Developing and Evaluating Rural Environmental Health Indicators: A Focus on Agricultural Pesticides and Health Outcomes in Manitoba

by

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ABSTRACT

The thesis objectives were to a) create environmental health indicators (EHIs) of the use and risk of crop farming pesticides; b) conduct an epidemiological study of the association between the pesticide EHIs and health outcomes, in rural crop farming areas of Manitoba. Pesticide indicators included the average annualized percent of Census Consolidated Subdivision land acreage where any pesticides, herbicides, fungicides, or insecticides were applied as well as an indicator of pesticide risk. In multilevel models, the use of insecticides was significantly associated with perinatal conditions (males: OR=1.08, p=0.005; females: OR=1.07, p=0.01), congenital anomalies in males (OR=1.04, p=0.04), and eye disorders (males: OR=1.03, p<0.001; females: OR=1.02, p=0.012). Eye disorders in males were also significantly associated with the use of any pesticide (OR=1.001, p<0.001) and pesticide risk (OR=1.06, p<0.001). Regular pesticide use in crop farming, especially insecticides, may be adversely affecting the health of the rural residents of Southern Manitoba.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF COPYRIGHTED MATERIAL FOR WHICH PERMISSION WAS OBTAINED

1. INTRODUCTION

1.1. Study Objective

Environmental health indicators[1] (EHIs) are needed, in Canada as well as globally, to aid in the monitoring and surveillance of environmental risks to human health. It is important to develop EHIs relevant to rural populations, considering the uniqueness of rural health concerns and the rural environment. Agricultural pesticides have been highlighted as an area in need of EHI development. In order to have empirical validity, an EHI of agricultural pesticides needs to have an identified link to health. The importance of agriculture in Manitoba and the wealth of available data on both pesticides used in crop farming and health outcomes makes developing rural EHIs of agricultural pesticide use and risk both relevant and feasible. Accordingly, the objectives of the study are to: (a) *create environmental health indicators (EHIs) of 'pesticide use in crop farming' and 'risk of pesticide use in crop farming';* (b) *evaluate empirical validity through conducting an epidemiological study of the association between the EHIs of agricultural pesticides and adverse physical and mental health outcomes, in rural farming areas of Manitoba, Canada.*

[1] Terms contained in the Glossary (Appendix A) are underlined the first time they appear in the text.

1.2. Environmental Health Indicators

Worldwide, there has been increasing recognition of the critical contribution of monitoring and surveillance to research, professional practice, and evidence-based decision making in the fields of both public health and environmental health (Eyles & Furgal, 2002; Gray & Schornack, 2002). In this context, monitoring and surveillance involve the regular collection and analysis of measurements intended to identify changes in the environment, the health status of human populations, or both (Eyles & Furgal, 2002; Furgal & Gosselin, 2002). Generally only those measurements that are indicative of the relationship between human health and the environment are chosen as environmental health indicators (Furgal & Gosselin, 2002): defined as "an expression of the link between environment and health, targeted at an issue of specific policy or management concern and presented in a form which facilitates interpretation for effective decision-making" (Briggs, 2003, p. 2).

Two categories of environmental health indicators (EHIs) are sometimes delineated based on the direction of the link between environment and health (Briggs, 2003; Wcislo, Dutkiewicz, & Konczalik, 2002). Health-related environmental indicators (HREIs) are environmental conditions that potentially affect health (Wcislo et al., 2002). Environmental-related health indicators (ERHIs) are health outcomes that have environmental causes or factors (Wcislo et al., 2002). As the fields of environment and health converged, HREIs were recognized as part of the physical environment determinant of health in the population health model and ERHIs were considered relevant to monitoring the state of the environment (Hodge & Longo, 2002; Sladden, Beard,

Simpson, & Luckie, 1999). The field of sustainability, which focuses on maintaining or improving both human and ecosystem well-being, also employs both types of EHIs (Hodge & Longo, 2002).

Generally, suites of indicators are developed where both types of EHIs are included (D. L. Combs, personal communication, September 2, 2005). The suites of EHIs are designed so that environmental risks to health can be assessed through monitoring of both HREIs and ERHIs (Briggs, 1999, 2003). EHIs are an instrument for facilitating decision-making processes as well as a tool for lobbying and raising awareness (Briggs, 1999; Centers for Disease Control and Prevention, 2006; United Nations Department of Economic and Social Affairs, 2001). Other roles of EHIs include measuring progress towards goals and evaluating the performance of policies or interventions (Briggs, 1999, 2003; Centers for Disease Control and Prevention, 2006; United Nations Department of Economic and Social Affairs, 2001). Epidemiological research also uses EHIs to investigate the association between health and the environment (Briggs, 1999; Centers for Disease Control and Prevention, 2006). The above mentioned roles of EHIs will not, however, be fulfilled simply through the existence of EHIs. EHIs must be designed and maintained rigorously as well as interpreted accurately in order to be meaningful (Briggs, 2003; Eyles & Furgal, 2002).

Environmental health indicator development aims to allow for comparisons between jurisdictions as well as to facilitate reporting at aggregate levels (Briggs, 1999, 2003; Ryan-Nicholls & Racher, 2004). EHIs that can be compared across jurisdictions enable

health disparities to be examined (Pitblado et al., 1999). The 1992 Earth Summit spurred the United Nations (UN) Commission on Sustainable Development to approve a Programme of Work on Indicators of Sustainable Development (United Nations Department of Economic and Social Affairs, 2001). The Programme had the goal of developing a core set of national-level sustainability indicators, which would allow for comparisons across nations as well as aggregation to the global level (Hodge & Longo, 2002; United Nations Department of Economic and Social Affairs, 2001). The Environmental Public Health Indicators Project of the American Centers for Disease Control and Prevention has proposed environmental public health indicators with the goal of using them within states as well as on a national scale (D. L. Combs, personal communication, September 2, 2005; Centers for Disease Control and Prevention, 2006). Other summaries of EHIs, as well as EHIs specific to children, have also been created in order to facilitate their uptake by various jurisdictions (Briggs, 1999, 2003; Commission for Environmental Cooperation Steering Group on Children's Health and Environment Indicators & Commission for Environmental Cooperation Secretariat, 2003). The above mentioned indicator projects, as well as the 2002 Health and Environment Ministers of the Americas emphasizing the need for environmental and public health indicator development and implementation, highlight the momentum that EHI development has at the regional, national, and international level (Gray & Schornack, 2002).

1.3. The Need for Rural Environmental Health Indicators in Canada

Rural Canada comprises over ninety percent of the nation's territory and one-third of the Canadian population, yet its sustainability impacts on all Canadians through its role in the economy, culture, and identity of Canada (Lyons & Gardner, 2001; Pitblado et al., 1999). Differences in health status, health behaviour, and heath services utilization are significant between rural and urban Canada (Canadian Institute for Health Information, 2006; Pitblado et al., 1999). A smaller proportion of rural residents rate their health as excellent, compared to urban Canadians (Mitura & Bollman, 2003). Health risk factors of smoking and having a higher body mass index are both more prevalent in rural areas of Canada (Mitura & Bollman, 2003). Generally, rural Canadians also have higher levels of disability, lower life expectancy, as well as higher accident and injury rates (Pong, Pitblado, & Irvine, 2002).

Despite differences in health between rural and urban Canadians, a set of rural health indicators, which "can be used to reflect or describe the health conditions of rural communities or populations" (Pitblado et al., 1999, p. 1-3), is not in common use (Pong et al., 2002). In their report, "Assessing Rural Health: Toward Developing Health Indicators for Rural Canada", Pitblado and colleagues (1999) emphasize that accurate descriptions of the health conditions in rural communities and populations is essential to understanding and improving rural health. A focus on rural heath in Canada is currently vital, as many rural communities are experiencing demographic, ecological, economic, and social challenges unique to the rural setting (Boyens, 2001; Pitblado et al., 1999).

The Manitoba Centre for Health Policy, in conjunction with representatives from the rural and northern health authorities of the Canadian prairie province of Manitoba, have produced a compilation report of indicators entitled "The Manitoba RHA Indicators Atlas: Population-Based Comparisons of Health and Health Care Use" (Martens et al., 2003). Both rural health status indicators and rural health service utilization indicators are included in the report.

Pitblado et al. (1999) believe that in order to have a complete understanding of health, indicators should not be limited to health status indicators but should also include health determinant indicators, as well as health behaviour indicators, health resources indicators, and health service utilization indicators. Health determinant indicators can focus on the state of any determinant of health (Pitblado et al., 1999). Environmental health indicators (EHIs) are health determinant indicators that focus on aspects of the physical environment (e.g. air quality). Upon compiling health indicators commonly used nationally in Canada, Pitblado et al. (1999) found 31% of them to be health determinant indicators, however, none of them were EHIs. Pitblado et al. (1999) emphasize the lack of EHIs in use in Canada and stress that there is "a long way to go…in developing EHIs that are sensitive to rural populations" (p. 2-5).

1.4. Rural Environmental Health Indicators of Agricultural Pesticides

Widely used in Canadian agriculture, pesticides prevent, destroy, repel, or mitigate pests (Costa, 1997). Pests include insects, fungi, unwanted plants, and other organisms that cause damage to crops (United States Environmental Protection Agency, 2006a). Acute adverse effects of pesticides on human health are well characterized due to 100,000 to 25 million occurrences (estimates vary) annually worldwide (Costa, 1997; Fleming & Herzstein, 1997). Death due to pesticide poisoning, however, is found almost exclusively in developing countries where regulations regarding pesticide approval and use are less stringent, and education and labeling are not as extensive (Coggen, 2002; He, 2000; Hurtig et al., 2003; Tinoco-Ojanguren & Halperin, 1998). A recent systematic review of pesticide human health effects produced by The Ontario College of Family Physicians indicated that pesticide exposure was associated with a variety of health risks in the Canadian context (Sanborn et al., 2004).

Due to the health concerns associated with pesticides, many organizations have recommended developing environmental health indicators (EHIs) related to agricultural pesticides. The Commission for Environmental Cooperation Secretariat and Steering Group on Children's Health and Environment Indicators recommended pesticides as one of their twelve priority indicators of children's environmental health (Commission for Environmental Cooperation Steering Group on Children's Health and Environment Indicators & Commission for Environmental Cooperation Secretariat, 2003). The Environmental Public Health Indicators Project in the United States includes in their list of proposed indicators those regarding the hazards, exposures, health effects, and

interventions related to agricultural pesticides (Centers for Disease Control and Prevention, 2006). In 2000, the UN Commission on Sustainable Development Programme of Work on Indicators of Sustainable Development presented a report outlining their core set of sustainability indicators that included "use of agricultural pesticides" (United Nations Department of Economic and Social Affairs, 2001, p. 16). Pesticide use has also been recommended as an EHI relevant to rural communities in agricultural regions of Canada (Pitblado et al., 1999; Pong et al., 2002).

Risk to human health due to agricultural pesticides is a product of both exposure and the hazard (intrinsic toxicity) of the pesticides (Levitan, 2000). If feasible, it is considered ideal to include both of these factors in an EHI that focuses on the risk due to agricultural pesticides. Many recommended EHIs of agricultural pesticides are based, however, only on measures of potential exposure such as the quantity of pesticides used (Centers for Disease Control and Prevention, 2006; Pitblado et al., 1999; Pong et al., 2002; United Nations Department of Economic and Social Affairs, 2001). This is primarily due to limitations in available data upon which the recommended EHIs are based (United Nations Department of Economic and Social Affairs, 2001). In order to include toxicity information in an EHI of agricultural pesticides, knowledge of the specific pesticides applied is essential.

In order for an EHI of agricultural pesticides to be valuable, it must satisfy general EHI criteria. Despite many different sets of EHI criteria, there is a general acceptance that an EHI must have both scientific validity as well as utility (Briggs, 2003; Eyles & Furgal,

2002). Utility criteria include that the EHI is measurable (based on available data), timely, specific, relevant, actionable, cost-effective, as well as understandable by the target audience (Briggs, 2003; Centers for Disease Control and Prevention, 2006; Commission for Environmental Cooperation Steering Group on Children's Health and Environment Indicators & Commission for Environmental Cooperation Secretariat, 2003; Eyles & Furgal, 2002; Pitblado et al., 1999; United Nations Department of Economic and Social Affairs, 2001; von Schirnding, 2002). Utility is meaningless, however, if the EHI is not scientifically sound. First and foremost, the EHI must be credible and thereby indicative of a link between the environment and health (Briggs, 2003; Commission for Environmental Cooperation Steering Group on Children's Health and Environment Indicators & Commission for Environmental Cooperation Secretariat, 2003; Eyles & Furgal, 2002). Knowledge regarding the effects of pesticides on human health give EHIs of agricultural pesticides face validity, yet specific indicators also need empirical validity, which is dependent on the context and measurement of the specific EHI (Centers for Disease Control and Prevention, 2006; Eyles & Furgal, 2002). In addition to being credible, an EHI must be unbiased, consistent, comparable, robust, reliable, and representative in order to be considered scientifically valid (Briggs, 2003; Commission for Environmental Cooperation Steering Group on Children's Health and Environment Indicators & Commission for Environmental Cooperation Secretariat, 2003; Eyles & Furgal, 2002; von Schirnding, 2002). Few indicators can satisfy all of the above mentioned criteria of utility and scientific credibility; the priority of different criteria will vary based on the situation (Briggs, 2003).

1.5. Developing Rural Environmental Health Indicators of Agricultural Pesticide Use and Risk in Manitoba, Canada

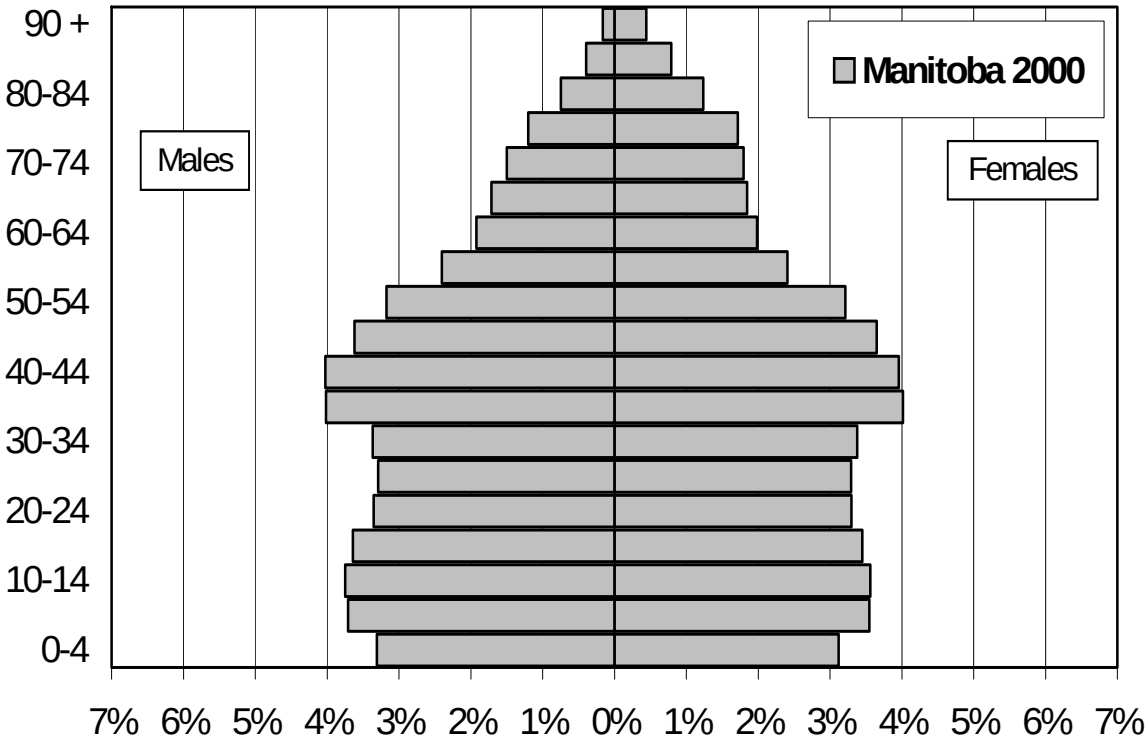
1.5.1. Manitoba Geography and Demography

Manitoba is located in Central Canada and is one of the three prairie provinces. It is bordered by the United States of America (USA) to the south, the province of Saskatchewan to the west, the territory of Nunavut to the north, the province of Ontario to the east, and Hudson Bay to the northeast. The province is 649,950 km^2 in area and spans 1225 kilometers from north to south (Travel Manitoba, n.d.a). Over fifty percent of northern Manitoba is Precambrian Shield with boreal forest, while the northernmost reaches of the province are tundra and permafrost (Travel Manitoba, n.d.a). A triangle of agricultural land borders Saskatchewan and the USA (Travel Manitoba, n.d.a). Just over 15% of Manitoba is covered with fresh water, the majority of it held in Lake Winnipeg and Lake Manitoba (Travel Manitoba, n.d.a).

Manitoba experiences warm summers and cold winters with average temperatures in the southern agricultural regions of 25ºC in July and August and slightly below -20ºC in December through February (Travel Manitoba, n.d.b). Across agricultural Manitoba the climate results in a relatively short growing season with the one-in-four-year risk of last spring frost being in the first week of June and the one-in-four-year risk of first fall frost being between August 28th and September 15th (Manitoba Agriculture Food and Rural Initiatives, 2005a). Slight variations in frost patterns occur due to micro-climates in certain agricultural areas (Manitoba Agriculture Food and Rural Initiatives, 2005a).

The population of Manitoba on July 1, 2005 numbered 1,177,556 (Manitoba Finance, 2005). Depending on the method of classification, between 55 and 72 percent of the province's population lives in an urban environment, with the major centre being the capital city of Winnipeg (Manitoba Agriculture Food and Rural Initiatives, 2003; Pitblado et al., 1999). In 2001, slightly over six percent of Manitobans lived on farms (Manitoba Agriculture Food and Rural Initiatives, 2003). The age and sex distribution of Manitoba's population in 2000 is shown in Figure 1. Each bar represents the percentage of the population within a specific five-year age group, with males on the left and females on the right (Martens et al., 2003). Population pyramids (Figure 1 for Manitoba) vary between regions of the province, with the northern areas exhibiting broader bases with narrower apexes and the southern rural areas resembling the Manitoba overall population demographic (Martens et al., 2003).

Figure 1: Age and Sex Profile of Manitoba, 2000



Note. The population pyramid is based on a population of 1,148,699. From *The Manitoba RHA Indicators Atlas: Population-Based Comparisons of Health and Health Care Use* (p. 33), by P. J. Martens, R. Fransoo, The Need to Know Team (funded through CIHR), E. Burland, L. Jebamani, C. Burchill, et al., 2003, Winnipeg, Manitoba: Manitoba Centre for Health Policy. Copyright 2003 by Manitoba Health. Adapted with permission.

1.5.2. Crop Farming in Manitoba

In 2001, according to the Canadian Census, 36,395,150 hectares of Canada was crop land (Manitoba Agriculture Food and Rural Initiatives, 2003). At that time, thirteen percent of Canada's crop land (4,714,830 hectares) was located in Manitoba and it comprised slightly over sixty percent of the province's total farm land (Manitoba Agriculture Food and Rural Initiatives, 2003). The total value of crop production in Manitoba was $2.3 billion in 2003, constituting approximately 55% of the total value of agricultural

production in the province that year (Manitoba Agriculture Food and Rural Initiatives, 2003). The primary crops harvested were wheat and canola, followed by barley, oats and *all tame hay* (Manitoba Agriculture Food and Rural Initiatives, 2003). Potatoes also contributed substantially to the total value of crop production (Manitoba Agriculture Food and Rural Initiatives, 2003).

The Manitoba Agricultural Services Corporation (MASC) provides insurance for Manitoba crop farmers against "financial losses because of reduced crop quantity and/or quality due to natural perils" (Manitoba Agricultural Services Corporation, 2006c, para. 3). MASC compiles the production and management information, which farmers are required to provide in order to register for crop insurance protection, and presents it at the aggregated CCS[2] level on the Manitoba Management Plus Program (MMPP), a publicly available online resource (available at http://www.mmpp.com/; Manitoba Agricultural Services Corporation, 2006d). The goals of the MMPP are to aid farmers in their decision-making and in turn reduce insurance payouts (Manitoba Agricultural Services Corporation, 2006d). Although registered for on a voluntary basis, approximately 85% of Manitoba crop farmers are included in the MMPP data (G. Martens, personal communication, April 21, 2004). Information on pesticide use and crop yields can be ascertained for Manitoba crop farming CCSs, through query tools on the MMPP website, allowing for the creation of environmental health indicators (EHIs) based on agricultural

[2] CCS = Census Consolidated Subdivision. A CCS is defined as: "A grouping of census subdivisions. Generally the smaller, more urban census subdivisions (towns, villages, etc.) are combined with the surrounding, larger, more rural census subdivision, in order to create a geographic level between the census subdivision and the census division." (Pitblado et al., 1999, p. 2-10)

pesticide use at the level of the CCS. There is also the potential for EHIs of pesticide risk to be formed since the MMPP provides details regarding which specific pesticides were used.

1.5.3. Health and Health Care in Manitoba

In Manitoba, the premature mortality rate[3], a measure of general health status, was 3.32/1000 in 1996 – 2000 (Martens et al., 2003). During this same time period the male life expectancy in the province was 75.9 years and the female life expectancy was 81.3 years (Martens et al., 2003). The Rural South of the province, where the majority of the province's agricultural activity is located, had a premature mortality rate slightly below the Manitoba average, a slightly above average female life expectancy, and a similar male life expectancy (Martens et al., 2003). Circulatory challenges and cancer were the main causes of death in the Rural South (including Brandon) in 1995 – 1999, as in the whole of Manitoba (Martens et al., 2003). Injuries accounted for six percent of deaths in the area with motor and other vehicle accidents, falls, and violence to self being the main causes of injury death (Martens et al., 2003). A recent report focusing on mental illness in Manitoba found that more than 25% of Manitobans had at least one mental illness diagnosis between 1997 and 2002 (Martens et al., 2004).

Manitoba residents are entitled to physician and hospital services as well as home care and personal care home benefits through the provincial health insurance program

[3] Rate of deaths per 1000 aged 0-74. The specified rate is age- & sex-adjusted to the Manitoba population on December 31, 1996 (Martens et al., 2003).

(Manitoba Health, n.d.). The Population Health Research Data Repository (PHRDR), housed at the Manitoba Centre for Health Policy, holds linkable de-identified (anonymous) administrative databases of the health services utilization history of individuals covered by the Manitoba Health Insurance Plan (Manitoba Centre for Health Policy, 2006a). Rates of the treatment prevalence for specific health conditions can be calculated by combining information from the physician claims, hospital files, and pharmaceutical files. Appropriate denominators are available because all Manitobans registered with the Manitoba Health Insurance Plan are included in the Repository, whether they contact the health care system or not. The Repository is able to provide information on the health status of people living in specific CCSs, allowing their health status to be examined in relation to agricultural pesticides.

1.6. Summary

The goals of this thesis are to: (a) create environmental health indicators (EHIs) of 'pesticide use in crop farming' and the 'risk of pesticide use in crop farming'; (b) evaluate empirical validity through conducting an epidemiological study of the association between the EHIs of agricultural pesticides and adverse physical and mental health outcomes, in rural farming areas of Manitoba, Canada. The importance of agriculture in Manitoba and the wealth of available data on both pesticides used in crop farming and health outcomes makes developing and evaluating rural EHIs of agricultural pesticide use and risk both relevant and feasible. The resultant EHIs have the potential to aid in the monitoring and surveillance of environmental risks to the health of rural Canadians.

2. CONCEPTUAL FRAMEWORK

2.1. Population Health Promotion Model

The conceptualization of health has evolved in Canada over the past century. The medical model, where an "absence of disease or disability" (Larson, 1999, p. 124) is indicative of health, was expanded to "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity"[4] in the 1948 Constitution of the World Health Organization. Due to criticisms of generality the World Health Organization revised their definition to reflect health as a resource for daily life (Last, Spasoff, Harris, & Thuriaux (Eds.), 2001, p. 81). Frankish and colleagues in 1996 articulated this concept of health as "the capacity of people to adapt to, respond to, or control life's challenges and changes" (Public Health Agency of Canada, 2002). Health, conceptualized in such a manner, is seen to be affected by various health determinants, including social well-being, rather than be synonymous with it (Public Health Agency of Canada, 2002). By extension, in 1997 the Federal, Provincial, Territorial Advisory Committee on Population Health stated that:

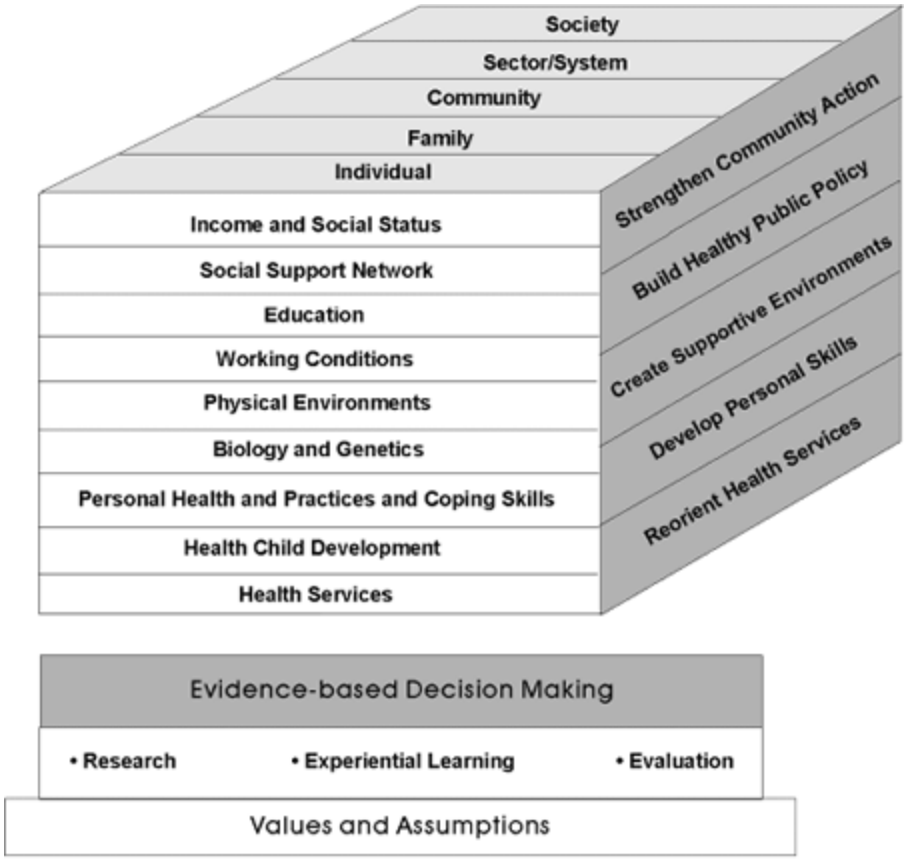
> Population health refers to the health of a population as measured by health status indicators and as influenced by social, economic and physical environments, personal health practices, individual capacity and coping skills, human biology, early childhood development, and health services.

[4] Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948. The Definition has not been amended since 1948.

> As an approach, population health focuses on the interrelated conditions and factors that influence the health of populations over the life course, identifies systematic variations in their patterns of occurrence, and applies the resulting knowledge to develop and implement policies and actions to improve the health and well-being of those populations. (Chomik & Health Canada, 2001)

The population health promotion model (Figure 2) illustrates the association between health promotion and population health, with the comprehensive action strategies of the former being applied to the determinants of health outlined in the latter (Hamilton & Bhatti, 1996). This model also highlights the importance of evidence-based decision-making as the foundation of population health promotion (Hamilton & Bhatti, 1996). Recently, the term evidence-*informed* decision-making has been preferred to evidence-*based* decision-making, recognizing the many stakeholders at the policy nexus and the many aspects beyond just the research evidence (i.e. values, beliefs, politics, economics, etc.) that go into a decision-making process (Clements, 2004). The spirit of health exemplified in this model forms the basis for the conceptualization of health used in this thesis.

Figure 2: Population Health Promotion Model



Source: Population Health Promotion: An Integrated Model of Population Health and Health Promotion prepared by Nancy Hamilton and Tariq Bhatti, Public Health Agency of Canada, February 1996. Reproduced with the permission of the Minister of Public Works and Government Services Canada, 2006.

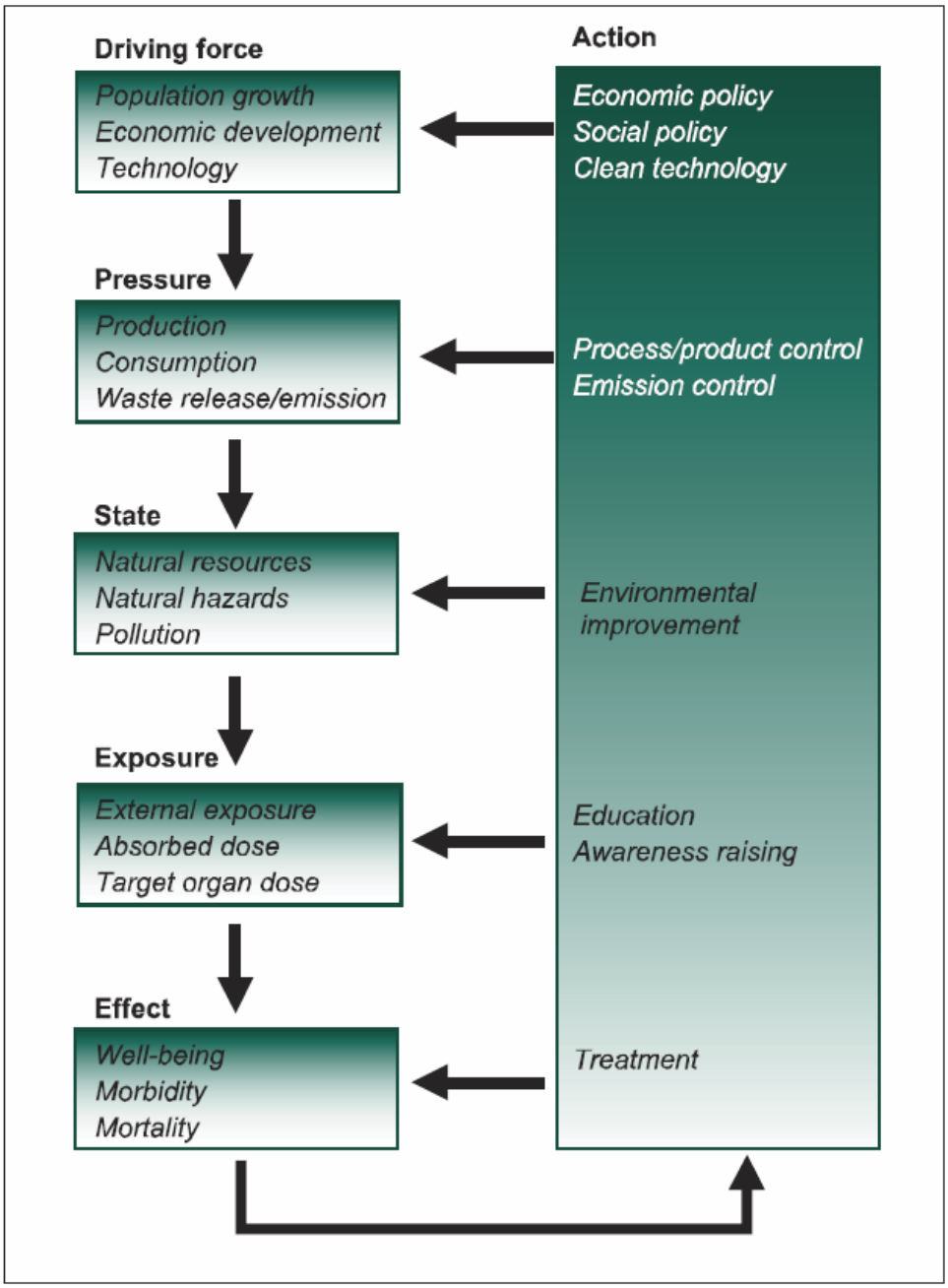
2.2. The DPSEEA Framework

This study expands upon the population health promotion model through focusing on pesticides as an element of the physical environment. Due to the nature of pesticides, like other environmental health concerns, a framework that discusses exposure is most appropriate for conceptualizing their effect on health. The DPSEEA (pronounced 'deep-sea') framework (Figure 3) has been commonly used for environmental health indicator organization and development (Briggs, 1999, 2003; Spiegel & Yassi, 1997; von Schirnding, 2002; Wcislo et al., 2002). The driving forces (D) component represents the root causes of the environmental concerns (Briggs, 2003). The pressures (P) on the environment occur as a result of the driving forces and the state of the environment (S) is in turn affected (Briggs, 2003). Human exposure (E_1) to the changed environmental state is possible and may lead to effects (E_2) on health (Briggs, 2003). The action (A) component of the framework influences all of the other components with the ultimate goal of curbing the adverse health effects (Briggs, 2003).

Although, to its credit, the DPSEEA framework clearly outlines the environment-health chain and illustrates the many different points for action, it also has limitations (Briggs, 2003). The framework is geared towards anthropogenic driving forces and is therefore not as suited to natural environmental hazards (Briggs, 1999, 2003). The linear nature of the framework is also an impediment since, in reality, "individual hazards often lead to a wide range of adverse health effects, while single health outcomes may derive from many different exposures and underlying causes. Ignoring this complexity can be dangerous,

for it may encourage us to seek simple, singular solutions to complex, multifactorial problems" (Briggs, 2003, p. 12).

Figure 3: The DPSEEA Framework

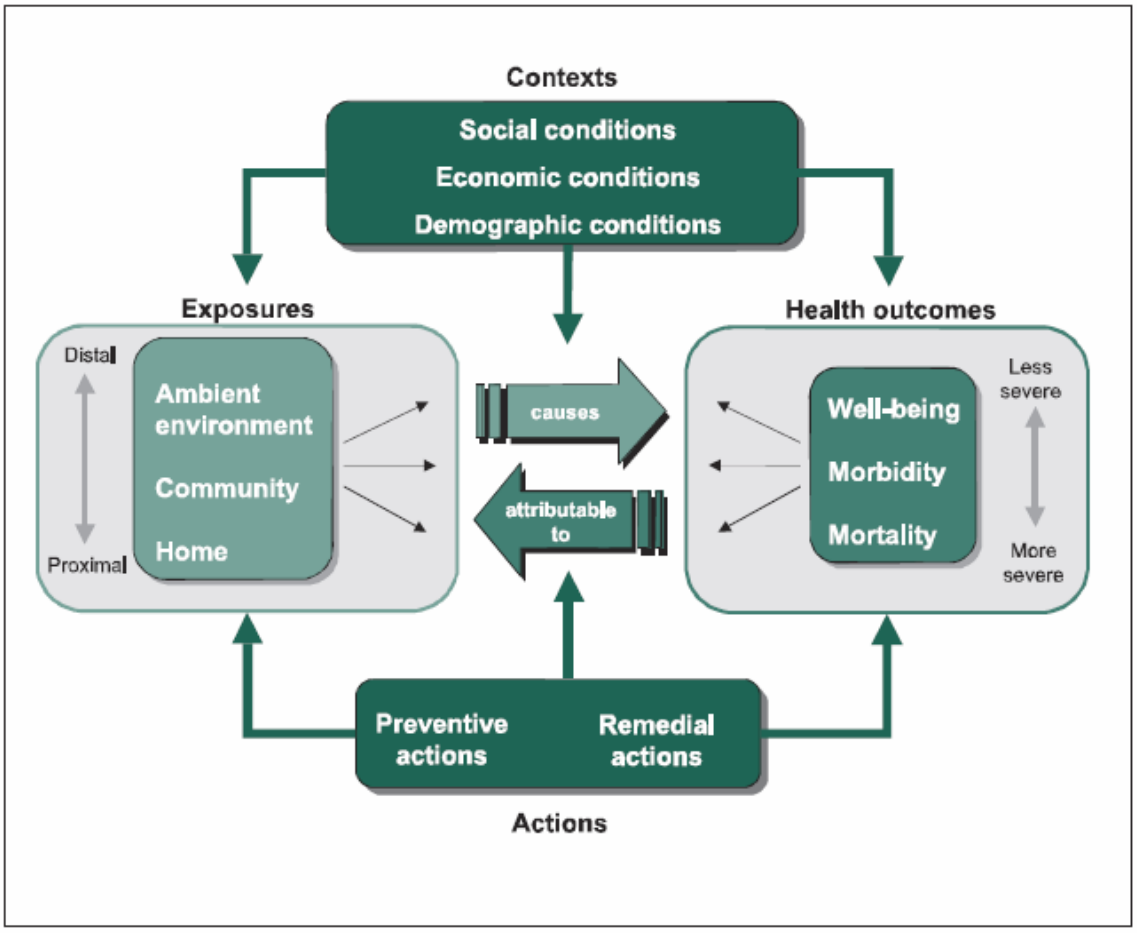


Note. From ***Making a Difference: Indicators to Improve Children's Environmental Health*** (p. 13), by D. Briggs, 2003, Geneva, Switzerland: World Health Organization. Copyright 2003 by World Health Organization. Reprinted with permission. Available at http://www.who.int/phe/children/childrenindicators/en/index.html

2.3. Multiple Exposures – Multiple Effects (MEME) Model

The Multiple Exposures – Multiple Effects (MEME) model (Figure 4) circumvents the linearity challenge of the DPSEEA framework. This model highlights how health outcomes are associated with multiple exposures in various settings, and how individual exposures can be connected to many different health outcomes (Briggs, 2003). The MEME model includes within exposures the DPSEEA framework components of pressure, state of the environment, and exposure; considering pressures and the state of the environment as distal exposures (Briggs, 2003). A positive aspect of the MEME model is that it recognizes the influence of contextual factors on both health outcomes and exposures, as well as the relationship between the them (Figure 4). The contexts outlined in the MEME model are similar to the population health determinants included in the population health promotion model. Like the population health promotion model and the DPSEEA framework, the MEME model also emphasizes the need for both preventive and remedial actions to address the adverse health outcomes (Briggs, 2003; Hamilton & Bhatti, 1996).

Figure 4: Multiple Exposures – Multiple Effects (MEME) Model



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2.4. Study Conceptual Framework

The population health promotion model (Figure 2), the DPSEEA framework (Figure 3), and the MEME model (Figure 4) all provide valuable contributions to the conceptual framework of this thesis. The MEME model provides the main framework through highlighting how multiple exposures lead to multiple health outcomes. Within the MEME model exposures component the DPSEEA framework provides a useful tool for understanding the potential pathways between pressures, the state of the environment, and the potential of proximal human exposure. The population health promotion model and its roots provide the lens through which the MEME model health outcomes component can be viewed. As well, in this study the contexts component of the MEME model will be seen as including the population health determinants included in the population health promotion model. In the conceptual framework chosen for this thesis the key concepts of the DPSEEA framework and the population health promotion model are attached to the structure of the MEME model.

3. LITERATURE REVIEW

3.1. Classification of Pesticides

Pesticides are known by many different types of names. Consumers generally know a pesticide by the product name under which it is sold, also known as its trade name (Manitoba Agriculture Food and Rural Initiatives, 2004). Normally products for sale contain more than one chemical and are more adeptly termed pesticide formulations. These formulations are composed of one or more active ingredients (common name pesticides) as well as other ingredients that have been termed inert ingredients (Rumsey, 2002). The active ingredients prevent, kill, or repel pests, or act as plant regulators, desiccants, defoliants, synergists, or nitrogen stabilizers (National Pesticide Telecommunications Network, 1999). The other (inert) ingredients are added to improve the storage, handling, safety, application, or effectiveness of the pesticide and can be solvents, carriers, adjuvants, or any other compound that is intentionally added to the active ingredients (National Pesticide Telecommunications Network, 1999). Most information regarding the toxicity of a pesticide is found under the common names, Chemical Abstract Services numbers (standard chemical identifier), or chemical names of its components rather than the trade name (Rumsey, 2002). Generally both the formulated pesticides (a.k.a. trade name pesticides) as well as the active ingredients (a.k.a. common name pesticides) are termed pesticides.

Pesticides can be classified based on their target pest, their mode/site of action or their chemical composition/group (Fait et al., 2001; Manitoba Agriculture Food and Rural

Initiatives, 2005b; Pest Management Regulatory Agency, 1999). Of the pesticides classifications based on target pest (Table 1) herbicides, insecticides and fungicides are the most important in Manitoba (Manitoba Agriculture Food and Rural Initiatives, 2005b). Insecticides, herbicides and fungicides are further classified into groups based

Table 1: Classification of Pesticides by Target Pest

Classification	**Target Pest**
Insecticides	Insects
Herbicides	Weeds
Fungicides	Fungi and molds

on their chemical composition and related mode/site of action on the pest (see http://www.pmra-arla.gc.ca/english/pdf/dir/dir9906-e.pdf for full listing; Pest Management Regulatory Agency, 1999). Although pesticides from the same group have the same mode of action, this does not mean that they control the same specific pests or have the same level of safety (Manitoba Agriculture Food and Rural Initiatives, 2005b).

3.2. Biological Plausibility of Pesticides Affecting Human Health

It is biologically plausible, due to the conservation of biochemical processes in many levels of life forms, that compounds designed to harmfully affect insect, fungi, or other pests, could also harm humans (D. L. Combs, personal communication, September 2, 2005; Blundell, 2005). For example, it is plausible that certain herbicide groups that inhibit lipid synthesis or mitosis as well as fungicide groups that affect cell division or the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) could impact upon the health of humans (Pest Management Regulatory Agency, 1999). As well, many insecticides function by influencing chloride, calcium, or sodium channels or by disrupting the function of acetylcholine or octopamine (Bloomquist, 1996; Pest Management Regulatory Agency, 1999). Through these mechanisms the insect nervous system is impaired, however, these chemicals also influence the basis of neurological function in humans.

Commonly used organophosphate and carbamate insecticides, which are responsible for most human pesticide intoxications worldwide, provide a specific example of how the biochemical processes shared by pests and humans can influence the human health effects of certain pesticide groups (Blundell, 2005; Wagner, 1997). The main physiologic effect in both insects and humans of organophosphates, and to a weaker degree carbamates, is the inhibition of acetylcholinesterase (Pest Management Regulatory Agency, 1999; Wagner, 1997). Without acetylcholinesterase, an enzyme that interrupts nerve transmissions, constant stimulation of the nervous system occurs, leading to over activity of the involuntary muscles, voluntary muscles, and exocrine glands (Wagner,

1997). Severe acute intoxication can be fatal (Costa, 1997). Organophosphates and carbamates could plausibly have physiological effects beyond the nervous system as they may also influence the non-neuronal acetylcholinesterase functions of cell differentiation, immune function regulation, and mitosis (Blundell, 2005).

3.3. The Pathway from Agricultural Pesticide Use to Adverse Human Health Effects

When examining the potential for agricultural pesticide use, a *pressure* (P) in the DPSEEA framework, to cause adverse health *effects* (E_2), the factors connecting the stages from *pressure* to *effect* in the framework must be considered (see Chapter 2 for description of DPSEEA framework). The methods and conditions of agricultural pesticide application affect the *state* of the environment (S), which in turn influences the potential for *exposure* (E_1). Characteristics of the exposure in combination with the intrinsic toxicity of the pesticide and the susceptibility of the exposed person influence whether a health effect is experienced and if so at what severity.

Characteristics of the agricultural pesticide application (pressure*)* will influence how the state of the environment is altered. How often an area is sprayed, with what pesticides it is sprayed, and the concentration of the active ingredient in the spray will all influence the amount of pesticide delivered to an area. The amount of pesticide in an area will also be influenced by the persistence of the sprayed pesticides, the length of time they last in the environment, and their bioaccumulative properties, the degree to which they accrue in the tissues of living organisms (Blundell, 2005). The size of area sprayed as well as the extent of pesticide drift influence the scale at which the pressure of agricultural pesticide use influences the state of the environment (Blundell, 2005). Pesticide drift is greatly influenced by the size of the pesticide droplet that is released from the pesticide spraying equipment: larger droplets settle sooner and therefore do not drift over as large an area as smaller droplets (Blundell, 2005). The design of the pesticide spray nozzle is a key

contributor to the size of the pesticide droplets (Blundell, 2005; Manitoba Agriculture Food and Rural Initiatives, 2005b). Other factors that effect the behaviour of spray droplets are "the type of formulation, nature of co-formulants, local topography and meteorological conditions (particularly temperature and wind conditions)" (Blundell, 2005, p. 48) as well as the type of application (aerial versus ground) and speed of application (van der Werf, 1996). The amount of crop foliage on a field also impacts upon the amount of pesticide drift with greater crop cover reducing drift (Blundell, 2005). Pesticide drift can be additionally curbed by field boundaries or buffer zones (Blundell, 2005). The range of land and water in which drifting pesticide droplets are deposited is based on many factors but is one of the ways in which the pressure of agricultural pesticide use influences the state of the environment. Another consideration is that the air surrounding fields upon which agricultural pesticides have been applied may also be altered due to the vaporization of pesticide droplets (van der Werf, 1996). Droplet size, type of formulation and nature of co-formulants, meteorological conditions (including humidity), as well as the ability of vegetative surfaces to collect the vapor influence the range of air that is affected by the agricultural spraying (Blundell, 2005; Dowling & Seiber, 2002). The manner in which agricultural pesticide application influences the state of the environment is complex, yet the type and amount of pesticides in the ground, water, and air, and the size of area affected in turn impacts the potential for exposure.

Exposure is defined as "an event that occurs when there is contact at a boundary between a human and the environment with a contaminant of a specific concentration for an interval of time" (National Academy of Sciences, 1991, p. 19). The presence of

pesticides in the air, water, or soil (state of the environment) provides the potential for human exposure. Exposure can occur through inhalation, ingestion, or dermal absorption and may occur directly through contact with pesticides or indirectly through contact with residues (Blundell, 2005; Briggs, 1999). Individuals who work with pesticides are most often exposed through a direct dermal route, however, highly volatile pesticides many also provide substantial exposure through inhalation (Dowling & Seiber, 2002). Agricultural pesticide residues have been found in the meals of both farm families (Melnyk, Berry, & Sheldon, 1997) and the general public (MacIntosh, Kabiru, & Ryan, 2001), resulting in indirect exposure through ingestion. Bystanders are also indirectly exposed to pesticides through pesticide drift from farmland (Alarcon et al., 2005). The quantity of the pesticide at the interface of a human and the environment is known as the *external exposure* (Briggs, 1999). The *absorbed dose* is the amount of pesticide which is absorbed and it is dependent on the dose of pesticide and the duration of the exposure (Briggs, 1999). Based on duration, exposure can be classified into acute exposure (less than 24 hours), sub-acute exposure (24 hours to 3 months), and chronic exposure (longer than 3 months) (Blundell, 2005). The level of exposure to a specific pesticide is sometimes measured through the use of biomarkers, which are biological or biochemical responses in the human body to the pesticide exposure (Blundell, 2005).

Personal behaviour influences the degree of exposure of individuals to agricultural pesticides that exist in the environment (Alavanja, Hoppin, & Kamel, 2004). Farm families risk exposure though storage of pesticides in their homes, mixing pesticides within close proximity of their houses, and washing clothes used for pesticide work with

other clothes (Gladen et al., 1998). The use of personal protective equipment and the use of tractors with cabs both decrease the risk of exposure for individuals who work with pesticides (Arbuckle, Cole, Ritter, & Ripley, 2005; Cessna & Grover, 2002). Although spills are unintentional, they contribute to lifetime pesticide exposure, even if they do not result in overt poisoning (Alavanja, Hoppin et al., 2004). In one study, over 15% of male farm residents had been accidentally exposed (at least once) through a spill (McDuffie et al., 2002).

Exposure is necessary, but not sufficient, for a health effect to occur (Briggs, 1999). The intrinsic toxicity of the pesticide and the susceptibility of the exposed person also play a key role in addition to the duration, magnitude, timing, and type (route into the body) of the exposure (Blundell, 2005; Myres & Betke, 2002). The intrinsic toxicity of a pesticide is a measure of its capability of causing adverse effects (Blundell, 2005). The most common measure of a pesticide's acute toxicity is the LD_{50} value, which "is a statistical estimate of the number of mg of toxicant per kg of bodyweight required to kill 50% of a large population of test animals" (International Programme on Chemical Safety, 2005, p. 2). The International Programme of Chemical Safety of the World Health Organization (2005) classifies pesticides according to the oral and dermal LD_{50} of their solid and liquid states into the categories of extremely hazardous, highly hazardous, moderately hazardous, slightly hazardous, and "unlikely to present acute hazard in normal use" (p. 5). A pesticide's polarity and reactivity also influence its potential for causing adverse health effects (Dowling & Seiber, 2002). In addition to the toxicity of the pesticide(s) that an individual is exposed to, their susceptibility influences whether a health effect will

occur. Certain persons may be more susceptible to pesticides because of their age, gender, health status, or pregnancy (Blundell, 2005; Fleming & Herzstein, 1997).

3.4. Epidemiological Studies of the Adverse Effects on Human Health of Agricultural Pesticides

3.4.1. Need for Epidemiological Studies

Epidemiological studies contribute to examining the adverse effects of pesticides on human health through their ability to study humans in their lived environments. Analytic epidemiology is able to examine associations between putative risk factors and human health effects without experimentation, which would be unethical in many pesticide health studies (Last et al. (Eds.), 2001). Epidemiological studies of the effects of pesticides on humans are especially important because risk assessments for the approval of new pesticides are only able to consider human studies when a pesticide has been previously used in another country, which is rare (C. Norman, personal communication, June 28, 2004). The Pest Management Regulatory Agency (PMRA) of Canada routinely approves pesticides based on standardized animal toxicity testing in combination with exposure assessment data, which is elucidated through human volunteer experiments or estimated based on pesticides with similar formulation types (Pest Management Regulatory Agency, 2000, 2005). Toxicity results that outline the effects of large regular doses of a single pesticide on an animal are used to estimate the effects of low, possibly intermittent, doses on humans through the addition of margins of error (Blundell, 2005; Pest Management Regulatory Agency, 2000). Decisions based on these estimates may not be sufficient to protect human health (Alavanja, Hoppin et al., 2004; Burns, 2005). Without epidemiological studies, the potential of pesticides to cause low-grade or chronic health effects, even if applied at levels and with methods approved by the PMRA, cannot

be eliminated due to the above mentioned limitations of the PMRA pesticide approval process (Alavanja, Hoppin et al., 2004).

An additional benefit of epidemiological studies is that they are able to examine the effects of concurrent exposure to multiple pesticide formulations. Also, through epidemiologically examining the health effects of exposure to various pesticide formulations the potential adverse effects of inert ingredients in the formulations, such as solvents, can be considered (Dich, Zahm, Hanberg, & Adami, 1997; Petrelli, Siepi, Miligi, & Vineis, 1993). Although studies of mixed pesticide exposure are unable to highlight the effect of specific active or inert ingredients, they provide important information for hypothesis generation and for use of the precautionary principle[5].

