ☐	31 ☐	41 ☐	51 ☐	61 ☐
1970 - 1979	12 ☐	22 ☐	32 ☐	42 ☐	52 ☐	62 ☐
1980 - 1989	13 ☐	23 ☐	33 ☐	43 ☐	53 ☐	63 ☐
1990 - present	14 ☐	24 ☐	34 ☐	44 ☐	54 ☐	64 ☐

When working with pesticides, how often did you use **protective glasses**?

	Always	Sometimes	Seldom	Never	N/A	Don't Know
1960 - 1969	11 ☐	21 ☐	31 ☐	41 ☐	51 ☐	61 ☐
1970 - 1979	12 ☐	22 ☐	32 ☐	42 ☐	52 ☐	62 ☐
1980 - 1989	13 ☐	23 ☐	33 ☐	43 ☐	53 ☐	63 ☐
1990 - present	14 ☐	24 ☐	34 ☐	44 ☐	54 ☐	64 ☐

PROTECTIVE EQUIPMENT, continued.

When working with pesticides, how often did you use **gloves**?

	Always	Sometimes	Seldom	Never	N/A	Don't Know
1960 - 1969	11 ☐	21 ☐	31 ☐	41 ☐	51 ☐	61 ☐
1970 - 1979	12 ☐	22 ☐	32 ☐	42 ☐	52 ☐	62 ☐
1980 - 1989	13 ☐	23 ☐	33 ☐	43 ☐	53 ☐	63 ☐
1990 - present	14 ☐	24 ☐	34 ☐	44 ☐	54 ☐	64 ☐

When working with pesticides, how often did you use a **uniform (coverall, protective suit)**?

	Always	Sometimes	Seldom	Never	N/A	Don't Know
1960 - 1969	11 ☐	21 ☐	31 ☐	41 ☐	51 ☐	61 ☐
1970 - 1979	12 ☐	22 ☐	32 ☐	42 ☐	52 ☐	62 ☐
1980 - 1989	13 ☐	23 ☐	33 ☐	43 ☐	53 ☐	63 ☐
1990 - present	14 ☐	24 ☐	34 ☐	44 ☐	54 ☐	64 ☐

When working with pesticides, how often did you use **long sleeve shirt and long trousers**?

	Always	Sometimes	Seldom	Never	N/A	Don't Know
1960 - 1969	11 ☐	21 ☐	31 ☐	41 ☐	51 ☐	61 ☐
1970 - 1979	12 ☐	22 ☐	32 ☐	42 ☐	52 ☐	62 ☐
1980 - 1989	13 ☐	23 ☐	33 ☐	43 ☐	53 ☐	63 ☐
1990 - present	14 ☐	24 ☐	34 ☐	44 ☐	54 ☐	64 ☐

MEDICAL HISTORY

What is your **present Height**? _____feet _____inches

What is your **present Weight**? _____pounds

What was your approximate **weight in 1975** (ie. 20 years ago)? ______pounds

Have you had any **Major Illnesses**?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

If Yes, please check which illness(es) and indicate the year diagnosed.

Illness	Year Diagnosed
☐ High Blood Pressure	________
☐ Asthma	________
☐ Breathing Problems	________
☐ Heart Problems	________
☐ Seizures/Convulsions	________
☐ Skin Problems	________
☐ Cancer (type:_______________)	________
☐ Arthritis	________
☐ Nerve Problems (including Parkinsons)	________
☐ Reproductive Problems	________
☐ Other:_________________	________

Has anyone in your **family** (ie. parents, siblings, children) ever had any **Major Illnesses**?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

If Yes, please check which illness(es), the relationship of the person to you, and indicate the year it was diagnosed.

Illness	Relationship	Year Diagnosed
☐ High Blood Pressure	________	________
☐ Asthma	________	________
☐ Breathing Problems	________	________
☐ Heart Problems	________	________
☐ Seizures/Convulsions	________	________
☐ Skin Problems	________	________
☐ Cancer (type:_______________)	________	________
☐ Arthritis	________	________
☐ Nerve Problems (including Parkinsons)	________	________
☐ Reproductive Problems	________	________
☐ Other:_________________	________	________
☐ Other:_________________	________	________

Do you take any **medications regularly** (both prescription and over-the-counter)?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

If Yes, please list these medications by name:

1. ______
2. ______
3. ______
4. ______

Have you ever taken any **medicine for seizures** (epilepsy) such as **dilantin, Phenobarbital, or valproic acid**?

