Profiling industrial air-pollutant mixtures and their associations with preterm birth and small for gestational age in Alberta, Canada

by

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Abstract

Background

Adverse birth outcomes (ABOs) are major causes of neonatal death and future adverse health outcomes. Gaps still exist in understanding the local distribution of maternal and social risk factors for ABOs, and the effect of air pollutant mixtures derived from industrial activities on pregnancy outcomes in Alberta.

Objectives

(1) To assess the prevalence of ABOs in Alberta, Canada and the relative contribution of associated known maternal risk factors and area-level socioeconomic status; (2) To characterize exposure to air pollutant mixtures from industrial emissions in Alberta and describe their associations with preterm birth (PTB) and small for gestational age (SGA).

Methods

For the first objective: I conducted a prevalence study of PTB, SGA and low birth weight at term (LBWT) using data from all singleton live births occurred in Alberta from 2006 to 2012. Birth records were provided by the Alberta Perinatal Health Program. Data included the postal code of residence at the time of birth and 21 maternal risk factors for ABOs. I used a Canadian area-level socioeconomic status index (SES-index) as a proxy for neighborhood socioeconomic status. Standardized prevalence ratios (age-adjusted and smoothed by an empirical Bayes approach) at small area level were estimated to locate areas of *low*, *medium* and *high*-ABO occurrence. The contribution of risk factors in the *high-ratio* areas were identified by their corresponding attributable fraction (AF).

For the second objective: I used industrial-facilities' emissions into the air from the Canadian National Pollutant Release Inventory. I profiled the *mixtures* based on the proportional content of ten broader chemical classes (*NO_2*, *SO_2*, *CO*, *PM*, *VOCs*, *PAHs*, *metals*, *other inorganics*, *other*

organics and *nitrosamines/ethers/alcohols*) in the individual emissions by applying cluster analysis. I used proximity (10-km buffer) of the maternal postal codes to the sources of the *mixtures* to assign exposure. I used multivariable logistic regression for estimating the associations of the *group of mixtures* with SGA, spontaneous-PTB (sPTB) and induced-PTB (iPTB) adjusted maternal covariates and the SES-index.

Main results

A total of 330,957 births was analyzed. The period prevalence of: PTB ranged from 4.4% to 10.9%; SGA ranged from 5.4% to 15.2%, and LBWT ranged from 0.8% to 3.8%. The higher prevalence of ABOs was observed in urban locations.

The key risk factors for spontaneous-PTB were: past-preterm (AF=18%), smoking during pregnancy (AF=15%), bleeding after the 20th week (AF=11%), low SES-index (AF=9%), substance use during pregnancy (AF=5%), and gestational diabetes (AF=4%). For induced-PTB: gestational hypertension (AF=19%), past preterm (12%), proteinuria (10%), and smoking during pregnancy (6%). For SGA: low SES-index (AF=12%), smoking during pregnancy (AF=6%), and gestational hypertension (AF=4%). For LBWT: low SES-index (AF=16%), smoking during pregnancy (AF=10%), and gestational hypertension (AF=7%).

A total of 6,259 facilities overall emitting 133 chemicals were classified into nine *groups of mixtures* based on the predominant chemical class (the chemical class with ≥ 60% of the proportional content) in the emissions: *NO_2-mixtures*, *CO-mix*tures, *SO_2-mixtures*, *PM-mixtures*, *VOCs-mixtures*, *Metals-mixtures*, *Other inorganics-mixtures*, *Other organics-mixtures*, and *Heterogeneous-mixtures*. *Mixtures* with a high proportional content of gases were common and densely present across the province; whereas mixtures with a high proportional content of *VOCs*, *Metals*-, *Other organics*- and *Other inorganic*- were scarce but associated with ABOs. The

VOCs-mixtures increased the odds of SGA by 37% (95% CI: 11-69%). *Metals-mixtures*, *other inorganic-mixtures*, and *other organic-mixtures* increased the odds of iPTB by 17% (95% CI: 5-30%), 17% (95% CI: 6-28%), and 24% (95% CI: 9-41%), respectively. *Heterogeneous-mixtures* increased the odds of sPTB by 36% (95%CI: 13-63%).

Conclusions

The areas with the highest prevalence of ABO were mainly urban. Low SES-index, smoking during pregnancy and gestational hypertension were the common main contributors of ABOs. *Mixtures* with a significant content of volatile organic compounds, metals, other toxic organic and inorganic substances were associated with preterm birth and small for gestational age. These results may motivate and justify further research in studying the health effects of mixtures of chemicals released into the air by industrial sources. Finally, our results suggest that other unmeasured factors and their interactions should be investigated to better understand the occurrence of adverse birth outcomes in Alberta.

Preface

This thesis is an original work by Jesús Arturo Serrano Lomelín, with the co-supervision of Dr. Alvaro Osornio-Vargas and Dr. Yutaka Yasui. The research project, of which this thesis is a part, received ethics approval and yearly renewal from the University of Alberta Research Ethics Board, Project Name "Spatial data mining exploring co-location of adverse birth outcomes and environmental variables". No. Pro00039545, July 25, 2013 – July 24, 2018.

Chapter 1 introduces the subject and the objectives, followed by a synoptic overview of the main topics: (i) the occurrence of preterm birth and small for gestational age at worldwide, national and local (Alberta) levels; (ii) ambient air pollution and health; (iii) multi-pollutant approaches in epidemiological studies; and (iv) the burden of industrial emissions in Alberta. The significance of this thesis finalizes the chapter.

Chapter 2 presents the prevalence of adverse birth outcomes in Alberta in areas identified as *low*-, *medium*-, and *high*- occurrence of small for gestational age, preterm birth, and low birth weight at term. It describes, additionally, the associated prevalence profiles of maternal risk factors and area-level socioeconomic status. This chapter resulted in a manuscript that will be submitted for publication in a scientific journal as: Serrano-Lomelin J, Nielsen C, Osornio-Vargas A, Kumar M, Chandra S, Aelicks N, Villeneuve PJ, Yasui Y, Agrawal, S. Aziz K. "Prevalence of adverse birth outcomes in Alberta, Canada and the relative contribution of associated known maternal risk factors and area-level socioeconomic status". I was responsible for preparing and analyzing the data, constructing the discussion topics, and drafting the manuscript. C. Nielsen (Earth and Atmospheric Sciences, University of Alberta) performed the geo-location of the maternal postal codes at time of birth and reviewed the manuscript. Dr. Osornio-Vargas, Dr. M. Kumar, Dr. S. Chandra, and Dr. K. Aziz (paediatrics, University of Alberta), participated in the formulation of the scientific questions, reviewed the manuscript and

provided theoretical feedback for the discussion. N. Aelicks provided the data, participated in the formulation of the scientific questions and reviewed the manuscript (Alberta Perinatal Health Program). Dr. S. Agrawal (Urban and Regional Planning Program, University of Alberta) reviewed the manuscript and provided feedback for the discussion. Dr. Villeneuve (Departmental of Health Sciences, Carleton University), and Dr. Y. Yasui (School of Public Health, University of Alberta) oversaw my research, reviewed the manuscript and provided theoretical feedback.