3.4.2. Focus of Epidemiological Literature Review

The literature regarding pesticides and health is broad. Only analytical epidemiological studies that examine the association between agricultural pesticides and human health effects are included in this review. Toxicological studies, laboratory studies, case studies, scientific news articles, and methodology papers are not reviewed. Both original articles and reviews are examined.

[5] Regarding the precautionary principle, the Wingspread Statement states that "when an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically" (Wingspread Conference Participants, 1998).

Only studies with exposures that can be attributed directly or by proxy to agricultural pesticides are included. Studies regarding home and garden pesticide use, vector control pesticides, structural fumigation, and pesticide manufacturing or formulation are not included. Research regarding pesticides in drinking water, food, and breast milk are not examined as such studies often do not focus on the entire pathway between agricultural pesticide use and health effects. Research studying the effect of occupational pesticide exposure is only included if it is specific to farmers, farm workers, or agricultural pesticide applicators.

The review of the epidemiological literature in this thesis focuses on studies where the potential of occupational or non-occupational exposure (with exposure broadly defined as in the MEME model described in Section 2.3.) due to agricultural pesticide use is similar to that presented by Manitoba crop farming. Mechanized crop farming that covers a broad acreage is comparable to practices on the majority of Manitoba's crop farms. Studies examining farming of predominantly fruits, vegetables, and vineyards are accordingly not included as these types of farming are more likely to involve non-mechanized work and smaller farms, both factors that increase the risk of pesticide exposure to people working on and/or living near the farms beyond levels generally seen in Manitoba. Research regarding the farming of predominantly cotton and tobacco is also excluded as these crops are not grown in Manitoba (Manitoba Agriculture Food and Rural Initiatives, 2003).

The literature review is limited to studies of Canadian and American crop farming as different regulatory environments in other regions alter the potential for exposure. Although based in the United States, studies of migrant farm workers and predominantly Hispanic Californian farm workers are excluded due to divergent risk factors. Research regarding organochlorine insecticides (e.g. DDT) is also excluded as they are not commonly used anymore in Manitoba.

Through varied research methods epidemiological studies examine a breadth of health outcomes. Only health outcomes measurable using the administrative data are included in this review. Genotoxic and biochemical endpoints are accordingly not considered. Studies focusing on neurobehavioural outcomes and general symptoms are also excluded. Fertility and fecundity research as well as research into sex ratios and timing of menopause are not included. The literature on acute poisonings and its sequelae is also not reviewed as severe intoxications are rare in Manitoba. Poisoning with agricultural pesticides is much more common in developing countries where application methods and rates of use of personal protective equipment differ from the Manitoba context. The combination of the extant literature with the limitations of this review result in some health outcomes (e.g. dermatologic outcomes) not being reviewed due to a lack of relevant studies.

3.4.3. Methodology of Epidemiological Literature Review

Initially the following databases were separately queried for relevant articles: Biological Abstracts, CAB Abstracts, CINAHL, EMBASE Cardiology, EMBASE Immunology,

EMBASE Neurosciences, EMBASE Pediatrics, General Science Full Text, Health Reference Center, PubMed/MEDLINE, PsycINFO, and Web of Science. The queries included four main concepts joined by AND terms. Within each concept, terms were joined by OR operators. The first concept represented pesticides and included the following terms in various databases: pesticide, insecticide, fungicide, herbicide, pesticide-adverse effects, pesticide-toxicity, and pesticide-analysis. The second concept represented the agricultural nature of the exposure and included some of the following terms depending on the database: farm, agriculture, environmental exposure, rural environment, occupational exposure, environmental effects, and disorders of environmental origin. The third concept represented health effects and in most databases included a selection of: human medicine, occupational health, public health, epidemiology, health, and disease(s). In the case of PubMed/MEDLINE multiple searches were conducted with each of the MeSH disease categories being employed separately as the third concept. The fourth concept was the term human and it was only included when the database had a broader focus. The queries were restricted to English language publications.

The results of the database queries were compiled and titles were reviewed. Duplicates and articles that were not relevant were discarded. The abstracts of the remaining articles were then examined in order to determine if they conformed to the focus of the review. Although the original database queries were performed for a 1992-2006 time span, upon reading the abstracts it was decided that the 2001-2006 literature would generally be sufficient. Select articles from before 2001 were included if they were deemed important

to the review. Hard copies of the selected articles and the articles lacking an abstract were sought. Full articles were examined and excluded if they did not fulfill the requirements for inclusion in the review.

Review articles were surveyed and used to expand the list of relevant references. Articles referenced in the included original work were also considered for the literature review. Original articles were reviewed in tabular format and grouped by health outcome. Articles that discuss multiple health outcomes were generally listed under each separate health outcome. The tables, in which the literature is reviewed, document whether a statistically significant adverse effect was found in the study. Only exposures relevant to crop farming were discussed (e.g. if livestock exposure was studied as well it was not reported). The measurement of the relevant exposures was described in the tables, however, the specific values of the measures of association were not reported. It is recognized that statistical significance is not equivalent to clinical significance and may be due to chance alone (Last et al. (Eds.), 2001). For this reason, studies that performed many comparisons and had very few significant results were not considered to have a significant effect but instead this association was reported in the notes section.

3.4.4. Review of Epidemiological Literature on the Adverse Effects of Agricultural Pesticides on Human Health

Farmers have often been the focus of studies into the adverse effects of agricultural pesticides, although they are not the only group affected. Farmers have tended to be in better health overall than the general population, particularly with respect to

cardiovascular diseases and diseases associated with tobacco use (Blair, Sandler, Tarone et al., 2005; Blair, Sandler, Thomas et al., 2005; Blair & Zahm, 1995; Fleming, Gomez-Marin, Zheng, Ma, & Lee, 2003; Gomez-Marin et al., 2004). Certain diseases, however, are more common in farmers, such as infectious diseases, non-malignant respiratory diseases, and certain cancers (Blair, Sandler, Tarone et al., 2005; Blair, Sandler, Thomas et al., 2005; Fleming et al., 2003). Many lifestyle factors and exposures influence the health of farmers. The adverse effects of agricultural pesticides, specifically, include a broad range of acute symptoms as well as a range of chronically developed ailments. Many studies of acute symptoms are not analytical but descriptive. Acute symptoms include skin and eye irritation, flu-like symptoms, headaches and dizziness, chest discomfort, and fatigue (Calvert et al., 2004; Frank, McKnight, Kirkhorn, & Gunderson, 2004; Martin et al., 2002). This review, which discusses analytical epidemiological studies of the adverse effects of agricultural pesticides on farmers and rural residents, is organized by health outcome.

Research where the exposure to agricultural pesticides is reasonably similar to that due to crop farming in Manitoba is included in this review. Many included articles are a product of the Agricultural Health Study (AHS), a prospective cohort study of 52,395 private licensed pesticide applicators, 4916 commercial applicators, and 32,347 spouses of farmer applicators from Iowa and North Carolina (Alavanja et al., 2005). The number of individuals in each article, however, varies depending on missing data considerations. The applicators in the AHS cohort are primarily white males and the spouses are predominantly white females (Alavanja et al., 1996; Blair, Sandler, Thomas et al., 2005).

AHS studies have reported both standardized incidence ratios for the cohort as well as the effects of exposure to specific pesticides. Exposure to the specific pesticides is commonly determined by the sophisticated measures of lifetime exposure-days and intensity-weighted exposure-days (Lee, Blair et al., 2004). Another benefit of AHS research is that it is able to adjust for the use of other pesticides whose use is highly correlated with the pesticide of interest (Rusiecki et al., 2006). The AHS provides a source of extensive high-quality research. A deficiency of the literature is that for many health outcomes AHS research is the only source of information, not allowing for corroboration from other study populations.

3.4.4.1. Mortality

Table 2 describes the three included studies that examined mortality. A study comparing farmers and pesticide workers to other occupations found an increased risk for a number of mortality causes (Fleming et al., 2003), whereas a cohort study of pesticide applicators did not find an increased, but rather a decreased, standardized mortality ratio for many causes (Blair, Sandler, Tarone et al., 2005). An ecologic study found an association between wheat acreage, a surrogate for chlorophenoxy herbicide use, and mortality from diabetes mellitus and mortality from ischemic heart disease (Schreinemachers, 2006).

Table 2: Studies Regarding Mortality

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
Fleming et al. 2003	Yes for mortality due to all causes, heart disease, overall cancer, nervous system cancer, lymphatic/hemato-poietic cancer, and motor vehicle and other accidents	Age-adjusted risk ratio comparing farmers/pesticide applicators to all other occupations	Survey linked to mortality data	American workers in the National Health Interview Survey cohort, a probability sample of US population; farmers/pesticide applicators (N=9,471) compared to all other employed persons (N=433,228)	
Blair, Sandler, Tarone et al., 2005	No	SMR based on being part of cohort	Prospective cohort (AHS)	Licensed pesticide applicators (N=52,393) and spouses of farmers (N=32,345) in Iowa and North Carolina	Mortality due to all causes, all cancers, buccal cavity and pharynx, digestive system, esophagus, pancreas, lung, prostate, bladder, diabetes, cardiovascular disease, COPD, nephritis, and suicide significantly lower than unity.
Schreinemachers 2006	Yes for mortality due to diabetes mellitus and mortality from ischemic heart	Average percentage of county's land area in wheat as surrogate measure of exposure to	Ecologic	White residents of rural agricultural counties of Minnesota, Montana, North Dakota, and South Dakota	ORs for mortality from ischemic heart disease and the subcategory of acute myocardial infarction were significantly increased, but

	disease	chlorophenoxy herbicides		aggregated by county (N=152)	mortality from the subcategory of coronary atherosclerosis was decreased.

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

3.4.4.2. Cancer

Despite the challenges of determining the etiology of a multifactorial disease such as cancer, pesticide exposure has been implicated as a risk factor for some cancers (Jaga & Dharmani, 2005). Many epidemiological reviews of cancer and pesticide exposure have a broader focus than this review, including studies from countries other than the USA and Canada, articles based on pesticide use in venues other than crop farming, as well as research regarding manufacturing workers (Alavanja, Hoppin et al., 2004; Jaga & Dharmani, 2005; Sanborn et al., 2004). Generally studies have not found an adverse pesticide effect on all cancers combined but have found an effect on specific cancers; concurrent with the differing etiologies of various cancers (Dich et al., 1997). Examining the literature with a more inclusive lens, Alavanja, Hoppin, and Kamel (2004) concluded that there is a general association between pesticides and the following cancers: non-Hodgkin's lymphoma, leukemia, multiple myeloma, soft-tissue sarcoma, prostate, pancreatic, lung, and ovarian. A systematic review from the Ontario College of Family Physicians found a strong association between pesticides and the following cancers: brain, kidney, pancreatic, prostate, non-Hodgkin's lymphoma, and leukemia (Sanborn et al., 2004).

As shown in Table 3, the reviewed literature generally did not show an adverse effect of agricultural pesticide exposure on all cancers combined (Alavanja et al., 2005; Beane Freeman et al., 2005; Bonner et al., 2005; De Roos et al., 2005; Lee, Hoppin et al., 2004; Rusiecki et al., 2006; Rusiecki et al., 2004; Wang, Lewis-Michl, Hwang, Fitzgerald, & Stark, 2002). Table 4 illustrates how there was also no significant adverse effect of

agricultural pesticides on the digestive system cancers of the colon (Alavanja et al., 2005; Bonner et al., 2005; De Roos et al., 2005; Lee, Hoppin et al., 2004; Rusiecki et al., 2006; Rusiecki et al., 2004), colorectal region (Beane Freeman et al., 2005; Wang et al., 2002), esophagus (Lee, Blair et al., 2004; Lee, Lijinsky et al., 2004; Rusiecki et al., 2004), gallbladder (Alavanja et al., 2005), liver (Alavanja et al., 2005; Wang et al., 2002), pancreas (Alavanja et al., 2005; De Roos et al., 2005; Rusiecki et al., 2004; Wang et al., 2002), and stomach (Lee, Hoppin et al., 2004; Lee, Lijinsky et al., 2004; Wang et al., 2002). Cancers of the rectum (Table 4), however, were significantly increased with exposure to the insecticide chlorpyrifos (Lee, Blair et al., 2004) and the herbicide metolachlor (Rusiecki et al., 2006), but not with exposure to any of the herbicides alachlor (Lee, Hoppin et al., 2004), atrazine (Rusiecki et al., 2004), or glyphosate (De Roos et al., 2005).

The limited number of studies focusing on cancers of the female genital system (Alavanja et al., 2005), cervical cancer (Wang et al., 2002), and uterine cancer (Wang et al., 2002) did not show significant adverse effects but were only based on standardized incidence ratios (Table 5). One study of ovarian cancer found that licensed restricted-use pesticide applicators had a higher standardized incidence ratio (Alavanja et al., 2005) but all other reviewed studies found no significant adverse effect (Alavanja et al., 2005; Hopenhayn-Rich, Stump, & Browning, 2002; Wang et al., 2002; Young, Mills, Riordan, & Cress, 2005). Cancer of the male genital system (Table 5), including of the prostate and testis, was significantly affected by agricultural pesticides in some studies (Alavanja et al., 2003; Alavanja et al., 2005; Morrison et al., 1993) but no specific pesticides were

implicated (Beane Freeman et al., 2005; Bonner et al., 2005; De Roos et al., 2005; Rusiecki et al., 2006; Rusiecki et al., 2004). Cancers of the urinary system in general, (Alavanja et al., 2005), the bladder (De Roos et al., 2005; Rusiecki et al., 2004; Wang et al., 2002), and the kidney (De Roos et al., 2005; Lee, Blair et al., 2004; Rusiecki et al., 2004; Wang et al., 2002) also did not in general appear to be affected significantly by agricultural pesticides (Tables 5), although alachlor exposure did significantly increase the risk of bladder cancer (Lee, Hoppin et al., 2004).

Cancers of the lymphatic and hematopoietic tissue show a more mixed picture with the effect of agricultural pesticides varying by the pesticide examined. Overall lymphohematopoetic cancers (Table 6) have been associated with the insecticide chlorpyrifos (Lee, Blair et al., 2004), the herbicide alachlor (Lee, Hoppin et al., 2004), and the insecticide diazinon (Beane Freeman et al., 2005) but not with the insecticide carbofuran (Bonner et al., 2005), the herbicide glyphosate (De Roos et al., 2005), or the herbicide metolachlor (Rusiecki et al., 2006). None of the reviewed studies (Alavanja et al., 2005; Pahwa et al., 2003; Pahwa et al., 2006) showed an association between agricultural pesticides and Hodgkin's disease. Leukemia risk was significantly affected by exposure to the insecticides diazinon (Beane Freeman et al., 2005) and chlorpyrifos (Lee, Blair et al., 2004) but not by the other pesticides and measures of exposure examined (Alavanja et al., 2005; Beane Freeman et al., 2005; De Roos et al., 2005; Lee, Hoppin et al., 2004; Rusiecki et al., 2004; Wang et al., 2002). Glyphosate, a herbicide, was the only pesticide that had a significant adverse effect (De Roos et al., 2005) on multiple myeloma (Alavanja et al., 2005; Lee, Blair et al., 2004; Lee, Hoppin et al., 2004;

Pahwa et al., 2003; Pahwa et al., 2006; Rusiecki et al., 2004; Wang et al., 2002). High levels of exposure to agricultural chemicals, in general, has been associated with mylodysplastic syndromes, formerly known as preleukemia (Strom, Gu, Gruschkus, Pierce, & Estey, 2005). Of the many studies on non-Hodgkin's lymphoma, six of the reviewed studies found a significant adverse effect (Chiu et al., 2004; De Roos et al., 2003; Kato et al., 2004; Lee, Cantor, Berzofsky, Zahm, & Blair, 2004; Waddell et al., 2001; Zheng et al., 2001), however, many of these were based on a similar study population. Agricultural Health Study research, on the other hand, has been unable to find a statistically significant association between agricultural pesticides and overall NHL (Alavanja et al., 2005; Beane Freeman et al., 2005; Bonner et al., 2005; De Roos et al., 2005; Lee, Blair et al., 2004; Lee, Hoppin et al., 2004; Rusiecki et al., 2006; Rusiecki et al., 2004). Other groups have also been unable to find this association (McDuffie et al., 2002; McDuffie et al., 2005; Wang et al., 2002). Two studies that have delineated non-Hodgkin's lymphomas based on t(14;18)-subtypes have found significant associations with t(14;18)-positive NHL but not t(14;18)-negative NHL (Chiu et al., 2006; Schroeder et al., 2001).

No reviewed studies of cancer in the orolaryngeal region found a significant effect of pesticides, although most were only based on standardized incidence ratios. Table 7 displays details of the studies examining cancer of the buccal cavity (Alavanja et al., 2005), larynx (Wang et al., 2002), lip (Alavanja et al., 2005), and oral cavity (De Roos et al., 2005; Rusiecki et al., 2006; Rusiecki et al., 2004; Wang et al., 2002).

Studies examining respiratory system cancers and lung cancer (Table 8) using standardized incidence ratios have not found increased risks for populations exposed to agricultural pesticides (Alavanja et al., 2005; Wang et al., 2002). Agricultural Health Study (AHS) research, however, has found a significant adverse effect on lung cancer risk of the herbicides metolachlor (Alavanja, Dosemeci et al., 2004; Rusiecki et al., 2006) and pendimethalin (Alavanja, Dosemeci et al., 2004) as well as the insecticides carbofuran (Bonner et al., 2005), chlorpyrifos (Alavanja, Dosemeci et al., 2004; Lee, Blair et al., 2004), and diazinon (Alavanja, Dosemeci et al., 2004; Beane Freeman et al., 2005). The herbicides atrazine (Rusiecki et al., 2004) and glyphosate (De Roos et al., 2005) have not been found to have a significant effect on lung cancer in other AHS work. An advantage of AHS research on lung cancer is that it adjusts for smoking history.

Reviewed studies provided mixed results regarding brain cancer and its most common form, gliomas (Table 9). Standardized incidence ratios for brain cancer were not significantly increased (Alavanja et al., 2005; Wang et al., 2002) but the insecticide chlorpyrifos significantly increased the risk (Lee, Blair et al., 2004). Risk of gliomas was not significantly increased in women exposed to agricultural pesticides (Carreon et al., 2005; Lee et al., 2005), but results were mixed for men (Lee et al., 2005; Ruder et al., 2004).

Although many of the reviewed studies of breast cancer (Table 10) did not find a significant adverse effect of agricultural pesticides (Alavanja et al., 2005; Hopenhayn-Rich et al., 2002; Reynolds, Hurley et al., 2005; Reynolds et al., 2004; Wang et al.,

2002), those that took into account menopausal status (through an age limitation or through actual status) did find significant results (Brophy et al., 2002; Engel et al., 2005). The reviewed studies described in Tables 11 to 14 did not find a significant adverse effect of agricultural pesticides on melanoma (Alavanja et al., 2005; Beane Freeman et al., 2005; De Roos et al., 2005; Rusiecki et al., 2004; Wang et al., 2002), mesothelioma (Alavanja et al., 2005), soft-tissue tumors (Alavanja et al., 2005; Pahwa et al., 2003; Pahwa et al., 2006), or thyroid cancer (Alavanja et al., 2005; Lee, Hoppin et al., 2004; Wang et al., 2002).

Pesticide exposure tends to have a greater impact on childhood cancers (Table 15) than on cancers in adulthood (Baldwin & Preston, 2004). Adverse impacts of residential pesticide use have been found for childhood cancers (Baldwin & Preston, 2004). Studies measuring agricultural pesticide exposure according to an ecological measure of pesticide use density have not found an association with childhood cancers (Reynolds, Von Behren, Gunier, Goldberg, Harnly et al., 2005; Reynolds, Von Behren, Gunier, Goldberg, & Hertz, 2005; Reynolds et al., 2002). Alternatively, a cohort of children of pesticide applicators were at a greater risk for certain types of cancer (Flower et al., 2004). The association between childhood cancer and parental occupation has been examined but studies do not have enough of a farming focus to be relevant to this review (Chen et al., 2005; Moore et al., 2005; van Wijngaarden, Stewart, Olshan, Savitz, & Bunin, 2003).

Table 3: Studies Regarding All Cancers Combined

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	Significantly lower than expected for those over 50 yrs of age
*Lee, Hoppin, et al. 2004	No	Alachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,980)	Significantly increased risk with medium exposure but trend not significant.
*Rusiecki et al. 2004	No	Atrazine (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=53,943)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	Significantly lower than expected
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	Significantly lower than expected
*Beane Freeman et al. 2005	Yes	Diazinon (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=23,106)	Dependent on referent group used

*Bonner et al. 2005	No	Carbofuran (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,877)	
*De Roos et al. 2005	No	Glyphosate (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,315)	
*Rusiecki et al. 2006	No	Metolachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=50,193)	

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

Table 4: Studies Regarding Digestive System Cancers

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
All digestive system cancers combined					
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	Significantly lower than expected
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	Significantly lower than expected
Adenocarcinomas of stomach and esophagus					
Lee, Lijinsky, et al. 2004	No	Ever living or working on a farm, duration of farming, size of farm; ever use of insecticides or herbicides; use of individual pesticides, including nitrosatable pesticides	Population-based case-control	White men and women (age ≥ 21 yrs) from eastern Nebraska Cases: dx with adenocarinoma of stomach (N=170) or oesophagus (N=137) Controls: matched by sex, age, and vital status (N=498)	Significant inverse association between stomach cancer and benzoic acid herbicide.
Esophageal cancer					
*Lee, Blair, et al. 2004	No	Chlorpyrifos (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,383)	

*Rusiecki et al. 2004	No	Atrazine (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=53,943)	
Stomach cancer					
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	
*Lee, Hoppin, et al. 2004	No	Alachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,980)	
Colorectal cancer					
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	Significantly lower than expected for those between ages 50 and 69 yrs
*Beane Freeman et al. 2005	No	Diazinon (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=23,106)	
Colon cancer					
*Lee, Hoppin, et al. 2004	No	Alachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,980)	

*Rusiecki et al. 2004	No	Atrazine (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=53,943)	
*Bonner et al. 2005	No	Carbofuran (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,877)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	
*De Roos et al. 2005	No	Glyphosate (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,315)	
*Rusiecki et al. 2006	No	Metolachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=50,193)	
Rectal cancer					
*Lee, Blair, et al. 2004	Yes	Chlorpyrifos (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,383)	
*Lee, Hoppin, et al. 2004	No	Alachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,980)	

*Rusiecki et al. 2004	No	Atrazine (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=53,943)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	Significantly lower than expected
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	Significantly lower than expected
*De Roos et al. 2005	No	Glyphosate (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,315)	
*Rusiecki et al. 2006	Yes	Metolachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=50,193)	Based on small numbers.
Gallbladder cancer					
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	

Liver cancer					
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	
Pancreatic cancer					
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	
*Rusiecki et al. 2004	No	Atrazine (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=53,943)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North	Significantly lower than expected

				Carolina (N=52,395)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	
*De Roos et al. 2005	No	Glyphosate (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,315)	

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

Table 5: Studies Regarding Cancers of the Genitourinary Organs

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
Female genital system cancers					
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Female licensed private pesticide applicators in Iowa and North Carolina (N=1,359)	Except for ovarian cancer that was significantly higher than expected
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Female spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,128)	Significantly lower than expected
Cervical cancer					
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	
Ovarian cancer					
*Hopenhayn-Rich et al. 2002	No	Atrazine (*herbicide*) in water, atrazine sales, acres of corn	Ecological	Population of State of Kentucky, USA (N=3.7 million) aggregated by county (N=120) and Area Development Districts (N=15)	All of the exposure variables had a significant inverse effect.

*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	
*Alavanja et al. 2005	Yes	SIR based on being part of cohort	Prospective cohort (AHS)	Female licensed private pesticide applicators in Iowa and North Carolina (N=1,359)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Female spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,128)	Significantly lower than expected
Young et al. 2005	No	Triazine herbicides (including atrazine, simazine, cyanazine)	Population-based case-control	Women (age ≥ 18 yrs) from Central California Cases: dx with epithelial ovarian cancer (N=256) Controls: Frequency matched by age and ethnicity (N=1,122)	
Uterine cancer					
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	

Male genital system cancers					
*Alavanja et al. 2005	Yes	SIR based on being part of cohort	Prospective cohort (AHS)	Male licensed private pesticide applicators in Iowa and North Carolina (N=51,036)	Except for testicular cancer
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Male spouses of licensed private pesticide applicators in Iowa and North Carolina (N=219)	
Prostate cancer					
Morrison et al. 1993	Yes	Acres sprayed with herbicides	Retrospective cohort	Male farmers (age ≥ 45 yrs) from Manitoba, Saskatchewan, and Alberta (Canada) identified in 1971 Canadian Censuses of population and agriculture.	Effect of herbicides stronger for farmers with no employees and/or those who reported no expenses for paid assistance.
Alavanja et al. 2003	Yes	SIR based on being part of cohort; *Fumigant* methyl bromide; *Insecticides:* aldrin, carbofuran, DDT, heptachlor	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=55,332)	If have family history *herbicide* butylate, and *insecticides* coumaphos, fonofos, phorate also significant adverse effect
*Rusiecki et al. 2004	No	Atrazine (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=53,943)	

*Alavanja et al. 2005	Yes	SIR based on being part of cohort	Prospective cohort (AHS)	Male licensed private pesticide applicators in Iowa and North Carolina (N=51,036)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Male spouses of licensed private pesticide applicators in Iowa and North Carolina (N=219)	
*Beane Freeman et al. 2005	No	Diazinon (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=23,106)	
*Bonner et al. 2005	No	Carbofuran (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,877)	
*De Roos et al. 2005	No	Glyphosate (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,315)	
*Rusiecki et al. 2006	No	Metolachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=50,193)	Significant decreased risk with higher exposure categories but trend not significant.
Testicular cancer					
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Male licensed private pesticide applicators in Iowa and North Carolina	

				(N=51,036)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Male spouses of licensed private pesticide applicators in Iowa and North Carolina (N=219)	
Urinary system cancers					
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	Significantly lower than expected
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	
Bladder cancer					
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	
*Lee, Hoppin, et al. 2004	Yes	Alachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,980)	
*Rusiecki et al. 2004	No	Atrazine (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=53,943)	

*De Roos et al. 2005	No	Glyphosate (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,315)	
Kidney cancer					
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	
*Lee, Blair, et al. 2004	No	Chlorpyrifos (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,383)	
*Rusiecki et al. 2004	No	Atrazine (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=53,943)	
*De Roos et al. 2005	No	Glyphosate (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,315)	

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

Table 6: Studies Regarding Lymphohematopoetic System Cancers

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
Lymphohematopoetic system cancers					
*Lee, Blair, et al. 2004	Yes	Chlorpyrifos (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,383)	Significantly increased risk with higher exposure but trend not significant.
*Lee, Hoppin, et al. 2004	Yes	Alachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,980)	
*Beane Freeman et al. 2005	Yes	Diazinon (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=23,106)	Depends on exposure measure and referent group used
*Bonner et al. 2005	No	Carbofuran (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,877)	
*De Roos et al. 2005	No	Glyphosate (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,315)	
*Rusiecki et al. 2006	No	Metolachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=50,193)	

Hodgkin's lymphoma					
*Pahwa et al. 2003	No	Pesticides or agricultural chemicals ≥ 10 h/yr, herbicides, insecticides, fungicides, fumigants, potato seed dust	Population-based case-control	Men from six Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec) who ever lived or worked on a farm Cases: dx with Hodgkin's disease (N=119) Controls: matched by age and province (N=673)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	
Pahwa et al. 2006	No	*Herbicides*: "any phenoxyherbicide", 2,4-D, mecoprop, MCPA, "any dicamba-containing herbicide"	Population-based case-control	Men from six Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec) who ever lived or worked on a farm Cases: dx with Hodgkin's lymphoma (N=117) Controls: matched by age and province (N=673)	Larger group including non-farm subjects also examined but not reported on here.

Leukemia					
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	
*Lee, Blair, et al. 2004	Yes	Chlorpyrifos (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,383)	Significantly increased risk with higher exposure but trend not significant.
*Lee, Hoppin, et al. 2004	No	Alachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,980)	
*Rusiecki et al. 2004	No	Atrazine (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=53,943)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	
*Beane Freeman et al. 2005	Yes	Diazinon (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=23,106)	Depends on exposure measure and referent group used

*De Roos et al. 2005	No	Glyphosate (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,315)	
Multiple myeloma					
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	
*Pahwa et al. 2003	No	Pesticides or agricultural chemicals ≥ 10 h/yr, herbicides, insecticides, fungicides, fumigants, potato seed dust	Population-based case-control	Men from six Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec) who ever lived or worked on a farm Cases: dx with multiple myeloma (N=178) Controls: matched by age and province (N=673)	
*Lee, Blair, et al. 2004	No	Chlorpyrifos (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,383)	
*Lee, Hoppin, et al. 2004	No	Alachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,980)	
*Rusiecki et al. 2004	No	Atrazine (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=53,943)	

*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	
*De Roos et al. 2005	Yes	Glyphosate (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,315)	Based on small number of cases but consistent across states
Pahwa et al. 2006	No	*Herbicides*: "any phenoxyherbicide", 2,4-D, mecoprop, MCPA, "any dicamba-containing herbicide"	Population-based case-control	Men from six Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec) who ever lived or worked on a farm Cases: dx with multiple myeloma (N=176) Controls: matched by age and province (N=673)	Larger group including non-farm subjects also examined but not reported on here.
Myelodysplastic syndromes (MDS)					
Strom et al. 2005	Yes	High exposure level and duration of agricultural chemicals (pesticides and fertilizers)	Hospital-based case-control	Cases: Adult de novo MDS cases dx at University of Texas MD Anderson Cancer Center (N=354) Controls: friends, family	Agricultural analyses limited to men.

				members, and patients' visitors frequency matched by age, gender, and ethnicity (N=452)	
Non-Hodgkin lymphoma (NHL)					
Waddell et al. 2001	Yes	Organophosphates (particularly the insecticide diazinon)	Three pooled population-based case-control studies	White men in Iowa, Minnesota, Kansas, and Nebraska Cases: dx with NHL (N=748) Controls: matched by age, state, and vital status (N=2,236)	Greater risk from proxy interviews than direct interviews. Risk of small lymphocytic lymphoma from diazinon use was significant both with direct and proxy interviews.
Zheng et al. 2001	Yes	Carbamate pesticides (particularly Sevin)	Three pooled population-based case-control studies	White men in Iowa, Minnesota, Kansas, and Nebraska Cases: dx with NHL (N=985) Controls: matched by age, state, and vital status (N=2,895)	Effect pronounced if personally handled product, used product for ≥ 20 yrs before disease dx, or used product ≥ 7 yrs. Effect of Sevin strongest on small-cell lymphoma.
McDuffie et al. 2002	No	Accidental pulmonary or dermal exposure to fungicides, slimicides, carbamate insecticides, organophosphate	Population-based case-control	Men from six Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec) who ever lived or worked on a	Reported conclusion based on conditional logistic model including exposure to livestock. In

		insecticides, and dicamba herbicides		farm Cases: dx with NHL (N=235) Controls: matched by age and province (N=673)	univariate analyses exposure to carbamate insecticides, organophosphate insecticides, and dicamba herbicides significant.
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	
De Roos et al. 2003	Yes	Atrazine (*herbicide*), diazinon (*insecticide*), diazinon and atrazine combined, alachlor (*herbicide*) and atrazine combined	Three pooled population-based case-control studies	White men in Iowa, Minnesota, Kansas, and Nebraska Cases: dx with NHL (N=650) Controls: matched by age, state, and vital status (N=1,933)	Aldrin (*insecticide*) had a significant inverse effect.
Chiu et al. 2004	Yes	Crop insecticides, fungicides, herbicides	Three pooled population-based case-control studies	White men in Iowa, Minnesota, Kansas, and Nebraska Cases: dx with NHL (N=973) Controls: matched by age, state, and vital status (N=2,853)	Effect on small lymphocytic NHL and 'other NHL' but not on follicular NHL or diffuse large cell NHL.
Kato et al. 2004	Yes	Worked on farm using pesticides for ≥ 10 yrs	Population-based case-control	Women aged 20-79 yrs from upstate counties of New York	Also significant effects of household

				State Cases: dx with NHL (N=376) Contorls: matched by age (N=463)	pesticides; not reported on here.
*Lee, Blair, et al. 2004	No	Chlorpyrifos (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,383)	
Lee, Cantor, et al. 2004	Yes	*Insecticides*: organophosphates, chlordane, diazinon, fonofos, lindane, malathion; *Herbicides*: cyanazine	Two pooled population-based case-control studies	White men from Iowa and Minnesota and white men and women from Nebraska Cases: dx with NHL (N=872) Controls: matched by sex, age, state and vital status (N=2,336)	Effects of pesticide exposure more pronounced for asthmatics.
*Lee, Hoppin, et al. 2004	No	Alachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,980)	
*Rusiecki et al. 2004	No	Atrazine (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=53,943)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	

*Beane Freeman et al. 2005	No	Diazinon (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=23,106)	
*Bonner et al. 2005	No	Carbofuran (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,877)	
*De Roos et al. 2005	No	Glyphosate (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,315)	
McDuffie et al. 2005	No	*Herbicides*: mecoprop, herbicides containing dicamba, phenoxy herbicides (only in combination with DEET and rubber glove use)	Population-based case-control	Men from six Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec) who ever lived or worked on a farm Cases: dx with NHL (N=235) Controls: matched by age and province (N=673)	Effects greater when used in conjunction with DEET and rubber gloves. Larger group including non-farm subjects also examined but not reported on here.
*Rusiecki et al. 2006	No	Metolachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=50,193)	
t (14;18) - positive non-Hodgkin lymphoma (NHL)					
Schroeder et al. 2001	Yes	*Insecticides*: dieldrin, toxaphene, lindane; *herbicides*: atrazine.	Population-based case-control	White male non-metropolitan residents aged 30 yrs. and older in Iowa and Minnesota Cases: dx with t(14;18)-positive NHL (N=62)	Similar effects were not found for t(14;18)-negative NHL

				Controls: matched by age, state, and vital status (N=1,245)	
Chiu et al. 2006	Yes	Crop insecticides including organochlorines, carbamates, organophosphates, pyrethroids; herbicides including phenoxyacetic acids, triazines, amides, benzoic acids, carbamates; fumigants	Population-based case-control	White male and female farmers aged 21 yrs. and older in eastern Nebraska Cases: dx with t(14;18)-positive NHL (N=65) Controls: matched by age, state, and vital status (N=229)	Similar effects were not found for t(14;18)-negative NHL

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

Table 7: Studies Regarding Cancers of the Orolaryngeal Region

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
Larynx cancer					
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	
Oral cavity cancer					
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	
*Rusiecki et al. 2004	No	Atrazine (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=53,943)	
*De Roos et al. 2005	No	Glyphosate (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,315)	
*Rusiecki et al. 2006	No	Metolachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=50,193)	

Buccal cavity cancer					
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	Significantly lower than expected, except for lip cancer
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	
Lip cancer					
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

Table 8: Studies Regarding Respiratory System Cancers

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
Respiratory system cancers					
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	Significantly lower than expected
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	Significantly lower than expected
Lung cancer					
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	Significantly lower than expected for those between ages 50 and 69 years
Alavanja, Dosemeci et al. 2004	Yes	*Herbicides*: metolachlor and pendimethalin; *Insecticides*: chlorpyrifos and diazinon	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina with no history of lung cancer at enrollment (N=57,284)	The herbicide dicamba and the insecticides carbofuran and dieldrin had significant effects with low-exposure group as referent but not with non-exposed group.

*Lee, Blair, et al. 2004	Yes	Chlorpyrifos (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,383)	
*Rusiecki et al. 2004	No	Atrazine (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=53,943)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	Significantly lower than expected
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	Significantly lower than expected
*Beane Freeman et al. 2005	Yes	Diazinon (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=23,106)	Depends on exposure measure used
*Bonner et al. 2005	Yes	Carbofuran (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,877)	Only significant when low-carbofuran exposed, not non-carbofuran exposed, group used as referent.
*De Roos et al. 2005	No	Glyphosate (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,315)	

*Rusiecki et al. 2006	Yes	Metolachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=50,193)	

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

Table 9: Studies Regarding Brain Cancer

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
Brain cancer					
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	
*Lee, Blair, et al. 2004	Yes	Chlorpyrifos (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,383)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	Included brain and central nervous system cancers
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	Included brain and central nervous system cancers
Gliomas					
Ruder et al. 2004	No	Ever lived/worked on farm; herbicides, insecticides, fungicides, fumigants ever used on farm; *pesticide classes*: arsenicals, benzoic acids,	Population-based case-control	Male (18-80 yrs) non-metropolitan residents of Iowa, Michigan, Minnesota, and Wisconsin Cases: dx with primary intracranial glioma (N=457)	

		carbamates, chloroacetanilides, dinitroanilines, inorganics, organochlorines, organophosphates, phenoxys, traizines, urea-based, estrogenic		Controls: age and state matched (N=648)	
Carreon et al. 2005	No	Ever lived/worked on farm; herbicides, insecticides, fungicides, fumigants ever used on farm; laundered pesticide-applicator clothes; pesticides stored in house; various pesticide categories and individual pesticides	Population-based case-control	Female (18-80 yrs) non-metropolitan residents of Iowa, Michigan, Minnesota, and Wisconsin Cases: dx with primary intracranial glioma (N=341) Controls: age and state matched (N=527)	
Lee et al. 2005	Men: Yes Women: No	Men: *Herbicides*: metribuzin, paraquat; *Insecticides*: bufencarb, chlorpyrifos, coumaphos	Population-based case-control	White men and women (age ≥ 21 yrs) from eastern Nebraska Cases: dx with primary glioma (N=251) Controls: matched by sex, age, and vital status (N=498)	Pesticides with recorded significant effects had significantly increased risks overall for men and ORs that increased among both self and proxy respondents.

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.

[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

Table 10: Studies Regarding Breast Cancer

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
Brophy et al. 2002	Yes	Ever farming for women ≤ 55 yrs, controlling for age and personal educational achievement	Hospital-based case-control	Female patients of the Windsor Regional Cancer Centre in Windsor, Ontario, Canada who through convenience sampling completed a computer-assisted interview on occupational histories Cases: women newly dx with breast cancer (N=299) Controls: women dx with cancers other than breast cancer or lymphoma (N=237)	When ecologic census tract median household income was controlled for instead of personal education, resulting in use of all cases, the OR was marginally non-significant.
*Hopenhayn-Rich et al. 2002	No	Atrazine (*herbicide*) in water, atrazine sales, acres of corn	Ecological	Population of State of Kentucky, USA (N=3.7 million) aggregated by county (N=120) and Area Development Districts (N=15)	
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses	Significantly lower than expected for those between ages

				or relatives (N=6,310)	50 and 69 yrs
Reynolds et al. 2004	No	Pounds per square-mile (in half-mile radius of subjects' residences) of recently applied probable or likely human carcinogens, possible or suggestive human carcinogens, endocrine disruptors, anticholinesterases, organochlorines, simazine (*herbicide*), diuron (*herbicide*), oryzalin (*herbicide*), propargite (*insecticide*), and methyl bromide (*fumigant*)	Prospective cohort (California Teachers Study)	Active and retired female enrollees in State Teachers Retirement System with no prior history of breast cancer (N=114,835). 1,552 developed invasive breast cancer.	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	
Engel et al. 2005	Yes	Husband's Use of *Insecticides*: aldrin, carbaryl, chlordane, DDT, dieldrin, heptachlor,	Prospective cohort (AHS)	Wives of male licensed restricted-use pesticide applicators in Iowa and North Carolina (N=30,454)	Husband's use only significant for postmenopausal women.

		lindane, malathion; *Herbicides*: 2,4,5-TP; *Fungicides*: captan Premenopausal wife's use of *Insecticides*: chlorpyrifos, dichlorvos, terbufos			Postmenopausal wife's use of organochlorines, DDT, and atrazine had significant inverse association.
Reynolds, Hurley et al. 2005	No	Pounds per square-mile (in half-mile radius of subjects' residences) of recently applied probable or likely human carcinogens, possible or suggestive human carcinogens, xenoestrogens, anticholinesterases, organochlorines, simazine (*herbicide*), diuron (*herbicide*), oryzalin (*herbicide*), propargite (*insecticide*), and methyl bromide (*fumigant*)	Ecological	Female population of State of California, USA (age ≥ 20) aggregated to US Census block group level (70,968,598 person-years of observation and 176,302 invasive breast cancer cases)	

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

Table 11: Studies Regarding Melanoma

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	
*Rusiecki et al. 2004	No	Atrazine (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=53,943)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	
*Alavanja et al. 2005	Yes	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	
*Beane Freeman et al. 2005	No	Diazinon (*insecticide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=23,106)	
*De Roos et al. 2005	No	Glyphosate (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=54,315)	

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.

[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

Table 12: Studies Regarding Mesothelioma

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

Table 13: Studies Regarding Soft-Tissue Tumors

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
*Pahwa et al. 2003	No	Pesticides or agricultural chemicals ≥ 10 h/yr, herbicides, insecticides, fungicides, fumigants, potato seed dust	Population-based case-control	Men from six Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec) who ever lived or worked on a farm Cases: dx with soft-tissue sarcoma (N=159) Controls: matched by age and province (N=673)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	
Pahwa et al. 2006	No	*Herbicides*: "any phenoxyherbicide", 2,4-D, mecoprop, MCPA, "any dicamba-containing herbicide"	Population-based case-control	Men from six Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec) who ever lived or worked on a farm Cases: dx with soft-tissue	Larger group including non-farm subjects also examined but not reported on here.

				sarcoma (N=156) Controls: matched by age and province (N=673)	

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

Table 14: Studies Regarding Thyroid Cancer

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
*Wang et al. 2002	No	SIR based on being part of cohort	Retrospective cohort	Female farm residents who were New York Farm Bureau members, or members' spouses or relatives (N=6,310)	
*Lee, Hoppin, et al. 2004	No	Alachlor (*herbicide*)	Prospective cohort (AHS)	Licensed pesticide applicators in Iowa and North Carolina (N=49,980)	
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=52,395)	Included thyroid and other endocrine cancers
*Alavanja et al. 2005	No	SIR based on being part of cohort	Prospective cohort (AHS)	Spouses of licensed private pesticide applicators in Iowa and North Carolina (N=32,347)	Included thyroid and other endocrine cancers

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

Table 15: Studies Regarding Childhood Cancer

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
Reynolds et al. 2002	No for childhood cancer (age < 15)	Pesticide use density of *toxicological groups*: probable carcinogens, possible carcinogens, genotoxic compounds, reproductive or developmental toxicants; *chemical classes*: organochlorides, organophosphates, carbamates, dithiocarbamates; *commonly used pesticides*: propargite (*insecticide*), methyl bromide (*fumigant*), trifluralin (*herbicide*), simazine (*herbicide*), metam sodium (*fumigant*), dicofol (*acaricide*), chlorothalonil (*fungicide*)	Ecologic	Individuals under 15 yrs of age in the State of California (USA)	Exception: highest usage level of propargite had significant adverse effect on childhood leukemia.
Flower et al. 2004	Yes for all cancers, all lymphomas, and Hodgkin's lymphoma. No for leukemia, non-Hodgkin's lymphoma, Burkitt's lymphoma, brain tumors, neuroblastoma, retinoblastoma, Wilms tumor, bone	SIR based on being part of cohort	Hybrid; retrospective and prospective cohort (AHS)	Children of licensed pesticide applicators in Iowa (N=17,357)	Testing for the effect of paternal use of specific chemicals before child's birth on subsequent overall childhood cancer risk, only aldrin (*insecticide*) significantly increased the risk.

	tumors, soft-tissue tumors, germ cell tumors.				
Reynolds, Behren, Gunier, Goldberg, Harnly, et al. 2005	No for early childhood cancer (age < 5)	Pesticide use density of *toxicological groups*: probable carcinogens, possible carcinogens, genotoxic compounds, reproductive or developmental toxicants; *chemical classes*: organochlorides, organophosphates, carbamates, dithiocarbamates; *commonly used pesticides*: propargite (*insecticide*), methyl bromide (*fumigant*), trifluralin (*herbicide*), simazine (*herbicide*), metam sodium (*fumigant*), dicofol (*acaricide*), chlorothalonil (*fungicide*)	Population-based case-control	Children in the State of California (USA) Cases: childhood cancer cases dx under age 5 yrs (N=2,189) Controls: two randomly selected controls matched on date of birth and sex (N=4,335)	Exception: metam sodium (*fumigant*) and dicofol (*acaricide*) use had significant adverse effect on childhood leukemia, but trend not significant.
Reynolds, Behren, Gunier, Goldberg, Hertz 2005	No for acute lymphoblastic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, and Burkitt's lymphoma	Pesticide use density of *toxicological groups*: probable carcinogens, possible carcinogens, genotoxic compounds, reproductive or developmental toxicants; *chemical classes*: organochlorides, organophosphates, carbamates, dithiocarbamates; *commonly used pesticides*: propargite (*insecticide*), methyl bromide (*fumigant*), trifluralin (*herbicide*), simazine (*herbicide*), metam sodium (*fumigant*), dicofol (*acaricide*), chlorothalonil (*fungicide*)	Ecologic	Individuals under 15 yrs of age in the State of California (USA)	Exceptions: (1) when urbanization adjusted for possible carcinogens, genotoxins, and reproductive and developmental toxins had significant adverse effect on Hodgkin's disease; (2) highest usage level of propargite had significant

					inverse effect on non-Hodgkin's lymphoma.

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

3.4.4.3. Diseases of the Respiratory System

Farmers have been found to be at an increased risk for respiratory ailments (Hoppin, Umbach, London, Alavanja, & Sandler, 2004; Mpofu, Lockinger, Bidwell, & McDuffie, 2002; Schenker, 2005). Many exposures contribute to these ailments including dusts, solvents, exhaust, infectious agents, endotoxins, and others (Hoppin et al., 2004; Mpofu et al., 2002; Schenker, 2005). Adverse pesticide effects were found for the development of early childhood asthma (Salam, Li, Langholz, & Gilliland, 2004) but not adult asthma (Jones et al., 2003), in the reviewed studies (Table 16). A limitation of the study on early childhood asthma is that it did not differentiate between home and agricultural pesticide exposure (Salam et al., 2004). Pesticides have also been associated with wheeze (Table 16) among both private and commercial pesticide applicators (Hoppin et al., 2006; Hoppin, Umbach, London, Alavanja, & Sandler, 2002).

Table 16: Studies Regarding Diseases of the Respiratory System

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
Adult asthma					
Jones et al. 2003	No	Cases did not differ from controls in prevalence of asthma symptoms following spray season	Prospective case-control	Residents aged 21-60 yrs of five agricultural counties in eastern Arkansas Cases: members of the Arkansas Agricultural Aviation Association; pesticide applicators included aviators, ground mixers and loaders, and on-site office personnel (N=50) Controls: Lion's Club members with only community-based pesticide exposure (N=49)	
Early childhood asthma					
Salam et al. 2004	Yes	Exposure in first year of life to herbicides, pesticides, farm crops/dust/animals	Case-control nested in Children's Health Study cohort	Children recruited to cohort from public school classrooms (grades 4, 7, & 10) in 12 communities in Southern California (USA) Cases: dx with asthma before 5 yrs of age (N=279) Controls: asthma-free at study	Limitation: study does not distinguish between farm and non-farm exposure settings for pesticides/herbicides.

				entry, frequency-matched on age, sex, and community of residence and counter-matched on in utero exposure to maternal smoking (N=412)	
Wheeze					
Hoppin et al. 2002	Yes	Total pesticides; total insecticides including chlorpyrifos, malathion, and parathion; total herbicides including alachlor, atrazine, chlorimuron ethyl, EPTC, paraquat, and petroleum oil; metalaxyl (*fungicide*)	Cross-sectional (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=20,468)	Examined wheeze within past year and chemical use in past year among AHS cohort.
Hoppin et al. 2006	Yes	In single-agent models the *herbicides* atrazine, chlorimuron-ethyl, glyphosate, imazethapyr, metolachlor, metribuzin, pendimethalin, and petroleum oil; the *insecticides* chlorpyrifos, dichlorvos, fonofos, phorate, and terbufos. When chlorimuron-ethyl was included in the models only phorate and dichlorvos (used	Cross-sectional (AHS)	Licensed commercial pesticide applicators in Iowa (N=2,255)	Limitation: most commercial applicators certified for agricultural work but also include applicators to lawns, golf courses, and homes.

		exclusively on animals) remained significant.			

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

3.4.4.4. Disorders of the Eye

Japanese research has implicated agricultural organophosphate pesticides as an factor increasing the risk of eye disorders in humans (Dementi, 1994). The limited North American epidemiological research that has been conducted on the subject (Table 17) has found an adverse effect of fungicides, in populations composed of both applicators (Kamel et al., 2000) and wives of applicators (Kirrane et al., 2005), on the risk of retinal degeneration, the most common form of visual impairment in older adults (Kamel et al., 2000). Among applicators a significant adverse effect of select organochlorines, carbamates, and organophosphates was also found although these associations were not as pronounced as the effect of fungicides (Kamel et al., 2000). The study examining applicators' wives also evaluated the relationship of retinal detachment, glaucoma, and cataracts with agricultural pesticide use but did not find significant effects (Kirrane et al., 2005).

Table 17: Studies Regarding Retinal Degeneration

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
Kamel et al. 2000	Yes	Ever use of fungicides including benomyl, captan, chlorothalonil, copper ammonia carbonate, ferbam, maneb, metalaxyl, PCNB, and sulfur; ever use of organochlorines including DDT, dicofol, and endosulfan; ever use of carbamates including carbaryl and oxanyl; ever use of the *organophosphates*: dichlorvos, cygon, guthion, imidan, malathion, orthene, and prolate	Cross-sectional (AHS)	Licensed private pesticide applicators in Iowa and North Carolina (N=17,958)	Few dose-response relationships found among the organochlorines and organophosphates.
Kirrane et al. 2005	Yes	Ever use of fungicides	Cross-sectional (AHS)	Wives of husbands who were the sole licensed private pesticide applicator in the couple in Iowa and North Carolina (N=31,173)	Limitation: agricultural and residential use not distinguished.

[a] Starred references appear for multiple health outcomes.
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[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

3.4.4.5. Fetal Death and Congenital Anomalies

Reviews of the literature have suggested an association between parental pesticide exposure and a number of adverse pregnancy outcomes, including fetal death and congenital anomalies (Arbuckle & Sever, 1998; Hanke & Jurewicz, 2004). Fetal death is defined as "death before the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy" (National Center for Health Statistics, 2006). In common parlance a distinction is often made between early fetal deaths (a.k.a. miscarriages or spontaneous abortions) and late fetal deaths (a.k.a. stillbirths). The cut-off employed to delineate early and late fetal death varies but is generally the 20^{th} or 28^{th} week of gestation (Last et al. (Eds.), 2001). Congenital anomalies (a.k.a. birth defects or congenital malformations) can lead to fetal death, but are also present in live births.