0 ☐ No 1 ☐ Yes

9 ☐ Don't Know

Have you ever taken any **medicine for Parkinson's Disease** such as **L-Dopa** or **Sinemet**?

0 ☐ No 1 ☐ Yes

9 ☐ Don't Know

When you were a child, did you ever take **Cod Liver Oil**?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

If Yes, in general, how often did you take the **Cod Liver Oil**?

1 ☐ 1 or more times per **week**

2 ☐ 1 or more times per **month**

3 ☐ Less than 1 time per **month**

Have you ever been **sick due to pesticides**?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

If Yes, was this due to your exposure to pesticides at work?

0 ☐ No 1 ☐ Yes

9 ☐ Don't Know

If Yes, did a doctor say this illness(es) was possibly related to pesticides?

0 ☐ No 1 ☐ Yes

9 ☐ Don't Know

If Yes, please describe the incident(s) (i.e. circumstances, symptoms, hospitalization, medications, and when happened.

______

______

______

______

______

______

______

~~please use the back of this page if more space is needed~~

Have you ever worked with **anyone else** who has been **sick** due to their **exposure to pesticides**?

- 0 ☐ No
- 9 ☐ Don't Know
- 1 ☐ Yes

Has anyone in your **family** ever been **sick** due to their **exposure to pesticides**?

- 0 ☐ No
- 9 ☐ Don't Know
- 1 ☐ Yes

Have you **ever** been **sick** (other than from pesticides) or **injured** due to **your work**?

- 0 ☐ No
- 9 ☐ Don't Know
- 1 ☐ Yes

If Yes, did a doctor say this illness(es) was possibly related to your work?

- 0 ☐ No
- 9 ☐ Don't Know
- 1 ☐ Yes

If Yes, please describe the incident(s) (i.e. circumstances, symptoms, hospitalization, medications, and when happened):

____

____

____

____

____

____

____

SUN EXPOSURE

Do you wear a **hat** for protection from the sun while working?

1 ☐ Always 3 ☐ Sometimes 5 ☐ Don't Know

2 ☐ Mostly 4 ☐ Never

Do you use **sunscreen** for protection from the sun while working?

1 ☐ Always 3 ☐ Sometimes 5 ☐ Don't Know

2 ☐ Mostly 4 ☐ Never

During what **part of the day** is the sun most hazardous to your skin?

1 ☐ Between 8 AM to 10 AM

2 ☐ Between 10 AM to 3 PM

3 ☐ Between 3 PM to 5 PM

4 ☐ Don't know

Have you ever had your **skin examined by a Doctor** for moles, spots, or other changes?

0 ☐ No

1 ☐ Yes

9 ☐ Don't Know

TOBACCO—Cigarettes

Do you presently live or have you lived with **persons who regularly smoke Cigarettes**?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

If Yes, how many years in total have you lived with smokers?

______years

Have you ever smoked **100 cigarettes** or more during your life?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

If Yes, how **old** were you when you first started smoking cigarettes?
______years old

If Yes, how many packs per day (ppd) have you usually smoked?
(a pack=20 cigarettes)

	< 1 ppd	1 ppd	2 ppd	> 2 ppd	N/A	Don't Know
1960 - 1969	11 ☐	21 ☐	31 ☐	41 ☐	51 ☐	61 ☐
1970 - 1979	12 ☐	22 ☐	32 ☐	42 ☐	52 ☐	62 ☐
1980 - 1989	13 ☐	23 ☐	33 ☐	43 ☐	53 ☐	63 ☐
1990 - present	14 ☐	24 ☐	34 ☐	44 ☐	54 ☐	64 ☐

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CIGARETTES—continued

Do you **presently smoke** cigarettes?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

If No, how old were you when you **stopped** smoking cigarettes?

______years

If No, how many packs per day (**ppd**) did you usually smoke before you quit.

