Mapping Congenital Heart Disease and the Emission of Developmental Toxicants in Alberta, Canada: A Geographic Information System Based Framework for Supporting Interdisciplinary Research and Surveillance Monitoring

by

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Abstract

Background: Congenital heart disease (CHD) is a significant global public health issue affecting 1% of all live births and the most common lethal congenital abnormality in infancy. Although CHD may occur in the presence of chromosomal abnormalities, in most affected children, the cause is unknown. The role of environmental pollutants and socioeconomic status (SES) has recently received attention. I sought to explore the association of developmental toxicants (DTs) from industrial sources and the additional role of SES at neighborhood level and CHD in Alberta, Canada through an interdisciplinary multistep study.

Objectives: 1) To track the trends of multipollutant groups of DTs emitted by industry and the trends of CHD and explore potential associations between trends of multipollutant groups of DTs and CHD in Alberta and its urban and rural regions.

2) To investigate the potential exposure to multiple pollutant exposures on CHD development by assigning the sum of the inverse distance weighted emissions on the maternal residential postal code in urban and rural Alberta.

3) To explore the role of neighborhood low SES and its association with CHD in urban and rural Alberta.

4) To map the geographic regions at risk of CHD development from DT exposures and low SES and to determine where the variables collocate.

Methods: I acquired the emissions data reported in the Canadian National Pollutant Release Inventory (n = 18 all emitted to air) and identified CHD patients born in Alberta from 2003–2010 (n = 2415). I identified three groups of emissions after principal component analysis: Groups 1, 2, and 3. I calculated yearly crude CHD and septal defect rates and tested for correlations using Spearman with the yearly sum of DT groups using amounts and the potential toxicity risk score of the emissions. I then assigned an inverse distance weighted (IDW) DT exposure to the maternal postal code and categorized the exposure

into percentile distributions. I used Poisson and negative binomial regression models in urban and rural regions respectively to calculate CHD relative risks (RR) and (95% CI) for the IDW exposure and for SES variables. I finally mapped the locations with high risk for CHD which collocated with DT exposures and low SES.

Results: Province-wide, I found associations between Group 1 DTs and CHD and septal defect rates, when using amounts (r = 0.86, CI 0.39, 0.97 and r = 0.89, CI 0.48, 0.98, respectively) and RS (r = 0.88, CI 0.47, 0.98 and r = 0.85, CI 0.36, 0.97, respectively). Rural Group 2 DTs were positively associated with septal defect rates in both amounts released and RS (r = 0.91, CI 0.55, 0.98 and r = 0.91, CI 0.55, 0.98, respectively). For IDW exposure, the adjusted RR in urban settings was 1.8 (95% CI: 1.5, 2.3) for Group 1 and 1.4 (95% CI: 1.3, 1.6) for both Groups 2 and 3. In rural postal codes, Groups 1 and 3 emissions had a RR of 2.6 (95% CI: 1.03, 7). For SES, there was a significant increased RR of CHD in the urban and rural lowest SES tertile, (RR = 1.1 (95% CI, 1.0, 1.3) and RR = 3.0 (95% CI, 1.9, 4.8), respectively). Rural postal codes with intermediate SES also had an increased RR = 1.6 (1.1, 2.5) when compared to the highest SES tertile. Maps revealed that few postal codes were exposed to very high levels of DT emissions and low SES was more randomly distributed in both urban and rural postal codes. However most of the postal codes were in fact exposed to all three DT groups. Few postal codes collocated with the three combined DT groups and SES suggesting a localized phenomenon of environmental injustice.

Conclusions: I found a temporal decrease in emissions and CHD rates in rural regions and a potential positive association between CHD and septal defect rates and mixtures of organic compounds with or without gases. Few postal codes exposed to high levels of emissions and low neighborhood SES were independently associated with an increased risk of CHD in both urban and rural regions of Alberta. Rural postal codes with intermediate SES also demonstrated an increased risk of CHD indicating that the impact of SES maybe more complex in those regions. Few postal codes collocated with the three combined DT groups and SES suggesting a localized phenomenon of environmental injustice.

Preface

This thesis is an original work of Deliwe Precious Ngwezi. The reported research studies which form this thesis received ethics approval from the University of Alberta Health Research Ethics Board: Study Name: ***" Mapping Congenital Heart Disease and the Emission of Developmental Toxicants in Alberta, Canada: A Geographic Information Systems (GIS) based Framework for Supporting Interdisciplinary Research and Surveillance Monitoring",*** Pro000254428, approved on January 27,2012 and from the University of Calgary's Conjoint Health Research Ethics Board of the Faculties of Medicine, Nursing and Kinesiology, Ethics ID: E-24758, approved on September 11,2012.

Chapter 2 of the thesis has been published as Deliwe Precious Ngwezi, Lisa K. Hornberger, Jose Luis Cabeza-Gonzalez, Sujata Chandra, Deborah Fruitman and Alvaro Osornio-Vargas, ***"Tracking Trends in Emissions of Developmental Toxicants and Potential Associations with Congenital Heart Disease in Alberta, Canada"***. *Challenges*. 2018,9,28. Chapter 3 of the thesis has been published as Deliwe P. Ngwezi, Lisa K. Hornberger, Jesus Serrano-Lomelin , Charlene C. Nielsen , Deborah Fruitman and Alvaro Osornio-Vargas***, "Industrial Developmental Toxicants and Congenital Heart Disease in Urban and Rural Alberta, Canada".*** *Challenges* 2018, 9, 26, 1-16. In both chapters, with the supervision of Drs Lisa K Hornberger and Alvaro Osornio-Vargas, I was responsible for 1) designing the study, 2) collecting and analyzing and interpreting the data, and 3) writing the first draft and revisions of the manuscript

Chapters 1, 4 and 5 will also be submitted for publication in peer reviewed journals shortly.

Dedication

This thesis is dedicated firstly to my father Professor Arthur August Ngwezi and my mother Jacobeth Matlotlo Ngwezi for their steadfast love, encouragement and for instilling the love of God and the pursuit of knowledge to all seven of their children.

To the memory of my Uncle Theophilus "Bigboy" Koopa and Professor Bongani Mayosi who went home to heaven too soon.

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Lastly, this labor of love is for all the children all over world who are born with congenital heart disease. They are the brave young hearts who strive to live and reach their best potential despite their imperfect hearts. I sincerely hope and pray that my research has contributed in small ways to the collective efforts of finding the answers that the families of affected children are seeking.

"It Always Seems Impossible Until It Is Done"

Nelson Mandela

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When I left South Africa in August 2011 to start this journey, little did I know it would take seven years to accomplish my mission in a very cold country, Alberta, Canada. It was an extremely lonely and trying endeavor peppered with highs and lows, laughs and cries, triumphs and defeat, courage and fear, strength and weariness, hope and despair. Through it all, I am glad God's grace, love and mercy kept my mind, body and soul in perfect peace: ***Isaiah 26:3 "You will keep him in perfect peace whose mind is stayed on You, because he trusts in You".***

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book***:" The North Face of God".*** She prophetically told me it would not be a walk in the park and all her predictions came to pass. My experiences have indeed been like climbing the metaphorical Mount Everest's North Face. It was oftentimes treacherous but exciting too. The view from the top however is worth every drop of tear, blood and sweat. Thank you for being my spiritual north star Nomi. Thank you to your loving husband and brother in law Mr Joseph Sebata, for taking time to visit me in Alberta and taking the road trip to Banff with me. That was the most joyous moment in my life to share life experiences with you. Thank you to my brothers, Sibusiso, Lwazi and Lifa for quietly supporting and praying for me. I love you very much my dear brothers. Thank you to all my relatives from the Ngwezi, Koopa, Maine, Moruke and Tshotlang families for your kindness bestowed to me over the years. One of my champions is my dear cousin, Mr Papi Nkoli who was instrumental in making the adventure to Canada come true. I started learning how to write a research proposal grant from you Cousy. Thank you for never losing faith in me. You are the best and I love you endlessly.

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List of Abbreviations

ACASS	**Alberta Congenital Anomalies Surveillance System**
APVR	Anomalous Pulmonary Venous Return
ASD	Atrial Septal Defect
AV	Average
AVSD	Atrio-Ventricular Septal Defect
CHD	Congenital Heart Disease
CI	Confidence Interval
CO	Carbon Monoxide
CSDH	Commission on Social Determinants of Health
DA	Dissemination Area
DT	Developmental Toxicant
DTEF	Developmental Toxicant Emitting Facility
d-TGA	Transposition of the Great Arteries
EF	Emitting Facility
GIS	Geographic Information Systems
IDW	Inverse Distance Weight
IQR	Inter Quartile Range
LHO	Left Heart Obstruction
MAUP	Modifiable Areal Unit Problem
NO_2	Nitrogen dioxide
NPRI	National Pollutant Release Inventory
NTD	Neural Tube Defects
OECD	Organization for Economic Cooperation and Development
PCA	Principal Component Analysis
PDA	Patent Ductus Arteriosus
$PM_{2.5}$	Particulate Matter less than 2.5 micrometers
PRTR	Pollutant Release and Transfer Registry
RHO	Right Heart Obstruction
RR	Relative Risk
RS	Risk Score
SD	Standard Deviation
SES	Socio-Economic Status
SO_2	Sulphur dioxide

SV	Single ventricle
TCE	Trichloroethylene
TEP	Toxic Equivalent Potential
TOF	Tetralogy of Fallot
WHO	World Health Organization
VOC	Volatile Organic Compound

Chapter 1 Introduction

1.1. Background

Heart broken families of children born with congenital heart disease/defect (CHD) always ask the following questions soon after the diagnosis is made: "What caused my child's defect?", "Is it something we did that caused the defect?", "Is there anything we could have done to prevent the defect?" and "Will it happen again in future pregnancies?" Like many pediatric cardiologists internationally, I was frequently asked these questions in my clinical practice in South Africa and found few answers for such families.

Less than half of all infants and children with CHD have an identifiable cause for their defect. A genetic abnormality, maternal disease and maternal drug/medication exposures are among the more commonly recognized causes. That for many the etiology of the CHD remains unknown, however, warrants a search for teratogenic factors that could potentially affect any pregnancy. The role of environmental exposures in cardiac maldevelopment has become an area of more recent interest.

In the fall of 2011, I embraced the opportunity to enter a graduate studies program at the University of Alberta, Department of Pediatrics to develop an interdisciplinary research initiative directed towards investigating the role of environmental industrial pollutants and factors associated with lower socioeconomic status (SES) in the development of CHD. I hypothesized that a multipollutant mix of industry-emitted developmental toxicants (DTs) could contribute to cardiac maldevelopment. I further hypothesized that circumstances related to lower SES could also contribute to CHD development.

This research endeavor represented a collaborative effort between me as the primary investigator, working in an interdisciplinary environment with fetal and pediatric cardiologists, perinatologists, epidemiologists, toxicologist, earth and atmospheric scientists, a geographic information systems analyst, a biostatistician and my supervisors, without whom it would not have been accomplished. This work contributes to the body of knowledge by providing new hypotheses as building blocks for ongoing research in this field.

This paper-based thesis includes four core chapters (Chapters 2 through 5). The current chapter introduces my thesis, examining the background literature, the knowledge gaps and the rationale for the proposed research objectives and hypotheses to be tested. Chapter 2 explores temporal relationships between CHD cases and mixtures of DTs released into the air as reported by the National Pollutant Release Inventory (NPRI) from 2003 to 2010 in Alberta (rural and urban). The manuscript has been accepted and published in Challenges Journal (1). Chapter 3 applies a geographic information systems (GIS) framework, to examine the effects of maternal residential proximity to DT emitting facilities using the maternal postal

codes as the unit of analysis. I assigned the sum of inverse distance weighted emissions in tonnes to the maternal postal code and determined their association with CHD cases. The manuscript has been accepted and published in Challenges Journal (2). Chapter 4 applied a validated SES score generated from several variables within the Statistics Canada population database, to explore the association between neighborhood SES and CHD. In Chapter 5, using GIS, I developed maps to visualize the areas where CHD cases, postal codes exposed to very high levels of DT emissions and low SES were situated and where they collocated. Finally, Chapter 6 provides a summary and conclusions of the research as well as potential future directions that substantiate and build on my findings with respect to the contribution of industry emitted DTs and factors associated with low SES in cardiac maldevelopment.

1.2. The Burden of Congenital Anomalies

At the beginning of the millennium, world leaders came together to formulate a vision to optimize the health of populations globally, particularly those exposed to extreme poverty and dehumanizing living conditions in countries with the lowest income per capita (3, 4). The outcome of the gathering produced eight millennium developmental goals of which the *fourth* was aimed at reducing child mortality initially from infectious diseases, pneumonia, diarrhea, prematurity, birth asphyxia and neonatal sepsis by 2015 (5). A progress report generated to track these achievements published in 2015 showed that whilst there was a marked reduction in the mortality of children less than five years of age from 90 down to 43 deaths per 1000 live births between 1990 and 2015, there was still room for more children's lives to be saved as expressed in the sustained developmental goals agenda (5-7).

Although the initial focus of the *fourth* millennium developmental goal did not include birth defects among the health issues targeted, it became clear with subsequent reviews, that birth defects are also important contributors to the ongoing mortality of infants and children of less than five years (8). They concluded that a reduction in birth defects and optimization of the care of affected infants and children were necessary next steps if further reduction of child mortality were to be realized (8, 9).

Birth defects or congenital anomalies are defined as structural or functional abnormalities, including metabolic disorders, which a newborn has from birth (10). Among all birth defects, CHD remains the most common and the most serious birth defect worldwide (4, 11). Furthermore, severe CHD is recognized as a leading cause of disability due to long term sequelae even after treatment among infants which contributes importantly to costly health care for governments and families (12) and to the emotional stress of affected families (13-15).

1.3. Epidemiology of CHD

CHD, defined as gross structural abnormalities of the heart and/or intrathoracic vessels, affects 1% of all live births, and their incidence may be higher due to a substantial number of affected conceptions which end in missed abortion or fetal loss (11, 16). Globally, the prevalence of CHD has increased in the last century, beginning from 0.6 per 1,000 live births in 1930 to 9.1 per 1,000 live births after 1995 (17, 18). With an annual birth rate of 150 million worldwide, 1.35 million infants are born with CHD every year (17) with highest rates of CHD observed in poor developing countries with high fertility and poor socio-economic circumstances (4). In Canada, major congenital anomalies occur in 3-5% of newborn infants and in 8-10% of stillbirths, and account for 23% of all infant deaths (19). Based on the Canadian Congenital Anomalies Surveillance System in 2013, the prevalence of CHD has decreased from 10.71 per 1,000 total births in 1998 to 8.51 per 1,000 total births in 2009 (19). However, these estimates may vary from province to province depending on the data source used to ascertain rates (19). In the province of Alberta, for instance, the birth prevalence of CHD has been reported to be 13 per 1,000 live births according to a report published in 2013, which is higher than the national reported prevalence (19).

Greater strides in the surgical and medical management of CHD have been achieved during the last 60 years with longer life expectancy into adulthood even for patients with severe cardiac pathologies (16). A study conducted in Quebec, in fact, showed in recent years a higher prevalence of CHD in general amongst adults (57%) than children (11%) due to increased survival to adulthood (20). A sub-analysis of severe CHD showed again a higher prevalence of CHD amongst adults (55%) compared to children (19%) (20). This has now created a new challenge, that of a growing adult population with CHD which exceeds the number of affected children born who require ongoing medical attention from repeated hospitalizations for surgical, catheter or non-surgical interventions (20). Consequently, the morbidity and mortality-related economic burden placed on healthcare systems, as well, as patients and their families are astronomical (12, 21-24). This economic burden underscores the urgency to identify the causes of CHD through collaborative research and innovative methodologies that could lead to strategies to prevent these defects in our children.

1.3.1. The Origins of CHD

Questions regarding the origin of CHD were eloquently articulated by one of the greatest pioneers of clinical pediatric cardiology, Dr. Maude Elizabeth Seymour Abbott (1869-1940) (25). She stated her questions as follows: *"Is it a fault in the germ plasm; is it true inheritance from one or other parent from their progenitors; does it lie in the environment of the developing embryo either in an altered or diseased state of maternal tissues or secretions; or does it lie in mechanical trauma inflicted in the uterus during the first weeks of pregnancy; or is there exhaustion of the parturient uterus; or is it due to disease of the*

embryo itself". It is her framework that has guided researchers in this complex subject of the etiology of CHD to date. The mechanisms of teratogenicity are classified into two categories: 1) those that occur due to errors in genetic programming of the embryo, and 2) those due to environmental factors that interact with the embryo during cardiac morphogenesis prior to 7-8 weeks (26). Approximately 15% of congenital heart defects are due to established genetic abnormalities which include single gene and larger chromosomal aberrancies (26-28). Another 5-10% of CHD cases are believed to relate to known maternal conditions (e.g., diabetes, phenylketonuria) or teratogenic drug exposures (e.g. vitamin A derivatives) (27, 29-31). However it is estimated that the combined non inherited risk factors (e.g., diabetes mellitus, infections, teratogenic drugs.) account for at least 30% of CHD (32, 33).The majority of CHD fall into the category of unknown etiology, which is thought to be polygenic or fit the criteria of multifactorial disease (28, 34). Therefore, for nearly 55% of affected children, the cause of the CHD is not known, but it is thought to be related at least in part to complex interactions between parental exposures to environmental toxicants with or without genetic interplay (35-37). The lack of sufficient and reliable information on what may constitute modifiable risks has contributed to the dearth of evidence-based strategies to reduce the burden of CHD (32, 38).

1.3.2. CHD and the Environment

A gravid woman most commonly becomes aware of her pregnancy between the 5nd and 8th week of gestation, past the critical period for cardiac development (39, 40). This results in a missed opportunity for women to modify their lifestyles and to avoid other hazardous exposures to reduce potential risks to the embryo during the vulnerable window of cardiac morphogenesis. Maternal exposure to potential environmental risk factors such as chemical pollutants could occur during the peri-conceptional period, which is defined as the three months before pregnancy through the first three months of pregnancy (41). However, there is also evidence that some of the chemicals may result in transgenerational epigenetic alterations of DNA which may be related to previous generation exposures or cause CHD in future pregnancies (36). It is in this context that the significance and the role of environmental exposures in the development of CHD are now gaining attention.

The term "environmental exposure" is a broad concept which denotes any non-genetic factors that are a part of the fetal-placental-maternal environment axis and that render the developing embryo susceptible to the accompanying ramifications. This exposure ranges from maternal factors impacting the embryo's environment such as alcohol consumption, smoking, maternal disease such as diabetes mellitus, use of teratogenic drugs including infections (e.g., rubella); to those factors associated with low SES and toxic environmental chemical and pollutant exposures.

Historically the importance of the environment in the evaluation and assessment of health was first recognized by the ancient physician Hippocrates in his monograph entitled: ***"On Airs, Waters and Places".*** He emphasized that for physicians to be able to reach the correct medical diagnosis, they should ask key questions about the patient's living environment such as the quality of air, water, and soil amongst other environmental factors (42).

1.4. Industrialization, Socio-Economic Status, Public Health and the Science of Where?

The observations made by Hippocrates of the relationship between the environment and adverse health effects were later amplified in the beginnings of industrial revolution in 1750, which began in Great Britain. Technological advances and access to coal and steel mineral resources and increasing consumer demands as a result of colonization in distant countries and growing trade relationships led to increasing exposures that ultimately had an important impact on the health of populations (43). As much as there were economic benefits with the technological innovation of machines used for mass production of goods, steam engines, construction of transportation networks by road, rail and water, and the development of financial sectors, there were simultaneous negative effects impacting particularly on the poor working class (43). The expansion of manufacturing factories created work opportunities for the populations. This was accompanied by rapid urbanization which saw a movement of people from rural subsistence to urban settlements. While this period created opportunities to enhance one's existence, the industrial revolution unfortunately created class, cultural and race divisions with extremely wealthy entrepreneurs on the one hand and very poor working class on the other. As this wave of industrialization spread across Europe and North America, environmental degradation of air, water and land ensued. These conditions were exacerbated by overcrowding, poor living conditions and sanitation and emergence of diseases such as tuberculosis, typhoid and cholera which claimed many lives amongst the poor working class (44).

The importance of the science of knowing the geographic location of disease occurrence was elegantly illustrated by Dr. John Snow in 1854 during the industrial revolution period. He demonstrated the link between cholera, poor sanitation and water contamination at a time when cholera was thought to be transmitted by air. Through what is known now as an ecologic study design, he manually mapped the residences of all the case fatalities and found a cluster around the vicinity of a contaminated water pump on Broad Street, London. This relationship was lost to the decision makers and public health professionals of the time. However, based on his analysis of the case fatalities and after much deliberations and persuasion, the authorities agreed to remove the water pump handle and the scourge of the cholera epidemic came to an abrupt halt(45). This provided strong evidence that indeed cholera was waterborne despite the absence of proof of a microbial organism at that time. The hesitation to act on behalf of the

wellbeing of populations or slow implementation of disease prevention strategies by authorities until irrefutable scientific evidence is produced is gradually diminishing today. In Canada. for example, the government has adopted a "precautionary principle" which recognizes that in certain circumstances where there are serious threats, lack of scientific evidence shall not be used to delay interventions that protect the health of the population and the environment (46).

Air pollution became a recognized issue in Canada as early as 1896 as a result of transboundary adverse effects of emissions from the Trail Smelter which was located in British Columbia (47). The pollution affected the crops of farmers in the neighboring Washington State of the United States of America. These concerns led to the establishment of the National Air Pollution Surveillance in 1969 and the promulgation of the Canadian Clean Air Act in 1971(47, 48). These regulations monitored levels of sulphur dioxide (SO_2) and particulate matter (PM) as a priority to ensure good air quality for the health of the population and environment. There have been gradual improvements in the acceptable threshold levels for criteria air pollutants (e.g. particulate matter, ozone) with the new and more stringent Canadian Ambient Air Quality Standards adopted in 2013 (49). The purpose of the environmental legislation is to protect the health of the public from these pollutants. However, recognition that people are exposed to far more chemicals than is represented by criteria pollutants largely spurred on by the Bhopal chemical disaster of 1984 in India (50), led to the establishment of pollutant inventories. This initiative is supported by the Organization of Economic Cooperation and Development (OECD) through its recommendation that its members establish pollutant release and transfer registries (PRTR) in 1996 (51). Canada, being a member and signatory of the OECD, followed suit and established the National Pollutant Release Inventory (NPRI), which made it mandatory for industries which meet the required set criteria for reporting emissions to do so annually through the promulgation of Canada's Environmental Protection Act of 1999 (52).

The Canadian NPRI tracks and manages onsite and offsite toxic chemical emissions driven by the notion that "you can only manage what you know." The advantage of the registry is that it has the capacity to capture information about which chemicals are being released, where, how much and by whom. The disadvantage is that the reported emissions are estimations based on the activity of a reporting facility. Becoming stable and most reliable in 2002, the registry has since provided opportunities to use the information in health-related research studies in Canada. Chemical exposures from either industry emissions or commercial manufacturers are becoming a serious public health concern all over the world. As an example, it is estimated that 80,000 new synthetic chemicals have been developed in the United States over the past 50 years and only 3,000 of these chemicals have been investigated for potential threat to human health and even fewer (8%) tested for potential effects on the development of infants and children (53). In addition, toxicological evaluations focus on evaluating individual pollutants with a

paucity of data available on the effect of pollutant mixtures. Despite concerns around the accuracy and validity of the self-reported emissions by industries, the NPRI registry nevertheless provides a useful tool to inform the public about the emissions. It also makes it possible for decision makers to implement strategies for surveillance and monitoring and implement necessary penalties and action where there are breaches by the industries according to section 272 and 273 of the Canadian Environmental Protection Act (52). There are also measures in place that safeguard the reliability of the information given by the industry operators such as penalties and the forfeiture of the operating license should any malfeasance be discovered on the part of the industry owners. Given the potential exposure of populations to industrial activities and the fact that little is known about the teratogenic impact of multiple pollutants, underscores the imperative to investigate the role of chemicals particularly multipollutant mixtures on the development of CHD. Some of the chemicals emitted by the industries are already known to cause some degree of biological dysfunction in the fetus or the developing child and are referred to as developmental toxicants (DTs) (54). Whether these DTs contribute to cardiac maldevelopment remains unknown for the vast majority of these chemicals.

1.4.1. Environmental Chemical Exposures, SES and CHD

1.4.1.1. Environmental Chemical Exposures: The pioneering work by Ferencz et al. in 1997, which examined occupational and domestic chemical exposures and CHD development (55), has led to a growing number of epidemiological studies which have attempted to examine the relationship between environmental chemical pollutants in various media such as air, water and soil and the development of CHD. Because of a comprehensive literature review, I have identified 74 published investigations that explore relationships between industrial chemical pollutants or environmental pollutants and CHD (Appendix A). Twenty-seven of 74 studies (36.5%) investigated occupational exposures to chemicals, the majority of which (n=23) examined maternal exposures (56-78) and only 4 examined paternal exposures (79-82). Maternal exposures to organic solvents and pesticides were associated with risk of CHD in most of these investigations (56, 58, 59, 61, 63, 70-72, 74, 76, 78); however, some demonstrated no association with CHD (57, 60, 62, 64, 65, 67-69, 73, 75). One study examined maternal occupational exposure to trace elements and heavy metals and found associations with lead (77). Among the four studies that have examined the role of paternal exposures, two studies of male firefighters exposed during emergency situations found both positive (79) and negative associations with CHD (81). The other two studies showed positive associations with CHD but examined different chemical exposures of fathers at work (80, 82). Although no systematic reviews examining the relationship between occupational exposures and CHD currently exist, my perusal of the literature suggests the majority of published studies have

focused on organic solvent exposures because these chemicals are commonly found in occupational settings, industries and the environment and the associations found are still equivocal at best (83).

Outdoor air exposures and their relationship with CHD have been the focus of 13 (18%) of the 74 studies, and most of these have examined proximity to industrial sites as a proxy for exposure (84-90). Others have used PRTR (85-88, 90, 91) which capture toxic emissions from industries to examine the relationship with CHD. Some have examined urban and rural differences in association with CHD and found residence in rural regions to be associated with septal defects, and these were largely related to agricultural pesticide exposures (92-94). Other studies examining the role of outdoor exposures related to residence in various geographic areas, such as municipality or census tract that hosted hazardous facility or facilities, found associations with CHD (91, 95). Finally, one outdoor study found that paternal exposure to phthalates was associated with ventricular septal defects (96).

With regards industrial chemical exposures, no systematic reviews have been performed examining outdoor industrial chemical exposures. Most studies published to date have used proximity to industrial facilities as a proxy for exposure and have not incorporated the actual amounts of chemicals released by the facilities in their analysis. However, in 2008, Wigle et al. (97) published a review on the epidemiological evidence of relationships between reproductive and child health outcomes and environmental chemicals. From this review, the evidence regarding chemical exposures and CHD occurrence generally remained inconclusive.

Several studies (20 of the 74 studies, 27%) have investigated the role of ambient air pollution and CHD in urban areas from sources such as traffic, coal-fired power stations and domestic heating and cooking (98-117). These studies examined criteria pollutants such as nitrogen dioxide (NO_2), sulphur dioxide (SO_2), carbon monoxide (CO), ozone and particulate matter less than 2.5 and 10 micrometers in aerodynamic diameter ($PM_{2.5}$) and (PM_{10}) measured from fixed monitoring stations (118). The studies revealed heterogeneity in the pollutant combinations assessed and CHD development. All the studies represented case control studies and assigned exposure to the vulnerable window of cardiogenesis; however, the effects observed varied between the studies. Interestingly, one study by Stingone et al. examined multipollutant exposures from urban air pollutants and found associations with left ventricular outflow tract obstructions (108).Two recent meta-analyses conducted by Vrijheid et al. 2011 and Chen et al. 2014 (119, 120) concluded that NO_2 and SO_2 were associated with increased risk of coarctation of aorta and tetralogy of Fallot (TOF). PM_{10} was also associated with an increased risk of atrial septal defects (ASD). In summary, urban air pollution thus far, carries the strongest evidence in relation to development of CHD as observed in these meta-analyses.

Very few studies, six (8%) of the 74, have examined the role of indoor exposures in CHD development. One study which examined the relationship between house renovations and CHD found associations with conotruncal and anomalous pulmonary venous return defects (121). Other studies examining heavy metals found in maternal hair identified associations with CHD (122-124). One other study demonstrated associations between indoor air pollution from soil contaminated by trichloroethylene (TCE) and tetrachloroethylene through soil vapor intrusion into the indoor environment and CHD (125).

Finally, ingestion of contaminated water has been the subject of focus in several studies. Metalloids such as arsenic have been associated with coarctation of aorta and CHD overall (126, 127). The relationship between organic compounds in water and CHD has been less definitive with some reporting associations (128-130) and others not (131-133).

In summary, the body of literature that examines the role of chemical pollutant exposures and CHD development has been expanding since the first published work from the Baltimore Washington Infant Study by Ferencz et al. (55); however, the studies have employed various methodologies and examined various media of exposure. A few meta-analyses on ambient air pollution demonstrated consistent associations between NO_2, SO_2 and CHD. Most of the empirical studies have investigated maternal occupational exposure to chemicals followed by studies on urban pollution exposures. Compared to other mediums of pollutant exposures, the level of evidence for ambient air pollution in urban settings is the strongest based on the meta-analyses published thus far. There is a paucity of investigations that have examined outdoor exposure to industrial chemicals, and most have used proximity to industrial facilities as a surrogate for exposure. Organic solvents have been more consistently associated with CHD from various mediums of exposure ranging from occupational studies, contaminated groundwater and industrial facilities emitting trichloroethylene (organic compound). Some experimental studies have demonstrated congenital heart anomalies in chick embryos injected with trichloroethylene (134). Even fewer studies have taken advantage of available PRTRs. There have also been a limited number of studies examining the role of indoor pollutant exposures. Finally, only a single previous study has examined multiple pollutant exposures as would occur in everyday life. Thus, there is still a need to explore further the relationships between pollutant exposures and particularly outdoor multipollutant mixtures and CHD. One other challenge related to the interpretation and comparisons of past studies that have examined the role of exposures in CHD etiology, is that different classification systems of CHD have been employed and this adds to the difficulty of reaching consensus regarding the etiology of CHD.

1.4.1.2. SES: In 1948, the World Health Organization (WHO) was established specifically to provide reliable and objective information that help to address public health concerns of all nations and also

provide evidence that would help in health policy formulations (135). In 1998, the first edition of social determinants of health was published by WHO which identified social disadvantage and poverty as the root cause of ill health even after provision of medical care (136). Earlier (1998) empirical studies examining the relationship between social determinants of health, mortality (137) and neural tube defects (138) concurred this positive association. In the 21st century today, debates around concerns of industrialization and the impacts of the social and economic factors on the well-being of human populations and the environment continue to prevail just as they did during the 18th century.

The economic, social, political and health inequalities continue to persist along class, race and gender lines and the gap between the rich and poor is growing larger daily (139). The people who generate the wealth are not the direct beneficiaries and often times are exploited, exposed to hazardous occupational conditions with no protection, and work long hours of hard labor with little income to show for their toil (139). In addition, poor people, due to lack of agency, might be exposed to hazardous environmental pollutants in the vicinity of their places of residences and thus suffer from a *"double jeopardy"* as shown in some concept papers and empirical studies on environmental justice in some places in the United States (140), including some locations in Canada (141-144). Empirical data on the relationship between socio-economic status and CHD development is still in evolution. The body of literature searched on the subject identified 28 studies including two systematic reviews using individual variables for maternal SES (145) and aggregated neighborhood SES (146) which are listed in (Appendix B). The majority of the studies (20/28, 71%) examined individual maternal SES variables and the risk of CHD (63, 65, 147-164), whilst (8/28, 29%) examined associations with SES at the area level or neighborhood level (148, 152, 165-170). Four out of the eight studies (50%) examined individual, family and neighborhood to weigh the relative contribution of each level of the SES variables in CHD development (148, 152, 167, 170).

Amongst the studies that examined individual socioeconomic variables and CHD, the variables that were examined were maternal levels of education, whether they had less than high school, completed high school or had a college education, income levels and occupation ranging from unskilled, semi-skilled or professional. Education was the variable most commonly assessed in these studies and this likely reflected the relative ease of acquiring that information through interviews rather than through registries (171). Some studies found associations between low maternal SES and CHD (147-149, 153-155, 158, 159, 164, 167), whilst other studies found no associations (63, 65, 150-152, 156, 157, 160). A recent systematic review and meta-analysis of 33 studies examining the role of SES using individual maternal variables found that maternal low education levels were associated with increased risk of CHD (145). Nevertheless, the authors concluded that despite the presence of modest evidence for a role of low SES in CHD development, this relationship has not been sufficiently explored for developed countries and there

is even less data for developing economies. Therefore, more investigations are necessary to make conclusive associations of the role of SES on CHD and to make comparisons between developed and developing economies.