The reviewed literature found an adverse effect of pesticides in many cases (Table 18). Studies of farm families and pesticide applicator families found significant adverse pesticide effects on fetal death (Arbuckle, Lin, & Mery, 2001; Garry, Harkins, Lyubimov, Erickson, & Long, 2002). Research examining the effect of proximity to agricultural pesticide use on the general population found a significant affect on fetal deaths due to congenital anomalies (Bell, Hertz-Picciotto, & Beaumont, 2001a), but not due to other causes (Bell, Hertz Picciotto, & Beaumont, 2001b). A cross-sectional study of congenital anomalies in live births fathered by pesticide applicators did not find a significant effect of most pesticides (Garry, Harkins, Erickson et al., 2002). Two other studies have found a significant adverse pesticide effect on congenital anomalies; an ecologic study of live

births (Schreinemachers, 2003), as well as a case-control study of neural tube defects in live births or fetal deaths (Rull, Ritz, & Shaw, 2006). Compared to other health outcomes reviewed, a greater percentage of these studies were conducted in regions bordering Manitoba.

Table 18: Studies Regarding Congenital Anomalies and Fetal Death

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
Early fetal death (< 20 wk)					
Arbuckle et al. 2001	Yes	Herbicides including phenoxy acetic acids and 2,4-D, insecticides, fungicides including thiocarbamates, organophosphates, miscellaneous class of pesticides	Retrospective cohort (Ontario Farm Family Health Study)	Pregnancies of couples living year round on farms in Ontario (Canada) with wife 44 yrs of age or younger and at least one member of couple working on the farm (3,936 pregnancies with 395 spontaneous abortions)	Women aged 35 yrs and older more susceptible to pesticide effects. In older age group carbaryl and triazines additionally had significant effects.
Early fetal death (<28 wk) and late fetal death (>28 wk)					
Garry, Harkins, Lyubimov, et al. 2002	Yes	Early or late fetal death with paternal use of herbicides, insecticides, and fungicides combined; *fungicides*: organotin and EBDC-containing fungicides (maneb and mancozeb); Early or late fetal death with maternal use of pesticides (including mixing, loading, and pesticide applications); Early fetal death in the	Cross-sectional	Self-reported singleton pregnancies fathered by randomly selected licensed pesticide applicators from five counties in the Red River Valley of Minnesota (1,602 pregnancies fathered by 522 applicators)	Number of first trimester miscarriages significantly elevated in spring.

		spring with paternal use of *herbicides*: sulfonylurea, imidizolinone, and Mixture 9100 (chlorophenoxy, sulfonylurea, and benzothiodiazole)			
Late fetal death (>20 wk) and infant death (within 24 hr) due to causes other than congenital anomalies					
Bell et al. 2001b	No	Residential proximity to the application of *pesticide classes* of phosphates, pyrethroids, halogenated hydrocarbons, carbamates, endocrine disruptors, estrogenic pesticides; acetylcholinesterase inhibitors: direct, indirect, and carbamate inhibitors	Case-cohort	Pregnancy outcomes in ten California counties with rural populations and high use of pesticides Cases: all infant deaths within 24 hrs of birth and fetal deaths after 20 wks of gestation, excluding congenital anomalies and causes not likely to be influenced by environmental exposures (N=319) Noncases: randomly selected from live normal births in same counties; frequency-match by county and age (N=611)	Borderline significant effects in second trimester with the pesticide classes of halogenated hydrocarbons, carbamates, and endocrine disruptors.

Late fetal death (>20 wk) and infant death (within 24 hr) due to congenital anomalies					
Bell et al. 2001a	Yes	Residential proximity to the application of the *pesticide classes* of phosphates, pyrethroids, or halogenated hydrocarbons	Population-based case-control	Pregnancy outcomes in ten California counties with rural populations and high use of pesticides Cases: all infant deaths within 24 hrs of birth and fetal deaths after 20 wks of gestation, due to congenital anomalies (N=73) Controls: randomly selected from live normal births in same counties; frequency-match by county and age (N=611)	Effects strongest when exposed during 3^{rd}-8^{th} wk of gestation.
Congenital anomalies in live births					
Garry, Harkins, Erickson, et al. 2002	No	Combinations of herbicides, insecticides, fungicides, and fumigants	Cross-sectional	Self-reported singleton live births fathered by randomly selected licensed pesticide applicators from five counties in the Red River Valley of Minnesota (1,532 live births fathered by 536 applicators)	Exceptions: phosphine fumigant associated with adverse central nervous system or neurobehavioural sequelae; phosphonamino herbicides (includes glyphosate) associated with ADD/ADHD. Conceptions in

					spring resulted in significantly more birth defects than other seasons.
Schreinemachers 2003	Yes	Above median percentage of county's land area in wheat, as surrogate measure of exposure to chlorophenoxy herbicides	Ecologic	White singleton births (N=43,634) to mothers 18 yrs or older from rural, agricultural counties of Minnesota, Montana, North Dakota, and South Dakota aggregated by county (N=147)	Significant effects for circulatory/ respiratory anomalies, musculoskeletal/ integumental anomalies, as well as (for males only) infant death from congenital anomalies.
Neural tube defects in live births or fetal deaths					
Rull et al. 2006	Yes	Residential proximity to the application of any pesticides, endocrine disruptors, cholinesterase inhibitors, and benzimidazoles	Two pooled case-control studies	Singleton live born infants and fetal deaths, including elective terminations in California (USA) Cases: confirmed dx of one of the neural tube defects of anencephaly, spina bifida cystica, craniorrhachischisis, or iniencephaly (N=731) Controls: infants without structural congenital anomalies dx before their first birthday (N=940)	In single-pesticide models some individual pesticides had significant effects that did not remain in multiple-pesticide models.

[a] Starred references appear for multiple health outcomes.

[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

3.4.4.6. Neurological Diseases and Mental Illness

The acute adverse effects of pesticide poisoning on the nervous system, although not included in the scope of this review, are well documented (Kamel & Hoppin, 2004). Many studies examining pesticides and neurological impacts focus on "symptom prevalence, neurobehavioural performance, sensory and motor dysfunction, and direct measures of nerve function" (Kamel & Hoppin, 2004, p. 952). As these effects can generally not be identified using administrative databases, articles concerning these outcomes are not contained in this review, but are discussed elsewhere (Colosio, Tiramani, & Maroni, 2003; Kamel & Hoppin, 2004; Sanborn et al., 2004). Accordingly the majority of the neurological outcomes reviewed here are neurodegenerative diseases.

Parkinson's disease is a neurodegenerative disease that affects at least 1% of the American population over the age of 55 (Sherer, Betarbet, & Greenamyre, 2001). Most reviews conclude that agricultural pesticides play a role in the development of Parkinson's disease (Di Monte, 2003; Kamel & Hoppin, 2004; Lai, Marion, Teschke, & Tsui, 2002; Sherer et al., 2001). Similarly a meta-analysis found both in worldwide studies and American studies a significant adverse effect on Parkinson's disease of rural living; pesticide exposure; and exposure to farming, living on a farm, or exposure to farm animals (Priyadarshi, Khuder, Schaub, & Priyadarshi, 2001). Others do not believe that the literature is consistent enough to provide sufficient evidence of a deleterious effect of pesticides on Parkinson's disease (Li, Mink, McIntosh, Teta, & Finley, 2005). Although these reviews are based on the many articles that have been published on Parkinson's disease and pesticides, few of these articles satisfy the requirements of this literature

review (partially due to being out of the date range). Of moderate relevance are two recent case-control studies that examined Parkinson's disease in predominantly urban populations with relatively low exposure to agriculture. One found a significant adverse effect of occupational insecticides (not limited to farming), while the other did not find a significant effect of pesticide exposure (Firestone et al., 2005; Gorell, Peterson, Rybicki, & Johnson, 2004). Table 19 describes the one study that met all the requirements of the literature review, which found a significant effect on Parkinson's disease of occupations with likely pesticide exposure (Park et al., 2005).

Alzheimer's disease (Table 19) is a neurodegenerative disease that is considered, in this study, as both a disease of the nervous system and as a form of dementia, a mental illness. In this study, presenile dementia (Table 19) is included only in the dementia category and motor neuron disease (Table 19) only in the nervous system disease category. All three of these ailments were examined in a study by Park et al. (2005) who found, for all outcomes, an increased risk from occupations in farming (Park et al., 2005). Another study examining Alzheimer's disease risk did not find a significant impact of pesticide use on the general population (Gauthier et al., 2001).

Depression, which can be measured using administrative data (Martens et al., 2004), is sometimes examined as a neurological symptom. Although some studies have examined depression as a sequelae of pesticide poisoning (Stallones & Beseler, 2002a, 2002b), few were found that examined the potential for pesticide exposure, similar to that in

Manitoba, to impact depression prevalence. Table 20 describes the one included study; it found a significant effect of agricultural pesticide use on depression.

Table 19: Studies Regarding Neurological Diseases

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
Alzheimer's disease					
Gauthier et al. 2001	No	Area (ha) sprayed with insecticides, herbicides, or pesticides averaged over subjects' municipalities of residence over 20 yrs	Population-based case-control	Randomly selected residents (age ≥ 70 yrs) of the Saguenay-Lac Saint-Jean region of Quebec (Canada) Cases: selected residents with neurologist-confirmed Alzheimer's disease (N=67) Controls: matched by age and sex (N=67)	
*Park et al. 2005	Yes	Farmer occupation (excluding farm workers, managers, graders, etc.)	Population-based case-control	Decedents in 27 American states between 1982-1991 Cases: death certificate mentioned Alzheimer's disease (N=47,783) Controls: all decedents with no mention of neurologic diseases, accidental deaths, or lymphopoietic/CNS cancers (N=2,485,518)	Only significant for death at age < 65 yrs.
Motor neuron disease					
*Park et al. 2005	Yes	All farm related occupations; farmer	Population-based case-control	Decedents in 27 American states between 1982-1991	

		occupation (excluding farm workers, managers, graders, etc.); farming occupations with likely pesticide exposure (excluded managers)		Cases: death certificate mentioned motor neuron disease (N=6,347) Controls: all decedents with no mention of neurologic diseases, accidental deaths, or lymphopoietic/CNS cancers (N=2,526,954)	
Parkinson's disease					
*Park et al. 2005	Yes	All farm related occupations; farmer occupation (excluding farm workers, managers, graders, etc.); farming occupations with likely pesticide exposure (excluded managers)	Population-based case-control	Decedents in 27 American states between 1982-1991 Cases: death certificate mentioned Parkinson's disease (N=33,678) Controls: all decedents with no mention of neurologic diseases, accidental deaths, or lymphopoietic/CNS cancers (N=2,499,623)	
Presenile dementia					
*Park et al. 2005	Yes	All farm related occupations; farmer occupation (excluding farm workers, managers, graders, etc.)	Population-based case-control	Decedents in 27 American states between 1982-1991 Cases: death certificate mentioned presenile dementia (N=27,374) Controls: all decedents with no mention of neurologic diseases, accidental deaths, or	Only significant for death at age < 65 yrs.

				lymphopoietic/CNS cancers (N=2,505,927)	

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

Table 20 Studies Regarding Depression

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
Kamel et al. 2005	Yes	Lifetime use of: any pesticide, any insecticide, organophosphates, organochlorines, and fumigants	Cross-sectional (AHS)	White, male (age = 18-75 yrs) licensed pesticide applicators in Iowa and North Carolina (N=18,782)	Adjusted for age, state, education, smoking, and alcohol use. Association did not change when accounted for pesticide poisoning, pesticide-related medical visits, and high-exposure events.

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.
[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

3.4.4.7. Musculoskeletal Autoimmune Diseases

The limited number of studies of pesticides and autoimmune diseases have found modest adverse effects (Cooper, Miller, & Germolec, 2002). These studies often focus on the musculoskeletal autoimmune diseases of rheumatoid arthritis, and to a lesser degree systemic lupus erythematosus (Cooper et al., 2004; Cooper et al., 2002). Only two studies were found regarding these types of health outcomes that met the requirements of the review (Table 21). Both studies focused predominantly on females, as they are more likely to experience such ailments (Cooper et al., 2002). The study of rheumatoid arthritis did not find a significant adverse effect (De Roos, Cooper, Alavanja, & Sandler, 2005). The research regarding systemic lupus erythematosus did find a significant effect of mixing pesticides, but not applying them (Cooper et al., 2004).

Table 21: Studies Regarding Musculoskeletal Autoimmune Diseases

Reference[a]	Significant[b] adverse effect	Exposure[c]	Study type	Population	Notes
Rheumatoid arthritis					
De Roos et al. 2005	No	Living on a farm; mixing/applying pesticides overall, any pesticide class, or any specific pesticides	Case-control nested in prospective cohort (AHS)	Female licensed pesticide applicators or spouses of applicators in Iowa and North Carolina Cases: physician-confirmed rheumatoid arthritis (N=135) Controls: 5 per case matched by birth date within one year (N=675)	The exception was 2,4-D which was associated with a significant decrease in risk.
Systemic lupus erythematosus					
Cooper et al. 2004	Yes	Mixing pesticides for agricultural work (no effect when only considered applying pesticides)	Population-based case-control	Predominantly female (90%) individuals from North Carolina and South Carolina (USA) who ever worked or lived on a farm Cases: recently dx with systemic lupus erythematosus (N=140) Controls: population based controls matched by sex, age, and state (N=140)	Although statistically significant, based on very low prevalence of exposure.

[a] Starred references appear for multiple health outcomes.
[b] Statistically significant with $p<0.05$.

[c] When significant adverse effects exist then exposure(s) associated with these effects are listed. Otherwise all tested measures, which did not result in a significant adverse effect, are listed. Group names given in italics are for readability and were not explicitly tested. Any significant inverse effects are recorded under notes.

3.4.5. Summary of Review of Epidemiological Literature on the Adverse Effects of Agricultural Pesticides on Human Health

Examining literature regarding the health effects of agricultural pesticide exposure, similar to that presented by Manitoba crop farming, provides an indication of what results may be found in this study. According to the reviewed literature agricultural pesticides have an adverse effect on some health outcomes. Risk of lymphohematopoetic cancers (especially leukemia and non-Hodgkin's lymphoma), lung cancer, cancers of the male genital system, brain cancer, breast cancer, and childhood cancers appear to be influenced by agricultural pesticides in some contexts. Fetal death and congenital anomalies are also likely affected by agricultural pesticide exposure. Certain respiratory outcomes, neurodegenerative diseases, and mental health outcomes also appear to be adversely affected by agricultural pesticides in some contexts. Agricultural pesticides additionally had adverse effects on disorders of the eye in the reviewed literature.

3.5. Environmental Health Indicators of Agricultural Pesticides

Indicators are by design a simplification of reality. Describing in entirety the factors that influence the risk of agricultural pesticides to human health would be exceedingly cumbersome. An ideal environmental health indicator (EHI) of agricultural pesticides would balance simplicity and its associated ease of use with complexity and its greater accuracy. The two key criteria of EHIs, scientific validity and utility, must often be balanced against one another in indicator development (Briggs, 2003; Eyles & Furgal, 2002). EHIs of agricultural pesticides that incorporate exposure and toxicity information more appropriately approximate the risk to human health due to the pesticides. Yet an EHI that examines only factors related to exposure, such as agricultural pesticide use, is simpler to create and therefore more feasible. In Manitoba, due to the wealth of crop farming data it is feasible to create both an indicator of agricultural pesticide use and risk.

3.5.1. Environmental Health Indicators Based on Exposure to Agricultural Pesticides

Exposure to agricultural pesticides, in its broadest sense according to the MEME framework, can be measured in many different ways, as is evident in the review of the epidemiological literature (see Section 3.4.4.). Some measurements of exposure that are feasible in epidemiological studies are not, however, conducive to being an environmental health indicator (EHI). An effective EHI must be scientifically valid as well as useful, which includes being both measurable and cost-effective (Briggs, 2003; Eyles & Furgal, 2002). Generally measures of proximal exposure (*exposure* in the

DPSEEA framework), such as biomarkers, are considered the best measure of exposure and are recommended for studying causation (Blundell, 2005; Commission for Environmental Cooperation Steering Group on Children's Health and Environment Indicators & Commission for Environmental Cooperation Secretariat, 2003). Such measures are costly in both time and money, however, since they must be collected from individuals for the purpose of the project. Information regarding the amount of pesticides in the environment or the use of pesticides (state and pressure in the DPSEEA framework) are more distal measures of exposure yet they are collected for other purposes and therefore may be cost-effective to use as secondary data. Due to their cost, measures of proximal exposure can only be ascertained for a sample of the population and for only one or two pesticides, whereas, more general measures of agricultural pesticide use can incorporate multiple pesticides and be applicable to the population. The Commission for Environmental Cooperation Secretariat and the Steering Group on Children's Health and Environment Indicators (2003) describe how biomarkers would be the most ideal measure of exposure to pesticides, but that pesticide residues on foods as well as pesticide use data are also valuable indicators.

Organizations that recommend the development of an indicator based on agricultural pesticide use, a distal exposure measure (*pressure* in the DPSEEA framework), have suggested different measures (Centers for Disease Control and Prevention, 2006; Pitblado et al., 1999; Pong et al., 2002; United Nations Department of Economic and Social Affairs, 2001). The United States Environmental Public Health Indicators Project suggests both "annual tons used" and "pounds applied" as feasible indicators of pesticide

use based on available data sources (Centers for Disease Control and Prevention, 2006, p. 14). Similarly, the UN Commission on Sustainable Development Programme of Work on Indicators of Sustainable Development has recommended an interim indicator of agricultural pesticide use to be defined as the "pesticide use in metric tons of active ingredients per 10 km^2 of agricultural land" (United Nations Department of Economic and Social Affairs, 2001, p. 132). Expressed limitations of this indicator is that it "provides an aggregation, which ignores toxicity, mobility, and level of persistence; and spatial and application variances" (United Nations Department of Economic and Social Affairs, 2001, p. 133). In Canada, Census of Agriculture information on the area sprayed with herbicides, insecticides and fungicides has been recommended (Pitblado et al., 1999; Pong et al., 2002). Giving the example of herbicide application, the "proportion of land in CCS[6] where herbicides applied" was the recommended indicator, although it was recognized that the indicator only "presents the possibility of potential exposure, but does not explicitly give actual exposure or dosage level" (Pitblado et al., 1999, p. 4-51). The latter measure regarding the proportion of land where pesticides were applied differs from the others in that the amount of active ingredient is not considered. Recommended application rates can be used to approximate the amount of active ingredient used on a certain area of land if the pesticide is known. All of above measures are limited in that they do not take into account characteristics of the pesticide application, which influences the probability of exposure (as described in Section 3.3.).

[6] CCS = Census Consolidated Subdivision. A CCS is defined as: "A grouping of census subdivisions. Generally the smaller, more urban census subdivisions (towns, villages, etc.) are combined with the surrounding, larger, more rural census subdivision, in order to create a geographic level between the census subdivision and the census division." (Pitblado et al., 1999, p. 2-10)

3.5.2. Environmental Health Indicators of Agricultural Pesticide Risk

Environmental health indicators (EHIs) based on agricultural pesticide use can be expanded into EHIs of agricultural pesticide "risk" through weighting them by toxicological information. Such weighting is suggested by the UN Commission on Sustainable Development in order to address some of the limitations in their interim agricultural pesticide use indicator: they state that "an indicator could be developed which would recognize the classification of pesticide into classes, ranging from less harmful to highly toxic. Such a pesticide index would show if pesticide use is becoming more sustainable or not" (United Nations Department of Economic and Social Affairs, 2001, p. 133). Toxicity weighting is especially relevant when an indicator includes the use of multiple pesticides, due to the potential range in pesticide toxicities.

Risk "is defined as the probability of an event multiplied by the magnitude of the outcome of that event" (Maud, Edwards-Jones, & Quin, 2001, p. 60). Therefore assessing risk due to pesticides requires the incorporation of the probability of exposure to the pesticides as well as an estimation of the magnitude of the putative outcome(s), which is dependent on both susceptibility factors and the intrinsic toxicity of the pesticides (Levitan, 2000; Maud et al., 2001; Myres & Betke, 2002). Despite their inaccuracies, indicators that include simpler characterizations of toxicology and potential or actual exposure are widely known as *pesticide risk indicators/indices* in the phraseology of those assessing the effect of pesticides on the environment (Levitan, 2000; Maud et al., 2001). With such understood simplification the term *pesticide risk*

indicators will also be used in this study. Due to the varying use of the terms *indicators* and *indices* to describe pesticide risk, indicators will be used in this study in order to conform to the environmental health literature and because indices can be seen as an sub-set of indicators (Levitan, 2000; Maud et al., 2001; Pitblado et al., 1999).

Indicators of pesticide risk to the environment that take into consideration human health impacts could potentially be employed directly, or after modification, as EHIs of agricultural pesticide risk to human health. A minority of environmental pesticide risk indicators take into consideration human health impacts and many of those that do are not feasible or suitable to use in this study (Vercruysse & Steurbaut, 2002). The Manitoba pesticide use data does not include site-specific information, such as the timing or type of pesticide application (Manitoba Agricultural Services Corporation, 2006b). Pesticide risk indicators that require site-specific information are therefore not currently feasible in Manitoba. Site-specific measures are more important for indicators that are developed as decision aids for farmers than for indicators that are designed for policy or research tools because of the difference in scale (Levitan, 2000).

3.5.2.1. Pesticide Risk Indicators with a Human Health Component

One of the earliest pesticide risk indicators that considered human health was Metcalf's Pest-Management Rating of Insecticides, which was first published in 1975 (as cited in Levitan, Merwin, & Kovach, 1995). It included measures of acute toxicity to humans but did not consider pesticide dose (as cited in: Levitan et al., 1995; Maud et al., 2001). Metcalf's rating referred only to insecticides and has since been expanded upon by other

indices (as cited in Levitan et al., 1995). The environmental economic injury levels of the 1992 study of Higley and Wintersteen (as cited in van der Werf, 1996) as well as the relative leaching potential index and relative runoff potential index of the 1992 study of Hornsby (as cited in van der Werf, 1996) consider human toxicity measures but are mainly environmental in focus (van der Werf, 1996). The Fruit Growers Pesticide Index (PI) presented in 1994 by Penrose, Thwaite, and Bower includes mammalian toxicity, however, it is focused on reducing pesticide residues in fruit rather than risk in general (Maud et al., 2001; Penrose, Thwaite, & Bower, 1994; van der Werf, 1996). The PI is dependent on site-specific information, such as the timing of pesticide application, which is not currently available in the Manitoba pesticide use data (Levitan et al., 1995; Penrose et al., 1994). Another challenge of the PI is that weights are assigned to the main component categories based on the values and opinions of the end-users (Maud et al., 2001; Penrose et al., 1994). Although weighting components makes the indicators more adaptable to the end-users, their results are highly dependent on these subjective rankings making the PI of questionable policy use (Maud et al., 2001).

The Chemical Hazard Evaluation for Management Strategies (CHEMS-1) chemical ranking and scoring method was designed by Swanson and colleagues (1997) as a chemical screening tool. CHEMS-1 was developed to rank toxic chemicals, including pesticides, based on their human health effects, environmental effects and exposure potential (Swanson et al., 1997). Human health effects are considered by CHEMS-1 through measurements of acute oral and inhalation toxicity, carcinogenicity, and other chronic effects (Swanson et al., 1997). As a screening tool designed to flag chemicals for

future observation, CHEMS-1 is biased towards giving chemicals higher scores (Levitan, 2000; Swanson et al., 1997). With its focus on ranking, the CHEMS-1 "results do not represent any quantitative measure of hazard or risk" (Swanson et al., 1997, p. 379). The challenges of being biased towards higher scores and not being intended as a quantitative measure of risk make CHEMS-1 unconducive to use in this study as a weighting factor of exposure.

The pesticide occupational and environmental risk (POCER) indicator, designed by Vercruysse and Steurbaut (2002), includes ten modules that focus on both human health and environmental risk. Human health is included in three modules regarding the risk to pesticide applicators, workers and bystanders (Vercruysse & Steurbaut, 2002). In each module exposure estimates are compared to reference toxicological values (Vercruysse & Steurbaut, 2002). The exposure estimates are based on site-specific data and, when possible, are estimated through computerized predictive exposure models (Vercruysse & Steurbaut, 2002). The estimates of exposure are formulated according to European farming practices and the Belgian pesticide registration procedure (Vercruysse & Steurbaut, 2002). The European context of POCER and its requirement for detailed site-specific information place limitations on its utility in Manitoba.

3.5.2.2. The Environmental Impact Quotient (EIQ)

The Environmental Impact Quotient (EIQ) is a pesticide risk indicator that was developed by Kovach and colleagues in 1992 as a decision aid for farmers and integrated pest management practitioners. Information on the EIQ has since been updated regularly and

is available online (Kovach, Petzoldt, Degni, & Tette, n.d.). The EIQ takes into consideration the impact of agricultural pesticides on the farm worker, the consumer, and the environment in three separate components that are then averaged (Kovach et al., n.d.). Each component of the EIQ is calculated by multiplying a pesticide's toxicological characteristics by its characteristics that influence the potential for exposure to the pesticide (Kovach et al., n.d.). The EIQ is designed to be subsequently integrated into an EIQ Field Use Rating that is a result of "multiplying the EIQ value for the specific chemical…by the percent active ingredient in the formulation by the rate per acre used" (Kovach et al., n.d., EIQ Field Use Rating section, para. 1). In order to aid in farm decision making, the Environmental Impact of different pest management strategies can then be determined by combining the involved pesticides' EIQ Field Use Ratings that have been weighted by the required number of applications (Kovach et al., n.d.). Although originally designed as a pre-application decision aid regarding pesticide use on horticultural crops, the EIQ has been adapted to post-application comparisons of risk on a broader range of crops (Kovach et al., n.d.; Levitan et al., 1995). In Canada, the EIQ has been employed in determining the reduction of pesticide risk due to pesticide use on a wide range of crops in Ontario (Gallivan, Berges, & McGee, 2005; Gallivan, Surgeoner, & Kovach, 2001). Another Canadian study examined the differences in Environmental Impact, through use of the EIQ, between pesticides used on herbicide-resistant and conventional canola (Brimner, Gallivan, & Stephenson, 2005).

The EIQ is not without limitations. Like many pesticide risk indicators the EIQ does not consider the synergistic effects of multiple pesticide exposure or the effects of varying

formulation types (Maud et al., 2001). The EIQ does not consider the volatilisation of pesticides or their toxicity from exposure due to inhalation: factors which may be especially important to bystander risk (van der Werf, 1996; Vercruysse & Steurbaut, 2002). Although making the use of the EIQ feasible, the omission of site-specific data does limit its exactness (Maud et al., 2001; van der Werf, 1996). The most commonly cited limitation of the EIQ is that it requires the measurements of the toxicological and exposure characteristics, upon which it is based, to be transformed into ratings of 1, 3, or 5 (Gallivan et al., 2005; Kovach et al., n.d.; Levitan et al., 1995; van der Werf, 1996). The narrow range of the ratings result in pesticides with extreme differences in toxicity having only a five-fold rating difference (Levitan et al., 1995; van der Werf, 1996). When, to determine the overall Environmental Impact, the transformed measures of toxicological and exposure characteristics are combined with untransformed information on the amount of pesticide used, the result will be biased towards the pesticide use data. Therefore, relatively toxic pesticides applied at low doses will have a lower Environmental Impact than less toxic pesticides applied at higher doses (van der Werf, 1996)

Recognizing the criticisms of the EIQ, the most recent evaluation of pesticide use and risk in Ontario employed for comparison two other pesticide risk indicators, in addition to the EIQ, that were also applicable to multiple pesticides used over time (Gallivan et al., 2005). One was the Environmental Hazard Index (EHI) of the Californian environmental health policy programme, which was presented by Pease, Liebman, Landy, and Albright in 1996 (as cited in: Gallivan et al., 2005; Maud et al., 2001). The EHI has been

criticized by Maud et al. (2001) for having components that were weighted by the end-user. Gallivan et al. (2005) circumvented this challenge by having the same weight for each component. The recent Ontario study also employed the Priority Substance List (PSL) score of Koniecki, Newhook, Long, de Beyssac, and Socha that was published in 1997 . The three risk indicators differ in their structure: They are based on different pesticide characteristics and "the EIQ multiplies toxicity by potential exposure to estimate the potential risk for each element of the score, whereas the EHI and PSL add toxicity and potential exposure as separate elements of the score" (Gallivan et al., 2005, p.25). All three pesticide risk indicators transformed the pesticide characteristics using a scoring system; that of the EHI was non-linear and that of the EIQ and PSL was linear, thereby reducing their sensitivity (Gallivan et al., 2005). Potentially due to their fundamental differences, there was limited agreement among the three pesticide risk indicators when comparing the risk scores for individual pesticides, however, trends in overall pesticide risk reduction were generally similar (Gallivan et al., 2005). All of the pesticide risk indicators were biased towards high use pesticides, therefore their differential treatment of glyphosate resulted in some divergent trends (Gallivan et al., 2005). Glyphosate had a higher risk score relative to many other herbicides according to the EIQ and a lower relative risk score based on the EHI and PSL, due to how the EIQ treats post-emergent herbicides (Gallivan et al., 2005). When Gallivan et al. scored glyphosate based on its foliar residue half-life - the way the EIQ treats pesticides that are not herbicides – the EIQ trends were comparable to those of the EHI and PSL (Gallivan et al., 2005; Kovach et al., n.d.).

The study by Gallivan et al. (2005) indicates that despite the limitations of the EIQ it produces similar results to the EHI and PSL when multiple pesticides are considered. In the Manitoba context it is feasible to utilize the EIQ because it is not site-specific and because the EIQ values are publicly available (Kovach et al., n.d.). The EIQ is greatly influenced, however, by the impact of the pesticide on honey bees and beneficial arthropods (Levitan et al., 1995). In order to make it more focused on the risk of pesticides to human health, the ecological component could be omitted. The resulting EIQ_{HUMAN} would be an average of the farm worker and consumer components. The EIQ is very conducive to this type of modification as each separate component includes toxicological and exposure characteristics (Gallivan et al., 2005; Levitan et al., 1995). The full benefits of the EIQ, or a modified $EIQ_{HUMAN,}$ can not be realized unless the EIQ Field Use Rating is calculated, which incorporates the dosage rate and the active ingredient concentration (Falconer, 2002). When exact application rates have not been known, previous studies have used the recommended application rates, hence the lack of known application rates in Manitoba is not prohibitive (Brimner et al., 2005; Maud et al., 2001). Weighting the area sprayed with pesticides by the EIQ_{HUMAN} Field Use Rating for each component pesticide will form the basis for a viable indicator of pesticide risk to human health.

4. METHODOLOGY

4.1. Data Sources

4.1.1. Population Health Research Data Repository (PHRDR)

The Population Health Research Data Repository (Repository) is housed at the Manitoba Centre for Health Policy (MCHP). The Repository includes the health services utilization history of every individual who has registered for the Manitoba Health Services Insurance Plan, whether they contacted the health care system or not, in linkable de-identified (i.e. anonymized) databases (Manitoba Centre for Health Policy, 2006b). Treatment prevalence rates for specific health conditions can be calculated by combining information from the physician claims, hospital separation abstracts, and pharmaceutical files. Treatment prevalence values are determined rather than the actual disease prevalence because the "administrative data used do not directly indicate who 'has' a disease, but rather who received health services 'treatment' for that disease" (Manitoba Centre for Health Policy, 2006a, Terms beginning with T section). The age and sex distribution of a region's population can also be described using the Repository, allowing this distribution to be controlled for in analyses. Canada Census data at the Dissemination Area (DA) level, such as average household income, as well as information from the Census of Agriculture are also contained in the Repository. Crosswalk files allow DA-level information to be aggregated.

The databases contained in the Repository were not originally designed for research. The secondary use of these administrative databases means that the cost of data collection is

low, a multi-year span of data is readily obtainable, and data for the entire insured population are available. A disadvantage of using this data source is that the actual disease prevalence is not available, only information on who received health services for the disease. Another limitation is the specificity of the medical claims data as a physician may only document one diagnosis code, which is limited to three digits, regardless of the number of complaints a patient presents with. The diagnosis codes are recorded in ICD-9-CM, a coding system "developed by the World Health Organization (WHO) that is used to classify diseases, health conditions and procedures" (Manitoba Centre for Health Policy, 2006a, Terms beginning with I section). In the hospital claims data 12 diagnostic codes and 16 diagnosis codes, with five digit specificity, are available and accordingly use of medical and hospital claims data in conjunction increases validity.

4.1.2. Manitoba Management Plus Program (MMPP)

The MMPP is a publicly available online resource (found at http://www.mmpp.com/ under Regional Analysis Tools…Pesticide Data) that provides information regarding production and management practices, including pesticide use, on Manitoba crop farms. The MMPP is provided by the Manitoba Agricultural Services Corporation (MASC) who state that "improved access to meaningful production and management information improves on farm decision making and in turn reduces Production Insurance payouts - a win-win situation for both farmers and MASC" (Manitoba Agricultural Services Corporation, 2006d, para. 1). The data found within the MMPP is a compilation of anonymous information that farmers provide to MASC in order to register for production insurance protection (Manitoba Agricultural Services Corporation, 2006a). Although

production insurance is registered for on a voluntary basis, 85% of Manitoba crop farmers are included in the MMPP data (G. Martens, personal communication, April 21, 2004).

The information provided by farmers is not verified by MASC for accuracy and the data are not standardized for management or environmental influences (Manitoba Agricultural Services Corporation, 2006a). Another stated limitation of the pesticide information is that:

> Producers report to MASC that they have used a product, but do not specify either the rate or percentage of acres that the product was actually applied. This means that pesticide acreage data for any product or group of products will tend to be overestimates. (Manitoba Agricultural Services Corporation, 2006a, Step 8 section, para. 6)

Overestimation is likely minimal, however, as most Manitoba farmers spray the entire area they report (G. Martens, personal communication, September 21, 2006). Based on the above mentioned limitations, MASC cautions that "data is most credible when it is obtained from a large acreage over many years" (Manitoba Agricultural Services Corporation, 2006a, Step 8 section, para. 9). Using data from multiple years or over a large acreage is also recommended because data are only displayed if they are the compilation of data from at least three farmers and a minimum of 200 acres, in order to maintain confidentiality (Manitoba Agricultural Services Corporation, 2006a).

Pesticide usage data from the MMPP can be compiled by repetitively querying the Pesticide Data Browser, which is able to provide the number of acres sprayed based on combinations of year, "municipality name"[7], crop name, and pesticide name (Manitoba Agricultural Services Corporation, 2006b). If the same acre is sprayed more than once with the same or a different pesticide it will be counted more than once (G. Martens, personal communication, September 21, 2006).

[7] Generally refers to areas that are considered Census Consolidated Subdivisions (CCS) in the Canada Census. CCS will be used throughout the remainder of the document. A CCS is defined as: "A grouping of census subdivisions. Generally the smaller, more urban census subdivisions (towns, villages, etc.) are combined with the surrounding, larger, more rural census subdivision, in order to create a geographic level between the census subdivision and the census division." (Pitblado et al., 1999, p. 2-10)

4.2. Linkage and Sampling

4.2.1. Linkage

Census consolidated subdivision[8] (CCS) names from the MMPP were matched with CCS names from the Statistics Canada electronic boundary files of the 2001 Canada Census (Statistics Canada, 2001a). In the MMPP Shellmouth and Boulton were listed as separate areas but they are combined in the Census into the CCS of Shellmouth-Boulton; the aggregation was used in this study. Similarly in the MMPP data the areas of Elton and Cornwallis were listed separately, however, in the Census they are listed together under the name of Elton and were used together in the study. The CCS identification numbers (CCSUID) from the Statistics Canada electronic boundary files (2001 Canada Census) were then matched with the Statistics Canada 2005 Postal Code Conversion File (PCCF) to provide Census subdivision (CSD) names and numbers (Statistics Canada, 2005). The CSD names were then matched with the Municipality names from the Manitoba Health electronic boundary files (Manitoba Health, 2002), which provided the MUNCODES necessary to pull the appropriate individuals from the MCHP Repository. Some First Nations communities go by different names in the PCCF and the Manitoba Health files, therefore these community names were matched manually to their synonyms (Martens et al., 2002).

[8] A CCS is defined as: "A grouping of census subdivisions. Generally the smaller, more urban census subdivisions (towns, villages, etc.) are combined with the surrounding, larger, more rural census subdivision, in order to create a geographic level between the census subdivision and the census division." (Pitblado et al., 1999, p. 2-10)

4.2.2. Criteria for Inclusion/Exclusion of Areas

The study included rural crop farming areas of Southern Manitoba. Taking the CCSs of Manitoba, the first to be excluded were those in the North, specifically in the Regional Health Authorities (RHAs) of Churchill, Burntwood, and NOR-MAN that are above the 53rd parallel. Farming is sparse in these regions and their social context is generally different from the Rural South. The city of Winnipeg was excluded due to its urban nature.

The goal of the study was to include crop farming areas. Different methods of determining whether there was crop farming in a CCS were proposed. It was decided that any CCS that was included in the MMPP database, excepting the above mentioned areas, would be considered. An exception to this rule was the exclusion of the CCS of St.Laurent that was included in the MMPP data but had very few acres recorded. These exclusions resulted in 114 CCSs being included in the study. The proportion of land in a CCS where pesticides were applied over four years according to the MMPP was highly correlated with the Census-based measure of the proportion of land in a CCS in crop and/or summerfallow (Pearson correlation co-efficient = 0.91, df = 112, $p<0.001$).

Larger population centres within the 114 included crop farming CCSs of the Rural South were also excluded so that they did not dilute the putative effects of agricultural pesticides on rural human health. The municipalities that are considered cities (Brandon, Portage la Prairie, Steinbach) were excluded, as were towns that according to the 2001 Canada Census had a population greater than 5,000 (Dauphin, Selkirk, Morden, Winkler).

The pesticide data was still based on the entire CCS, as this is the level of data available in the MMPP. Considering towns and cities compose a small proportion of the acres of a CCS this limitation is minor.

4.2.3. Criteria for Inclusion/Exclusion of Individuals

Individuals were only included if they were considered to reside, for the purposes of the study, in one of the included municipalities within one of the included CCSs. Residency requirements differed based on coverage status. Coverage was determined over an eight-year period, including the four-year study period, January 1, 2001 to December 31, 2004, and the four years before it. Coverage was complete over the interval if a person was born or died during the interval or was completely covered by Manitoba Health over the entire interval. For those with complete coverage, the total number of days spent at each CCS was counted, and the longest duration was compared with the total length of coverage. If the length of this longest segment was 50% or more of the total coverage duration and it was located at one of the included CCSs then that person met the residency requirement. If the individual was born or died in the time period then 50% of their coverage duration may not be 50% of 8 years. For those with incomplete coverage, at least 4 years at one of the included CCSs was required in the 8-year period to meet the residency requirement. Individuals who met the residency requirement were included in the study and were considered to reside in the CCS where they spent the longest duration.

Using the MCHP Repository it was determined that 443,986 individuals had had contact with at least one of the included CCSs at some point between January 1, 1997 and

December 31, 2004. Due to data challenges, such as a coverage end date prior to start date, 522 individuals were excluded. Another 29,059 were excluded because they were not covered at all during the 2001-2004 study period. The resulting 414,405 were then tested based on the above mentioned residency requirements; seventy-eight percent (N=323,368) met the requirements.

4.3. Variable Creation

4.3.1. Individual Characteristics

The individual characteristics of sex, age, and income were utilized in this study. The MCHP Research Registry was used to determine the sex and age of each individual. Age was determined as of the end of the study period (December 31, 2004) so that all ages were positive values. For individuals who died during the study period, age describes how old they would have been if they had lived until the end of the study period. Individual income measures were not available; average household income values from the 2001 Canada Census were used as proxies (Statistics Canada, 2001b). The postal codes of individuals, according to the MCHP Research Registry, were assigned to their most likely Census Dissemination Area (DA) with the Statistics Canada 2005 Postal Code Conversion File (Statistics Canada, 2005). For 128 individuals (0.04%) their recorded postal code did not match to a valid Manitoba DA; these individuals were eliminated from analyses that used income. If the average household income for the DA was missing or suppressed the average household income for the Census Subdivision was used instead, if this value was not available then the average household income for the Census Division was employed (Statistics Canada, 2001b). Area-level income attributed to the individual was then grouped into deciles of individuals and the median of the decile divided by 1,000 was used as the income measure. Therefore each one-unit increase in the income measure represents a $1,000 increase in average household income. Canadian dollars are used throughout this thesis.

4.3.2. Health Status Indicators

The physician claims, hospital separation abstracts, pharmaceutical files, and Research Registry of the Repository were used to create individual- and ecological-level health status indicators. Overall mortality and premature mortality were included as indicators of overall health status. Specific morbidity measures were grouped according to body system (e.g. diseases of the respiratory system) or type of disease (e.g. cancer), generally following the chapter categories of version 9 of the International Classification of Diseases (ICD-9-CM) (HCIA Inc., 1994). Disorders of the eye, spontaneous abortion, and cancer in young children were examined separately due to the reported association with pesticides in the literature (see Section 3.4.4.). Instead of utilizing the Mental Disorders chapter of the ICD-9-CM, the mental illness indicators of dementia, depression, and cumulative mental illnesses were created using definitions that have been previously developed at MCHP (Martens et al., 2004). The cumulative mental illnesses indicator identifies individuals who were treated for one or more of depression, anxiety disorders, substance abuse, schizophrenia, and personality disorders (Martens et al., 2004). Two ICD-9-CM measures that refer to pesticide-specific diagnoses are included in the hospital separation abstracts. The pesticide-specific indicators were created for descriptive purposes to elucidate whether direct measurement of pesticide effects is feasible.

The study period was January 1, 2001 to December 31, 2004. Mortality measures were based on the MCHP Registry data. For the physical illnesses, physician claims for fiscal years 2000/01 to 2004/05 were used to search for claims within the study period. At the

time of analysis the hospital separation abstracts file for fiscal year 2004/05 was not available, therefore, for physical disorders and pesticide-specific diagnoses only fiscal years 2000/01 to 2003/04 were used to search for hospital separations within the study period. Mental disorders claims were searched for in a five year period, between January 1, 2000 and December 31, 2004, based on the specifications of previously developed indicators (Martens et al., 2004). Accordingly, the 1999/2000 fiscal year physician claims and hospital separation abstracts were employed in addition to those used to search for physical disorders. The depression indicator also required the use of the Drug Product Information Network. The fiscal years 1999/2000 to 2004/05 were used to search for prescriptions between January 1, 2000 and December 31, 2004. Although the lack of the 2004/05 hospital separation abstracts file is a limitation, many hospital visits are also captured in the physician claims file due to physician billing, reducing the impact of this limitation as the two types of files are used in combination. Another limitation of the data is the use of hospital separations; if an individual is admitted but not discharged during the time period of interest then they will not be counted.

Age restrictions were placed on some of the health outcomes. The indicators of cumulative mental illness and depression were limited to individuals age 10 and older, and the indicator of dementia was limited to individuals age 55 and older, based on previously validated definitions (Martens et al., 2004). The pregnancy related health outcomes of complications of pregnancy, childbirth, and the puerperium and its subset spontaneous abortion were limited to females age 15 to 49 years. The health outcomes of conditions originating in the perinatal period, congenital anomalies, and cancer in young

children were limited to individuals under 5 years of age. Age was calculated at the end of the study period.

At the individual level, health status indicators were binary variables that designated whether the individual had been treated for the health outcomes defined in Table 22. The ecological CCS-level health status indicators were sex-disaggregated age-adjusted period prevalences for the health outcomes (Table 22). The ecological measure for females of disorders of the eye therefore represented the age-adjusted percentage of females in each CCS who had at least one physician claim or hospital separation for a disorder of the eye over the study period. If an individual had multiple diagnoses for eye disorders over the 4-year study period they were only counted once. Although rule out visits were counted it is assumed that the incidence of rule out visits is constant across CCSs and will therefore not impact upon the detected associations. Rule out visits are contacts with the health care system where an individual is diagnosed with a condition, which later it is determined they don't actually suffer from. Prevalence values generated from this study must, accordingly, be interpreted with some caution as the study is designed to accurately measure association, not prevalence.

Table 22: Definitions of Health Outcomes

Health outcome	**Definition**
Mortality	
Overall mortality	Death according to MCHP Registry
Premature mortality	Death before age 75 according to MCHP Registry
Physical illness	
Cancer	At least one physician claim or hospital separation with a diagnosis code for a neoplasm (ICD-9-CM 140-239) and an

	age of 5 years or older
Cancer in young children	At least one physician claim or hospital separation with a diagnosis code for a neoplasm (ICD-9-CM 140-239) before age 5
Complications of pregnancy, childbirth, and the puerperium	At least one physician claim or hospital separation with a diagnosis code for complications of pregnancy, childbirth, or the puerperium (ICD-9-CM 630-677); females age 15 to 49 years
Spontaneous abortion	At least one physician claim or hospital separation with a diagnosis code for a spontaneous abortion (ICD-9-CM 634); females age 15 to 49 years
Conditions originating in the perinatal period	At least one physician claim or hospital separation with a diagnosis code for a condition originating in the perinatal period (ICD-9-CM 760-779) before age 5
Congenital anomalies	At least one physician claim or hospital separation with a diagnosis code for a congenital anomaly (ICD-9-CM 740-759) before age 5
Diseases of the blood and blood-forming organs	At least one physician claim or hospital separation with a diagnosis code for a disease of the blood or blood-forming organs (ICD-9-CM 280-289)
Diseases of the circulatory system	At least one physician claim or hospital separation with a diagnosis code for a disease of the circulatory system (ICD-9-CM 390-459)
Diseases of the digestive system	At least one physician claim or hospital separation with a diagnosis code for a disease of the digestive system (ICD-9-CM 520-579)
Diseases of the genitourinary system	At least one physician claim or hospital separation with a diagnosis code for a disease of the genitourinary system (ICD-9-CM 580-629)
Diseases of the musculoskeletal system and connective tissue	At least one physician claim or hospital separation with a diagnosis code for a disease of the musculoskeletal system or the connective tissue (ICD-9-CM 710-739)
Diseases of the nervous system	At least one physician claim or hospital separation with a diagnosis code for a disease of the nervous system (ICD-9-CM 320-359)
Disease of the respiratory system	At least one physician claim or hospital separation with a diagnosis code for a disease of the respiratory system (ICD-9-CM 460-519)

Diseases of the skin and subcutaneous tissue	At least one physician claim or hospital separation with a diagnosis code for a skin or subcutaneous tissue disease (ICD-9-CM 680-709)
Disorders of the eye	At least one physician claim or hospital separation with a diagnosis code for a disorder of the eye (ICD-9-CM 360-379)
Endocrine, nutritional and metabolic diseases, and immunity disorders	At least one physician claim or hospital separation with a diagnosis code for an endocrine, nutritional, metabolic disease or immunity disorder (ICD-9-CM 240-279)
Ill-defined conditions	At least one physician claim or hospital separation with a diagnosis code for an ill-defined condition (ICD-9-CM 780-799)
Infectious and parasitic disease	At least one physician claim or hospital separation with a diagnosis code for an infectious or parasitic disease (ICD-9-CM 001-139)
Injury and poisoning	At least one physician claim or hospital separation with a diagnosis code for an injury or poisoning (ICD-9-CM 800-999)
Mental illness	
Cumulative mental illnesses	Treatment for any of the following mental illnesses: depression (as defined within table), anxiety states (at least one hospital separation with a diagnosis code for anxiety states (ICD-9-CM 300.0), phobic disorders (ICD-9-CM 300.2), or obsessive-compulsive disorders (ICD-9-CM 300.3) OR a physician claim with a diagnosis code for neurotic disorders (ICD-9-CM 300) at least three times in the five-year span), substance abuse (at least one physician claim or hospital separation with a diagnosis code for alcoholic psychoses (ICD-9-CM 291), drug psychoses (ICD-9-CM 292), alcohol dependence (ICD-9-CM 303), drug dependence (ICD-9-CM 304), or nondependent abuse of drugs (ICD-9-CM 305)), personality disorders (ICD-9-CM 301), and schizophrenia (ICD-9-CM 295); age of 10 years or older
Dementia	At least one physician claim or hospital separation with a diagnosis code for organic psychotic conditions (ICD-9-CM 290-292), other organic psychotic conditions (ICD-9-CM 294), cerebral degenerations (ICD-9-CM 331), or senility (ICD-9-CM 797); age of 55 years or older
Depression	At least one physician claim or hospital separation with a diagnosis code for affective psychoses (ICD-9-CM 296 in physician and 296.2-296.8 in hospital), adjustment reaction (ICD-9-CM 309), depressive disorder (ICD-9-CM 311), or

	neurotic depression (ICD-9-CM 300.4, available only in hospital) OR at least one physician claim or hospital separation with a diagnosis code for neurotic disorders (ICD-9-CM 300) plus a prescription for an antidepressant or mood stabilizer (excluding the anti-anxiety drugs paroxetine, citalopram and venflaxamine); age of 10 years or older
Pesticide-specific diagnoses	
Accidental poisoning by agricultural and horticultural chemical and pharmaceutical preparations other than plant food and fertilizers	At least one hospital separation with an external cause of injury code for an accidental poisoning by agricultural and horticultural chemical and pharmaceutical preparations other than plant food and fertilizers (ICD-9-CM E863)
Toxic effects of substances chiefly nonmedicinal as to source (pesticides)	At least one hospital separation with a diagnosis code for a toxic effect of a chiefly nonmedicinal substance including organophosphates and carbamates, and other pesticides not elsewhere classified (ICD-9-CM 989.3-989.4)

Note. For all health outcomes, if an individual had multiple diagnoses within the same category they were only counted once.

Age adjustment was achieved through modeling proportions using SAS® software, Version 9.1 of the SAS System for Unix[9] (SAS Institute Inc., 2003). First the sex-disaggregated outcome variables were modeled with the CCS identifiers and age as predictors. Depending on the outcome variables, models used a Poisson or a negative binomial distribution. The manner in which age was grouped depended on the fit of the model. Table 23 describes for each ecological health outcome the chosen age groupings. To calculate the age-adjusted prevalences, the parameter estimates for each CCS were exponentiated and then multiplied by the crude prevalence of the health outcome in the reference CCS. The CCS of St. Andrews was used as the reference as it had the largest

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population of both males and females and would therefore have the most stable proportion.