Chapter 3 characterizes the air-pollutant mixtures extracted from over one hundred chemicals emitted into the air and reported by the industrial and commercial facilities in Alberta from 2006 to 2012. The characterization includes their geographical distribution across the province and the principal industrial sector sources. Additionally, it reports statistical associations of the industrial air pollutant mixtures with preterm birth and small for gestational age, considering proximity to the industrial air pollutant mixtures (postal codes of the mothers at time of birth within a 10-km buffer) as a proxy of environmental exposure. This chapter resulted in a manuscript that will be submitted for publication in a scientific journal as: Serrano-Lomelin J, Nielsen C, Villeneuve PJ, Yasui Y, Osornio-Vargas A. "Associations between maternal residential proximity to air-pollutant mixtures from industrial sources and preterm birth and small for gestational age". I was responsible for the conceptualization and development of the research objectives, preparing and analyzing the data, constructing the discussion topics, and drafting the manuscript. C. Nielsen (Earth and Atmospheric Sciences, University of Alberta) performed GIS tasks and reviewed the manuscript. Dr. P. Villeneuve (Departmental of Health Sciences, Carleton University), Dr. Y. Yasui (School of Public Health, University of Alberta), and Dr. A. Osornio-Vargas (paediatrics, University of Alberta) oversaw my research, reviewed the manuscript, and provided feedback on the discussion and recommendations.

Chapter 4 provides conclusions and a general summary of results, with emphasis on the significance of the findings and their potential implications for environmental health researchers.

Chapters 2 and 3 are presented in a paper-based format. Each chapter has standard sections (i.e., introduction, methods, results, and discussion) written as stand-alone manuscripts for future publication. Therefore, there may be some redundancy in the introductions, methods, and references in these chapters. The references for the four chapters were included in the corresponding section at the end of the document.

Finally, appendices include materials that support some procedures used in this thesis as well as the letter of ethics approval from the University of Alberta Health Research Ethics Board (Appendix 3).

To Aura,

Nora, Aranza, Ivannia,

My lovely mother and family,

My father's memory

Acknowledgements

Surely, at some future time clever minds will bring
circulatory diseases, cancer and mental diseases under control.
And if the life sciences learn how to eliminate the physical diseases on man,
there remains the challenge to deal with crime, greed and hate.

Dwight J. Ingle (Principles of Research in Biology and Medicine. 1958)

The completion of this academic work was possible by the union of many wills and individual commitments. So, I am infinitely in debt to many people who have helped me to expand and strengthen my academic training but also overcome challenges, limitations, and difficult times. It is impossible to name them all and to explain in a fair way what they have taught me. All have my deepest gratitude.

I was lucky to have as main supervisors, Dr. Yutaka Yasui and Dr. Alvaro Osornio-Vargas, from whom I always received constructive feedback, support, and motivation to continue learning and improving my academic skills. By working with them, I have confirmed that not just passion for science, but open-mindedness, respect, commitment, ethics, and humanity, must guide our behaviour as researchers and individuals. Thank you, Dr. Osornio-Vargas, for inviting me to participate in environmental health research since 2005, and for giving me the opportunity to study this Ph.D. project. Thank you, Dr. Yasui, for accepting me as a student on your team and for your valuable guidance during my Ph.D.

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Of course, thanks to my whole and lovely family (more than 40!!) for your remote support but close love. This achievement is thanks to you.

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List of Abbreviations (Alphabetical)

Acronyms

ABO	Adverse birth outcome
AF	Attributable fraction
ATSDR	Agency for Toxic Substances and Disease Registry
CO	Carbon monoxide
LBW	Low birth weight
LBWT	Low birth weight at term
NAICS	North America Industry Classification System
NPRI	National Pollutant Release Inventory
NOx	Nitrogen oxides
NO_2	Nitrogen dioxide
PAH	Polycyclic aromatic hydrocarbon
PM	Particulate matter
$PM_{2.5}$	Particles of median aerodynamic diameter < 2.5 μm
PM_{10}	Particles of median aerodynamic diameter < 10 μm
PTB	Preterm birth
TPM	Total particulate matter
SGA	Small for gestational age
SO_2	Sulphur dioxide
VOC	Volatile organic compounds
WHO	World Health Organization

Chapter 1

1. Introduction

1.1. Thesis overview

This thesis investigates the association of mixtures of air pollutants from industrial sources with preterm birth (PTB) and small for gestational age (SGA), and the local/regional distribution of PTB- and SGA-related maternal risk factors. These health outcomes are of worldwide public health concern due to their current prevalence and health implications. They are important causes of neonatal death and are related to short- and long-term adverse health conditions that negatively affect the lives of newborns, their families, and society to some extent. Regarding air pollution, it is a worldwide ubiquitous condition affecting the health of human populations and ecosystems. I focused on mixtures of air pollutants from industrial sources because it is a research gap in air pollution and perinatal epidemiology. Past and current research on air pollution has mainly focused on understanding the associations of traffic-related pollutants or air pollutants such as ground-level ozone, nitrogen dioxide, sulphur dioxide, carbon monoxide, and particulate matter with adverse birth outcomes. Consequently, the associations of a large number of hazardous chemicals released into the air by industrial sources with adverse birth outcomes are still unknown.

I followed a multi-pollutant perspective by recognizing that air pollution is composed of mixtures of chemicals that vary both spatially and temporally. Multi-pollutant approaches in air pollution and perinatal epidemiology may contribute to better understanding the relationships between ambient air pollution and health outcomes, and, consequently, to better protect the health of human populations.

This thesis research was framed within an interdisciplinary research project of an exploratory nature based on an engaged scholarship design (in which the stakeholders participated in

problem and question formulation).[1] The project's main goal was to identify potential associations between adverse birth outcomes and outdoor industrial pollutants in Canada for postulating new hypotheses. Its main goal was accomplished by using innovative data mining algorithms to search for association rules. The resulting association rules were contrasted by analyzing the same data set under epidemiological and geographic methods. The validated rules will inform future research. The project received financial support from The Canadian Institutes of Health Research (CIHR) and The Natural Sciences and Engineering Research Council of Canada (NSERC) (Application number 290275). The study received ethics approval from the University of Alberta Research Ethics Board and institutional approval from the Alberta Perinatal Health Program.

1.1.1. Aims and objectives

Within this research framework, this thesis used data from births occurring in Alberta, Canada, from 2006 to 2012, and industrial emissions from the National Pollutant Release Inventory (NPRI) of Canada, to pursue the following general aims:

1) To assess the prevalence of adverse birth outcomes and the relative contribution of associated known maternal risk factors and area-level socioeconomic status;
2) To characterize air pollutant mixtures from industrial emissions to analyze their associations with PTB and SGA.