Beyond the individual SES, poor material living conditions including deprived neighborhoods are increasingly being recognized as important contributors to the overall wellbeing of the populations(172). Neighborhood SES has been examined using various geographic units such as census tract or dissemination area or postal code. Composite scores or indices for the geographic unit have been generated using SES variables such as unemployment, poverty, education levels, occupation, rental occupancy, crowding of people living in the corresponding spatial unit. Amongst published studies that utilize these scores or indices, some have found associations between maternal residence in deprived neighborhoods and CHD (148, 151, 166-170), whilst others have found no associations (152, 165). In a recent meta-analysis that included four published investigations, Deguen et al. found no relationship between maternal SES and CHD (146). Interestingly, SES and its relationship with health is a complex and multifaceted construct requiring interventions at all levels and, as such, few studies have also examined the interaction of maternal individual SES with composite SES index at family or neighborhood area level to determine if they each contribute independently to CHD development (148, 152, 167, 170). The relevance of understanding which SES construct represents the most important determinant of adverse health outcomes as stated in the literature will enable decision makers to craft policies aimed at individual intervention or large-scale social policy interventions to improve the quality of life. Out of the four studies that examined multilevel SES indices, only one study found positive associations of highly deprived neighborhoods and CHD, but these effects were confounded after adjusting for individual and family SES and showed that the association was not independent of those measures of SES (170). The three remaining studies reported an increased risk of CHD; however, the confidence intervals for the effects were not significant. In addition to neighborhood SES, other factors such as neighborhood characteristics (e.g. recreational resources, services, built environment, quality of housing, natural spaces, walkability, access to healthy food options, safety, violence, social connections, and culture) could modify the effects of the neighborhood SES positively on populations living in those regions (172, 173). For example a study by Roubinov et al., found that cortisol levels as indicators of stress, were elevated in children from low SES families who lived in lower opportunity neighborhoods compared to children from low SES families who lived in higher opportunity neighborhoods(173).

In total, the studies examining SES and CHD have used varying SES indicators with predominant use of maternal education indicator. They also employed various methodologies such as cohort, case control or ecologic studies with case control method being most commonly used. Although there are modest

associations of individual maternal SES and CHD, the studies are still insufficient to provide conclusive associations. When looking at neighborhood SES and CHD, the data is inconclusive at best. Furthermore, there is a paucity of studies in developed countries which examine the relationship between air pollution, SES and development of CHD.

1.5. Knowledge Gaps

The literature review identified a wide variety of studies examining the association between environmental chemical pollutants and CHD using many different methodologies and classifications of CHD subtypes. All the studies examined single pollutant exposures and only one study to date has examined multiple pollutant exposures. Furthermore, fewer studies have utilized the PRTRs to study industrial chemical emissions and CHD (85-87, 174). With regards SES, the evidence to date suggests the presence of modest associations between individual maternal SES and CHD and the impact of neighborhood SES remain inconclusive.

The rationale of the current thesis was to explore spatiotemporal trends of DTs emitted by industry in Alberta and CHD rates. I also sought to determine if there were associations between multipollutant DTs, SES and CHD in Alberta using the maternal postal code as the unit of analysis.

Over the past six decades Alberta has transitioned from agricultural to industrial development with the establishment of a publicly accessible pollution data registry known as the NPRI. There are two centralized pediatric cardiology referral centers, one in Northern Alberta (Stollery Children's Hospital) and the other in Southern Alberta (Alberta Children's Hospital) with access to a comprehensive CHD database. These resources have provided me with an opportunity to undertake a population-based study to examine the potential role of multiple industrial DT emissions and exposures related to SES on the development of CHD in Alberta. Figure 1.1 is an illustration of the conceptual framework adapted partly from one of Dr. Abbott's questions regarding the etiology of CHD: ***"does it lie in the environment of the developing embryo either in an altered or diseased state of maternal tissues or secretions?"***

1.6. Pilot Study of Industrial Toxicant Emissions and CHD in Alberta

In the fall of 2011, I was admitted as an MSc student and began a research initiative directed towards developing a system that harmonizes and integrates data from various sources to construct a geospatial/temporal framework for generating hypotheses about the potential associations between industrial emissions and CHD by using GIS framework and statistical methodologies. From the initial population data retrieved through the Stollery and Alberta Children's Hospital echocardiographic databases, and using Statistics Canada for Alberta's annual births, the average rate of CHD in Alberta during the study period was 5.8±1.09/1,000 live births with the most commonly encountered including

septal (47.9%), left ventricular outflow tract obstruction (15.2%) and conotruncal (e.g. tetralogy of Fallot, truncus arteriosus, double outlet right ventricle) (12.2%) defects. During this period an overall decrease in the rates of CHD was observed most likely secondary to a decrease in septal defects (175). Using Canada's NPRI, I identified 18 DTs out of 139 chemicals reported to have been emitted to the air by industries operating in Alberta. The study found that 99.9% of the DTs emissions were released to air and therefore I chose to focus this research initiative on DTs released into air in the years 2003 through 2010, the timeframe in which the infants identified would have been in their first trimester of fetal development, during cardiac morphogenesis.

Overall, there was a temporal decreasing trend in the emission of DTs and this was accompanied by a parallel decrease in the rates of CHD particularly after 2006. I also observed positive associations between individual organic compounds and CHD rates whilst there were negative associations with heavy metals. This observation opened the door to transition my studies into the University of Alberta Department of Pediatrics Ph.D. program through which I would explore in more depth the relationship of multipollutant groups of DTs and CHD by employing the principal component analysis (PCA) methodology, Poisson regression models and GIS, which will be discussed in subsequent Chapters.

1.7. Research Objectives & Outline of Thesis

The overarching focus of my thesis was to explore for potential associations of DTs, co-varying subgroups of DTs and SES with CHD and specific embryological derivations of CHD in Alberta using conventional statistics and GIS. To address this overarching goal, I used an exploratory ecologic design to examine initially the temporal relationships and trends of DT emissions and CHD cases in the whole province and its urban and rural regions. The outline of the subsequent chapters is as follows:

- Chapter 2: The first objective was to use PCA to derive subgroups of DTs. I used linear regression models to determine the trends of emissions and CHD rates. I used Spearman correlation to determine associations between the DTs and the subgroups with rates of CHD and specific embryological derivations in the province and its urban and rural regions.
- Chapter 3: Since my initial approach examined temporal associations of CHD and DTs at a large spatial scale, the objective for this chapter was to examine relationships at a higher spatial resolution. I used an inverse distance weighted approach to assign the sum of DTs and the subgroups to the maternal residential postal code adjusted for SES and traffic related pollutants and calculated relative risks using Poisson regression models.

- Chapter 4: I used a recently developed socioeconomic index to determine if there was a relationship between neighborhood low SES and CHD adjusting for all the DTs and traffic related pollutants
- Chapter 5: Provides maps of the geographic distribution of CHD, DTs subgroups and SES to define areas with collocation of CHD cases and risk factors related to DTs exposure and neighborhood SES in urban and rural regions.
- Chapter 6: Concludes my thesis by summarizing the major findings, strengths and limitations of my research, implications and future research directions.

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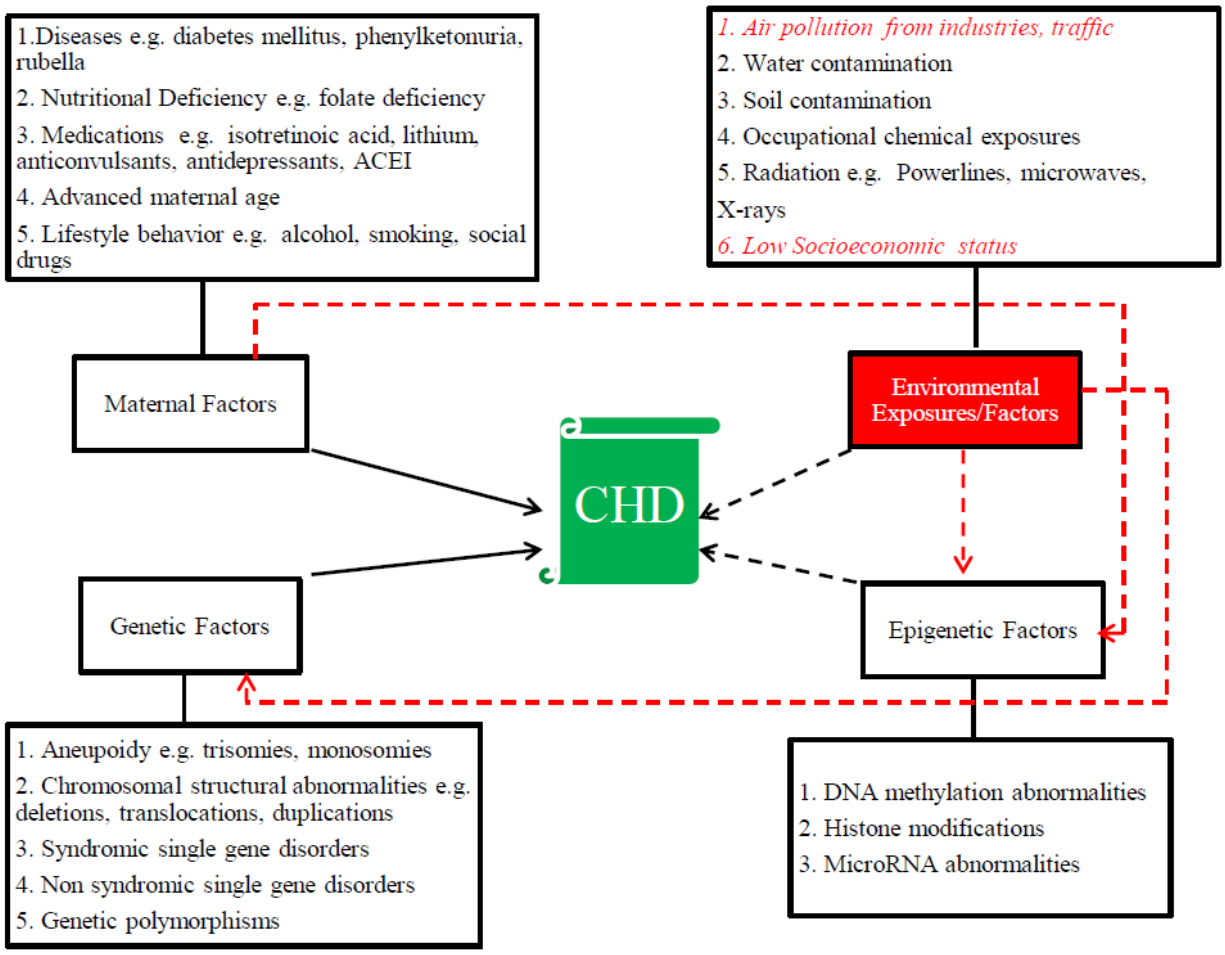

Figure 1. 1. Conceptual Framework

Conceptual Framewok on the etiology of CHD. Some of the maternal and genetic factors known to cause CHD are listed with solid arrows. Evidence is now emerging that suggests the presence of associations between environmental pollution and of low SES with CHD shown in dashed black arrows. However, the literature also suggests possible interactions between maternal factors and epigenetic factors as well as environmental exposures and genetic/epigenetic factors in susceptible individuals as shown in dashed red arrows supporting the theory of multifactorial etiology. For the present research, I will focus on exploring environmental factors (red box) represented with variables in red italics (industrial air emissions, SES at neighborhood level adjusted for traffic related such as NO_2 and $PM_{2.5}$) and CHD in Alberta.

Chapter 2 Tracking Trends in Emissions of Developmental Toxicants and Potential Associations with Congenital Heart Disease in Alberta, Canada

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2.1. Abstract: Congenital heart disease (CHD) is a serious anomaly for which the etiology remains elusive. We explored temporal trend associations between industrial developmental toxicant (DT) air emissions and CHD in Alberta. Patients born between 2004–2011 with a diagnosis of CHD and 18 DTs from the National Pollutant Release Inventory (2003–2010) were identified. We applied principal component analysis (PCA) to DT amounts and toxicity risk scores (RS) and defined yearly crude CHD and septal defects rates for urban and rural regions. Correlations between DT groups and CHD rates were examined with Spearman test and Bonferroni correction was conducted for multiple comparisons. PCA identified three DT groups: Group 1 (volatile organic compounds (VOCs) and other gases,) Group 2 (other VOCs), and Group 3 (mainly heavy metals). Province-wide, we found associations between Group 1 DTs and CHD and septal defect rates, when using amounts (r = 0.86, CI 0.39, 0.97 and r = 0.89, CI 0.48, 0.98, respectively) and RS (r = 0.88, CI 0.47, 0.98 and r = 0.85, CI 0.36, 0.97, respectively). Rural Group 2 DTs were positively associated with septal defect rates in both amounts released and RS (r = 0.91, CI 0.55, 0.98 and r = 0.91, CI 0.55, 0.98, respectively). In this exploratory study, we found a temporal decrease in emissions and CHD rates in rural regions and a potential positive association between CHD and septal defect rates and mixtures of organic compounds with or without gases.

Keywords: congenital heart disease; planetary health; industrial emissions; air pollution; developmental toxicants

2.2. Introduction

Congenital heart disease (CHD) is the most common and serious congenital anomaly affecting 1% of all live births and a higher number of conceptions worldwide (1). CHDs are the most common cause of neonatal death among birth defects and they importantly contribute to mortality and morbidity-related economic costs (2). Genetic risk factors, such as Mendelian inheritance in some families, and non-syndromic single gene and chromosomal anomalies account for 15% of CHD (3,4). A further 30% of CHD is thought to be multifactorial and is attributed to recognized non-inherited risk factors, such as diabetes mellitus, infections, like rubella, and exposures to teratogenic medications (5,6). However, for more than half of the affected children the cause is not known. It has been long suspected that CHD may, in part, relate to complex interactions between parental environmental exposures with or without a genetic predisposition (7). The Baltimore–Washington Infant Study was the largest epidemiological study to document a potential role for chemical exposures (domestic and occupational) in the development of CHD (8). Possible associations between ambient urban air pollutants such as sulphur dioxide, nitrogen dioxide, carbon monoxide, and particulate matter, as well as organic solvents have also been reported by other groups (9,10). The majority of these investigations have explored associations of single pollutants

with very few studies examining the relationship between multipollutant exposures and CHD (11). This area of study has also been largely limited to the use of a few monitored ambient air pollutants as listed above. Finally, access to regional and national CHD databases has further limited research in this area.

Canada established a National Pollutant Release Inventory (NPRI) (12), a mandatory government registry that maintains annual reports of industrial chemical releases to air, water, soil, and transferred off-site for treatment from the whole country. Among the reported pollutants are developmental toxicants (DTs), chemicals believed to have some impact on fetal and childhood development and health but have not been definitively recognized as cardiac teratogens by the Office of Environmental Health Hazard Assessment Proposition 65 (13).

Alberta is a Canadian province located in Western Canada along the Canada-US border. It spans 661,185 square kilometers and boasts a rich diverse landscape consisting of forests, prairies, the Rocky Mountains, glaciers, lakes and rivers, amongst others. Over the past five decades it has witnessed an exponential population growth from one million people to currently 4.2 million people of whom 80% reside in urban vs. 20% in rural regions (14). This trend has been attributed to rapid industrialization and accompanying economic opportunities. The footprint from various industrial sectors varies in urban and rural Alberta (professional, scientific, and technical services vs. mining and oil and gas extraction, agricultural and forestry, respectively) (15,16). Concerns around the exploitation of the oil sands and its impact on the planetary health of the ecosystems, biodiversity, natural landscapes, and human population have been raised (17). In addition, the Public Health Agency of Canada has reported that the CHD prevalence in Alberta is higher than the national average (18).

Given access to the NPRI which captures toxic releases by industry and the fact that the Province of Alberta has two centralized pediatric cardiology referral centers with a captive population of CHD patients, we conducted an exploratory study to investigate the potential relationship between industrial pollutants and CHD through an ecologic study in Alberta and its urban and rural regions. The aims of this study were two-fold: (1) to track the trends of multipollutant groups of developmental toxicants (DTs) emitted by industry and the trends of CHD, and (2) to explore potential associations between trends of multipollutant groups of DTs and CHD in Alberta and its urban and rural regions.

2.2. Materials and Methods

This is an exploratory ecologic study, which examined industrial DTs and CHD rate trends aggregated temporarily in the province of Alberta and its urban and rural regions. Ecologic study designs have been

used to explore research ideas around rare diseases with limited knowledge in a time- and cost-effective manner, and to generate hypotheses for testing in more robust research methods (19)

2.2.1. Study Population

We searched for all children born in Alberta between January 2004 and August 2011 with echocardiography-confirmed CHD from the pediatric echocardiographic Xcelera (Philips, Markham, ON, Canada) regional databases. Other data for each case included birth date, study date, and postal code at the time of diagnosis. Ethics approval from the participating institutions was obtained.

Case ascertainment was performed by retrieving all echocardiographic and surgical reports to confirm a diagnosis of CHD. Cases were aggregated according to their suspected embryological derivations as previously described (20). For patients with multiple echocardiographic examinations, the most consistent major umbrella diagnosis was accepted as the diagnosis, and when there was uncertainty regarding the primary embryological group, the echocardiogram was reviewed by a pediatric echocardiographer or the operative diagnosis was used. We considered all cases with structural heart abnormalities, including those with a patent ductus arteriosus (PDA) present at >6 months and those with an atrial septal defect (ASD) after one year, or in whom surgical or device closure was necessary. Patients with cardiomyopathies and no structural CHD, neonatal peripheral pulmonary stenosis, a PDA at less than six months, an ASD at <1 year, and all cases born outside of the province were excluded.

2.2.2. Pollution Data

We accessed the NPRI to identify annual reports of all chemicals released and geographic coordinates of emitting facilities in Alberta from 2003–2010. We found that overall, 99% of emissions had been released to air, and therefore we focused on air emissions. We then identified chemicals recognized as DTs based on a list compiled by the US Environmental Protection Agency from the State of California known as Proposition 65 (13).

2.2.3. Spatio-Temporal Aggregation of DTs

As the study population consisted of births between January 2004 and August 2011, we used the DTs emitted to air in the year in which the first trimester occurred between 2003 and 2010, as a surrogate for exposure during the period of cardiac morphogenesis. We worked under the assumption that the cases were born at term. For the cases, whose first trimester straddled two years, the case was assigned to the preceding year as the year of exposure. Live births for the study period were obtained from Statistics Canada and assigned to the year when the first trimester occurred for the sake of consistency.

2.2.4. Statistical Methods

2.2.4.1. CHD rates: We calculated yearly crude rates for all CHD and for septal defects observed for the exposure years 2003–2010 and described their trends. We used the second digit of first three characters of the Alberta postal code to identify cases in urban and rural areas. The population at <1 year of age was aggregated at the postal code level using Statistics Canada population data in order to calculate CHD rates.

2.2.4.2. DT emissions: We sought to explore potential associations using the amounts of DTs reported as tonnes or taking into consideration the potential toxicity of the DTs to the neighborhood defined as a Risk Score (RS). The RS is calculated by multiplying the amount of pollutant released by its corresponding toxic equivalent potential (TEP) which is determined by international agencies and the US government and then reported in Scorecard, which is a website compiled by Environmental Defense, a US nongovernmental agency (21, 22). This solution allows for comparisons of chemical releases on a common scale that considers differences in their chemical toxicity.

To reduce the number of pollutant variables in the analyses and create multipollutant groups, we applied principal component analysis (PCA) to both provincial amounts and RS metrics. The correlation matrix of the PCA used standardized individual DTs due to large variations in emitted amounts. To fulfill the required criteria that the number of observations should be greater than the number of variables (23), we selected the DTs according to sectors using the North American Industrial Classification System at level 2 (24). We used orthogonal varimax rotation and we retained three uncorrelated principal components (PCs) which accounted for 74% of cumulative variability in tonnes and 83% of cumulative variability for RS. We selected DTs with a correlation coefficient $\geq \left| 0.6 \right|$ to keep in the corresponding groups, which we named Groups 1 to 3. We then summed the yearly amounts and RS of the DTs in their respective groups and determined their annual trends. We used simple linear regression to determine coefficients for the amounts of emissions and RS and Bonferroni adjusted p-trend values. Since we did not have many comparisons for the CHD trends, we accepted a p value of ≤ 0.05 to be significant.

We tested potential associations between yearly sum of the amount and RS of each DT group and CHD rates at provincial, rural and urban levels using Spearman test. We considered associations with r values >0.7, scatter plots with a linear tendency and reported the 95% CI for the correlation coefficient. Although Bonferroni adjustments are not strictly recommended in exploratory studies (25), here we are presenting conservative p values to avoid inflated type 1 error due to multiple tests. Applying Bonferroni approach, we obtained the adjusted p-value threshold by dividing α (0.05) by the number of the independent hypotheses. Due to a high correlation between CHD and Septal ($r = 0.90$, $p = 0.002$), we

consider CHD and Septal as one outcome in term of multiple-testing adjustment. As province data is just the sum of urban and rural, the province overall model is, therefore, not independent of rural-urban stratified models. On the other hand, due to the low correlation between amounts and risk score ($r = -0.33$, $p = 0.42$), we consider them two independent exposures. Similarly, the models with three chemical groups are independent as the three PCA groups are uncorrelated. Therefore, the total number of "independent" tests is 12 (= 2 × 3 × 2; 2 for two different metrics of the exposure (amounts and risk score) × three chemical groups × two rural/urban strata, and considered a p value ≤0.004 to be significant after Bonferroni correction. All analyses were performed using STATA 12 (StataCorp LP, College Station, TX, USA) and SPSS 21 (IBM Corp, Armonk, NY, USA).

2.3. Results

2.3.1. CHD in Alberta

A total of 2415 CHD infants were born in Alberta between 2004–2011 representing an overall incidence rate of 6.6 per 1000 live births with a slightly higher incidence in rural regions (6.9 per 1000 live births vs. 6.5 per 1000 live births in urban regions). The proportions of all of the embryological groups of CHDs are shown in Table 2.1. Temporally, CHD rates revealed a statistically significant downward trend in the province, and in its rural regions paralleled by changes specifically in septal defects (Table 2.2), (Figure 2.1A, B, respectively). CHD rates did not change significantly in urban regions during this same period. The other embryological groups were small, and no further analysis was attempted.

Table 2. 1. Proportions of CHD in Alberta 2004–2011.

Embryological Group	Count (n = 2415)	Percentage (%)	Prevalence (per 1000 Live Births)
Septal	1320	54.7	3.67
LHO	360	14.9	1.00
Conotruncus	263	10.9	0.73
RHO	220	9.1	0.61
AVSD	109	4.5	0.30
PDA	48	1.9	0.13
Heterotaxy	34	1.4	0.09
APVR	34	1.4	0.09
Complex/SV	21	0.9	0.06
Other	6	0.2	0.002

APVR = anomalous pulmonary venous return, AVSD = atrio-ventricular septal defect, LHO = left heart obstruction, PDA = patent ductus arteriosus, RHO = right heart obstruction, SV = single ventricle, other = abnormal valves (3), anomalous left coronary from pulmonary artery (2) and pulmonary vein stenosis (1).

Table 2. 2. Trends of CHD and septal defects rates for exposure years 2003–2010 in Alberta and its urban and rural regions.

Variables	Region	Regression Coefficient	95% CI	* *p* Value
CHD Rates	Province	−0.4	−0.6; −0.2	0.005 *
	Rural	−0.3	−0.5; −0.2	0.003 *
	Urban	−0.2	−0.4; 0.1	0.133
Septal Defect Rates	Province	−0.2	−0.3; −0.1	0.012 *
	Rural	−0.2	−0.3; −0.02	0.025 *
	Urban	−0.1	−0.3; 0.03	0.105

* p value ≤ 0.05 = significant.

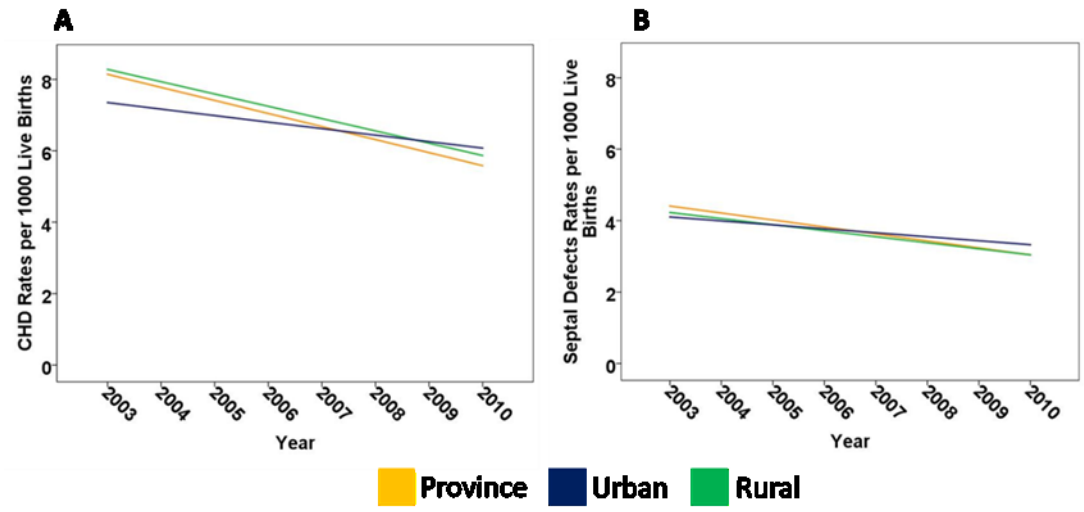

Figure 2. 1. Trends of CHD

(A) Crude CHD rates in the province and rural regions show a significant decreasing trend, (* p = 0.005 and 0.003, respectively) not found in urban regions (p = 0.133); and **(B)** crude septal defects rates showed a significant downward trend in the province and rural regions (* p = 0.012 and 0.025, respectively), but not urban regions (p = 0.105).

2.3.2. DTs in Alberta

2.3.2.1. Emission proportions in absolute amount and risk score: Of the 139 reported chemicals emitted to air in Alberta, 18 were DTs, representing 51% of the provincial emissions. Of the 18 DTs, 59% of the amounts in tonnes were emitted by facilities located in rural areas and 40.3% in urban areas. There was a total of 3537 developmental toxicant emitting facilities (DTEF) in the province, 2700 (76%) in rural and 837 (24%) in urban regions for the study period. The PCA matrix revealed three groups of DTs which were selected based on the correlation coefficient ≥0.6 (Table 2.3). Group 1 predominantly had four volatile organic compounds (VOCs) and two gases; Group 2 had six other VOCs; and Group 3 consisted primarily of four heavy metals. Group1 DTs represented the largest group emitted in Alberta (urban and rural) (Table 2.4). DT RS were higher in rural compared to urban areas (71.5% vs. 28.5%). RS of Group 3 had the highest proportion of the emitted DTs (province > rural > urban), whilst Group 2 contributed the least.

Table 2. 3. Principal component analysis of 18 developmental toxicants.

Developmental Toxicants	Principal Components		
	Group 1	**Group 2**	**Group 3**
Benzene	***0.98***	0.11	0.01
Carbon Disulfide	***0.95***	−0.09	−0.04
Carbon Monoxide	***0.95***	0.21	0.12
Sulphur Dioxide	***0.86***	−0.11	0.47
Toluene	***0.86***	−0.04	0.04
1,3-Butadiene	***0.64***	***0.66***	0.01
Chloroform	0.02	***0.85***	0.04
Ethylene Oxide	0.17	***0.96***	0.06
Methanol	0.03	***0.86***	0.06
Methyl-isobutyl-ketone	0.11	***0.90***	0.05
Trichloroethylene	0.11	***0.79***	0.05
Arsenic	0.16	0.11	***0.95***
Cadmium	0.36	0.06	***0.60***
Hexachlorobenzene	−0.15	−0.05	***0.91***
Lead	0.29	0.29	***0.72***
Mercury	−0.52	−0.08	***0.97***
2-Ethoxyethanol	−0.05	−0.04	−0.08
N-Methyl-2-Pyrrolidone	−0.03	0.04	0.01

DTs with a correlation coefficient ≥0.6 (bold italics) were selected and kept in the principal component they represent. DTs = developmental toxicants.

Table 2. 4. Proportions of emissions by region using amounts and risk scores.

Region	Groups	Amount	%	Risk Score	%
Province	Group 1	4,834,586	99.6	9,773,565	15.2
	Group 2	18,220	0.4	3623	0.01
	Group 3	36	0.00	54,578,189	84.8
Total		4,852,844		64,355,377	
(AV ± SD)		95,153 ± 145,728		2,681,474 ± 2,986,681	
Urban	Group 1	1,946,446	99.4	4,274,371	23.3
	Group 2	11,637	0.6	3031	0.02
	Group 3	15	0.00	14,059,472	76.7
Total		1,958,101	40.3	18,336,874	28.5
(AV ± SD)		92,984 ± 141,235		6,112,291 ± 5,883,839	
Rural	Group 1	2,888,139	99.7	5,499,194	11.9
	Group 2	6583	0.3	592	0.00
	Group 3	21	0.00	40,518,716	88
Total		2,894,743	59.7	46,018,502	71.5
(AV ± SD)		98,669 ± 147,335		15,339,501 ± 17,945,349	

AV = Average, SD = Standard Deviation.

2.3.2.2. Emission trends of DTs in amounts and RS: DT emissions decreased in total amounts provincially and were driven by the rural emissions (Table 2.5). Based on total amounts, Group 1 and 2 showed a significant downward trend in rural regions whilst Group 3 showed a significant increasing trend in the whole province (Figure 2.2 A–C). Based on RS, urban regions showed an overall significant increase in DT emissions. Comparing the three groups by RS, Group 1 showed a significant downward trend in the province driven by rural regions, Group 2 showed a significant decrease in all regions, whilst Group 3 showed a significant increase only in urban regions (Table 2.5).

Table 2. 5. Trends of developmental toxicant emissions in Alberta, 2003–2010.

Variables	Region	Regression Coefficient	95% CI	* *p* Value
DT Amounts				
Overall	Province	−14,003	−21,446; −6539	0.004 *
	Rural	−9226	−16,016; −2436	0.016
	Urban	−4634	−9337; 69	0.053
Group 1	Province	−13,962	−21,427; −6497	0.004 *
	Rural	−9188	−15,970; −2405	0.016
	Urban	−4658	−9372; 58	0.052
Group 2	Province	−42	−87; 3	0.060
	Rural	−39	−67; −10	0.016
	Urban	23	−18; 63	0.221
Group 3	Province	0.4	0.3; 0.6	<0.001 *
	Rural	0.5	0.05; 0.4	0.021
	Urban	0.2	0.04; 0.3	0.016
DT Risk Scores				
Overall	Province	128,140	−44,647; 300,928	0.120
	Rural	−68,809	−338,413; 200,794	0.555
	Urban	196,950	72,289; 321,611	0.008
Group 1	Province	−33,772	−45,486; −22,057	<0.001 *
	Rural	−29,410	−36,996; −21,824	<0.001 *
	Urban	−4361	−17,512; 8789	0.448
Group 2	Province	−65	−107; −24	0.008
	Rural	−4	−6; −1	0.016 *
	Urban	−62	−102; −22	0.009
Group 3	Province	161,977	−7609; 331,563	0.058
	Rural	−39,396	−305,239; 226,447	0.729
	Urban	201,373	71,479; 331,268	0.009

* p value ≤ 0.004 = significant after Bonferroni adjustment.

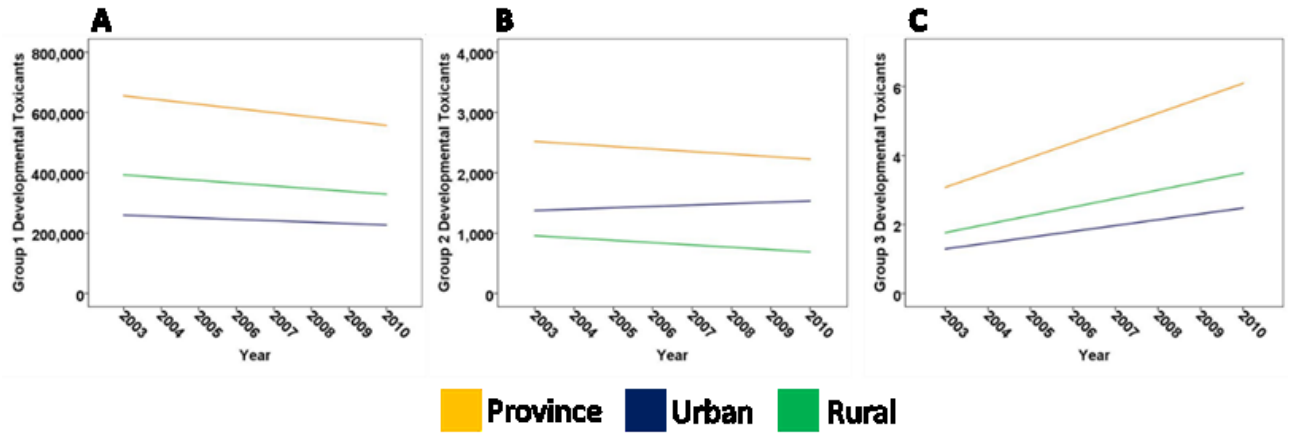

Figure 2. 2. Developmental toxicants in amounts (tonnes).

(A) Group 1 DTs demonstrated a decreasing trend in the province, (* p = 0.004); **(B)** There was no statistically significant decrease in Group 2 emissions in the province and its urban and rural regions; **(C)** Group 3 DTs showed a statistically significant increase in the province overall, (* p < 0.001). DT = developmental toxicant, * p value ≤ 0.004 = significant post Bonferroni adjustment.

Table 2. 6. Associations of CHD and Septal Defect Rates with DT Groups.