	< 1 ppd	1 ppd	2 ppd	> 2 ppd	N/A	Don't Know
1960 - 1969	11 ☐	21 ☐	31 ☐	41 ☐	51 ☐	61 ☐
1970 - 1979	12 ☐	22 ☐	32 ☐	42 ☐	52 ☐	62 ☐
1980 - 1989	13 ☐	23 ☐	33 ☐	43 ☐	53 ☐	63 ☐
1990 - present	14 ☐	24 ☐	34 ☐	44 ☐	54 ☐	64 ☐

CIGARS

Have you ever regularly smoked **cigars**?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

If Yes, how many **cigars per day** do/did you usually smoke?

1 ☐ 1 - 3

3 ☐ 7 - 10

2 ☐ 4 - 6

4 ☐ more than 10

If Yes, for how many **years** have you or did you regularly smoke cigars? ______years

PIPE

Have you ever regularly used a **pipe**?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

If Yes, for how many years have/did you regularly use a pipe?

______years

CHEWING TOBACCO OR SNUFF

Have you ever regularly used **chewing tobacco or snuff**?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

If Yes, for how many **years** have/did you regularly use chewing tobacco or snuff?

______years

ALCOHOL

Have you ever regularly used **alcohol**?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

If Yes, for how many **years** have/did you regularly use alcohol?

_______years

If Yes, what **kinds** of alcohol do/did you regularly drink? (check all that apply)

1 ☐ Beer

2 ☐ Wine

3 ☐ Liquor

If Yes, for each type of alcohol, approximately how much do/did you drink regularly **per week**? (Check all that apply)

	< 1 six pack	1 six pack	2 six packs	1 case or more
Beer	11 ☐	12 ☐	13 ☐	14 ☐

	< 1 glass	1 glass	1 bottle	2 + bottles
Wine	21 ☐	22 ☐	23 ☐	24 ☐
Liquor	31 ☐	32 ☐	33 ☐	34 ☐

OTHER

Have you ever used any **drugs not prescribed by a physician** (including marijuana, cocaine or crack, heroin, angel dust, speed, valium, or barbiturates)?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

NERVOUS SYSTEM				
Since many pesticides can affect the nerves, the following questions deal with symptoms from your nervous system which you might have experienced regularly over the past 10 years; please indicate if you have experienced these symptoms, and if Yes, for how many years.				
	No (0)	Don't Know (9)	Yes (1)	Number of Years
Have you had **trouble rising** from a chair?	☐	☐	☐	____
Has your **handwriting gotten smaller** than it once was?	☐	☐	☐	____
Do people tell you that your **voice is softer** than it once was?	☐	☐	☐	____
Has your **balance gotten poor**?	☐	☐	☐	____
Have your **feet ever seemed to get stuck** to the floor?	☐	☐	☐	____
Do people tell you that **your face seems less expressive** than it once did?	☐	☐	☐	____
Have your **arms or legs shaken**?	☐	☐	☐	____
Have you had **trouble buttoning buttons**?	☐	☐	☐	____
Do you **shuffle your feet and/or take tiny steps** when you walk?	☐	☐	☐	____
Have you had any **blurred vision** or times when you see **distant objects double**?	☐	☐	☐	____
Have you had complete or partial **temporary loss of sight** in your eyes?	☐	☐	☐	____
Have there been times when your **speech was slurred**?	☐	☐	☐	____
Have there been times when you had **difficulty swallowing**?	☐	☐	☐	____
Have you experienced **muscle weakness** which made it hard to walk fast or to climb stairs?	☐	☐	☐	____
Have you had **frequent headaches** (3 or more/week) ?	☐	☐	☐	____
Have you had spells of **dizziness or lightheadedness**?	☐	☐	☐	____
Have you **fainted or "blacked out"** (i.e. lost consciousness) ?	☐	☐	☐	____
Have you had a **convulsion, seizure or fit**?	☐	☐	☐	____
Have you had difficulty **getting to sleep or trouble staying asleep**?	☐	☐	☐	____
Have you **tired more easily** for the amount of activity you do?	☐	☐	☐	____
Have you had any trouble with **forgetfulness**?	☐	☐	☐	____
Have your **relatives** noted that you have any trouble with **forgetfulness**?	☐	☐	☐	____
Have you had any trouble with your **coordination** (for example, trouble handling or picking up objects) ?	☐	☐	☐	____
Have you noticed any **unexplained numbness, or tingling** in your hands or feet?	☐	☐	☐	____
Have you had **trouble concentrating** or keeping your mind on things?	☐	☐	☐	____
Have you had frequent and severe **mood swings**?	☐	☐	☐	____
Have there been periods of time when you found that you were easily **depressed**, or had **crying spells**?	☐	☐	☐	____