For the first aim, the objectives were:

1) To estimate the period prevalence of PTB, SGA and low birth weight at term (LBWT) within the province;
2) To identify areas of low, moderate (average) and high occurrence of PTB, SGA and LBWT;

3) To profile the prevalence of risk factors in the areas of low, moderate (average) and high occurrence of adverse birth outcome;

4) To identify the key risk factors impacting the areas with the high occurrence.

For the second aim, two objectives were defined:

1) To characterize mixtures of air pollutants released by industrial facilities in Alberta;

2) To estimate the association of the characterized industrial air-pollutant mixtures with PTB (spontaneous and induced) and SGA.

1.2. Synoptic overview

1.2.1. Preterm birth, and small for gestational age

Preterm birth is defined as a birth occurring before 37 weeks of completed gestation.[2] It is the leading cause of perinatal and neonatal mortality in developed and developing countries[2], and the second leading cause of death - after pneumonia - in children under five years.[3] PTB is closely related to several newborn diseases (e.g., cerebral palsy, cognitive disabilities and respiratory illness),[4] which impact significantly the health care costs:[5] US $4.5 billion in the United Kingdom,[6] and CAN $587 million in Canada[7]. PTB is a complex condition due to its multifactorial nature. Mother's age and lifestyle factors (e.g., tobacco smoke), medical conditions, socio-economic characteristics, and environmental exposure to hazardous chemicals have been associated with PTB.[2,8,9]

Worldwide, an estimated 12 to 15 million babies are preterm each year, with annual crude rates ranging from 5-18% across 184 countries,[3] and increasing in almost all countries.[10] In Canada, the crude rates of PTB increased from 7.0% in 1999 to 8.2% in 2004[11], while between 2005 and 2010 they slightly decreased from 7.9% to 7.7%.[12] Across the country, Nunavut

(10.7%), Yukon (9.6%), Alberta (8.6%), and Ontario (8.1%) have observed the highest PTB rates in 2010-2011.[13] Alberta also reported PTB rates above the national average during 2006-2007 (**Figure 1.1**).

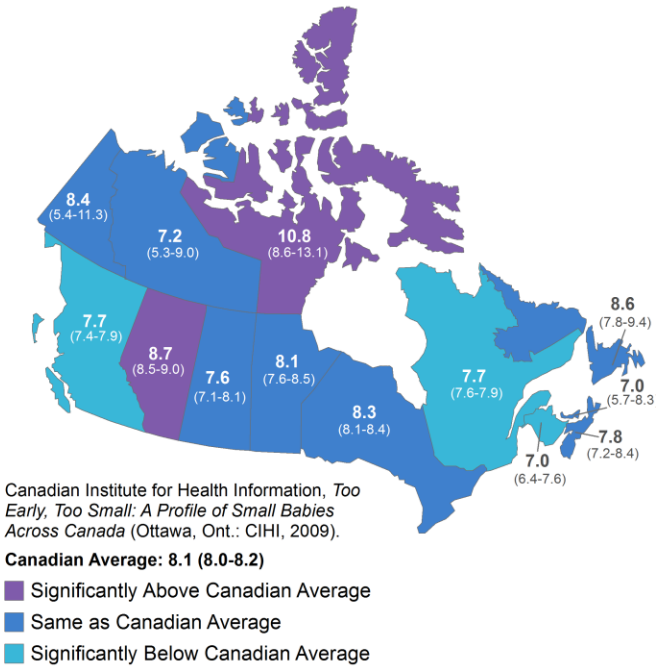

Figure 1.1. Preterm birth rates. Canada (2006-2007)

Source: Canadian Institute for Health Information, Too Early, Too Small: A Profile of Small Babies Across Canada (Ottawa, Ont.: CIHI, 2009).

Small for gestational age birth refers to a newborn with a birth weight below the tenth percentile for their gestational age and sex using a standard reference population.[4] SGA is an indicator related to fetal growth restriction[4] with perhaps a distinct etiology of PTB.[14,15] It is an important indicator used by health institutions because the perinatal mortality rate for growth-restricted infants has been estimated to be 10 to 20 times higher than newborns who are not growth restricted.[4] Some risk factors associated with SGA overlap with PTB (i.e., smoking during pregnancy, diabetes and hypertension).[4, 14,15] The immigrant condition[14] and exposure to air pollution have been associated with SGA[16].

It was estimated in 2010 that 27% of all births in low- and middle-income countries (32.4 million babies) were born SGA.[17] In Canada, the SGA birth rates varied between 7.8% and 8.3% between 2001 and 2010 (excluding Ontario)[12]. Alberta had the higher average SGA crude rate (8.8%) from 2006 to 2010 compared with the rest of the provinces.[12]

1.2.2. Ambient air pollution

Ambient air pollution involves changes in the "natural" chemical composition of the atmosphere at local levels in a way that can be harmful to ecosystems[18]. It is generally composed of a variety of chemical compounds derived from multiple natural (i.e., volcanos and bushfires) and anthropogenic emission sources (i.e., vehicle traffic, industrial processes).[18] Chemical compounds such as nitrogen oxides (NOx), sulphur dioxide (SO_2), carbon monoxide (CO), particulate matter (PM), some metals and organic compounds (e.g., polycyclic aromatic hydrocarbons [PAH], formaldehyde, volatile organic compounds[VOC]) are recognized as air pollutants.[18,19] As the human population has grown accompanied with urbanization, diversification of industrial processes, and an extensive use of fossil fuels, the emissions of chemicals into the local atmosphere have affected the quality of the air.[20-22] Primary pollutants (those emitted directly from sources into the air) are subject to photochemical reactions in the troposphere in the presence of oxygen to form secondary air pollutants, such as ozone (O_3; resulted from the oxidation of nitrogen dioxide [NO_2] or nitric oxide, or of some VOC), and sulphuric acid (resulting from the oxidation of SO_2).[20] Others chemicals exist in particulate or aerosol phase in equilibrium with the surrounding gases and may be composed of pure compounds or a complex mixture of inorganic and organic constituents. Chemicals in particles may potentially be transported over large distances (i.e., hundreds of kilometers).[20,21]

During the last 60 years, historical events have changed the profile of air pollution:[22] (i) the implementation of environmental legislation to control and reduce emissions (i.e., the Clean Air Acts); (ii) the use of cleaner technologies (i.e., catalytic converters, elaboration of cleaner fuels); (iii) the diversification of industrial activities and the intensification of traffic; and (iv) the changes in the local atmospheric conditions (i.e., the increment in the average temperature associated with climate change). The first two events have resulted in reductions in gas emissions (i.e., SO_2 and NO_2). [22] Conversely, industrialization and traffic intensity have added emissions of a variety of chemicals (i.e., metals and organic compounds) and increased the production of PM.[22] In addition; the observed increment of the global average air temperature exacerbates the production of secondary air pollutants in the atmosphere such as PM[21] and organic aerosols.[23]