Region	Variable	Spearman's Rho (95% CI)	* *p* Value	Spearman's Rho (95% CI)	* *p* Value
DT Amounts					
		CHD		**Septal**	
Province	Group 1	0.86 (0.39, 0.97)	0.007	0.89 (0.48, 0.98)	0.003 *
	Group 2	0.50 (−0.32, 0.89)	0.207	0.79 (0.16, 0.96)	0.023
	Group 3	−0.74 (−0.95, −0.07)	0.037	−0.76 (−0.95, −0.12)	0.031
Rural	Group 1	0.62 (−0.15, 0.92)	0.102	0.60 (−0.19, 0.92)	0.120
	Group 2	0.79 (0.18, 0.96)	0.021	0.91 (0.55, 0.98)	0.002 *
	Group 3	−0.64 (−0.93, 0.11)	0.086	−0.81 (−0.96, −0.24)	0.015
Urban	Group 1	0.71 (0.02, 0.94)	0.047	0.74 (0.07, 0.95)	0.037
	Group 2	−0.07 (−0.74, 0.67)	0.867	−0.02 (−0.72, 0.69)	0.955
	Group 3	−0.88 (−0.98, −0.47)	0.004 *	−0.83 (−0.97, −0.31)	0.010
DT Risk Scores					
		CHD		**Septal**	
Province	Group 1	0.88 (0.47, 0.98)	0.004 *	0.85 (0.36, 0.97)	0.007
	Group 2	0.86 (0.39, 0.97)	0.007	0.97 (0.84, 0.99)	<0.001 *
	Group 3	−0.41 (−0.86, 0.42)	0.320	−0.50 (−0.89, 0.31)	0.204
Rural	Group 1	0.88 (0.47, 0.98)	0.004 *	0.76 (0.12, 0.95)	0.028
	Group 2	0.79 (0.18, 0.96)	0.021	0.91 (0.55, 0.98)	0.002 *
	Group 3	−0.02 (−0.72, 0.69)	0.955	−0.12 (−0.76, 0.64)	0.779
Urban	Group 1	0.69 (−0.03, 0.94)	0.058	0.64 (−0.11, 0.93)	0.086
	Group 2	0.69 (−0.03, 0.94)	0.058	0.86 (0.39, 0.97)	0.007
	Group 3	−0.79 (−0.96, −0.18)	0.021	−0.81 (−0.96, −0.24)	0.015

CHD = congenital heart disease, DT = developmental toxicants, * p value ≤ 0.004 post Bonferroni adjustment.

2.3.2.3. Emissions Amount: There were marginal statistically significant associations between the total amount of the 18 DTs emitted in the province and with CHD rates ($r = 0.86$, 95% CI: 0.39, 0.97, $p < 0.007$), whilst the total of the remaining 121 chemicals showed no association ($r = 0.38$, 95% CI: −0.44, 0.86, $p = 0.352$). We found positive associations between Group 1 emissions in the province and septal defect rates. For Group 2 DTs, we found positive associations with septal defects in rural regions, whilst in the urban regions there were negative between Group 3 DTs and CHDs overall (Table 2.6).

2.3.2.4. Risk Scores: Although there were no associations with the total RS of the 18 DTs emitted in the province and CHD, we found positive associations between Group 1 and CHD rates and also with Group 2 and septal defects rates. In the rural regions, we found positive associations with Group 1 and CHD and Group 2 with septal defect rates (Table 2.6).

2.4. Discussion

Our exploratory study found important downward air emission trends in both amounts and RS (potential toxicity) which differed between rural and urban regions of Alberta, with a reduction in emissions potentially influencing CHD rates in rural regions only. They reflected province-wide positive associations between Group 1 emissions (benzene, carbon monoxide, carbon disulfide, sulphur dioxide, toluene, and 1,3 butadiene) and CHD and septal defect rates using both amounts and risk scores. Group 2 emissions (1,3 butadiene, chloroform, ethylene oxide, methanol, methyl-isobutyl-ketone, and trichloroethylene) were associated with septal defects when using both the amounts and RS in rural regions. In addition, we found positive associations between rural Group 1 emissions and CHD rates based on the RS only. In urban regions, we found negative associations between Group 3 emission amounts (arsenic, lead, cadmium, hexachorobenzene, mercury) and CHD. To our knowledge, this is one of very few studies that utilize a national pollutant registry to explore multipollutant groups of industrial emissions and their potential relation to CHD (26).

Investigations examining associations between air pollution and CHD rates have largely relied on data from monitoring stations in urban settings which capture ambient concentrations of a few monitored pollutants (e.g., carbon monoxide, sulphur oxides, nitrogen oxides) (9). This approach has less capacity to examine a broader range of emitted industrial pollutants and the impact of multipollutant combinations on health outcomes. Therefore, our study generates new hypotheses as to how multiple pollutants could potentially contribute to CHD, a direction recently recognized as important in understanding how environmental exposures contribute to health (27).

In this study, we examined trends of DT emitted by facilities located in rural and urban regions without considering the impact they may have in neighboring regions. That rural regions host the greatest proportion of industrial facilities compared to urban regions could have accounted for the higher proportion of DT emissions in those regions. There were greater decreases in DT emission amounts in rural compared to urban regions over the study period. Likewise, the proportion of CHD cases was higher in rural regions compared to urban regions and we found a significant temporal decrease in CHD and septal defects rates in the province and rural regions. In contrast, the urban facilities demonstrated a marginally statistically significant temporal decrease in emissions and CHD rates.

Throughout the study period, Group 1 DTs had a greater geographic footprint in both urban and rural regions compared to Group 2 and 3 DTs. Associated reductions in emissions of Group 1 and 2 DTs and CHDs could suggest that a reduction in industrial emissions in rural regions positively impacted the health in those areas. The urban located facilities continued to emit significantly more toxic Group 3 DTs into the environment. The combination of those two factors and additional factors not examined here (e.g., other pollutants, socioeconomic status) may have contributed to the lack of change in CHD rates in urban areas. The observed decreasing trend in the emission of DTs in our study can be attributed to multiple factors which may act alone or in combination, including new legislation, use of prevention and mitigation technology, cycles and variation in production, implementation of government strategy for environmentally sustainable development and industrial self-regulation (28). Studies of environmental regulations suggest that legislation alone does not seem to explain the observed decrements in emission (29). To this effect, economic factors may be stronger contributors to the behavior of emissions in time. For example, the 2008 economic downturn affected the manufacturing sector particularly wood manufacturing resulting in a decrease of benzene emissions (15).

To better examine the association between multiple pollutants groups with CHD rates, we explored both the trends of emission amounts as well as their RS. The use of pollutant toxicity has been found to be important, particularly in equity studies, to better quantify the risk posed by industries to nearby communities (30). Some of the DTs may be emitted in small quantities but are highly toxic when factoring their toxic equivalent potential (e.g., heavy metals). In the current exploratory study, the most significant associations found with Group 1 and 2 DTs remained regardless of using amounts or RS. Recently, using an inverse distance weighted (IDW) approach to understand the effect of maternal residential proximity to industrial facilities on the development of CHD (31), we identified that only the highest exposures to the three DTs Groups were associated with urban CHD while, in rural regions, associations occurred with Group 1 and 3 DTs and not Group 2 DTs (31). Even though rural regions had more facilities and emissions, their impact was larger in surrounding urban postal codes. In the current

study it is not clear whether urban or rural regions are the main driver of the Group 1 associations at province level.

The Group 3 emissions which are dominated by heavy metals present contradictory and intriguing results. We found strong negative associations with CHD in urban regions based on amounts emitted. In fact, in our previous study, (31) using a more precise exploratory approach, we found positive associations in both urban and rural postal codes exposed to the highest levels of Group 3 emissions (31). Our findings are consistent with published studies where the relationship between heavy metals and CHD remains inconclusive with some studies reporting positive and others negative associations (32). This suggests that the associations between CHD and Group 3 DTs may be more complex.

Reported experimental animal models have demonstrated congenital anomalies with exposure to some of the chemicals we examined in our study, however whether there is a truly causal effect is still to be explored. A study by Holson et al. which examined arsenic (present in Group 3 chemicals in our study), demonstrated congenital anomalies only at very high metal exposures (33), suggesting that very high doses of metals may be required to produce effects in humans. In addition, there is evidence that some of the volatile organic compounds (VOCs) identified in our study, trichloroethylene (TCE) in drinking water resulted in CHD in animal models; however, exposure to inhaled TCE, as would be the case in the present study, has not clearly affected cardiac morphogenesis in these models (34). No previous experimental models have been used to examine the role of multipollutant (e.g., VOCs and gases), and yet, based on the findings of our study, possible chemical combinations could be teratogenic. Mechanisms through which these chemicals contribute to CHD evolution could include oxidative stress-mediated dysregulation of developmental signals during cardiac morphogenesis (35), complex gene–environmental interactions during the vulnerable window of cardiac embryogenesis, and/or altered epigenetic transcription factors involved in neural crest migration or other cell processes during cardiomorphogenesis (36-38). Further investigations that explore the impact of exposure to pollutant mixtures on cardiac development are necessary to better define this relationship on a whole organ, cellular, and molecular level.

2.5. Study Limitations

Although our study sheds light on a potential association between multipollutant organic compounds and gases emitted into air by industry and CHD, certain limitations must be recognized. Being an ecological study, the observations made at aggregate level cannot be inferred to individuals. Given our source of patient data, we were unable to account for other variables associated with CHD including genetic abnormalities, maternal health and exposure to drugs, and the impact of folic acid supplementation (39). In addition, other subtypes of CHD were not examined because they did not reveal any temporal trend

and most likely due to small sample size. Therefore, we committed to report only the septal group of CHDs and this could contribute to selection bias. We were also unable to include other environmental confounders like the socio-economic status and traffic related pollutants and, therefore, the estimates observed in our study could be an over or under estimation of the associations of industrial pollutants and CHD.

We did not have data on gestational age at birth and yet some of our CHD cases could have been delivered prematurely which could have resulted in exposure misclassification errors. In addition, the emissions are reported annually making it difficult to assign them more closely to the window of cardiac morphogenesis.

We did not include terminated pregnancies with fetal CHD; however, the observed temporal decrease in CHD rates was unlikely to have occurred due to pregnancy terminations, as we had previously observed no increase in pregnancy terminations for CHD in the province during the study period, and absolute termination rates are quite low in our province (40). Furthermore, the CHD rates we reported are consistent with previously published Alberta case ascertainment rates (41).

2.6. Conclusions and Recommendations

In this exploratory study, we have observed downward temporal patterns of emissions accompanied by a parallel decrease in CHD rates in rural regions which potentially implies that efforts at reducing emissions could impact positively on reducing CHD in our children and the general health of all living organisms on the planet. Furthermore, we observed consistent positive associations between VOC emissions and CHDs in Alberta, predominantly in rural areas between 2003 and 2010. The relationship between industrial DTs and CHD may not represent the effect of exposure to a single pollutant, but rather multipollutant exposures which require further investigation by the research community. We believe that the approach of using amounts and RS in this study complemented each other in attempting to quantify the risk posed by industries to nearby communities. We would like to recommend the establishment of comprehensive prospective birth defect registries which will capture maternal environmental factors, detailed perinatal variables, genetic, socio-economic, and pollutant environmental factors from various sources which will enhance more robust future epidemiological studies. Finally, our study was limited to human populations and the evidence from studies on other species (42, 43) needs to be consolidated in order to begin to understand the role industrial chemical pollution and adverse health outcomes on the planet and its inhabitants.

Author Contributions: D.P.N. contributed to the conceptualization, design, acquisition of data, and statistical analysis of the data, and wrote the paper. L.K.H. contributed to the conceptualization, design, acquisition of data, resources, and reviewed the manuscript. J.L.C.-G. contributed to the conceptualization of the discussion and reviewed the manuscript. S.C. contributed to the conceptualization of the study and reviewed the manuscript. D.F. provided the data and reviewed the manuscript. A.O.-V. contributed to the conceptualization, design, acquisition of data, and resources, and reviewed the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Ethics Approval: Ethics approval was obtained from the two participating institutions' boards: University of Alberta's Health Research Ethics Board-Health Panel approved the study and assigned it a project number, study ID: Pro00025428. University of Calgary's Conjoint Health Research Ethics Board of the Faculties of Medicine, Nursing and Kinesiology, ethics ID: E-24758.

Availability of data materials: The air pollution dataset generated for the current study is publicly available from the Government of Canada's National Pollutant Release Inventory, https://www.ec.gc.ca/inrp-npri/default.asp?lang=en&n=0EC58C98 (Accessed 11 July 2018). The CHD dataset is not publicly available due to privacy and confidentiality clauses of the Government of Alberta's Health Information Act Section 2.

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Chapter 3 Industrial Developmental Toxicants and Congenital Heart Disease in Urban and Rural Alberta, Canada

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3.1. Abstract: The etiology of congenital heart defects (CHD) is not known for many affected patients. In the present study, we examined the association between industrial emissions and CHD in urban and rural Alberta. We acquired the emissions data reported in the Canadian National Pollutant Release Inventory (n = 18) and identified CHD patients born in Alberta from 2003–2010 (n = 2413). We identified three

groups of emissions after principal component analysis: Groups 1, 2, and 3. The distribution of exposure to the postal codes with births was determined using an inverse distance weighted approach. Poisson or negative binomial regression models helped estimate associations (relative risk (RR), 95% Confidence Intervals (CI)) adjusted for socioeconomic status and two criteria pollutants: nitrogen dioxide and particulate matter with a mean aerodynamic diameter of ≤2.5 micrometers. The adjusted RR in urban settings was 1.8 (95% CI: 1.5, 2.3) for Group 1 and 1.4 (95% CI: 1.3, 1.6) for both Groups 2 and 3. In rural postal codes, Groups 1 and 3 emissions had a RR of 2.6 (95% CI: 1.03, 7). Associations were only observed in postal codes with the highest levels of emissions and maps demonstrated that regions with very high exposures were sparse.

Keywords: congenital heart disease; developmental toxicants; air pollution; industrial emissions; planetary health; National Pollutant Release Inventory

3.2. Introduction

Congenital heart disease (CHD) affects nearly 1% of newborns worldwide (1, 2) and is the most common cause of neonatal death among babies with birth defects (3). Although the etiology for some CHD can be directly attributed to known chromosomal anomalies, Mendelian syndromes, and non-syndromic single gene disorders (4, 5), the majority are thought to be multifactorial and related to complex interactions between intrauterine exposures and developmental processes with or without a genetic predisposition (6, 7).

With the lack of a defined etiology for most CHD, there has been an increasing interest in investigating the potential role of exposures to environmental toxicants; however, the results have been inconsistent and have focused primarily on urban criteria pollutants such as sulphur dioxide, nitrogen dioxide, carbon monoxide, particulate matter, and ozone (8). Two recent meta-analyses examining studies that reported a relationship between criteria air pollutants and CHD found a consistent positive association between nitrogen dioxide and coarctation of the aorta (9, 10). Fewer studies have examined the association between industrial emissions and CHD, and of those, the most consistent positive associations for CHD have been with organic compounds (e.g., benzene, trichloroethylene, toluene) (11-14). Finally, most investigations have concentrated on single pollutant exposures with only one previous report having examined the relationship between urban multipollutant exposures and CHD (15).

Over the past five decades, the province of Alberta has witnessed growing industrial development owing to the discovery and exploitation of the oil sands in the 1970s, which was accompanied by rapid

population growth. Naturally, concerns have been raised about the adverse impact of industrial pollution sources on planetary health such as the health of ecosystems, biodiversity, and natural landscapes in which people live (16). Human beings have a complex connection and dependency on the health of the ecosystems. If anthropogenic sources of environmental pollution challenge the natural systems, it results in adverse health effects that impact all living species. The Public Health Agency of Canada has documented that the prevalence of CHD in the province is greater than the national average (17). Furthermore, Canada is part of the initiative established by the Organization for Economic Co-operation and Development (OECD) in 1996 to develop registries that capture toxic emissions from industries operating in those countries. Thus the government of Canada established a National Pollutant Release Inventory (NPRI) to capture and track emissions released onsite or offsite into air, water, and soil, for monitoring and management purposes. Given public access to the NPRI and the fact that we have centralized pediatric cardiology services with two referral centers in Alberta, we sought to investigate the potential exposure to multiple pollutant exposures on CHD development by assigning the sum of the inverse distance weighted emissions on the maternal residential postal code in urban and rural Alberta.

3.3. Materials and Methods

3.3.1. Study Population

We searched for all children with echocardiography confirmed CHD born in Alberta between January 2004 and August 2011 from the pediatric echocardiographic Xcelera (Philips, Markham, ON, Canada) regional databases. The databases covered every single case occurring in the province. Data for each case included only birth date and mothers' residential postal code at time of diagnosis. We used the second digit of the first three characters of the Alberta postal code to identify cases in urban and rural areas as defined elsewhere (18). Ethics approval was obtained from the participating institutions (Stollery and Alberta Children's Hospitals). They included a clause indicating that privacy and confidentially regulation prevents displaying maps showing individual postal codes where a low number of cases exists.

Case ascertainment was performed by retrieving all echocardiographic and surgical reports to confirm a diagnosis of CHD. For patients with multiple echocardiographic examinations, the most consistent major umbrella diagnosis was accepted as the diagnosis, and when there was uncertainty regarding the primary embryological group, the echocardiogram was reviewed by a pediatric echocardiographer or the operative diagnosis was chosen. We considered all cases with structural heart abnormalities, including those with a patent ductus arteriosus present at >6 months and those with an atrial septal defect after one year or in whom surgical or device closure was necessary. We excluded patients with cardiomyopathies and no

structural CHD, neonatal peripheral pulmonary stenosis, a patent ductus arteriosus at <6 months, an atrial septal defect at <1 year, and all cases born outside of the province.

3.3.2. Pollution Data

We accessed the NPRI to obtain annual reports of all chemicals released regardless of the processes involved, and the geographic coordinates of the emitting facilities in Alberta from 2003–2010. We then identified chemicals recognized as developmental toxicants (DTs) but not known to have cardiac teratogenicity from the Proposition 65 list compiled by the Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency (19) (referred for simplicity as industrial emissions/emissions/chemicals or pollutants throughout the manuscript). We found that overall, 99% of the emissions had been released to air, and therefore we focused on air emissions. In order to reduce the number of pollutant variables in the analyses and examine multipollutant groups, we applied principal components analysis (PCA) (20) to provincial amounts in tonnes. The correlation matrix of the PCA used standardized individual chemicals because of large variations in emitted amounts. To fulfill the required criteria that the number of observations should be greater than the number of variables (20), we selected the chemicals according to sectors using the North American Industrial Classification System at Level 2 (21). We retained three rotated principal components which accounted for 74% of cumulative variability and 21% of variance for amounts released in tonnes. We selected chemicals with a correlation coefficient $\geq |0.6|$ to keep in the corresponding groups, which we named Group 1 to 3.

3.3.3. Exposure Assessment

As the study population consisted of CHD cases born between January 2004 and August 2011, we used the chemicals emitted to air in the year in which the first trimester occurred between 2003 and 2010, assuming that the cases were born at term. For the cases whose first trimester straddled two years, we assigned the case to the preceding year as the year of exposure. In order to obtain all the postal codes where a birth and a potential chemical exposure occurred, we accessed the Alberta Perinatal Health Program database (22). We obtained partial data indicating the postal codes where at least one birth occurred, but not the number of births. We characterized the percentile distribution of the potentially exposed population, by assigning estimated chemical exposure to every postal code (see below) where at least one birth occurred during the study period. On the basis of postal code, we assigned the CHD cases to those categories of exposure for further analysis. We used the sum of the tonnes of chemicals emitted within 10 km of the postal code after weighting by the inverse distance from the emitting facilities (EF) to the centroid of the postal code of the maternal residence, as a proxy to account for higher or lower chemical exposures as a function of the proximity to emitting facilities. We first estimated the Euclidean distance from the population-weighted centroid of the postal codes obtained from Digital Mapping

Technology Incorporated Spatial CanMap Postal Code Suite 2013 (23) to all the surrounding EF within a 10-km radius using ArcGIS 10.4, and calculated the inverse distance. Then, we multiplied the inverse distance by the tonnes emitted from each facility within the 10-km radius and summed the product for the postal codes for the eight-year study period (2003–2010). We used a 10-km radius because in our exploratory analysis we found that 90% of the CHD cases were within 10-km of an industrial emitting facility, and in our analysis, all the CHD cases were within 10 km. We analyzed the exposure to all chemicals emitted in the province and the identified multipollutant groups using percentile categories to define exposure gradients. Most of the postal codes (96% urban; 77% rural) were exposed to all and Group 1 chemicals allowing categorization in deciles. Since larger urban/rural differences were observed for Groups 2 and 3 (70% urban; 10% rural), we assigned these two groups of chemicals to tertile categories (most of the exposure was very small, approaching zero). The lowest exposure category was designated as the reference in the analysis.

3.3.4. Statistical Analysis

We examined overall counts of CHD in urban and rural postal codes and did not attempt to analyze according to subtypes of CHD as the sample sizes were small. We used descriptive statistics for the percentile distribution of the inverse distance weighed exposure at the postal code where births occurred and the corresponding counts of CHD cases per exposure category in urban and rural postal codes. Differences in exposure categories were measured using the non-parametric tests—Mann–Whitney U test (two groups) and Kruskal–Wallis (more than two groups)—because of non-normal distributions of the data. In addition to non-normal distributions, the fact that CHD is a rare disease and we only had CHD counts by postal code, we applied Poisson regression models for the urban postal codes. However, for the rural postal codes we used negative binomial regression models because the observed variance was greater than the mean of CHD cases by postal code, probably related to the small sample size. We reported adjusted associations of relative risk (RR) and (95% CI) between CHD occurrence and all emissions and the three multipollutant groups. Confounders included in the analysis were: (1) a previously developed socio-economic status (SES) index by Chan et al. (24) applied at the postal code level; and (2) land use regression models for nitrogen dioxide (NO_2) and particulate matter with a mean aerodynamic diameter ≤2.5 micrometers ($PM_{2.5}$) constructed by Hystad et al. (25) to estimate pollutant concentrations at the postal code level across Alberta. To assess whether our results were robust to changes in model specification with regards to exposure, we conducted sensitivity analyses including subsamples at distances <10 km. We used STATA 13 and IBM SPSS 24 for statistical analysis and ESRI ArcGIS 10.4 for mapping.

3.4. Results

3.4.1. Principal Component Analysis (PCA)

The PCA matrix revealed three groups of industrial emissions which were selected based on the correlation coefficient ≥0.6, highlighted in Table 3.1. Group 1 consisted of benzene, carbon disulfide, carbon monoxide, toluene, sulphur dioxide, toluene, and 1,3 butadiene; Group 2 consisted of ethylene oxide, methyl-isobutyl-ketone, methanol, chloroform, trichloroethylene, and 1,3 butadiene; Group 3 consisted of mercury, arsenic, hexachlorobenzene, lead, and cadmium (the chemicals are presented in the order of their correlation coefficient from the highest to lowest). Out of the 17 industrial sectors operating in Alberta, only 11 sectors reported emissions released to air to the NPRI for the study period (2003–2010). The total number of emitting facilities (EF) was greater in rural (n = 1172, 75%) compared to urban regions (n = 388, 25%). The rural postal codes had the highest proportion of emissions in tonnes (2,894,743, 60%) compared to urban (1,958,101, 40%) for the study period (Appendix I) and Group 1 emissions in amounts were dominant compared to Group 2 and 3 emissions. The mining, utilities, and manufacturing sectors contributed 99.6% of the total emissions in the province. The proportions of the emissions based on the three main sectors for the three multipollutant groups are shown in Appendix I. The mining sector contributed the largest proportion of the emissions followed by manufacturing and utilities sectors. The utilities sector was more dominant in rural postal codes.

Table 3. 1.Principal Component Analysis matrix of the 18 industrial emissions included in the study.

Industrial Emissions	Principal Components		
	Group 1	**Group 2**	**Group 3**
Benzene	*0.98*	0.11	0.01
Carbon Disulfide	*0.95*	−0.09	−0.04
Carbon Monoxide	*0.95*	0.21	0.12
Sulphur Dioxide	*0.86*	−0.11	0.47
Toluene	*0.86*	−0.04	0.04
1,3-Butadiene	*0.64*	*0.66*	0.01
Chloroform	0.02	*0.85*	0.04
Ethylene Oxide	0.17	*0.96*	0.06
Methanol	0.03	*0.86*	0.06
Methyl-isobutyl-ketone	0.11	*0.90*	0.05
Trichloroethylene	0.11	*0.79*	0.05
Arsenic	0.16	0.11	*0.95*
Cadmium	0.36	0.06	*0.60*
Hexachlorobenzene	−0.15	−0.05	*0.91*
Lead	0.29	0.29	*0.72*
Mercury	−0.52	−0.08	*0.97*
2-Ethoxyethanol	−0.05	−0.04	−0.08
N-Methyl-2-Pyrrolidone	−0.03	0.04	0.01

Industrial emissions with a correlation coefficient ≥0.6 (bold italics) were selected and kept in the principal component they represent.

3.4.2. Distribution of Emitting Facilities and Exposure on Alberta Postal Codes

We worked with a total of 54,240 postal codes, where 52,077 postal codes had emitting facilities within a 10 km radius and 2163 other postal codes had emitting facilities beyond a 10 km radius. The postal codes with no facilities within the 10 km radius were included as part of the distribution of exposures fitting in the lowest category of exposure. Most of the postal codes (n = 53,561, 98.7%) were urban, whereas (n = 679, 0.01%) were rural (Table 3.2). However, because of the likelihood that an emitting facility could impact both urban and rural postal codes based on distance regardless of the location, we found that the median number of emitting facilities impacting urban postal codes was higher (n = 60, IQR 84) than the rural postal codes (n = 10, IQR 15) due to a larger number of postal codes with births in urban regions

compared to rural postal codes. After calculating the inverse distance weighted (IDW) exposure by the facilities within 10 km of the postal codes of interest, the median total exposure was significantly higher in urban (0.6 tonnes, IQR 2.4) compared to rural postal codes (0.07 tonnes, IQR 0.3). Similarly, when considering the median exposure of the three multipollutant groups, it was significantly higher in urban compared to rural postal codes (Table 3.2). Figure 1 presents the decile distribution of the IDW exposure for all and Group 1 emissions and the tertile distribution of Groups 2 and 3, comparing urban and rural postal codes.

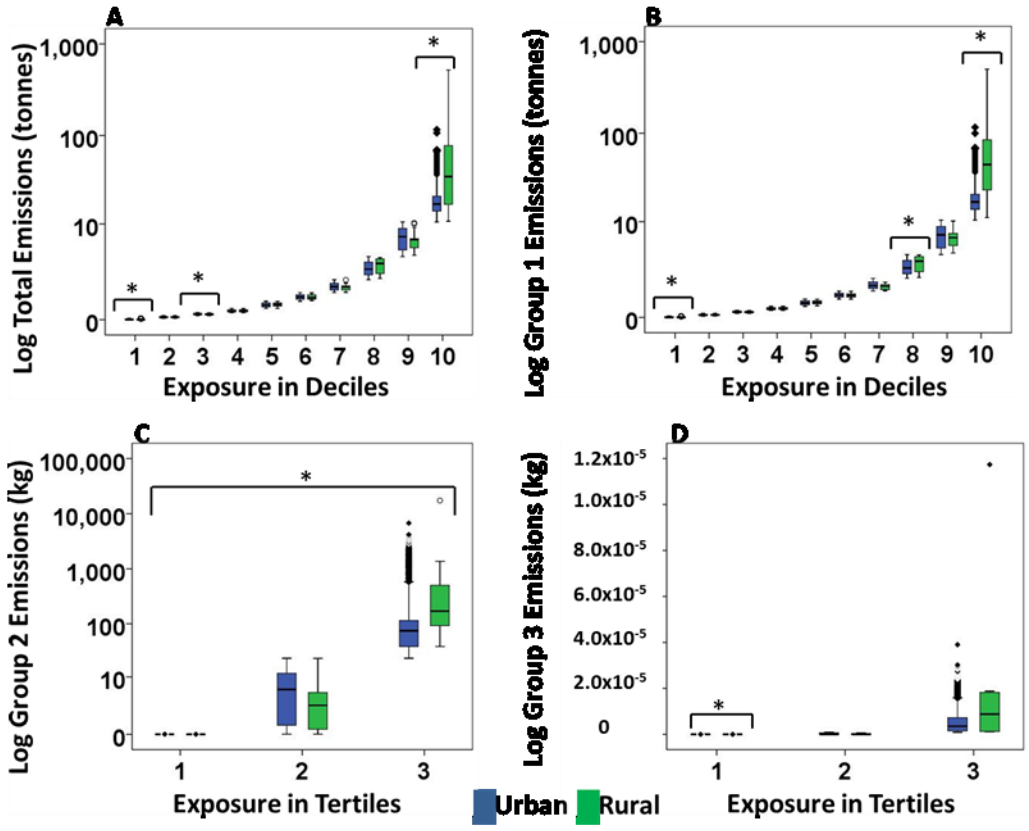

Figure 3.1. Distribution of inverse distance weighted (IDW) exposure in urban and rural Alberta.

(A) Total sum of exposure from all emissions showed significantly higher medians in urban 1st and 3rd deciles and higher median in rural 10th decile. (B) Group 1 showed significantly higher median differences in urban 1st and 8th deciles and rural 10th decile. (C) Tertiles of Group 2 emissions with significantly higher median in urban 1st and 2nd tertiles and rural 3rd tertile. (D) Tertiles of Group 3 emissions with significantly higher median in urban 1st tertile (Mann Whitney U test, * $p < 0.05$).

Table 3. 2. Descriptive statistics of the emissions, postal codes exposed to the emissions, and congenital heart defect (CHD) counts in urban and rural Alberta.

Variable	Urban	Rural	* *p* Value
Total postal codes	53,561	679	
Number of postal codes with EF in a 10 km radius	51,546	531	
Number of postal codes without EF in a 10 km radius	2015	148	
Count of EF per Postal Code (Min)	1	1	
Count of EF per Postal Code (Max)	252	183	
Median number of EF impacting each postal code (IQR)	60 (84)	10 (15)	
Sum total IDW emissions in tonnes	170,497	1632	
Sum Group 1 IDW emissions in tonnes	168,434	1608	
Sum Group 2 IDW emissions in kg	205,089,526	23,689	
Sum Group 3 IDW emissions in kg	9043	21	
Median total emissions in tonnes (IQR)	0.6 (2.4)	0.07 (0.3)	<0.001
Median Group 1 emission in tonnes (IQR)	0.6 (2.3)	0.07 (0.3)	<0.001
Median Group 2 emissions in kg (IQR)	6 (39)	0.0000 (0.00) †	<0.001
Median Group 3 emissions in kg (IQR)	$2.2x10^{-9}$ ($1.5x10^{-7}$)	0.0000 (0.00) †	<0.001
Total CHD counts *n* = 2413 (%)	1967 (81.5)	446 (18.4)	
Poisson mean of CHD counts (95% CI)	0.04 (0.04, 0.04)	0.66 (0.59, 0.72)	

* $p < 0.005$ = statistically significant. EF = Emitting Facilities. IDW = Inverse Distance Weight. CI = Confidence Intervals. IQR = Interquartile range. † = Group 2 and 3 were emitted in small quantities in rural postal codes and are represented in kilograms.

3.4.3. Distribution of CHD in Urban and Rural Alberta

There were a total of 2413 CHD cases that had an emitting facility within 10 km for the eight study years. The number of postal codes with CHD cases was higher in the urban (n = 1967, 82%) than in the rural regions (n = 446, 18%) (Table 3.2), consistent with the number of urban and rural postal codes and the distribution of the Alberta population (80% residing in urban and 20% in rural postal codes). Nevertheless, the Poisson mean CHD counts by postal code were higher in rural 0.66 (95% CI: 0.59,

0.72) compared to urban postal codes 0.04 (95% CI: 0.04, 0.04). CHD cases assigned to each one of the decile exposure categories (all and Group 1) and to the tertile categories (Groups 2 and 3) emissions are presented in Figure 3.2.

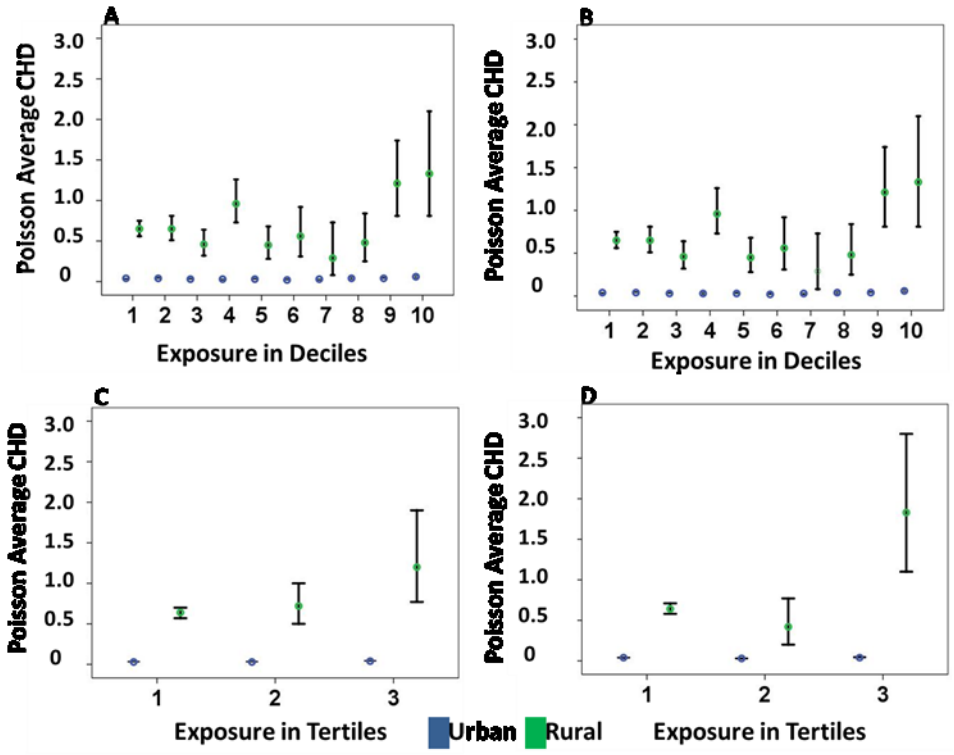

Figure 3.2 Poisson distribution of average of congenital heart defect (CHD) cases and 95% confidence intervals (CI) in urban and rural postal codes.