Nervous System—continued

	No (0)	Don't Know (9)	Yes (1)	Number of Years
Have there been periods of time when you were easily **irritated** or unusually irritable?	☐	☐	☐	______
Have you experienced **slowed or fuzzy thinking**?	☐	☐	☐	______
Have you had **difficulty remembering** things?	☐	☐	☐	______
Do you find that you are **more anxious than before**?	☐	☐	☐	______
Do you feel that you have been **persecuted or threatened** by others?	☐	☐	☐	______
Sometimes people claim that they see, smell, or feel things when other people are not able to notice them; have you ever experienced such **sensations**?	☐	☐	☐	______
Have you been treated for any **mental or psychiatric or nervous condition** of any kind?	☐	☐	☐	______

Do you think that exposure or work with **pesticides is hazardous to your health**?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

If Yes, which types of health hazards? ______________________________

If Yes, which types of pesticides? ______________________________

Do you think that exposure or work with **pesticides increases the risk for cancer**?

0 ☐ No

9 ☐ Don't Know

1 ☐ Yes

If Yes, which types of cancer? ______________________________

If Yes, which types of pesticides? ______________________________

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Do you have any other comments? (Please use the back of this page if more space is needed)

Thank you very much for your time and cooperation.

Please return the completed Questionnaire and <u>one</u> copy of the <u>signed</u> Consent Form in the stamped addressed envelope included in your packet. As soon as both of these forms are received you will be sent $10.00 for your time and effort.

Please call or write if you have any questions or comments.

Lora E. Fleming, MD, MPH (Principal Investigator)
University of Miami School of Medicine
Department of Epidemiology & Public Health (R-669)
PO Box 016069
Miami, FL 33101

Tel: (305)243-5912 FAX: (305)243-5544

Pesticide Applicator's Questionnaire Consent

University of Miami School of Medicine
Department of Epidemiology & Public Health (R-669)
Lora E. Fleming, MD, MPH (Principal Investigator)

Status of Pesticide Applicator 1 ☐ Alive

2 ☐ Dead Year Died 19____

Phone contact	___/___/___	9 -5 wkday	___/___/___	5 -9 wkday	___/___/___	wkend
1st #	___/___/___	9 -5 wkday	___/___/___	5 -9 wkday	___/___/___	wkend
Phone contact	___/___/___	9 -5 wkday	___/___/___	5 -9 wkday	___/___/___	wkend
2nd #	___/___/___	9 -5 wkday	___/___/___	5 -9 wkday	___/___/___	wkend
Phone contact	___/___/___	9 -5 wkday	___/___/___	5 -9 wkday	___/___/___	wkend
3rd #	___/___/___	9 -5 wkday	___/___/___	5 -9 wkday	___/___/___	wkend

Date of actual contact ___/___/___

Consent Information Paragraph

You are invited to participate in a research study of Florida Pesticide Applicators by investigators from the University of Miami School of Medicine. You were selected from the complete list of licensed Pesticide Applicators provided by the Florida Department of Agriculture. This Study is examining the possible connection between work-related pesticide exposure and health effects. This is a Study of the University of Miami, not the Florida Department of Agriculture.

You will be asked 5 to 10 minutes of questions concerning your work and possible health risks such as cigarette smoking. There are no risks or benefits to participating in this study. Participation is voluntary, and you can withdraw at any time.

Your information is confidential. Your records and results will not be identified individually in any publication. The Florida Department of Agriculture will receive only the Final Summary of Results, never any individual information.

Dr. Fleming, the Principal Investigator, can answer any questions that you may have regarding the investigation at (305)243-5912. If you have any questions about your rights as a research subject, you may contact Ms. Marie Arnold, administrator of University of Miami Human Subjects, at (305)243-3327.

Spoke to:

Name:______________________________ Relationship:____________________

Does the subject (or proxy) consent to phone interview?