During the last decade, PM has received great attention by its impact on air quality and health. PM is a mixture of solid and liquid particles suspended in the air, including biological material (i.e., bacteria, virus, pollen).[21] Its composition and physical-chemical properties vary according to its sources and local meteorological conditions.[21,23] For routine monitoring and regulatory purposes, PM is quantified by particle size:[21] the smaller fractions are ultrafine particles (UFPs < 0.1 μm) and $PM_{2.5}$ (< 2.5 μm); while the larger particles are PM_{10} (< 10 μm). The major constituents are sulphates (SO_4^{2-}), nitrates (NO_3^-), ammonium (NH_4^+), sodium and chloride ions (Na^+, Cl^-, respectively), elemental and organic carbon, mineral material (i.e., Al, Si, Fe and Ca), metals (i.e., Pb, Cd, Hg, Ni, Cr. Zn), and water-soluble components (i.e., ammonium sulphate $(NH_4)_2SO_4$), although the exact composition of PM depends on the location, air pollution sources, and prevailing meteorology.[21] Since exposure to commonly measured air pollutants, such as PM, O_3, NO_2 and SO_2, has been associated with respiratory and cardiovascular morbidity and mortality[24,25] and other health outcomes (i.e., adverse birth

outcomes[26]) the World Health Organization (WHO) have published air quality guidelines for their corresponding ambient concentrations.[27]

1.2.3. Air pollution and health

The WHO has qualified air pollution exposure as the world's largest single environmental health risk.[28] In 2014, the WHO reported that in 2012 around 7 million deaths worldwide were related, in some way, to air pollution exposure.[28] Air pollution is directly linked to human activities to the point that it "has been considered an unavoidable concomitant of economic development".[29] It is projected it will remain a problem of concern in the near future since it is expected that the application of recent measures to reduce air pollutant emissions and the use of clean technologies will only partially reduce its impact.[29]

Ambient air pollution and its effects on human health have been largely studied by epidemiologists. Since 1952, when a heavy smog event covered the city of London causing excessive mortality,[30] ambient air pollution started receiving substantial attention by environmental-health authorities and researchers. Nowadays, compiled worldwide evidence from toxicological and epidemiological studies indicate that ambient air pollutants are related to mortality,[31] the development of acute and chronic diseases (i.e., asthma, cardiovascular diseases, cognitive and psychomotor development in childhood), and the shortening of life expectancy.[32,33]

Based on scientific studies, a large list of air pollutants has been identified, continuously monitored, controlled, and, in some cases, reduced or eliminated.[22] As a result of those studies, the WHO has suggested that countries should consider the implementation of air quality standards to protect human health.[27] However, in 2016 the WHO estimated that more than 80% of the population living in urban areas that monitor air pollutants are exposed to air quality levels that exceed the international air quality guidelines.[34] This indicated that, despite the great

progress in controlling local levels of ambient air pollutants, considerable quantities continue to be released into the air from anthropogenic (i.e., traffic, industrial facilities) and natural sources (i.e., wildfires), affecting human populations living in urban settlements, near to industrial facilities, and in areas with high transportation emissions.[35]

1.2.4. Multi-pollutant approaches in air pollution epidemiology.

During the last decade, a growing scientific interest exists in quantifying the health consequences of being exposed to air pollution mixtures by recognizing that people are simultaneously exposed to a mixture of air pollutants.[36] It has been presupposed that multi-pollutant approaches could help us identify the most harmful pollution emission sources and to provide a better understanding of the health effects of ambient air pollution. Thus, it will improve air-emissions regulations and protect human health.[36]

However, elucidating the health effects of "real world" air pollutant mixtures is a challenging task.[37] There is a need of developing (i) research frameworks and reliable and practical methods for measuring a complex mixture of chemicals,[38,41,43,44] (ii) optimal statistical methods for assessing additive effects, effect measure modification, and dimension reduction,[39,45,46] (iii) metrics that properly represent the multi-pollutant environment,[40] and (iv) improved air quality management frameworks.[42] The major progress in this field has come from studying air pollutant mixtures where air pollution monitoring stations exist, providing a vast quantity of information (i.e., hourly concentrations) of a reduced list of chemicals (i.e., criteria pollutants such as SO_2, NO_2, CO, and O_3). Data from monitoring stations allows researchers to model spatial and temporal changes in atmospheric concentrations and environmental deposition to better estimate population exposure and health effects.[39-41] However, the study of mixtures from industrial facilities (which may release dozens or hundreds of chemicals into the air that are not

captured by air monitoring stations) and their potential health effects have been barely explored.[42]

The Health Effects Institute in the United States has designed an interdisciplinary strategy supporting methodological developments to characterize the health effects of "real word" air pollutant mixtures.[45,46] The Southeastern Centre for Air Pollution and Epidemiology is leading an interdisciplinary approach for studying air pollution mixtures and health outcomes; they have developed a novel method to measure ambient fine particulate reactive oxygen species as a measure of toxicity of PM.[47] Recently, health researchers have reported some associations between outdoor (and indoor) air pollutant mixtures with health outcomes. For example: (i) an increase in mortality (3.7%) associated with a mix of elements related to traffic pollution and oil combustion emissions composed of $PM_{2.5}$-black carbon, NO, NO_2, SO_2 and O_3 on total mortality in the greater Boston area;[48] (ii) positive associations between a mixture of 27 correlated chemicals (5 polychlorinated biphenyls, 7 polycyclic aromatic hydrocarbons, and 15 pesticides) measured in house dust (indoor pollution) and increased risk of Non-Hodgkin Lymphoma in a population-based case control study in Detroit, Iowa, and Los Angeles;[49] (iii) positive associations between $PM_{2.5}$ and ozone with low birth weight and preterm birth;[26] (iv) positive associations between low birth weight at term with pollutant clusters with elevated NO_2, NO, and $PM_{2.5}$ in Los Angeles County;[50] (v) positive associations between mortality and NO_2 and limited impact with $PM_{2.5}$ and O_3 in a long-term exposure study in Canada.[51]

The study of the biological mechanisms implicated in the pathway between air pollution and adverse health outcomes is also challenging due to the complex nature of the air pollutant mixtures. Oxidative stress induced by organic compounds, and inflammatory potential associated with size and soil-related chemical compounds in PM, are two of the different biological mechanisms that have been suggested to explain the toxic effect of air pollutants.[52,53] However,

different types of interaction among pollutants[44] (additive, synergism, antagonism, inhibition, potentiation, and masking) may alter biological responses. For example, it has been suggested that a threshold-dose in the proportional content of PAH in $PM_{2.5}$ may inhibit the dose-response relationship between soil-content and cellular inflammatory response.[54]

Currently, the science of pollutant mixtures is in the developing phase and no simple approach exists to solve all challenges. The study of pollutant mixtures requires interdisciplinary research, including: molecular and cell biology, toxicology, eco-toxicology, epidemiology, exposure assessment, risk assessment, and atmospheric chemistry[55,63] to better understand the relationships between air pollutant mixtures and human health.