Table 23: Age Groupings Used for Age-Adjustment of Ecological Health Outcomes

Health Outcome	Males	Females
Overall mortality	0-14, 15-29, 30-44, 45-59, 60-74, 75+	0-14, 15-29, 30-44, 45-59, 60-74, 75+
Premature mortality	0-14, 15-29, 30-44, 45-59, 60-74, 75+	0-49, 50+
Cancer	0-14, 15-29, 30-44, 45-59, 60-74, 75+	0-14, 15-29, 30-44, 45-59, 60-74, 75+
Cancer in young children	N/A	N/A
Complications of pregnancy, childbirth, and the puerperium	N/A	15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49
Spontaneous abortion	N/A	15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49
Conditions originating in the perinatal period	N/A	N/A
Congenital anomalies	N/A	N/A
Diseases of the blood and blood-forming organs	0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+	0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+
Diseases of the circulatory system	0-14, 15-29, 30-44, 45-59, 60-74, 75+	0-14, 15-29, 30-44, 45-59, 60-74, 75+
Diseases of the digestive system	0-14, 15-29, 30-44, 45-59, 60-74, 75+	0-14, 15-29, 30-44, 45-59, 60-74, 75+
Diseases of the genitourinary system	0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+	0-14, 15-29, 30-44, 45-59, 60-74, 75+
Diseases of the musculoskeletal system and connective tissue	0-14, 15-29, 30-44, 45-59, 60-74, 75+	0-14, 15-29, 30-44, 45-59, 60-74, 75+
Diseases of the nervous system	0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+	0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+

Disease of the respiratory system	0-49, 50+	0-49, 50+
Diseases of the skin and subcutaneous tissue	0-14, 15-29, 30-44, 45-59, 60-74, 75+	0-14, 15-29, 30-44, 45-59, 60-74, 75+
Disorders of the eye	0-14, 15-29, 30-44, 45-59, 60-74, 75+	0-14, 15-29, 30-44, 45-59, 60-74, 75+
Endocrine, nutritional and metabolic diseases, and immunity disorders	0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+	0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+
Ill-defined conditions	0-19, 20-39, 40-59, 60+	0-19, 20-39, 40-59, 60+
Infectious and parasitic disease	0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+	0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+
Injury and poisoning	0-19, 20+	0-19, 20-39, 40-59, 60+
Cumulative mental illnesses	0-14, 15-29, 30-44, 45-59, 60-74, 75+	0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+
Dementia	0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+	0-14, 15-29, 30-44, 45-59, 60-74, 75+
Depression	0-14, 15-29, 30-44, 45-59, 60-74, 75+	0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+

4.3.3. Pesticide Indicators

4.3.3.1. Indicators of Pesticide Use in Crop Farming

Four CCS-level indicators of pesticide use in crop farming were created based on the MMPP data (see Section 4.1.2.): the average percent of CCS land acreage, annualized over four years (2001-2004), where any pesticide, herbicides, insecticides, or fungicides were applied. The sum of the acres where any pesticides (or a sub-group) were applied over the four-year study period, divided by four, was used as the numerator of the

indicators and the acreage of the CCS as the denominator. The indicators were then multiplied by 100 to form percents. Hence, a value of one indicates that every year, on average, the equivalent of one percent of the acres in the CCS had pesticides applied to them once. Values greater than 100% are possible since an acre sprayed more than once is counted multiple times (G. Martens, personal communication, September 21, 2006).

The indicator of *average annualized percent of CCS land acreage where any pesticide applied* includes herbicides, insecticides, and fungicides. In order to create this indicator the MMPP Pesticide Data Browser was queried by only CCS, which produced the amount of acres included in the Pesticide Data Browser for each CCS over the four year study period (2001-2004; at the time of data retrieval these were the only years available). Subtracted from this overall amount of acres were, as determined by additional queries, the amount of acres per CCS that over the four years were classified as no chemicals applied, no fungicide/insecticides, no herbicide applied, and organically grown. Forming a percent, the resulting amount of acres, divided by four, was used as the numerator and the CCS acreage as the denominator of the average annualized percent of CCS land acreage where any pesticide applied.

The indicators of *average annualized percent of CCS land acreage where herbicides applied*, *average annualized percent of CCS land acreage where insecticides applied*, *average annualized percent of CCS land acreage where fungicides applied* were created by analogous processes. First the MMPP Pesticide Data Browser was queried by CCS and pesticide name, which produced the amount of acres included in the Pesticide Data

Browser for each pesticide by CCS over the four year time period (2001-2004). The results of the query were modified to aid in future categorization, based on expert advice[10], in the following ways: acres of 2,4-D were split between 2,4-D amine and 2,4-D ester, acres of Champion and Champion Plus were added to those of Champion Extra, all the acres attributed to some variety of MCPA were considered MCPA ester since it is the most common, acres of Puma/Attain Virtual Pak were added to both Puma and Attain, acres of Puma/Buctril M Virtual Pak were added to both Puma and Buctril M, and acres of Vitavax were split between Vitavax Single Solution and Vitavax Dual Solution.

Using the 2004 Guide to Crop Protection (Manitoba Agriculture Food and Rural Initiatives, 2004) and expert advice each pesticide was categorized according to its pesticide type: herbicide, insecticide, fungicide, fungicide and insecticide, or none of the above (included Merge, Easout, Zinc Chelate, no chemicals applied, no fungicide/insecticides, no herbicide applied, and organically grown). For each CCS the acres of herbicides, insecticides, and fungicides were summed and used as the numerators for the percent indicators, with CCS acreage as the denominator. Pesticides that were both fungicides and insecticides were included in the acreage of both types. Querying by pesticide name led to some suppression of data, therefore, the sum of the acres of herbicides, insecticides, and fungicides does not add up to the amount of acres where any pesticides were applied. The pesticides of Ultimax and Advantage were excluded

[10] Expert pesticide advice was provided throughout the thesis by Gary Martens, Field Manager and Instructor, Department of Plant Sciences, University of Manitoba; and Dr. Rene van Acker, Professor and Department Head, Department of Plant Agriculture, University of Guelph.

because they could not be assigned a pesticide type. However, they accounted for a small amount of acres (1202 and 7413 acres over the four years respectively).

4.3.3.2. Indicators of Risk of Pesticide Use in Crop Farming

One CCS-level indicator of pesticide risk was created. The reasoning for utilizing a modification of the Environmental Impact Quotient (EIQ), and EIQ_{HUMAN}, as the basis of this pesticide risk indicator was described in Section 3.5.2.2.. The EIQ is a measure of the putative exposure and toxicological properties of each active ingredient. The EIQ_{HUMAN} includes the average of the farm worker and consumer components of the EIQ and excludes the ecological component. Weighting the amount of active ingredient used by the EIQ_{HUMAN} results in a measure of risk.

In order to create the indicator of pesticide risk the amount of each active ingredient used per CCS needed to be derived from the amount of acres where each trade name pesticide was applied per CCS. The MMPP Pesticide Data Browser was queried by CCS and pesticide name to find the amount of acres per CCS where each trade name pesticide had been applied over the four-year study period (2001-2004). The same data cleaning methods and exclusions that were previously described for the other pesticide indicators were employed.

The pesticide name given in the MMPP is the trade name of the pesticide. Some trade name pesticides are intended to be tank mixes, where the components have not yet been combined and are applied at varying application rates. The *amount of trade name or tank*

mix component applied (measured in litres or kilograms) was calculated as the product of (i) the number of acres where the trade name or tank mix component was applied according to MMPP, (ii) the Recommended Application Rate (RAR) of the trade name or tank mix component (measured in kg/acre or L/acre depending on the formulation and in L/kg seed or kg/kg seed if a seed treatment), and (iii) the kilograms of seed per acre (for seed treatments, in other cases set to unity). In previous studies when exact application rates have not been known, RARs were used instead as was done in this study (Brimner et al., 2005; Maud et al., 2001). Some RARs were found in the 2004 Guide to Crop Protection (Manitoba Agriculture Food and Rural Initiatives, 2004), however, the RAR of many pesticides varies by crop. Accordingly most RARs were determined through consultation with experts[11].

Many trade name pesticides and tank mix components are themselves composed of multiple active ingredients (a.k.a. common name pesticides). The *kilograms of active ingredient applied* was calculated as the product of the amount of trade name or tank mix component applied and the proportion of the active ingredient in the trade name or tank mix component (measured as a unit-less proportion or in kg/L depending on the formulation of the pesticide).

As discussed in Section 3.5.2.2., one of the most commonly cited limitations of the EIQ is that the measures of toxicological and exposure characteristics are transformed to a

[11] Expert pesticide advice was provided throughout the thesis by Gary Martens, Field Manager and Instructor, Department of Plant Sciences, University of Manitoba; and Dr. Rene van Acker, Professor and Department Head, Department of Plant Agriculture, University of Guelph.

limited scale, yet are combined with untransformed information on the amount of pesticide used (Levitan et al., 1995; van der Werf, 1996). This limitation results in the outcome being biased towards pesticide use data. Addressing this source of bias, the kilograms of active ingredient applied was natural log-transformed before being weighted by the EIQ_{HUMAN}.

Within each CCS the products of the log-transformed kilograms of active ingredient applied and the EIQ_{HUMAN} for each active ingredient were summed and then this value was used as the numerator of the pesticide risk indicator for the CCS. This measure was divided by the natural log-transformed acreage of the CCS and the resultant value was used as the CCS-level indicator of pesticide risk. Without the log-transformation of the CCS acreage, small CCSs had abnormally high values of the indicator. In order to be on a similar scale as the other variables the pesticide risk indicator was divided by 100 before being used in analyses. Table 24 includes the steps of calculating the pesticide risk in a hypothetical CCS where only five pesticides were used over the study period.

EIQ values were first sought in the Gallivan et al. report (2005) that provided EIQ values updated in 2005. Values were then looked for in the online resource of the Integrated Pest Management Program of New York State (Kovach et al., n.d.). Based on the recommendations of Gallivan et al. (2005), discussed in Section 3.5.2.2., the EIQ_{HUMAN} of glyphosate was modified to reflect a plant surface half life based on its foliar dissipation rather than based on being a post-emergent herbicide. For four active ingredients the EIQ could not be found. The documentation of the American

Environmental Protection Agency and the Canadian Pest Management Regulatory Agency was searched in order to find the toxicological information with which the EIQ_{HUMAN} could be calculated. No information could be found for flamprop methyl and quinclorac and therefore these active ingredients were excluded from the pesticide risk indicator calculation. Information was found on florasulam and flucarbazone-sodium. When calculated both of these active ingredients had an EIQ_{HUMAN} of 7.5.

Table 24: Example of Pesticide Risk Calculation

Pesticide (Type)	Acres		RAR		kg seed/ acre[a]		Amount of trade name or tank mix component applied		Proportion of active ingredient in trade name or tank mix component		Kilograms (kg) of active ingredient		Active ingredient	EIQ_{HUMAN}	ln(kg)* EIQ_{HUMAN}
Buctril M (herbicide)	86400	*	0.4	*	1	=	34560.0	*	0.28	=	9676.8	of	bromoxynil	15.5	61.8
							34560.0	*	0.28	=	9676.8	of	MCPA ester	9.25	36.9
Puma (herbicide)	60915	*	0.268	*	1	=	16325.2	*	0.12	=	1959.0	of	fenoxaprop-p-ethyl	5.5	18.1
Touchdown (herbicide)	25303	*	0.5	*	1	=	12651.5	*	0.36	=	4554.5	of	glyphosate	4.5	16.5
Decis (insecticide)	13317	*	0.06	*	1	=	799.0	*	0.05	=	40.0	of	deltamethrin	4.5	7.2
Dividend (fungicide)	2020	*	0.0065	*	50	=	656.5	*	0.0321	=	21.1	of	difenoconazole	19.25	25.5
							656.5	*	0.0027	=	1.8	of	metalxyl-M	13.5	3.4
															SUM = 169.3

[a] If not a seed treatment then kg seed/acre is equal to one.

Let CCS acreage = 191,794 acres; then ln(CCS acreage) = 5.283

Pesticide Risk = $[\sum(\ln(kg)*EIQ_{HUMAN})/ \ln(\text{CCS acreage})]/ 100$
= (169.3/ 5.283)/ 100
= 32.04/ 100
= 0.32

4.4. Statistical Approaches

4.4.1. Descriptive Analyses

The sex, age, and income profiles of the cohort (N = 323,368) were examined (Tables 26, 27, and 28). The distribution of the cohort by CCS can be found in Appendix B. Descriptive statistics for the pesticide indicators were calculated (Table 29), as were Spearman correlations between the various pesticide indicators (Table 30). The frequency of the pesticide-specific health indicators were calculated for the entire cohort. The descriptive statistics were conducted using SAS® software, Version 9.1 of the SAS System for Unix (SAS Institute Inc., 2003).

4.4.2. Exploratory Analyses

Spearman correlations were calculated between combinations of the pesticide indicators and the sex-disaggregated age-adjusted ecological health status indicators in order to highlight pairings potentially of interest for further analyses (Tables 31 and 32). The non-parametric Spearman correlation tests were chosen because a number of the pesticide indicators had a non-normal distribution. Correlations with a p-value below 0.05 were considered for further analyses. This cut-off value was not reduced, despite multiple tests, because of the exploratory nature of this stage of the study. SAS® software, Version 9.1 of the SAS System for Unix (SAS Institute Inc., 2003), was used to conduct the analyses.

4.4.3. Analytical Analyses

Multilevel analyses were employed to further examine potential associations between pesticide indicators and health status indicators. Multilevel analysis "allows the simultaneous examination of the effects of group-level and individual-level predictors…[and]…the nonindependence of observations within groups is accounted for" (Diez-Roux, 2000, p. 174). Individuals were nested within CCSs; both the individual characteristics of age and income, as well as a CCS-level pesticide indicator, were included in the sex-disaggregated multilevel models. Income was included due to its role as a key determinant of health (Section 2.1). The results of the exploratory ecological correlations were used to focus upon select statistically correlated combinations of pesticide and health outcome indicators. The results of the descriptive analyses were also used to determine which pesticide indicators to utilize in the analytical analyses.

Hierarchical generalized linear models (HGLMs) provide a method to model multilevel data that has a nonlinear structure. HGLMs have both a level-1 and a level-2 model. The level-1 model includes three parts: a sampling model, a link function, and a structural model (Raudenbush & Bryk, 2002). In this study the outcome variables were individual level health status indicators: binary variables indicating whether an individual was treated for the health outcome of interest during the four year study period. With a binary outcome (zero or one) the level-1 sampling model utilizes a special case of the binomial distribution, the Bernoulli distribution. With the Bernoulli sampling model the predicted value of the level-1 outcome is equal to the probability of an individual being treated for

the health outcome ($Ø_{ij,}$ for case *i* in level-2 unit *j*) (Raudenbush, Bryk, Cheong, & Congdon, 2000). The level-1 link function is the logit link function

$$\eta_{ij} = \log (Ø_{ij} / (1- Ø_{ij}))$$

where η_{ij} is the log-odds (or 'logit') of an individual being treated for the health outcome (Raudenbush et al., 2000). The level-1 structural model and the level-2 model change based on which variables are included in the model and whether they are fixed or random effects.

For each selected sex-disaggregated individual-level health indicator a null model was first run with no level-1 or level-2 predictors. The level-1 structural model for the null model only included the level-1 intercept

$$\log (Ø_{ij} / (1- Ø_{ij})) = \beta_{0j}$$ (Raudenbush et al., 2000).

In HGLM the level-1 coefficients (β_{qj}) become outcome variables in the level-2 model (Raudenbush et al., 2000). Therefore, in the level-2 null model only the level-1 intercept was an outcome variable

$$\beta_{0j} = \gamma_{00} + \mu_{0j}$$

predicted by the level-2 intercept, γ_{00}, and the level-2 random effect, μ_{0j} (Raudenbush et al., 2000). The variance of the random intercept in the null model was inspected in order to determine whether there was significant variation across level-2 units. The statistical program HLM2 Version 5.0 was used to conduct the multilevel analyses (Scientific Software International Inc., 2000).

The specifications of the final HGLM models for the pesticide and health indicator combinations (Table 25) depended on the fit of the models compared to the null model. Fit was measured based on the deviance output from the Laplace6 method of estimation, which approximates but does not replicate maximum likelihood (Raudenbush et al., 2000). A regular chi-squared distribution was used to determine the significance in the change in deviances between models that had the same number of random effects. When comparing a model to one with an additional random effect a 50:50 mixture of chi-squared distributions was employed (Fitzmaurice, Laird, & Ware, 2004). The pesticide indicators of interest were forced into the models because they were the focus on the study. Income was included in all models and age was included in models describing health outcomes that were not limited to individuals under age 5. The intercept and the income coefficient were initially allowed to vary across level-2 units and were therefore considered random effects. The final estimation of variance components indicated whether the income coefficient significantly varied across level-2 units; i.e. whether the relationship between income and the health outcome of interest differed across CCSs. Income was fixed in subsequent models ($\beta_{1j} = \gamma_{10}$) if its effect did not significantly vary over level-2 units and having it vary was not important to the fit of the model. Age was initially included as a variable with 5-year age groups (AGE5). AGE5 had the lowest age in each range, with age 90 being the highest value: it was employed as a continuous variable. An age-squared term (AGESQ) was also initially included along with age. The age and age-squared terms were fixed effects; i.e. not allowed to vary across level-2 units. The age-squared term was deleted from some models in order to improve their fit. Age was re-grouped for female disorders of the eye and male cancers to accommodate

bimodal distributions. In the model of female disorders of the eye age was grouped into 20 years of age and under, between 20 and 65 years of age, and 65 years of age and older. Similarly, in the model for male cancers age was grouped into 50 years of age and under, between 50 and 75 years of age, and 75 years of age and older.

Table 25: Final HGLM Models for each Pesticide-Health Indicator Combination

Health outcome	Pesticide indicator	Level-1 model	Level-2 model[a]
Males			
Cancer	Average annualized percent of CCS land acreage where any pesticide applied	$\log (Ø_{ij} / (1- Ø_{ij})) = \beta_{0j} + \beta_{1j}(INCOME)_{ij} + \beta_{2j}(AGE\leq50)_{ij} + \beta_{3j}(AGE\geq75)_{ij}$	$\beta_{0j} = \gamma_{00} + \gamma_{01}(ANY)_j + \mu_{0j}$ $\beta_{1j} = \gamma_{10} + \mu_{1j}$ $\beta_{2j} = \gamma_{20}$ $\beta_{3j} = \gamma_{30}$
Cancer	Average annualized percent of CCS land acreage where insecticides applied	$\log (Ø_{ij} / (1- Ø_{ij})) = \beta_{0j} + \beta_{1j}(INCOME)_{ij} + \beta_{2j}(AGE\leq50)_{ij} + \beta_{3j}(AGE\geq75)_{ij}$	$\beta_{0j} = \gamma_{00} + \gamma_{01}(INSECT)_j + \mu_{0j}$ $\beta_{1j} = \gamma_{10} + \mu_{1j}$ $\beta_{2j} = \gamma_{20}$ $\beta_{3j} = \gamma_{30}$
Cancer	Pesticide risk	$\log (Ø_{ij} / (1- Ø_{ij})) = \beta_{0j} + \beta_{1j}(INCOME)_{ij} + \beta_{2j}(AGE\leq50)_{ij} + \beta_{3j}(AGE\geq75)_{ij}$	$\beta_{0j} = \gamma_{00} + \gamma_{01}(RISK)_j + \mu_{0j}$ $\beta_{1j} = \gamma_{10} + \mu_{1j}$ $\beta_{2j} = \gamma_{20}$ $\beta_{3j} = \gamma_{30}$
Conditions originating	Average annualized	$\log (Ø_{ij} / (1- Ø_{ij})) = \beta_{0j} +$	$\beta_{0j} = \gamma_{00} + \gamma_{01}(INSECT)_j$

in the perinatal period	percent of CCS land acreage where insecticides applied	$\beta_{1j}(\text{INCOME})_{ij}$	$+ \mu_{0j}$ $\beta_{1j} = \gamma_{10}$
Congenital anomalies	Average annualized percent of CCS land acreage where any pesticide applied	$\log (\text{Ø}_{ij} / (1- \text{Ø}_{ij})) = \beta_{0j} +$ $\beta_{1j}(\text{INCOME})_{ij}$	$\beta_{0j} = \gamma_{00} + \gamma_{01}(\text{ANY})_j +$ μ_{0j} $\beta_{1j} = \gamma_{10} + \mu_{1j}$
Congenital anomalies	Average annualized percent of CCS land acreage where insecticides applied	$\log (\text{Ø}_{ij} / (1- \text{Ø}_{ij})) = \beta_{0j} +$ $\beta_{1j}(\text{INCOME})_{ij}$	$\beta_{0j} = \gamma_{00} + \gamma_{01}(\text{INSECT})_j$ $+ \mu_{0j}$ $\beta_{1j} = \gamma_{10} + \mu_{1j}$
Disorders of the eye	Average annualized percent of CCS land acreage where any pesticide applied	$\log (\text{Ø}_{ij} / (1- \text{Ø}_{ij})) = \beta_{0j} +$ $\beta_{1j}(\text{INCOME})_{ij} + \beta_{2j}(\text{AGE5})_{ij} +$ $\beta_{3j}(\text{AGESQ})_{ij}$	$\beta_{0j} = \gamma_{00} + \gamma_{01}(\text{ANY})_j +$ μ_{0j} $\beta_{1j} = \gamma_{10} + \mu_{1j}$ $\beta_{2j} = \gamma_{20}$ $\beta_{3j} = \gamma_{30}$
Disorders of the eye	Average annualized percent of CCS land acreage where insecticides applied	$\log (\text{Ø}_{ij} / (1- \text{Ø}_{ij})) = \beta_{0j} +$ $\beta_{1j}(\text{INCOME})_{ij} + \beta_{2j}(\text{AGE5})_{ij} +$ $\beta_{3j}(\text{AGESQ})_{ij}$	$\beta_{0j} = \gamma_{00} + \gamma_{01}(\text{INSECT})_j$ $+ \mu_{0j}$ $\beta_{1j} = \gamma_{10} + \mu_{1j}$ $\beta_{2j} = \gamma_{20}$ $\beta_{3j} = \gamma_{30}$
Disorders of the eye	Pesticide risk	$\log (\text{Ø}_{ij} / (1- \text{Ø}_{ij})) = \beta_{0j} +$	$\beta_{0j} = \gamma_{00} + \gamma_{01}(\text{RISK})_j +$

		$\beta_{1j}(\text{INCOME})_{ij} + \beta_{2j}(\text{AGE5})_{ij} +$ $\beta_{3j}(\text{AGESQ})_{ij}$	μ_{0j} $\beta_{1j} = \gamma_{10} + \mu_{1j}$ $\beta_{2j} = \gamma_{20}$ $\beta_{3j} = \gamma_{30}$
Diseases of the circulatory system	Average annualized percent of CCS land acreage where any pesticide applied	$\log (\text{Ø}_{ij} / (1- \text{Ø}_{ij})) = \beta_{0j} +$ $\beta_{1j}(\text{INCOME})_{ij} + \beta_{2j}(\text{AGE5})_{ij}$	$\beta_{0j} = \gamma_{00} + \gamma_{01}(\text{ANY})_j +$ μ_{0j} $\beta_{1j} = \gamma_{10}$ $\beta_{2j} = \gamma_{20}$
Females			
Conditions originating in the perinatal period	Average annualized percent of CCS land acreage where insecticides applied	$\log (\text{Ø}_{ij} / (1- \text{Ø}_{ij})) = \beta_{0j} +$ $\beta_{1j}(\text{INCOME})_{ij}$	$\beta_{0j} = \gamma_{00} + \gamma_{01}(\text{INSECT})_j$ $+ \mu_{0j}$ $\beta_{1j} = \gamma_{10}$
Disorders of the eye	Average annualized percent of CCS land acreage where any pesticide applied	$\log (\text{Ø}_{ij} / (1- \text{Ø}_{ij})) = \beta_{0j} +$ $\beta_{1j}(\text{INCOME})_{ij} + \beta_{2j}(\text{AGE}\leq 20)_{ij}$ $+ \beta_{3j}(\text{AGE}\geq 65)_{ij}$	$\beta_{0j} = \gamma_{00} + \gamma_{01}(\text{ANY})_j +$ μ_{0j} $\beta_{1j} = \gamma_{10} + \mu_{1j}$ $\beta_{2j} = \gamma_{20}$ $\beta_{3j} = \gamma_{30}$
Disorders of the eye	Average annualized percent of CCS land acreage where insecticides applied	$\log (\text{Ø}_{ij} / (1- \text{Ø}_{ij})) = \beta_{0j} +$ $\beta_{1j}(\text{INCOME})_{ij} + \beta_{2j}(\text{AGE}\leq 20)_{ij}$ $+ \beta_{3j}(\text{AGE}\geq 65)_{ij}$	$\beta_{0j} = \gamma_{00} + \gamma_{01}(\text{INSECT})_j$ $+ \mu_{0j}$ $\beta_{1j} = \gamma_{10} + \mu_{1j}$ $\beta_{2j} = \gamma_{20}$ $\beta_{3j} = \gamma_{30}$

Disorders of the eye	Pesticide risk	$\log (\emptyset_{ij} / (1- \emptyset_{ij})) = \beta_{0j} +$ $\beta_{1j}(\text{INCOME})_{ij} + \beta_{2j}(\text{AGE}\leq 20)_{ij}$ $+ \beta_{3j}(\text{AGE}\geq 65)_{ij}$	$\beta_{0j} = \gamma_{00} + \gamma_{01}(\text{RISK})_j +$ μ_{0j} $\beta_{1j} = \gamma_{10} + \mu_{1j}$ $\beta_{2j} = \gamma_{20}$ $\beta_{3j} = \gamma_{30}$
Diseases of the circulatory system	Average annualized percent of CCS land acreage where any pesticide applied	$\log (\emptyset_{ij} / (1- \emptyset_{ij})) = \beta_{0j} +$ $\beta_{1j}(\text{INCOME})_{ij} + \beta_{2j}(\text{AGE5})_{ij} +$ $\beta_{3j}(\text{AGESQ})_{ij}$	$\beta_{0j} = \gamma_{00} + \gamma_{01}(\text{RISK})_j +$ μ_{0j} $\beta_{1j} = \gamma_{10} + \mu_{1j}$ $\beta_{2j} = \gamma_{20}$ $\beta_{3j} = \gamma_{30}$

[a] In the level-2 models the pesticide indicators were coded as follows: ANY = average annualized percent of CCS land acreage where any pesticide applied; INSECT = average annualized percent of CCS land acreage where insecticides applied; RISK = pesticide risk.

The results of population-average models with robust standard errors were reported. The parameter estimates in a population-average model represent the expected difference in the log-odds of the health outcome "associated with a unit increase in the predictors, holding constant the other predictors, but averaging over the distribution of level-2 random effects" (Raudenbush & Bryk, 2002, p. 303). Only in models with a nonlinear link function does a distinction arise between population-average and unit-specific models (Raudenbush & Bryk, 2002). In unit-specific models the estimates are dependent on the level-2 random effects being held constant, in addition to the other predictors, and are therefore not appropriate for generalizing to the population. Laplace6 estimations, which approximate maximum likelihood, are based on a unit-specific model and

therefore were not reported as the main results. These estimations were compared to those of the population-average models, however, and divergences were documented. This technique optimized the strengths of both types of models because the population-average model is more appropriate for this study but it is based on a less exact method of estimation, full penalized quasi-likelihood.

In addition to reporting the regression coefficients of the full models, the coefficients of similar models that only included level-1 variables (lacked the pesticide variables) were also reported so that the coefficients of these variables could be compared. Odds ratios for the predictors were calculated by exponentiating the parameter estimates. The odds ratios represent the factor by which the odds of the examined health outcome increases with a one unit increase in the independent variable of interest. The 95% confidence intervals of the odds ratios were calculated by exponentiating the parameter estimates ± (1.96*standard error of the parameter estimates). Accordingly, confidence intervals that do not cross one are statistically significant with a p-value of 0.05 or lower. The specific p-values recorded by the HLM2 Version 5.0 program were also documented (Scientific Software International Inc., 2000).

An advantage of odds ratios (ORs) compared to risk ratios (RRs), especially when outcomes are common as is the case in this study, is that "homogeneity of ORs is a more tenable assumption than the assumption of homogeneity of RRs and thus it is more likely that an estimate of the OR can be reliably applied to all individuals within a population" (Cook, 2002, p. 1432). An advantage of RRs, however, is that they are more intuitive,

being the ratio of probabilities rather than of odds. In order to support ease of interpretation, and to allow individuals to calculate RRs if they so choose, probabilities were also calculated. The intercept of the population-average models is the expected log-odds of the health outcome for an individual with zero on all predictors (Raudenbush et al., 2000). In these analyses all of the predictors were centered around their grand mean, therefore, it is an average individual that has a value of zero on all predictors (Subramanian, Jones, & Duncan, 2003). The predicted probability of an outcome ($Ø_{ij}$) is calculated from the predicted log-odds ($ŋ_{ij}$) as follows:

$Ø_{ij} = 1/ (1+ \exp\{- ŋ_{ij}\})$ (Raudenbush & Bryk, 2002).

The probability based on the intercept, therefore, represents the probability of diagnosis with the health outcome of interest for an individual of average income and average age (for models where age included) who lives in a CCS with an average value of the pesticide indicator. For each health outcome the probabilities for individuals who differ from the average in either a one-unit increase or a one standard deviation increase in the pesticide measures were also calculated.

Confidence in a result that is not statistically significant is related to power. Power calculations for multilevel models, especially nonlinear models, are not well developed (Subramanian et al., 2003). General guidelines for the number of groups (level-2 units) and individuals (level-1) per group include: 30 with 30 each, 50 with 20 each, and 100 with 10 each (Subramanian et al., 2003). This study conforms to each of these guidelines with 114 areas and an average of 2836 individuals per area.

4.5. Knowledge Translation

Knowledge translation is the "exchange, synthesis and ethically-sound application of knowledge - within a complex system of interactions among researchers and users" (Canadian Institutes of Health Research, 2004, Defining and framing knowledge translation section, para. 2). The broad intended audience of this study was health policy decision-makers, health researchers, and agricultural policy decision-makers. The immediate intended audience, a sub-set of the larger audience, was *The Need To Know* Team. The Team is made up of representatives from all of the rural and Northern Regional Health Authorities (RHAs) of Manitoba, the Manitoba Centre for Health Policy, and Manitoba Health (Bowen, Martens, & The Need to Know Team, 2005). This research was presented, at an interim stage and upon completion, to *The Need To Know* Team. At the interim stage, feedback regarding the study was solicited from the Team. The broader audience was accessed through the results of the study being presented in Prince George, British Columbia at the Seventh National Conference of the Canadian Rural Health Research Society (poster presentation, October 19-21, 2006) and in Winnipeg, Manitoba at the Thirteenth Annual Rural and Northern Health Care Meeting (oral presentation, October 24, 2006). The study was also written up for publication in the scientific literature. Although these actions work towards knowledge translation, they are mostly restricted to dissemination.

4.5.1. Maps

Maps were created as a key tool for disseminating information on the indicators used in the study. All of the pesticide indicators were mapped in order to better understand their relationship. Only those health indicators that were utilized in the HGLM models were mapped so as not to overload the audience. The maps were created with the mapping software ArcView GIS 3.3 (Environmental Systems Research Institute, 2002). Values were assigned to classes in the graduated colour maps by the ArcView's system of natural breaks, which uses Jenk's optimization to minimize the variation within each class (Environmental Systems Research Institute, 1996, p. 104).

4.6. Ethics Approval

Ethical approval for this study was received from the Health Research Ethics Board of the University of Manitoba (H2004:091). Approval for the project was also obtained from the Health Information Privacy Committee of Manitoba Health (File No. 2004/2005-09).

5. RESULTS

5.1. Descriptive Results

The profile of the study cohort, by sex, is outlined in table 26. The cohort is almost evenly split between males and females.

Table 26: Sex Profile of Cohort (N=323,368)

Sex	N	Percent
Male	163,798	50.65
Female	159,570	49.35

The mean age of the cohort was 39.7 years (SD = 24.3 years). The age profile of the cohort is displayed in table 27.

Table 27: Age Profile of Cohort (N=323,368)

Ten year age groups	N	Percent
0-9	37,327	11.54
10-19	47,894	14.81
20-29	41,569	12.85
30-39	33,234	10.28
40-49	48,082	14.87
50-59	41,443	12.82
60-69	29,869	9.24
70-79	23,575	7.29
80-89	15,243	4.71

90+	5,132	1.59

The mean household income of the cohort was $46,079 (SD = $15,448). Table 28 presents the income profile of the cohort.

Table 28: Average Household Income Profile of Cohort Based on Canada Census Data (N=323,368)

Income groups (Canadian dollars)	N	Percent
< 20,000	723	0.22
20,000 – 29,999	28,150	8.71
30,000 – 39,999	104,074	32.18
40,000 – 49,999	91,915	28.42
50,000 – 59,999	46,579	14.40
60,000 – 69,999	31,062	9.61
70,000 – 79,999	11,334	3.50
80,000 – 89,999	4,979	1.54
> 90,000	4,424	1.37
Missing	128	0.04

The characteristics of the pesticide variables are outlined in Table 29. The Spearman correlations between the various pesticide indicators are presented in Table 30.

Table 29: Characteristics of Pesticide Indicators

Pesticide type[a]	Mean	Standard deviation	Median	Minimum	Maximum
Any Pesticide	73.57	49.41	72.98	0.27	208.42
Herbicides	58.51	38.55	58.25	0.08	166.00
Insecticides	2.43	2.00	2.08	0.00	9.56
Fungicides	11.57	10.29	8.27	0.00	41.69
Pesticide Risk	2.36	0.98	2.46	0.04	5.04

[a] All pesticide variables, other than pesticide risk, represent the average annualized percent of CCS land acreage where the pesticide type was applied.

Table 30: Spearman Correlations between Pesticide Indicators

Pesticide type[a]	Any pesticide	Herbicides	Insecticides	Fungicides
Any pesticide	1.00			
Herbicides	0.99	1.00		
Insecticides	0.81	0.80	1.00	
Fungicides	0.95	0.92	0.79	1.00
Pesticide risk	0.80	0.78	0.83	0.86

Note: All correlations statistically significant at $p < 0.0001$.

[a] All pesticide variables, other than pesticide risk, represent the average annualized percent of CCS land acreage where the pesticide type was applied.

The frequency of the pesticide-specific health outcomes were calculated for the entire cohort in order to elucidate whether direct measurement of pesticide effects is feasible.

During the study period, only six individuals had a hospital separation with an accidental poisoning by agricultural and horticultural chemical and pharmaceutical preparations other than plant food and fertilizers, and no individuals had a diagnosis of toxic effects of substances chiefly nonmedicinal as to source (pesticides).

5.2. Exploratory Results

Table 31 outlines the Spearman correlations between the pesticide and health indicators at the ecological level for males, while table 32 includes the analogous measures for females. In a number of cases the treatment prevalence of health outcomes significantly increased as pesticide use and risk increased. For males the results of the correlation analyses indicated that treatment prevalence for cancer, conditions originating in the perinatal period, congenital anomalies, and disorders of the eye increased significantly as pesticide use or risk increased (Table 31). For females the treatment prevalence for conditions originating in the perinatal period and disorders of the eye increased significantly as pesticide use or risk increased (Table 32).

Table 31: Spearman Correlations between Pesticide and Health Indicators for Males (p-values in parentheses)

	Average annualized percent of CCS land acreage where any pesticide applied	Average annualized percent of CCS land acreage where herbicides applied	Average annualized percent of CCS land acreage where insecti-cides applied	Average annualized percent of CCS land acreage where fungicides applied	Pesticide risk
Overall mortality	-0.18 (0.06)	-0.17 (0.07)	-0.07 (0.49)	-0.15 (0.11)	-0.11 (0.26)
Premature mortality	**-0.28 (<0.01)**	**-0.26 (<0.01)**	-0.13 (0.17)	**-0.28 (<0.01)**	**-0.22 (0.02)**
Cancer	**0.28 (<0.01)**	**0.26 (<0.01)**	**0.25 (<0.01)**	**0.23 (0.01)**	**0.20 (0.03)**
Cancer in young children	0.06 (0.56)	0.03 (0.72)	0.08 (0.40)	0.11 (0.25)	0.14 (0.14)

Complications of pregnancy, childbirth, and the puerperium	N/A	N/A	N/A	N/A	N/A
Spontaneous abortion	N/A	N/A	N/A	N/A	N/A
Conditions originating in the perinatal period	0.05 (0.59)	0.06 (0.52)	**0.23 (0.01)**	0.0002 (0.99)	0.02 (0.83)
Congenital anomalies	**0.20 (0.04)**	**0.18 (0.05)**	**0.23 (0.01)**	0.18 (0.06)	0.18 (0.06)
Diseases of the blood and blood-forming organs	-0.14 (0.14)	-0.14 (0.13)	-0.14 (0.15)	-0.11 (0.24)	-0.09 (0.32)
Diseases of the circulatory system	**-0.21 (0.03)**	**-0.19 (0.04)**	-0.11 (0.25)	-0.17 (0.07)	-0.10 (0.27)
Diseases of the digestive system	-0.18 (0.06)	-0.17 (0.07)	0.02 (0.80)	-0.16 (0.09)	-0.09 (0.34)
Diseases of the genitourinary system	-0.09 (0.32)	-0.08 (0.37)	0.0003 (0.99)	-0.14 (0.13)	-0.09 (0.34)
Diseases of the musculoskeletal system and connective tissue	-0.004 (0.97)	0.0002 (0.99)	-0.15 (0.11)	0.02 (0.83)	-0.05 (0.61)
Diseases of the nervous system	-0.16 (0.09)	-0.16 (0.09)	**-0.26 (<0.01)**	-0.11 (0.24)	-0.15 (0.11)
Disease of the respiratory system	-0.09 (0.35)	-0.07 (0.47)	0.03 (0.72)	-0.12 (0.19)	-0.08 (0.37)
Diseases of the skin and subcutaneous tissue	-0.13 (0.16)	-0.14 (0.12)	-0.17 (0.07)	-0.08 (0.38)	-0.06 (0.55)
Disorders of the eye	**0.54 (<0.0001)**	**0.54 (<0.0001)**	**0.56 (<0.0001)**	**0.49 (<0.0001)**	**0.47 (<0.0001)**
Endocrine, nutritional and metabolic diseases, and immunity disorders	-0.07 (0.46)	-0.07 (0.46)	0.02 (0.82)	-0.08 (0.38)	-0.10 (0.31)

Ill-defined conditions	-0.006 (0.95)	-0.02 (0.80)	-0.07 (0.47)	0.06 (0.53)	0.07 (0.45)
Infectious and parasitic disease	0.02 (0.82)	0.03 (0.77)	-0.01 (0.91)	0.04 (0.69)	0.03 (0.79)
Injury and poisoning	-0.02 (0.83)	-0.01 (0.88)	0.09 (0.33)	-0.02 (0.84)	0.02 (0.83)
Cumulative mental illnesses	-0.10 (0.30)	-0.09 (0.35)	**-0.21 (0.03)**	-0.12 (0.19)	-0.16 (0.09)
Dementia	-0.04 (0.63)	-0.05 (0.63)	-0.05 (0.61)	-0.08 (0.42)	-0.11 (0.24)
Depression	-0.03 (0.78)	-0.01 (0.88)	-0.12 (0.20)	-0.11 (0.24)	-0.09 (0.32)

Note. Correlations with p-values of 0.05 and below in bold.

Table 32: Spearman Correlations between Pesticide and Health Indicators for Females (p-values in parentheses)

	Average annualized percent of CCS land acreage where any pesticide applied	Average annualized percent of CCS land acreage where herbicides applied	Average annualized percent of CCS land acreage where insecti-cides applied	Average annualized percent of CCS land acreage where fungicides applied	Pesticide risk
Overall mortality	**-0.28 (<0.01)**	**-0.29 (<0.01)**	**-0.18 (0.05)**	**-0.23 (0.01)**	-0.13 (0.16)
Premature mortality	**-0.33 (<0.001)**	**-0.32 (<0.001)**	**-0.20 (0.03)**	**-0.28 (<0.01)**	**-0.21 (0.02)**
Cancer	0.10 (0.27)	0.10 (0.29)	0.04 (0.65)	0.04 (0.66)	0.01 (0.95)
Cancer in young children	0.11 (0.25)	0.10 (0.31)	0.07 (0.48)	0.14 (0.14)	0.15 (0.12)

Complications of pregnancy, childbirth, and the puerperium	-0.13 (0.18)	-0.13 (0.16)	-0.08 (0.37)	-0.10 (0.30)	-0.12 (0.22)
Spontaneous abortion	-0.10 (0.29)	-0.10 (0.27)	-0.08 (0.40)	-0.08 (0.41)	-0.11 (0.24)
Conditions originating in the perinatal period	0.02 (0.81)	0.03 (0.74)	**0.19 (0.04)**	-0.06 (0.56)	-0.003 (0.98)
Congenital anomalies	-0.04 (0.68)	-0.04 (0.69)	0.02 (0.82)	-0.06 (0.53)	0.01 (0.93)
Diseases of the blood and blood-forming organs	**-0.19 (0.04)**	-0.18 (0.06)	-0.05 (0.57)	**-0.22 (0.02)**	-0.16 (0.08)
Diseases of the circulatory system	**-0.30 (<0.01)**	**-0.27 (<0.01)**	-0.14 (0.13)	**-0.36 (<0.0001)**	**-0.27 (<0.01)**
Diseases of the digestive system	**-0.42 (<0.0001)**	**-0.41 (<0.0001)**	**-0.21 (0.02)**	**-0.41 (<0.0001)**	**-0.29 (<0.01)**
Diseases of the genitourinary system	**-0.20 (0.03)**	**-0.20 (0.03)**	-0.17 (0.07)	**-0.22 (0.02)**	**-0.22 (0.02)**
Diseases of the musculoskeletal system and connective tissue	**-0.19 (0.04)**	**-0.18 (0.05)**	-0.13 (0.17)	**-0.19 (0.04)**	-0.18 (0.06)
Diseases of the nervous system	-0.08 (0.42)	-0.07 (0.44)	-0.15 (0.10)	-0.06 (0.54)	-0.07 (0.47)
Disease of the respiratory system	**-0.24 (0.01)**	**-0.21 (0.02)**	-0.10 (0.29)	**-0.28 (<0.01)**	**-0.27 (<0.01)**
Diseases of the skin and subcutaneous tissue	-0.13 (0.15)	-0.13 (0.16)	-0.16 (0.09)	-0.12 (0.19)	-0.14 (0.15)
Disorders of the eye	**0.26 (<0.01)**	**0.27 (<0.01)**	**0.35 (<0.001)**	**0.23 (0.02)**	**0.21 (0.02)**
Endocrine, nutritional and metabolic diseases, and	**-0.44 (<0.0001)**	**-0.41348 (<0.0001)**	**-0.28 (<0.01)**	**-0.47 (<0.0001)**	**-0.42 (<0.0001)**

immunity disorders					
Ill-defined conditions	**-0.22 (0.02)**	**-0.23 (0.01)**	**-0.21 (0.03)**	-0.16 (0.08)	-0.13 (0.16)
Infectious and parasitic disease	-0.12 (0.20)	-0.11 (0.25)	-0.14 (0.13)	-0.11 (0.24)	-0.10 (0.29)
Injury and poisoning	**-0.22 (0.02)**	**-0.21 (0.02)**	-0.04 (0.68)	**-0.23 (0.01)**	-0.15 (0.12)
Cumulative mental illnesses	-0.15 (0.11)	-0.15 (0.12)	**-0.20 (0.03)**	-0.18 (0.06)	-0.14 (0.14)
Dementia	-0.04 (0.67)	-0.06 (0.52)	-0.04 (0.66)	-0.04 (0.69)	-0.01 (0.90)
Depression	-0.10 (0.29)	-0.11 (0.26)	-0.14 (0.14)	-0.13 (0.16)	-0.08 (0.42)

Note. Correlations with p-values of 0.05 and below in bold.

The treatment prevalence of various health indicators significantly decreased as pesticide use or risk increased. For females this was the case for many health outcomes including: overall mortality, premature mortality, diseases of the blood and blood-forming organs, diseases of the circulatory system, diseases of the digestive system, diseases of the genitourinary system, diseases of the musculoskeletal system and connective tissue, disease of the respiratory system, ill-defined conditions, injury and poisoning, cumulative mental illnesses, as well as endocrine, nutritional and metabolic diseases and immunity disorders (Table 32). For males a similar statistically significant inverse correlation was observed for premature mortality, diseases of the circulatory system, diseases of the nervous system, and cumulative mental illnesses (Table 31). It is possible that these inverse relationships were due to higher income areas using more pesticides, as higher

income areas generally have less health concerns. Accordingly, income needed to be controlled for in the analytical analyses.

5.3. Analytical Results

The purpose of the study was to focus upon potential adverse health effects of agricultural pesticide use and risk. In the exploratory stage of the analysis, age-adjusted and sex-disaggregated health outcomes were correlated with the pesticide indicators but no other potential confounders were accounted for. The next stage of the analysis employed multilevel models to examine the influence of selected CCS-level pesticide indicators on individual health outcomes controlling for age and income (models were sex-disaggregated). In doing so any bias due to wealthier areas using more pesticides, and also being healthier, would be controlled for.

The number of pesticide indicators used in the multilevel models was delimited based on the results of the exploratory correlations. It was decided that the pesticide indicators focusing on herbicides and fungicides would not be used in this analytical stage of the study, as their pattern of correlations with the health outcomes was extremely similar to that of the any pesticide indicator (Tables 31 and 32). Although the pesticide risk indicator also had a similar pattern of correlations, it was employed in the analytical stage in order to determine its value compared to the simpler measures of pesticide use. The insecticide indicator appeared to have a different pattern of correlations with the health indicators than the other indicators of pesticide use, and was therefore retained in the analytical analyses.

All of the statistically significant correlations in the exploratory analyses involving the average annualized percent of CCS land acreage where any pesticide applied, the average

annualized percent of CCS land acreage where insecticides applied, or pesticide risk that highlighted a potential adverse effect on health, the focus of this study, were further examined in multilevel models (Table 33). As noted, the treatment prevalence of various health indicators significantly decreased as pesticide use and risk increased. As following up on potential effects of this nature was not the original focus of the study, only one example combination was chosen for multilevel modeling in order to determine how such an association responded to controlling for other confounders. The combination of the average annualized percent of CCS land acreage where any pesticide was applied with diseases of the circulatory system was chosen, as it was one of the only pairings that was significantly correlated for both males and females (Tables 31 and 32).

Table 33: Combinations of Health Outcomes and Pesticide Indicators Examined in Multilevel Models

Health outcome	**Pesticide indicator**
Males	
Cancer	Average annualized percent of CCS land acreage where any pesticide applied
Cancer	Average annualized percent of CCS land acreage where insecticides applied
Cancer	Pesticide risk
Conditions originating in the perinatal period	Average annualized percent of CCS land acreage where insecticides applied
Congenital anomalies	Average annualized percent of CCS land acreage where any pesticide applied
Congenital anomalies	Average annualized percent of CCS land acreage where insecticides applied
Disorders of the eye	Average annualized percent of CCS land acreage where any pesticide applied
Disorders of the eye	Average annualized percent of CCS land acreage where insecticides applied

Disorders of the eye	Pesticide risk
Diseases of the circulatory system	Average annualized percent of CCS land acreage where any pesticide applied
Females	
Conditions originating in the perinatal period	Average annualized percent of CCS land acreage where insecticides applied
Disorders of the eye	Average annualized percent of CCS land acreage where any pesticide applied
Disorders of the eye	Average annualized percent of CCS land acreage where insecticides applied
Disorders of the eye	Pesticide risk
Diseases of the circulatory system	Average annualized percent of CCS land acreage where any pesticide applied

5.3.1. Cancer in Males

The ecological age-adjusted 4-year period prevalence of cancer in males was significantly correlated at the ecological level with the indicators of average annualized percent of CCS land acreage where any pesticide applied, average annualized percent of CCS land acreage where insecticides applied, and pesticide risk. Table 34 outlines the results of the null model, the model with only level-1 predictors, and a full model for each pesticide indicator.

Table 34: Multilevel Model Results for Cancer in Males Ages Five and Older (N=154,785)

	Null	Level-1 predictors	Level-2 predictors: Any pesticide	Level-2 predictors: Insecticides	Level-2 predictors: Pesticide risk
Intercept (γ_{00})	-1.932 (0.021) $p < 0.001$	-2.197 (0.017) $p < 0.001$	-2.199 (0.018) $p < 0.001$	-2.198 (0.018) $p < 0.001$	-2.196 (0.018) $p < 0.001$
Income	---	0.006 (0.001) $p < 0.001$	0.006 (0.001) $p < 0.001$	0.006 (0.001) $p < 0.001$	0.006 (0.001) $p < 0.001$
Age ≤ 50	---	-1.375 (0.029) $p < 0.001$	-1.376 (0.029) $p < 0.001$	-1.376 (0.029) $p < 0.001$	-1.375 (0.029) $p < 0.001$
Age ≥ 75	---	0.847 (0.023) $p < 0.001$	0.847 (0.023) $p < 0.001$	0.847 (0.023) $p < 0.001$	0.848 (0.023) $p < 0.001$
Any Pesticide	---	---	0.00032 (0.00029) $p = 0.266$	---	---
Insecticides	---	---	---	0.010 (0.007) $p = 0.127$	---
Pesticide risk	---	---	---	---	-0.007 (0.018) $p = 0.689$
Variance of random intercept (μ_{0j})	0.04556 $p < 0.001$	0.01215 $p < 0.001$	0.01153 $p < 0.001$	0.01141 $p < 0.001$	0.01193 $p < 0.001$
Variance of random slope for income (μ_{1j})	---	0.00003 $p < 0.001$	0.00003 $p < 0.001$	0.00003 $p < 0.001$	0.00003 $p < 0.001$

Number of estimated parameters	2	7	8	8	8

Note. Coefficients with standard errors in parentheses, followed by p-values. Significant differences ($p<0.0005$) between null model (deviance = 438,832.3) and all models with level-2 predictors. Deviance difference: any pesticide = 490, insecticide = 479.8, pesticide risk = 489.8; $\chi^2_{0.0005, q=6} = 25.23$. All pesticide variables, other than pesticide risk, represent the average annualized percent of CCS land acreage where the pesticide type was applied.

Table 35 provides the odds ratios, and their confidence intervals, based on the coefficients provided in the models in Table 34 that include level-2 predictors. The odds ratios for the pesticide measures represent the change in odds based on a one-unit increase in the pesticide measure; none were significant. Therefore, the odds of having cancer were related to age and income but not to pesticides.

Table 35: Odds Ratios with Confidence Intervals from Multilevel Model Results for Cancer in Males Ages Five and Older

Pesticide measure	**Age**	**Income**	**Pesticide measure**
Any pesticide	Age ≤ 50: **0.253 (0.239-0.267)** Age ≥ 75: **2.334 (2.230-2.442)**	**1.006 (1.004-1.008)**	1.000 (1.000-1.001)
Insecticides	Age ≤ 50: **0.253 (0.239-0.267)** Age ≥ 75: **2.333 (2.229-2.441)**	**1.006 (1.004-1.008)**	1.010 (0.997-1.024)
Pesticide risk	Age ≤ 50: **0.253 (0.239-0.268)** Age ≥ 75: **2.334 (2.231-2.442)**	**1.006 (1.004-1.008)**	0.993 (0.857-1.029)

Note: Statistically significant results in bold. All pesticide variables, other than pesticide risk, represent the average annualized percent of CCS land acreage where the pesticide type was applied.