(A) Decile distribution of overall emissions. Rural postal codes had a larger average and variability of CHD cases per postal code in all the deciles of exposure. In urban postal codes, the average and variability were constant. **(B)** Decile distribution of Group 1 emissions which were similar to overall emissions. For Group 2 **(C)** and Group 3 emissions **(D),** the average and variability of CHD cases by postal code was high in rural compared to urban postal codes, with the highest average in the 3rd tertile where the exposure was the highest.

3.4.4. Adjusted Inverse Distance Weighted Exposure on CHD in Urban and Rural Postal Codes

3.4.4.1. Urban Postal Codes

Adjusted values indicated an increased association with CHD in the highest decile of exposure to all and Group 1 emissions [RR = 1.8 (1.50, 2.3) for both] (Figure 3.3A, B). The postal codes with the highest exposures from all and Group 1 emissions equally accounted for 16% of all CHD urban cases, which were found in 10% of the urban postal codes (Appendix C, D). In addition, there was a decreased association with CHD in the 4th and 6th decile of moderate exposure to all emissions [RR =0.73 (0.58, 0.93), and RR=0.66 (0.0.51, 0.84), respectively] (Figure 3.3A). Group 1 also showed decreased

associations in the 4th, 6th, and 7th deciles [RR= 0.75 (0.59, 0.95), RR =0.65 (0.51, 0.84) and RR =0.78 (0.62, 0.98), respectively] (Figure 3.3B). Similar to all and to Group 1 emissions, Groups 2 and 3 also showed associations in the postal codes with the highest exposure [RR =1.4 (1.3, 1.6) and RR = 1.4 (1.2, 1.6), respectively]. The postal codes in the highest tertile accounted for 40% of CHD cases and 34% of the postal codes (Appendix E). There was a decreased association with Group 3 in the 2nd tertile [RR = 0.84 (0.73, 0.96)] (Figure 3.4A, B).

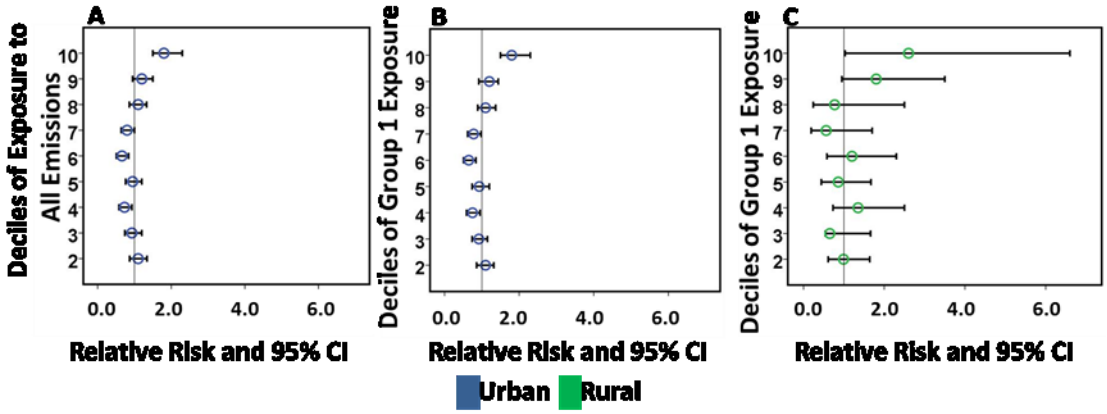

Figure 3. 3. Adjusted relative risk of postal codes exposed to the sum of all and Group 1 only emissions in urban and rural regions.

(A) Shows a significant increased risk ratio in the 10th decile with the highest exposure and inverse associations in the 4th and 6th deciles with modest exposure in urban postal codes. (B) Shows an increased risk ratio in the 10th decile with the highest exposure and inverse associations in the 4th, 6th and 7th deciles with modest exposure in urban postal codes. (C) Shows a significantly increased risk ratio in the 10th decile with the highest exposure in rural postal codes.

3.4.4.2. Rural Postal Codes

Although there was no effect observed for all emissions combined and Group 2 emissions in rural postal codes, there was an increased association with CHD in the postal codes with the highest exposure to Group 1 emissions [relative risk (RR) = 2.6 (1.0, 6.6)] (Figure 3.3C). The postal codes with the highest exposure represented only 2% of rural postal codes and had 5% of all rural CHD cases (Appendix D). Postal codes exposed to Group 3 emissions also showed associations in the highest tertile [RR = 2.6 (1.0, 7)] (Figure 3.4D). The postal codes in this tertile included 2% of all rural postal codes and it contained 5% of all rural CHD cases (Appendix E).

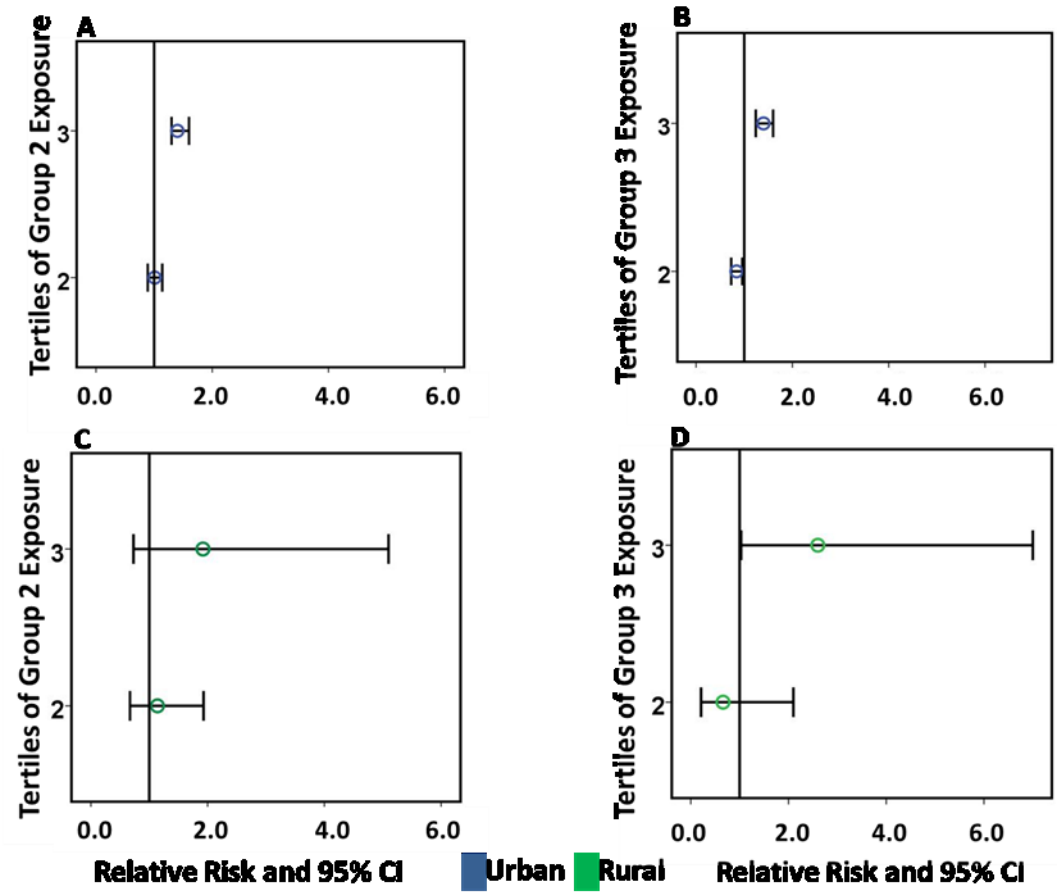

Figure 3. 4. Adjusted relative risk of postal codes exposed to Group 2 and 3 emissions on CHD in urban and rural regions.

(A, B) show increased risk ratio in the 3rd tertile with the highest exposure to Group 2 and 3 in urban postal codes. Group 3 also showed a significant inverse association in the 2nd tertile of exposure. (C) Shows the rural postal codes exposed to Group 2 emissions with no effect which may have been related to the small sample size. (D) Shows increased risk ratio (RR) of exposure to Group 3 in the 3rd tertile in rural postal codes.

The sensitivity analysis to explore the effects of changes in model specification did not show any difference with the results analyzed at 10 km. We retained the effects in urban postal codes for all emissions and the three groups of emissions when applying an eight or nine km radius. In the rural postal codes, we gained effects for postal codes exposed to all the emissions and retained effects for Group 1 and 3 emissions. We attempted analysis at five km but only 35% of the CHD cases were within those areas and the models did not work because of the small sample size.

3.4.5. Geographic Distribution of Urban and Rural Postal Codes with the Highest Exposure to Emissions

In urban regions, there were a total of 5410 postal codes with the highest exposure to Group 1 emissions (Table 3.3) and (Figure 3.5A). However, all of the CHD cases in this category (n = 317) were located in only 293 (5%) of the postal codes (Table 3.3). For Group 2, the highest exposure tertile contained a total of 18,062 postal codes (Table 3.3) (Figure 3.5B), and only 730 (4%) contained all the CHD cases (n = 786) in this category (Table 3.3). For Group 3, the highest exposure tertile contained a total of 18,068 postal codes (Table 3.3) (Figure 3.5C), and only 741 (4%) contained all the CHD cases (n = 799) in this category (Table 3.3). The postal codes for the individual three multipollutant groups showed similar distributions and were situated in the central, south, and western parts of Alberta, but mainly in the two largest cities of the province (Edmonton and Calgary).

In the rural regions, there were a total of 14 postal codes that had the highest exposure to Group 1 emissions (Table 3.3). Seven (50%) of the postal codes with the highest exposure had CHD cases (Table 3.3). Furthermore, there were a total of 12 postal codes in the highest exposure tertile to Group 3 emissions (Table 3.3) and six (50%) of the postal codes had CHD cases (Table 3.3). The postal codes with the highest exposure to Groups 1 and 3 emissions were few and sparse. They were situated in the central and northern parts of Alberta. Because the rural postal codes had low numbers of cases, we cannot present a map displaying their location. Because of confidentiality concerns, the ethics approval for this work did not permit presentation of maps with postal codes having less than ten individuals.

Table 3. 3. Distribution of postal codes exposed to the highest emissions and CHD in Alberta.

Region	Exposure Category	Total Postal Codes Count	Postal Codes with CHD (%)	Number of CHD Cases	Min Cases	Max Cases	Min Exposure (tonnes)	Max Exposure (tonnes)
Urban	Group 1 in 10th Decile	5410	293 (5)	317	1	4	10	116
	Group 2 in 3rd Tertile	18,062	730 (4)	786	1	4	23	2461 ‡
	Group 3 in 3rd Tertile	18,068	741 (4)	799	1	4	0.091	3.9 ‡
Rural	Group 1 in 10th Decile	14	7 (50)	20	1	9	11	500
	Group 2 in 3rd Tertile	18	6(33)	22	1	9	38	17,340 ‡
	Group 3 in 3rd Tertile	12	6 (50)	22	1	9	0.1	12 ‡

‡ = Group 2 and 3 emissions were emitted in small amounts and were not detectable in tonnes, therefore we chose to show them in kilograms.

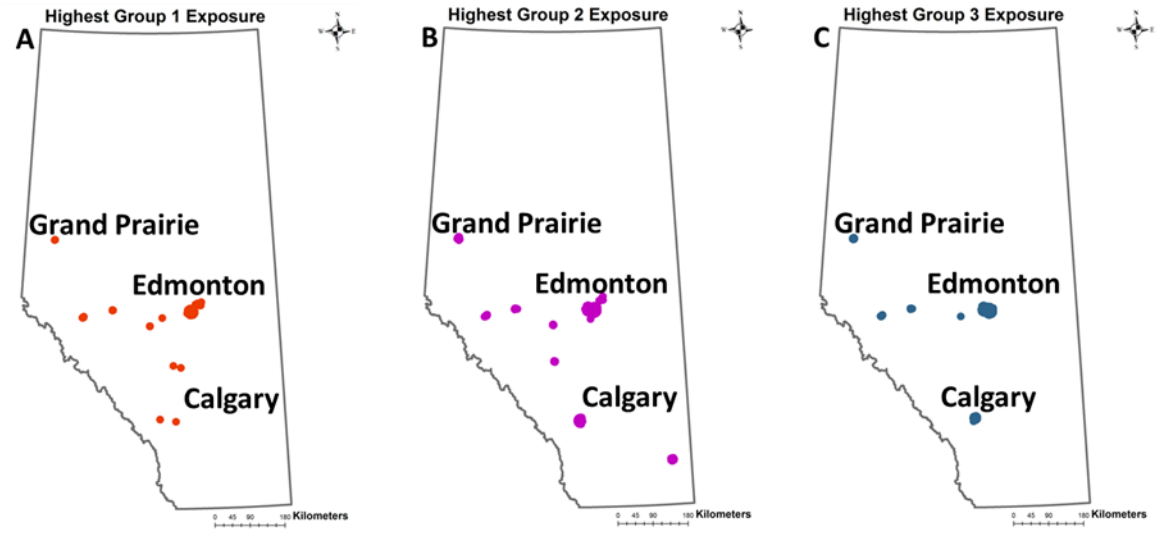

Figure 3.5 Geographic location of urban postal codes with the highest exposure to emissions.

(A) Displays postal codes exposed to Group 1 emissions (5410). (B) Displays postal codes exposed to Group 2 emissions (18,062). (C) Displays postal codes exposed to Group 3 emissions (18,068). Similar patterns are observed for the three groups and most the exposed postal codes are situated in the two main cities of the province: Edmonton and Calgary.

3.5. Discussion

Our investigation found positive associations of CHD occurrence in the postal codes with the highest air emissions of multipollutant groups (identified by the principal component analysis) from industrial sources in the province. Specifically, we found associations with urban postal codes exposed to the highest levels of all emissions and the three multipollutant groups individually, whilst the rural postal codes had associations with highest exposures to Group 1 and 3 emissions. In addition, we found the associations to be stronger in rural compared to urban postal codes. We also observed a decreased association in urban postal codes with moderate exposure from all and Groups 1 and 3 emissions. Mapping the postal codes with the highest emissions revealed that very few postal codes were exposed to the highest levels of emissions.

3.5.1. Multipollutant Exposures and CHD

An advantage of our study is that we used a comprehensive list of chemicals emitted to the air (from the NPRI) that otherwise would not be available since not many chemicals are routinely monitored in the environment. Although our study did not examine the interactions of these chemicals in the atmosphere, the positive associations we observed were found in the context of independent groups of industrial

emissions and not of chemicals acting individually. These new associations for groups of industrial emissions potentially support the notion of multipollutant human exposures and adverse health outcomes as a new paradigm that requires exploration by the research community (26).

To assess the association of emissions and CHD development, we modeled exposures of all air emissions released by industries in Alberta and a subset of three multipollutant groups we identified using Principal Component Analysis (PCA). This analysis only provides information about co-variating chemicals regardless of location, participation of multiple or single industrial facilities, or processes involved. PCA has been used in only one previously reported study to examine the role of groups of urban pollutants and CHD (15). In that case-control study, three pollutant groups were identified: nitrogen dioxide and carbon monoxide; particulate matter and ozone; and sulphur dioxide alone. Although their results are not fully comparable to ours since they utilized urban monitored pollutants from various sources, they found positive associations which did not reach statistical significance with groups containing sulphur dioxide and carbon monoxide. This was consistent with our observations for Group 1 emissions which contained both gases. Interestingly and contrary to our study, the associations in their study were attenuated in the highest levels of exposure.

The combinations of pollutants we identified have not been previously reported to have an association with CHD and they were released by three main sectors (manufacturing, utilities, and mining) operating in urban and rural regions. However, other studies have explored the association between individual chemicals or categories of chemicals found among our multipollutant groups and CHD. For instance, an earlier study by Gilboa et al. examined the potential role of maternal occupational exposures to classes of organic solvents and CHD (27). They had found positive associations of maternal exposure to any solvent or class of chlorinated solvents (e.g., trichloroethylene) with ventricular septal defects specifically. Of the single pollutant studies, only CO, SO_2, and trichloroethylene have been associated with CHD (9, 12, 28). Our study did not examine occupational exposures and we did not have the statistical power to examine subtypes of CHD; however, we identified heterogeneous groups and mixtures of toxicants which were associated with CHD in general. Group 1 emissions, which were more ubiquitous, consisted of volatile organic compound gases (VOCs) (1, 3 -butadiene, carbon disulfide, benzene, toluene) and other gases (SO_2, CO) and these were emitted in large amounts compared to Group 2 and 3 emissions. Group 2 contained chlorinated solvents (chloroform, trichloroethylene), alcohol-based solvents (methanol, methyl-isobutyl-ketone), and a VOC (ethylene oxide) and Group 3 contained arsenic, cadmium, lead, mercury, and hexachlorobenzene. It is plausible that the positive associations we observed were driven by individual toxicants in the groups they cohabit, such as SO_2 in Group 1; trichloroethylene in Group 2; and

lead in Group 3. However, it is also possible that the combination of toxicants, given their covariation as defined by PCA, may have been equally or even more contributory.

In our study we found positive associations between heavy metals and CHD in both urban and rural postal codes. However, previous studies have shown inconsistent associations between heavy metals and CHD, reporting both negative and positive associations (14). According to our PCA results, the participation of heavy metals in Group 1 and 2 was minimal based on the loading factors. Nevertheless, we do not know how they could interact with the other dominant chemicals in the groups they cohabit or whether they originate from the same industrial processes or are emitted by the same sources.

The proportion of the pollutant mixtures in terms of the dose and concentrations requires further exploration and determination in future studies. Overall, the urban postal codes showed positive associations with all three multipollutant groups in the highest levels of exposure whereas the associations in rural postal codes were only observed with highest levels of Groups 1 and 3 emissions. This observation suggests that the exposure from emissions is more in urban populations as this was also borne out by the positive associations with the overall sum of all the emissions. Interestingly, the size of the risk was higher in rural postal codes possibly related to higher concentrations of pollutants in the highest level of exposure in rural postal codes. The wide confidence interval including the large variance which was greater than the average of cases in rural postal codes is suggestive of clustering of CHD in some rural postal codes which require further geographic spatial analysis. Given our observations, we could suggest that the monitoring of emissions identified in this paper should initially focus on locations exposed to the highest levels of exposure in both urban and rural regions.

3.5.2. Negative Associations of Multipollutant Exposures and CHD in Urban Postal Codes

Urban postal codes presented us with both modest associations in the highest levels of exposure and smaller magnitude, but statistically significant, decreased associations in the moderately exposed postal codes, a phenomenon not observed in rural postal codes. These differences could potentially be due to other unmeasured variables such as wind dispersion, terrain, the effect of buildings and meteorological factors, and stack height that may protect some postal codes from the exposure of air pollutants in urban populations (29-31). Our study assigned exposure to the maternal residential postal code by considering the influence of distance on the tonnes emitted by the surrounding industrial facilities. However, it has been shown that intra-urban differences in air pollutant dispersion do exist, and, as such, more sophisticated dispersion models should be undertaken to assign more accurate exposure estimates in environmental epidemiology studies (32-34).

3.5.3. Rural Higher Average of CHD by Postal Code

We found a consistently higher average of CHD in rural postal codes for all levels of exposure compared to urban postal codes. However, positive associations accounted only for those postal codes exposed to the highest emissions after adjusting for neighborhood socio-economic status (SES) and other predominantly traffic related confounders such as nitrogen dioxide (NO_2) and particulate matter with a mean aerodynamic diameter ≤2.5 micrometers ($PM_{2.5}$). Exposures to environmental hazards present in water or soil were not measured in our study. There are also unique genetic risks independent of or potentially contributing to the effect of emissions in the different ethnicities common in rural areas of Alberta (e.g., First Nations, Hutterite) that warrant further exploration.

3.5.4. Plausible Pathogenetic Mechanisms for Industrial Multipollutants and CHD

The groups of chemicals identified in the study present an opportunity for the discussion of potential pathogenic mechanisms that may require their interactions to culminate in abnormal cardiac morphogenesis. No previous experimental models have been used to examine the role of multipollutants in CHD. The cellular and molecular mechanisms responsible for cardiac dysmorphogenesis are known for some specific chemical/pollutant exposures. For instance, organic solvents including chlorinated solvents such as trichloroethylene, one of the pollutants in our study, have been shown to alter cardiac morphogenesis through oxidative stress-mediated dysregulation of developmental signals (27, 35, 36). Genetic variations in the ability of the fetus or pregnant mother to eliminate some chemicals may explain abnormalities. Glutathione S-transferases (GSTs), for example, are enzymes essential for detoxification of many chemicals (8). In a small number of human pregnancies exposed to organic solvents and resultant fetal pathology, Ronan et al. (37) found fetal genetic abnormalities in this enzyme to be associated with the occurrence of congenital anomalies which included CHD.

Epigenetic modifications of the DNA secondary to chemical exposures in children are now gaining attention. A literature review by Bitto et al. proposed that environmental toxicant exposures during the vulnerable period of fetal development and early childhood could be responsible for adverse health outcomes in children (38). Interestingly, all of the heavy metals in Group 3 (cadmium, lead, mercury, arsenic) have been proposed to induce epigenetic alterations in children which could result in neurodevelopmental disorders such as autism, attention deficit disorders, and cancer or endocrine disorders (38). Although there are currently no studies which have demonstrated epigenetic alterations due to chemical toxicant exposures in the context of CHD, including the reported chemicals in our study, preliminary investigations are emerging which document the relevance of epigenetic changes in synchrony with genetic transcription factors that play a crucial role in abnormal cardiac morphogenesis (39-41). Further animal/translational investigations that explore the impact of exposure to pollutant

mixtures on cardiac development are necessary to better define this relationship on a whole organ, cellular, and molecular level.

3.6. Strengths and Limitations

Because of the centralized pediatric cardiology services in Alberta, the strength of our study is that we used a database which captured all CHD cases born in Alberta with complete case ascertainment. Our study sheds light on a potential association between industrial air-emitted chemicals, Group 1 (benzene, carbon disulfide, toluene, 1, 3 butadiene, carbon monoxide, and sulphur dioxide); Group 2 (1, 3 butadiene, chloroform, ethylene oxide, methanol, methyl-isobutyl-ketone and trichloroethylene), and Group 3 (arsenic, cadmium, mercury, lead, and hexachlorobenzene) and CHD, but certain limitations must be recognized. Being an ecological study, the observations made at aggregate level cannot be inferred to individuals. Given our source of patient data, we were unable to account for other variables associated with CHD including genetic abnormalities, maternal health, and exposure to drugs, the exposure of folic acid supplementation, and meteorological data (42). We may have underestimated the CHD counts because we did not include stillbirths and terminated pregnancies with fetal CHD; however, we had previously observed no increase in pregnancy terminations for CHD in the province during the study period and absolute termination rates are quite low in our province (43). In addition, associations with specific subtypes of CHD were not examined because of the small number of cases.

We did not have data on gestational age at birth and yet some of our CHD cases could have been delivered prematurely, which could have resulted in exposure misclassification. The chemical exposure assigned to the postal code in tonnes is the sum of all distance weighted emissions from the neighboring facilities over a period of eight years. However, the actual dose that would potentially reach the human population requires precise pollutant measurements in addition to biomonitoring data.

Another limitation of the study is that because the emissions were reported annually in the NPRI, we were unable to assign the precise exposure to the critical window of cardiomorphogenesis. We did not have a maternal residential history at the time of conception and the first trimester of pregnancy. We obtained the postal code address given at the time of the initial echocardiogram and assumed it to be the same address as the first trimester of pregnancy which would be the period of cardiomorphogenesis. Previous studies have shown that a minority of women move during pregnancy (44, 45), but we still acknowledge the existence of a potential exposure misclassification.

Another source of exposure misclassification is the fact that we had a measurement bias of the emissions because we used annual estimates reported in the NPRI and not monitored pollutants data. Our work

represents an initial approach motivated by the fact that there is no existing comprehensive database of as many chemicals monitored in the environment as the ones reported in the NPRI.

3.7. Conclusions and Recommendations

We found regional variation in associations between the sum of all emissions and multipollutant groups in the postal codes with the highest exposure and CHD. The maps indicated that few postal codes were exposed to high emissions. The exposed urban postal codes concentrated in the main cities of the province and had positive associations with the sum of all the emissions and the three groups of the pollutants, whilst for the rural postal codes, the associations were detected for Group 1 and 3 pollutants only, perhaps as the number of postal codes exposed in these regions was extremely small. Furthermore, the other rural postal codes which had higher numbers of CHD cases not explained by chemicals require ongoing exploration of other potential contributors.

The findings from our study support the need to conduct more robust epidemiological studies which will include maternal risk factors and meteorological data to further validate these findings. We recommend that future studies should investigate the role of multiple pollutants in the evolution of CHD. The fact that we found associations only in the highest exposure categories in both urban and rural postal codes suggests the presence of a threshold of exposure to pollutants for CHD to develop not confounded by SES or other urban pollutants. This observation warrants future investigations to determine the threshold which would require the use of more precise data (e.g., monitored data) to identify the critical concentration of exposure in which CHD may occur.

Finally, we have shown potential associations between mixtures of industrial emissions and children's heart maldevelopment. However, there is still a need to incorporate the findings from other species [e.g., (46, 47)] to capture the complexity involved on the planetary health implications of environmental pollution.

Supplementary Materials: The following are available online at www.mdpi.com/link. Appendix I. (A) Shows the proportion and trends of 18 chemicals in tonnes for urban and rural postal odes. The rural postal codes had the highest proportion of emissions released to air for the period 2003–2010. (B) Shows the distribution of the three groups of emissions derived from principal component analysis and the 3 main sectors (mining, manufacturing and utilities) which emitted the chemicals in urban and rural postal codes. Appendix C. Regional Decile Distribution of the Sum of All Inverse Distance Weighted (IDW) Emissions and Congenital Heart Disease (CHD), Appendix D. Regional Decile Distribution of Group1 Inverse Distance Weighted (IDW) Emissions and Congenital Heart Disease, Appendix E. Regional

Tertile Distribution of Group 2 and 3 Inverse Distance Weighted (IDW) Emissions and Congenital Heart Disease (CHD).

Author Contributions: Deliwe P Ngwezi, contributed to the conceptualization, design, acquisition of data, analysis of the data and wrote the paper. Lisa K Hornberger contributed to the conceptualization, design, acquisition of data, resources and reviewed the manuscript. Jesus Serrano-Lomelin contributed to the conceptualization, assisted with database management, statistical analysis and reviewed the manuscript. Charlene Nielsen assisted with the spatial analysis and reviewed the manuscript. Deborah Fruitman provided the data and reviewed the manuscript. Alvaro Osornio-Vargas contributed to the conceptualization, design, acquisition of data, resources and reviewed the manuscript.

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Declarations: The air pollution dataset generated for the current study is publicly available from the Government of Canada's National Pollutant Release Inventory, https://www.ec.gc.ca/inrp-npri/. Accessed 5 May 2018. The CHD dataset is not publicly available due to privacy and confidentiality clauses of the Government of Alberta's Health Information Act Section 2.

Abbreviations

CHD Congenital Heart Disease

EF Emitting Facility

IDW Inverse Distance Weight

NPRI National Pollutant Release Inventory

PCA Principal Component Analysis

RR Relative Risk

SES Socio-Economic Status

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Chapter 4 Neighborhood socio-economic status and congenital heart disease in urban and rural Alberta

4.1. Abstract

Introduction

Congenital heart disease (CHD) is one of the most significant and serious congenital anomalies affecting 1% of live births worldwide. Despite its impact on populations globally, the etiology for most CHD remains unknown. It has been suggested that the cause for many is multifactorial and potentially involving environmental factors with or without a genetic predisposition. Some have explored potential contributing factors associated with maternal socioeconomic status (SES) and several studies have found associations between individual SES and CHD. However, neighborhood SES has also been found to adversely impact health outcomes and the contribution of neighborhood SES on CHD development is currently unknown. In this study I sought to explore the role of neighborhood SES and its association with CHD in urban and rural Alberta.

Methods

I identified all children born with CHD in Alberta between January 2004 and August 2011 from echocardiography databases of the Stollery and Alberta Children's Hospitals. I used Chan's SES index which was constructed at dissemination area level from 22 variables obtained from Census Canada 2006 which included cultural identities and housing characteristics, variables from environmental injustice studies and Pampalon's index. The index was assigned to the postal codes belonging to the respective DA's. I categorized the index into tertiles and assigned the CHD cases to the tertiles for urban and rural regions with tertile (1) reflecting the lowest SES and tertile (3) the highest SES. I conducted Poisson and non-negative binomial regression models adjusted for traffic related variables like NO_2 and $PM_{2.5}$ and all industrial developmental toxicants (DTs) released to air.

Results

In urban regions of Alberta, there was a significant increased risk ratio of CHD in the urban lowest SES tertile (1^{st} tertile) [RR = 1.1 (1.0, 1.3)], whilst in the rural regions, there was an increased risk ratio which was significant in the lowest and intermediate SES tertile [RR = 3.0 (1.9, 4.8) and RR = 1.6 (1.1, 2.5), respectively] when compared to the highest SES tertile.

Conclusions

Low neighborhood SES was independently associated with an increased risk of CHD in both urban and rural regions of Alberta. Furthermore, there was an increase risk also in the intermediate SES rural regions but was higher in the low SES regions. Future studies will examine the relationship of individual maternal, family and neighborhood SES to ascertain the unique contribution of the neighborhood as a risk factor for CHD. Furthermore, we will examine if the phenomenon of environmental injustice exists in Alberta by examining interactions between neighborhood SES and industrial DTs.

4.2. Introduction

In Chapter 3, the analysis of maternal exposure to developmental toxicants (DTs) and the association with congenital heart disease (CHD) showed that overall the average CHD case number by postal code was higher in rural compared to urban regions in all decile categories of exposure. In rural regions, I found an increased risk ratio in the highest decile of exposure to Group 1 DTs and the highest tertile of exposure to Group 3 DTs after adjusting for socioeconomic status (SES) and urban pollution-related confounders such as NO_2 and $PM_{2.5}$. In urban regions, the associations were found with all 3 DT Groups and DTs overall. Although the average CHD cases by postal code were high in the rural regions, not all of the cases could be explained by DT exposures. Therefore, in this chapter, I sought to explore if SES at the neighborhood level, had an independent association with CHD in Alberta particularly in the rural regions given the high incidence of CHD in those regions.

It is becoming increasingly apparent that there is a relationship between social and economic factors and the health of populations (1-3). Although there have been improvements in the health indices for most populations around the world, health inequities as a result of social injustices persist in some parts of the world and account for the majority of unnecessary deaths amongst the most vulnerable populations (2). Indeed, an attempt has been made by the WHO to address the health inequities globally by establishing a commission on social determinants of health (CSDH) in 2008. The commission concluded that health inequities are determined by conditions in which people are born, live, work, access to health care, education, food security, shelter and recreational facilities in determining their well-being and full potential in life (2, 4). Decision makers at political and economic levels need to play an active role in closing the gaps that contribute to the inequities.

Canada, one of the richest countries internationally, has for a long time prided itself as having one of the best health care systems in the world. Despite good health policies and the wealth of the country, health inequities exist as a result of poor living conditions, access to healthcare, working conditions, lack of recreational facilities (5, 6). It has been postulated that people in poor socioeconomic position have an excess burden of exposure to environmental hazards compared to their rich counterparts that predisposes them to adverse health outcomes leading to a *"double jeopardy"* (7, 8). However, the findings from Chapter 3 showed that exposure to DTs after controlling for SES, was independently associated with the risk of CHD in regions with the highest exposure. I concluded that not all CHD cases can be explained by DT exposures and therefore SES may potentially explain CHD occurrence in regions with low to moderate exposures to DTs.

CHD is one of the most common and significant among all congenital anomalies affecting 1% of live births worldwide (9). The etiology of CHD is believed to be multifactorial; however, for most CHD, the cause is not known (10). Environmental factors such as environmental pollution with or without a genetic predisposition are thought to be at play (11). Previous studies have examined SES in relation to access to health care for management of CHD, prenatal diagnosis of CHD, mortality, morbidity and economic costs in treating patients with CHD (12-16). However, the role of SES in the development of CHD is increasingly gaining attention. The majority of studies published to date have examined SES at an individual level. A recent meta-analysis which examined 33 studies (17) found that there was an association with low maternal education, income and employment and CHD. However, more evidence is emerging as previously determined by the CSDH, that neighborhood living conditions in addition to individual socioeconomic position may be important determinants of health (2). There is paucity of data on the role of neighborhood SES in the development of CHD. A recent meta- analysis of nine studies exploring the effect of neighborhood SES and congenital anomalies, found that cleft lip with or without palate was associated with neighborhood SES (18). Out of the nine studies included, only four case control studies were eligible for inclusion in the meta-analysis for the subtypes of CHD (18). One other study which was conducted in Canada was not included in the meta-analysis because it was a cohort study (19). The pooled effects of the four studies suggested no association between neighborhood SES and CHD, however some of these studies individually showed positive and negative associations with CHD. For example, Carmichael et al. in 2003 and 2009(20, 21) examined neighborhood SES at census tract level and individual maternal SES in the United States and found no association between either level of SES and conotruncal CHD. Vrijheid et al. (22), examined neighborhood SES using enumeration areas and the Carstairs deprivation index for Great Britain. They found increased odds ratio with increasing deprivation for septal defects only. Finally, one other study included in the meta-analysis by Pawluk et al. (23) and was conducted in Argentina, used a regional based SES index and found low SES to be a risk factor for ventricular septal defects. The differences in the associations discovered in these studies could be due to the heterogeneity of the spatial unit of analysis used, the small number of studies analyzed and the variation in the grouping and subtypes of CHD reported.