1.2.5. Air toxic inventories and industrial emissions into the air in Alberta (2006-2012)

Industrial facilities are continuously emitting large quantities of chemicals into the air. According to Agarwal and collaborators[56] 75,000 different chemical substances are registered under the Toxic Substances Control Act of the United States. Large uncertainty exists about the number and amounts of chemicals that are released into the environment (air, water, land) by industrial activities and their associated impact on human health and ecosystems; mainly because not all chemicals released by industry into the environment are tracked.[57] Some developed countries have legislated to track hazardous emissions to air, water, and land by industrial activities.[58] The annual amounts of those chemicals, recognized as toxic for human health, are reported by facilities into databases known as Pollutant Release and Transfer Register Databases (PRTR). Generally, hundreds of these chemicals have been tracked by PRTR and data are publicly available. Health researchers have used these data for investigating associations among industrial chemicals and adult and childhood cancer, neurodevelopmental diseases, and other health outcomes; their use in environmental health research has increased in the last decade.[58]

In Canada, industrial facilities that manufacture, process, use or release substances listed in the Canadian Environmental Protection Act 1999,[59] report their annual emissions to air, land, and water to the National Pollutant Release Inventory (NPRI).[60] In 2012, 42% of all facilities across the country reporting to the NPRI were located in Alberta.[60] The industrial facilities from Alberta were the principal emitters of chemicals to the air in the country during 2006-2012, accounting for 29.8% of the total chemicals emitted (**Table 1.1**). Conventional and non-conventional oil and gas extraction, electricity, and wood products manufacturing are the main sectors accounting for 88% of the chemicals discharged to the air in Alberta (**Table 1.2**). They have jointly emitted 136 chemicals, averaging almost one million tonnes per year during the study period (**Table 1.2**). However, few studies have estimated health effects from industrial emissions in this province.[62]

Table 1.1 Total industrial emissions reported by province or territory to NPRI (2006-2012)*

Province or Territory	#of chemicals and groups of chemicals reported	*Tonnes*	Annual mean	%
Alberta	**136**	7,826,250	**1,118,036**	**29.8**
Quebec	161	4,803,173	686,168	18.3
Ontario	199	4,393,760	627,680	16.7
British Columbia	122	3,062,427	437,490	11.6
Manitoba	72	2,102,495	300,356	8.0
Saskatchewan	82	1,749,686	249,955	6.7
Nova Scotia	85	1,012,687	144,670	3.8
New Brunswick	78	645,206	92,172	2.5
Newfoundland and Labrador	63	567,074	81,011	2.2
Northwest Territories	51	87,617	12,517	0.3
Nunavut	20	37,977	5,425	0.1
Prince Edward Island	24	12,474	1,782	0.0
Yukon	5	4,290	613	0.0
Overall		26,305,116	3,757,874	100.0

*Source: Extracted from NPRI databases (2006-2012). Based on initial extraction data (before a complete evaluation of guidelines for all Provinces).

Table 1.2 Total industrial emissions reported by sector. Alberta, 2006-2012

Industrial Sector	Tonnes	%	cum.%
Conventional Oil and Gas Extraction	3,177,490	40.6	40.6
Non-Conventional Oil Extraction (including Oilsands and Heavy Oil)	1,778,269	22.7	63.3
Electricity	1,623,774	20.7	84.1
Wood Products	310,845	4.0	88.0
Chemicals	241,637	3.1	91.1
Pulp and Paper	149,343	1.9	93.0
Petroleum and Coal Prod. Refining and Manufacturing	149,012	1.9	94.9
Oil & Gas Pipelines and Storage	101,502	1.3	96.2
Cement, Lime and Other Non-Metallic Minerals	84,288	1.1	97.3
All other activities*	210,090	2.7	100.0
Total	7,826,250	100.0	

* Source: Extracted from NPRI databases (2006-2012). Based on initial data before data analysis and evaluation. Other Manufacturing, Mining and Quarrying, Aluminum, Metals (Except Aluminum and Iron and Steel) Iron and Steel, Water and Wastewater Systems, Plastics and Rubber, Waste Treatment and Disposal Transportation Equipment Mfg.). Based on initial extraction data (before a complete evaluation of guidelines for all Provinces).

1.3. Significance

Adverse birth outcomes such as preterm birth and small for gestational age significantly affect the survival of neonates and their future health. They also affect the economic burden of healthcare systems. The past observed rates of these adverse birth outcomes in Alberta showed values above the reported national average. The potential participation of a wide set of known risk factors, including maternal, social and environmental, related to the occurrence of these adverse birth outcomes in Alberta has been barely explored. Consequently, more research is needed to identify local/regional risk factors associated with preterm birth and small for gestational age. Additionally, the associations of the large industrial emissions occurred in Alberta with preterm birth and small for gestational in Alberta have not been explored. Their study may provide important insights in air pollution epidemiology. This thesis research aims to contribute to reducing, to some extent, these knowledge gaps by (i) identifying areas of high prevalence of preterm birth and small for gestational age and their related maternal risk factors,

and (ii) taking the first steps in exploring the potential associations of mixtures of air pollutants from industrial sources on adverse birth outcomes. The results of this thesis may (i) provide a better understanding of key-maternal risk factors for preterm birth and small for gestational age in Alberta, and (ii) identify harmful industrial mixtures released to air to guide future research aimed to elucidate the health effects of ambient air pollution.

Chapter 2

2. Prevalence of adverse birth outcomes, and related maternal and area-level socioeconomic status factors in Alberta, Canada, (2006-2012).

2.1. Abstract

Background. The annual crude rates of adverse birth outcomes (ABO) such as preterm birth (PTB) and small for gestational age (SGA) in Alberta has been among the highest in Canada from 2004-2011. An evaluation of the provincial distribution of ABO in conjunction with a large set of known risk factors sets the path towards understanding the ABO occurrence within the province.

Objectives. To identify areas of high PTB, SGA and low birth weight at term (LBWT) occurrence, and to estimate the prevalence and attributable fraction (AF) of known maternal risk factors and area-level socioeconomic status in those areas.

Methods: This prevalence study used data from the Alberta Perinatal Health Program including all singleton live births (2006-2012), 21 maternal risk factors, and an area-level socioeconomic status index (SES-index). Smoothed age-adjusted standardized prevalence ratios at small area level were estimated to locate areas of *low*-, *medium*- and *high*-ABO occurrence. Key sets of risk factors in the *high*-ratio areas were identified by calculating their attributable fraction (AF).

Results: A total of 330,957 births were analyzed. The highest prevalence of ABOs was predominantly in urban areas. Across the three areas of occurrence: the period PTB prevalence ranged from 4.4% to 10.9%; the period SGA prevalence ranged from 5.4% to 15.2%, and; the period LBWT prevalence ranged from 0.8% to 3.8%. The key risk factors for spontaneous-PTB were: past-preterm (AF=18%), smoking during pregnancy (AF=15%), bleeding after the 20th week (AF=11%), low SES-index (AF=9%), substance use during pregnancy (AF=5%), and gestational diabetes (AF=4%). For induced-PTB: gestational hypertension (AF=19%), past

preterm (12%), proteinuria (10%), and smoking during pregnancy (6%). For SGA: low SES-index (AF=12%), smoking during pregnancy (AF=6%), gestational hypertension (AF=4%) and past-SGA (AF=3%). For LBWT: low SES-index (AF=16%), smoking during pregnancy (AF=10%), and gestational hypertension (AF=7%).