Table 36 presents the probabilities of males age five and older being diagnosed with cancer over the four year study period. The probability of the average individual is reported as well as the probabilities for individuals who differ from the average in either a one-unit increase or a one standard deviation increase in the pesticide measures. Emphasizing the lack of statistical association between pesticides and cancer in males, differences in pesticide use and risk did not change the probability of males having cancer.

Table 36: Probabilities Based on Multilevel Model Results for Cancer in Males Ages Five and Older

	Probability of diagnosis with cancer in males of average income and age who live in CCSs with:		
Pesticide measure	**Average value of pesticide measure**	**Value of pesticide measure one unit greater than average**	**Value of pesticide measure one standard deviation greater than average**
Any pesticide	0.100	0.100	0.101
Insecticides	0.100	0.101	0.102
Pesticide risk	0.100	0.099	0.099

Note: All pesticide variables, other than pesticide risk, represent the average annualized percent of CCS land acreage where the pesticide type was applied. The standard deviations of the pesticide measures are 49 % for any pesticide, 2 % for insecticides, and 0.98 for pesticide risk.

5.3.2. Conditions Originating in the Perinatal Period in Males

The ecological age-adjusted 4-year period prevalence of conditions originating in the perinatal period in males was significantly correlated at the ecological level with the

indicator of average annualized percent of CCS land acreage where insecticides applied. Table 37 outlines the results of the null model, the model with only level-1 predictors, and a full model that includes the insecticide indicator. Results for income based on Laplace estimation differed; larger standard errors (0.003) resulted in results that were not significant (p=0.096 for the model with level-1 predictors and p=0.058 for the model with level-2 predictors).

Table 37: Multilevel Model Results for Conditions Originating in the Perinatal Period in Males Under Five Years of Age (N=8,947)

	Null	**Level-1 predictors**	**Level-2 predictors: Insecticides**
Intercept (γ_{00})	-0.688 (0.054) p < 0.001	-0.710 (0.053) p < 0.001	-0.722 (0.050) p < 0.001
Income	---	-0.006 (0.002) p = 0.013	-0.006 (0.002) p = 0.007
Insecticides	---	---	0.073 (0.025) p = 0.005
Variance of random intercept (μ_{0j})	0.23462 p < 0.001	0.20956 p < 0.001	0.18731 p < 0.001
Number of estimated parameters	2	3	4

Note. Coefficients with standard errors in parentheses, followed by p-values. Significant difference ($0.01<p<0.025$) between null model (deviance = 25,414.1) and model with level-2 predictor. Deviance difference: insecticide = 7.5; $\chi^2_{0.025, 2} = 7.378$. Insecticide indicator represents the average annualized percent of CCS land acreage where insecticides were applied.

Based on the model including insecticides in Table 37, the odds ratios (and confidence intervals) for income and the insecticides indicator were 0.994 (0.989-0.998) and 1.076 (1.023-1.131), respectively. Therefore, a one percent increase in the average annualized percent of CCS land acreage where insecticides were applied significantly increased the odds, for males under five year of age, of being diagnosed with a condition originating in the perinatal period by 7.6%. For an increase in insecticide application of two percent, the standard deviation, the odds ratio is 1.157, resulting in a 15.7% increase in the odds.

The probability of diagnosis with a condition originating in the perinatal period in males under five years of age of average income who live in CCSs with average insecticide use is 32.7%. For a similar individual who only differs by living in a CCS with a one percent greater average annualized percent of CCS land acreage where insecticides were applied the probability is 34.3%. A two percent (standard deviation) increase in insecticide use results in a probability of 36.0%, an increase of over 3%.

5.3.3. Congenital Anomalies in Males

The ecological age-adjusted 4-year period prevalence of congenital anomalies in males was significantly correlated at the ecological level with the indicators of average annualized percent of CCS land acreage where any pesticide applied and average annualized percent of CCS land acreage where insecticides applied. Table 38 outlines the results of the null model, the model with only level-1 predictors, and a full model for each pesticide indicator.

Table 38: Multilevel Model Results for Congenital Anomalies in Males Under Five Years of Age (N=8,947)

	Null	Level-1 predictors	Level-2 predictors: Any pesticide	Level-2 predictors: Insecticides
Intercept (γ_{00})	-2.013 (0.037) p < 0.001	-2.011 (0.036) p < 0.001	-2.012 (0.035) p < 0.001	-2.015 (0.035) p < 0.001
Income	---	0.003 (0.002) p = 0.252	0.003 (0.002) p = 0.270	0.003 (0.002) p = 0.160
Any pesticide	---	---	0.0002 (0.0007) p = 0.779	---
Insecticides	---	---	---	0.0419 (0.020) p = 0.038
Variance of random intercept (μ_{0j})	0.01955 p = 0.051	0.02161 p = 0.233	0.02092 p = 0.203	0.02013 p = 0.189
Variance of random slope for income (μ_{1j})	---	0.00552 p = 0.167	0.00003 p = 0.167	0.00003 p = 0.205
Number of estimated parameters	2	5	6	6

Note. Coefficients with standard errors in parentheses, followed by p-values. Significant differences between null model (deviance = 25,312.7) and all models with level-2 predictors. Deviance difference: any pesticide = 20.2 ($0.0005<p<0.001$), insecticide = 16.8 ($0.0025<p<0.005$); $\chi^2_{0.005, q=4} = 15.97$; $\chi^2_{0.001, q=4} = 19.69$. Pesticide variables represent the average annualized percent of CCS land acreage where the pesticide type was applied.

Table 39 provides the odds ratios, and their confidence intervals, based on the coefficients provided in the models in Table 38 that include level-2 predictors. The odds ratios for the pesticide measures represent the change in odds based on a one unit increase in the pesticide measure. The indicator of any pesticide use was not significant, however, a one percent increase in the average annualized percent of CCS land acreage where insecticides were applied significantly increased the odds, for males under five years of age, of being diagnosed with a congenital anomaly by 4.3%. For an increase in insecticide application of two percent, the standard deviation, the odds ratio is 1.087, resulting in an 8.7% increase in the odds.

Table 39: Odds Ratios with Confidence Intervals from Multilevel Model Results for Congenital Anomalies in Males Under Five Years of Age

Pesticide measure	**Income**	**Pesticide measure**
Any pesticide	1.003 (0.998-1.007)	1.000 (0.999-1.002)
Insecticides	1.003 (0.999-1.008)	**1.043 (1.002-1.085)**

Note: Statistically significant results in bold. Pesticide variables represent the average annualized percent of CCS land acreage where the pesticide type was applied.

Table 40 presents the probabilities of males under age five being diagnosed with congenital anomalies over the four-year study period. The probability of the average individual is reported as well as the probabilities for individuals who differ from the average in either a one-unit increase or a one standard deviation increase in the pesticide measures. Although insecticide use was significantly associated with congenital anomalies in males, the corresponding increase in probabilities is relatively small (approximately 1%) for a standard deviation increase in the use of insecticides.

Table 40: Probabilities Based on Multilevel Model Results for Congenital Anomalies in Males Under Five Years of Age

	Probability of diagnosis with a congenital anomaly in males under age five of average income who live in CCSs with:		
Pesticide measure	**Average value of pesticide measure**	**Value of pesticide measure one unit greater than average**	**Value of pesticide measure one standard deviation greater than average**
Any pesticide	0.118	0.118	0.119
Insecticides	0.118	0.122	0.127

Note: Pesticide variables represent the average annualized percent of CCS land acreage where the pesticide type was applied. The standard deviations of the pesticide measures are 49 % for any pesticide and 2 % for insecticides.

5.3.4. Disorders of the Eye in Males

The ecological age-adjusted 4-year period prevalence of disorders of the eye in males was significantly correlated at the ecological level with the indicators of average annualized percent of CCS land acreage where any pesticide applied, average annualized percent of CCS land acreage where insecticides applied, and pesticide risk. Table 41 outlines the results of the null model, the model with only level-1 predictors, and a full model for each pesticide indicator.

Table 41: Multilevel Model Results for Disorders of the Eye in Males (N=163,732)

	Null	Level-1 predictors	Level-2 predictors: Any pesticide	Level-2 predictors: Insecticides	Level-2 predictors: Pesticide risk
Intercept (γ_{00})	-0.614 (0.016) $p < 0.001$	-0.666 (0.014) $p < 0.001$	-0.671 (0.014) $p < 0.001$	-0.669 (0.014) $p < 0.001$	-0.674 (0.013) $p < 0.001$
Income	---	0.001 (0.001) $p = 0.372$	0.0003 (0.001) $p = 0.757$	0.0009 (0.001) $p = 0.404$	0.0003 (0.0009) $p = 0.738$
Age	---	-0.088 (0.002) $p < 0.001$	-0.088 (0.002) $p < 0.001$	-0.088 (0.002) $p < 0.001$	-0.088 (0.002) $p < 0.001$
Age squared	---	0.001 (0.00002) $p < 0.001$	0.001 (0.00002) $p < 0.001$	0.001 (0.00002) $p < 0.001$	0.001 (0.00002) $p < 0.001$
Any pesticide	---	---	0.0014 (0.0003) $p < 0.001$	---	---
Insecticides	---	---	---	0.0338 (0.0065) $p < 0.001$	---
Pesticide risk	---	---	---	---	0.0579 (0.0118) $p < 0.001$
Variance of random intercept (μ_{0j})	0.02345 $p < 0.001$	0.01485 $p < 0.001$	0.01235 $p < 0.001$	0.01205 $p < 0.001$	0.01272 $p < 0.001$
Variance of random slope for income (μ_{1j})	---	0.00004 $p < 0.001$	0.00004 $p < 0.001$	0.00004 $p < 0.001$	0.00003 $p < 0.001$

Number of estimated parameters	2	7	8	8	8

Note. Coefficients with standard errors in parentheses, followed by p-values. Significant differences ($p<0.0005$) between null model (deviance = 464,733.6) and all models with level-2 predictors. Deviance difference: any pesticide = 1,639, insecticide = 1,641.9, pesticide risk = 1,640.5; $\chi^2_{0.0005, q=6} = 25.23$. All pesticide variables, other than pesticide risk, represent the average annualized percent of CCS land acreage where the pesticide type was applied.

Table 42 provides the odds ratios, and their confidence intervals, based on the coefficients provided in the models in Table 41 that include level-2 predictors. The odds ratios for the pesticide measures represent the change in odds based on a one-unit increase in the pesticide measure; all were significant.

Table 42: Odds Ratios with Confidence Intervals from Multilevel Model Results for Disorders of the Eye in Males

Pesticide measure	**Age**	**Income**	**Pesticide measure**
Any pesticide	Age: **0.916 (0.913-0.919)** Age-Squared: **1.001 (1.001-1.001)**	1.000 (0.998-1.002)	**1.001 (1.001-1.002)**
Insecticides	Age: **0.916 (0.913-0.919)** Age-Squared: **1.001 (1.001-1.001)**	1.001 (0.999-1.003)	**1.034 (1.021-1.048)**
Pesticide risk	Age: **0.916 (0.913-0.919)** Age-Squared: **1.001 (1.001-1.001)**	1.000 (0.998-1.002)	**1.060 (1.035-1.084)**

Note: Statistically significant results in bold. All pesticide variables, other than pesticide risk, represent the average annualized percent of CCS land acreage where the pesticide type was applied.

Table 43 presents the probabilities of males being diagnosed with disorders of the eye over the four-year study period. The probability of the average individual is reported as well as the probabilities for individuals who differ from the average in either a one-unit increase or a one standard deviation increase in the pesticide measures.

Table 43: Probabilities based on Multilevel Model Results for Disorders of the Eye in Males

	Probability of diagnosis with a disorder of the eye in males of average income and age who live in CCSs with:		
Pesticide measure	**Average value of pesticide measure**	**Value of pesticide measure one unit greater than average**	**Value of pesticide measure one standard deviation greater than average**
Any pesticide	0.338	0.339	0.354
Insecticides	0.339	0.346	0.354
Pesticide risk	0.338	0.351	0.350

Note: All pesticide variables, other than pesticide risk, represent the average annualized percent of CCS land acreage where the pesticide type was applied. The standard deviations of the pesticide measures are 49 % for any pesticide, 2 % for insecticides, and 0.98 for pesticide risk.

5.3.5. Diseases of the Circulatory System in Males

The ecological age-adjusted 4-year period prevalence of diseases of the circulatory system in males was significantly and inversely correlated at the ecological level with the indicator of average annualized percent of CCS land acreage where any pesticide applied. This multilevel model tested the inverse relationship between the use of any pesticide and male circulatory diseases in order to determine whether it persisted after controlling for

income and age. Table 44 outlines the results of the null model, the model with only level-1 predictors, and a full model that includes the any pesticide indicator.

Table 44: Multilevel Model Results for Diseases of the Circulatory System in Males (N=163,732)

	Null	**Level-1 predictors**	**Level-2 predictors: Any pesticide**
Intercept (γ_{00})	-1.229 (0.021) $p < 0.001$	-1.819 (0.014) $p < 0.001$	-1.816 (0.014) $p < 0.001$
Income	---	-0.0006 (0.001) $p = 0.551$	-0.0003 (0.001) $p = 0.768$
Age	---	0.062 (0.0005) $p < 0.001$	0.062 (0.0005) $p < 0.001$
Any pesticide	---	---	-0.0006 (0.0003) $p = 0.014$
Variance of random intercept (μ_{0j})	0.04617 $p < 0.001$	0.01009 $p < 0.001$	0.00866 $p < 0.001$
Number of estimated parameters	2	4	5

Note. Coefficients with standard errors in parentheses, followed by p-values. Significant difference ($p<0.001$) between null model (deviance = 464,617.8) and model with level-2 predictor. Deviance difference: any pesticide = 4,713.9; $\chi^2_{0.001,\,3} = 16.266$. Any pesticide indicator represents the average annualized percent of CCS land acreage where any pesticide was applied.

Table 45 provides the odds ratios, and their confidence intervals, based on the coefficients provided in the model in Table 44 that include the level-2 predictor. The odds ratios for the any pesticide measure represent the change in odds based on a one unit increase in the pesticide measure; it was significant but only slightly different than unity.

Table 45: Odds Ratios with Confidence Intervals from Multilevel Model Results for Diseases of the Circulatory System in Males

Pesticide measure	Age	Income	Pesticide measure
Any pesticide	**1.064 (1.064-1.065)**	1.000 (0.998-1.002)	**0.999 (0.999-1.000)**

Note: Statistically significant results in bold. Any pesticide indicator represents the average annualized percent of CCS land acreage where any pesticide was applied.

Table 46 presents the probabilities of males being diagnosed with diseases of the circulatory system over the four-year study period. The probability of the average individual is reported as well as the probabilities for individuals who differ from the average in either a one-unit increase or a one standard deviation increase in the pesticide measures. The use of pesticides had an extremely small effect on the probability of circulatory diseases, even a 49% increase (the standard deviation) in the acreage of the CCS where pesticides were applied only resulted in a 0.4% decrease in male circulatory diseases.

Table 46: Probabilities based on Multilevel Model Results for Diseases of the Circulatory System in Males

	Probability of diagnosis with cancer in males of average income and age who live in CCSs with:		
Pesticide measure	**Average value of pesticide measure**	**Value of pesticide measure one unit greater than average**	**Value of pesticide measure one standard deviation greater than average**
Any pesticide	0.140	0.140	0.136

Note: Any pesticide indicator represents the average annualized percent of CCS land acreage where the any pesticide type was applied. The standard deviation of the any pesticide measures is 49 %.

5.3.6. Conditions Originating in the Perinatal Period in Females

The ecological age-adjusted 4-year period prevalence of conditions originating in the perinatal period in females was significantly correlated at the ecological level with the indicator of average annualized percent of CCS land acreage where insecticides applied. Table 47 outlines the results of the null model, the model with only level-1 predictors, and a full model that includes the insecticide indicator.

Table 47: Multilevel Model Results for Conditions Originating in the Perinatal Period in Females Under Five Years of Age (N=8,608)

	Null	**Level-1 predictors**	**Level-2 predictors: Insecticides**
Intercept (γ_{00})	-0.791 (0.054) $p < 0.001$	-0.826 (0.052) $p < 0.001$	-0.829 (0.049) $p < 0.001$
Income	---	-0.010 (0.003) $p = 0.001$	-0.010 (0.003) $p = 0.001$
Insecticides	---	---	0.0677 (0.0263) $p = 0.010$
Variance of random intercept (μ_{0j})	0.22871 $p < 0.001$	0.19849 $p < 0.001$	0.18237 $p < 0.001$
Number of estimated parameters	2	3	4

Note. Coefficients with standard errors in parentheses, followed by p-values. Significant difference ($0.025<p<0.05$) between null model (deviance = 24,437.6) and model with level-2 predictor. Deviance difference: insecticide = 7.2; $\chi^2_{0.05, 2} = 5.991$. The insecticides measure represents the average annualized percent of CCS land acreage where insecticides were applied.

Based on the model including insecticides in Table 47, the odds ratios (and confidence intervals) for income and the insecticides indicator were 0.990 (0.984-0.996) and 1.070 (1.016-1.127), respectively. Therefore, a one percent increase in the average annualized percent of CCS land acreage where insecticides were applied significantly increased the odds, for females under five year of age, of being diagnosed with a condition originating in the perinatal period by 7.0%. For an increase in insecticide application of two

percent, the standard deviation, the odds ratio is 1.145, resulting in a 14.5% increase in the odds.

The probability of diagnosis with a condition originating in the perinatal period in females under five years of age of average income who live in CCSs with average insecticide use is 30.4%. For a similar individual who only differs by living in a CCS with a one percent greater average annualized percent of CCS land acreage where insecticides were applied the probability is 31.8%. A two percent (standard deviation) increase in insecticide use results in a probability of 33.3%, an increase of almost 3%.

5.3.7. Disorders of the Eye in Females

The ecological age-adjusted 4-year period prevalence of disorders of the eye in females was significantly correlated at the ecological level with indicators of the average annualized percent of CCS land acreage where any pesticide applied, the average annualized percent of CCS land acreage where insecticides applied, and pesticide risk. Table 48 outlines the results of the null model, the model with only level-1 predictors, and a full model for each pesticide indicator. With Laplace estimation the standard error of the coefficient for pesticide risk increases to 0.017, resulting in a higher p-value of 0.187.

Table 48: Multilevel Model Results for Disorders of the Eye in Females (N=159,508)

	Null	Level-1 predictors	Level-2 predictors: Any pesticide	Level-2 predictors: Insecticides	Level-2 predictors: Pesticide risk
Intercept (γ_{00})	-0.317 (0.016) $p < 0.001$	-0.378 (0.014) $p < 0.001$	-0.381 (0.014) $p < 0.001$	-0.382 (0.014) $p < 0.001$	-0.382 (0.014) $p < 0.001$
Income	---	0.0005 (0.001) $p = 0.684$	0.0002 (0.001) $p = 0.889$	0.0003 (0.0012) $p = 0.805$	0.0002 (0.001) $p = 0.841$
Age ≤ 20	---	1.409 (0.023) $p < 0.001$	1.409 (0.023) $p < 0.001$	1.409 (0.023) $p < 0.001$	1.409 (0.023) $p < 0.001$
Age ≥ 65	---	1.830 (0.023) $p < 0.001$	1.830 (0.023) $p < 0.001$	1.830 (0.023) $p < 0.001$	1.830 (0.023) $p < 0.001$
Any pesticide	---	---	0.0005 (0.0003) $p = 0.131$	---	---
Insecticides	---	---	---	0.0183 (0.0073) $p = 0.012$	---
Pesticide risk	---	---	---	---	0.0229 (0.013) $p = 0.075$
Variance of random intercept (μ_{0j})	0.02437 $p < 0.001$	0.01209 $p < 0.001$	0.01195 $p < 0.001$	0.01125 $p < 0.001$	0.01191 $p < 0.001$
Variance of random slope for income (μ_{1j})	---	0.00006 $p < 0.001$	0.00006 $p < 0.001$	0.00006 $p < 0.001$	0.00006 $p < 0.001$

Number of estimated parameters	2	7	8	8	8

Note. Coefficients with standard errors in parentheses, followed by p-values. Significant differences ($p<0.0005$) between null model (deviance = 452,783.4) and all models with level-2 predictors. Deviance difference: any pesticide = 47.6, insecticide = 48.8, pesticide risk = 48.1; $\chi^2_{0.0005, q=6} = 25.23$. All pesticide variables, other than pesticide risk, represent the average annualized percent of CCS land acreage where the pesticide type was applied.

Table 49 provides the odds ratios, and their confidence intervals, based on the coefficients provided in the models in Table 48 that include level-2 predictors. The odds ratios for the pesticide measures represent the change in odds based on a one unit increase in the pesticide measure; insecticides had a significant effect but the measures of pesticide risk and any pesticide use did not.

Table 49: Odds Ratios with Confidence Intervals from Multilevel Model Results for Disorders of the Eye in Females

Pesticide measure	**Age**	**Income**	**Pesticide measure**
Any pesticide	Age ≤ 20: **4.093 (3.916-4.279)** Age ≥ 65: **6.235 (5.962-6.522)**	1.000 (0.998-1.003)	1.000 (1.000-1.001)
Insecticides	Age ≤ 20: **4.094 (3.917-4.279)** Age ≥ 65: **6.236 (5.962-6.522)**	1.000 (0.998-1.003)	**1.018 (1.004-1.033)**
Pesticide risk	Age ≤ 20: **4.094 (3.916-4.279)** Age ≥ 65: **6.235 (5.961-6.521)**	1.000 (0.998-1.003)	1.023 (0.998-1.049)

Note: Statistically significant results in bold. All pesticide variables, other than pesticide risk, represent the average annualized percent of CCS land acreage where the pesticide type was applied.

Table 50 presents the probabilities of females being diagnosed with disorders of the eye over the four-year study period. The probability of the average individual is reported as well as the probabilities for individuals who differ from the average in either a one-unit increase or a one standard deviation increase in the pesticide measures. Although insecticide use was significantly associated with eye disorders in males, the corresponding increase in probabilities is relatively small (0.8%) for a standard deviation increase in the use of insecticides.

Table 50: Probabilities based on Multilevel Model Results for Disorders of the Eye in Females

	Probability of diagnosis with a disorder of the eye in females of average income and age who live in CCSs with:		
Pesticide measure	**Average value of pesticide measure**	**Value of pesticide measure one unit greater than average**	**Value of pesticide measure one standard deviation greater than average**
Any pesticide	0.406	0.406	0.412
Insecticides	0.406	0.410	0.414
Pesticide risk	0.406	0.411	0.411

Note: All pesticide variables, other than pesticide risk, represent the average annualized percent of CCS land acreage where the pesticide type was applied. The standard deviations of the pesticide measures are 49 % for any pesticide, 2 % for insecticides, and 0.98 for pesticide risk.

5.3.8. Diseases of the Circulatory System in Females

The ecological age-adjusted 4-year period prevalence of diseases of the circulatory system in females was significantly and inversely correlated at the ecological level with

the indicator of average annualized percent of CCS land acreage where any pesticide applied and pesticide risk. As described earlier only the correlation with the 'any pesticide' indicator will be modeled at this point in time. This multilevel model tested the inverse relationship between the use of any pesticide and female circulatory diseases in order to determine whether it persisted after controlling for income and age. Table 51 outlines the results of the null model, the model with only level-1 predictors, and a full model that includes the any pesticide indicator.

Table 51: Multilevel Model Results for Diseases of the Circulatory System in Females (N=159,508)

	Null	**Level-1 predictors**	**Level-2 predictors: Any Pesticide**
Intercept (γ_{00})	-1.046 (0.024) $p < 0.001$	-1.609 (0.016) $p < 0.001$	-1.606 (0.016) $p < 0.001$
Income	---	-0.004 (0.001) $p < 0.001$	-0.004 (0.001) $p = 0.001$
Age	---	0.080 (0.002) $p < 0.001$	0.080 (0.002) $p < 0.001$
Age squared	---	-0.0002 (0.00002) $p < 0.001$	-0.0002 (0.00002) $p < 0.001$
Any pesticide	---	---	-0.0007 (0.0002) $p = 0.003$
Variance of random intercept (μ_{0j})	0.05922 $p < 0.001$	0.01056 $p < 0.001$	0.00950 $p < 0.001$

Variance of random slope for income (μ_{1j})	---	0.00003 p = 0.002	0.00003 p = 0.002
Number of estimated parameters	2	7	8

Note. Coefficients with standard errors in parentheses, followed by p-values. Significant difference ($p<0.0005$) between null model (deviance = 452,711.6) and model with level-2 predictor. Deviance difference: any pesticide = 2,442.8; $\chi^2_{0.0005, q=6} = 25.23$. The any pesticide indicator represents the average annualized percent of CCS land acreage where any pesticide was applied.

Table 52 provides the odds ratios, and their confidence intervals, based on the coefficients provided in the model in Table 51 that includes the any pesticide indicator. The odds ratio for the any pesticide measure represents the change in odds based on a one unit increase in the pesticide measure.

Table 52: Odds Ratios with Confidence Intervals from Multilevel Model Results for Diseases of the Circulatory System in Females

Pesticide measure	Age	Income	Pesticide measure
Any pesticide	Age: **1.0834 (1.079-1.087)** Age-squared: **1.000 (1.000-1.000)**	**0.996 (0.994-0.998)**	**0.999 (0.999-1.000)**

Note: Statistically significant results in bold. The any pesticide indicator represents the average annualized percent of CCS land acreage where any pesticide was applied.

Table 53 presents the probabilities of females being diagnosed with diseases of the circulatory system over the four-year study period. The probability of the average individual is reported as well as the probabilities for individuals who differ from the average in either a one-unit increase or a one standard deviation increase in the pesticide

measures. The use of pesticides had an extremely small effect on the probability of circulatory diseases, even a 49% increase (the standard deviation) in the acreage of the CCS where pesticides were applied only resulted in a 0.5% decrease in female circulatory diseases.

Table 53: Probabilities Based on Multilevel Model Results for Diseases of the Circulatory System in Females

	Probability of diagnosis with cancer in males of average income and age who live in CCSs with:		
Pesticide measure	**Average value of pesticide measure**	**Value of pesticide measure one unit greater than average**	**Value of pesticide measure one standard deviation greater than average**
Any pesticide	0.167	0.167	0.162

Note: The any pesticide indicator represents the average annualized percent of CCS land acreage where any pesticide was applied. The standard deviation of the any pesticide measure is 49 %.

5.3.9. Summary of Significant Analytical Results

The analytical analyses were conducted using multilevel modeling that adjusted for income and age (when appropriate). All of the investigated pesticide indicators were significantly associated with certain health outcomes. Insecticide use was associated with many different health outcomes. Table 54 summarizes the significant associations found in the multilevel models. The odds ratios and their 95% confidence intervals are reported. The probabilities associated with standard deviation increases in the pesticide measures are also shown. The standard deviation increase is used because of the variation in the scope of the different pesticide indicators, for example a one-unit increase

in the use of any pesticide is 1/49th of its standard deviation whereas it is half of the insecticide indicator's standard deviation.

Table 54: Summary of Significant Analytical Results from Multilevel Models

	Odds ratio[a] (95% CI)	Baseline probability[b] (%)	Probability with SD increase (%)	Change in probability[c] (%)
Insecticide Use				
Male				
Perinatal conditions	1.08 (1.02 – 1.13)	32.7	36.0	+ 3.3
Congenital anomalies	1.04 (1.002-1.08)	11.8	12.7	+ 0.9
Eye disorders	1.03 (1.02-1.05)	33.9	35.4	+ 1.5
Female				
Perinatal conditions	1.07 (1.02-1.13)	30.4	33.3	+ 2.9
Eye disorders	1.02 (1.004-1.03)	40.6	41.4	+ 0.8
Any Pesticide Use				
Male				
Eye disorders	1.001 (1.001-1.002)	33.8	35.4	+ 1.6
Circulatory System Diseases	0.99 (0.99-1.00)	14.0	13.6	- 0.4
Female				
Circulatory System Diseases	0.99 (0.99-1.00)	16.7	16.2	- 0.5

Pesticide Risk				
Male				
Eye disorders	1.06 (1.04-1.08)	33.8	35.0	+ 1.2

Note. CI = confidence interval; SD = standard deviation. All pesticide variables, other than pesticide risk, represent the average annualized percent of CCS land acreage where the pesticide type was applied.

[a]Odds ratio given for one unit increase in pesticide measure. [b]Baseline probability represents probability of individual with average income and age, living in CCS with the average on the pesticide measure, experiencing the health outcome. [c]Change in probability is the change associated with standard deviation increase in pesticide measure.

5.4. Maps

Maps were created for all of the pesticide indicators (Figures 5 – 9) as well as the health indicators that were examined with multilevel models (Figures 10 – 17). A map labeling the included CCSs was also created (Figure 18). The maps were created with the mapping software ArcView GIS 3.3 (Environmental Systems Research Institute, 2002). Values were assigned to classes in the graduated colour maps by ArcView's system of natural breaks, which uses Jenk's optimization to minimize the variation within each class (Environmental Systems Research Institute, 1996, p. 104).

5.4.1. Maps of Pesticide Indicators

Figure 5: Map of Any Pesticide Use

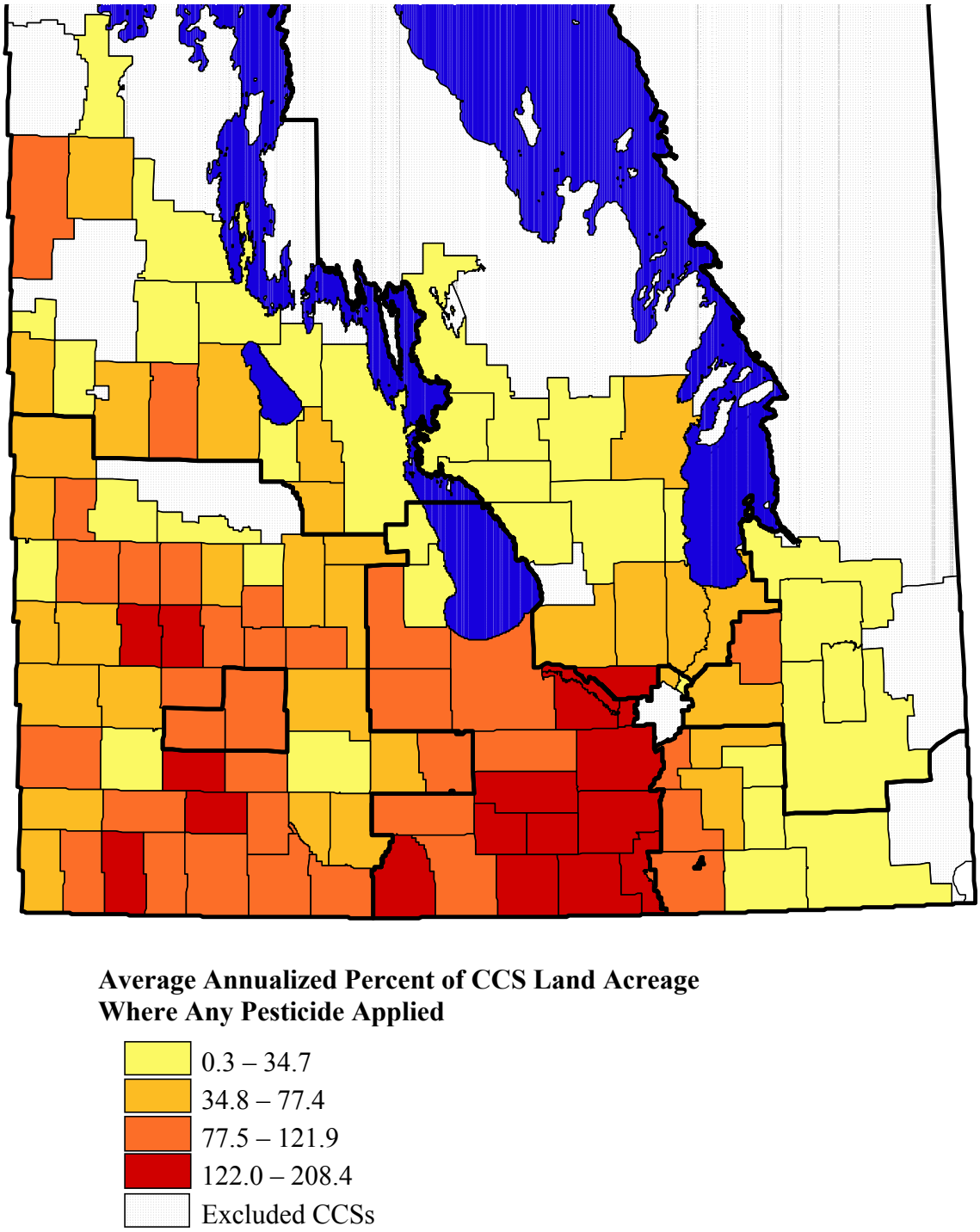
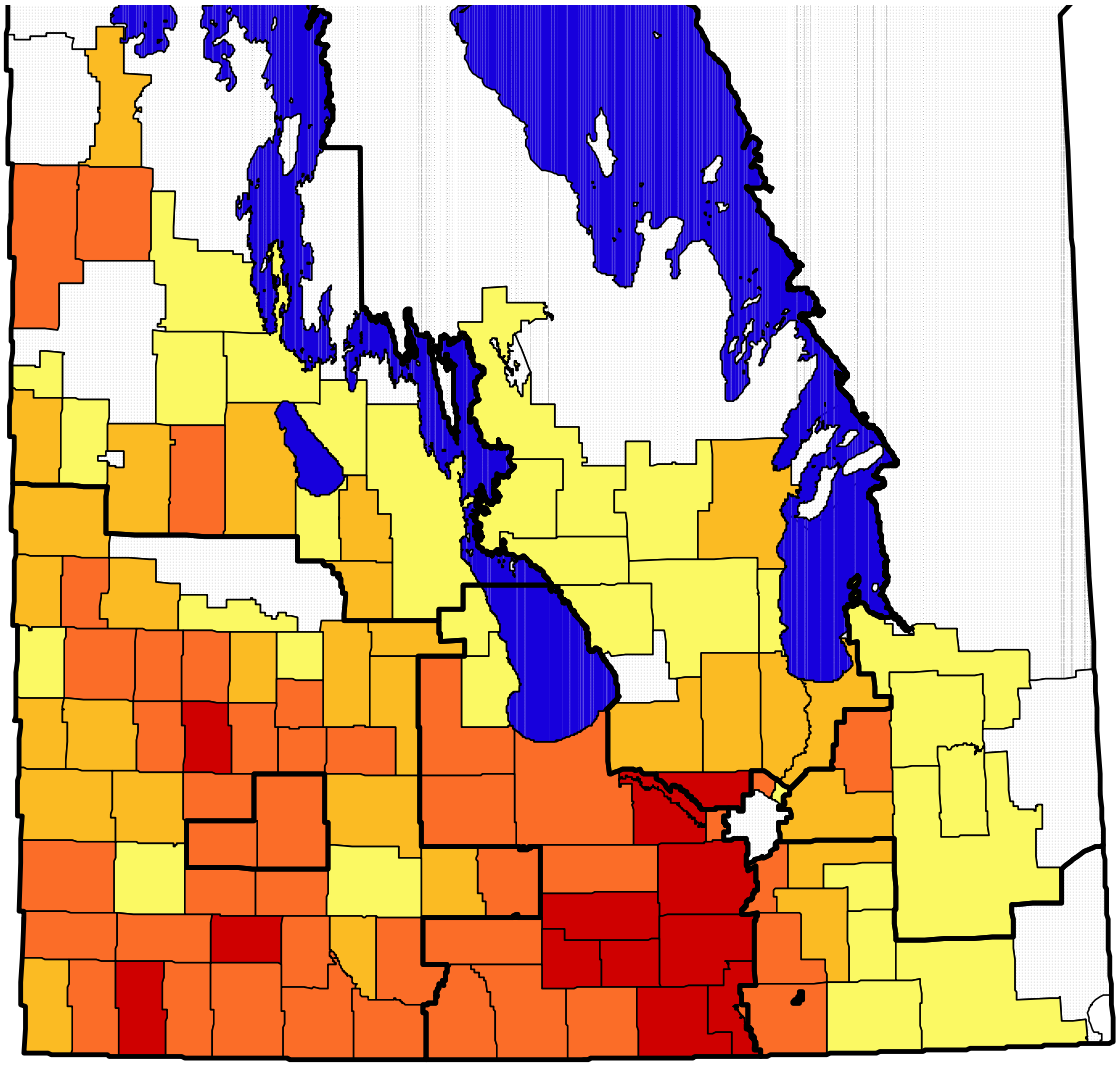


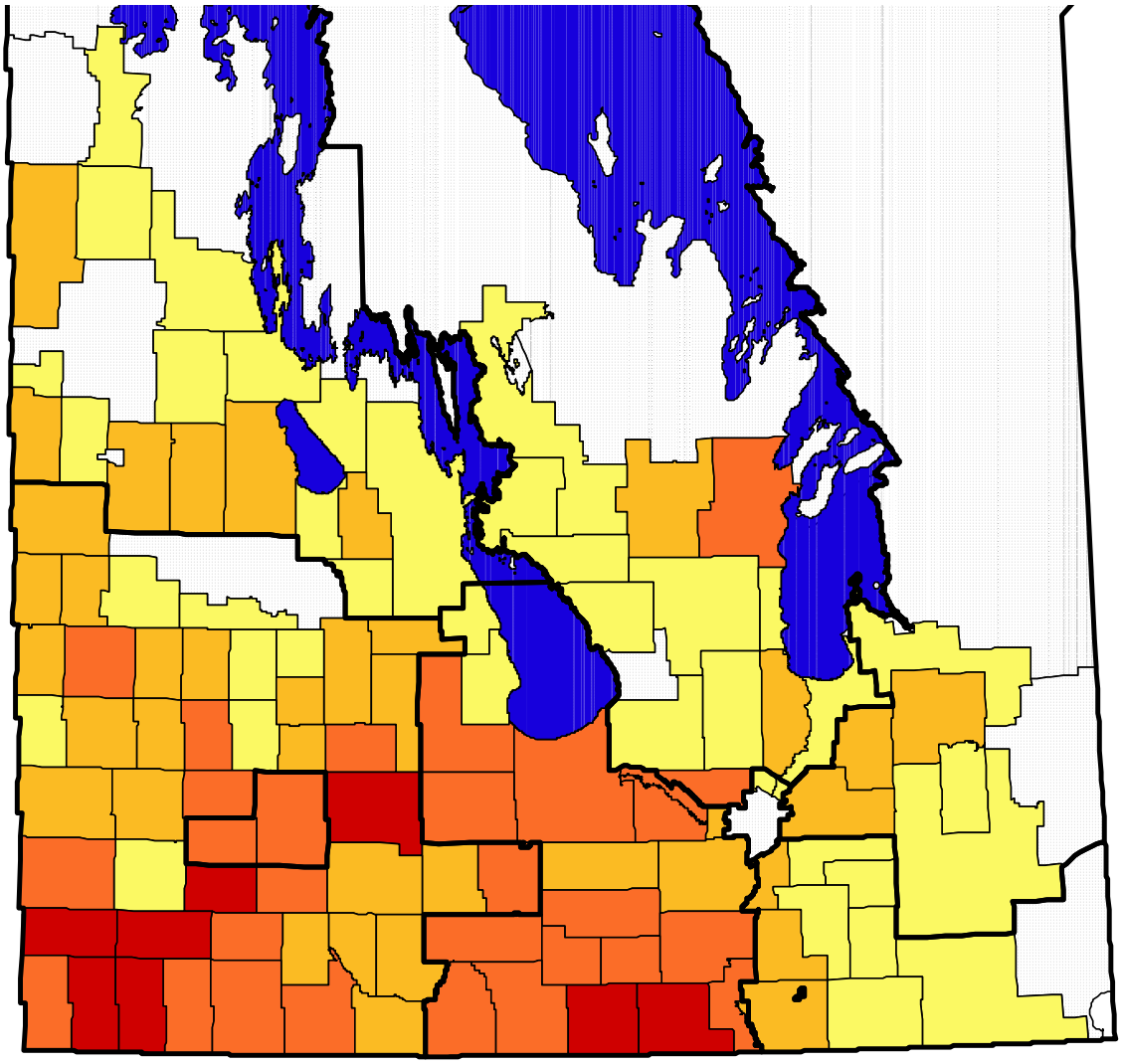
Figure 6: Map of Herbicide Use



Average Annualized Percent of CCS Land Acreage Where Herbicides Applied

- 0.1 – 26.4
- 26.5 – 59.3
- 59.4 – 102.2
- 102.3 – 166.0
- Excluded CCSs

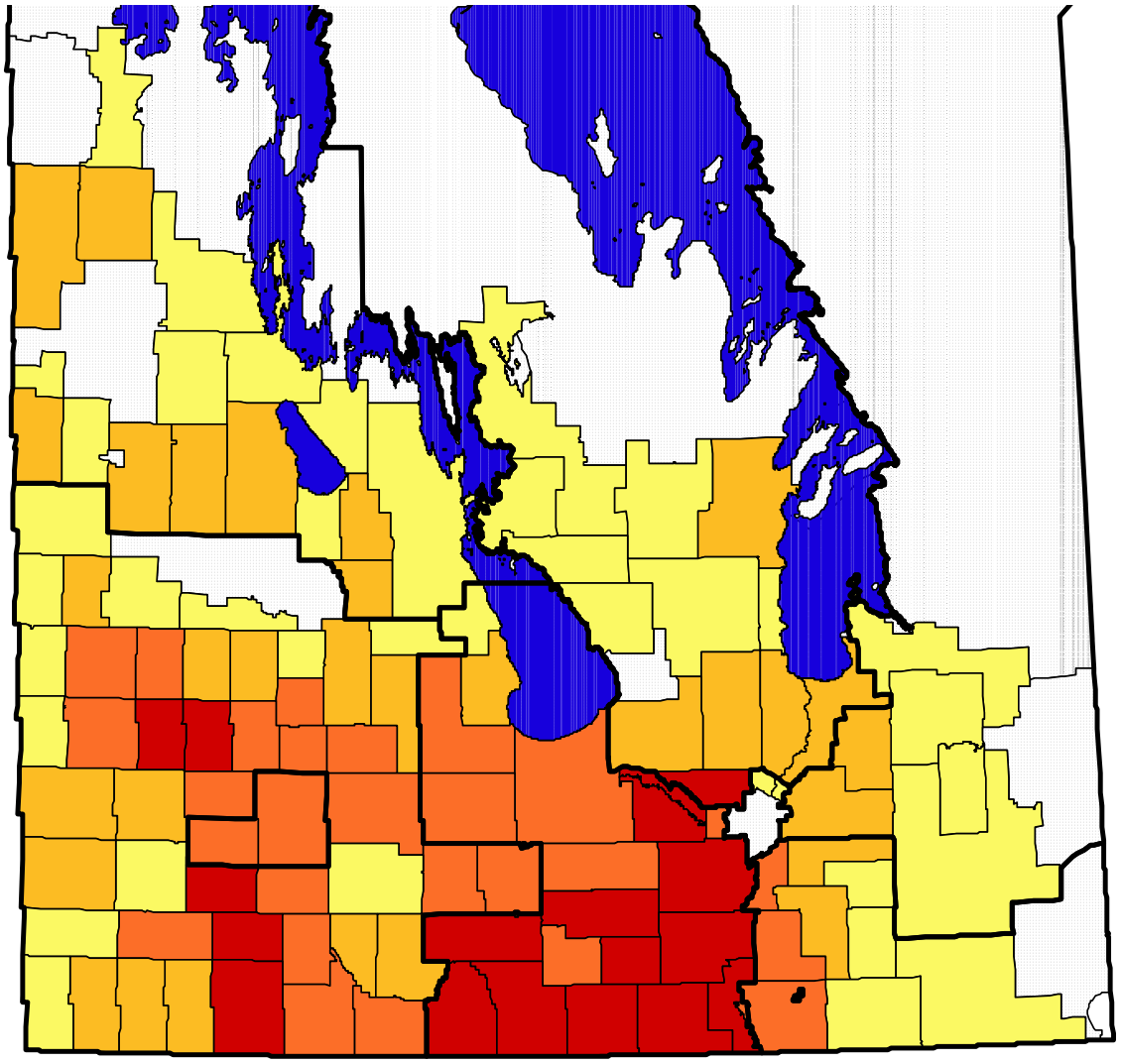
Figure 7: Map of Insecticide Use



Average Annualized Percent of CCS Land Acreage Where Insecticides Applied

- 0.0 – 1.2
- 1.3 – 3.0
- 3.1 – 5.5
- 5.6 – 9.6
- Excluded CCSs

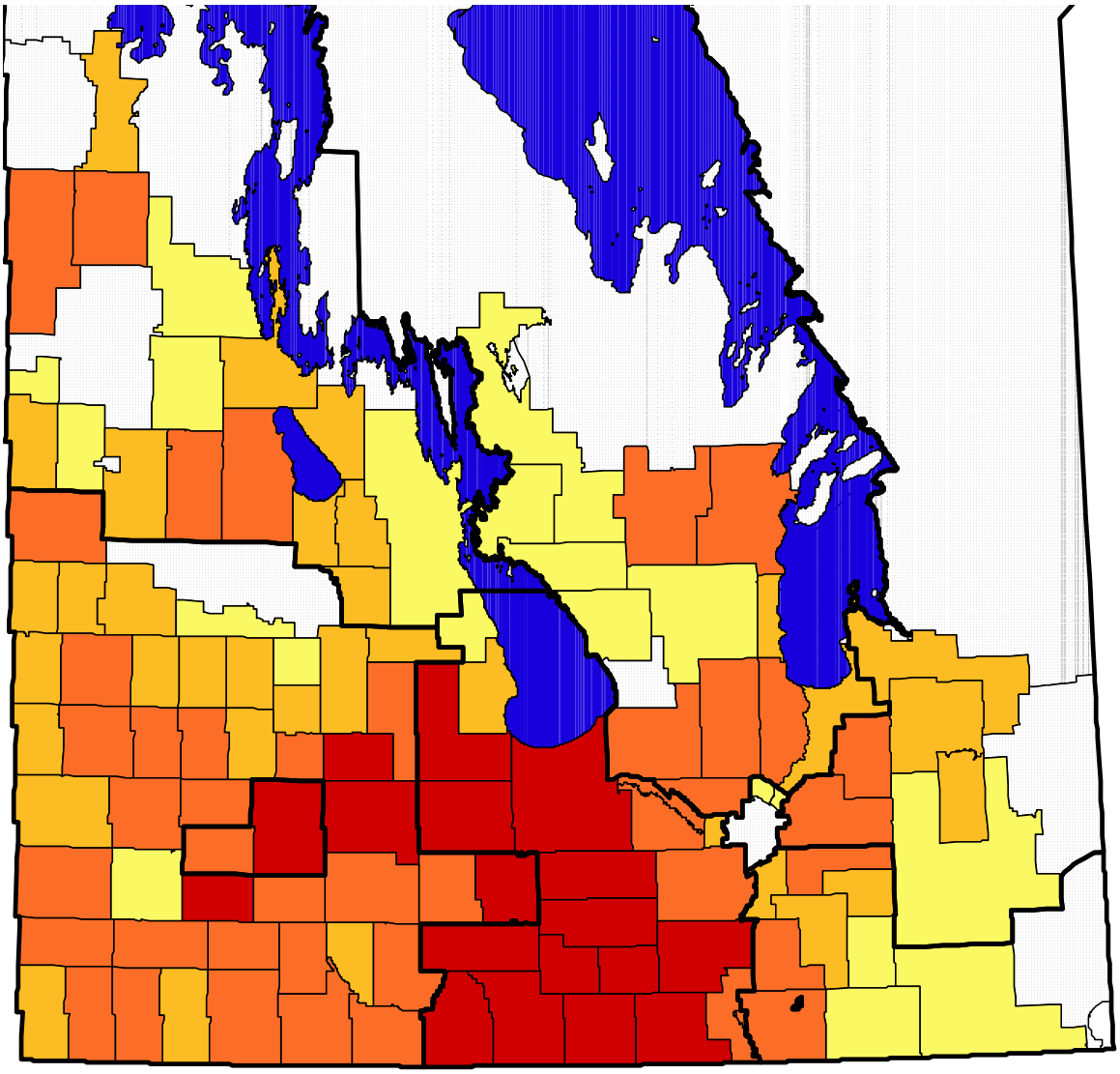
Figure 8: Map of Fungicide Use



Average Annualized Percent of CCS Land Acreage Where Fungicides Applied

- 0.0 – 4.7
- 4.8 – 12.0
- 12.1 – 21.7
- 21.8 – 41.7
- Excluded CCSs

Figure 9: Map of Pesticide Risk



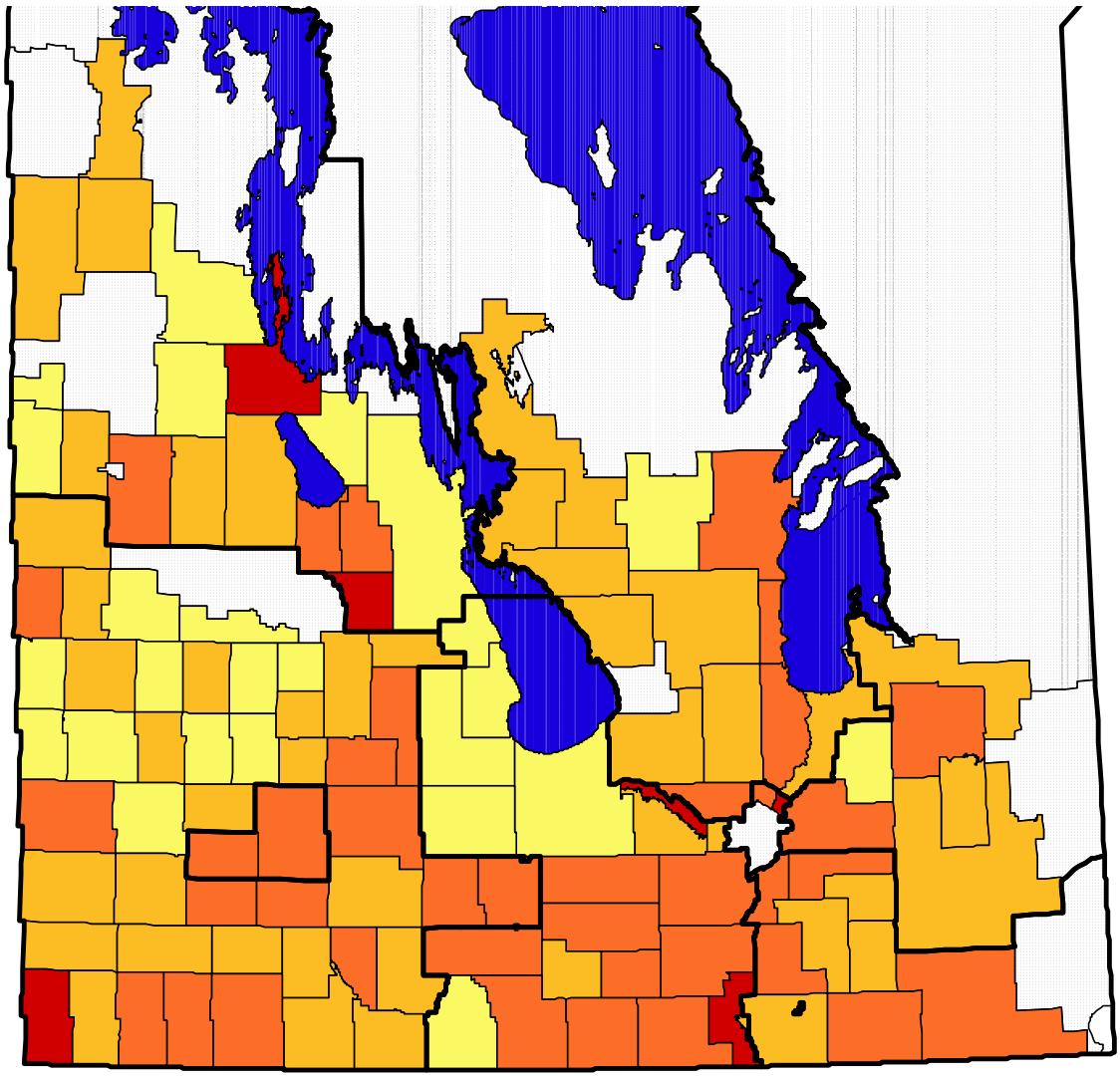
Pesticide Risk

- 0.04 – 1.26
- 1.27 – 2.37
- 2.38 – 3.25
- 3.26 – 5.04
- Excluded CCSs

5.4.2. Maps of Health Indicators Examined in Multilevel Models

The health outcomes that were examined in the multilevel models were mapped. The maps show the age-adjusted period prevalence, except for perinatal conditions and congenital anomalies that were not age-adjusted as they were restricted to individuals under five years of age. The maps are at the ecological level, with the values the same as those that were employed in the initial correlations, whereas, the analytical multilevel models used individual-level health indicators instead. If an individual had multiple diagnoses of the mapped health outcome during the study period they were only counted once. Appendix C includes the female age-adjusted prevalence values, and the crude period prevalence values upon which they are based, by CCS. Appendix D outlines the male crude period prevalence values by CCS and Appendix E the corresponding age-adjusted prevalence values.