0 ☐ No

1 ☐ Yes

2 ☐ Unable to contact

If No, may I ask you why? ____________________________

ID#

Pesticide Applicator's Questionnaire

University of Miami School of Medicine
Department of Epidemiology & Public Health (R-669)

Have you ever worked with:

	No	Yes	Don't Know	Year Started	Year Ended	Still Working
Herbicides	11 ☐	21 ☐	31 ☐	________	________	41 ☐
Pesticides	12 ☐	22 ☐	32 ☐	________	________	41 ☐

Did you **apply pesticides for others** before getting your license?

0 ☐ No

1 ☐ Yes

9 ☐ Don't Know

If Yes, exactly which years did you apply pesticides for others?
19_____ to 19_____

What pesticides have you most commonly worked with by **decade**?

- aldrin
- arsenic
- chlordane
- DBCP
- DDT
- endrin
- heptachlor
- lindane
- methyl bromide
- parathion
- paraquat
- temik
- herbicides
- organochlorines
- organophosphates
- carbamates
- pyrethrums
- other ______________

Pesticide Applied	Amount/day	Unit (circle)	Number of days/year	Decade
		gal. / lbs.		1960 - 1969
		gal. / lbs.		1960 - 1969
		gal. / lbs.		1960 - 1969
		gal. / lbs.		1960 - 1969
		gal. / lbs.		1970 - 1979
		gal. / lbs.		1970 - 1979
		gal. / lbs.		1970 - 1979
		gal. / lbs.		1970 - 1979
		gal. / lbs.		1980 - 1989
		gal. / lbs.		1980 - 1989
		gal. / lbs.		1980 - 1989
		gal. / lbs.		1980 - 1989
		gal. / lbs.		1990 - present
		gal. / lbs.		1990 - present
		gal. / lbs.		1990 - present
		gal. / lbs.		1990 - present

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Have you ever lived on a **Farm or Agricultural Enterprise**?

0 ☐ No
1 ☐ Yes
9 ☐ Don't Know

If Yes, can you estimate the number of years?
_______ yrs.

Have you regularly applied **pesticides at home**?

0 ☐ No
1 ☐ Yes
9 ☐ Don't Know

If Yes, can you estimate the number of years?
_______ yrs.

Have you ever smoked **100 cigarettes** (5 packs) or more during your life?

0 ☐ No
1 ☐ Yes
9 ☐ Don't Know

If Yes, how **old** were you when you first **started** smoking cigarettes?
______years old

	< 1 ppd	1-1½ ppd	1½-2 ppd	> 2 ppd	N/A	Don't Know
1960 - 1969	11 ☐	21 ☐	31 ☐	41 ☐	51 ☐	61 ☐
1970 - 1979	12 ☐	22 ☐	32 ☐	42 ☐	52 ☐	62 ☐
1980 - 1989	13 ☐	23 ☐	33 ☐	43 ☐	53 ☐	63 ☐
1990 - present	14 ☐	24 ☐	34 ☐	44 ☐	54 ☐	64 ☐

Are you a **current cigarette smoker**?

0 ☐ No
1 ☐ Yes
9 ☐ Don't Know

If No, how **old** were you when you **stopped** smoking cigarettes?
______years old

Do you regularly have more than 2 **alcoholic beverages** per week?

0 ☐ No
1 ☐ Yes
9 ☐ Don't Know

If Yes, for how many **years** have/did you regularly use **alcohol**?
______years

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Have you had any of the following **illnesses**:

- 1 ☐ Nerve Problems (including Parkinson's and Alzheimer's Disease)
- 2 ☐ Asthma
- 3 ☐ Breathing Problems
- 4 ☐ Heart Problems
- 5 ☐ Seizures/Convulsions
- 6 ☐ Skin Problems
- 7 ☐ Cancer (type____________________)
- 8 ☐ Arthritis
- 9 ☐ High Blood Pressure
- 10 ☐ Reproductive Problems
- 11 ☐ Other:____________________
- 12 ☐ Other:____________________

Please indicate your **sex**?

- 1 ☐ Male
- 2 ☐ Female

How many years of **school** have you <u>completed</u>?