Conclusion: The *high*-ABO prevalence areas were mainly urban. Low SES-index, smoking during pregnancy, and gestational hypertension were the main common risk factors in the *high-ratio* areas. The attributable fractions of the risk factors explored suggests that other unmeasured factors (e.g. diet, ethnicity, air pollutants) and their interactions should be investigated to better understand the occurrence of adverse birth outcomes in Alberta.

2.2. Introduction

Adverse birth outcomes (ABOs) such as preterm birth (PTB), small for gestational age (SGA) and low birth weight (LBW) are of great concern in public health. Babies born prematurely, or with fetal growth restrictions, have a lower chance of survival and a higher probability of developing chronic diseases, including physical and cognitive outcomes.[1-5] The perinatal and life-long health care needed by individuals with these health conditions significantly impact health systems. For example, premature babies in Canada cost approximately $587 million over the first ten years of life[6] and decrease the human capital over the life course.[7] Although considerable efforts have been made by health authorities to reduce the ABO occurrence and related health impacts[8,9] the current prevalence of ABOs is still a public health concern.[2,10]

The control and reduction of the ABOs occurrence is complicated due, in part, to their multifactorial nature. The mechanisms that regulate the timing of birth and the quality of the fetal growth are susceptible to the maternal, social and natural conditions relating to the fetus.[11] Risk-factors and prevalence-based epidemiological approaches have contributed to identify risk factors for ABOs. The first, has shown that a large variety of individual, social, and environmental factors have been associated with PTB, SGA and LBW.[12-16] Examples include, maternal age (too young or too old), low maternal body mass index, smoking and alcohol consumption,[2] obstetric history,[16] low income or education,[17] ethnicity,[18] the role of urban and rural context,[19,20] and exposure to urban air pollutants.[14,21-23] The second, has helped identify those sets of factors that result in the greatest harm to local populations,[24] and are useful in configuring target interventions,[25] helping to understand to what extent risk factors may explain ABOs' occurrence, identifying potential risk factor interactions for further research, and hypothesizing about other unmeasured but probable factors affecting ABOs.

In Alberta, the occurrence of SGA and PTB has been consistently above the national average during the last decade. The average SGA crude rate in Canada from 2004 to 2008 was estimated to be 8% (95%CI: 7.9-8.0), whereas in Alberta it was 8.7% (95%CI: 8.6-8.8).[26] Similarly, the national PTB crude rate was estimated to be 7.9% (95%CI: 7.9-8.0), whereas in Alberta it was 8.8% (95%CI: 8.7-8.9)[26]. More recently (2006-2011), the national SGA and PTB crude rates have decreased, remaining high in Alberta.[27,28] Previous studies on the prevalence of maternal risk factors in Alberta reported a high prevalence of maternal prenatal smoking (26%) and advanced maternal age (35 or older) (12%).[29,30] However, they did not include data describing other maternal risk factors such as gestational diabetes, or gestational hypertension. Thus, exploring how the prevalence of ABOs and of an extensive range of relevant risk factors varies within the province of Alberta could help us understand to what extent known risk factors could explain their occurrence.

We carried out a prevalence study in Alberta to (1) quantify the occurrence of PTB, SGA, and LBWT (low birth weight at term) at small area-level resolution; (2) estimate the prevalence of known maternal risk factors and the prevalence of cases by area-level socioeconomic status in three levels of occurrence: low, moderate (average) and high; and (3) identify the relatively more important set of maternal risk factors in areas with high ABO occurrence. This study will inform future research since is part of an ongoing project that investigates the geographic variability of ABO and maternal, social and environmental factors in Canada.[31]

2.3. Methods

2.3.1 Study design and definitions

We carried out a prevalence study of PTB, SGA, LBWT in Alberta, Canada, including all singletons live births born in the province between 2006 and 2012. We defined PTB as newborns

less than 37 weeks and zero days of gestational age; SGA as newborns below the tenth percentile weight from a sex-age specific Canadian-population reference;[32] and LBWT as newborns weighing less than 2500 grams at term (gestational age equal or higher than 37 weeks and 0 days).

2.3.2 Birth data and area-level socioeconomic index

Birth data and maternal information were extracted from the birth registry of the Alberta Perinatal Health Program, which covers the entire population of births in Alberta, whether in hospital or planned home births with a registered midwife. Anonymous data of every singleton live birth with gestational age between 22 and 42 completed weeks were analyzed. Our data included maternal age, six-character postal code of residence at the time of birth, newborns' birth date, birth weight, type of labour (spontaneous, induced, no-labour, unknown) and gestational age at delivery in completed weeks. Additionally, we included 21 maternal variables from the following three categories: current pregnancy (i.e., gestational hypertension/diabetes, smoking, substance use, proteinuria, anemia, bleeding anytime, blood antibodies), pre-pregnancy (i.e., pre-existing diabetes/hypertension, low/high mothers' weight), and past obstetrical history (i.e., past preterm/SGA/abortions/stillbirths, parity, neonatal deaths) (Supplementary Table 2.1 shows the definitions for the 21 maternal variables). We identified spontaneous and induced PTB as indicated by the type of labour registered in the data registry.

We used the Canadian socioeconomic status index (SES-index) developed by Chan *et al*.[33] as a proxy for area-level socioeconomic status, since no individual socioeconomic data were included in the APHP database. This index incorporates data from the 2006 National Census including: educational certificate, employment status, income, marital status, owning a home or renting, transport mode, year of home-construction, and the aboriginal status or human

developmental index of the individuals' country-origin. The SES-index was previously found to perform well in capturing gradients of the prevalence of adverse pregnancy outcomes[33]. It is reported in both continuous and quintile values at the dissemination area (DA) level, i.e., census geography areas with a population of 400 to 700 persons.[34] A low SES-index value, or quintile, indicates low socioeconomic status.

2.3.3 Geo-coding

The geographical coordinates of the centroids of the six-character postal codes of the mothers' residences were assigned to the corresponding DA. There were 5,357 DAs in Alberta based on the 2006 geographical framework. Because the Statistic Canada Postal Code Conversion File for 2006 did not include all postal codes instituted after 2006, a vector overlay of the postal code locations[35] with the DA boundary file[36] was performed to capture, at the DA level, all postal codes included in the study. We identified the type of DA as urban, rural, or neither urban nor rural, by using the attribute information product GeoSuite provided by Statistics Canada as the standard to identify geographical characteristics of georeferenced data.[37] For the Census year 2006, Statistics Canada classified an area as urban as those with a minimum population concentration of 1,000 persons and a population density of at least 400 persons per square kilometer; otherwise, it was classified as rural.[37]

2.3.4 Statistical Analysis

The prevalence of SGA, PTB and LBWT for the province and by type of location (urban/rural), maternal age groups, and SES-index quintiles was calculated. Maternal age groups were based on the age categories used by the Canadian Institute of Health Information to disseminate perinatal indicators:[38] (1) less than 20 years; (2) 20-34 years; (3) 35-39 years; and (4) +40 years old. The 20-34 age group was used as reference to study differences in ABO's

prevalence by maternal age (we applied independent proportions tests with Bonferroni correction of p-values).