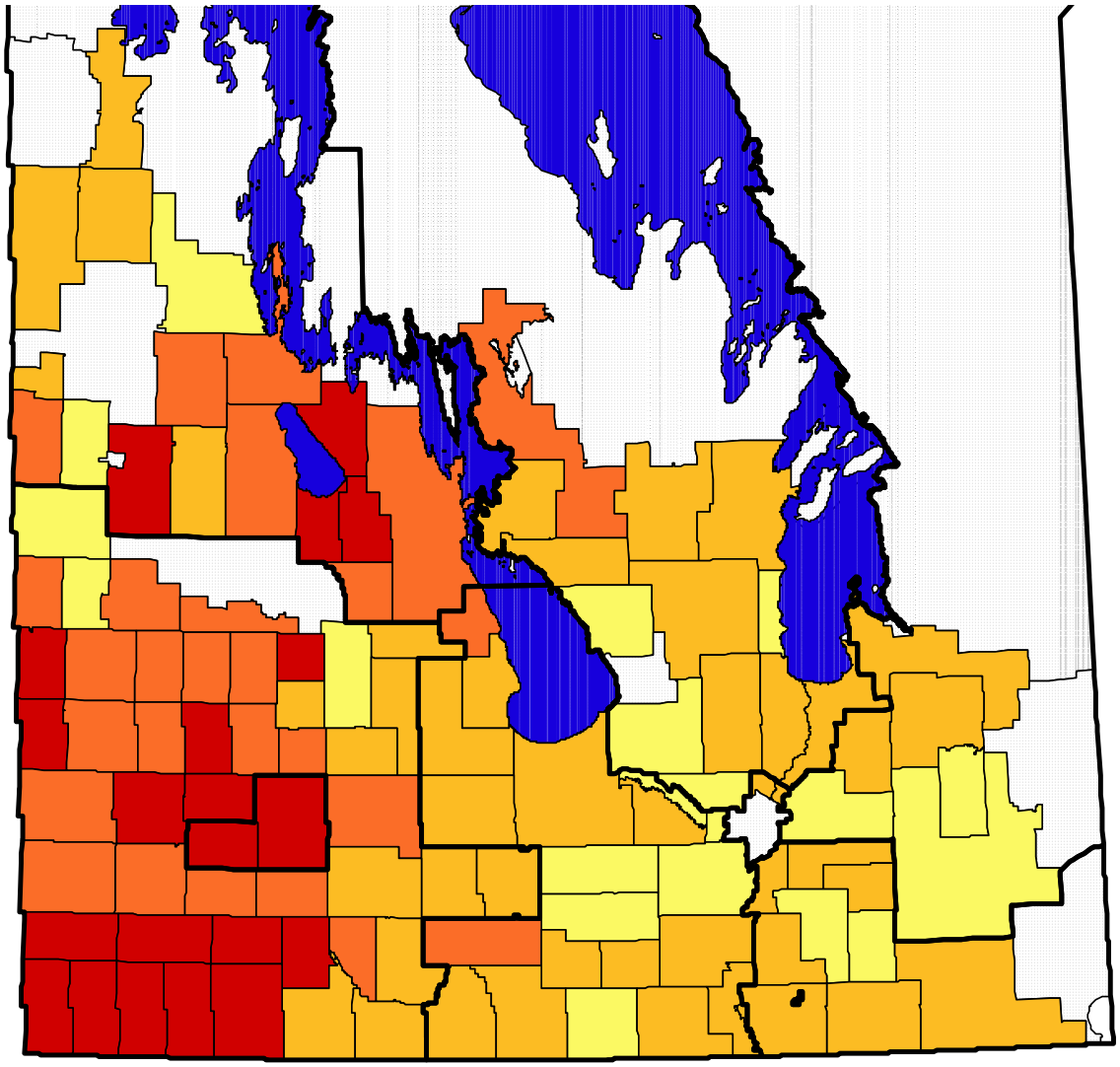
Figure 10: Map of Cancer in Males



Age-Adjusted Four-Year Period Prevalence (%) of Cancer in Males Ages Five and Older

- 6.7 – 10.3
- 10.4 – 12.3
- 12.4 – 14.4
- 14.5 – 16.7
- Excluded CCSs

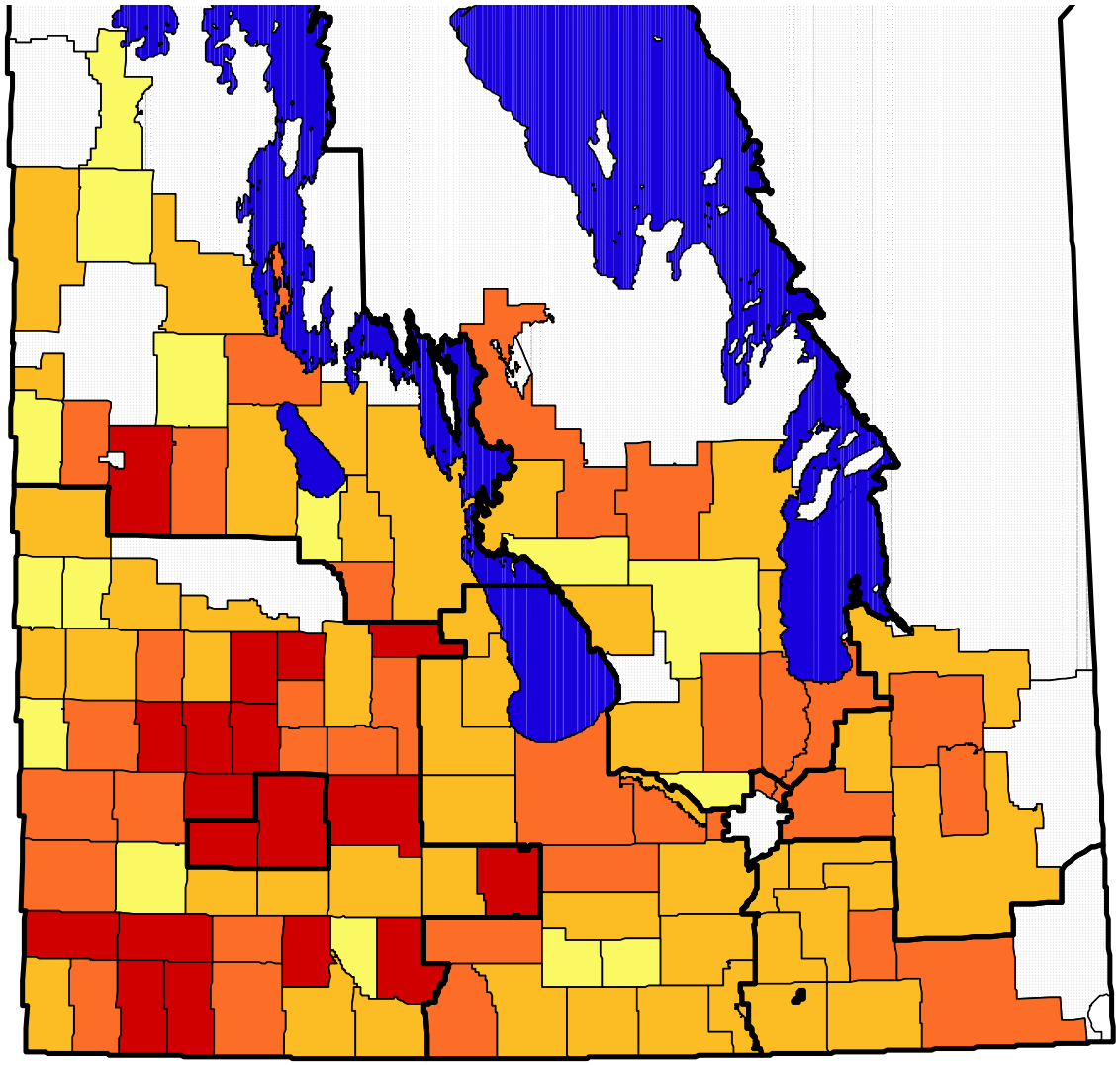
Figure 11: Map of Perinatal Conditions in Males



Four-Year Period Prevalence (%) of Conditions Originating in the Perinatal Period in Males Under Five Years of Age

- 0.0 – 21.6
- 21.7 – 34.7
- 34.8 – 48.0
- 48.1 – 80.0
- Excluded CCSs

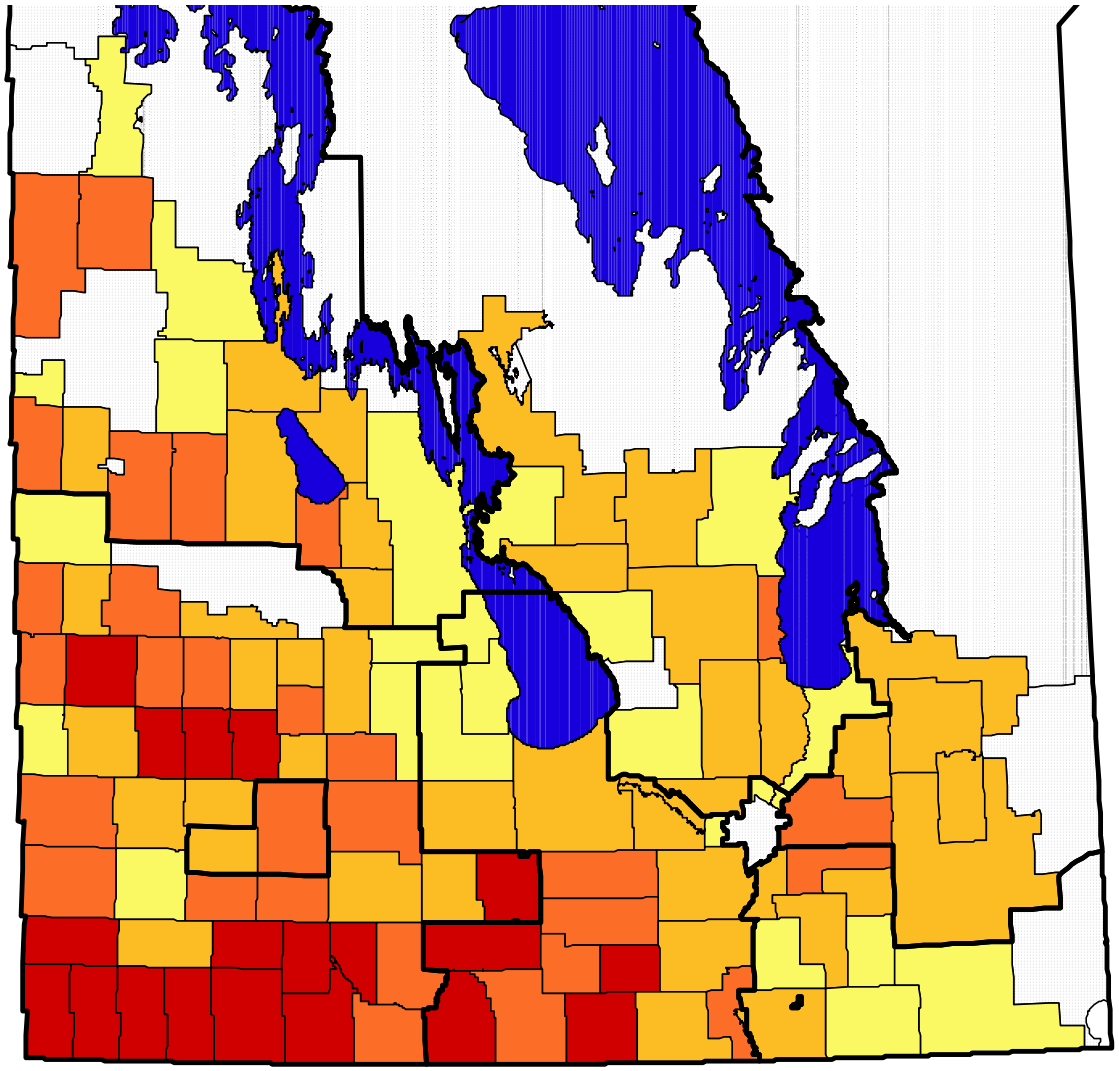
Figure 12: Map of Congenital Anomalies in Males



Four-Year Period Prevalence (%) of Congenital Anomalies in Males Under Five Years of Age

- 0.0 – 6.0
- 6.1 – 11.5
- 11.6 – 17.5
- 17.6 – 27.8
- Excluded CCSs

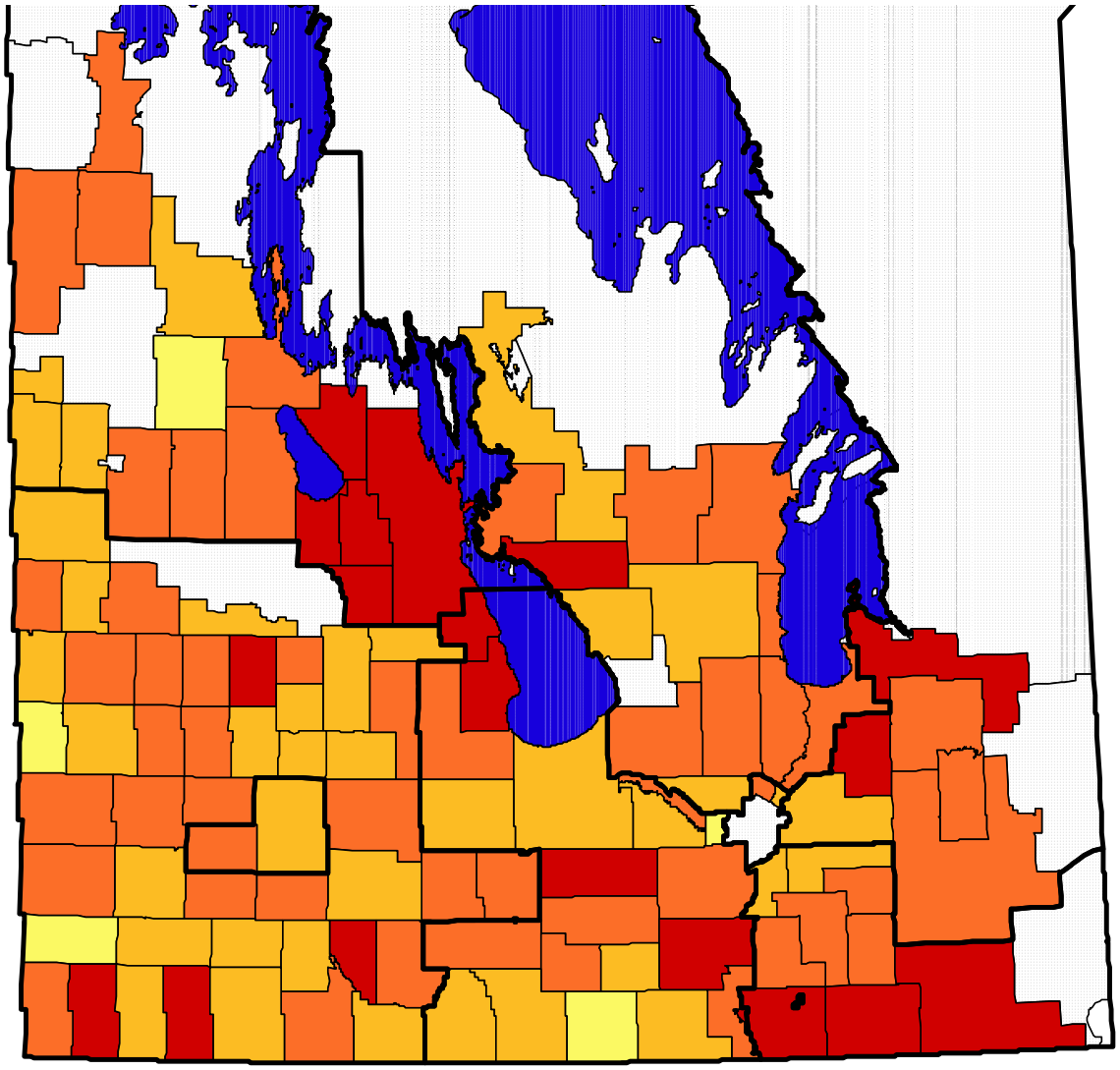
Figure 13: Map of Disorders of the Eye in Males



Age-Adjusted Four-Year Period Prevalence (%) of Disorders of the Eye in Males

- 0.0 – 6.0
- 6.1 – 11.5
- 11.6 – 17.5
- 17.6 – 27.8
- Excluded CCSs

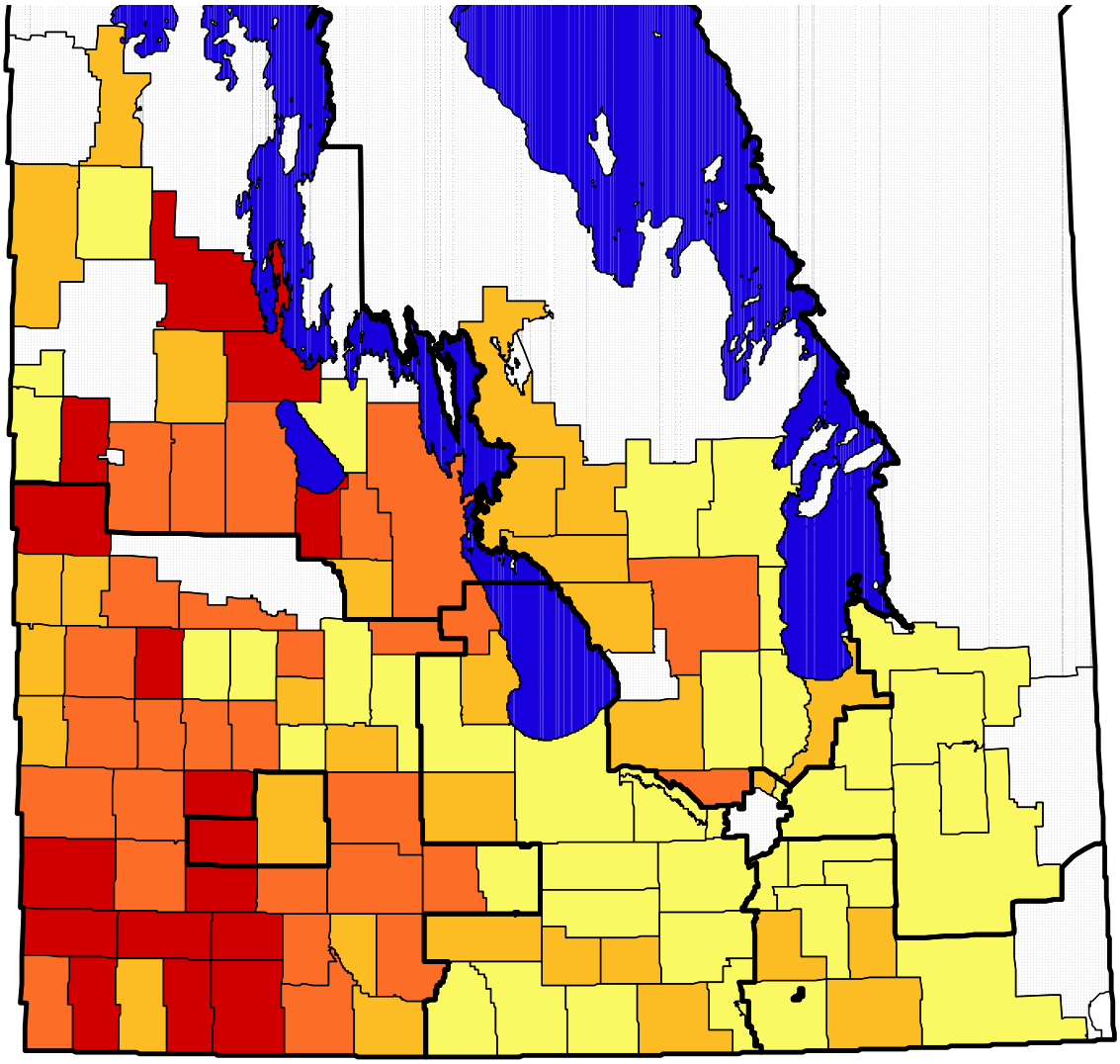
Figure 14: Map of Diseases of the Circulatory System in Males



Age-Adjusted Four-Year Period Prevalence (%) of Diseases of the Circulatory System in Males

- 12.2 – 18.0
- 18.1 – 21.1
- 21.2 – 23.2
- 23.3 – 27.4
- Excluded CCSs

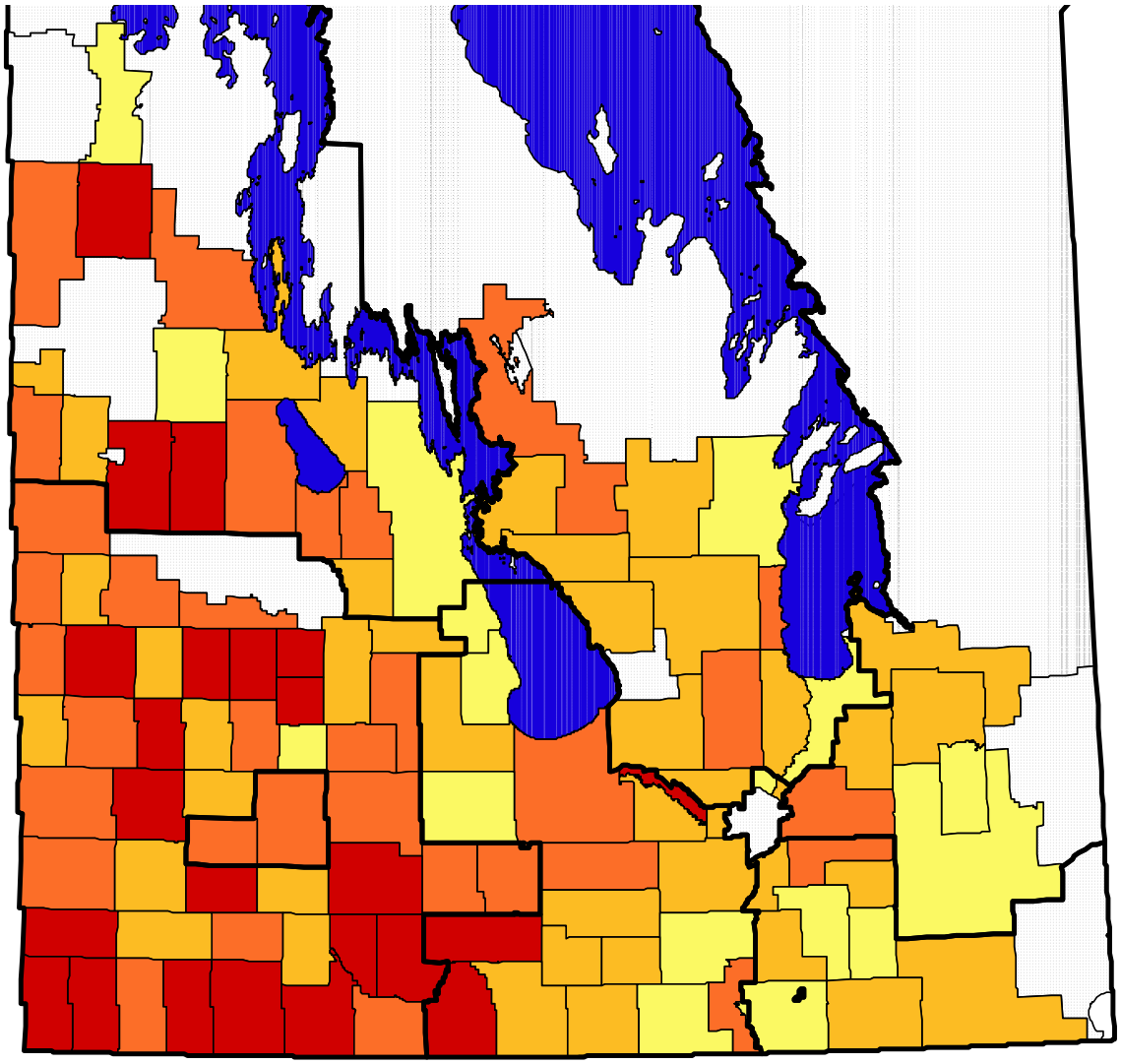
Figure 15: Map of Perinatal Conditions in Females



Four-Year Period Prevalence (%) of Conditions Originating in the Perinatal Period in Females Under Five Years of Age

- 4.0 – 24.2
- 24.3 – 34.4
- 34.5 – 48.1
- 48.2 – 66.7
- Excluded CCSs

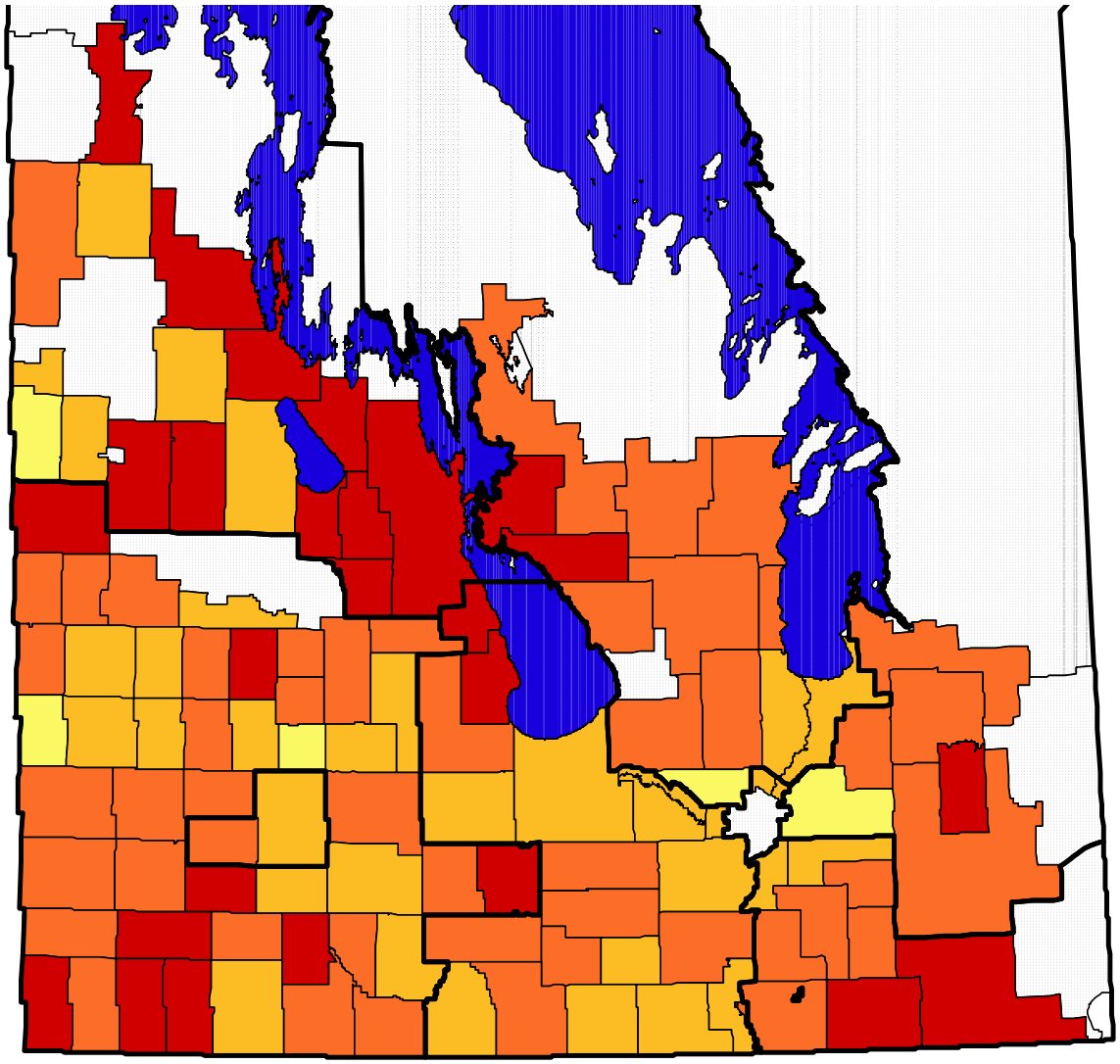
Figure 16: Map of Eye Disorders in Females



Age-Adjusted Four-Year Period Prevalence (%) of Eye Disorders in Females

- 29.5 – 35.6
- 35.7 – 38.4
- 38.5 – 41.4
- 41.5 – 45.4
- Excluded CCSs

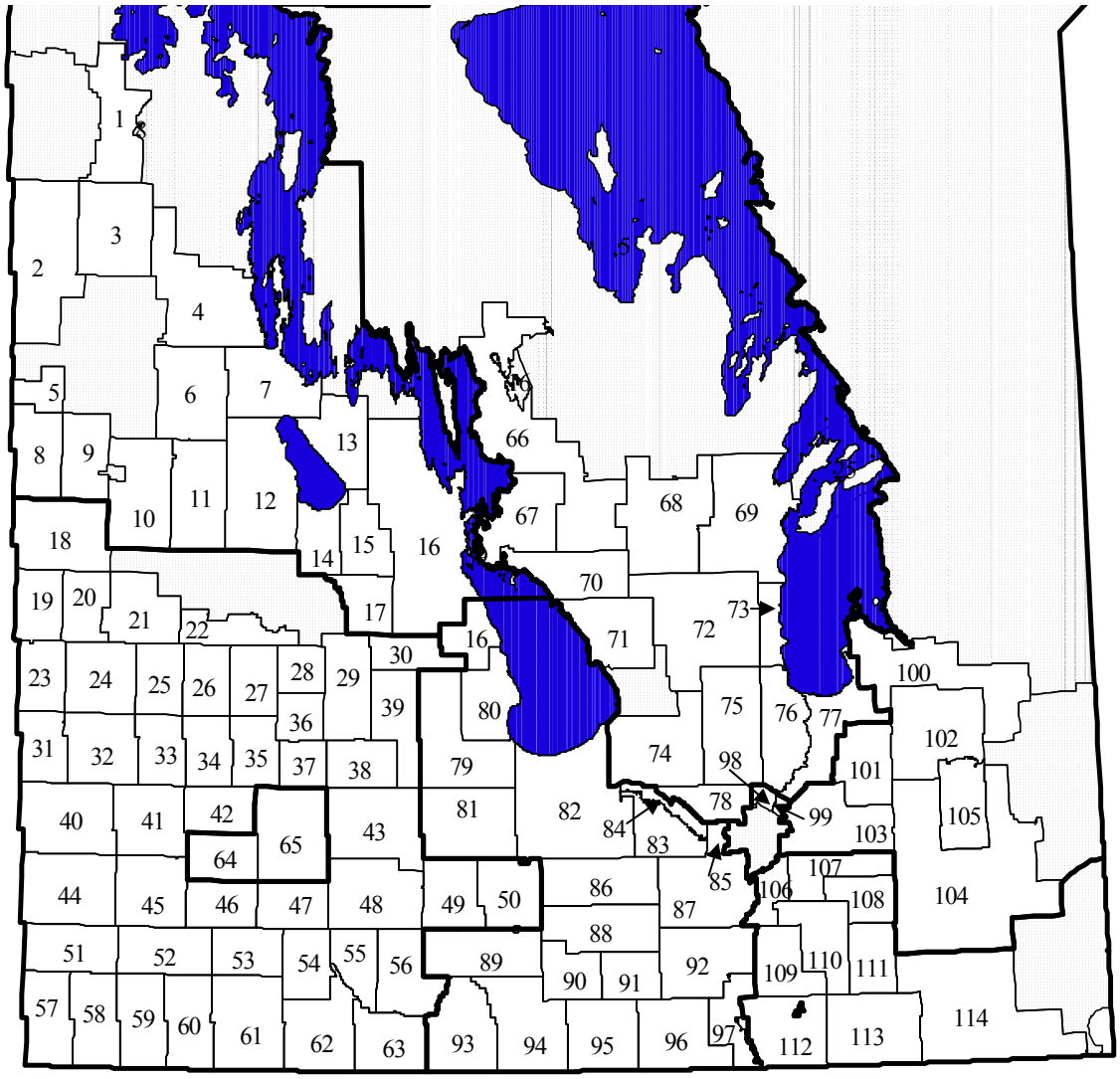
Figure 17: Map of Diseases of the Circulatory System in Females



Age-Adjusted Four-Year Period Prevalence (%) of Diseases of the Circulatory System in Females

- 14.8 – 19.3
- 19.4 – 22.6
- 22.7 – 24.8
- 24.9 – 30.3
- Excluded CCSs

Figure 18: Map of Included Census Consolidated Subdivisions (CCSs) by Regional Health Authority



Parkland Regional Health Authority (1 – 17)

1 Mountain (North)
2 Swan River
3 Minitonas
4 Mountain (South)
5 Park (North)
6 Ethelbert
7 Mossey River

8 Shell River
9 Hillsburg
10 Grandview
11 Gilbert Plains
12 Dauphin
13 Lawrence
14 Ochre River
15 Ste. Rose
16 Alonsa
17 McCreary

Assiniboine Regional Health Authority (18 – 63)

18 Shellmouth-Boulton
19 Russell
20 Silver Creek
21 Rossburn
22 Park (South)
23 Ellice
24 Birtle
25 Shoal Lake
26 Strathclair
27 Harrison
28 Clanwilliam
29 Rosedale
30 Glenella
31 Archie
32 Miniota
33 Hamiota
34 Blanshard
35 Saskatchewan
36 Minto
37 Odanah
38 Langford
39 Lansdowne
40 Wallace
41 Woodworth
42 Daly
43 North Cypress

44 Pipestone
45 Sifton
46 Glenwood
47 Oakland
48 South Cypress
49 Victoria
50 South Norfolk
51 Albert
52 Cameron
53 Whitewater
54 Riverside
55 Strathcona
56 Argyle
57 Edward
58 Arthur
59 Brenda
60 Winchester
61 Morton
62 Turtle Mountain
63 Roblin

Brandon Regional Health Authority (64 – 65)

64 Whitehead
65 Elton

Interlake Regional Health Authority (66 – 78)

66 Grahamdale
67 Siglunes
68 Fisher
69 Bifrost
70 Eriksdale
71 Coldwell
72 Armstrong
73 Gimli
74 Woodlands
75 Rockwood
76 St. Andrews

77 St. Clements
78 Rosser

Central Regional Health Authority (16, 79 – 97)

16 Alonsa
79 Westbourne
80 Lakeview
81 North Norfolk
82 Portage la Prairie
83 Cartier
84 St. Francois Xavier
85 Headingley
86 Grey
87 Macdonald
88 Dufferin
89 Lorne
90 Thompson
91 Roland
92 Morris
93 Louise
94 Pembina
95 Stanley
96 Rhineland
97 Montcalm

Winnipeg Regional Health Authority (98 – 99)

98 West St. Paul
99 East St. Paul

North Eastman Regional Health Authority (100 – 105)

100 Alexander
101 Brokenhead
102 Lac du Bonnet
103 Springfield
104 Reynolds
105 Whitemouth

South Eastman Regional Health Authority (106 – 114)

106 Ritchot
107 Tache
108 Ste. Anne
109 De Salaberry
110 Hanover
111 La Broquerie
112 Franklin
113 Stuartburn
114 Piney

6. DISCUSSION

6.1. Discussion of Health Outcomes Examined in Multilevel Models

This study initially examined the correlations between the developed pesticide indicators and many broad health outcomes in order to determine which health outcomes should be the focus of further analyses. Significant correlations that suggested a potential adverse effect of pesticides were examined in subsequent multilevel models. Additionally, the association between the use of any pesticides and circulatory system diseases was explored as an example of an inverse correlation (as pesticide use increased the health outcome decreased). The following sections discuss the multilevel model results for each health outcome.

6.1.1. Conditions Originating in the Perinatal Period

The ICD-9-CM[12] chapter regarding conditions originating in the perinatal period incorporates a wide variety of outcomes (HCIA Inc., 1994). Diagnosis of short and long gestation lengths, low and high birth weights, birth trauma, as well as maternal causes of challenges for the newborn or fetus are included (HCIA Inc., 1994). The chapter also comprises diseases specific to the fetus or newborn (under 28 days) that affect a variety of body systems (HCIA Inc., 1994). Diagnosis with intrauterine hypoxia or birth asphyxia, which may lead to fetal death, are also included in this chapter (HCIA Inc., 1994).

[12] The ICD-9-CM is a coding system "developed by the World Health Organization (WHO) that is used to classify diseases, health conditions and procedures" (Manitoba Centre for Health Policy, 2006a, Terms beginning with I section). See sections 4.1.1. and 4.3.2. for further information on its use in this thesis.

This study found that the treatment prevalence of conditions originating in the perintal period, in both males and females under age five, was significantly correlated with insecticide use at the ecological level (Tables 31 and 32). No other pesticide indicators were correlated with these conditions (Tables 31 and 32). For both males and females a significant association was maintained in the multilevel analyses; these associations were the strongest found in the study (Table 54). For males of average household income, when insecticide use was one standard deviation higher the probability of having a perinatal condition was 36.0%, compared to 32.7% in areas of average insecticide use. For females of average household income, when insecticide use was one standard deviation higher the probability of having a perinatal condition was 33.3%, compared to 30.4% in areas of average insecticide use.

Although literature regarding early and late fetal death was reviewed in Chapter 3 the outcomes examined in these studies are more comparable to the pregnancy outcomes of spontaneous abortion and intrauterine death in the ICD-9-CM, which are not included in the perinatal conditions chapter (HCIA Inc., 1994). Studies of low birth weight and small-for-gestational-age have generally not found an effect of agricultural pesticides (Hanke & Jurewicz, 2004; Schreinemachers, 2003). Although only the focus of a limited number of studies, parental work in agriculture has been associated with preterm delivery (Hanke & Jurewicz, 2004).

No literature was found that discussed the bulk of the diagnoses included in the conditions originating in the perinatal period chapter; general health concerns specific to the fetus or newborn. These outcomes include respiratory conditions, infections, jaundice, digestive concerns, and others (HCIA Inc., 1994). The lack of research into these outcomes may be due to the limited use of administrative definitions to study perinatal health outcomes. Future studies, moving beyond this exploratory research, need to be conducted to elucidate which diagnoses in the perinatal chapter were associated with insecticides. If preterm delivery is affected it is possible that this in turn influences the prevalence of adverse perinatal health outcomes (Health Canada, 2003).

6.1.2. Congenital Anomalies in Males

Diagnosis with congenital anomalies in males under age five was significantly correlated at the ecological level with the use of any pesticides, herbicides (not investigated in multilevel models), and insecticides (Table 31). Similar correlations were not found for congenital anomalies in females (Table 32). For males a significant association was maintained in the multilevel models between congenital anomalies and insecticides but not the indicator of the combined use of any pesticides (Table 38). The level of effect was relatively small, however: For males of average household income, when insecticide use was one standard deviation higher the probability of having a congenital anomaly was 12.7%, compared to 11.8% in areas of average insecticide use.

The treatment prevalence of congenital anomalies in this study (mean = 11.8%) is higher than most reported prevalences because the entire ICD-9-CM congenital anomalies

chapter (HCIA Inc., 1994) was included. The chapter includes a wide variety of anomalies spanning from anencephaly, the fatal absence of most of the brain, to birth marks (HCIA Inc., 1994). More common is the reporting of only severe congenital anomalies that are diagnosed in 2 –3 % of births (Health Canada, 2002, 2003). Future studies examining which congenital anomalies are predominantly associated with insecticides would expand on this exploratory study.

The reviewed epidemiological literature included studies that examined congenital anomalies in both live births and fetal deaths (Section 3.4.4.5.). Most comparable to this research are two studies that examined congenital anomalies in live births; both conducted in states directly south of Manitoba. The cross-sectional study of Garry, Harkins, Erickson et al. (2002) did not find an association between paternal pesticide use and congenital anomalies, although spring conceptions resulted in more birth defects. On the other hand, the ecological study of Schreinemachers (2003) did find an association between wheat acreage, used as a proxy for herbicide use, and congenital anomalies. This study is similar to that of Schreinemachers (2003) in that pesticides are measured at the ecological level and that live births to a rural population are examined. The two case-control studies that considered congenital anomalies in fetal deaths, exclusively or in conjunction with those in live births, also found significant adverse effects. Both of these studies measured pesticide exposure by residential proximity to application. Significant adverse effects were also generally found in earlier literature (Hanke & Jurewicz, 2004). As found in this study, the greater susceptibility of males to congenital anomalies

associated with pesticide exposure has been found elsewhere (Garry, Harkins, Erickson et al., 2002; Schreinemachers, 2003).

A more complex definition of congenital anomalies, than that used in this research, would encapsulate fetal deaths caused by congenital anomalies and elective pregnancy terminations after prenatal congenital anomaly diagnosis (Dolk & Vrijheid, 2003; Rull et al., 2006). Potential confounding could exist in this study if regions with lower pesticide use have higher rates of elective terminations due to prenatal diagnosis with congenital anomalies. Accordingly, future studies should attempt to include prenatally diagnosed congenital anomalies and fetal deaths due to congenital anomalies. Even with such a definition "it is possible that environmental exposures may act on the probability of survival of the malformed fetus, rather than causing abnormal morphological development itself" (Dolk & Vrijheid, 2003, p. 28).

Additional factors in this study may have led to the association between agricultural pesticides and congenital anomalies being underestimated. Due to the exploratory nature of this study all congenital anomalies were grouped together despite known aetiologic and pathogenetic heterogeneity (Dolk & Vrijheid, 2003). As in the study of combined cancers, it is possible that stronger effects on certain types of congenital anomalies are diluted by a lack of effect on others (Dolk & Vrijheid, 2003). A similar averaging of effects may have occurred due to the fact that the timing of potential pesticide exposure, with regards to week of gestation, was not considered. During the period of organogenesis, approximately the 3^{rd} – 8^{th} week of pregnancy, pesticide exposure has

been shown to have a stronger effect on congenital anomalies (Bell et al., 2001a). Future longitudinal studies utilizing population-based administrative databases may have sufficient numbers to create relevant subgroups of congenital anomalies by outcome type and timing of exposure.

6.1.3. Disorders of the Eye

The period prevalence of disorders of the eye in both men and women was significantly correlated at the ecological level with the use of any pesticides, herbicides (not investigated in multilevel models), insecticides, fungicides (not investigated in multilevel models), and pesticide risk (Tables 31 and 32). For males a significant association was maintained in all the multilevel models (Table 41), whereas, for females an association only remained with insecticides (Table 48). Income was adjusted for in the multilevel models but not in the initial correlations. As diagnosis with eye disorders has been associated with higher socioeconomic status in Manitoba (Mustard et al., 1995), adjusting for income likely caused the attenuation of the associations for females, as areas of higher socioeconomic status are more likely to have higher pesticide use.

Adverse effects on the eye disorder of retinal degeneration were found in Agricultural Health Study research focusing on both applicators and wives of applicators (Kamel et al., 2000; Kirrane et al., 2005). In their research the strongest associations were seen with fungicides (Kamel et al., 2000; Kirrane et al., 2005). Fungicides were not directly examined in the multilevel models of this study but they contribute to the use of any pesticides and the pesticide risk indicators. Applicators in the Agricultural Health Study

research also experienced significant adverse effects on retinal degeneration from a number of insecticide classes.

Epidemiological research on eye disorders has been extremely limited in North America to date. The Agricultural Health Study research and this study emphasize the importance of monitoring and investigating the effect of agricultural pesticides on eye disorders in both the occupationally exposed and the general population.

6.1.4. Cancer in Males

Period prevalence of cancer in males age five and older was ecologically correlated with all of the agricultural pesticide indicators (Table 31), however, no significant associations were found in multilevel models that adjusted for age and income (Table 34). The epidemiological literature on cancer, summarized in Section 3.4.4.2., provided mixed results with the presence of a significant adverse effect varying by both the pesticide and type of cancer examined. It is possible that through examining the effect of broad groups of pesticides on all cancers combined any potential associations were masked. The general lack of adverse effect of agricultural pesticide exposure on all cancers combined (Table 3) corroborates this hypothesis (Alavanja et al., 2005; Beane Freeman et al., 2005; Bonner et al., 2005; De Roos et al., 2005; Lee, Hoppin et al., 2004; Rusiecki et al., 2006; Rusiecki et al., 2004; Wang et al., 2002).

The map of male cancers (Figure 10) highlights the limited variance in the health indicator, which could account for the lack of detected association in the multilevel

models. The significant correlation may have been the product of the select number of areas with extreme prevalences (Figure 10). Alternatively, the inclusion of income in the multilevel models could account for the results that diverge from the correlations.

A general challenge of examining cancer in this study is its cross-sectional nature. Examination of cancer in this context is based on the assumption that areas of high pesticide use remain high use areas over time as they are areas of greater crop farming, which is in turn dependent on relatively constant soil quality (G. Martens, personal communication, May 21, 2006). Although a valid assumption, residency in this study is only based on an eight year period. Future studies could overcome these challenges by utilizing a longitudinal design, examining specific pesticides and cancers, as well as through employing measures from the Canada Census of Agriculture on historical pesticide use.

6.1.5. Diseases of the Circulatory System

The focus of this research was the adverse effects of agricultural pesticides on health outcomes. Nevertheless the initial Spearman correlations indicated that certain health outcomes were inversely associated with the pesticide indicators; when pesticide use or risk was higher the age-adjusted period prevalence of the ecological health outcomes was lower. This pattern was more common for females than males (Tables 32 and 31). The maps of diseases of the circulatory system in both males (Figure 14) and females (Figure 17) also demonstrate an inverse geographic pattern with pesticide use.

An example inverse correlation was chosen for further investigation in a multilevel model in order to determine the effect of controlling for age and income. The association between the use of any pesticides and diseases of the circulatory system was chosen, as it was common to both males and females. The association was maintained, for both sexes, in the multilevel models that adjusted for individual age and for income, however, it was very small. Although the effect was slightly larger for females, when the use of any pesticides was one standard deviation higher the probability of average females having a circulatory disease was only 16.2%, compared to 16.7% in areas of average pesticide use. The general inverse pattern of association between pesticide use and circulatory diseases, coupled with the extremely small associations found in the multilevel models, suggests potential confounding by other rural factors.

6.1.6. Summary of Health Outcomes

The results of this study indicate that some health outcomes may be more susceptible to pesticides than others. Associations were found, in the initial correlations and in the multilevel models, between the developed pesticide indicators and perinatal conditions, congenital anomalies in males, and eye disorders. Male cancers were significantly associated with pesticides in the initial correlations but not in the multilevel models. Other health outcomes were inversely associated with the pesticide indicators in the initial correlations, and for circulatory system diseases this association was maintained in the multilevel models but it was very small.

The results of the initial correlations were designed to aid in choosing the health outcomes for further study in the more rigourous multilevel models. The ecological-level correlations only took into account age and did not control for any other confounders. As such, a lack of initial adverse association does not confirm a general lack of effect of pesticides on these health outcomes. Future research employing different methodologies would be beneficial in examining the health outcomes that were not significantly correlated with pesticide use in the initial exploratory correlations.

6.2. Discussion of Pesticide Indicators

6.2.1. Pesticide Use Indicators

Four indicators of pesticide use were created in this study; the use of any pesticide and the use of the subgroups of herbicides, insecticides, and fungicides. The use of any pesticide was highest in the Red River Valley south of Winnipeg and also high in the southwest of Manitoba (Figure 5). Areas with the highest use applied pesticides to the equivalent of all acres in the CCS twice every year (Figure 5). Since the use of any pesticide was measured in percent each one-unit value represented a small proportion of the range of the variable that had a standard deviation of 49% (Table 29). Accordingly, small odds ratios corresponded to noticeable effects on the probability of the examined health outcomes. In the multilevel models the use of any pesticide was significantly associated with an increase in eye disorders in males as well as a slight reduction in circulatory system diseases.

The use of herbicides was extremely correlated (Table 30) with the use of any pesticide, as herbicides are applied to many more acres in Manitoba than insecticides or fungicides. The geographical pattern of herbicide use, accordingly, was also very similar to that of the use of any pesticide (Figure 6). These similarities, in conjunction with the fact that the initial correlations with the health outcomes showed very similar results for the use of any pesticide and the use of herbicides, resulted in the herbicide indicator not being selected for examination in the multilevel models.

Fungicide use was also not examined in the multilevel models due to the high correlation between it and the use of any pesticide (Table 30) as well as its associations with similar health outcomes in the initial correlational analyses (Tables 31 and 32). The slight differences between the geographic pattern of the use of fungicides (Figure 8) and that of the use of all pesticides combined (Figure 5) may warrant independent examination of fungicide use in multilevel models in the future. Such an investigation would be especially relevant to eye disorders, as Agricultural Health Study research has found an association between these disorders and fungicide use (Kamel et al., 2000; Kirrane et al., 2005).