- 1 ☐ Elementary (Grades 1-6)
- 2 ☐ Junior High School (Grades 7-9)
- 3 ☐ High School (Grades 10-12)
- 4 ☐ Junior College or Technical School
- 5 ☐ College
- 6 ☐ College (4 years +)
- 7 ☐ Other ____________________
- 8 ☐ Don't Know

What is your **date of birth** (mm/dd/yy) ______/______/______

How would you describe your **Race/Ethnic Group**?

- 1 ☐ White Non Hispanic
- 2 ☐ Black Non Hispanic
- 3 ☐ White Hispanic
- 4 ☐ Black Hispanic
- 5 ☐ Asian
- 6 ☐ Polynesian
- 7 ☐ Native American
- 8 ☐ Other ____________________
- 9 ☐ Don't Know

Comments: ____

____

____

____

____

Would you like to recieve a copy of the **Final Results of the Study**?

- 0 ☐ No
- 1 ☐ Yes

If Yes, verify address on label

Correct Address: ____

____

____

Thank you very much for your time and co-operation. Your answers are greatly appreciated!!!

Appendix C: Letters

a) Original Case Control Mailing Letter

b) Follow up Case Control Mailing Letter

October 31, 1995

UNIVERSITY OF MIAMI

SCHOOL OF MEDICINE

Dear

You are invited to participate in a research Study of Florida Pesticide Applicators conducted by Investigators from the University of Miami School of Medicine. You have been selected to participate in this Study from the complete list of licensed Pesticide Applicators provided by the Florida Department of Agriculture Bureau of Pesticides through public access.

This Study will examine the connection between work-related pesticide exposure and health effects. This is a Study of the University of Miami School of Medicine, not the Florida Department of Agriculture Bureau of Pesticides. This Study has been approved by the University of Miami Human Subjects Committee (see the enclosed Consent Form). We hope that the results of this study will prevent health effects in pesticide applicators and other people in the future.

We invite you to participate by filling out and returning the enclosed Questionnaire and 1 signed copy of the Consent Form in the enclosed stamped addressed envelope. We are seeking information concerning the types and amounts of pesticides you have used, as well as the equipment for application and protection. It also asks for information concerning other health risks such as cigarette smoking and demographic information.

If you return the completed Questionnaire and 1 signed copy of the Consent Form in the enclosed stamped self-addressed envelope, you will receive a remuneration of $10.00 for your participation in this study. In addition, if you wish to receive a copy of the Final Summary of Results when this study is completed, then indicate this at the end of the Consent Form.

If you do not wish to participate in this study, please tell us briefly why:__

____

____

and return these materials in the enclosed stamped addressed envelope. You will not be contacted any further.

If for some reason, a person other than you needs to fill out the questionnaire for you, please indicate this in the space provided on the Questionnaire.

If we do not receive any response from you within 3 weeks, we will call your house to see if we can assist you in answering the Questionnaire or with any other questions you might have.

If you have any questions or concerns about this study, the Questionnaire or the Consent Form, please feel free to call (305-243-5912) or write us at the address listed below.

Sincerely,

Lora E. Fleming MD MPH
Principal Investigator
enc:

Department of Epidemiology and Public Health (R-669)
Daughtry Building
P.O. Box 016069, Miami, Florida 33101
Location: 1029 N.W. 15 Street, Miami, Florida 33136
Telephone: (305) 547-6972 Fax: (305) 547-5544

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UNIVERSITY OF
Miami
SCHOOL OF MEDICINE

December 8, 1995

Dear

You were invited to participate in a research Study of Florida Pesticide Applicators conducted by Investigators from the University of Miami School of Medicine.

As we explained, the Study will examine the connection between work-related pesticide exposure and health effects. This is a Study of the University of Miami School of Medicine, not the Florida Department of Agriculture Bureau of Pesticides. This Study has been approved by the University of Miami Human Subjects Committee (see the enclosed Consent Form). We hope that the results of this study will prevent health effects in pesticide applicators and other people in the future.

We invite you to participate by filling out and returning the enclosed Questionnaire and 1 signed copy of the Consent Form in the enclosed stamped addressed envelope. If you return the completed Questionnaire and 1 signed copy of the Consent Form in the enclosed stamped self-addressed envelope, you will receive a remuneration of $10.00 for your participation in this study. In addition, if you wish to receive a copy of the Final Summary of Results when this study is completed, then indicate this at the end of the Consent Form.