Indeed, some studies have found that the characteristics of the neighborhood weighed more in determining adverse health outcomes after controlling for individual SES (24, 25). For example, if neighborhoods lack quality spaces for physical activity, recreation, access to healthy food options, exposed to violence and poverty which leads to stress, these factors will result in adverse health for individuals living in those neighborhoods even if at individual level, they have the knowledge and means to be able to make healthy lifestyle choices. However, their unhealthy environments may limit their

capacity to execute their lifestyle choices. Conversely, unhealthy individual lifestyles may also be reinforced by the neighborhoods which are poorly resourced. Another study by Roubinov et al., found that children from families with low SES but living in higher opportunity neighborhoods, had lower stress levels as determined from their cortisol levels which were not raised compared to children who came from low SES families and living in low advantage neighborhoods (26).

Based on the findings from the two meta-analyses to date, the role of SES on CHD incidence remains inconclusive and even more so when using the variable as neighborhood SES. To explore health outcomes related to environmental pollution and SES in Canada, an SES index at neighborhood level was developed by Chan et al. (27). This index identified 22 variables from the 2006 Census which included housing characteristics as a proxy for indoor pollution, variables from Canadian environmental injustice studies and from a previous deprivation index (Pampalon). The Chan index found an association between lower quintiles of SES and adverse birth outcomes such low birth weight, small for gestational age and preterm birth in urban Alberta, however it did not examine associations with birth defects including CHD.

With this in mind, I sought to investigate the association of neighborhood SES and the risk of CHD using the Chan index at postal codes level without considering the influence of the characteristics of the neighborhoods in urban and rural Alberta.

4.3. Materials and Methods

4.3.1. Study Population

I searched for all children born in Alberta between January 2004 and August 2011 with echocardiography confirmed CHD from the pediatric echocardiographic Xcelera (Philips, Canada) regional databases. Other data for each case included birth date, study date, and postal code at time of diagnosis. Ethics approval from the participating institutions was obtained.

Case ascertainment was performed by retrieving all echocardiographic and surgical reports to confirm a diagnosis of CHD. Cases were aggregated according to their suspected embryological derivations as previously described (Botto et al., 2007). For patients with multiple echocardiographic examinations, the most consistent major umbrella diagnosis was accepted as the diagnosis, and when there was uncertainty regarding the primary embryological group, the echocardiogram was reviewed by a pediatric echocardiographer or the operative diagnosis was used. I considered all cases with structural heart abnormalities, including those with a patent ductus arteriosus (PDA) present at >6 months and those with an atrial septal defect (ASD) after one year or in whom surgical or device closure was necessary. Patients with cardiomyopathies and no structural CHD, neonatal peripheral pulmonary stenosis, a PDA at less than 6 months, an ASD at <1 year, and all cases born outside of the province were excluded.

4.3.2. Derivation of SES Index

I worked with the SES index which was designed to investigate the relationship of environmental related indices and SES in adverse health outcomes in Canada (27). The index used principal component analysis (PCA) based on 22 SES variables which included cultural identities, housing characteristics identified from Census Canada 2006, variables identified in Canadian environmental injustice studies and variables included in an existing Canadian deprivation index (Pampalon), like house income, highest educational level attained, etc. The PCA analysis was performed for all the dissemination areas (DA) in Canada (n=52,974) of which there are 5,517 in Alberta. A DA is defined as small neighboring regions consisting of 400 to 700 people (28). I used the postal code conversion file (PCCF) to identify the postal codes belonging to each DA and I assigned the SES index value of the DA to each of the postal codes aggregated to the individual DAs, assuming a homogenous distribution within the DA. The highest category of SES index was designated as the reference in the analysis.

4.3.3. Covariates

4.3.3.1. Overall Developmental Toxicants (DTs)

I accessed the NPRI to identify annual reports of all DTs as previously defined in Chapters 2 and 3 which were released to air and geographic coordinates of emitting facilities in Alberta from 2003-2010.

4.3.3.2. NO_2 and $PM_{2.5}$

I used national land use regression models for NO_2 and $PM_{2.5}$ constructed by Hystad et al. (29). They used data from fixed site air pollution stations, satellite-based estimates and geographic predictor variables in multiple linear regression models to estimate pollutant concentrations across Alberta that were applied to the postal codes of interest in this study to assign their exposures as potential confounders.

4.3.4. Statistical Analysis

The SES index was categorized into tertiles of SES: tertile 1 = lowest SES, tertile 2 = intermediate SES and tertile 3 = highest SES, of which the latter was the reference. CHD cases were then assigned to each tertile of the SES. I used descriptive statistics to describe the distribution of the SES tertile categories and the counts of CHD cases assigned to the SES categories in urban and rural regions. Differences in SES median categories between urban and rural regions were measured using Mann-Whitney U test and Kruskal Wallis for the differences in tertile categories. Poisson and negative binomial regression models were constructed to determine the risk ratios (RR) and 95% CI adjusted for overall DTs and urban related exposures using surrogates such as NO_2 and $PM_{2.5}$.

4.4. Results

4.4.1. Distribution of SES Index and CHD Cases in Urban and Rural Regions

Overall, urban regions had a higher SES compared to rural regions, with a median SES index of 0.19, IQR =0.74 versus 0.00 (IQR=0.59) in rural regions ($p<0.001$). After stratifying the SES indices into tertiles, I found significant higher median SES for the 1st (low SES) of the rural postal codes and a higher median for the 3rd (high SES) tertiles in urban postal codes. There was no difference in median for the 2nd (middle) tertile. The overall average CHD counts by postal code remained high in rural compared to urban postal codes, particularly in the postal codes impacted by the lowest tertile of SES (Fig 4.1) and (Table 4.1).

4.4.2. Adjusted Effects of SES Index on CHD Cases in Urban and Rural Regions

After controlling for DT emissions, and urban related pollution variables, there was a significantly increased association of CHD in the lowest SES tertile (1st tertile) (RR = 1.1 (1.0, 1.3)), whilst in the rural regions, there was a gradient in the association which was significantly increased in the lowest and middle SES tertiles (1st & 2nd tertile) (RR = 3.0 (1.9, 4.8) and RR = 1.6 (1.1, 2.5), respectively) when compared to the highest SES tertile (3rd tertile) (Fig 4.2)&(Table 4.2). The postal codes in the lowest urban SES accounted for 38% of all CHD cases, whilst in the rural regions, 51% and 37% of all CHD cases were found in the lowest and middle SES postal codes respectively Table 4.1.

4.5 Discussion

My study found statistically significant positive associations between neighborhood SES index and CHD after adjusting for industrial DT exposures and traffic related pollutant such as NO_2 and $PM_{2.5}$ in both urban and rural regions of Alberta. However, the impact was larger in the rural regions with both the lowest and middle SES regions associated with increased risk of CHD, whilst in the urban regions; the risk was only observed in the lowest SES regions.

The association of low neighborhood SES and adverse health outcomes is well documented (30-32). Several studies have reported on the association of low SES and congenital anomalies (33-35), however there have been very few studies that have examined the association between low SES and CHD with largely inconclusive findings as suggested from a recent meta-analysis (18). Some studies have found a positive association of neighborhood SES and CHD (19, 22) whilst others have found no association (20, 21). In an earlier study (21), the authors found both positive associations between low SES at neighborhood level and d-Transposition of the Great Arteries (d-TGA), and reduced risk of Tetralogy of Fallot (TOF). In a subsequent investigation where they assigned an SES index at household level, they observed no associations with conotruncal heart defects, but found positive associations with cleft lip with or without palate. Another study by Yang et al. which examined individual SES based on both parents' education attainment, occupation, household income and a household SES index created from the joint effects of the individual SES variables, found differential increased odd ratios for d-TGA and TOF, although the effects were not significant (36). For example, individual paternal low education and maternal low occupation was associated with d-TGA and TOF. Maternal low education, and low household SES index was associated with risk of d-TGA whilst TOF was associated only with low household income.

My study utilized an SES index at DA level but extrapolated to postal codes and found an independent increasing risk ratio for CHD overall from 1.6 times in the rural middle SES to three times the risk in rural low SES postal codes. In the urban postal codes, there was an increased risk ratio for CHD in the low SES postal codes only. The finding of an increased risk of CHD for the rural middle SES neighborhood populations is contrary to the notion that good social position is associated with the well-being of people. A plausible explanation could be the fact that we used the SES index at postal code level which was extrapolated from the DA area level, therefore resulting in a misclassification of the SES index known as the modifiable areal unit problem (MAUP) where different results are observed as a function of the change in the geographic unit of analysis (37). The rural DA's are larger compared to urban and have fewer postal codes compared to smaller urban DA's which have many postal codes. This difference may account for the more stable estimates I observed in urban compared to rural postal codes.

Studies have attempted to discriminate the relative weight of the contribution of individual SES versus neighborhood SES in relation to adverse health outcomes (24, 38, 39) and have found that neighborhood SES maybe more important than individual SES. However, some studies have shown that both individual and neighborhood SES together confer an increased risk of congenital anomalies and are not mutually exclusive (33). My study did not evaluate the contribution of individual SES, and because I used an index, I was also unable to quantify the relative contribution of composite variables which informed the construction of the SES index. Nonetheless, a Canadian study by Agha et al., found both area level low income and education to be associated with non-severe CHD, whilst only low education was found to be a significant predictor for severe CHD (19). My study could not examine severe CHD (conotruncal heart defects, single ventricle physiology, hypoplastic left heart syndrome) due to small numbers. The largest proportion of CHD was septal heart defects which would be classified as non-severe CHD. The positive associations with neighborhood SES in my study could have been driven by the septal defects which would support the findings by Agha et al (19). Other studies which corroborate my findings, reported positive association between ventricular septal defects and low neighborhood SES (33, 34). However, there were studies which found no association with CHD (22, 23). This observation suggests that indeed SES is a complex multifaceted construct with a host of factors at individual, family and neighborhood level acting in concert and in a mutually reinforcing fashion which results in adverse health outcomes (3).

Although studies have demonstrated neighborhood SES to be more important than individual SES in health outcomes such as coronary heart disease, adolescent health and survival of children with CHD (24, 38, 39) respectively, some studies have shown that both individual and neighborhood SES together confer an increased risk of congenital anomalies and are not mutually exclusive (33). For example, the study by Wasserman et al., found that neural tube defects (NTD) were associated with both neighborhood and

maternal individual low SES. Although my study did not include NTDs, it is known that perinatal folate supplementation is associated with decreased risk of NTD and CHD (40). Pregnant women with lack of access to healthy nutrition and access to health care because of where they live, maybe at risk of giving birth to a child with CHD. Whilst the data on maternal individual SES and CHD is currently very scanty as recently shown in a meta-analysis of 33 studies by Yu et al 2014 (17) and even more so for neighborhood SES (18), future studies should examine the role of multilevel SES on CHD to elucidate the extent to which neighborhood, individual and family SES may represent the SES factors that could have contributed to CHD in their models. This finding would confirm the importance of neighborhood as an independent determinant of risk for CHD development or determine whether there is an interaction with maternal individual or family SES.

The concept of environmental justice is well documented in the United States of America (41). This resulted in the issuing of executive orders by former President Bill Clinton which made it compulsory for agencies to be sensitive about the impact of environmental hazards on minority populations (42). In Canada, the concept has also been explored (7, 8, 43) and findings suggest that poor people are also disproportionately exposed to environmental pollutants (43). In contrast, my study found that low neighborhood SES after adjusting for DT exposure and traffic related variables, was independently associated with risk of CHD in both urban and rural regions of Alberta. This observation suggests that both socioeconomic factors and DT exposures independently play an important role in the development of CHD. My data, however, was at this point unable to allow me to conclude with certainty whether or not environmental injustice exists in Alberta. Geographic mapping of the locations of the cases and the associated risk factors could help elucidate the existence or lack of the phenomenon in Alberta.

The province of Alberta was developed in 1905 and its economy was largely dependent on agriculture for the past 70 years. Approximately 80 % of the Alberta population resides in urban and 20% rural regions and this disparity in the population distribution has been driven by economic and job opportunities in urban regions (44). Municipal services ranging from access to health services, safe water, electricity and sanitation, safe spaces for recreation and physical activity, access to stores with healthy food options may not be optimum for these rural communities due to financial constraints despite the industrial economic boom in the province (44). Therefore, the increased magnitude of CHD risk observed in these rural regions maybe a reflection of the health inequities and social injustices, including other unmeasured confounders that rural populations and some minority populations such as indigenous peoples are confronted with in some parts of Alberta. Although I did not specifically identify indigenous populations in my study, a majority of them (42% versus 19% of the total Alberta population) live in rural and small-town areas (45) and suffer adverse health effects from water pollution from hazardous environmental

toxicants. For example, there are some strongly held perceptions that the industrial oil exploration in rural Alberta has impacted negatively on the livelihood, health, culture and spiritual wellbeing of indigenous populations as a result of water pollution, dumping of toxic waste and degradation of environment (46, 47). Therefore, these environmental risk factors may potentially contribute to the increased CHD risk and point to the health inequities and social injustices that the minority populations are confronted with in some parts of Alberta.

The strengths of my study are that it is population based and I had access to a validated database of all CHD in the province of Alberta. I also used a comprehensive neighborhood SES index which was created to examine health outcomes attributed to environmental pollution specifically in Canada. The limitation of the study was that I was unable to adjust for individual maternal SES indicators in order to be certain of the effect of the neighborhood SES index. Extrapolation of the DA generated SES index to postal codes may have created a misclassification of the SES index due to a modifiable area unit problem. Another limitation is that I was unable to adjust for other risk factors associated with CHD at neighborhood level, individual and family level and therefore the estimates maybe overestimated.

4.6. Conclusions and Recommendations

Low neighborhood SES independent of DT exposure was associated with an increased risk of CHD in both urban and rural regions of Alberta. Furthermore, rural regions appear to be more greatly impacted with a much higher risk ratio in the low SES neighborhood. Living in intermediate SES neighborhoods also confers a risk of CHD in rural regions which points to the presence of other unmeasured confounders in the development of CHD. Further investigations are necessary currently to examine the relationship of individual maternal, family and neighborhood SES to ascertain the unique contribution of the neighborhood as a risk factor for CHD or any interactions for that matter. Furthermore, I need to examine if the phenomenon of environmental injustice exists in Alberta and contributes to CHD by examining interactions between neighborhood SES and industrial DTs.

Table 4. 1. Regional Tertile Distribution of SES and CHD in Urban and Rural Alberta

Region	Tertile	Postal Code Count	% of Postal Codes	Median SES Index	SES Index IQR	Min SES Index	Max SES Index	Mean SES Index ±SD	CHD Count (%)	Average CHD by Postal Code	Variance of CHD by Postal Code
Urban	1	18,009	34	-0.36	0.43	-1.9	0.01	-0.4±0.34	743(38)	0.04 (0.04, 0.04)	0.05
	2	17,809	33	0.23	0.2	0.02	0.41	0.2±0.11	580(29)	0.03 (0.03, 0.04)	0.04
	3	17,710	33	0.6	0.2	0.42	1.4	0.6±0.2	644(33)	0.04 (0.03, 0.04)	0.04
Total		53,561							1,967	0.04 (0.04, 0.04)	0.04
Rural	1	223	33	-0.2	0.4	-2.4	0.01	-0.4±0.6	227(51)	1.02 (0.89, 1.2)	4.6
	2	296	44	0.24	0.2	0.02	0.4	0.2±0.11	165(37)	0.56 (0.48, 0.65)	1.4
	3	159	23	0.6	0.2	0.4	1.0	0.6±0.11	54(12)	0.34 (0.26, 0.44)	0.7
		679							446	0.66	2.33

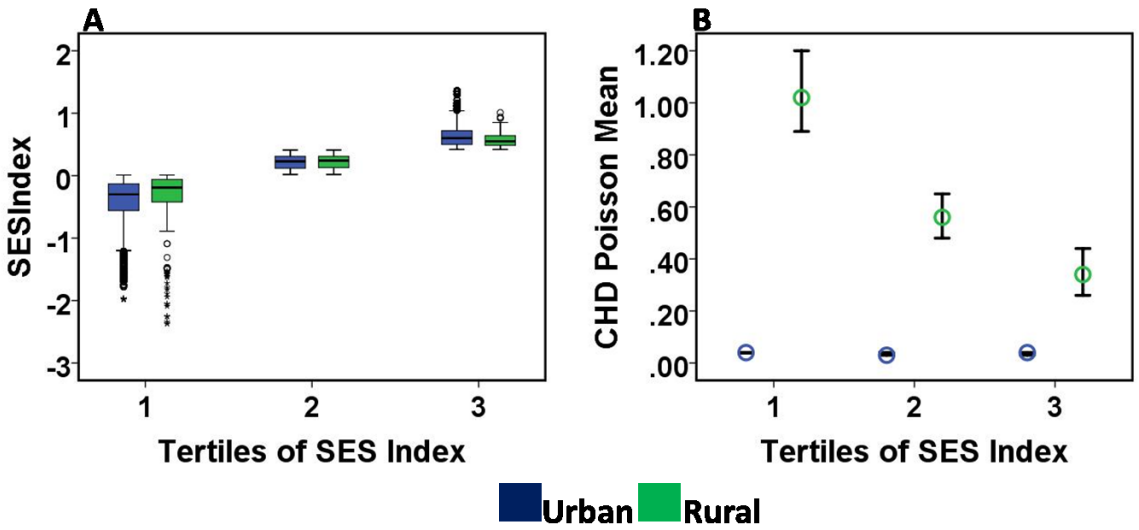

Figure 4. 1. Tertile Distribution of SES Index in Urban and Rural Regions.

(A) Tertile 1 and 3 showed statistically significant differences in the median SES in favor of rural and urban regions respectively. (**B)** Poisson mean distribution and 95% confidence intervals of CHD cases within the SES tertiles. The rural regions had higher average cases by postal code compared to urban regions with tertile 1 having the highest average CHD cases.

Table 4. 2. Effects of SES on CHD adjusted by DTs-IDW, NO_2 and $PM_{2.5}$ in Urban and Rural Alberta

Region	Tertile	Unadjusted RR (95% CI)	[a]RR (95% CI)	[b]RR (95% CI)	[c]RR (95% CI)	†RR (95% CI)
Urban	1	***1.13 (1.0, 1.3)***	***1.1 (0.96, 1.2)***	***1.2 (1.1, 1.3)***	***1.1, 1.02, 1.3)***	***1.1(1.0,1.3)***
	2	0.89 (0.79, 1.01)	0.9 (0.8, 0.9)	0.93(0.83, 1.1)	0.89 (0.79, 1.01)	0.9(0.8,1.0)
	3	Ref	Ref	Ref	Ref	
Rural	1	***2.9 (1.9, 4.8)***	***3.1 (1.9, 2.5)***	***3 (1.9, 4.8)***	***2.9 (1.9, 4.7)***	***3.0(1.9,4.8)***
	2	***1.6 (1.1, 2.6)***	***1.6 (1.04, 2.5)***	***1.6 (1.1, 2.6)***	***1.7 (1.1, 2.6)***	***1.6(1.1,2.5)***
	3	Ref	Ref	Ref	Ref	

a = DTs-IDW, b = NO2, c = PM2.5, †All Covariates

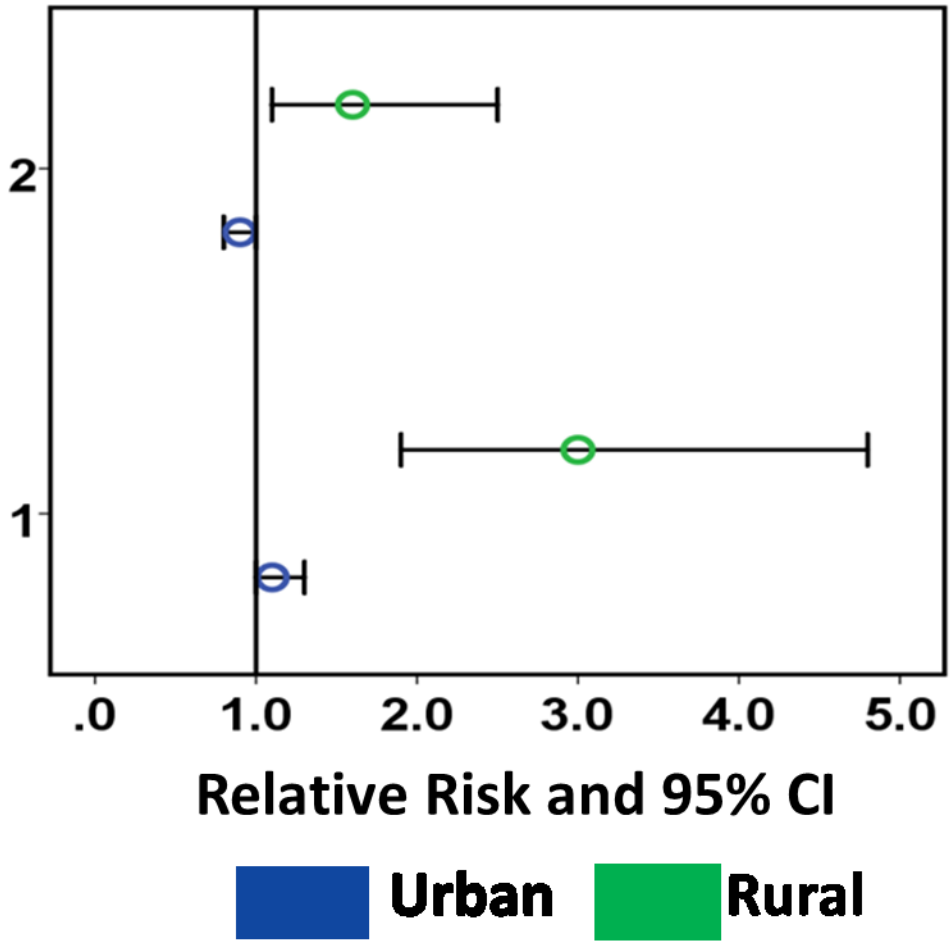

Figure 4. 2. Shows the effects of SES Index on CHD in urban and rural Alberta. The effect was stronger in rural compared to urban regions.

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Chapter 5 Geographic Distribution of Postal Codes Exposed to High levels of Developmental Toxicants, Low Socio-Economic Status and Congenital Heart Disease in Alberta

5.1. Abstract

Introduction

Previous analysis showed differences in the exposure to developmental toxicants (DTs) emitted to air by industry on urban and rural Alberta. I found that very high levels of DTs were necessary to identify associations between congenital heart disease (CHD) and DTs. Independently, low socioeconomic status (SES) was associated with CHD. The objective of this chapter was to visualize the geographic distribution of the regions that are exposed to the highest levels of DTs, low SES and those regions with and without CHD cases in Alberta. I then sought to determine the locations where all three variables collocate by using geographic information systems (GIS) software.

Methods

I worked with postal codes that were exposed to the highest DT levels of all the three DT groups. Likewise, I extracted the urban postal codes with low SES and for the rural postal codes I extracted both low and intermediate SES categories given my findings in the preceding chapter. In order to identify postal codes that were exposed to more than one group of DTs, I computed the various permutations of DT combinations using the whole dataset and then conducted an overlay analysis of the postal codes exposed to the highest DT groups based on the DT combinations. I overlaid the highest level of DT combinations with low or intermediate SES index and CHD cases to determine regions where all of the variables collocate. I used Poisson models to calculate the adjusted relative risk (RR) for urban postal codes exposed to the three DTs combined alone and also with low SES included. I included SES, NO_2 and $PM_{2.5}$ as covariates accordingly. The reference for the former was postal codes exposed to the lowest emissions of the three DTs combined. For the latter, the reference was postal codes exposed to the lowest emissions of the three DTs combined and had intermediate or high SES. The rural sample size was too small and therefore I did not estimate the RR. In order to display the centroids of the postal codes with the highest DT exposure, low SES and the CHD cases, I used ESRI ArcGIS 10.4 software to create dots of the groups of DTs and CHD cases. To project the maps, we used the 1983 North American Datum 10 degrees Transverse Mercator, using the Alberta Forest Projection Coordinate System.

Results

The analysis revealed that in fact few postal codes were exposed to the highest levels of the three DT groups. For the urban postal codes, the geographic pattern was similar for all the three DT groups and they were located in central, western and southern parts of Alberta. The postal codes in urban regions with lowest SES were randomly distributed with a slight predominance in central and southern parts of Alberta. In the rural regions, the postal codes exposed to the highest Group 1 and 3 DTs were situated in central Alberta and one isolated region in the north. The rural regions with low SES were widely dispersed throughout Alberta. The postal codes with CHD cases were few in both urban and rural postal codes.

Overlay analysis revealed that 5% of urban postal codes which were exposed to the highest levels of all the three DTs combined, had 16% of the total CHD cases in urban regions. When I included low SES to the three DT combinations, 7% of these postal codes had CHD cases which accounted for 10% of the total CHD cases in urban postal codes and these were mainly in Edmonton. In contrast, for the rural postal codes, 75% of the postal codes exposed to the highest levels of the three DTs combined had 3% of the total CHD cases in rural regions and these were in central and northern region of Alberta. The adjusted RR for the urban postal codes exposed to the highest levels of the three DT groups was 1.55, CI: 1.03, 2.30. This risk doubled after SES was overlaid with the three DT groups, RR 1.96, CI: 1.53, 2.51.

Conclusions

The maps generated have facilitated identification of regions in Alberta exposed to the highest levels of the DTs and low or intermediate (rural only) SES independently. Overall, few postal codes were exposed to the highest levels of DT emissions and I discovered similar patterns in the geographic locations of the postal codes exposed to the three DT groups. The overlay analysis confirmed the collocations of the three DT groups with and without low SES and intermediate SES (rural only). The risk ratio however was amplified for low SES combined with the three DTs and not with the three DT combinations alone. The findings suggest the presence of a localized environmental injustice in Alberta. In the rural regions, the collocation of the DT groups with intermediate SES suggests a much more complex phenomenon.

Keywords: Congenital heart disease, developmental toxicants, socioeconomic status, environmental justice, environmental injustice

5.2. Introduction

In my previous work (Chapter 3 accepted as a publication) I found positive associations between CHD occurrence and postal codes exposed to high DT emissions. In urban regions this included all three groups of DTs and DTs overall and in rural regions, postal codes impacted most by Group 1 and 3 DTs were positively associated with CHDs. In Chapter 4, I also found independent positive associations in urban regions between low neighborhood SES and CHD and in rural regions between both low and intermediate SES and CHD however I did not know the location of those postal codes.

Mapping of disease and understanding where adverse health concerns occur are very important aspects of public health research as was demonstrated by John Snow when he mapped the case fatalities from cholera in London 1854 to a central water well (1). With advances in technology in the 21st century, this process has been tremendously simplified with universal availability of computers and digital technology making health research more feasible; this has resulted in the emergence of a new field of medical geographic information systems (GIS) (2). For example, by harnessing the technology offered by GIS, I have been able to assign an inverse distance weighted exposure to DT groups on the maternal residential postal codes and quantify the risk ratio associated with exposure to those environmental variables (3). Furthermore, through GIS technology, public health officials can conduct surveillance and monitoring of public health for adverse health outcomes associated with environmental and social risk factors (4, 5). Surveillance is defined as "the systematic and continuous collection, analysis, and interpretation of health-related data closely integrated with the timely and coherent dissemination of the results and assessment to those who have a right to know so that action can be taken. It is an essential feature of epidemiological and public health practice. The final phase in the surveillance chain is the application of the information to health promotion and to disease prevention and control" (6). Monitoring is distinguished from surveillance and defined as "the intermittent performance and analysis of measurements aimed at detecting changes in the health status of populations or in the physical or social environment" (6).

Although I had demonstrated the relationship between DT exposures, low and intermediate SES and CHD in Alberta, by identifying the geographic regions exposed to those individual risk factors acting alone or in combinations, could potentially inform and complement the already existing Alberta Congenital Anomalies Surveillance System (ACASS). The health authorities could begin to monitor those regions and intervene through programs and policies that reduce the risks of these exposures and improve adverse social factors that have a potential negative effect on the developing heart.

Therefore, the objectives of this chapter were three-fold: 1) to map postal codes which were exposed to high DT emissions, those with low SES in urban and those with both low and intermediate SES in rural regions and overlay these maps with postal codes that had CHD cases; 2) to map the postal codes where there is collocation of the highest DT groups' exposures and 3) to determine if there is collocation of the postal codes where highest DT exposure occurred, low SES and CHD to detect if there is environmental injustice in Alberta.

5.3. Methods and Materials

5.3.1. Mapping High DT Impact Postal Codes and CHD

5.3.1.1. Data:

In this chapter, I focused on urban and rural postal codes exposed to the highest DT levels. I also focused on urban postal codes with lowest SES and rural postal codes with lowest and intermediate SES. The study population, SES Index and DT exposure assignment methodology and the DT group variables were detailed in Chapters 3 (DT emissions and CHD) and 4 (SES and CHD). I first created maps of the postal codes based on the centile categories of DT exposures and the various categories were symbolized with dots of different colors. I then extracted postal codes exposed to the highest concentrations of the three DT groups and mapped those high levels of the three DT groups. I overlaid CHD cases exposed to the highest DT concentrations of the three DT groups. Likewise, the SES index was categorized into tertiles using dots of varying colors. I extracted the urban postal codes with low SES and for the rural postal codes; I extracted both lowest and intermediate SES categories. I obtained coordinates for the centroid of the maternal postal codes where the CHD cases occurred from Digital Mapping Technology Inc.

5.3.1.2. Overlay Analysis

To identify the postal codes exposed to the highest levels of 1, 2 or all 3 of the DT groups I used the whole distribution of postal codes exposed to DTs emitted by facilities within a 10 km radius in the province. I then filtered the postal codes exposed to the highest DT emissions from the three DT groups. For each DT group, I computed the various combinations listed above. The same process was repeated for the postal codes exposed to high DT emissions of the three groups and low SES in urban postal codes and both low and intermediate SES for rural postal codes. These combinations would inform the spatial overlay analysis to determine the regions with collocation of all three variables: high DT emissions, low SES and CHD. In order to display the centroids of the postal codes exposed to the highest DT emissions, low SES and CHD cases, I used ESRI ArcGIS 10.4 software to locate as dots the postal codes with the groups of DTs, SES and CHD cases. To project the maps, I used the 1983 North American Datum 10 degrees Transverse Mercator, using the Alberta Forest Projection Coordinate System. Because of confidentiality concerns, the ethics approval for this work did not permit presentation of maps with postal codes having less than ten individuals.

5.3.2. Statistical Methods

I used Poisson regression models to calculate adjusted relative risks (RR) for postal codes exposed to all three DT groups combined in urban postal codes. I included SES, NO_2 and $PM_{2.5}$ as covariates accordingly. There were too few rural postal codes to allow for statistical testing. I compared the RR of postal codes exposed to all three DT groups to the postal codes with low exposure to all three DT groups. I also compared the RR of the postal codes exposed to all three DT groups and low SES to those with low exposure to all three DT groups and intermediate or high SES. I used STATA 13 (StataCorp LP,College Station, TX, USA) for analysis of data.

5.4. Results

5.4.1. Description of Postal Codes Exposed to High Levels of DTs, Low and Intermediate SES

5.4.1.1. Urban

The decile or tertile distributions of the urban Group 1, 2 and 3 DTs are shown in different colors in Fig 5.1A, Fig 5.2A and Fig 5.3A, respectively. In urban regions, all three DT groups were located in the central, southern and western parts of Alberta. There were a total of 5,410 postal codes exposed to the highest levels of Group 1 DTs, (Table 5.1, and Fig. 5.1B). The CHD cases found in this category (n=317, 16%) out of a total of 1,967 cases, were located in only 293 (5%) of the postal codes (Table 5.1, Fig. 5.1 C). For group 2 DTs, there were a total of 18,062 postal codes exposed to the highest DT levels (Table 5.1, Fig 5.2B). The cases found in this category (n=786, 40%) out of a total of 1,967 cases, were located in 730 (4%) of those postal codes (Table 5.1, Fig. 5.2 C). For group 3 DTs, there were a total of 18,068 postal codes exposed to the highest DT levels (Table 5.1, Fig 5.3B). The cases found in this category (n=799, 40%) out of a total of 1,967 were located in 741 (4%) of the postal codes (Table 5.1, Fig 5.3C).