To identify low, average, and high-ABO occurrence areas, we (1) estimated age-adjusted standardize prevalence ratios (SPRs) of SGA, PTB, and LBWT per DA; and (2) smoothed the SPRs by applying an empirical Bayesian approach based on a Poisson random intercept regression model, which accounts for unstable proportions existing in DAs with low numbers of births and cases.[39] SPRs by DA were based on the age-specific group proportion per ABO in the whole province and the age group distribution in each DA (see Appendix 1). We labeled *low*- and *high*-ratio areas where the smoothed SPRs were two standard deviations below or above the corresponding SPR average (≈1). The DAs with smoothed SPRs between the *low*- and *high*-ratio areas were labeled as *middle*-ratio areas. We created maps for displaying the *low-, middle*- and *high*-ratio areas of SGA, PTB and LBWT at the DA-level. The use of smoothed SPRs preserved individual's privacy when mapped.

We identified key risk factors in areas of *high* occurrence by ranking them according to their attributable fraction (AF). AF values were calculated according to methods described elsewhere.[25,40] The AF combines the associative effect (e.g., relative risk or odds ratio) of a specific risk factor and the proportion of the exposed population to that factor to quantify the proportion of the disease burden among the exposed people that is attributed to a specific risk factor (if a causal effect exists and it is not distorted by any bias).[41] By calculating AFs, we assumed that all selected risk factors were causative of the studied ABO. The odds ratios (ORs) of the maternal risk factors on Spontaneous-PTB, Induced-PTB, SGA, and LBWT, were estimated by applying a DA-specific logistic random-intercept model. This model accounts for the exposure to similar unmeasured conditions that are potentially linked to the health outcomes in mothers living in the same DA. We reported adjusted odds ratios (adjORs); potential

confounders were identified by creating directed acyclic graphs.[42] The associations of the ABOs with SES-index quintiles and maternal age groups were estimated by logistic regression by using as reference the highest SES-index quintile (most socially-advantaged areas) for the former, and the 20-34 age group for the latter. We selected those risk factors with statistically significant positive associative effect (adjORs > 1) to estimate their prevalence in the *low*-, *middle*-, and *high*-ratio areas. We tested whether the proportions in the *low*- and *high*-ratio areas were statistically equal compared with their corresponding proportions in the *middle*-ratio areas by applying independent proportions tests (with Bonferroni correction of p-values). Reported confidence intervals are at 95% and are referred to as CI to facilitate the reading of results. We tested the distribution of cases across the SES-index quintiles and maternal age groups by applying chi-square homogeneity test. We performed statistical analysis by using Stata (v.13)[43] and SPSS (v.22)[44], and made maps by using ArcGIS (v.10.4).[45]

2.3.5 Ethics approval

The study received ethics approval from the University of Alberta Research Ethics Board and institutional approval from the Alberta Perinatal Health Program (APHP).

2.4. Results

The total number of births registered in Alberta from 2006 to 2012 was 349,762. Ninety-six percent (n=334,894) of the births corresponded to singleton live births with a gestational age between 22 and 42 completed weeks. Approximately 0.5% of these births (n=1,653) had an invalid postal code and were excluded from the analysis. Births were registered in 4,422 of the current 5,357 DAs in Alberta. Ninety-nine percent (n=4,396) of those, matched as urban or rural location and had an SES-index value. Therefore, we included a total of 330,957 singleton live births with a gestational age between 22 and 42 weeks for further analysis (Figure 2.1). Table 2.1

shows the corresponding numbers and proportions of the variables included in the study. Most births occurred in urban locations (88.34%), in the mothers aged 20 to 34 (79.53%), and in the highest two SES-index quintiles (47.63% *vs.* 33.77% in the combined SES-index quintiles 1 and 2). The most prevalent conditions during pregnancy were: smoking (16.20%), gestational hypertension (5.25%), gestational diabetes (5.03%), bleeding before the 20th week (5.06%), and bleeding after the 20th week (3.26%). Mothers' weight > 91 kg and other medical disorders were the pre-pregnancy conditions most relevant (9.21% and 7.25%, respectively). Past preterm and past abortions were the past obstetrical conditions more frequent (4.46% and 4.20%, respectively).

2.4.1 Preterm Birth (PTB)

Prevalence of PTB. Table 2.2 shows the results of this section. The period prevalence of PTB in the province was estimated at 6.82% (CI: 6.49, 7.15). From the PTB cases, 68% were spontaneous and 32% induced. Among the spontaneous labors, the PTB prevalence was 6.27% (CI: 5.84, 6.69); whereas among the induced labors, the PTB was 6.59% (CI: 5.96, 7.22). Mothers over 40 years old had a statistically higher PTB prevalence (8.95%; CI:6.94, 10.96) compared with the mothers aged 20-34 (6.54%; CI: 6.17, 6.91) (p=0.004). The prevalence of PTB was statistically higher in the three lowest SES-index quintiles compared with the highest SES-index quintile: the PTB prevalence ranged from 8.00% (CI: 7.77, 8.23) in the lowest to 6.11% (CI:5.95, 6.27) in the highest quintile.

The PTB prevalence in the *low*-, *middle*-, and *high*-ratio areas was: 4.44% (CI: 3.35, 5.53), 6,72% (CI: 6.36, 7.08), and 10.95% (CI: 9.76, 12.13), respectively. Eighty five percent of the *high*-PTB ratio areas were urban and mainly located within 10 of the 14 census metropolitan areas (CMAs) that exist in Alberta (Table 2.2, Figure 2.2).

PTB's risk factors: prevalence and key factors. Table 2.3 shows the prevalence of the positively associated maternal risk factors with PTB, across the three areas of occurrence (*low-, middle,* and *high*-), as well as the proportion of PTB cases by SES-index quintiles and maternal age-groups. The adjusted-ORs for all variables studied are presented in the Supplementary Table 2.2.

In the case of spontaneous PTB, comparisons between the *middle*- and the *high*-PTB ratio areas showed differences (statistically significant) mainly related to: (i) an increased prevalence of smoking during pregnancy from 24.2% (CI: 23.4, 25.0) to 36.9% (CI: 34.4, 39.3), and substance use during pregnancy from 6.3% (CI: 5.8, 6.8) to 11.4% (CI: 9.8, 13.0); (ii) more proportion of PTB cases in the lowest SES-index from 17.6% (CI: 16.9, 18.3) to 39.3% (CI: 36.9, 41.8); and a more proportion of cases in the age group < 20 from 6.3% (CI: 5.8, 6.8] to 8.7% [CI: 7.2, 10.1). Bleeding after the 20th week and gestational diabetes were maternal conditions with homogenous prevalence across the areas with values around 13% and 6% respectively. The factors with the highest AF values were past-preterm (17.6%), smoking during pregnancy (14.7%), bleeding after the 20th week (10.9%) and living in a low SES-index status area (9.3%) (Table 2.4).