The use of insecticides (Figure 7) had a noticeably different geographic pattern than the use of any pesticide (Figure 5) and was correlated with different health outcomes (Tables 31 and 32). Although due to being a component of the use of any pesticide indicator one would expect them to be correlated, insecticide use was not as highly correlated as herbicide and fungicide use (Table 30). For these reasons insecticide use was separately

examined in the multilevel models, where it was found to be associated with more health outcomes than the use of any pesticide and pesticide risk. Insecticide use was significantly associated, in multilevel models that adjusted for income and age (when appropriate), with conditions originating in the perinatal period, congenital anomalies in males, and eye disorders. These results are biologically plausible as insecticides are generally considered to be one of the most toxic types of pesticides, partially due to the conservation of biochemical processes between insects and humans (Section 3.2.).

6.2.2. Pesticide Risk Indicator

The pesticide risk indicator was developed since indicators that include measures of the toxicity and exposure potential of pesticides are considered superior. The EIQ_{HUMAN} was used because of the availability of the EIQ values upon which it is based, the previous use of the EIQ in the Canadian context, and its utility in a context where site-specific characteristics are not known (Section 3.5.2.2.). The process of creating the indicator was time consuming, as it required transforming the acres where each pesticide was applied into the amount applied. The tank mix compositions, recommended application rates, seed treatment characteristics, and percent active ingredients were all required to achieve this calculation (Section 4.3.3.2.). These required values were not all readily available and expert advice was necessary.

The pesticide risk indicator had a pattern of initial correlations with the ecological-level health outcomes that was relatively similar to the use of any pesticide indicator (Tables 31 and 32). In some of the cases where the use of any pesticide was inversely correlated

with health outcomes, pesticide risk was not significantly correlated. In other cases the effect was similar but did not reach statistical significance. The geographic distribution of the pesticide risk indicator (Figure 9) was, like the use of any pesticide, high in the southwest of Manitoba and south of Winnipeg but the geographic pattern was not identical to that of the use of any pesticide (Figure 5).

The pesticide risk indicator was examined separately in the multilevel models in order to determine its utility compared to the measures of pesticide use. Like the other indicators it was not associated significantly with male cancer in the multilevel models (Section 6.1.4.). Pesticide risk was significantly associated with eye disorders in males but not in females (Tables 41 and 48), as was the case for the use of any pesticide indicator. Although in the case of male eye disorders the odds ratio for the pesticide risk indicator appears much larger than the odds ratio for the use of any pesticide indicator, an increase of one standard deviation in pesticide risk actually results in a smaller increase in probability than a one standard deviation increase in the use of any pesticide because of the difference in scale of the indicators. Therefore in most situations the pesticide risk indicator performed similarly to the use of any pesticide indicator, despite requiring considerably more work to create.

Although the EIQ_{HUMAN} was the best feasible basis for the pesticide risk indicator, its limitations (as described in Section 3.5.2.2.) may have weakened the indicator beyond utility in this context. First, the pesticide risk indicator was biased towards high use pesticides. This bias was attenuated but not eliminated through the amount of pesticide

being log-transformed before being weighted by the EIQ_{HUMAN}. Another consideration is that the farm worker and consumer components of the EIQ, which form the EIQ_{HUMAN}, do not consider the likelihood of exposure to bystanders, which is based primarily on the characteristics of a pesticide that increase its potential for drift. In this study, where the entire rural population is included, bystander exposure may have been relevant to the majority of individuals. Another limitation of the EIQ_{HUMAN} is that it only includes dermal and chronic toxicity measures. Inclusion of respiratory toxicity may have been needed to make the indicator sensitive to the health outcomes of bystanders. Also, if teratology measures had been included then the pesticide risk indicator may have been more sensitive to congenital anomalies.

Before deciding on the EIQ_{HUMAN} as the basis for a single pesticide risk indicator, the original plan of this study was to weight the amount of each active ingredient by different toxicity measures relevant to each health outcome examined. For example, toxicity measures of teratology would have been used when examining congenital anomalies, neurotoxicity measures would have been employed for neurological outcomes, and measures of dermal irritation would have been included for diseases of the skin. Regrettably these toxicity measures were not available for enough of the active ingredients. Although the Pest Management Regulatory Agency (PMRA) of Canada produces Proposed Regulatory Decision Documents (PRDDs) that include the desired toxicity measures for each pesticide they approve, these documents are not available to the public except during the approval process. A PMRA representative (personal communication, August 4, 2004) stated that this toxicity information is proprietary to the

companies that produce the pesticides. The PMRA evaluates the toxicity information that the companies submit and therefore this information belongs to the companies themselves. Based on this system the Canadian public does not have access to knowledge regarding the toxicity of pesticides approved in Canada, an extreme lack of transparency. The Environmental Protection Agency (EPA) of the United States has a much more transparent system and provides on their website both Fact Sheets of New Active Ingredients and Reregistration Eligibility Decisions (REDs). The EPA only has information posted, however, on pesticides that were approved or reapproved in 1997 or later, thereby excluding a number of pesticides. Based on these limitations in data availability, creating more specific toxicity weighted measures of pesticide risk was not possible in this study.

6.3. Study Limitations

6.3.1. Study Design

The cross-sectional design of the study limits it ability to determine causation. The relative simplicity of the cross-sectional design was balanced, however, by the exploratory nature and breadth of this research. As the first step in examining whether environmental health related data could be utilized in conjunction with the Population Health Research Data Repository, housed at the Manitoba Center for Health Policy (Section 4.1.1.), the study had broad exploratory goals. Also contributing to the scope of the study is the fact that agricultural pesticides have been associated with a wide range of health outcomes, which were explored. Therefore the cross-sectional design presents limitations but was suitable to the exploratory nature of the study.

6.3.2. Health Outcomes

Key to the exploratory nature of the study, but also limiting its conclusions, are the broad groupings of health outcomes that were utilized. Health outcomes were based, for the most part, on the chapter level of the ICD-9-CM (Section 4.3.2.). This resulted in health outcomes grouped according to body system or type of disease. Due to the differences in health outcomes included within these chapters it is possible that significant associations between pesticide indicators and specific health outcomes may have been masked or underestimated (Sections 6.1.2. and 6.1.4.).

The associations between health outcomes and agricultural pesticides may have also been underestimated due to affected individuals not seeking treatment (Kirkhorn & Schenker, 2002). Examining Iowa farmers, from a sub-set of the Agricultural Health Study cohort, it was determined that "among those with symptoms [from a high pesticide exposure event], approximately 35% sought medical treatment from a health care provider" (Alavanja et al., 2001, p. 560). The associations found in this study would be underestimations if individuals with a health outcome due to pesticides were less likely to go to a heath care professional than others with the same condition. If the tendency for individuals, consciously or unconsciously affected by pesticides, to contact the health care system varies by CCS then this could present a potential source of bias.

6.3.3. Pesticide Indicators

The pesticide indicators were grouped by broad pesticide type rather than by specific pesticides or pesticide chemical classes. The use of pesticide types could have led to the underestimation of detected associations with the health outcomes as the biological pathways by which pesticides affect health vary greatly by pesticide (Cantor et al., 1992). Despite this epidemiological limitation, the creation of pesticide indicators based on pesticide type served the purpose of creating and validating an indicator that would have utility as an environmental health indicator of agricultural pesticides. Pesticide application by type is easily understood and data by type is easier to acquire. For example, the amount of agricultural herbicides, fungicides, and insecticides applied in Canada is included in the Census of Agriculture. The limitations of the pesticide risk indicator have been previously discussed (Sections 3.5.2.2. and 6.2.2.).

6.3.4. Potential Confounding

It is possible that factors that were not accounted for have confounded the results of this study. For example, data on lifestyle factors such as smoking or exercise levels were not included in the study. Also individuals who are at the greatest risk of pesticide exposure will also most likely be exposed to the potential confounders of diesel fumes, livestock, or dusts. Studies have examined the level of confounding between pesticides and other farm exposures, however, and found that the ”magnitude of bias due to confounding is likely to be minimal” (Coble et al., 2002, p. 418).

Additionally there may be social factors that impact the treatment prevalence of certain health outcomes in a region that are also related to the amount of pesticides used. For example, the association between insecticides and congenital anomalies in live births found in this study could be confounded if women in areas with higher pesticide use have fewer elective pregnancy terminations of congenital anomalies following prenatal diagnosis. Factors such as less access to prenatal screening or social norms that deter elective pregnancy terminations could contribute to such a situation and should, if possible, be examined in future studies.

6.4. Study Strengths and Contributions

6.4.1. Validation of Environmental Health Indicators of Agricultural Pesticide Use and Risk

The main contribution of this study is the validation of the indicators of agricultural pesticide use and risk as environmental health indicators (EHI) through the confirmation of their association with health outcomes. The use of insecticides indicator was associated with multiple health outcomes and is therefore strongly supported as an EHI. The pesticide risk indicator and the use of any pesticide indicator (and by association herbicide and fungicide use) were also highlighted as valid EHIs, although to a lesser degree as they were only significantly associated with male eye disorders. The findings of this study, therefore, support the use of these EHIs of pesticide use and risk, especially insecticide use, in public health monitoring and surveillance.

6.4.2. Linking Pesticide Data with Administrative Health Data

This research was the first to link environmental health data, specifically agricultural pesticide data, to the Manitoba Population Health Research Data Repository (Repository). Through this linkage, the association between individual-level health outcomes and area-level agricultural pesticide use and risk was able to be determined. A positive aspect of using the Repository is that health outcomes that may not be feasibly investigated otherwise can be examined. For example, few studies have examined perinatal conditions yet these were significantly associated with insecticide use. Another

benefit of using the Repository is that all individuals enrolled in the provincial health plan, not just those who contacted the health system, were included in the study. This is a key advantage of working with administrative databases as it results in appropriate denominators as well as population-based figures. This study included 323,368 people from crop farming areas in the rural south of Manitoba.

Focusing on the entire rural population in crop farming areas made the epidemiological portion of the study relevant to the validation of the pesticide measures as environmental health indicators. Many studies focus only on occupational exposures to farmers. These studies are more appropriate for confirming causation, as more specific exposure estimates are possible. Yet, the number of farmers is decreasing despite farmland still composing a substantial proportion of the rural environment. From a population health perspective, therefore, it could be considered most appropriate to be investigating the impact of agricultural practices, not only on farm families, but on the entire rural population, as was done in this study by linking the pesticide data with the Repository.

The potential of using the Manitoba Management Plus Program (MMPP) pesticide data in health research was also confirmed through linking this data to the Repository. The fact that the pesticide data identifies which pesticides were applied is a strength of this study. This information was used to create the pesticide risk indicator. Future research, based on this work, could use knowledge of the specific pesticides applied to analyze the association between health outcomes and specific pesticides or pesticide classes.

6.4.3. Pesticide Risk Indicator Development and Evaluation

This study created an indicator of pesticide risk after examining the most feasible and appropriate way to weight the pesticide use data by toxicity and exposure potential (Section 3.5.2.). This risk indicator was not associated with as many health outcomes as the use of insecticides (Section 6.2.2.). The workload of creating the pesticide risk indicator, compared to those of pesticide use, coupled with its performance in this study, does not recommend it for future use in its current form. The development of more specific risk indicators based on toxicological properties relevant to the specific health outcome of interest still has potential (Section 6.2.2.).

6.4.4. Relevant and Comprehensive Literature Review

The scope of the comprehensive review of the epidemiological literature provided in this thesis is unique (Section 3.4.2.). It focused on studies where the potential for exposure due to agricultural pesticides was similar to that provided by Manitoba crop farming (Section 3.4.2.). Most reviews of the pesticide literature focus generally on whether pesticides are implicated in the causation of specific health problems. As such they often include many different types of pesticide exposure (e.g. pesticide manufacturing), a worldwide scope, or broad farming exposures (e.g. intensive horticulture, livestock, etc.). This review provides an assessment of the health outcomes that might be expected, in the Canadian and American context, due to agricultural pesticide use in the crop farming of broad acreages.

6.4.5. Foundation for Future Research

As an exploratory research study, one of the goals of this study was to provide direction for future research (Section 6.5.1.). Satisfying this goal, the study has highlighted health outcomes that are potentially being influenced by pesticides that could be the focus of future analysis. Also, through validating the pesticide measures organized by pesticide type, this study supports the use of the Canada Census of Agriculture measures of pesticide use in longitudinal research (Section 6.5.1.).

6.5. Recommended Future Actions

6.5.1. Recommended Future Research

This exploratory study provides the foundation for many future research projects. Initially further exploration of the same data and results could be conducted to determine which specific health outcomes or specific pesticides were responsible for the associations found in this study. Longitudinal studies could then be performed, overcoming the limitations of the cross-sectional study (Section 6.3.1.), to test these associations with more rigor. Longitudinal studies could be conducted by linking past years of the MMPP pesticide data, if they were made available, with the Repository in order to examine the impact of specific pesticides over time. However, this study also confirmed the validity of broad pesticide groups. Similar measures of herbicide, fungicide, and insecticide use are available in the Canada Census of Agriculture. Therefore, Census data could also be employed in longitudinal research.

A separate research study could revisit the ecological associations between agricultural pesticide use and risk and human health outcomes using a spatial approach. These techniques would allow for the consideration of correlations in pesticide use between adjacent areas. Such an analysis could also account for the effect of income when examining all of the health outcomes rather than only those examined in the multilevel models. Such research would address the fact that it is possible that the correlation between pesticides and certain health outcomes was masked in this study when income was not considered in the initial correlations. Using yield data, which is also available

from the MMPP, an estimation of area level gross farming income could be calculated. This measure could also be included in future ecological-level research.

6.5.2. Recommended Future Policy Actions

6.5.2.1. Monitor Environmental Health Indicators of Agricultural Pesticides

The findings of this study support the monitoring of the examined pesticide indicators as environmental health indicators. The availability of similar Census values, in addition to the MMPP pesticide data available in Manitoba, makes this feasible. This research found associations between select health outcomes and all of the developed pesticide indicators, but the indicator of insecticide use was associated with an increase in multiple health outcomes (eye diseases, congenital anomalies, and perinatal conditions). Hence, monitoring of insecticide use and its associations with these health outcomes seems especially prudent.

Creation of a Canadian database for the systematic monitoring of pesticide use and the health effects of pesticides would be also advantageous. In California such reporting systems for both pesticide use and pesticide-related illness exist (Alarcon et al., 2005; Reynolds, Behren, Gunier, Goldberg, Harnly et al., 2005; Reynolds et al., 2004). In Canada, the Office of the Auditor General has also recommended the monitoring of both pesticide use and the health effects of pesticides (Commissioner of the Environment and Sustainable Development, 2003).

6.5.2.2. Reduce Pesticide Use and Level of Harm of Pesticide Use

To what extent the results of this study are employed is dependent on how much one follows the precautionary principle. As a cross-sectional study, it cannot be confirmed that agricultural pesticides, especially insecticides, are adversely affecting health. Yet the fact that an association was found, even when the entire population of the rural south of Manitoba was included, not just those who were occupationally exposed, may be cause for concern. Simultaneous to further research, it is prudent to work towards a reduction in pesticide use and the harm associated with pesticide use. That being said, it is important to remember the strong effect of income on health and to strive towards reductions in pesticides that do not negatively affect the livelihood of farmers.

A full analysis of appropriate agronomical methods for reducing pesticide use and risk is beyond the scope of this thesis, but many different types of policies would be warranted. Farmers need to be aided in reducing their pesticide use through greater education and support. The uptake of integrated pest management techniques is a move in this direction. Shifts to less toxic pesticides, such as *Bacillus thuringiensis Kurstaki* (Pearce, Habbick, Williams, Eastman, & Newman, 2002), would also be beneficial. Additionally, many specific changes, such as choosing lower volatility pesticides or changing the pesticide droplet size, can effect the potential for pesticide exposure (Section 3.3) (Dowling & Seiber, 2002). The reduction of pesticide use and risk needs to be a priority, with a variety of actions being undertaken.

6.5.2.3. Increase Public Education

Considering the potential harmful effects of pesticides on the health of rural Manitobans it would be prudent to increase public education regarding the potential risks to health of pesticides. Based on the results of this study, where perinatal conditions and congenital anomalies were both significantly associated with insecticide use, it seems reasonable to adopt a precautionary principled approach and educate couples who are planning on conceiving or who are pregnant. Educating couples who have not yet conceived is recognizably challenging as they have not yet accessed the health care system for prenatal care.

6.5.2.4. Modify Pesticide Approval Process

Despite the limitations of the study, the fact that associations were found when the entire rural population was included and broad pesticide groupings were employed highlights cause for concern regarding the health impacts of agricultural pesticides under normal practices. Considering the fact that both perinatal conditions and congenital anomalies were significantly associated with insecticide use, it is possible that the pesticide approval process performs better at safeguarding adult health than that of the fetus.

The Office of the Auditor General of Canada has documented many concerns about the pesticide approval process that could lead to approved pesticides harming human health (Commissioner of the Environment and Sustainable Development, 2003). First, many pesticides have not been recently re-evaluated and therefore older pesticides may not

meet current standards (Commissioner of the Environment and Sustainable Development, 2003). Also many pesticides are repetitively approved with emergency or temporary registrations, which do not receive the same testing rigor (Commissioner of the Environment and Sustainable Development, 2003). Additionally, exposure estimations used in the pesticide approval process are based on assumptions of full compliance with guidelines (Commissioner of the Environment and Sustainable Development, 2003). These assumptions may be incorrect, which leads to an underestimation of risks. Based on these and others factors Sears and colleagues (2006), in their examination of the pesticide approval process, state that pesticide "assessment does not approach standards for ethics, rigour or transparency in medical research. Canada needs a stronger regulator for pesticides" (Sears, Walker, van der Jagt, & Claman, 2006, p. 229). The challenges of the pesticide approval process need to be addressed in order to adequately safeguard the health of Canadians.

Additionally, information regarding pesticides approved by the Pest Management Regulatory Agency (PMRA) should be available to the Canadian public (Section 6.2.2.). Without this information Canadians are reliant solely the decisions of the PMRA and are not able to make informed choices for themselves. In combination with the potential limitations of the pesticide approval process, the lack of transparency is especially alarming. Greater access to information on approved pesticides would also allow researchers to perform more rigourous studies of pesticide health effects, further enhancing the health of Canadians.

7. REFERENCE LIST

Alarcon, W. A., Calvert, G. M., Blondell, J. M., Mehler, L. N., Sievert, J., Propeck, M., et al. (2005). Acute illnesses associated with pesticide exposure at schools. *JAMA, 294,* 455-465.

Alavanja, M. C., Dosemeci, M., Samanic, C., Lubin, J., Lynch, C. F., Knott, C., et al. (2004). Pesticides and lung cancer risk in the Agricultural Health Study cohort. *American Journal of Epidemiology, 160,* 876-885.

Alavanja, M. C. R., Hoppin, J. A., & Kamel, F. (2004). Health effects of chronic pesticide exposure: Cancer and neurotoxicity. *Annual Review of Public Health, 25,* 155-197.

Alavanja, M. C., Samanic, C., Dosemeci, M., Lubin, J., Tarone, R., Lynch, C. F., et al. (2003). Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. *American Journal of Epidemiology, 157,* 800-814.

Alavanja, M. C. R., Sandler, D. P., Lynch, C. F., Knott, C., Lubin, J. H., Tarone, R., et al. (2005). Cancer incidence in the Agricultural Health Study. *Scandinavian Journal of Work, Environment and Health., 31(Suppl. 1),* 39-45.

Alavanja, M. C., Sandler, D. P., McMaster, S. B., Zahm, S. H., McDonnell, C. J., Lynch, C. F., et al. (1996). The Agricultural Health Study. *Environmental Health Perspectives, 104,* 362-369.

Alavanja, M. C. R., Sprince, N. L., Oliver, E., Whitten, P., Lynch, C. F., Gillette, P. P., et al. (2001). Nested case-control analysis of high pesticide exposure events from the Agricultural Health Study. *American Journal of Industrial Medicine, 39,* 557-563.

Arbuckle, T. E., Cole, D. C., Ritter, L., & Ripley, B. D. (2005). Biomonitoring of herbicides in Ontario farm applicators. *Scandinavian Journal of Work, Environment and Health, 31(Suppl. 1),* 90-97.

Arbuckle, T. E., Lin, Z., & Mery, L. S. (2001). An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. *Environmental Health Perspectives, 109,* 851-857.

Arbuckle, T. E., & Sever, L. E. (1998). Pesticide exposures and fetal death: A review of the epidemiologic literature. *Critical Reviews in Toxicology, 28,* 229-270.

Baldwin, R. T., & Preston, M. S. (2004). Epidemiology of brain tumors in childhood: A review. *Toxicology and Applied Pharmacology, 199,* 118-131.

Beane Freeman, L. E., Bonner, M. R., Blair, A., Hoppin, J. A., Sandler, D. P., Lubin, J. H., et al. (2005). Cancer incidence among male pesticide applicators in the Agricultural Health Study cohort exposed to diazinon. *American Journal of Epidemiology, 162,* 1070-1079.

Bell, E. M., Hertz-Picciotto, I., & Beaumont, J. J. (2001a). A case-control study of pesticides and fetal death due to congenital anomalies. *Epidemiology, 12,* 148-156.

Bell, E. M., Hertz Picciotto, I., & Beaumont, J. J. (2001b). Case-cohort analysis of agricultural pesticide applications near maternal residence and selected causes of fetal death. *American Journal of Epidemiology, 154,* 702-710.

Blair, A., Sandler, D., Tarone, R., Lubin, J., Thomas, K., Hoppin, J. A., et al. (2005). Mortality among participants in the Agricultural Health Study. *Annals of Epidemiology, 15,* 279-285.

Blair, A., Sandler, D., Thomas, K., Hoppin, J. A., Kamel, F., Coble, J., et al. (2005). Disease and injury among participants in the Agricultural Health Study. *Journal of Agricultural Safety and Health, 11,* 141-150.

Blair, A., & Zahm, S. H. (1995). Agricultural exposures and cancer. *Environmental Health Perspectives, 103(Suppl. 8),* 205-208.

Bloomquist, J. R. (1996, January 9). *Insecticides: Chemistries and characteristics*. Retrieved October 9, 2005, from University of Minnesota Web site: http://ipmworld.umn.edu/chapters/bloomq.htm

Blundell, T. (2005). *Crop spraying and the health of residents and bystanders*. London, United Kingdom: Royal Commission on Environmental Pollution.

Bonner, M. R., Lee, W. J., Sandler, D. P., Hoppin, J. A., Dosemeci, M., & Alavanja, M. C. (2005). Occupational exposure to carbofuran and the incidence of cancer in the Agricultural Health Study. *Environmental Health Perspectives, 113,* 285-289.

Bowen, S., Martens, P., & *The Need to Know* Team (2005). Demystifying knowledge translation: Learning from the community. *Journal of Health Services Research and Policy, 10,* 203-211.

Boyens, I. (2001). *Another season's promise: Hope and despair in Canada's farm country*. Toronto, Ontario, Canada: Penguin Canada.

Briggs, D. J. (1999). *Environmental health indicators: Framework and methodologies*. Geneva: World Health Organization.

Briggs, D. J. (2003). *Making a difference: Indicators to improve children's environmental health*. Geneva, Switzerland: World Health Organization.

Brimner, T. A., Gallivan, G. J., & Stephenson, G. R. (2005). Influence of herbicide-resistant canola on the environmental impact of weed management. *Pest Management Science, 61,* 47-52.

Brophy, J. T., Keith, M. M., Gorey, K. M., Laukkanen, E., Hellyer, D., Watterson, A., et al. (2002). Occupational histories of cancer patients in a Canadian cancer treatment center and the generated hypothesis regarding breast cancer and farming. *International Journal of Occupational and Environmental Health, 8,* 346-353.

Burns, C. J. (2005). Cancer among pesticide manufacturers and applicators. *Scandinavian Journal of Work, Environment and Health, 31(Suppl. 1),* 9-17.

Calvert, G. M., Plate, D. K., Das, R., Rosales, R., Shafey, O., Thomsen, C., et al. (2004). Acute occupational pesticide-related illness in the US, 1998-1999: Surveillance

findings from the SENSOR-pesticides program. *American Journal of Industrial Medicine, 45,* 14-23.

Canadian Institute for Health Information. (2006). *How healthy are rural Canadians? An assessment of their health status and health determinants*. Ottawa, Ontario, Canada: Author.

Canadian Institutes of Health Research. (2004). *Knowledge translation strategy 2004-2009: Innovation in action*. Ottawa, Ontario, Canada: Author.

Cantor, K. P., Blair, A., Everett, G., Gibson, R., Burmeister, L. F., Brown, L. M., et al. (1992). Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Research, 52,* 2447-2455.

Carreon, T., Butler, M. A., Ruder, A. M., Waters, M. A., Davis King, K. E., Calvert, G. M., et al. (2005). Gliomas and farm pesticide exposure in women: The Upper Midwest Health Study. *Environmental Health Perspectives, 113,* 546-551.

Centers for Disease Control and Prevention, National Center for Environmental Health, Division of Environmental Hazards and Health Effects, Environmental Public Health Indicators Project. (2006, January). *Environmental public health indicators*. Retrieved December 6, 2006, from http://www.cdc.gov/nceh/indicators/pdfs/ephi.pdf

Cessna, A. J., & Grover, R. (2002). Exposure of ground-rig applicators to the herbicide bromoxynil applied as a 1:1 mixture of butyrate and octanoate. *Archives of Environmental Contamination and Toxicology, 42,* 369-382.

Chen, Z., Stewart, P. A., Davies, S., Giller, R., Krailo, M., Davis, M., et al. (2005). Parental occupational exposure to pesticides and childhood germ-cell tumors. *American Journal of Epidemiology, 162,* 858-867.

Chiu, B. C. H., Dave, B. J., Blair, A., Gapstur, S. M., Zahm, S. H., & Weisenburger, D. D. (2006). Agricultural pesticide use and risk of t(14;18)-defined subtypes of non-Hodgkin lymphoma. *Blood, 108,* 1363-1369.

Chiu, B. C. H., Weisenburger, D. D., Zahm, S. H., Cantor, K. P., Gapstur, S. M., Holmes, F., et al. (2004). Agricultural pesticide use, familial cancer, and risk of non-Hodgkin lymphoma. *Cancer Epidemiology Biomarkers and Prevention, 13,* 525-531.

Chomik, T. A., & Health Canada, Population and Public Health Branch, Strategic Policy Directorate. (2001). *The population health template: Key elements and actions that define a population health approach*. Ottawa, Ontario, Canada: Health Canada.

Clements, D. (2004). *What counts? Interpreting evidence-based decision-making for management and policy*. Ottawa, Ontario, Canada: Canadian Health Services Research Foundation.

Coble, J., Hoppin, J. A., Engel, L., Elci, O. C., Dosemeci, M., Lynch, C. F., et al. (2002). Prevalence of exposure to solvents, metals, grain dust, and other hazards among farmers in the Agricultural Health Study. *Journal of Exposure Analysis and Environmental Epidemiology, 12,* 418-426.

Coggen, D. (2002). Work with pesticides and organophosphates sheep dips. *Occupational Medicine, 52,* 467-470.

Colosio, C., Tiramani, M., & Maroni, M. (2003). Neurobehavioral effects of pesticides: State of the art. *Neurotoxicology, 24,* 577-591.

Commission for Environmental Cooperation Steering Group on Children's Health and Environment Indicators, & Commission for Environmental Cooperation Secretariat. (2003, June 2). *Recommendations for the development of children's health and the environment indicators in North America*. Retrieved October 12, 2005, from http://www.cec.org/files/pdf/POLLUTANTS/CHE-Recommendations_en.pdf

Commissioner of the Environment and Sustainable Development (2003). Managing the safety and accessibility of pesticides. In *Report of the Commissioner of the Environment and Sustainable Development to the House of Commons - 2003* (pp. 1-41). Ottawa, Ontario, Canada: Minister of Public Works and Government Services Canada.

Cook, T. D. (2002). Advanced statistics: Up with odds ratios! A case for odds ratios when outcomes are common. *Academic Emergency Medicine, 9,* 1430-1434.

Cooper, G. S., Miller, F. W., & Germolec, D. R. (2002). Occupational exposures and autoimmune diseases. *International Immunopharmacology, 2,* 303-313.

Cooper, G. S., Parks, C. G., Treadwell, E. L., St Clair, E. W., Gilkeson, G. S., & Dooley, M. A. (2004). Occupational risk factors for the development of systemic lupus erythematosus. *Journal of Rheumatology, 31,* 1928-1933.

Costa, L. G. (1997). Basic toxicology of pesticides. *Occupational Medicine: State of the Art Reviews, 12,* 251-268.

De Roos, A. J., Blair, A., Rusiecki, J. A., Hoppin, J. A., Svec, M., Dosemeci, M., et al. (2005). Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. *Environmental Health Perspectives, 113,* 49-54.

De Roos, A. J., Cooper, G. S., Alavanja, M. C., & Sandler, D. P. (2005). Rheumatoid arthritis among women in the Agricultural Health Study: Risk associated with farming activities and exposures. *Annals of Epidemiology, 15,* 762-770.

De Roos, A. J., Zahm, S. H., Cantor, K. P., Weisenburger, D. D., Holmes, F. F., Burmeister, L. F., et al. (2003). Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occupational and Environmental Medicine, 60(9),* E11.

Dementi, B. (1994). Ocular effects of organophosphates: A historical perspective of Saku disease. *Journal of Applied Toxicology, 14,* 119-129.

Dich, J., Zahm, S. H., Hanberg, A., & Adami, H. O. (1997). Pesticides and cancer. *Cancer Causes and Control, 8,* 420-443.

Diez-Roux, A. V. (2000). Multilevel analysis in public health research. *Annual Review of Public Health, 21,* 171-192.

Di Monte, D. A. (2003). The environment and Parkinson's disease: Is the nigrostriatal system preferentially targeted by neurotoxins? *The Lancet Neurology, 2,* 531-538.

Dolk, H., & Vrijheid, M. (2003). The impact of environmental pollution on congenital anomalies. *British Medical Bulletin, 68,* 25-45.

Dowling, K. C., & Seiber, J. N. (2002). Importance of respiratory exposure to pesticides among agricultural populations. *International Journal of Toxicology, 21,* 371-381.

Du Plessis, V., Beshiri, R., Bollman, R. D., & Clemenson, H. (2002). *Definitions of "rural"* (Agriculture and Rural Working Paper Series, No. 61). Ottawa, Ontario, Canada: Statistics Canada, Agriculture Division.

Engel, L. S., Hill, D. A., Hoppin, J. A., Lubin, J. H., Lynch, C. F., Pierce, J., et al. (2005). Pesticide use and breast cancer risk among farmers' wives in the Agricultural Health Study. *American Journal of Epidemiology, 161,* 121-135.

Environmental Systems Research Institute, Inc. (1996). *ArcView GIS: Using ArcView GIS*. Redlands, California: Author.

Environmental Systems Research Institute, Inc. (2002). ArcView GIS software. Version 3.3. Redlands, California, Author.

Eyles, J., & Furgal, C. (2002). Indicators in environmental health: Identifying and selecting common sets. *Canadian Journal of Public Health, 93,* S62-S67.

Fait, A., Iverson, B., Tiramani, M., Visentin, S., Maroni, M., & He, F. (2001). *Preventing health risks from the use of pesticides in agriculture* (Protecting Workers' Health Series No. 1). Geneva, Switzerland: World Health Organization.

Falconer, K. (2002). Pesticide environmental indicators and environmental policy. *Journal of Environmental Management, 65,* 285-300.

Firestone, J. A., Smith-Weller, T., Franklin, G., Swanson, P., Longstreth, W. T., Jr., & Checkoway, H. (2005). Pesticides and risk of Parkinson disease: A population-based case-control study. *Archives of Neurology, 62,* 91-95.

Fitzmaurice, G., Laird, N., & Ware, J. (2004). *Applied longitudinal analysis*. Hoboken, New Jersey: Wiley.

Fleming, L. E., Gomez-Marin, O., Zheng, D., Ma, F., & Lee, D. (2003). National Health Interview Survey mortality among US farmers and pesticide applicators. *American Journal of Industrial Medicine, 43,* 227-233.

Fleming, L. E., & Herzstein, J. A. (1997). Emerging issues in pesticide health studies. *Occupational Medicine: State of the Art Reviews, 12,* 387-397.

Flower, K. B., Hoppin, J. A., Lynch, C. F., Blair, A., Knott, C., Shore, D. L., et al. (2004). Cancer risk and parental pesticide application in children of Agricultural Health Study participants. *Environmental Health Perspectives, 112,* 631-635.

Frank, A. L., McKnight, R., Kirkhorn, S. R., & Gunderson, P. (2004). Issues of agricultural safety and health. *Annual Review of Public Health, 25,* 225-245.

Furgal, C., & Gosselin, P. (2002). Challenges and directions for environmental public health indicators and surveillance. *Canadian Journal of Public Health, 93,* S5-S8.

Gallivan, G. J., Berges, H., & McGee, B. (2005, June 22). *Evaluation of the changes in pesticide risk* (New Directions in Agri-Food & Rural Research, Research Project SR9128). Retrieved October 15, 2005, from http://www.agcare.org/uploadattachments/OMAFRA-Evaluation-Pesticide-Risk.pdf

Gallivan, G. J., Surgeoner, G. A., & Kovach, J. (2001). Pesticide risk reduction on crops in the province of Ontario. *Journal of Environmental Quality, 30,* 798-813.

Garry, V. F., Harkins, M. E., Erickson, L. L., Long Simpson, L. K., Holland, S. E., & Burroughs, B. L. (2002). Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA. *Environmental Health Perspectives, 110,* 441-449.

Garry, V. F., Harkins, M., Lyubimov, A., Erickson, L., & Long, L. (2002). Reproductive outcomes in the women of the Red River Valley of the north. I. The spouses of pesticide applicators: pregnancy loss, age at menarche, and exposures to pesticides. *Journal of Toxicology and Environmental Health.Part A, 65,* 769-786.

Gauthier, E., Fortier, I., Courchesne, F., Pepin, P., Mortimer, J., & Gauvreau, D. (2001). Environmental pesticide exposure as a risk factor for Alzheimer's disease: A case-control study. *Environmental Research, 86,* 37-45.

Gladen, B. C., Sandler, D. P., Zahm, S. H., Kamel, F., Rowland, A. S., & Alavanja, M. C. R. (1998). Exposure opportunities of families of farmer pesticide applicators. *American Journal of Industrial Medicine, 34,* 581-587.

Gomez-Marin, O., Fleming, L. E., Lee, D. J., LeBlanc, W., Zheng, D., Ma, F., et al. (2004). Acute and chronic disability among U.S. farmers and pesticide applicators: The National Health Interview Survey (NHIS). *Journal of Agricultural Safety and Health, 10,* 275-285.

Gorell, J. M., Peterson, E. L., Rybicki, B. A., & Johnson, C. C. (2004). Multiple risk factors for Parkinson's disease. *Journal of the Neurological Sciences, 217,* 169-174.

Gray, H., & Schornack, D. (2002). Environmental public health surveillance for healthy environments. *Canadian Journal of Public Health, 93,* S4.

Hamilton, N., & Bhatti, T. (1996, February). *Population health promotion: An integrated model of population health and health promotion*. Retrieved February 1, 2006, from http://www.phac-aspc.gc.ca/ph-sp/phdd/php/php.htm

Hanke, W., & Jurewicz, J. (2004). The risk of adverse reproductive and developmental disorders due to occupational pesticide exposure: An overview of current epidemiological evidence. *International Journal of Occupational Medicine and Environmental Health, 17,* 223-243.

HCIA Inc. (1994). *International classification of diseases 9th revision clinical modification: Vol. 1. Diseases: Tabular List*. Baltimore, Maryland: Author.

He, F. (2000). Neurotoxic effects of insecticides - Current and future research: A review. *Neurotoxicology, 21,* 829-836.

Health Canada. (2002). *Congenital anomalies in Canada - A perinatal health report, 2002*. Ottawa, Ontario, Canada: Minister of Public Works and Government Services Canada.

Health Canada. (2003). *Canadian perinatal health report 2003*. Ottawa, Ontario, Canada: Minister of Public Works and Government Services Canada.

Hodge, R. A., & Longo, J. M. J. (2002). International monitoring for environmental health surveillance. *Canadian Journal of Public Health, 93,* S16-S23.

Hopenhayn-Rich, C., Stump, M. L., & Browning, S. R. (2002). Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. *Archives of Environmental Contamination and Toxicology, 42,* 127-136.

Hoppin, J. A., Umbach, D. M., London, S. J., Alavanja, M. C. R., & Sandler, D. P. (2002). Chemical predictors of wheeze among farmer pesticide applicators in the Agricultural Health Study. *American Journal of Respiratory and Critical Care Medicine, 165,* 683-689.

Hoppin, J. A., Umbach, D. M., London, S. J., Alavanja, M. C. R., & Sandler, D. P. (2004). Diesel exhaust, solvents, and other occupational exposures as risk factors for wheeze among farmers. *American Journal of Respiratory and Critical Care Medicine, 169,* 1308-1313.

Hoppin, J. A., Umbach, D. M., London, S. J., Lynch, C. F., Alavanja, M. C., & Sandler, D. P. (2006). Pesticides associated with wheeze among commercial pesticide

applicators in the Agricultural Health Study. *American Journal of Epidemiology, 163 ,* 1129-1137.

Hurtig, A. K., Sebastian, M. S., Soto, A., Shingre, A., Zambrano, D., & Guerrero, W. (2003). Pesticide use among farmers in the Amazon basin of Ecuador. *Archives of Environmental Health, 58,* 223-228.

International Programme on Chemical Safety. (2005). *The WHO recommended classification of pesticides by hazard and Guidelines to classification 2004*. Geneva, Switzerland: World Health Organization.

Jaga, K., & Dharmani, C. (2005). The epidemiology of pesticide exposure and cancer: A review. *Reviews on Environmental Health, 20,* 15-38.

Jones, S. M., Burks, A. W., Spencer, H. J., Lensing, S., Roberson, P. K., Gandy, J., et al. (2003). Occupational asthma symptoms and respiratory function among aerial pesticide applicators. *American Journal of Industrial Medicine, 43,* 407-417.

Kamel, F., Boyes, W. K., Gladen, B. C., Rowland, A. S., Alavanja, M. C., Blair, A., et al. (2000). Retinal degeneration in licensed pesticide applicators. *American Journal of Industrial Medicine, 37,* 618-628.

Kamel, F., & Hoppin, J. A. (2004). Association of pesticide exposure with neurologic dysfunction and disease. *Environmental Health Perspectives, 112,* 950-958.

Kato, I., Watanabe-Meserve, H., Koenig, K. L., Baptiste, M. S., Lillquist, P. P., Frizzera, G., et al. (2004). Pesticide product use and risk of non-Hodgkin lymphoma in women. *Environmental Health Perspectives, 112,* 1275-1281.

Katz, A., De Coster, C., Bogdanovic, B., Soodeen, R.-A., & Chateau, D. (2004). *Using administrative data to develop indicators of quality in family practice*. Winnipeg, Manitoba, Canada: Manitoba Centre for Health Policy.

Kirkhorn, S. R., & Schenker, M. B. (2002). Current health effects of agricultural work: Respiratory disease, cancer, reproductive effects, musculoskeletal injuries, and pesticide-related illnesses. *Journal of Agricultural Safety and Health, 8,* 199-214.

Kirrane, E. F., Hoppin, J. A., Kamel, F., Umbach, D. M., Boyes, W. K., Deroos, A. J., et al. (2005). Retinal degeneration and other eye disorders in wives of farmer pesticide applicators enrolled in the Agricultural Health Study. *American Journal of Epidemiology, 161,* 1020-1029.

Kovach, J., Petzoldt, C., Degni, J., & Tette, J. (n.d.). *A method to measure the environmental impact of pesticides*. Retrieved September 5, 2006, from New York State Integrated Pest Management Program Web site: http://nysipm.cornell.edu/publications/eiq/default.asp

Lai, B. C. L., Marion, S. A., Teschke, K., & Tsui, J. K. C. (2002). Occupational and environmental risk factors for Parkinson's disease. *Parkinsonism and Related Disorders, 8,* 297-309.

Larson, J. S. (1999). The conceptualization of health. *Medical Care Research and Review, 56,* 123-136.

Last, J. M., Spasoff, R. A., Harris, S. S., & Thuriaux, M. C. (Eds.). (2001). *A dictionary of epidemiology* (4th ed.). New York: Oxford University Press.

Lee, W. J., Blair, A., Hoppin, J. A., Lubin, J. H., Rusiecki, J. A., Sandler, D. P., et al. (2004). Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. *Journal of the National Cancer Institute, 96,* 1781-1789.

Lee, W. J., Cantor, K. P., Berzofsky, J. A., Zahm, S. H., & Blair, A. (2004). Non-Hodgkin's lymphoma among asthmatics exposed to pesticides. *International Journal of Cancer, 111,* 298-302.

Lee, W. J., Colt, J. S., Heineman, E. F., McComb, R., Weisenburger, D. D., Lijinsky, W., et al. (2005). Agricultural pesticide use and risk of glioma in Nebraska, United States. *Occupational and Environmental Medicine, 62,* 786-792.

Lee, W. J., Hoppin, J. A., Blair, A., Lubin, J. H., Dosemeci, M., Sandler, D. P., et al. (2004). Cancer incidence among pesticide applicators exposed to alachlor in the Agricultural Health Study. *American Journal of Epidemiology, 159,* 373-380.

Lee, W. J., Lijinsky, W., Heineman, E. F., Markin, R. S., Weisenburger, D. D., & Ward, M. H. (2004). Agricultural pesticide use and adenocarcinomas of the stomach and oesophagus. *Occupational and Environmental Medicine, 61,* 743-749.

Levitan, L. (2000). "How to" and "why": Assessing the enviro-social impacts of pesticides. *Crop Protection, 19,* 629-636.

Levitan, L., Merwin, I., & Kovach, J. (1995). Assessing the relative environmental impacts of agricultural pesticides: The quest for a holistic method. *Agriculture, Ecosystems and Environment, 55,* 153-168.

Li, A. A., Mink, P. J., McIntosh, L. J., Teta, M. J., & Finley, B. (2005). Evaluation of epidemiologic and animal data associating pesticides with Parkinson's disease. *Journal of Occupational and Environmental Medicine, 47,* 1059-1087.

Lyons, R. F., & Gardner, P. (2001). *CIHR menu of rural health research themes: For discussion purposes only*. Ottawa, Ontario, Canada: Canadian Institutes for Health Research.

MacIntosh, D. L., Kabiru, C. W., & Ryan, P. B. (2001). Longitudinal investigation of dietary exposure to selected pesticides. *Environmental Health Perspectives, 109,* 145-150.

Manitoba Agricultural Services Corporation. (2006a, January). *Pesticide browser help*. Retrieved September 6, 2006, from http://www.mmpp.com/mcweb400.nsf/pageHelp.html?OpenPage

Manitoba Agricultural Services Corporation. (2006b, January). *Pesticide data browser*. Retrieved September 6, 2006, from http://www.mmpp.com/mcweb400.nsf/formPesticideSearch?Openform

Manitoba Agricultural Services Corporation. (2006c, March). *Production insurance: Introduction*. Retrieved September 6, 2006, from http://www.masc.mb.ca/masc_ins.nsf/webpages_allrisk1.html?OpenPage&charset=iso-8859-1

Manitoba Agricultural Services Corporation. (2006d, January). *Welcome to the Manitoba Management Plus Program (MMPP) website*. Retrieved September 5, 2006, from http://www.masc.mb.ca/mmpp.nsf/Home_Page.html?OpenPage

Manitoba Agriculture Food and Rural Initiatives, Program and Policy Analysis Branch. (2003). *2003 Manitoba agriculture yearbook*. Winnipeg, Manitoba, Canada: Author.

Manitoba Agriculture Food and Rural Initiatives (with Saskatchewan Agriculture, Food and Rural Revitalization). (2004). *Guide to crop protection 2004*.

Manitoba Agriculture Food and Rural Initiatives. (2005a, June). *Agricultural climate of Manitoba*. Retrieved September 30, 2005, from http://www.gov.mb.ca/agriculture/climate/waa50s04.html

Manitoba Agriculture Food and Rural Initiatives (with Saskatchewan Agriculture, Food and Rural Revitalization). (2005b). *Guide to crop protection 2005*.

Manitoba Centre for Health Policy. (2006a, September 30). *MCHP glossary and related terms*. Retrieved October 6, 2006, from http://www.umanitoba.ca/centres/mchp/concept/thesaurus/thesaurus.glossary.html

Manitoba Centre for Health Policy. (2006b, August 18). *Protocol for conducting administrative research* (step 4). Retrieved September 18, 2006, from http://www.umanitoba.ca/centres/mchp/protocol_external/databases.shtml

Manitoba Finance. (2005, October 7). *Manitoba economic highlights*. Retrieved October 8, 2005, from http://www.gov.mb.ca/finance/reports/pdf/highlights.pdf

Manitoba Health. (n.d.). *Are you covered?* Retrieved September 23, 2005, from http://www.gov.mb.ca/health/mhsip/index.html

Manitoba Health. (2002). Municipal electronic boundary files. hmun2002 ESRI shape file. Winnipeg, Manitoba, Canada, Manitoba Health, Health Information Management.

Martens, P., Bond, R., Jebamani, L., Burchill, C., Roos, N., Derksen, S., et al. (2002). *The health and health care use of registered First Nations people living in Manitoba: A population-based study*. Winnipeg, Manitoba, Canada: Manitoba Centre for Health Policy.

Martens, P., Fransoo, R., McKeen, N., *The Need To Know* Team (funded through CIHR), Burland, E., Jebamani, L., et al. (2004). *Patterns of regional mental illness disorder diagnoses and service use in Manitoba: A population-based study*. Winnipeg, Manitoba, Canada: Manitoba Centre for Health Policy.

Martens, P., Fransoo, R., *The Need to Know* Team (funded through CIHR), Burland, E., Jebamani, L., Burchill, C., et al. (2003). *The Manitoba RHA indicators atlas:*

Population-based comparisons of health and health care use. Winnipeg, Manitoba, Canada: Manitoba Centre for Health Policy.

Martin, S. A., Jr., Sandler, D. P., Harlow, S. D., Shore, D. L., Rowland, A. S., & Alavanja, M. C. R. (2002). Pesticide use and pesticide-related symptoms among black farmers in the Agricultural Health Study. *American Journal of Industrial Medicine, 41,* 202-209.

Maud, J., Edwards-Jones, G., & Quin, F. (2001). Comparative evaluation of pesticide risk indices for policy development and assessment in the United Kingdom. *Agriculture, Ecosystems and Environment, 86,* 59-73.

McDuffie, H. H., Pahwa, P., Robson, D., Dosman, J. A., Fincham, S., Spinelli, J. J., et al. (2005). Insect repellents, phenoxyherbicide exposure, and non-Hodgkin's lymphoma. *Journal of Occupational and Environmental Medicine, 47,* 806-816.

McDuffie, H. H., Pahwa, P., Spinelli, J. J., McLaughlin, J. R., Fincham, S., Robson, D., et al. (2002). Canadian male farm residents, pesticide safety handling practices, exposure to animals and non-Hodgkin's lymphoma (NHL). *American Journal of Industrial Medicine, 42(Suppl. 2),* 54-61.

Melnyk, L. J., Berry, M. R., & Sheldon, L. S. (1997). Dietary exposure from pesticide application on farms in the Agricultural Health Pilot Study. *Journal of Exposure Analysis and Environmental Epidemiology, 7,* 61-80.

Mitura, V., & Bollman, R. D. (2003). *The health of rural Canadians: A rural-urban comparison of health indicators* (Rural and Small Town Canada Analysis Bulletin, Vol. 4, No. 6). Ottawa, Ontario, Canada: Statistics Canada, Agriculture Division.

Moore, L. E., Gold, L., Stewart, P. A., Gridley, G., Prince, J. R., & Zahm, S. H. (2005). Parental occupational exposures and Ewing's sarcoma. *International Journal of Cancer, 114,* 472-478.

Morrison, H., Savitz, D., Semenciw, R., Hulka, B., Mao, Y., Morison, D., et al. (1993). Farming and prostate cancer mortality. *American Journal of Epidemiology, 137,* 270-280.

Mpofu, D., Lockinger, L., Bidwell, J., & McDuffie, H. H. (2002). Evaluation of a Respiratory Health Program for farmers and their families. *Journal of Occupational and Environmental Medicine, 44,* 1064-1074.

Mustard, C., Derksen, S., Berthelot, J.-M., Wolfson, M., Roos, L. L., & Carriere, K. (1995). *Socioeconomic gradients in mortality and the use of health care services at different stages in the life course*. Winnipeg, Manitoba, Canada: Manitoba Centre for Health Policy and Evaluation.

Myres, A. W., & Betke, K. (2002). Healthy environments = Healthy people. *Health Policy Research Bulletin, 4,* 5-8.

National Academy of Sciences. (1991). *Human exposure assessment for airborne pollutants: Advances and Opportunities*. Washington: National Academy Press.

National Center for Health Statistics. (2006, April 10). *NCHS definitions: Fetal death*. Retrieved from http://www.cdc.gov/nchs/datawh/nchsdefs/fetaldeath.htm

National Pesticide Telecommunications Network. (1999, December). *Pesticide formulations*. Retrieved October 6, 2006, from http://npic.orst.edu/factsheets/formulations.pdf

Pahwa, P., McDuffie, H. H., Dosman, J. A., McLaughlin, J. R., Spinelli, J. J., Robson, D., et al. (2006). Hodgkin lymphoma, multiple myeloma, soft tissue sarcomas, insect repellents, and phenoxyherbicides. *Journal of Occupational and Environmental Medicine, 48,* 264-274.

Pahwa, P., McDuffie, H. H., Dosman, J. A., Robson, D., McLaughlin, J. R., Spinelli, J. J., et al. (2003). Exposure to animals and selected risk factors among Canadian farm residents with Hodgkin's disease, multiple myeloma, or soft tissue sarcoma. *Journal of Occupational and Environmental Medicine, 45,* 857-868.

Park, R. M., Schulte, P. A., Bowman, J. D., Walker, J. T., Bondy, S. C., Yost, M. G., et al. (2005). Potential occupational risks for neurodegenerative diseases. *American Journal of Industrial Medicine, 48,* 63-77.

Pearce, M., Habbick, B., Williams, J., Eastman, M., & Newman, M. (2002). The effects of aerial spraying with Bacillus thuringiensis Kurstaki on children with asthma. *Canadian Journal of Public Health, 93,* 21-25.

Penrose, L. J., Thwaite, W. G., & Bower, C. C. (1994). Rating index as a basis for decision making on pesticide use reduction and for accreditation of fruit produced under integrated pest management. *Crop Protection, 13,* 146-152.

Pest Management Regulatory Agency, Submission Management and Information Division. (1999). *Voluntary pesticide resistance-management labelling based on target site/mode of action* (Regulatory Directive No. DIR99-06). Ottawa, Ontario, Canada: Author.

Pest Management Regulatory Agency, Submission Management and Information Division. (2000). *Technical paper: A decision framework for risk assessment and risk management in the Pest Management Regulatory Agency* (Science Policy Notice No. SPN2000-01). Ottawa, Ontario, Canada: Author.