5.4.1.2. Rural

The decile distribution of the rural Group 1 and 3 DTs is shown in different colors in Fig 5.4A and Fig 5.5A, respectively. In the rural regions, Group 1 and 3 DTs were located in central and northern parts of Alberta. There were a total of 14 postal codes that were exposed to the highest group 1 DTs (Table 5.1, Fig 5.4B). Cases found in this category (n=20, 5%) out of a total of 446 cases were located in 7 (50%) of those postal codes (Table 5.1, Fig 5.4C). Furthermore, there were a total of 12 postal codes exposed to the highest group 3 DTs (Table 5.1, Fig 5.5B) and all cases found in this category (n=22,5%) out of a total of 446 cases were located in 6 (50%) of those postal codes (Table 5.1, Fig 5. C). There were no

associations with CHD in postal codes exposed to the highest levels of Group 2 DTs in rural regions and as such I did not map these postal codes.

5.4.2. Distribution of SES Index

The tertile distribution of the SES index in urban and rural postal codes is shown in Fig 5.6A and Fig 5.7A, respectively. In urban regions, there were a total of 18,009 postal codes with low SES which were in central and southern parts (Fig 5.6B) of Alberta. The CHD cases found in this category (n=743, 38%) out of 1,967 cases were located in 692 (4%) of those postal codes (Table 5.1, Fig 5.6C). In rural regions, there were a total of 223 postal codes with low SES which were widely dispersed throughout Alberta (Fig 5.7B). All of the cases found in this category (n=227, 50%) out of 446 total rural cases were located in 86 (39%) of those postal codes (Table 5.1, Fig 5.7C). Furthermore, in the rural regions, there were a total of 296 postal codes in the intermediate SES category (Fig 5.8B). The CHD cases found in this category (n=165, 37%) out of 446 total rural cases were located in 88 (30%) of those postal codes (Table 5.1, Fig 5.8C).

5.4.3. Combinations of the Postal Codes Impacted with Highest DT levels in Urban and Rural Postal Codes

Table 5.2 provides the counts of postal codes exposed to the highest DT concentrations from the three groups in various combinations. Ninety -nine percent of the urban postal codes were exposed to the highest levels of the three DT groups combined. Only 290 (5%) of these postal codes had all of the CHD cases (n=313, 16%) in this category of highest exposure, out of the total number of urban CHD cases (n= 1,967). I mapped the postal codes exposed to the three highest DT levels which collocated with CHD cases and they are depicted as red dots in (Fig 5.9). When examining the proportional contribution of the 3 DTs, Group 1 DTs had the highest concentration compared to groups 2 and 3 DTs indicating that Group 1 DTs are most commonly found in the highest exposure category and likely drove the associations (Appendix F)

In the rural regions, there was more heterogeneity in the DT exposures. Forty percent of the postal codes were exposed to the highest levels of Group 1 and 3 DT together, followed by all the 3 DT groups (30%) and Group 1 DT only (21%). Approximately 1% of CHD cases were exposed to Group 1 only and Group 1 and 3 DTs combined (Table 5.2). Although the majority of the postal were exposed to Groups 1 and 3 combined, the majority of the rural CHD cases (n=11, 3%), were exposed to all three DTs combined (n=446).

I analyzed the postal codes exposed to the various combinations of DT groups with the highest concentrations and to low SES in urban and rural postal codes including the rural postal codes with

intermediate SES (Table 5.3). Forty-five percent of the urban postal codes had the highest exposure to the three DT groups and low SES. Only (n=174, 7%) postal codes had CHD cases (n=189, 10%) in this category of highest exposure out of the total number of urban CHD cases (n=1,967). No postal codes were exposed to the highest group 2 or 3 DT levels alone. I mapped the postal codes exposed to the three highest DT levels which collocate with low SES and CHD cases and they are depicted as yellow dots in (Fig 5.9). These collocations predominantly occurred in Edmonton.

In the rural regions where there was more heterogeneity, eleven to seventeen percent of the postal codes had the combinations of the highest concentrations of all the three DTs and low SES or intermediate SES. All the postal codes in the former (n=2, 100%), had CHD cases (n=4, 0.9%) out of the total number of 446 rural cases. The postal codes in the latter (n=1, 50%), had CHD cases (n=9, 2%) out of the total number of rural cases (n=446) (Table 5.3). Approximately 25% of the postal codes were exposed to Group 1 and 3 DTs and intermediate SES. Sixty-six percent of the postal codes had CHD cases (n=4, 0.9%) out of the total of 446 rural CHD cases. There were no cases exposed to the highest Group 1 and 3 DTs and low SES. Only one postal code was exposed to Group 1 DTs alone and low SES and had CHD cases (n=2, 0.4%). No postal codes were exposed to the highest group 2 or 3 DT levels alone. Because there were less than 10 CHD cases in the rural postal codes, these have not been mapped to protect the privacy of the patients. The average DT exposures in the postal codes without CHD cases and the overall combinations of the DT groups irrespective of the concentration of the DTs respectively are presented in Appendix G and H as supplementary Tables.

5.4.4. Adjusted Relative Risk of Urban Postal Codes Exposed the Highest Levels of All the Three DT Groups

I found an adjusted RR of 1.55 (95% CI: 1.03, 2.30) in the postal codes exposed to the highest concentrations of all the three DT groups combined compared to the postal codes exposed to the lowest levels of the three DT groups in urban regions after adjusting for SES, NO_2 and $PM_{2.5}$. I then included low SES with the three highest DT groups, and compared the variable to postal codes with intermediate, high SES and exposure to the lowest concentrations of three DT groups adjusted for NO_2 and $PM_{2.5}$, the adjusted RR doubled to 1.96 CI: 1.53, 2.51.

5.5. Discussion

The maps revealed a similar and focal pattern in the distribution of the postal codes exposed to the highest concentrations of DT emissions and CHD in urban and rural regions of Alberta. Overall, 4-5% of the urban postal codes with CHD cases were exposed to the highest levels of the three groups of DTs and

these were in central, western and southern Alberta. Fifty percent of the rural postal codes with CHD were exposed to Group 1 and 3 DTs compared to urban postal codes, and these were in central and northern Alberta. The urban postal codes exposed to low SES were mostly in the main cities of the province, whilst for the rural postal codes, they were more widely distributed for both the low and intermediate SES. The overlay analysis revealed that CHD occurred in postal codes exposed to the combination of all the three DT groups in urban and rural postal codes.

By mapping the postal codes exposed to the highest DT levels, low or intermediate SES and those with CHD cases, I learned firstly that there were differences in the geographic patterns between the urban and rural postal codes. For the urban postal codes, the distribution was focally impacting the two major metropolitan cities of the province, whilst for the rural postal codes the distribution was more dispersed. In chapter 3, I had found that DT groups were associated with CHD after adjusting for SES. However, in chapter 4, I also demonstrated independent associations of CHD and low SES. The maps showed differences in the distribution of the postal codes exposed to the highest DT emissions and low SES which potentially explains the observation that not all CHD occurrences is associated with DT exposures. In addition, SES effects in rural regions are more complex with populations residing in intermediate SES postal codes also demonstrating a risk of CHD.

Although there was a mathematical value in deriving the three independent groups of DTs using principal component analysis (PCA), the geographic patterns of the postal codes exposed to the three groups were similar suggesting that there was a geographic confounding of the three DT groups. Hence, I determined the postal codes exposed to all the highest levels of the three DT groups combined and I found that these postal codes collocated with CHD in urban regions. For the rural postal codes, I also demonstrated that most of the CHD cases occurred in postal codes exposed to the highest emissions of the three DT groups combined, followed by Group 1 only and lastly Group 1 and 3 DTs combined. This observation could suggest the potency of the mixtures of the three DT groups. Interestingly the risk ratio for the urban postal codes exposed to the highest levels of the three DTs combined did not increase when compared to the models using the individual DT groups. I was however unable to estimate the risk ratios in the rural postal codes because of the small numbers. In addition, Group 1 DTs contributed the greatest proportion of DTs compared to group 2 and 3 DTs in urban and rural postal codes and is therefore the main driver of the associations. A unique exposure to group 2 or 3 alone is rare in both urban and rural regions and the findings suggest that the 3 DT groups I had identified impact postal codes in some combination or the other. Another observation with respect to Group 2 DTs is that they were not emitted in high enough concentration in rural regions and thus did not participate in the evaluation of the associations.

The United States Environmental Protection Agency defines environmental justice as equitable treatment and meaningful involvement of all people irrespective of race, color, income or national origin with respect to development, implementation and enforcement of environmental laws which ensure protection from harmful hazards (7). It has been recognized that populations with low SES tend to be disproportionately exposed to environmental hazards (8, 9). Most empirical studies describing this situation, also known as environmental injustice, and the consequent adverse health outcomes have been conducted in the United States (10) albeit with mixed results. For example, studies which have examined the relationship between maternal residential proximity to industries emitting hazardous chemicals and waste site chemicals such as solvents, metals, pesticides, dioxins and furans have found associations with congenital malformations (10-15). A study by Langlois et al., examining maternal residential proximity to waste sites and CHD (16) and another by Yauck et al. (17) which examined maternal residential proximity to trichloroethylene emitting facilities, found associations with CHD. Other studies have found no associations between maternal residential proximity to hazardous waste sites (solvents, pesticides, furans, dioxins, metals) and congenital malformations (18-20). Although I had not necessarily directed my work to explore the possibility of environmental injustice in Alberta, the localized co-occurrence of low SES and DT exposures in certain postal codes suggests that environmental injustice is a localized phenomenon in urban and rural Alberta.

In Canada, there are no studies that have examined maternal residential proximity to hazardous waste sites or industries and CHD development; however, a study by Jerret et al., conducted in Ontario, examined variables that predicted the location of environmental pollution sources (15). This study found a negative association between property values and environmental pollution. This fact points to the potential for environmental injustice in Ontario. Furthermore, Jerret et al. demonstrated a positive association between pollution and low-income variables and he proposed that polluting industries may compensate for environmental degradation by paying more wages to employees. This relationship may potentially explain why I observed collocation of middle SES postal codes with high DT exposures in rural regions. The SES index does not offer the ability to discriminate between individual SES predictors such as housing value and income, however, the findings of the co-occurrence of the low SES index with high DT levels in my study indirectly strengthens the observations made by Jerret et al. for some regions of Alberta.

5.6. Conclusions and Recommendations

Even though most of the postal codes in Alberta are exposed to DT emissions, only a few are exposed to high levels in urban and rural postal codes. Low SES impacted a wider range of postal codes in both urban and rural postal regions. Urban and rural postal codes were exposed to the highest levels of all the three DT groups combined; however, this risk was not accentuated in urban postal codes and remained the same as the risk of being exposed to individual DT groups. There were no postal codes exposed to Group 2 or 3 alone in urban or rural postal codes. When overlaying the highest emissions of three DT groups combined, low SES index and CHD layers, I found twice the risk of CHD in urban postal codes and these were mainly in the major metropolitan areas. The findings suggest the presence of a localized environmental injustice phenomenon in urban postal codes. There were fewer rural postal codes with CHD exposed to the highest levels of all the three DT groups and low SES however the risk ratios were not estimated because of the small sample size. Although theoretically I derived three independent DT groups, I found that geographically there was confounding which could suggest an interaction of the combined DT groups with and without low SES in urban postal codes. I therefore suggest that future studies should thoroughly investigate for interactions as this was beyond the scope of the thesis.

Table 5. 1. Descriptive of Postal Codes with the Highest DT Exposures, Low and Intermediate SES and CHD in Alberta

Region	Exposure Category	Total Postal Codes Count	Postal Codes with CHD (%)	Number of CHD Cases (%)	Min Cases	Max Cases	Min DT Exposure (tonnes)	Max DT Exposure (tonnes)
Urban	Group 1 DTs Decile 10	5,410	293(5)	317(16)	1	4	10	116
	Group 2 DTs Tertile 3	18,062	730(4)	786(40)	1	4	23	2,461‡
	Group 3 DTs Tertile 3	18,068	741(4)	799(41)	1	4	0.091	3.9‡
Rural	Group 1 DTs Decile 10	14	7(50)	20(5)	1	9	11	500
	Group 2 DTs Tertile 3	18	6(33)	22(5)	1	9	38	17,340‡
	Group 3 DTs Tertile 3	12	6(50)	22(5)	1	9	0.1	12‡
			SES Index					
Urban	Tertile 1	18,009	692(4)	743 (38)	1	4		
	Tertile 2	17,809	550 (3)	580 (29)	1	6		
Rural	Tertile 1	223	86(39)	227 (50)	1	17		
	Tertile 2	296	88(30)	165 (37)	1	9		

‡ = Group 2 and 3 emissions were emitted in small amounts and were not detectable in tonnes, therefore I chose to show them in kilograms.

Table 5. 2. Summary Statistics of the Combinations of Postal Codes Exposed to the Highest Levels of DT Emissions

Region	Combinations of Highest DT Exposures	Group 1 DTs			Group 2 DTs			Group 3 DTs		
Urban		Postal Code Count (%)	Postal Code Count with Cases (%)	Sum CHD Cases	Postal Code Count (%)	Postal Code Count with Cases (%)	Sum CHD Cases	Postal Code Count (%)	Postal Code Count with Cases (%)	Sum CHD Cases
	1	1 (0.02)	0	0	0		0	0	0	0
	2	0	0	0	0		0	0	0	0
	3	0	0	0	0		0	0	0	0
	1+2	1(0.02)	0	0	1		0	0	0	0
	1+3	1(0.02)	0	0	0		0	1	0	0
	2+3	0	0	0	0		0	0	0	0
	1+2+3	5,357 (99)	290(5)	313(16)	5,357 (30)	313(16)	290(5)	5,357(30)	290(5)	313(16)
	+Non-Highest DT Combinations	50 (0.9)			12,704 (70)			12,710 (70)		
Total		5,410			18,062			18,068		
Rural	1	3(21)	2(66)	5(1.1)	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0

	3	0	0	0	0	0	0	0	0	0
	1+2	0	0	0	0	0	0	0	0	0
	1+3	5(36)	2(40)	4(0.9)	0	0	0	5(42)	2(40)	4(0.9)
	2+3	0	0	0	0	0	0	0	0	0
	1+2+3	4(29)	3(75)	11(2.5)	4(22)	3(75)	11(2.5)	4(33)	3(75)	11(2.5)
	+Non-Highest DT Combinations	2(14)			14(78)			3(25)		
Total		14	7	20	18	3	11	12	5	15

The Table is an aggregation of the postal codes exposed to the highest-levels of DT concentrations of any group based on the various combinations.

Table 5. 3. Summary Statistics of the Postal Codes Impacted by Highest DTs Alone or in Combinations, Low and Intermediate SES Index

Region	Combinations of Highest DT Exposures	Group 1 DTs			Group 2 DTs			Group 3 DTs		
Urban		Postal Code Count (%)	Postal Code Count with Cases (%)	Sum CHD Cases	Postal Code Count(%)	Postal Code Count with Cases (%)	Sum CHD Cases	Postal Code Count(%)	Postal Code Count with Cases	Sum CHD Cases
	1+low SES	0	0	0	0		0	0	0	0
	2+low SES	0	0	0	0		0	0	0	0
	3+low SES	0	0	0	0		0	0	0	0
	1+2+low SES	1	0	0	1		0	0	0	0
	1+3+low SES	0	0	0	0		0	1	0	0
	2+3+low SES	0	0	0	0		0	0	0	0
	1+2+3+low SES	2,447(45)	174(7)	189(10)	2,447(14)	174(7)	189(10)	2,447(14)	174(7)	189(10)
	Non-Highest DT +non low SES	2,963(55)			15,615(86)			15,621(86)		
Total		5,410	174	189	18,062	174	189	18,068	174	189
Rural	1+low SES	1(7)	1(100)	2(0.4)	0	0	0	0	0	0
	1+intermediate SES	0	0	0	0	0	0	0	0	0
	2+low SES	0	0	0	0	0	0	0	0	0

	2+intermediate SES	0	0	0	0	0	0	0	0	0
	3+low SES	0	0	0	0	0	0	0	0	0
	3+intermediate SES	0	0	0	0	0	0	0	0	0
	1+2+low SES	0	0	0	0	0	0	0	0	0
	1+2+intermediate SES	0	0	0	0	0	0	0	0	0
	1+3+low SES	1(7)	0	0	0	0	0	1(8)	0	0
	1+3+intermediate SES	3(21)	2(66)	4(0.9)	0	0	0	3(25)	2	4
	1+2+3+low SES	2(14)	2(100)	2(0.4)	2(11)	2(100)	2(0.4)	2(17)	2(100)	2(0.4)
	1+2+3+intermediate SES	2(14)	1(50)	9(2)	2(11)	1(50))	9(2)	2(17)	1(50)	9(2)
	Non-Highest DT+high SES	5(36)			14(78)					
Total		14	6	17	18	3	11	12	5	15

The Table is an aggregation of the postal codes exposed to the highest levels of DT combinations plus postal codes with low SES in urban and rural regions and those with intermediate SES in rural postal codes.

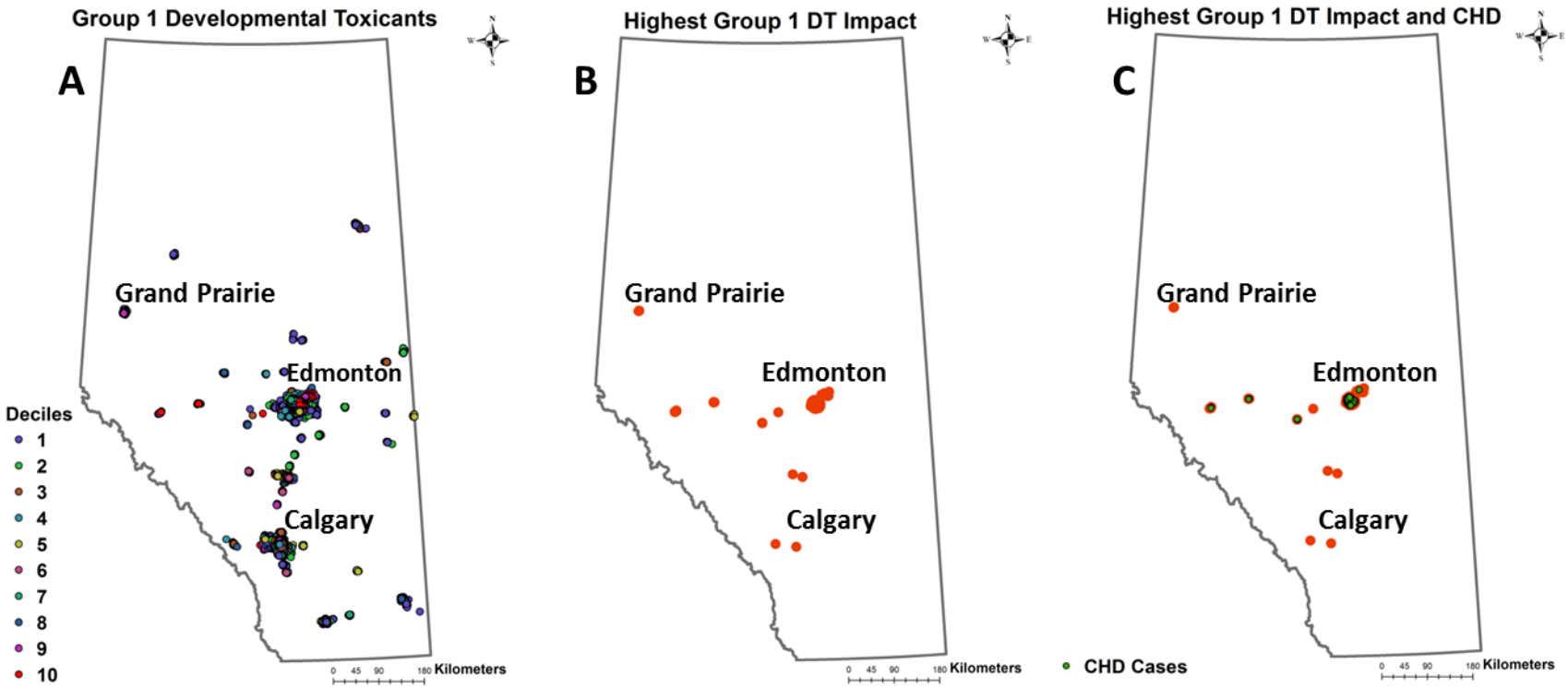

Figure 5. 1. Urban Distribution of the postal codes exposed to Group 1 Developmental Toxicants.

A, Distribution of all the Alberta postal codes exposed to Group 1 DTs categorized into deciles. B, Postal codes exposed to the highest group 1 DTs. C, Postal codes exposed to the highest group 1 DT impact and those with CHD cases (green dots).

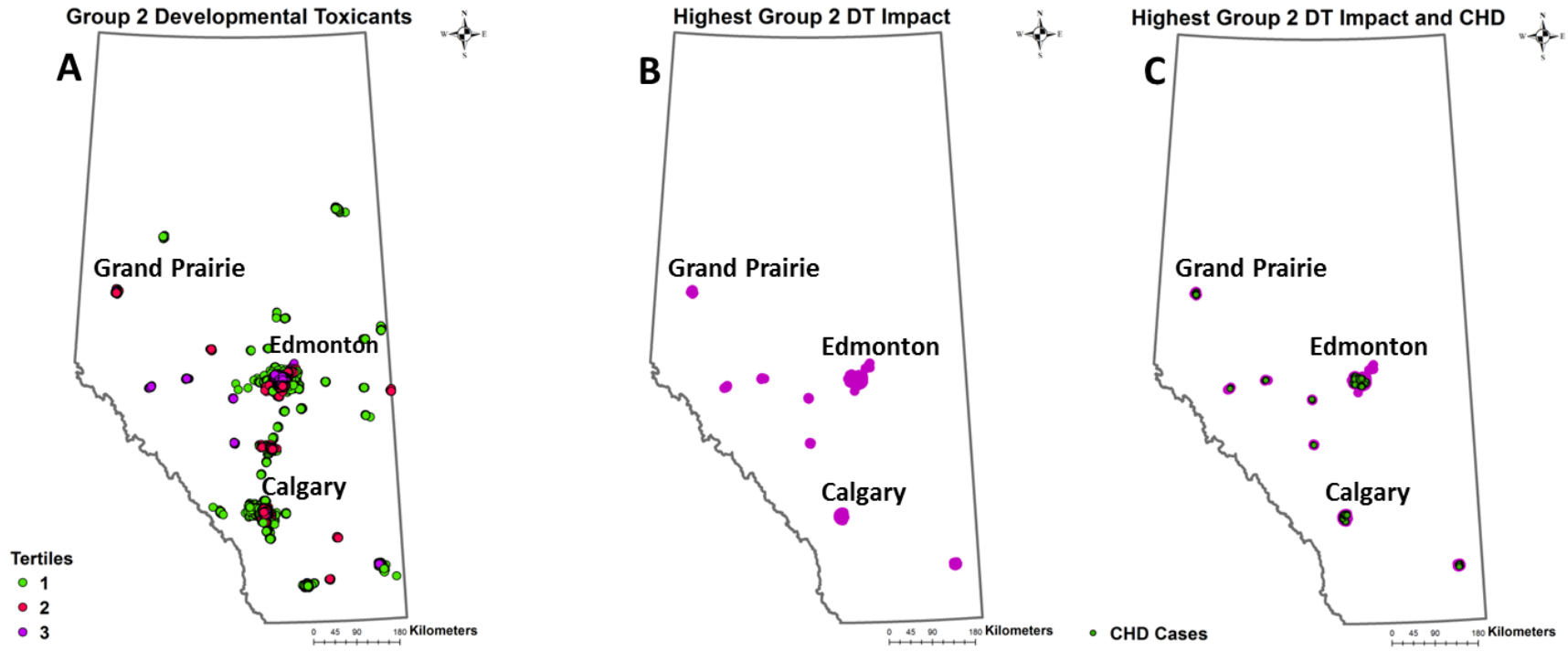

Figure 5. 2. Urban Distributions of Group 2 Developmental Toxicants.

A, Distribution of group 2 DTs categorized into tertiles. B, Postal codes exposed to the highest Group 2 DTs. C, Postal codes exposed to the highest Group 2 DTs and those with CHD cases (green dots)

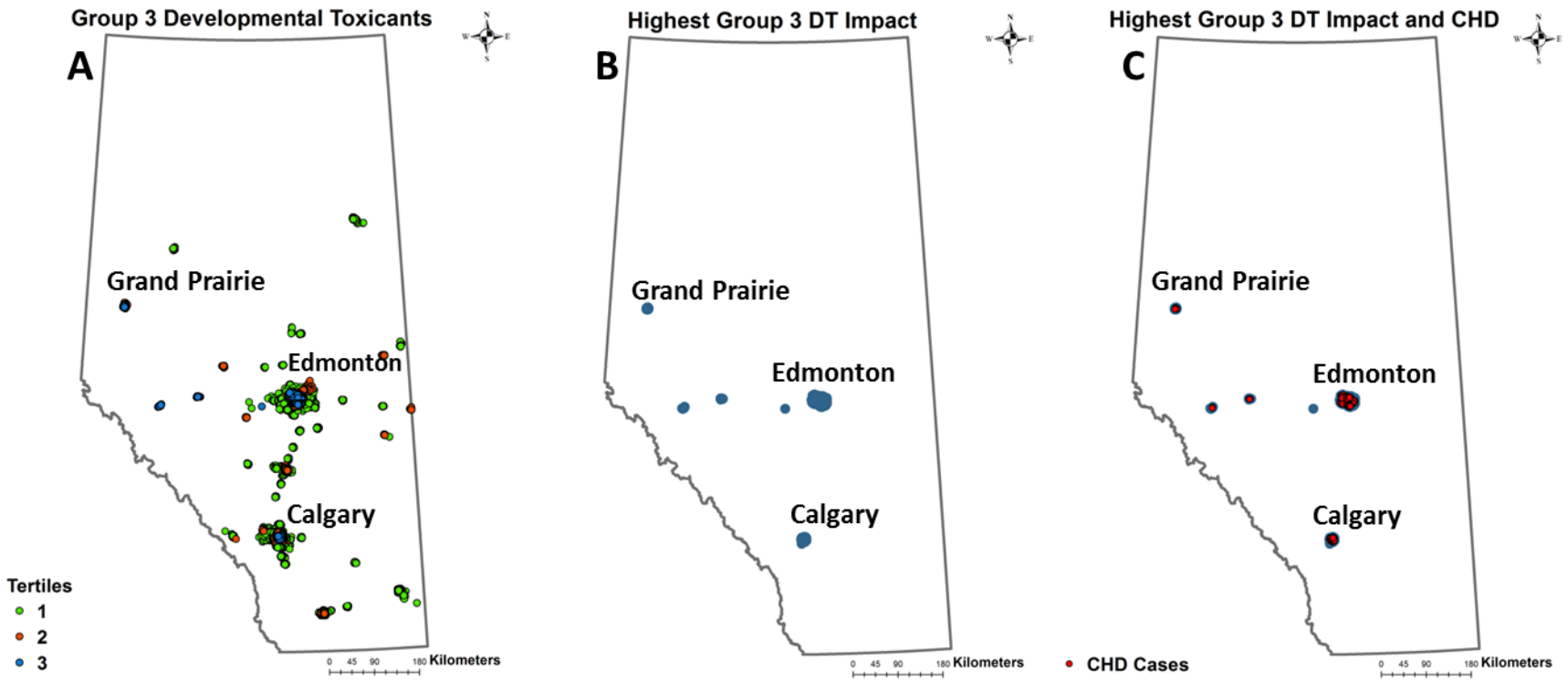

Figure 5. 3. Urban Distributions of Group 3 Developmental Toxicants.

A, Distribution of group 3 DTs categorized into tertiles. B, Postal codes exposed to the highest Group 3 DTs. C, Shows postal codes exposed to the highest Group 3 DTs and those with CHD cases in red dots.

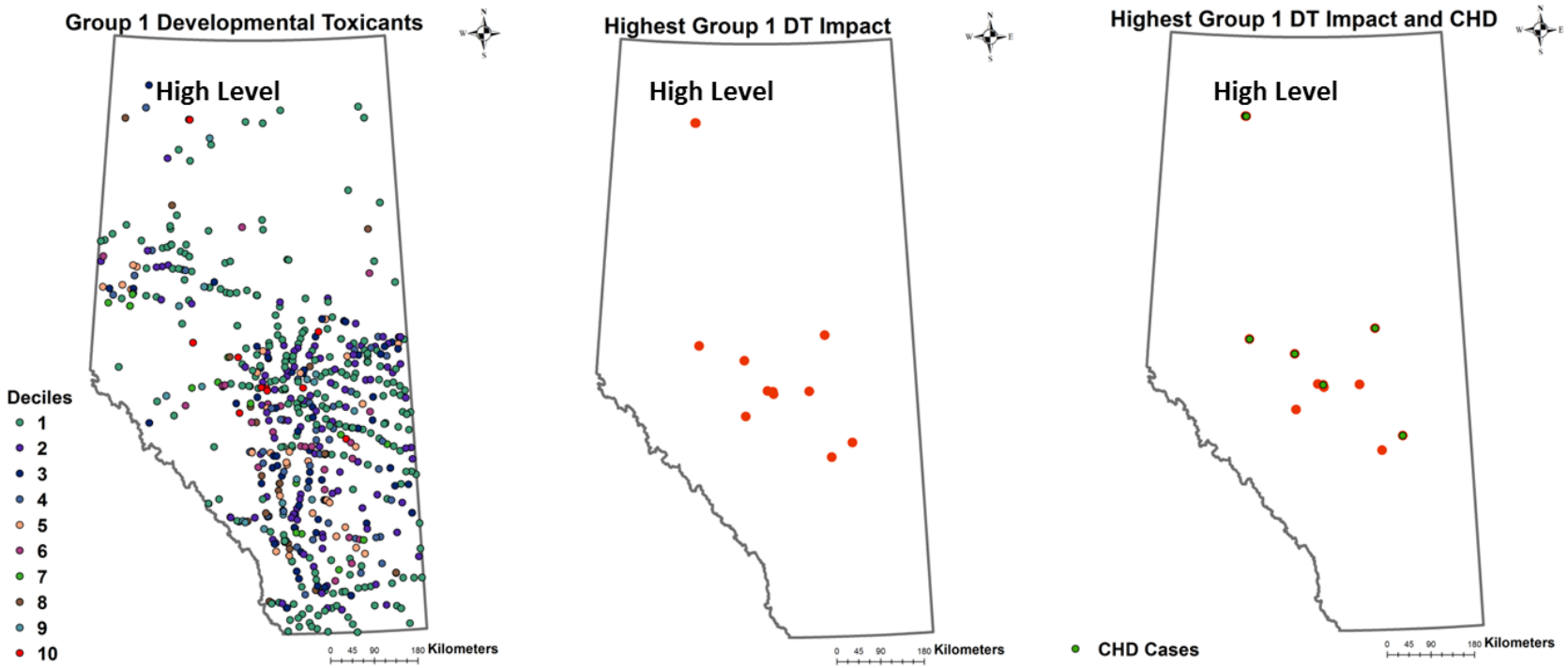

Figure 5. 4. Rural Distribution of Group 1 Developmental Toxicants.

A, Distribution of group 1 DTs categorized into deciles. B, Postal codes exposed to the highest Group 1 DTs. C, Shows postal codes exposed to the highest Group 1 DTs and those with CHD.

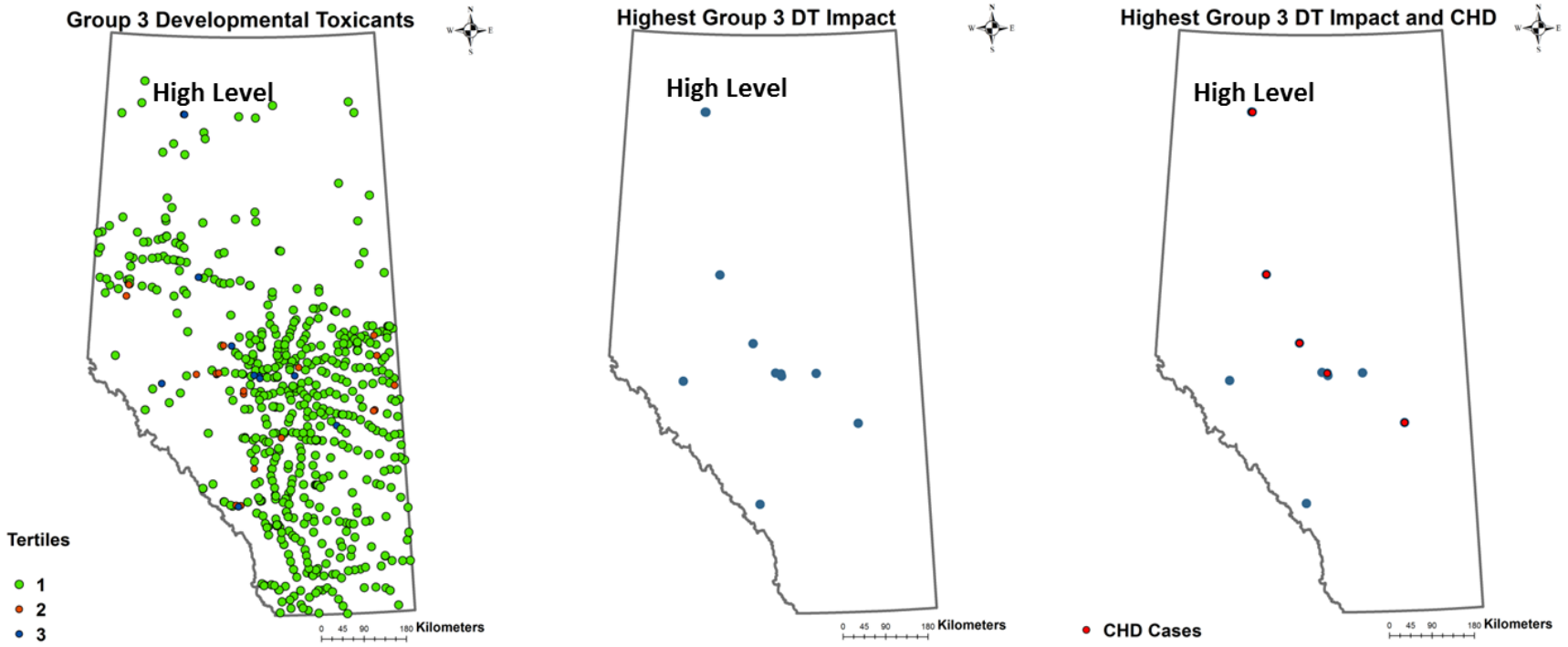

Figure 5. 5. Rural Distribution of Group 3 Developmental Toxicants.