If you do not wish to participate in this study, please tell us briefly why:__

____

____

and return these materials in the enclosed stamped addressed envelope. You will not be contacted any further.

If for some reason, a person other than you needs to fill out the questionnaire for you, please indicate this in the space provided on the Questionnaire.

If we do not receive any response from you within 3 weeks, we will call your house to see if we can assist you in answering the Questionnaire or with any other questions you might have.

If you have any questions or concerns about this study, the Questionnaire or the Consent Form, please feel free to call (305-243-5912) or write us at the address listed below.

Sincerely,

Lora E. Fleming MD MPH
Principal Investigator

enc:

Department of Epidemiology and Public Health (R-669)
Daughtry Building
P.O. Box 016069, Miami, Florida 33101
Location: 1029 N.W. 15 Street, Miami, Florida 33136
Telephone: (305) 547-6972 Fax: (305) 547-5544

Attachment D: Questionnaire Protocol Manual

3/5/96 LEF

Protocol: **Pesticide Applicators Questionnaire**

FRONT PAGE

The Database should provide a label with the Serial Number, Name, Address, telephone number and known vital status. The label should be pasted at the top of FRONT PAGE of each questionnaire.

Vital Status of the Pesticide Applicator should be filled in for:

a) cases after making telephone contact confirmation;
b) controls following their matched case;

Phone Contact will be made according to the following protocol:

a) 2 calls separated by at least one hour should be made in each of the 3 time periods (eg. 9-5 weekdays, 5-9 pm weekdays, and weekends) for each available phone number;
b) Messages should not be left on message machines, although these do count as attempted calls and should be indicated as "MM";
c) This process is repeated for up to 3 different phone numbers, if available, before declaring the subject "lost to follow up" = **Unable to Contact** at the bottom of FRONT PAGE;
d) The initial phone number should be taken from the database, with subsequent phone numbers from either:
    a) the initial phone contact;
    b) the CD Rom Phone Book Listing; and/or,
    c) the FCDS database for the cases;
e) Note the dates of all phone call attempts, and any results if relevant.

After noting the date of the contact, the following will be read upon establishing contact with the subject:

a) Subject Respondent
"Mr/Ms. (Name of Respondent), my name is ______________. I am calling from the University of Miami School of Medicine. As you know from the letter you recently received, you have been selected to participate in a study about pesticides and health by the University of Miami. I would like to ask you a few questions about your work locations, use of certain kinds of chemicals, and overall health."

If the **Case** subject has died, then enroll this person in the study after ascertaining the date of death.

If the **Control** subject has died, then do not enroll this person in the study; ascertain the date of death, thank them for their cooperation, and get a new Control name from the database.

b) Surrogate Respondent
"Mr/Ms. (Name of Respondent), my name is ______________. I am calling from the University of Miami School of Medicine. As you know from the letter you recently received, you have been selected to participate in a study about pesticides and health by the University of Miami. I would like to ask you a few questions about your (deceased/RELATIONSHIP, NAME OF STUDY SUBJECT's) work locations, use of certain kinds of chemicals, and brief medical history."

Surrogate = the spouse or significant other, or first degree relative.

If the Surrogate has questions concerning their selection for participation, especially in the case of a matched control, explain that it is the surrogate information which is of interest at this time; try not to allow the alive subject to assist the surrogate! If there are further questions, have them speak directly with the Principal Investigator.

If no Surrogate is available, then the subject is considered "lost to follow up" = **Unable to Contact** which should be documented at the bottom of FRONT PAGE.

In the situation of seeking a Surrogate, if the **Control** subject (not the Surrogate) has died, continue to enroll the Surrogate in the study after ascertaining the date of death of the Control subject.

With Surrogate interview, it is important to rephrase all questions beginning **"deceased/RELATIONSHIP, NAME OF STUDY SUBJECT's"**.....; all questions pertain to the pesticide applicator and you may wish to continually remind the Surrogate during the interview.

If the person allows you to continue, then read the **Consent Information Paragraph**. Note the name and relationship of the person responding to the phone call, and if they agree to participate. Make sure that this is a convenient time to administer this brief questionnaire. If not, then arrange a telephone appointment for a more convenient time.