Pest Management Regulatory Agency. (2005, August 15). *Data requirements for use site category (USC#14): Terrestrial food crops - EP*. Retrieved December 6, 2006, from http://www.pmra-arla.gc.ca/english/pdf/daco/EnglishEP/USC_14_EP_1.m.pdf

Petrelli, G., Siepi, G., Miligi, L., & Vineis, P. (1993). Solvents in pesticides. *Scandinavian Journal of Work, Environment and Health, 19,* 63-65.

Pitblado, J. R., Pong, R. W., Irvine, A., Nagarajan, K. V., Sahai, V., Zelmer, J., et al. (1999). *Assessing rural health: Toward developing health indicators for rural Canada*. Sudbury, Ontario, Canada: Laurentian University, Centre for Rural and Northern Health Research.

Pong, R. W., Pitblado, J. R., & Irvine, A. (2002). A strategy for developing environmental health indicators for rural Canada. *Canadian Journal of Public Health, 93,* S52-S55.

Priyadarshi, A., Khuder, S. A., Schaub, E. A., & Priyadarshi, S. S. (2001). Environmental risk factors and Parkinson's disease: A metaanalysis. *Environmental Research, 86,* 122-127.

Public Health Agency of Canada. (2002, November 29). *What is the population health approach*. Retrieved February 2, 2006, from http://www.phac-aspc.gc.ca/ph-sp/phdd/approach/index.html

Raudenbush, S. W., & Bryk, A. S. (2002). Hierarchical generalized linear models. In *Hierarchical linear models: Applications and data analysis methods* (2nd ed., pp. 291-335). Thousand Oaks, California: Sage Publications.

Raudenbush, S. W., Bryk, A. S., Cheong, Y. F., & Congdon, R. T., Jr. (2000). *HLM 5: Hierarchical linear and nonlinear modeling*. Lincolnwood, Illinois: Scientific Software International.

Reynolds, P., Hurley, S. E., Goldberg, D. E., Yerabati, S., Gunier, R. B., Hertz, A., et al. (2004). Residential proximity to agricultural pesticide use and incidence of breast cancer in the California Teachers Study cohort. *Environmental Research, 96,* 206-218.

Reynolds, P., Hurley, S. E., Gunier, R. B., Yerabati, S., Quach, T., & Hertz, A. (2005). Residential proximity to agricultural pesticide use and incidence of breast cancer in California, 1988-1997. *Environmental Health Perspectives, 113,* 993-1000.

Reynolds, P., Von Behren, J., Gunier, R. B., Goldberg, D. E., Harnly, M., Hertz, A., et al. (2005). Agricultural pesticide use and childhood cancer in California. *Epidemiology, 16,* 93-100.

Reynolds, P., Von Behren, J., Gunier, R., Goldberg, D. E., & Hertz, A. (2005). Agricultural pesticides and lymphoproliferative childhood cancer in California. *Scandinavian Journal of Work, Environment and Health, 31(Suppl. 1),* 46-54.

Reynolds, P., Von Behren, J., Gunier, R. B., Goldberg, D. E., Hertz, A., & Harnly, M. E. (2002). Childhood cancer and agricultural pesticide use: An ecologic study in California. *Environmental Health Perspectives, 110,* 319-324.

Ruder, A. M., Waters, M. A., Butler, M. A., Carreon, T., Calvert, G. M., Davis-King, K. E., et al. (2004). Gliomas and farm pesticide exposure in men: The Upper Midwest Health Study. *Archives of Environmental Health, 59,* 650-657.

Rull, R. P., Ritz, B., & Shaw, G. M. (2006). Neural tube defects and maternal residential proximity to agricultural pesticide applications. *American Journal of Epidemiology, 163,* 743-753.

Rumsey, K. (2002, June). *Researching health effects of pesticides on the web*. Retrieved October 9, 2005, from Northwest Coalition for Alternatives to Pesticides Web site: http://www.pesticide.org/ResPHealth.html

Rusiecki, J. A., De Roos, A., Lee, W. J., Dosemeci, M., Lubin, J. H., Hoppin, J. A., et al. (2004). Cancer incidence among pesticide applicators exposed to atrazine in the Agricultural Health Study. *Journal of the National Cancer Institute, 96,* 1375-1382.

Rusiecki, J. A., Hou, L., Lee, W. J., Blair, A., Dosemeci, M., Lubin, J. H., et al. (2006). Cancer incidence among pesticide applicators exposed to metolachlor in the Agricultural Health Study. *International Journal of Cancer, 118,* 3118-3123.

Ryan-Nicholls, K. D., & Racher, F. E. (2004). Investigating the health of rural communities: Toward framework development. *The International Electronic Journal of Rural and Remote Health Research, Education, Practice and Policy, 4(244),* 1-10.

Salam, M. T., Li, Y. F., Langholz, B., & Gilliland, F. D. (2004). Early-life environmental risk factors for asthma: Findings from the children's health study. *Environmental Health Perspectives, 112,* 760-765.

Sanborn, M., Cole, D., Kerr, K., Vakil, C., Sanin, L. H., & Bassil, K. (2004). *Systematic review of pesticide human health effects*. Toronto, Ontario, Canada: The Ontario College of Family Physicians.

SAS Institute Inc. (2003). SAS software. Version 9.1 for Unix. Cary, North Carolina, Author.

Schenker, M. B. (2005). Farming and asthma. *Occupational and Environmental Medicine, 62,* 211-212.

Schreinemachers, D. M. (2003). Birth malformations and other adverse perinatal outcomes in four U.S. wheat-producing states. *Environmental Health Perspectives, 111,* 1259-1264.

Schreinemachers, D. M. (2006). Mortality from ischemic heart disease and diabetes mellitus (type 2) in four U.S. wheat-producing states: A hypothesis-generating study. *Environmental Health Perspectives, 114,* 186-193.

Schroeder, J. C., Olshan, A. F., Baric, R., Dent, G. A., Weinberg, C. R., Yount, B., et al. (2001). Agricultural risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma. *Epidemiology, 12,* 701-709.

Scientific Software International Inc. (2000). HLM2 software. Version 5.0. Lincolnwood, Illinois, Author.

Sears, M., Walker, C., van der Jagt, R., & Claman, P. (2006). Pesticide assessment: Protecting public health on the home turf. *Paediatric Child Health, 11,* 229-234.

Sherer, T. B., Betarbet, R., & Greenamyre, J. T. (2001). Pathogenesis of Parkinson's disease. *Current Opinion in Investigational Drugs, 2,* 657-662.

Sladden, T., Beard, J., Simpson, J., & Luckie, K. (1999). Population health environmental indicators: Ecologic monitoring of environment-related health and disease trends. *Australian and New Zealand Journal of Public Health, 23,* 486-493.

Spiegel, J., & Yassi, A. (1997). The use of health indicators in environmental assessment. *Journal of Medical Systems, 21,* 275-289.

Stallones, L., & Beseler, C. (2002a). Pesticide illness, farm practices, and neurological symptoms among farm residents in Colorado. *Environmental Research, 90,* 89-97.

Stallones, L., & Beseler, C. (2002b). Pesticide poisoning and depressive symptoms among farm residents. *Annals of Epidemiology, 12,* 389-394.

Statistics Canada. (2001a). Census consolidated subdivisions, 2001 Census. cartographic boundary file, gccs046b02a_e.exe, Statistics Canada Catalogue No.: 92F0167XCE. Ottawa, Ontario, Canada, Author. 10-8-2002a.

Statistics Canada. (2001b). Profile of census divisions and subdivisions in Manitoba, 2001 Census. Beyond 20/20 data file, 95F0495XCB01002-Man.ivt, Statistics Canada Catalogue No.: 95-221-XPB. Ottawa, Ontario, Canada, Author. 2-24-2004b.

Statistics Canada. (2005). Postal code conversion file (PCCF): Update. data file, pccf46_feb05_fccp46.exe, Statistics Canada Catalogue No.: 92F0153UCE2005002. Ottawa, Ontario, Canada, Author.

Strom, S. S., Gu, Y., Gruschkus, S. K., Pierce, S. A., & Estey, E. H. (2005). Risk factors of myelodysplastic syndromes: A case-control study. *Leukemia, 19,* 1912-1918.

Subramanian, S. V., Jones, K., & Duncan, C. (2003). Multilevel methods for public health research. In I.Kawachi & L. F. Berkman (Eds.), *Neighborhoods and health* (pp. 65-111). New York: Oxford University Press.

Swanson, M. B., Davis, G. A., Kincaid, L. E., Schultz, T. W., Bartmess, J. E., Jones, S. L., et al. (1997). A screening method for ranking and scoring chemicals by potential human health and environmental impacts. *Environmental Toxicology and Chemistry, 16,* 372-383.

Tinoco-Ojanguren, R., & Halperin, D. C. (1998). Poverty, production, and health: Inhibition of erythrocyte cholinesterase via occupational exposure to organophosphate insecticides in Chiapas, Mexico. *Archives of Environmental Health, 53,* 29-35.

Travel Manitoba. (n.d.a). *Geography of Manitoba*. Retrieved September 5, 2006, from http://www.travelmanitoba.com/default.asp?page=130&node=585&menu=436

Travel Manitoba. (n.d.b). *Manitoba climate*. Retrieved September 6, 2006, from http://www.travelmanitoba.com/default.asp?page=136&node=591&menu=436

United Nations Department of Economic and Social Affairs, Division for Sustainable Development. (2001, April). *Indicators of sustainable development: Framework and methodologies* (Background Paper No. 3). Retrieved October 13, 2005, from http://www.un.org/esa/sustdev/csd/csd9_indi_bp3.pdf

United States Department of Health and Human Services, Environmental Health Policy Committee, Risk Communication and Education Subcommittee. (1998, November

20). *An ensemble of definitions of environmental health*. Retrieved October 6, 2006, from http://www.health.gov/environment/DefinitionsofEnvHealth/ehdef2.htm

United States Environmental Protection Agency. (2006a, December 1). *About pesticides*. Retrieved December 1, 2006, from http://www.epa.gov/pesticides/about/

United States Environmental Protection Agency. (2006b, May 2). *Pesticides: Glossary*. Retrieved October 4, 2006, from http://www.epa.gov/pesticides/glossary/index.html

Van der Werf, H. M. G. (1996). Assessing the impact of pesticides on the environment. *Agriculture, Ecosystems and Environment, 60,* 81-96.

Van Wijngaarden, E., Stewart, P. A., Olshan, A. F., Savitz, D. A., & Bunin, G. R. (2003). Parental occupational exposure to pesticides and childhood brain cancer. *American Journal of Epidemiology, 157,* 989-997.

Vercruysse, F., & Steurbaut, W. (2002). POCER, the pesticide occupational and environmental risk indicator. *Crop Protection, 21,* 307-315.

Von Schirnding, Y. E. (2002). Health-and-environment indicators in the context of sustainable development. *Canadian Journal of Public Health, 93,* S9-S15.

Waddell, B. L., Zahm, S. H., Baris, D., Weisenburger, D. D., Holmes, F., Burmeister, L. F., et al. (2001). Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). *Cancer Causes and Control, 12,* 509-517.

Wagner, S. L. (1997). Diagnosis and treatment of organophosphate and carbamate intoxication. *Occupational Medicine: State of the Art Reviews, 12,* 239-249.

Wang, Y., Lewis-Michl, E. L., Hwang, S. A., Fitzgerald, E. F., & Stark, A. D. (2002). Cancer incidence among a cohort of female farm residents in New York State. *Archives of Environmental Health, 57,* 561-567.

Wcislo, E., Dutkiewicz, T., & Konczalik, J. (2002). Indicator-based assessment of environmental hazards and health effects in the industrial cities of Upper Silesia, Poland. *Environmental Health Perspectives, 110,* 1133-1140.

Wingspread Conference Participants (1998). Wingspread statement on the precautionary principle. Paper presented at the Wingspread Conference, Racine, Wisconsin.

Young, H. A., Mills, P. K., Riordan, D. G., & Cress, R. D. (2005). Triazine herbicides and epithelial ovarian cancer risk in central California. *Journal of Occupational and Environmental Medicine, 47,* 1148-1156.

Zheng, T., Zahm, S. H., Cantor, K. P., Weisenburger, D. D., Zhang, Y., & Blair, A. (2001). Agricultural exposure to carbamate pesticides and risk of non-Hodgkin lymphoma. *Journal of Occupational and Environmental Medicine, 43,* 641-649.

8. APPENDICES

Appendix A: Glossary of Terms

Note: Definitions are quoted directly from referenced sources unless otherwise noted.

Active ingredient (A.I.)

The chemical or substance component of a pesticide product that can kill, repel, attract, mitigate or control a pest or that acts as a plant growth regulator, desiccant, or nitrogen stabilizer. The remainder of a formulated pesticide product consists of one or more "inert ingredients" (such as water, solvents, emulsifiers, surfactants, clay and propellants), which are there for reasons other than pesticidal activity. (United States Environmental Protection Agency, 2006b, A section)

Acute effect

An adverse effect on any living organism in which severe symptoms develop rapidly and often subside after the exposure stops. (United States Environmental Protection Agency, 2006b, A section)

Acute toxicity

Adverse effects that result from a single dose or single exposure of a chemical; any poisonous effect produced within a short period of time, usually less than 96 hours. This term normally is used to describe effects in experimental animals. (United States Environmental Protection Agency, 2006b, A section)

Adjuvants

Adjuvants often help make the pesticide stick to or spread out on the application surface….Other adjuvants aid in the mixing of some formulations when they are diluted for application. (National Pesticide Telecommunications Network, 1999, What makes up a formulation? section, para. 4)

Administrative Data / Databases

A collection of data that documents services provided by hospitals, nursing homes, and physicians. The data tracks hospital discharge summaries, physician billing claims, claims for prescription drugs, and other health related data. Using this data, researchers can study the utilization of health resources over time and the variations in rates within and across the provinces. (Katz, De Coster, Bogdanovic, Soodeen, & Chateau, 2004, p. 73)

Biomarkers

A biomarker is a biological or biochemical response to an environmental chemical which gives a measure of exposure and sometimes also of a toxic effect. (Blundell, 2005, p. 161)

Carcinogen or **carcinogenic**

Capable of causing cancer. A suspected carcinogen is a substance that may cause cancer in humans or animals but for which the evidence is not conclusive. (United States Environmental Protection Agency, 2006b, C section)

Carriers

Liquids or solid chemicals that are added to a pesticide product to aid in the delivery of the active ingredient. (National Pesticide Telecommunications Network, 1999, What makes up a formulation? section, para. 4)

Chronic effect

An adverse effect on any living organism in which symptoms develop slowly over a long period of time or recur frequently. (United States Environmental Protection Agency, 2006b, C section)

Environment

Many definitions of environment exist. In the environmental health context environment can be seen as "the suite of external factors that are important to human health" (Hodge & Longo, 2002, p. S16).

Environmental health

Many definitions of environmental health exist (United States Department of Health and Human Services, 1998). The following is the draft definition developed at a World Health Organization consultation in Sofia, Bulgaria in 1993:

> Environmental health comprises those aspects of human health, including quality of life, that are determined by physical, chemical, biological, social and psychological factors in the environment. It also refers to the theory and practice of assessing, correcting, controlling, and preventing those factors in the environment that can potentially affect adversely the health of present and future generations. (United States Department of Health and Human Services, 1998)

Environmental health indicators

An expression of the link between environment and health, targeted at an issue of specific policy or management concern and presented in a form which facilitates interpretation for effective decision-making. (Briggs, 2003, p. 2)

Fungicides

A pesticide used to control or destroy fungi on food or grain crops. (United States Environmental Protection Agency, 2006b, F section)

Fungi / Fungus

Funguses, or fungi, are types of plants that have no leaves, flowers or roots. Both words, funguses and fungi, are the plural of fungus. (United States Environmental Protection Agency, 2006b, F section)

Health indicator

A quantitative or qualitative measure that describes the state of health of a population or a community. (Pitblado et al., 1999, p. 1-2)

Health status

An indication of the risk of death of patients based on the type and number of comorbid conditions or on a number of socio-economic indicators. (Manitoba Centre for Health Policy, 2006a, Terms beginning with H section)

Herbicide

A pesticide designed to control or kill plants, weeds, or grasses. Almost 70% of all pesticide used by farmers and ranchers are herbicides. These chemicals have wide-ranging effects on non-target species. (United States Environmental Protection Agency, 2006b, H section)

International Classification of Diseases, 9th Revision, with Clinical Modifications (ICD-9-CM)

The 9th version of the ICD (International Classification of Disease) coding system (with Clinical Modifications), developed by the World Health Organization (WHO) that is used to classify diseases, health conditions and procedures. (Manitoba Centre for Health Policy, 2006a, Terms beginning with I section)

Inert ingredients

Substances that are not "active," such as water, petroleum distillates, talc, corn meal, or soaps. When discussing pesticides, inert ingredients do not attack a particular pest, but some are chemically or biologically active, causing health and environmental problems. (United States Environmental Protection Agency, 2006b, I section)

Insecticide

A pesticide compound specifically used to kill or prevent the growth of insects. (United States Environmental Protection Agency, 2006b, I section)

Integrated Pest Management (IPM)

The use of pest and environmental information in conjunction with available pest control technologies to prevent unacceptable levels of pest damage by the most economical means and with the least possible hazard to persons, property and the environment. (United States Environmental Protection Agency, 2006b, I section)

Lethal Dose 50 (LD 50)

The dose of a toxicant that will kill 50% of test organisms within a designated period of time. The lower the LD 50, the more toxic the compound. (United States Environmental Protection Agency, 2006b, L section)

Pests

Pests are living organisms that occur where they are not wanted or that cause damage to crops or humans or other animals. Examples include: insects, mice and other animals, unwanted plants (weeds), fungi, and microorganisms such as bacteria and viruses, and prions. (United States Environmental Protection Agency, 2006a, What is a pest? section)

Pesticide

Any substance or mixture of substances intended for: preventing, destroying, repelling, or mitigating any pest. Though often misunderstood to refer only to insecticides, the term pesticide also applies to herbicides, fungicides, and various other substances used to control pests. Under United States law, a pesticide is also any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant. (United States Environmental Protection Agency, 2006a, What is a pesticide? section)

Pesticide Formulation

Mixture of chemicals which effectively controls a pest. Formulating a pesticide involves processing it to improve its storage, handling, safety, application, or effectiveness. (National Pesticide Telecommunications Network, 1999, What are pesticide formulations? section)

Population Health Research Data Repository (PHRDR)

A comprehensive collection of administrative, registry, survey and other databases primarily comprising residents of Manitoba housed at Manitoba Centre for Health Policy (MCHP). It was developed to describe and explain patterns of health care and profiles of health and illness, facilitating inter-sectoral research in areas such as health care, education, and social services. The administrative health database, for example, holds records for virtually all contacts with the provincial health care system, the *Manitoba Health Services Insurance Plan* (including physicians, hospitals, personal care homes, home care, and pharmaceutical prescriptions) of all registered individuals. MCHP acts as a steward of the information in the PHRDR for agencies such as Manitoba Health. (Manitoba Centre for Health Policy, 2006a, Terms beginning with P section)

Rural

A standard definition of rural is not in use in Canada (du Plessis, Beshiri, Bollman, & Clemenson, 2002; Mitura & Bollman, 2003; Pong et al., 2002). Many definitions are socially or culturally based, however, these are rarely able to be used in the context of administrative databases (Pong et al., 2002). See *Definitions of "Rural"* by du Plessis and colleagues (2002) for a full discussion of six definitions of "rural" that can be used for national level analysis in Canada. The six definitions are based on different criteria "such as population size, population density, labour market context or settlement context" (du Plessis et al.,

2002, p. 15). The definitions also have different thresholds and are based on different geographical units (du Plessis et al., 2002).

Rural Health Indicators

Measures that can be used to reflect or describe the health conditions of rural communities or populations, relative to non-rural communities or populations. (Pitblado et al., 1999, p. 1-2)

Treatment Prevalence

The Manitoba Center for Health Policy describes treatment prevalence as follows:

> The term prevalence refers to the proportion of the population that 'has' a given disease at a given time. The administrative data used do not directly indicate who 'has' a disease, but rather who received health services 'treatment' for that disease; that is, they received some combination of physician visits, hospitalizations, or prescription drugs. Therefore, we call our indicators Treatment Prevalence values, as they reflect the use of health services for that disease. (Manitoba Centre for Health Policy, 2006a, Terms beginning with T section)

Volatile

Any substance which evaporates quickly. (United States Environmental Protection Agency, 2006b, V section)

Appendix B: Distribution of Cohort by CCS

CCS Name	CCSUID	N	Percent
Albert	4605058	377	0.12
Alexander	4601071	2,950	0.91
Alonsa	4617026	3,162	0.98
Archie	4615046	392	0.12
Argyle	4604057	1,211	0.37
Armstrong	4618037	1,692	0.52
Arthur	4605050	1,781	0.55
Bifrost	4618071	5,037	1.56
Birtle	4615055	1,592	0.49
Blanshard	4615033	644	0.20
Brenda	4605043	907	0.28
Brokenhead	4612052	4,779	1.48
Cameron	4605061	970	0.30
Cartier	4610043	3,074	0.95
Clanwilliam	4615091	1,148	0.36
Coldwell	4618044	1,335	0.41
Daly	4607075	2,000	0.62
Dauphin	4617048	1,975	0.61
De Salaberry	4602032	3,643	1.13
Dufferin	4603072	5,486	1.70
East St. Paul	4613032	7,307	2.26
Edward	4605055	691	0.21
Ellice	4615048	827	0.26
Elton	4607071	4,209	1.30
Eriksdale	4618052	1,457	0.45
Ethelbert	4617063	835	0.26
Fisher	4618068	2,684	0.83
Franklin	4602025	2,750	0.85
Gilbert Plains	4617053	1,735	0.54
Gimli	4618031	6,196	1.92
Glenella	4608072	615	0.19
Glenwood	4607051	2,208	0.68
Grahamdale	4618060	3,277	1.01
Grandview	4617057	1,711	0.53
Grey	4609017	2,941	0.91
Hamiota	4615036	1,392	0.43
Hanover	4602041	12,111	3.74
Harrison	4615069	1,118	0.35
Headingley	4611042	2,150	0.66
Hillsburg	4616045	676	0.21

CCS Name	CCSUID	N	Percent
La Broquerie	4602053	2,003	0.62
Lac du Bonnet	4601057	5,392	1.67
Lakeview	4608066	2,862	0.88
Langford	4615018	4,230	1.31
Lansdowne	4608054	931	0.29
Lawrence	4617076	655	0.20
Lorne	4604063	2,916	0.90
Louise	4604039	2,225	0.69
Macdonald	4610035	5,589	1.73
McCreary	4617034	1,108	0.34
Miniota	4615041	1,375	0.42
Minitonas	4620037	1,487	0.46
Minto	4615073	3,476	1.08
Montcalm	4603030	2,011	0.62
Morris	4603065	4,784	1.48
Morton	4605031	2,355	0.73
Mossey River	4617071	1,496	0.46
Mountain (North)	4620055	1,266	0.39
Mountain (South)	4620032	682	0.21
North Cypress	4607065	3,331	1.03
North Norfolk	4608045	4,425	1.37
Oakland	4607045	1,444	0.45
Ochre River	4617045	1,040	0.32
Odanah	4615023	443	0.14
Park (North)	4616063	431	0.13
Park (South)	4615095	959	0.30
Pembina	4604033	2,699	0.84
Piney	4601039	1,773	0.55
Pipestone	4606023	2,092	0.65
Portage la Prairie	4609024	7,173	2.22
Reynolds	4601043	1,194	0.37
Rhineland	4603036	9,012	2.79
Ritchot	4602075	5,146	1.59
Riverside	4605070	888	0.28
Roblin	4604051	2,447	0.76
Rockwood	4614036	12,816	3.96
Roland	4603062	901	0.28
Rosedale	4615078	1,725	0.53
Rossburn	4616002	2,318	0.72
Rosser	4614015	1,199	0.37
Russell	4616024	2,787	0.86
Saskatchewan	4615027	1,093	0.34
Shell River	4616049	1,905	0.59
Shellmouth-Boulton	4616038	1,041	0.32

CCS Name	CCSUID	N	Percent
Shoal Lake	4615060	1,441	0.45
Sifton	4606015	1,437	0.44
Siglunes	4618057	1,800	0.56
Silver Creek	4616019	563	0.17
South Cypress	4607038	1,421	0.44
South Norfolk	4608031	2,666	0.82
Springfield	4612047	12,262	3.79
St. Andrews	4613043	13,149	4.07
St. Clements	4613056	8,812	2.72
St. Francois Xavier	4610052	928	0.29
Stanley	4603047	3,467	1.07
Ste. Anne	4602057	6,520	2.02
Ste. Rose	4617040	2,085	0.64
Strathclair	4615064	1,353	0.42
Strathcona	4605076	650	0.20
Stuartburn	4601035	1,649	0.51
Swan River	4620041	8,308	2.57
Tache	4602069	7,809	2.42
Thompson	4603058	1,211	0.37
Turtle Mountain	4605024	3,417	1.06
Victoria	4608042	1,417	0.44
Wallace	4606028	5,418	1.68
West St. Paul	4613037	3,916	1.21
Westbourne	4608059	2,927	0.90
Whitehead	4607057	860	0.27
Whitemouth	4601046	1,851	0.57
Whitewater	4605067	758	0.23
Winchester	4605037	1,650	0.51
Woodlands	4614031	3,595	1.11
Woodworth	4606037	1,859	0.58

Appendix C: Crude and Age-Adjusted Period Prevalence of Mapped Health Outcomes by CCS for Females

CCSNAME	Crude Period Prevalence (%)			Age-Adjusted Period Prevalence (%)	
	Perinatal Conditions	Eye Disorders	Circulatory Diseases	Eye Disorders	Circulatory Diseases
Albert	50.0%	44.7%	26.3%	42.8%	24.1%
Alexander	19.0%	40.0%	29.1%	36.8%	24.8%
Alonsa	37.2%	36.1%	23.0%	33.9%	28.7%
Archie	25.0%	39.3%	18.5%	36.6%	14.8%
Argyle	42.1%	46.2%	23.4%	42.1%	20.4%
Armstrong	40.6%	40.0%	28.1%	37.2%	23.1%
Arthur	50.0%	46.8%	30.6%	41.9%	24.8%
Bifrost	20.0%	39.2%	23.9%	35.6%	23.3%
Birtle	48.0%	48.0%	27.4%	42.4%	21.5%
Blanshard	40.0%	39.7%	25.0%	37.9%	23.8%
Brenda	33.3%	44.4%	29.3%	41.4%	26.0%
Brokenhead	20.4%	38.8%	26.8%	36.1%	24.8%
Cameron	55.2%	40.4%	30.2%	36.0%	25.4%
Cartier	22.0%	36.7%	19.4%	35.9%	22.6%
Clanwilliam	39.5%	50.3%	29.4%	43.9%	24.7%
Coldwell	32.3%	40.0%	27.6%	36.2%	24.0%
Daly	54.1%	41.4%	28.3%	37.7%	24.0%
Dauphin	38.7%	41.3%	24.7%	39.9%	22.2%
De Salaberry	26.2%	39.8%	24.8%	37.4%	24.5%

CCSNAME	Crude Period Prevalence (%)			Age-Adjusted Period Prevalence (%)	
	Perinatal Conditions	Eye Disorders	Circulatory Diseases	Eye Disorders	Circulatory Diseases
Dufferin	15.9%	42.0%	27.8%	37.5%	23.6%
East St. Paul	21.9%	37.4%	19.4%	37.4%	19.9%
Edward	44.4%	49.9%	31.6%	45.3%	25.9%
Ellice	25.0%	44.5%	21.6%	41.1%	23.8%
Elton	34.4%	39.5%	18.0%	39.7%	21.5%
Eriksdale	30.2%	39.0%	29.6%	36.6%	30.2%
Ethelbert	29.4%	38.3%	30.2%	33.3%	22.2%
Fisher	20.7%	41.2%	24.5%	37.7%	24.2%
Franklin	17.8%	38.7%	22.5%	35.5%	24.3%
Gilbert Plains	41.0%	48.6%	32.4%	43.1%	25.8%
Gimli	17.8%	46.4%	32.9%	40.7%	23.4%
Glenella	42.3%	39.5%	24.5%	35.9%	22.8%
Glenwood	62.8%	48.1%	35.8%	42.0%	26.9%
Grahamdale	29.7%	43.3%	20.6%	39.9%	23.5%
Grandview	45.5%	48.7%	36.8%	41.9%	26.2%
Grey	20.0%	42.1%	24.4%	38.9%	23.0%
Hamiota	48.1%	50.8%	31.0%	42.9%	21.8%
Hanover	18.3%	36.3%	18.8%	34.4%	23.1%
Harrison	21.1%	48.8%	35.8%	42.7%	27.3%
Headingley	20.9%	37.8%	21.0%	37.6%	22.2%
Hillsburg	52.9%	39.4%	17.5%	37.9%	20.9%
La Broquerie	26.7%	35.6%	20.9%	34.3%	22.8%

CCSNAME	Crude Period Prevalence (%)			Age-Adjusted Period Prevalence (%)	
	Perinatal Conditions	Eye Disorders	Circulatory Diseases	Eye Disorders	Circulatory Diseases
Lac du Bonnet	14.9%	40.2%	30.0%	37.1%	23.6%
Lakeview	29.8%	31.3%	17.7%	29.5%	30.3%
Langford	27.8%	47.4%	29.2%	41.1%	22.2%
Lansdowne	20.0%	40.7%	21.3%	38.9%	20.4%
Lawrence	20.0%	41.5%	33.0%	36.9%	25.7%
Lorne	28.9%	46.2%	22.9%	42.0%	22.8%
Louise	22.7%	48.9%	28.4%	42.2%	21.6%
Macdonald	22.0%	38.1%	17.7%	38.1%	21.3%
McCreary	33.3%	42.7%	33.8%	36.8%	25.4%
Miniota	46.9%	45.2%	22.5%	40.7%	22.1%
Minitonas	20.7%	45.9%	25.5%	42.1%	22.6%
Minto	30.8%	47.5%	29.3%	41.6%	22.8%
Montcalm	19.0%	44.2%	26.4%	40.0%	22.4%
Morris	21.1%	38.5%	23.2%	35.3%	23.1%
Morton	49.3%	47.1%	26.1%	42.4%	21.6%
Mossey River	53.6%	40.5%	30.6%	36.5%	25.4%
Mountain (North)	25.7%	36.1%	26.7%	33.3%	25.4%
Mountain (South)	66.7%	43.0%	32.7%	38.8%	26.1%
North Cypress	44.7%	43.2%	26.6%	40.3%	24.2%
North Norfolk	28.0%	38.7%	20.4%	35.7%	21.0%
Oakland	42.1%	40.8%	22.1%	38.1%	20.2%
Ochre River	60.9%	43.8%	30.1%	41.3%	26.6%

CCSNAME	Crude Period Prevalence (%)			Age-Adjusted Period Prevalence (%)	
	Perinatal Conditions	Eye Disorders	Circulatory Diseases	Eye Disorders	Circulatory Diseases
Odanah	11.1%	38.2%	19.8%	34.4%	17.1%
Park (North)	22.2%	40.5%	24.9%	37.4%	21.7%
Park (South)	38.9%	44.0%	27.7%	40.2%	20.9%
Pembina	23.9%	41.0%	26.9%	37.5%	23.4%
Piney	16.7%	39.3%	33.3%	35.9%	27.8%
Pipestone	55.6%	45.1%	25.0%	41.0%	23.1%
Portage la Prairie	22.8%	40.9%	20.5%	39.0%	22.0%
Reynolds	20.0%	36.6%	27.5%	34.8%	24.6%
Rhineland	25.6%	39.0%	20.7%	35.7%	22.2%
Ritchot	19.1%	38.5%	18.0%	38.4%	21.1%
Riverside	40.9%	41.9%	26.3%	38.1%	25.6%
Roblin	32.5%	47.2%	34.4%	39.6%	24.6%
Rockwood	22.5%	40.9%	24.0%	39.8%	23.3%
Roland	29.6%	41.6%	22.7%	38.0%	22.1%
Rosedale	14.8%	40.6%	26.4%	37.1%	24.1%
Rossburn	39.8%	45.8%	24.3%	40.8%	24.8%
Rosser	47.4%	38.7%	19.7%	37.8%	18.5%
Russell	30.2%	45.4%	31.2%	39.7%	24.3%
Saskatchewan	37.5%	41.1%	23.0%	39.0%	21.1%
Shell River	19.6%	43.4%	19.4%	39.8%	19.1%
Shellmouth-Boulton	52.4%	42.7%	29.8%	39.0%	25.3%
Shoal Lake	50.0%	45.6%	31.9%	38.3%	22.0%

CCSNAME	Crude Period Prevalence (%)			Age-Adjusted Period Prevalence (%)	
	Perinatal Conditions	Eye Disorders	Circulatory Diseases	Eye Disorders	Circulatory Diseases
Sifton	38.3%	39.4%	24.6%	36.6%	24.0%
Siglunes	31.9%	41.1%	28.9%	37.6%	25.3%
Silver Creek	28.6%	40.4%	26.8%	37.6%	23.8%
South Cypress	38.5%	47.8%	25.6%	42.3%	21.1%
South Norfolk	22.9%	45.8%	30.5%	40.4%	25.4%
Springfield	22.0%	38.7%	18.2%	39.3%	19.3%
St. Andrews	17.8%	36.3%	22.5%	36.3%	22.5%
St. Clements	26.0%	35.1%	24.1%	34.0%	21.3%
St. Frantois Xavier	4.0%	41.4%	21.1%	42.4%	21.8%
Stanley	21.3%	38.7%	17.5%	37.7%	21.0%
Ste. Anne	23.3%	38.5%	23.3%	36.3%	24.2%
Ste. Rose	47.7%	43.0%	31.8%	39.1%	26.5%
Strathclair	24.2%	47.8%	26.5%	43.5%	24.0%
Strathcona	33.3%	52.4%	32.6%	45.4%	23.1%
Stuartburn	25.8%	43.0%	33.0%	37.4%	26.5%
Swan River	33.0%	45.0%	28.1%	40.7%	23.7%
Tache	19.2%	39.4%	17.0%	40.1%	21.1%
Thompson	28.0%	40.9%	27.3%	36.3%	24.5%
Turtle Mountain	47.8%	50.3%	30.1%	44.3%	23.3%
Victoria	38.2%	44.5%	27.5%	39.2%	22.7%
Wallace	42.9%	45.4%	28.5%	40.0%	22.9%
West St. Paul	26.5%	37.6%	25.5%	35.4%	22.4%

CCSNAME	Crude Period Prevalence (%)			Age-Adjusted Period Prevalence (%)	
	Perinatal Conditions	Eye Disorders	Circulatory Diseases	Eye Disorders	Circulatory Diseases
Westbourne	18.1%	41.4%	26.9%	36.6%	23.3%
Whitehead	56.3%	42.0%	25.3%	40.9%	24.7%
Whitemouth	23.9%	37.7%	30.5%	34.6%	27.3%
Whitewater	55.6%	42.8%	26.0%	39.8%	24.2%
Winchester	58.8%	51.6%	38.2%	43.3%	26.2%
Woodlands	28.2%	38.3%	22.2%	37.5%	22.9%
Woodworth	45.1%	45.3%	21.3%	43.3%	23.2%

Note: The crude period prevalence of perinatal conditions was mapped (Section 5.4.2.).

Appendix D: Crude Period Prevalence of Mapped Health Outcomes by CCS for Males

CCS Name	Crude Period Prevalence (%)				
	Perinatal Conditions	Congenital Anomalies	Eye Disorders	Cancer	Circulatory Diseases
Albert	75.0%	25.0%	38.9%	14.2%	20.7%
Alexander	24.4%	6.7%	33.5%	13.5%	28.1%
Alonsa	46.3%	10.3%	30.9%	7.8%	20.5%
Archie	80.0%	0.0%	27.4%	6.5%	13.7%
Argyle	33.3%	18.2%	37.8%	12.4%	23.7%
Armstrong	33.3%	6.1%	33.6%	13.2%	25.4%
Arthur	54.5%	13.6%	39.4%	13.8%	26.7%
Bifrost	27.5%	7.7%	32.7%	13.8%	20.8%
Birtle	40.0%	8.6%	39.5%	12.6%	24.6%
Blanshard	54.5%	18.2%	41.6%	10.3%	22.0%
Brenda	51.9%	25.9%	38.8%	13.0%	21.9%
Brokenhead	24.8%	8.5%	32.0%	10.3%	23.1%
Cameron	65.5%	20.7%	35.9%	13.8%	21.4%
Cartier	23.6%	14.3%	33.7%	9.1%	16.4%
Clanwilliam	55.6%	27.8%	36.4%	10.6%	24.9%
Coldwell	7.4%	11.1%	29.9%	13.6%	23.8%
Daly	51.9%	25.0%	36.2%	13.1%	24.6%
Dauphin	46.2%	11.5%	32.0%	13.1%	25.0%
De Salaberry	27.1%	9.3%	29.0%	11.9%	19.4%
Dufferin	17.5%	11.3%	38.1%	13.5%	21.7%
East St. Paul	22.4%	12.6%	29.4%	15.8%	20.0%
Edward	55.6%	11.1%	39.7%	18.4%	26.8%
Ellice	66.7%	8.3%	35.7%	10.0%	19.5%
Elton	53.5%	20.1%	35.9%	11.7%	18.6%
Eriksdale	29.1%	3.6%	33.6%	10.7%	25.4%
Ethelbert	36.4%	0.0%	34.2%	13.8%	25.8%
Fisher	30.7%	13.3%	33.4%	10.3%	23.3%
Franklin	28.2%	10.0%	34.3%	10.3%	20.0%
Gilbert Plains	34.1%	12.2%	39.3%	14.5%	27.1%
Gimli	17.7%	10.6%	40.1%	17.9%	30.2%
Glenella	34.6%	23.1%	28.3%	10.8%	21.2%

CCS Name	Crude Period Prevalence (%)				
	Perinatal Conditions	Congenital Anomalies	Eye Disorders	Cancer	Circulatory Diseases
Glenwood	44.4%	9.3%	38.7%	15.7%	26.7%
Grahamdale	36.0%	13.2%	35.0%	9.8%	17.4%
Grandview	58.1%	22.6%	39.2%	17.5%	29.1%
Grey	18.1%	16.0%	35.8%	12.8%	23.7%
Hamiota	46.7%	23.3%	42.8%	13.2%	26.2%
Hanover	21.7%	9.4%	32.7%	9.7%	16.8%
Harrison	45.0%	20.0%	36.0%	11.1%	30.8%
Headingley	18.0%	16.0%	25.0%	10.8%	14.7%
Hillsburg	14.3%	14.3%	33.8%	9.2%	17.2%
La Broquerie	21.5%	13.8%	32.3%	10.2%	18.7%
Lac du Bonnet	24.0%	12.5%	34.2%	15.6%	27.7%
Lakeview	33.9%	8.0%	23.8%	4.2%	12.8%
Langford	28.1%	13.5%	37.8%	15.4%	23.8%
Lansdowne	25.8%	12.9%	32.3%	15.0%	24.2%
Lawrence	55.6%	11.1%	35.0%	12.2%	32.9%
Lorne	37.6%	15.1%	41.7%	12.3%	20.1%
Louise	24.0%	12.0%	40.2%	11.6%	23.1%
Macdonald	20.1%	8.9%	32.2%	12.0%	17.2%
McCreary	48.0%	16.0%	36.4%	20.4%	31.6%
Miniota	45.7%	14.3%	35.2%	9.3%	18.3%
Minitonas	23.3%	3.3%	36.6%	13.7%	25.6%
Minto	34.8%	14.1%	37.2%	13.8%	23.3%
Montcalm	28.6%	11.4%	36.9%	15.7%	23.0%
Morris	28.2%	10.9%	35.0%	12.6%	22.4%
Morton	50.9%	17.5%	42.0%	13.8%	22.4%
Mossey River	45.8%	12.5%	32.6%	18.0%	26.1%
Mountain (North)	32.3%	3.2%	32.5%	12.2%	23.3%
Mountain (South)	13.3%	6.7%	31.9%	11.7%	24.9%
North Cypress	41.7%	19.8%	35.6%	12.9%	22.4%
North Norfolk	30.6%	10.6%	33.7%	7.7%	18.5%
Oakland	46.3%	7.3%	38.5%	14.2%	21.8%
Ochre River	65.2%	4.3%	38.3%	14.8%	28.2%
Odanah	37.5%	12.5%	32.6%	11.0%	21.6%
Park (North)	30.0%	10.0%	27.0%	11.1%	20.4%
Park (South)	42.9%	7.1%	32.3%	11.8%	27.4%

CCS Name	Crude Period Prevalence (%)				
	Perinatal Conditions	Congenital Anomalies	Eye Disorders	Cancer	Circulatory Diseases
Pembina	31.9%	6.9%	36.6%	14.0%	21.3%
Piney	23.5%	11.8%	31.8%	16.2%	29.2%
Pipestone	47.8%	15.2%	37.5%	13.4%	23.8%
Portage la Prairie	31.7%	15.6%	34.3%	9.7%	18.3%
Reynolds	14.8%	7.4%	31.9%	12.1%	25.4%
Rhineland	27.3%	9.6%	34.8%	11.9%	16.4%
Ritchot	23.7%	8.9%	31.0%	11.1%	17.0%
Riverside	65.4%	23.1%	40.4%	12.0%	18.6%
Roblin	27.7%	10.8%	39.5%	15.1%	25.4%
Rockwood	25.8%	13.4%	32.0%	11.3%	21.2%
Roland	24.2%	0.0%	40.1%	12.1%	18.4%
Rosedale	21.3%	10.6%	36.1%	10.9%	20.4%
Rossburn	42.7%	11.2%	39.0%	9.5%	20.1%
Rosser	5.3%	5.3%	32.2%	13.7%	21.7%
Russell	36.1%	4.9%	38.7%	15.8%	25.0%
Saskatchewan	35.5%	25.8%	37.8%	10.5%	19.5%
Shell River	36.1%	5.6%	38.1%	10.0%	21.6%
Shellmouth-Boulton	20.0%	10.0%	32.1%	12.4%	22.2%
Shoal Lake	40.0%	12.0%	37.6%	12.9%	27.3%
Sifton	46.8%	4.3%	32.2%	12.1%	18.6%
Siglunes	31.1%	9.8%	32.1%	11.5%	21.6%
Silver Creek	0.0%	0.0%	32.9%	10.6%	20.1%
South Cypress	27.8%	11.1%	35.6%	12.5%	19.8%
South Norfolk	30.6%	19.4%	39.4%	15.7%	24.5%
Springfield	18.4%	12.4%	33.8%	12.1%	19.4%
St. Andrews	25.6%	12.2%	31.0%	13.2%	22.0%
St. Clements	25.0%	12.2%	28.9%	12.6%	24.9%
St. Frantois Xavier	11.1%	11.1%	32.6%	16.2%	21.1%
Stanley	17.3%	9.3%	37.8%	10.7%	14.6%
Ste. Anne	26.8%	11.3%	34.4%	11.6%	20.2%
Ste. Rose	51.7%	10.0%	33.2%	13.8%	25.0%
Strathclair	42.5%	7.5%	38.4%	12.3%	24.4%
Strathcona	44.4%	0.0%	41.4%	17.1%	29.3%
Stuartburn	26.7%	8.3%	32.7%	15.9%	30.5%

CCS Name	Crude Period Prevalence (%)				
	Perinatal Conditions	Congenital Anomalies	Eye Disorders	Cancer	Circulatory Diseases
Swan River	29.4%	9.5%	37.4%	12.3%	23.9%
Tache	25.7%	10.4%	33.4%	10.9%	16.1%
Thompson	32.0%	0.0%	36.8%	12.0%	22.5%
Turtle Mountain	30.7%	9.3%	45.5%	14.2%	24.8%
Victoria	28.2%	10.3%	36.0%	16.2%	25.5%
Wallace	46.5%	14.0%	37.3%	15.6%	26.1%
West St. Paul	25.3%	13.8%	30.3%	14.0%	22.5%
Westbourne	27.5%	7.5%	33.1%	11.4%	24.0%
Whitehead	57.9%	21.1%	32.7%	14.3%	23.7%
Whitemouth	19.3%	17.5%	34.6%	12.8%	24.0%
Whitewater	56.0%	12.0%	39.1%	11.5%	20.8%
Winchester	52.8%	19.4%	41.8%	17.7%	30.8%
Woodlands	19.2%	10.6%	30.5%	11.0%	21.4%
Woodworth	50.9%	15.8%	33.5%	8.5%	18.7%

Note: The crude period prevalence of perinatal conditions and congenital anomalies was mapped (Section 5.4.2.).

Appendix E: Age-Adjusted Period Prevalence of Mapped Health Outcomes by CCS for Males

CCS Name	Age-Adjusted Period Prevalence (%)		
	Eye Disorders	Cancer	Circulatory Diseases
Albert	37.6%	12.1%	17.3%
Alexander	31.8%	11.7%	24.0%
Alonsa	29.1%	8.8%	25.0%
Archie	26.3%	7.4%	12.2%
Argyle	35.4%	11.2%	21.7%
Armstrong	31.6%	11.1%	21.1%
Arthur	36.4%	12.1%	23.7%
Bifrost	30.3%	13.8%	22.0%
Birtle	36.8%	11.0%	21.5%
Blanshard	39.8%	10.3%	21.3%
Brenda	37.2%	12.7%	21.1%
Brokenhead	31.0%	10.3%	23.5%
Cameron	32.3%	12.1%	19.3%
Cartier	32.7%	10.6%	20.5%
Clanwilliam	32.6%	9.4%	22.3%
Coldwell	28.0%	11.9%	20.9%
Daly	33.2%	11.7%	22.3%
Dauphin	30.7%	11.4%	21.4%
De Salaberry	28.0%	12.6%	21.4%
Dufferin	35.0%	12.7%	21.3%
East St. Paul	29.6%	16.6%	20.9%
Edward	37.1%	15.7%	22.5%
Ellice	33.7%	10.3%	20.4%
Elton	33.7%	12.5%	21.0%
Eriksdale	31.6%	10.9%	27.4%
Ethelbert	29.9%	10.0%	18.0%
Fisher	30.6%	10.2%	23.0%
Franklin	31.4%	11.3%	23.5%
Gilbert Plains	35.7%	12.3%	23.1%
Gimli	35.8%	13.6%	22.5%
Glenella	26.2%	11.0%	19.9%

CCS Name	Age-Adjusted Period Prevalence (%)		
	Eye Disorders	Cancer	Circulatory Diseases
Glenwood	35.2%	13.3%	22.9%
Grahamdale	32.9%	11.0%	20.8%
Grandview	35.1%	13.4%	22.0%
Grey	34.1%	12.9%	24.9%
Hamiota	38.8%	11.0%	22.1%
Hanover	31.4%	11.8%	22.2%
Harrison	32.6%	8.8%	24.2%
Headingley	27.8%	11.6%	15.3%
Hillsburg	32.1%	10.8%	19.9%
La Broquerie	30.3%	11.0%	21.3%
Lac du Bonnet	31.8%	12.9%	22.6%
Lakeview	21.5%	6.7%	25.1%
Langford	34.6%	13.2%	20.7%
Lansdowne	30.0%	13.6%	22.6%
Lawrence	31.7%	9.9%	24.3%
Lorne	39.1%	12.9%	22.2%
Louise	36.5%	10.1%	20.4%
Macdonald	32.1%	14.4%	21.5%
McCreary	32.8%	16.3%	25.2%
Miniota	32.4%	9.3%	19.1%
Minitonas	34.4%	12.2%	22.1%
Minto	34.4%	12.0%	20.7%
Montcalm	35.2%	14.8%	21.8%
Morris	32.9%	13.0%	24.2%
Morton	39.1%	12.4%	20.4%
Mossey River	30.6%	15.9%	22.9%
Mountain (North)	30.0%	11.2%	21.8%
Mountain (South)	29.3%	9.4%	19.8%
North Cypress	34.3%	12.9%	23.0%
North Norfolk	31.1%	8.1%	20.8%
Oakland	36.2%	13.6%	21.5%
Ochre River	35.1%	12.8%	24.6%
Odanah	31.2%	11.2%	19.8%
Park (North)	25.9%	10.1%	18.3%
Park (South)	30.6%	9.5%	21.0%
Pembina	33.8%	13.1%	20.3%

CCS Name	Age-Adjusted Period Prevalence (%)		
	Eye Disorders	Cancer	Circulatory Diseases
Piney	29.0%	13.1%	23.6%
Pipestone	34.4%	12.2%	22.0%
Portage la Prairie	32.7%	10.3%	20.5%
Reynolds	30.6%	10.8%	22.5%
Rhineland	32.5%	13.4%	20.2%
Ritchot	31.1%	13.0%	20.7%
Riverside	38.0%	12.3%	18.7%
Roblin	34.5%	12.0%	20.5%
Rockwood	31.8%	12.0%	22.7%
Roland	37.9%	12.5%	19.7%
Rosedale	33.3%	10.6%	20.4%
Rossburn	34.6%	9.7%	21.9%
Rosser	31.7%	13.1%	20.4%
Russell	35.0%	13.7%	21.9%
Saskatchewan	36.3%	10.3%	19.3%
Shell River	35.7%	9.7%	21.1%
Shellmouth-Boulton	30.1%	10.8%	19.2%
Shoal Lake	33.6%	10.3%	21.8%
Sifton	30.2%	12.1%	19.4%
Siglunes	29.5%	11.0%	21.5%
Silver Creek	31.9%	11.5%	19.3%
South Cypress	33.0%	11.5%	18.6%
South Norfolk	36.4%	14.4%	22.9%
Springfield	34.0%	12.8%	20.7%
St. Andrews	31.0%	13.2%	22.0%
St. Clements	28.5%	11.5%	22.1%
St. Frantois Xavier	32.8%	16.7%	22.3%
Stanley	36.8%	12.7%	18.0%
Ste. Anne	33.1%	12.0%	21.6%
Ste. Rose	31.1%	12.8%	23.7%
Strathclair	35.9%	11.1%	22.5%
Strathcona	39.1%	14.0%	23.6%
Stuartburn	29.5%	13.0%	25.8%
Swan River	34.4%	11.1%	21.9%
Tache	34.0%	13.3%	20.6%

CCS Name	Age-Adjusted Period Prevalence (%)		
	Eye Disorders	Cancer	Circulatory Diseases
Thompson	34.8%	11.3%	21.6%
Turtle Mountain	41.0%	12.2%	21.4%
Victoria	32.9%	14.2%	22.8%
Wallace	33.7%	13.6%	23.3%
West St. Paul	30.2%	13.6%	21.6%
Westbourne	29.8%	10.1%	21.7%
Whitehead	31.7%	14.2%	22.8%
Whitemouth	32.3%	11.6%	22.2%
Whitewater	36.8%	11.5%	20.7%
Winchester	36.6%	13.9%	24.3%
Woodlands	30.0%	11.5%	22.8%
Woodworth	32.9%	9.4%	21.5%

Note: The crude period prevalence of perinatal conditions and congenital anomalies was mapped (Section 5.4.2.).