A, Distribution of group 3 DTs categorized into tertiles. B, Postal codes exposed to the highest Group 3 DTs. C, Shows postal codes exposed to the highest Group 3 DTs and those with CHD cases (red dots).

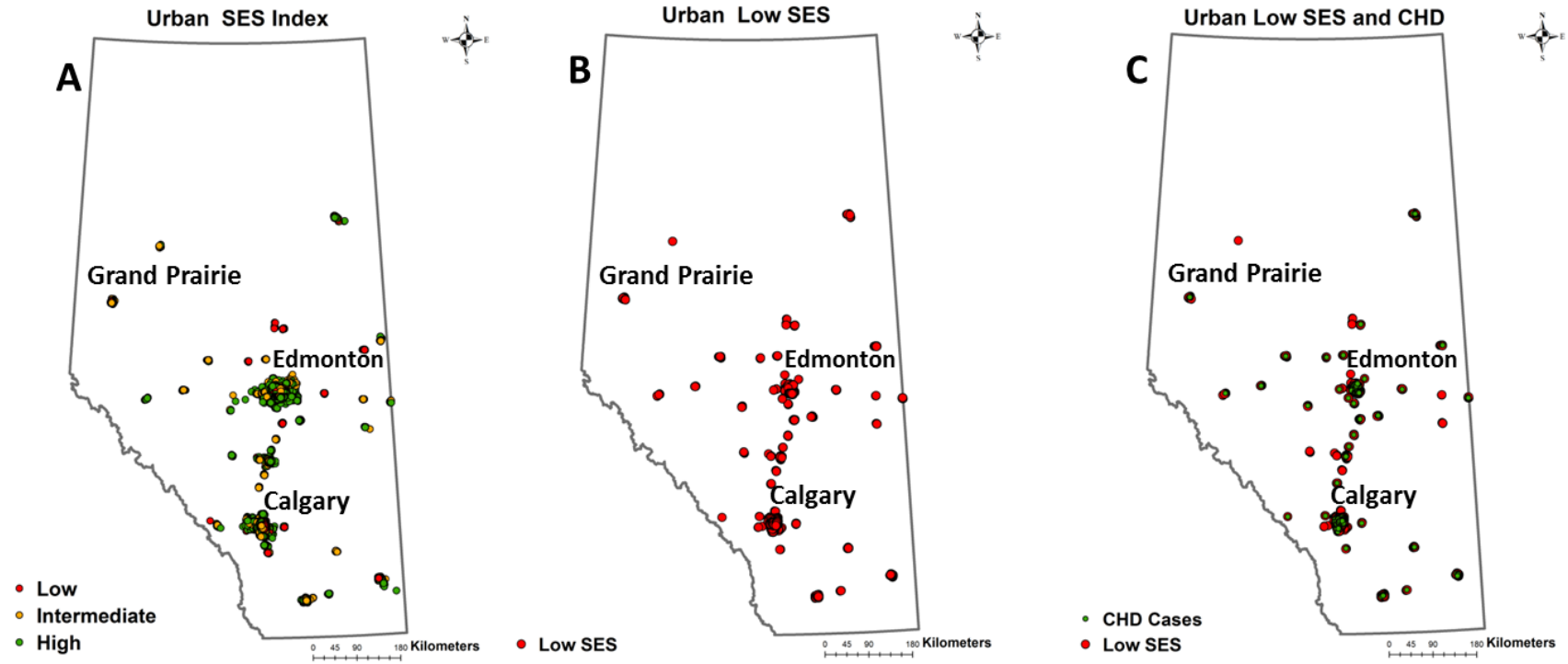

Figure 5. 6. Urban Distribution of Low Socioeconomic Status Index.

A, Shows the 3 levels of SES Index, Red = low, Yellow= intermediate and Green color= high SES Index. B, Distribution of postal codes with low SES in urban regions, C, Distribution of postal codes with low SES and CHD cases in green dots.

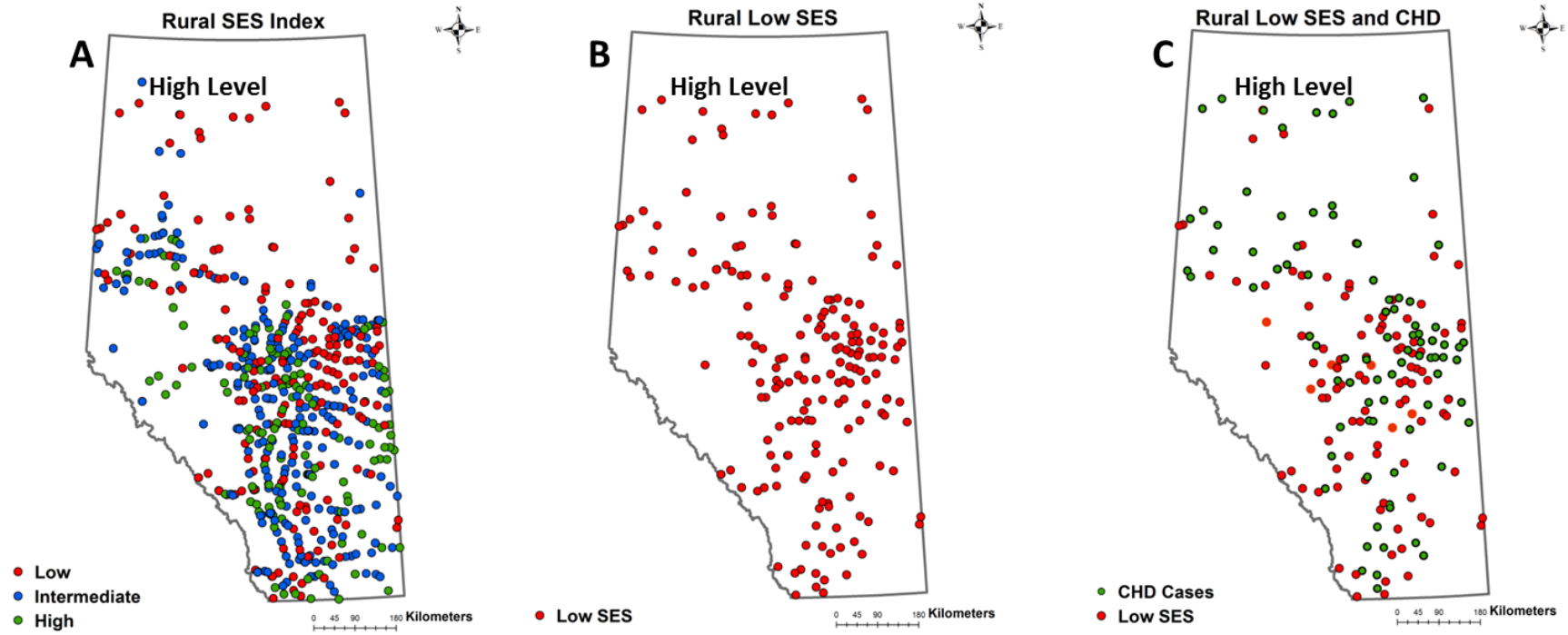

Figure 5. 7. Rural Distribution of Low Postal Codes with Socioeconomic Status Index.

A, Shows the 3 levels of SES Index, Red = low, Blue= Intermediate and Green color= high SES Index. B, Distribution of postal codes with low SES in rural regions, C, Distribution of postal codes with low SES and CHD cases in green.

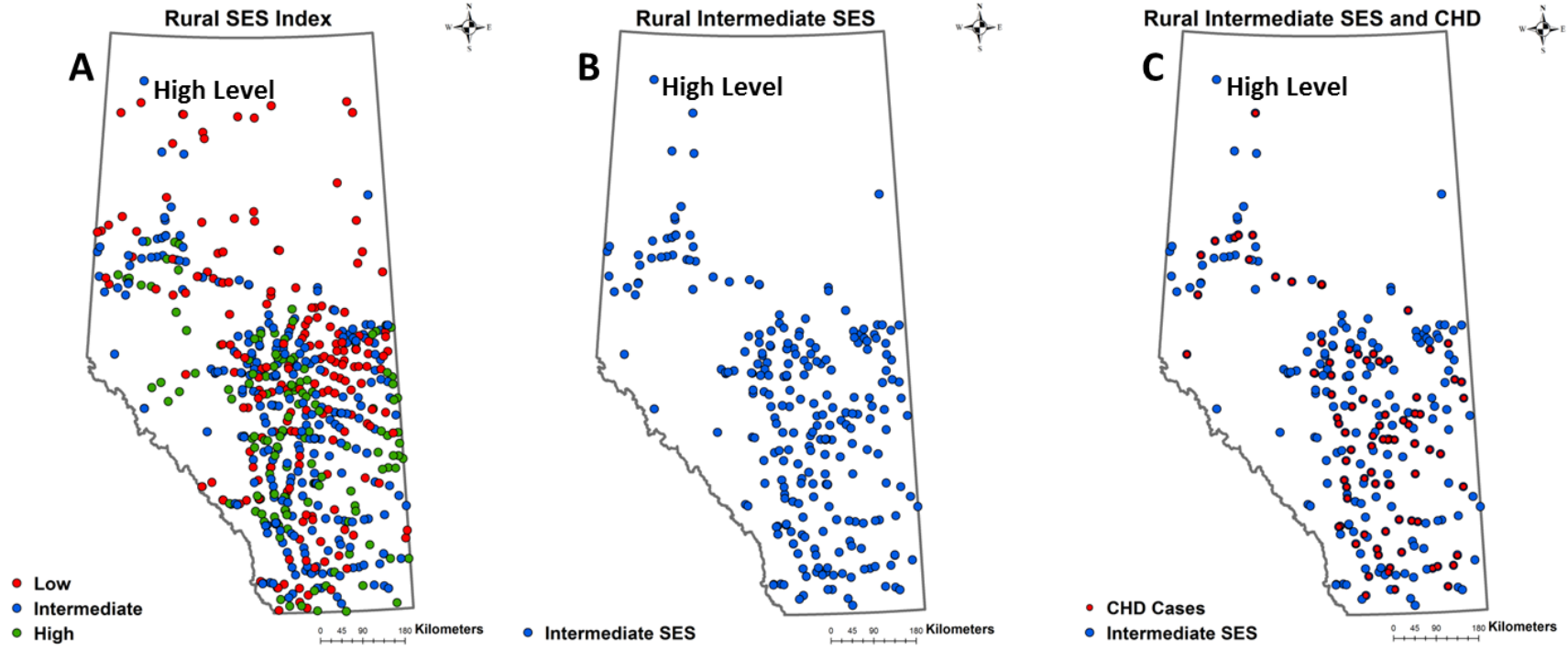

Figure 5. 8. Rural Distributions of Postal Codes with Intermediate Socioeconomic Status Index.

A, Shows the 3 levels of SES Index, Red = low, Blue= Intermediate and Green color= high SES Index. B, Distribution of postal codes with intermediate SES in rural regions. C, Distribution of postal codes with intermediate SES and CHD cases in red.

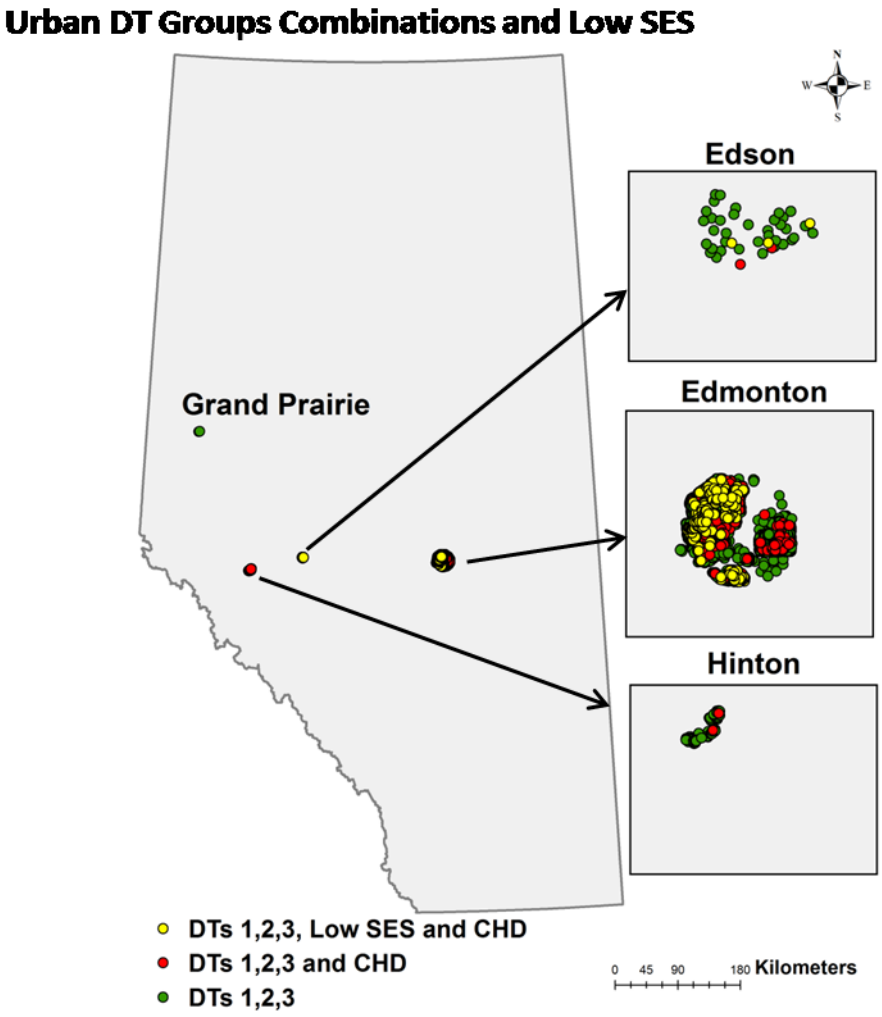

Figure 5. 9. Urban postal codes exposed to the highest emissions of the combinations of the three DT groups, low SES and CHD.

Edmonton had the most postal codes where CHD collocates with the 3 DT groups and low SES followed by Edson. Hinton had postal codes impacted by the 3 DT groups with CHD. Grand Prairie had postal codes impacted by the 3 DTs but did not have low SES or CHD. Yellow dot = Postal codes where the

3DTs, Low SES and CHD occur together, Red dot = Postal codes where the three DTs and CHD occur together, Green dot = Postal codes impacted by the three DT groups only.

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Chapter 6 Conclusions and Recommendations

6.1. Overview of Findings

The overarching goal of the present thesis was to examine, through an ecological study design, the potential relationships between industrial DT emissions, neighborhood SES and the development of CHD in the province of Alberta. I undertook a literature review and discovered that there was a paucity of studies which examined multipollutant exposures to industrial chemicals and CHD. Furthermore, the evidence of associations between CHD and SES was still inconclusive. I capitalized on the centralized pediatric cardiac health services in Alberta allowing for access to all live-born infants with CHD within the study period of 2004-2011, and the public access to industrial emissions database from Canada's NPRI from 2003-2010. I also had access to recently developed neighborhood SES index by Chan et al.; models of traffic related data (NO_2 and $PM_{2.5}$) created by Hystad et al., and provincially acquired SES data from Statistics Canada.

Initially, I explored trends of DT emissions and CHD rates in the province as a whole, and in the urban and rural locations of the province. I used both the amounts of DTs (tonnes) and the potential toxicity associated with the DTs. I derived three groups of DTs: Group 1) organic compounds and gases (benzene, carbon disulfide, carbon monoxide, Sulphur dioxide, toluene, and 1,3 butadiene), Group 2) organic compounds only (1,3 butadiene, chloroform, ethylene oxide, methanol, methyl-isobutyl-ketone and trichloroethylene), and Group 3) heavy metals and organic compound (arsenic, mercury, lead, cadmium and hexachlorobenzene) using PCA methodology to investigate the associations with multiple DT pollutants and to gain knowledge about the role of chemical mixtures. I found that rural regions hosted the majority of DT emitting facilities and had a higher proportion of emissions compared to urban regions. I also found a higher proportion of CHD cases in rural regions compared to urban regions. I found a significant temporal decrease in Group 1 and 2 DTs in the province and rural regions of Alberta. This trend was accompanied by a parallel significant temporal decrease in CHD rates in the rural regions of Alberta which was not observed in urban regions. The approach of using the amounts and risk scores complemented each other in attempting to quantify the risk posed by industries to nearby communities. Although I had discovered significant downward temporal trends in emissions and CHD rates, I could not make definitive conclusions as it was an exploratory assessment which assigned the yearly emissions at a coarse spatial scale in urban and rural regions.

In the second phase of the study, I examined at a higher spatial resolution, by using the maternal postal code as the unit of analysis, the effects of maternal residential proximity to the industries emitting the DTs

adjusted for SES and NO_2 and $PM_{2.5}$. I used an inverse distance weighted (IDW) approach to assign the sum of DT exposure to the maternal postal code for the study period (2003-2010). I generated percentile exposure categories and I found a significantly increased risk of CHD in postal codes exposed to the highest concentrations of the DTs overall and the three DT groups in urban regions, whilst in rural regions I found associations with Group 1 and 3 DTs only. Furthermore, the rural postal codes had a higher average number of cases by postal code in regions with moderate exposures. I deduced that not all CHD cases can be explained by DT exposure alone.

In the 3rd phase of study I tested for an independent association of neighborhood SES and CHD development after adjusting for DTs exposure and traffic related pollutants. I found an increased risk of CHD in postal codes with low SES in urban and rural regions. In addition, for rural postal codes I found an association between postal codes with an intermediate SES and CHD.

Finally, I mapped CHD, postal codes exposed to high levels of DTs and postal codes with low SES in urban and rural regions of Alberta in order to determine their geographic distribution and also to determine if there was collocation of the variables. I found that very few postal codes were exposed to the highest levels of DTs and these were located centrally and the south western part of Alberta for urban regions. The rural postal codes exposed to high DT levels were centrally situated and also found in the northern part of Alberta. Based on overlay analysis, I discovered that in fact postal codes where CHD occurred were exposed to the three DTs combined, although the risk was not amplified compared to the estimates of individual DT groups. The risk only doubled when the three DT groups combined collocated with low SES. I obtained the risk ratios for urban postal codes only and not rural postal codes due to the small sample size in the latter.

6.2. Conclusions

My study first established clear temporal decreasing trends of DT emissions overall and Group 1 and 2 DTs, particularly in rural regions. Although the rural regions had higher proportions of DT emissions, the associated reductions in those regions potentially impacted positively on the health of rural populations with an associated temporal decrease in CHD rates. The decrease in the emissions could have been due to a combination of factors such as the economic and financial meltdown that occurred a decade ago and also the implementation of regulations to curb the emissions from the industrial sectors. Irrespective of the reason, the significant observation from this exploratory study was that when emissions decreased, the incidence of CHD decreased as well. Whether it was due to government efforts or a fortuitous economic climate, this evolution potentially had a positive impact on the health of the Albertan children.

I used an IDW approach to assign the impact of the sum of the product of the DTs to the maternal postal code in a 10 km radius. I used this distance as my exploratory analysis demonstrated 90% of the CHD cases to be within this distance of an industrial emitting facility. The impact assigned to the postal code in tonnes was the sum of all emissions from the neighboring facilities over a period of eight years. When I factored the IDW exposure, I discovered that the urban postal codes had a higher burden of emissions compared to rural postal codes. This is because there were more postal codes in urban regions and these were exposed to the emissions irrespective of the location of the emitting facility. An increased risk of CHD was associated with exposure to the highest concentration of all three DT groups and overall DTs in urban postal codes. I observed similar associations in rural postal codes except for Group 2 DTs and for DTs overall. This is because Group 2 DT was emitted in smaller concentrations and hence I was unable to detect positive associations. Another potential explanation is that no postal codes were exposed to Group 2 or 3 DTs alone. I would like to emphasize that the actual dose that would potentially reach the human population was not determined and requires measurements at the area and personal level in addition to biomonitoring studies. Therefore, the interpretation of the associations observed should be with caution, bearing in mind that the exposure assignment may not have been completely accurate. Still, this approach afforded me an opportunity to identify postal codes with high DT impact and the risk associated with specific DT groups.

I also found positive associations between low SES and CHD in both urban and rural postal codes consistent with the published literature (1, 2). However, the associations in rural regions were more complex with some postal codes with intermediate SES demonstrating a risk of CHD. This could be due to other unmeasured confounders such as genetic risk and environmental factors amongst some of the unique populations who reside in those regions e.g. (First Nations and Hutterite).

When I mapped the postal codes exposed to the highest emissions of the three DT groups, I found that few postal codes were exposed to very high emissions and these accounted for about 16% of CHD cases in urban regions and 5% in rural regions. The postal codes affected by low SES accounted for 40% and 50% of urban and rural CHD cases, respectively. The maps also helped to elucidate the independent associations of SES and CHD I had observed in my Poisson models. The geographic pattern of SES was more widely dispersed particularly in rural postal codes, however for urban postal codes I observed that the major cities (Edmonton and Calgary) were affected by low SES.

The most important finding from the study is that I found collocation of CHD with the postal codes exposed to the highest levels of the three DTs combined in urban regions and more heterogeneity for rural postal codes. This finding suggests that people are exposed to all three DT groups and not individual DT

groups. Despite this observation, there was a value and need to use principal component analysis (PCA) to derive the three independent DT groups a priori to test the hypothesis of exposures to mixtures of chemicals. What I learned is that geographically there is no differential exposure to the three groups of DTs in urban and rural postal codes and more importantly that the risk was not amplified in urban postal codes where I obtained risk estimates. However, low SES compounded the risk estimates for urban postal codes exposed to the highest concentrations of the three DT groups combined. I therefore surmised based on these observations that there are few postal codes exposed to high levels of emissions. Furthermore, there is a localized phenomenon of environmental injustice in urban and rural Alberta and all the identified problems may require surveillance and monitoring.

6.2.1. Surveillance and Monitoring

Surveillance is defined as: *"the systematic and continuous collection, analysis, and interpretation of health-related data closely integrated with the timely and coherent dissemination of the results and assessment to those who have a right to know so that action can be taken. It is an essential feature of epidemiological and public health practice. The final phase in the surveillance chain is the application of the information to health promotion and to disease prevention and control" (*3). Surveillance is distinguished from monitoring which *is "the intermittent performance and analysis of measurements aimed at detecting changes in the health status of populations or in the physical or social environment "*(3). Historically, the critical role of disease surveillance can be traced back to Hippocrates who emphasized the importance of making observations, collecting and recording facts and then analyzing them for effective diagnosis and management of disease (4). However, the first public action can be traced back to the detection of cases of bubonic plague in the early 1300 when public officials boarded ships in Venice to prevent people afflicted from disembarking from the ship (4). This surveillance process, initially not well-appreciated, became organized and overtime, with more responsive governments, began to organize health care systems, assisting with creation of consensus on uniform disease classification and methods of measurements, and ultimately evolving to include prevention and control activities (4, 5).

Mapping of disease and understanding where adverse health concerns occur are also important elements of public health surveillance as initially demonstrated by John Snow when he mapped the case fatalities from cholera in London 1854 to a central water well (6)). With the advances in technology in the 21st century, this process has been made easier by the universal availability of computers and digital technology making public health surveillance of disease occurrence and environmental risk factors easy to monitor on large scales from regional to national and even global trends using geographic information systems (GIS). Therefore, my efforts at mapping CHD, the postal codes exposed to the highest emissions

from all the three DT groups and low SES inform the initial stages of a GIS based framework for surveillance and monitoring in order to reduce environmental chemical exposures and improve the socioeconomic well-being of vulnerable populations in Alberta.

6.3. Strengths and Limitations

The novelty of my study was that I was able, for the first time, to harness a health-related database, an environmental pollutant emissions database and a newly developed Canadian neighborhood SES index, linking these databases to examine if there were associations with CHD in Alberta through an interdisciplinary research approach. My work represents an initial approach motivated by the fact that there is no existing comprehensive database of as many chemicals monitored in the environment as the ones reported in the National Pollutant Release Inventory (NPRI). I examined multiple pollutant groups some of which had not been studied before using the NPRI and gained new insight into new associations with CHD.

Another strength of my endeavor was the centralized health care of Alberta, with only two pediatric cardiology referral centers, in conjunction with NPRI which details the release of toxic emissions by industry in the province annually. These resources provided a unique opportunity to investigate the potential role of environmental multipollutant mixtures in CHD development. I had access to a CHD echocardiographic database which captured all children born and diagnosed with a CHD in Alberta with complete case ascertainment. I was limited in that the database did not capture other risk factors and associations including maternal disease (e.g. diabetes) and known genetic syndromes or family histories in the infant which may have confounded my results. Nevertheless, for many children born with CHD, the etiology remains unknown and is thought to be multifactorial with an additional contribution of environmental exposures (7, 8). Furthermore, it is plausible that the substantial variability in cardiac phenotypes among patients with known risk factors could relate to environmental influences in cardiac maldevelopment (e.g. genetic predisposition + environment)

Ecologic studies are undertaken at aggregate level and usually employ secondary databases. They are very useful for hypothesis generation in health conditions that are relatively rare and have a complex etiology because they are inexpensive and fast to execute (9). The limitation of ecologic studies is that, without caution, results may lead to an “ecologic inference fallacy.” Observations made at aggregate level cannot be inferred to individual people. Thus, my decision to use this method was informed by the fact that CHD is a relatively rare disease with a complex etiology and I had limited access to all other risk factors associated with CHD and therefore the interpretation of my findings was cautious and cognizant of these limitations. Furthermore, there is a paucity of population studies investigating the role of toxic

industrial emissions and CHD largely due to the lack of accurate birth defect and industrial toxicant emissions registries. In addition, most of the studies to date have examined single pollutant exposures and only one study, to my knowledge, has examined the role of multipollutant mixtures using pollutant data from monitoring stations. The understanding of how multiple pollutants could potentially impact on the health of populations is only now a new research direction being pursued by the research community (10).

The limitations with the NPRI database are that the emissions were self-reported based on whether the industries fulfill the eligibility criteria of reporting. Although the emission data gathered was limited as the annual reports did not allow for accurate maternal spatio-temporal assignment of DT exposures, NPRI provided access to many industrial pollutants which had never been examined in isolation or together in relation to CHD development based on a detailed perusal of the reported literature.

With respect to the population studied, I did not have data on gestational age at birth and yet some of my CHD cases could have been delivered prematurely which could have resulted in exposure misclassification errors. I did not include terminated pregnancies with fetal CHD, which may underestimate the rates of CHD; however, the observed temporal decrease in CHD rates was unlikely to have occurred due to pregnancy terminations, as I had previously observed no increase in pregnancy terminations for CHD in the province during the study period and absolute termination rates have remained low (11). Furthermore, the CHD rates I reported are consistent with previously published Alberta case ascertainment rates (12).

The DT exposure assigned to the postal code in tonnes was the sum of all emissions from the neighboring facilities over a period of eight years. However, the actual dose that would potentially reach the human population requires measurements at the area and personal level in addition to biomonitoring studies. Another limitation of the study was that I did not have a precise spatiotemporal assessment of the DT impact. I did not have a definitive maternal residential history at the time of conception and the first trimester of pregnancy. I obtained the address given at the time of the initial echocardiogram and assumed it to be the same address as the first trimester of pregnancy which would be the period of cardiac morphogenesis. Previous studies have shown that a minority of women move during pregnancy (13, 14), but I still acknowledge the existence of a potential DT exposure misclassification.

6.4. Future Directions

6.4.1. Research

The findings from my study support the need to conduct more robust epidemiological studies such as cohort or case control studies to further validate these findings and in order to be able to initiate surveillance programs to monitor the postal codes exposed to highest DT levels. I recommend that future studies should investigate the role of multiple pollutants in the evolution of CHD to better understand the interactive effect of the combination of these pollutants in the development of CHD. The fact that I found associations only in the postal codes with the highest DT exposures in both urban and rural postal codes, suggests the presence of a threshold of exposure to DTs for CHD evolution, not confounded by SES or other urban pollutants. This observation warrants future investigations to determine the threshold requiring the use of more precise data such as monitored data to identify the critical concentration of exposure for CHD to occur. Furthermore, the fact that some postal codes were exposed to all the three DT groups would require further analyses to understand whether chemical mixtures have synergistic or antagonist interactions. Exposure to other environmental hazards such as pesticides, DTs found in water or soil contamination was not measured in my study. Furthermore, I did not examine other industrial pollutants which could have as yet an unrecognized teratogenic consequence on cardiac embryogenesis. I did not examine temporal variations of the IDW exposures or seasonal effects of CHD development. Unique genetic risks independent of or potentially contributing to the effect of DTs in the different ethnicities common in rural areas of Alberta (e.g. first nations, Hutterite) among other factors are also likely contributory and warrant further exploration or consideration in the design of future initiatives.

6.5. Recommendations

I recommend the establishment of comprehensive prospective birth defect registries which will capture maternal risk factors, detailed perinatal variables, genetic, socio-economic and pollutant environmental exposures from various sources which will enhance more robust future epidemiological studies in my quest to understand the etiology of CHD**.** Findings from such registries will provide more definitive associations of CHD with environmental factors which can be further tested and refined through biomonitoring of tissues such maternal hair, cord blood and placenta for chemical exposures and experimental animal studies.

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Appendices

Appendix A. Literature review of air pollution studies and CHD

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutants	Pollutant Data Source	Findings
Maternal Occupation	Tikkanen et al.	1988	Finland	CC	1982-1984	Organic solvents	Maternal interviews on solvent exposure (lacquer, petrol, white spirit	Organic solvents associated with VSD
	Tikkanen et al.	1988	Finland	CC	1980-1981	Type of Occupation	Maternal interviews	No associations with CHD
	Tikkanen et al.	1990	Finland	CC	1982-1983	Occupational exposures: organic solvents,	Maternal interviews	Positive associations with organic solvents, alcohol
	Tikkanen et al.	1991	Finland	CC	1982-1983	Organic solvents,	Maternal interviews	Positive association with organic solvents

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutants	Pollutant Data Source	Findings
Maternal Occupation	Tikkanen et al.	1991	Finland	CC	1982-1984	Organic solvents:	Maternal interviews	No association found between the exposures and CHD
	Tikkanen et al.	1992	Finland	CC	1982-1983	Organic solvents	Maternal interviews	Positive association between conotruncal defects and organic solvents
	Tikkanen et al.	1992	Finland	CC	1982-1983	Domestic exposures to organic , solvents, pesticides, glues, disinfectants, maternal habits, ultrasound examination	Maternal Interviews	No association with CHD

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutants	Pollutant Data Source	Findings
	Tikkanen et al.	1992	Finland	CC	1982-1983	Organic solvents: (dyes, lacquers, paints),glues, plastic raw materials, wood preservatives, pesticides, anesthetic gases,	Maternal interviews	Organic solvents associated with VSD
	Tikkanen	1992	Finland	CC	1982-1983	Organic solvents: (dyes, lacquers, paints), glues, plastic raw materials, wood preservatives, pesticides,	Maternal Interviews	No association with ASD

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutants	Pollutant Data Source	Findings
Maternal Occupation	Tikkanen J et al.	1993	Finland	CC	1982-1983	Mineral oils, organic solvents	Maternal interviews	Mineral oils were associated with CoA
	Tikkanen J et al.	1994	Finland	CC	1982-1983	Organic solvents: (dyes, lacquers, paints),glues, plastic raw materials, wood preservatives, pesticides,	Maternal interviews	No association with HLHS
	Pradat P	1993	Sweden	CC	1982-1986	Maternal type of work	census data and medical birth registry	No association found with CHD
	Cordier et al.	1997	France, Italy, United Kingdom and Netherlands	CC	1989-1992	Glycol ethers	Maternal interviews	No association with CHD.