If the person does not allow you to continue, or decides after hearing the Consent Information Paragraph that they do not wish to participate, then note this and ask for a brief statement of why they do not wish to participate.

If the Respondent decides not to continue in the middle of the questionnaire administration, note the reason why on FRONT PAGE and draw a line after the last answered question. Offer the Final Report and thank the Respondent for their cooperation and important contribution.

PAGE ONE

Write in or place a label with the serial number of the case or control subject at the top of the page.

Ask if the person has ever worked with Herbicides (eg. chemicals which kill plants):

a) If yes, note the year started and ended or continued working;
b) If no, then go to the next question;
c) If don't know, then go to the next question;

Ask if the person has ever worked with Pesticides (eg. chemicals which kill pests, including bugs, funguses, plants, etc):

a) If yes, note the year started and ended or continued working;
b) If no, then go to the next question;
c) If don't know, then go to the next question;

Regardless of answer to above, ask if they have ever applied pesticides for others before getting the Florida Pesticide Applicators (Restricted Use) License; if yes, get calendar years of use.

Even if answered "don't know" or "no" to use of herbicides and Pesticides, ask if you can read the Pesticide List to see if anything sounds familiar.

If answered "yes" to the use of herbicides and/or Pesticides:

a) Then fill in the decades;

b) Ask if they remember the names of any specific pesticides;

    1) If yes, then ask about the approximate amounts (in gallons or lbs) for an average application, and number of days/year for each specific pesticide by decade;

c) Whether they remember a specific pesticide or not, then read the Pesticide List,

    1) If "yes" for a pesticide on the Pesticide List, ask about the approximate amounts (in gallons or lbs) for an average application, and number of days/year for each specific pesticide by decade;

    2) Finish asking about all the decades before going onto the next pesticide on the Pesticide List;

d) Go to the back or labeled extra sheets if more space is needed, keeping to the same format;

PAGE TWO

Write in or place a label with the serial number of the case or control subject at the top of the page.

When asking about a) living on a Farm or Agricultural Enterprise, or b) applying pesticides at home, you can calculate the number of years for the Respondent by asking calendar years.

For the Cigarette question, a pack = 20 cigarettes. The "first started smoking cigarettes" would be more than 1 cigarette per day use.

Alcoholic beverages = beer, wine, "hard" liquor, mixed drinks. The same definition of "regular use" = >2 alcoholic beverages/week applies to both questions.

PAGE THREE

Write in or place a label with the serial number of the case or control subject at the top of the page.

The medical questions can be introduced by saying "I am now going to ask you a few questions about your medical history". Read the entire list and then ask for any other chronic or major medical problems not mentioned.

Sex = gender (can be marked by the interviewer without asking the Respondent) is of the study subject, not the Surrogate.

The years of school definitions can be interpreted by the interviewer without having to read through the entire list.

If the Respondent is hesitant throughout the interview, just ask to give the year of birth rather than the entire date of birth.

For the Race/Ethnic Group, first ask the respondent how they would describe the Race/Ethnic Group; only read the list if none of the listed answers are given or if there is significant hesitancy.

Ask an open-ended question concerning possible issues which the Respondent might wish to raise concerning the possible health effects of occupational pesticide exposure.

Offer a copy of the Final Results of the Study (probably available in the Spring to Summer of 1997); if the

Respondent expresses interest in a copy, then verify correct mailing address from Label and check the "if yes, verify address on label" box on the bottom of PAGE THREE if correct; if different address, note.

Thank the Respondent for their cooperation and important contribution. Remind that if there are any questions or concerns, they can call the Principal Investigator (305-243-5912) whose name, address and phone number are on the letter.

OVERALL

Write comments and extra information on the Questionnaire Forms, and discuss with the Principal Investigator afterwards.

Fill in some answer for all questions or write a reason why no answer.

If answer is not applicable, write "N/A".

If Respondent does not wish to answer, write "No Response".

If there are questions or problems, arrange for the Respondent to speak at a later date with the Principal Investigator.

With Surrogate interview, it is important to rephrase all questions beginning "**deceased/RELATIONSHIP, NAME OF STUDY SUBJECT's**".....; all questions pertain to the pesticide applicator and you may wish to continually remind the Surrogate during the interview.