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutants	Pollutant Data Source	Findings
Maternal Occupation	Fixler et al.	1998	Dallas, Texas	CC	-	Maternal exposures to paint, organic solvents, varnishing, welding, lead, mercury, cadmium, arsenic, textiles and hair dyes, plastic, pesticides	Maternal interviews	No association with environmental exposures
	Bassili et al.	2000	Alexandria, Egypt	CC	1995-1997	Maternal or paternal exposure to organic solvents, printing, metal and textile industry occupation	Maternal interviews	Maternal or paternal hazardou occupation was associated wit risk of CHD overall and VSD

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutant	Pollutant Data Source	Findings
Maternal Occupation	Loffredo et al.	2001	Baltimore-Washington Infant Study	CC	1987-1989	Exposure to pesticides for killing fleas, flying/ crawling insects, weeds and rodents at work or home.	Maternal interviews	Association of herbicides and rodenticides with TGA
	Gilboa et al.	2012	USA, NBDPS	CC	1997-2002	Occupational exposures to organic solvents	Maternal interviews on chemical exposures	Positive associations between solvents and VSD, TGA, RHO, AS
	Lupo et al.	2012	USA, NBDPS	CC	1997-2002	Occupational exposures to PAHs	Maternal interviews on chemical exposures	No association between PAHs and CHD
	Patel et al.	2012	USA, NBDPS	CC	1997-2005	Maternal exposures including occupational, smoking, alcohol	Maternal interviews	No association with AVSD

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutant	Pollutant Data Source	Findings
Maternal Occupation	Loffredo et al.	2001	Baltimore-Washington Infant Study	CC	1987-1989	Exposure to pesticides for killing fleas, flying/ crawling insects, weeds and rodents at work or home.	Maternal interviews	Association of herbicides and rodenticides with TGA
	Gilboa et al.	2012	USA, NBDPS	CC	1997-2002	Occupational exposures to organic solvents	Maternal interviews on chemical exposures	Positive associations between solvents and VSD, TGA, RHO, AS
	Lupo et al.	2012	USA, NBDPS	CC	1997-2002	Occupational exposures to PAHs	Maternal interviews on chemical exposures	No association between PAHs and CHD
	Patel et al.	2012	USA, NBDPS	CC	1997-2005	Maternal exposures including occupational, smoking, alcohol	Maternal interviews	No association with AVSD

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutant	Pollutant Data Source	Findings
Paternal Occupation	Ou et al.	2017	China	CC	2012-2013	Maternal exposure to toxic trace elements and heavy metals	Maternal interviews and blood samples for analysis using inductively couples plasma mass spectrometry	Lead was associated with CHD
	Olshan et al.	1990	British Columbia, Canada	CC	1952-1973	Firefighters exposed to: acrolein, benzene, CO_2, CO, dichlorofluoromethane, formaldehyde, hydrogen chloride, hydrogen cyanide, methylene chloride, nitrogen dioxide, sulfur dioxide, toluene, trichloroethylene, trichlorophenol.	Paternal occupation was linked with birth registration	Positive association with ASD and VSD

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutants	Pollutant Data Source	Findings
Paternal Occupation	Correa-Villasenor et al.	1993	Baltimore – Washington Infant Study	CC		Type of work: jewelry maker, lead soldering, welding, paint stripping	Interviews	Positive associations between septal defects and jewelry makers, lead soldering and pulmonary atresia, welding and ECD with Down Syndrome
	Aronson et al.	1996	Ontario, Canada	CC	1979-1986	Firefighters exposed to: acrolein, benzene, CO_2, CO, dichlorofluoromethane, formaldehyde, hydrogen chloride, hydrogen cyanide, methylene chloride, nitrogen dioxide, sulfur dioxide, toluene, trichloroethylene	Firefighter Registry	No association with CHD

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutants	Pollutant Data Source	Findings
Paternal Occupation	Correa-Villasenor et al.	1993	Baltimore – Washington Infant Study	CC		Type of work: jewelry maker, lead soldering, welding, paint stripping	Interviews	Positive associations between septal defects and jewelry makers, lead soldering and pulmonary atresia, welding and ECD with Down Syndrome
	Aronson et al.	1996	Ontario, Canada	CC	1979-1986	Firefighters exposed to: acrolein, benzene, CO_2, CO, dichlorofluoromethane, formaldehyde, hydrogen chloride, hydrogen cyanide, methylene chloride, nitrogen dioxide, sulfur dioxide, toluene, trichloroethylene	Firefighter Registry	No association with CHD

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutant	Pollutant Data Source	Findings
Outdoor Air Pollution	Malik et al.	2004	Dallas, Texas	CC	1979 -1984	Exposure to hazardous waste sites (HWS)	US EPA	Associations with overall CHD and ECD when living within 1 mile of HWS.
	Yauck et al.	2004	Milwaukee, Wisconsin	CC	1997 - 1999	Proximity to trichloroethylene (TCE) emitting site	Toxics Release Inventory (TRI)	Association of older mothers exposed to TCE and congenital heart disease
	Kuehl et al.	2006	Baltimore Washington Infant Study	CC	1981 -1989	Exposure to hazardous waste sites (HWS)	Toxics Release Inventory and National Priority List	HLHS cluster found in region with industrial emission of solvents, dioxin and polychlorinated biphenyls to air.

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutant	Pollutant data Source	Findings
Outdoor Air Pollution	Batra et al.	2007	Washington	CC	1987 - 2003	Exposure to agricultural pesticides based on residence or occupation. Eastern Washington economy is dominated by agricultural industry	Birth certificates	Living in eastern Washington. Associated with VSD.
	Langlois et al.	2009	Dallas, Texas	CC	1996 - 2000	Proximity to HWS and industrial facilities	TRI, ATSDR Hazardous Substances Release/Health Effect Database, TCEQ	Association found with truncus arteriosus
	Langlois et al.	2009	Dallas, Texas	Ecologic	1999 - 2003	Pesticides		ASD associated with pesticides in rural regions.

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutant	Pollutant Data Source	Findings
Outdoor Air Pollution	Gianicolo et al.	2012	Brindisi, Italy	Ecologic	2001 - 2010	Pollutants from petrochemical, manufacturing and power generating plants		Increased risk of CHD
	Brender et al.	2014	Texas, USA	CC	1996 - 2008	Chlorinated solvents	TRI	TCE associated with septal heart defects
	Carmichael et al.	2014	California, USA	CC	1997 - 2006	Pesticides exposure		TOF, HLHS,CoA, PVS, septal defects associated with pesticides
	McKenzie et al.	2014	Colorado, USA	CC	1996 - 2009	Proximity to natural gas development	Colorado Oil and Gas Information System	CHD associated with NGD exposure to
	Wijnans et al.	2014	Netherlands	CC	2003 - onwards	Pesticides, phthalates, alkylphenolic compounds, heavy metals, polychlorinated compounds	Maternal interviews	Phthalates associated with VSD

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutants	Pollutant Data Source	Findings
Ambient Air Pollution	Ritz et al.	2002	Southern California	CC	1987-1993	Data from ambient monitoring stations: CO, NO_2, ozone, PM_{10}	Fixed site monitoring stations	Association between CO and VSD; and Pulmonary/ aortic artery anomalies and ozone
	Hansen et al.	2009	Brisbane, Australia	CC	1998-2004	Ozone, NO_2,SO_2, CO,PM_{10}	Fixed site monitoring stations	Ozone associated pulmonary artery and valve defects. SO_2 associated with aortic artery and valve defects. Inverse associations of CO and VSD and with conotruncal defects
	Rankin et al.	2009	United Kingdom	CC	1985-1990	Black smoke, SO_2	Fixed site monitoring stations	No association with CHD..

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutants	Pollutant Data Source	Findings
Ambient Air Pollution	Strickland et al.	2009	Atlanta, Georgia	Cohort	1986-2003	CO, NO_2,PM_{10}, SO_2, ozone	Fixed site monitoring stations	Associations between PDA and PM_{10}.
	Dadvand et al.	2011	Northeast England	CC	1993-2003	PM_{10}, SO_2,NO_2,NO,ozone,CO	Fixed site monitoring stations	CO and NO associated with septal defects. CO associated with PV stenosis.

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutants	Pollutant Data Source	Findings
Ambient Air Pollution	Strickland et al.	2009	Atlanta, Georgia	Cohort	1986-2003	CO, NO_2,PM_{10}, SO_2, ozone	Fixed site monitoring stations	Associations between PDA and PM_{10}.
	Dadvand et al.	2011	Northeast England	CC	1993-2003	PM_{10}, SO_2,NO_2,NO,ozone,CO	Fixed site monitoring stations	CO and NO associated with septal defects. CO associated with PV stenosis.

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutants	Pollutant Data Source	Findings
Ambient Air Pollution	Dadvand et al.	2011	Northeast England	CC	1985-1996	Black smoke , SO_2	Distance was calculated for cases and controls and the monitoring stations within 16km	No associations between SO_2 and CHD overall and subtypes.
	Agay-Shay et al.	2013	Tel Aviv, Israel	Cohort	2000-2006	Exposure from ozone, NO_2,SO_2, CO, $PM_{2.5}$ and PM_{10}	Fixed site monitoring stations	Associations of PM_{10} and multiple CHD
	Padula et al.	2013	California, USA	CC	1997-2006	Exposure to seven ambient air pollutants and traffic exposures	Fixed site monitoring stations	PM_{10} associated with PVS, VSD. $PM_{2.5}$ associated with TGA. Traffic density associated with MuscVSD and PMVSD

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutants	Pollutant Data Source	Findings
Ambient Air Pollution	Gianicolo et al.	2014	Brindisi, Italy	CC	2001-2010	Ambient pollutant exposure to SO_2, NO_2 and TSP	Fixed site monitoring stations	SO_2 associated with congenital heart disease and VSD
	Schembari et al.	2014	Barcelona, Spain	CC	1994-2006	Exposure to traffic related pollutants: NO_2, $PM_{2.5}$ and PM_{10}	Land use regression models used to assign exposure to residential addresses of cases	NO_2 associated with CoA
	Stingone et al.	2014	North Carolina, USA	CC	1997-2006	Exposure to CO,SO_2,NO_2,ozone,$PM_{2.5}$ and PM_{10}	Fixed site monitoring stations	NO_2 associated with CoA and PVS. $PM_{2.5}$ associated with HLHS.
	Hwang et al.	2015	Taiwan	CC	2001-2007	Exposure to CO,SO_2,NO_2,ozone and PM_{10}	Fixed site monitoring stations	Ozone and PM_{10} associated with VSD, ASD and PDA

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutant	Pollutant Data Source	Findings
Ambient Air Pollution	Jin et al.	2015	Lanzhou, China	CC	2010-2012	Maternal exposure to PM_{10}, NO_2 and SO_2	Fixed site monitoring stations	PM_{10} and NO_2 associated with CI and TGA. PM_{10} a SO2 associated wi septal defects. PM10 and NO2 associated with PDA.
	Vinikoor-Imler et al.	2015	Texas	CC	2002-2006	Exposure to ozone, $PM_{2.5}$	Fixed monitoring sites	No associations between ozone, $PM_{2.5}$ and CHD
	Girguis et al.	2016	Massachusetts	CC	2001-2008	Exposure to traffic related air pollution	Satellite remote sensing, meteorological and land use data	No associations found with CHD

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutants	Pollutant Data Source	Findings
Ambient Air Pollution	Vinceti et al.	2016	Milan, Italy	CC	2001-2008	Exposure to traffic related air pollution: PM_{10}, benzene	Stationary plume dispersion model from the California LINE Source Dispersion Model Version 4	No association with congenital heart disease
	Yao et al.	2016	China	CC	2010-2012	Exposure to SO_2, NO_2 and PM_{10}	Fixed monitoring stations	SO_2 associated with birth defects in the second trimester
	Zhang et al.	2016	China	CC	2011-2013	Exposure to $PM_{2.5}$ and PM_{10}	Fixed monitoring stations	Associations between $PM_{2.5}$ and congenital heart disease
	Liu et al.	2017	China	CC	2007-2013	Exposure to PM_{10}	Fixed site monitoring station	PM10 associated with ASD, VSD, PDA ,and TOF and congenital heart disease.

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutant	Pollutant Data Source	Findings
Ambient Air Pollution	Stingone et al.	2017	USA	CC	1997-2006	Exposure to traffic related air pollutants (TRAP), intake of methyl nutrients and CHD	Fixed site monitoring stations	Association between NO2 and PMVSD.
Indoor air pollution	Forand et al	2012	New York	Ecologic	1978 – 2002, 1983 - 2000	Indoor exposure to TCE, PCE and other VOCs through soil vapor intrusion	Sampling of indoor air for TCE, PCE and other VOCs	TCE and PCE associated with congenital heart disease, and conotruncal defects
	Liu et al.	2013	China	CC	2010-2011	Exposure to chemicals during house renovations e.g. marbles, plywood, laminated board, carpets, ceramic tile, oil based paint, latex or acrylic coating.	Maternal interviews	Renovations associated with conotruncal and APVR defects

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutants	Pollutant Data Source	Findings
Indoor air pollution	Liu et al.	2015	China	CC	2010-2011	Exposure to lead based sources	Maternal hair lead levels were measured by using inductively coupled plasma mass spectometry	Association between lead and congenital heart disease , septal, conotruncal, LHO RHO defects
	Jin et al.	2016	China	CC	2010-2011	Exposure to arsenic, cadmium	Maternal hair arsenic and cadmium levels were measured by using inductively coupled plasma mass spectometry	Association between arsenic, cadmium and congenital heart disease.
	Liu et al.	2016	China	CC	2010-2011	Exposure to aluminum	Maternal hair metals measured as above	Association of aluminum with septal, conotruncal defects

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutant	Pollutant Data Source	Findings
Water	Zierler et al.	1988	Massachusetts	CC	1980 - 1983	arsenic, lead, mercury, selenium, cadmium, chromium, silver, fluoride, nitrate and sodium	Monitored data from department of environmental quality engineering of the commonwealth of Massachusetts	No association with congenital heart disease . Arsenic associated with coarctation of aorta
	Swan et al.	1989	California	CC	1981 - 1983	1,1,1-trichloroethane, methyl chloroform	Solvent leak from manufacturing plant	No association with congenital heart disease
	Shaw et al.	1990	California	CC	1981 - 1983	Maternal water consumption during pregnancy	Maternal interviews on water consumption	No association of drinking water and congenital heart disease
	Goldberg et al.	1990	Tucson Valley	CC	1969 -1987	Well water contaminated with TCE	Parental interviews	Positive association of TCE with congenital heart disease

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutant	Pollutant Data Source	Findings
Water	Grazuleviciene et al.	2013	Lithuania	Cohort	2007 -2009	Maternal water uptake contaminated with trihalomethane (THM)	Measured THM from tap water samples for each water treatment plant	Brominated THM associated with increased risk of congenital heart disease
	Rudnai et al.	2014	Budapest	CC	1987 -2003	Maternal exposure to arsenic in drinking water		Association of arsenic with congenital heart disease PDA, ASD
	Sanders et al.	2014	North Carolina	Semi-Ecologic	2003 -2008	Maternal exposure to arsenic, lead, cadmium and manganese from well water	Measurements from water well	High manganese level associated with conotruncal defects
	Kim et al.	2017	Texas	CC	1999 -2005	Pesticide exposure (Atrazine) in drinking water		No associations between atrazine and congenital heart disease
	Wright et al.	2017	Massachusetts	CC	1999 -2004	Disinfectant By Products (DBP) exposure in drinking water	Massachusetts EPA	Associations between and TOF and septal defects.

Appendix B. Literature review on socioeconomic status and congenital heart disease

Author	Year	Study Location	Study Design	Study Period	SES Measure	Level of SES Assignment	Findings
Tikkanen et al.	1992	Germany	CC	1982-1983	Education and occupation	Individual	No association with CHD
Fixler et al.	1993	USA	Cohort	1971-1984	Income and education	Census tract	No association with CHD
Pradat P	1993	Sweden	CC	1982-1986	Occupation	Individual	No association with CHD
Bassili et al.	2000	Egypt	CC	1995-1997	Education and occupation	Individual	Hazardous occupation associated with CHD risk
Vrijheid et al.	2000	United Kingdom	CC	1986-1993	Carstairs deprivation index	Census tract	Increased risk of CHD with increased deprivation
Carmichael et al.	2003	USA	CC	1987-1989	Education, occupation and neighborhood SES index	Individual, Census tract	Individual low SES and neighborhood SES associated with dTGA,
Williams et al.	2004	USA	CC	1968-1980	Education	Individual	Low SES associated with VSD

Author	Year	Study Location	Study Design	Study Period	SES Measure	Level of SES Assignment	Findings
McBride et al.	2005	USA	Cohort	1999-2001	Education	Individual	No association between SES and noncomplex left ventricular outflow tract obstructions
Batra et al.	2007	USA	CC	1987-2003	Occupation	Individual	Parental occupation not associated with VSD
Yang et al.	2008	USA	CC	1997-2000	Parental education, income, occupation, SES Index	Individual and household index	Low SES at individual and neighborhood level associated with CHD
Carmichael et al.	2009	USA	CC	1999-2004	Education, income, occupation	Individual, household index	Low SES not associated with conotruncal heart defects
Kuciene et al.	2009	Lithuania	CC	1999-2005	Education, occupation	Individual	Low SES associated with risk of CHD
Liu et al.	2009	China	CC	2004-2005	Education	Individual	Low SES associated with CHD
Long et al.	2010	USA	Cohort	1999-2004	Education	Individual	Low SES associated with TOF

Author	Year	Study Location	Study Design	Study Period	SES Measure	Level of SES Assignment	Findings
Agha et al.	2011	Canada	Cohort	1994-2007	Income, education	Dissemination Area	CHD prevalence higher in low SES regions
Agopian et al.	2012	USA	Cohort	1999-2008	Education	Individual	No association with non syndromic AVSD
Patel et al.	2012	USA	CC	1997-2005	Education, income	Individual	No association with non syndromic AVSD
Vereczkey et al.	2012	Hungary	CC	2009-2010	Occupation	Individual	Low SES associated with increased risk of left sided obstructive defects in unskilled mothers
Vereczkey et al.	2012	Hungary	CC	2009-2010	Occupation	Individual	Low SES associated with increased risk of VSD in unskilled mothers and housewives
Vereczkey et al.	2013	Hungary	CC	1980-1996	Occupation	Individual	No association of SES with AVCD
Egbe et al.	2014	USA	Cohort	1999-2008	Income	Individual	Decreased prevalence of CHD among upper class whites

Author	Year	Study Location	Study Design	Study Period	SES Measure	Level of SES Assignment	Findings
Egbe et al.	2014	USA	Cohort	Jan –Dec 2008	Income	Individual	Lower incidence of CHD in the lowest SES class compared to higher SES class
Pawluk	2014	Argentina	CC	1992-2001	Regional SES	Unmet Basic Need Index	Low SES associated with VSD
Yu et al.	2014	China	Systematic review and meta-analysis	Inception of medline database - 2014	Education, Income, occupation	Individual	Low SES associated with risk of CHD
Egbe et al.	2015	USA	Cohort	1998-2008	Income	Individual	Increased prevalence of mild CHD among higher SES Caucasians
Li et al.	2015	Sweden	Cohort	2000-2010	Education, income, occupation	Individual, family, neighborhood index	Deprived neighborhoods associated with CHD. Association not independent of individual or family SES

Author	Year	Study Location	Study Design	Study Period	SES Measure	Level of SES Assignment	Findings
Deguen et al.	2016	France	Systematic review and meta-analysis	Inception of medline database - 2015	Education, income, occupation, poverty, overcrowding	Various spatial aggregation	No association with CHD
Ou et al.	2016	China	CC	2004-2013	Education, income, occupation	Individual	Low SES associated with CHD

Appendix C . Regional Decile Distribution of the Sum of All Inverse Distance Weighted (IDW) Emissions and Congenital Heart Disease (CHD)

Region	Decile	Postal Code Count (%)	Median (tonnes)	IQR (tonnes)	Min (tonnes)	Max (tonnes)	CHD Count (%)	Average CHD by Postal Code (95% CI)	Variance of CHD by Postal Code
Urban	1	5142 (10)	0.003	0.017	0.00	0.03	201 (10)	0.04 (0.03, 0.04)	0.05
	2	5308 (10)	0.07	0.04	0.03	0.11	217 (11)	0.04 (0.04, 0.05)	0.05
	3	5352 (10)	0.15	0.05	0.11	0.19	185 (9)	0.03 (0.03, 0.04)	0.04
	4	5367 (10)	0.24	0.06	0.19	0.32	142 (7)	0.03 (0.02, 0.03)	0.03
	5	5377 (10)	0.44	0.14	0.32	0.59	183 (9)	0.03 (0.03, 0.04)	0.04
	6	5397 (10)	0.77	0.19	0.59	0.97	129 (7)	0.02 (0.02, 0.03)	0.03
	7	5410 (10)	1.28	0.39	0.96	1.72	159 (8)	0.03 (0.02, 0.03)	0.03
	8	5399 (10)	2.55	1.15	1.72	3.86	215 (11)	0.04 (0.03, 0.05)	0.04
	9	5400 (10)	6.98	4.1	3.86	10.50	221 (11)	0.04 (0.04, 0.05)	0.05
	10	5409 (10)	17	6.86	10.5	116	315 (16)	0.06 (0.05, 0.07)	0.07
Total		**53,561**					**1,967**	**0.04 (0.04, 0.04)**	**0.04**
Rural	1	282 (42)	0.00	0.01	0.00	0.03	182 (41)	0.65 (0.56, 0.75)	1.95
	2	116 (17)	0.07	0.03	0.03	0.11	75 (17)	0.65 (0.51, 0.81)	3.47
	3	72 (11)	0.14	0.04	0.11	0.19	33 (7)	0.46 (0.32, 0.64)	1.09
	4	57 (8)	0.24	0.07	0.19	0.32	55 (12)	0.96 (0.73, 1.26)	4.64
	5	47 (7)	0.46	0.12	0.33	0.59	21 (5)	0.45 (0.28, 0.68)	0.64
	6	27 (4)	0.74	0.21	0.61	0.95	15 (3)	0.56 (0.31, 0.92)	0.72
	7	14 (2)	1.26	0.27	0.99	1.71	4 (1)	0.29 (0.08, 0.73)	0.37
	8	25 (4)	3.08	1.42	1.81	3.74	12 (3)	0.48 (0.25, 0.84)	1.43
	9	24 (4)	6.4	1.57	4.02	10.30	29 (7)	1.21 (0.81, 1.74)	4.43
	10	15 (2)	34.9	72	10.8	518	20 (5)	1.33 (0.81, 2.1)	5.67
Total		**679**					**446**	**0.66 (0.59, 0.72)**	**2.33**

Appendix D. Regional Decile Distribution of Group1 Inverse Distance Weighted (IDW) Emissions and Congenital Heart Disease

Region	Decile	Postal Code Count (%)	Median (tonnes)	IQR (tonnes)	Min (tonnes	Max (tonnes)	CHD Count (%)	Average CHD by Postal Code (95% CI)	Variance of CHD by Postal Code
Urban	1	5142 (10)	0.002	0.17	0.00	0.03	201 (10)	0.04 (0.03, 0.04)	0.05
	2	5308 (10)	0.07	0.04	0.01	0.11	217 (11)	0.04 (0.04, 0.05)	0.05
	3	5352 (10)	0.15	0.05	0.07	0.19	185 (9)	0.03 (0.03, 0.04)	0.04
	4	5367 (10)	0.24	0.06	0.18	0.32	142 (7)	0.03 (0.02, 0.04)	0.03
	5	5377 (10)	0.44	0.14	0.29	0.59	183 (9)	0.03 (0.03, 0.04)	0.04
	6	5397 (10)	0.75	0.18	0.48	0.96	129 (7)	0.02 (0.02, 0.03)	0.03
	7	5410 (10)	1.22	0.37	0.79	1.72	159 (8)	0.03 (0.02, 0.03)	0.03
	8	5399 (10)	2.44	1.19	1.46	3.86	215 (11)	0.04 (0.03, 0.05)	0.04
	9	5400 (10)	6.9	4.06	3.33	10.5	221 (11)	0.04 (0.04, 0.05)	0.05
	10	5410 (10)	17	6.87	9.23	116	317 (16)	0.06 (0.05, 0.07)	0.07
Total		**53,561**					**1,967**	**0.04 (0.04, 0.04)**	**0.04**
Rural	1	282 (42)	0.00	0.01	0.00	0.03	182 (41)	0.65 (0.56, 0.75)	1.95
	2	116 (17)	0.07	0.03	0.03	0.11	75 (17)	0.65 (0.51, 0.81)	3.45
	3	72 (11)	0.14	0.04	0.11	019	33 (7)	0.46 (0.32, 0.64)	1.09
	4	57 (8)	0.24	0.07	0.18	0.32	55 (12)	0.96 (0.73, 1.26)	4.64
	5	47 (7)	0.46	0.12	0.32	0.58	21 (5)	0.45 (0.28, 0.68)	0.64
	6	27 (4)	0.74	0.19	0.61	0.95	15 (3)	0.56 (0.31, 0.92)	0.72
	7	14 (2)	1.24	0.25	0.98	1.71	4 (1)	0.29 (0.08, 0.73)	0.37
	8	25 (4)	3.08	1.46	1.81	3.74	12 (3)	0.48 (0.25, 0.84)	1.43
	9	24 (4)	6.4	1.61	3.8	10	29 (7)	1.21 (0.81, 1.74)	4.43
	10	15 (2)	35	72	9.4	500	20 (5)	1.33 (0.81, 2.06)	5.67

Total	**679**		**446**	**0.66 (0.59, 0.72)**	**2.33**

Appendix E Regional Tertile Distribution of Group 2 and 3 Inverse Distance Weighted (IDW) Emissions and Congenital Heart Disease (CHD).

Region	Tertiles	Postal Code Count (%)	Median (kg)	IQR (kg)	Min (kg)	Max (kg)	CHD Count (%)	Average CHD by Postal Code (95% CI)	Variance of CHD by Postal Code
Group 2 Emissions									
Urban	1	17,466 (33)	0.00	0.00	0.00	0.006	592 (30)	0.03 (0.03, 0.04)	0.04
	2	18,033 (34)	3.3	9.4	0.006	23	589 (30)	0.03 (0.03, 0.04)	0.04
	3	18,062 (34)	80	72	23	2,461	786 (40)	0.04 (0.04, 0.05)	0.05
Total		53,561					1,967	0.04 (0.04, 0.04)	0.04
Rural	1	614 (90)	0.00	0.00	0.00	0.003	390 (87)	0.64 (0.57, 0.70)	2.3
	2	47 (7)	2.3	4.6	0.006	23	34 (8)	0.72 (0.50, 1.0)	1.6
	3	18 (3)	171	472	38	17,340	22 (5)	1.2 (0.77, 1.9)	6.7
Total		679					446	0.66 (0.59, 0.72)	2.33
Group 3 Emissions									
Urban	1	17, 437 (33)	0.00	0.00	0.00	0.00004	664 (34)	0.04 (0.04,0.04)	0.04
	2	18, 056 (34)	0.002	0.058	0.00004	0.091	504 (26)	0.03 (0.03,0.03)	0.03
	3	18, 068 (34)	0.349	0.576	0.091	3.9	799 (41)	0.04 (0.04, 0.05)	0.05
Total		53, 561					1,967	0.04 (0.04, 0.04)	0.04
Rural	1	643 (95)	0.00	0.00	0.00	0.00004	414 (93)	0.64 (0.58,0.71)	2.2

	2	24 (4)	0.004	0.033	0.0002	0.064	10 (2)	0.42 (0.2,0.77)	1.5
	3	12 (2)	0.874	1.74	0.1	12	22 (5)	1.83 (1.1,2.8)	9.2
Total		679					446	0.66 (0.59,0.72)	2.33

Appendix F. Summary Statistics of the Postal Codes with the Highest DT Exposures and No CHD Cases

Region	Combinations of Highest DT Exposures	Postal Code Count (%)	Postal Code Count without Cases (%)	Postal Code average exposure without cases	Average Group1 DTs without Cases (%)	Average Group2 DTs without Cases (%)	Average Group3 DTs without Cases (%)
Urban	Group 1	1 (0.02)	0	13	0	0	0
	Group 2	0	0	0	0	0	0
	Group 3	0	0	0	0	0	0
	Group 1&2	1	0	22	0	0	0
	Group 1&3	1 (0.02)	0	11	0	0	0
	Group 2&3	0	0	0	0	0	0
	Group 1,2,3	5,357 (99.9)	5,067	19	19 (99.3)	0.13 (0.7)	0.001 (0.01)
Total		**5,360**	**5,067**				
Rural	Group 1	3 (25)	1 (20)	31	81	0	0
	Group 2	0	0	0	0	0	0
	Group 3	0	0	0	0	0	0
	Group 1&2	0	0	0	0	0	0
	Group 1&3	5 (42)	3 (60)	58	58	0	0.001
	Group 2&3	0	0	0	0	0	0
	Group 1,2,3	4 (33)	1 (20)	224	35	0.09	0.001
Total		**12**	**5**		**151 (99.9)**	**0.09 (0.06)**	**0.001 (0.01)**

Appendix G .Summary Statistics of CHD Distribution and DT Group Combinations in Any Level of Concentration in Urban and Rural Alberta

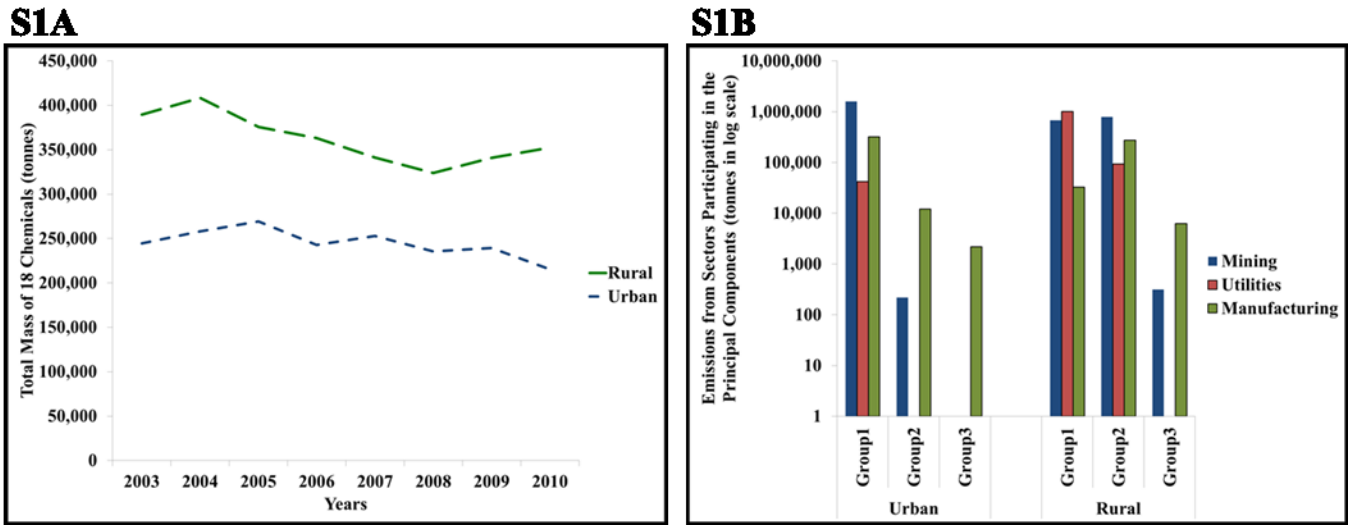
Region	DT Exposure Categories	Postal Code Count (%)	Sum CHD (%)
Urban	No Exposure	2097 (4)	81 (4)
	Group 1	8,145 (15)	351 (18)
	Group 2	22 (0 04)	2 (0.1)
	Group 3	1 (0.002)	0
	Group 1,2	5,076 (9.5)	175 (8.9)
	Group 1,3	5,026 (9.4)	114 (5.8)
	Group 2,3	1 (0.002)	0
	Group 1,2,3	33,193 (62)	1,244 (63)
Total		**53,561**	**1,967**
Rural	No Exposure	155 (23)	97 (22)
	Group 1	423 (62)	285 (64)
	Group 1,2	47 (7)	28 (6.3)
	Group 1,3	33 (5)	8 (1.8)
	Group 1,2,3	21 (3)	28 (6.3)
Total		**679**	**446**

The Table is an aggregation of the postal codes impacted by any level of DT concentrations based on the various combinations.

Appendix H . Composite Summary Statistics of the Postal Codes Exposed to the Three DT Groups Combined

Region	Combinations of Highest DT Exposures	Postal Code Count (%)	Postal Code Count with Cases (%)	Sum CHD Cases (%)	PC average exposure without cases	PC average exposure with cases	Average Group1 DTs with Cases (%)	Average Group2 DTs with Cases (%)	Average Group3 DTs with Cases (%)
Urban CHD n=1,967	Group 1	1 (0.02)	0	0	13	0	0	0	0
	Group 2	0	0	0	0	0	0	0	0
	Group 3	0	0	0	0	0	0	0	0
	Group 1&2	1	0	0	22	0	0	0	0
	Group 1&3	1 (0.02)	0	0	11	0	0	0	0
	Group 2&3	0	0	0	0	0	0	0	0
	Group 1,2,3	5,357 (99.9)	290	313 (16)	19	19	19 (99.3)	0.13 (0.7)	0.001 (0.01)
Rural CHD n=446	Group 1	3 (25)	2 (29)	5 (1.1)	31	41	81	0	0
	Group 2	0	0	0	0	0	0	0	0
	Group 3	0	0	0	0	0	0	0	0
	Group 1&2	0	0	0	0	0	0	0	0
	Group 1&3	5 (42)	2 (29)	4 (0.9)	58	59	119 (100)	0	0.002 (0)
	Group 2&3	0	0	0	0	0	0	0	0
	Group 1,2,3	4 (33)	3 (43)	11 (2.5)	224	287	1,416 (98.5)	23(1.6)	0.02(0.00)

Appendix I. Trends of overall emissions and proportions by sectors in urban and rural regions



(S1A) Shows the proportion and trends of 18 chemicals in tonnes for urban and rural postal odes. The rural postal codes had the highest proportion of emissions released to air for the period 2003-2010.

(S1B) Shows the distribution of the three groups of emissions derived from principal component analysis and the 3 main sectors (mining, manufacturing and utilities) which emitted the chemicals in urban and rural postal codes.