In the case of the induced PTB, comparisons between the *middle*- and the *high*-PTB ratio areas showed differences (statistically significant) related to: (i) an increased prevalence of smoking during pregnancy from 19.1% (CI: 17.9, 20.1) to 25.9% (CI: 22.6, 29.2), and substance use during pregnancy from 3.5% (CI: 3.0, 4.1) to 6.1% (CI: 4.3, 7.8); (ii) more proportion of PTB cases in the lowest SES-index quintile from 16.0% (CI: 15.0, 17.0) to 36.3% (CI: 32.7, 40.0); and a more proportion of cases in the mothers aged < 20 years from 4.3% (CI: 3.7, 4.8) to 6.8% (CI: 4.9, 8.7). Gestational hypertension and proteinuria were noticeably prevalent across the three areas of PTB occurrence (≈26% and ≈14%, respectively), followed by gestational

diabetes (≈10%), and bleeding before or after the 20th week (≈7%). The key factors with the highest AF values were gestational hypertension (18.5%), past preterm (11.6%), and proteinuria (10.2%) (Table 2.4).

2.4.2 Small for gestational age (SGA)

Prevalence of SGA. Table 2.5 shows the results of this section. The prevalence of SGA during the study period was 8.92% (CI:8.59, 9.25). In urban settings, the prevalence of SGA was higher compared with the rural ones (9.20% [CI:8.59, 9.25] *vs* 6.78% [CI:5.82, 7.77]; p< 0.001). No significant differences among SGA prevalence according to maternal age groups were detected when compared with the age group 20-34 (8.88% [CI: 8.52, 9.24]). The prevalence of SGA was statistically higher in the four lowest SES-index quintiles compared with the highest SES-index quintile: the SGA prevalence ranged from 10.56% (CI: 10.30, 10.82) in the lowest to 7.78% (CI:7.60, 7.96) in the highest quintile.

The prevalence of SGA in the *low*-, *middle*- and *high*-ratio areas was: 5.44% (CI: 4.36, 6.52), 8.81% (CI: 8.45, 9.17), and 15.23% (CI: 14.01, 16.45), respectively. Ninety-eight percent of the *high*-SGA ratio areas were urban and mainly located within five of the 14 of the current census metropolitan areas (CMAs) in Alberta (Table 2.5, Figure 2.3).

SGA's risk factors: prevalence and key factors. Table 2.6 shows the prevalence of the positively associated maternal risk factors with SGA, across the three areas of occurrence, as well as the proportion of SGA cases by SES-index quintiles and maternal age groups. The adjusted-ORs for all variables studied are presented in the Supplementary Table 2.3.

Comparisons between the *middle*- and the *high*-SGA ratio areas showed, interestingly: (i) a decrease in the prevalence of maternal risk factors during pregnancy mainly for smoking from 23.3% (CI: 22.7, 23.8) to 14.3% (CI: 13.1, 15.5), and substance use from 4.3% (CI: 4.1, 4.6) to

2.3% (CI: 1.8, 2.8); (ii) an small increase in the prevalence of mothers' weight <45 kg from 1.7% (CI: 1.6, 1.9) to 2.6% (CI: 2.0, 3.1); (iii) a more proportion of cases in the lowest SES-index quintile from 15% (CI: 14.5, 15.4) to 45.7% (CI: 44.0, 47.4). By contrast, smoking and substance use during pregnancy were notably higher in the *low*-ratio areas compared with the *middle*-ratio areas: their corresponding prevalence were: 34.5% (CI: 32.2, 36.7), and 10.4% (CI: 8.9, 11.8), respectively. Importantly, the prevalence of gestational hypertension was homogenous across the areas with values around 8.5%. The factors with the highest AF values were: living in areas with the lowest SES-index (11.6%), smoking during pregnancy (5.7%), gestational hypertension (4%), past-SGA (2.8%), and pre-pregnancy mothers' weight <45 kg (1.8%) (Table 2.4).

2.4.3 Low birth weight at term (LBWT)

Prevalence of LBWT. The prevalence of LBWT during the study period was 1.65% (CI: 1.31, 1.99). No significant differences among the LBWT prevalence according to the maternal age groups were detected compared to the age group 20-34. The prevalence of LBWT was statistically higher in the three lowest SES-index quintiles compared with the highest SES-index quintile: the LBWT prevalence ranged from 2.12 % (CI: 1.99, 2.24) in the lowest to 1.40% (CI: 1.32, 1.48) in the highest SES-index quintile. (Table 2.7).

The prevalence of LBWT in the *low*-, *middle*- and *high*-ratio areas was: 0.76% (CI: 0.00, 1.98), 1.51% (CI: 1.14, 1.88), and 3.77% (CI: 2.64, 4.90), respectively (Table 2.7, Figure 2.4). Ninety-eight percent of the *high*-ratio areas were urban and mainly located within eight of the 14 census metropolitan areas (CMAs) defined in Alberta in the 2006 geographical framework (Table 2.7).

LBWT's risk factors: prevalence and key factors. Table 2.8 shows the prevalence of the positively associated maternal risk factors with LBWT across the three areas of occurrence, as

well as the proportion of LBWT cases by SES-index quintiles and maternal age groups. The adjusted-ORs for all variables studied are presented in the Supplementary Table 2.4.

Comparisons between the *middle*- and the *high*-LBWT ratio areas showed: (i) a lightly but significant decrease in the prevalence of smoking during pregnancy from 2.6% (CI: 2.1, 3.1) to 3.7% (CI: 2.6, 4.8); and (ii) a more proportion of cases in the lowest SES-index quintile from 17.9% (CI: 16.7, 19.0) to 32.2% (CI: 29.5, 35.0). The prevalence of gestational hypertension was homogenous (≈ 12%) across the three areas of occurrence (Table 2.8).

The factors with the highest AF values were: smoking during pregnancy (9.7%), living in the two lowest SES-index areas (9.7% for quintile 1, and 5.9% for quintile 2), gestational hypertension (7.2%), past-SGA (4.8%), pre-existing other medical disorders (3.2%), past-preterm (2.9%) and pre-pregnancy mothers' low weight (2.9%) (Table 2.4).

2.5. Interpretation

This study showed that the areas with the highest statistically-significant ratios of preterm birth (spontaneous and induced), small for gestational age, and low birth weight at term among singletons live births, occurred predominantly in urban locations, where 88% of the live births occurred. Alberta has urbanized more than other provinces in Canada over the last five decades,[46] and around 80% of its population lives in urban settlements.[47] These results are consistent with other reports indicating an elevated SGA occurrence in urban settings in Canada[48]; whereas they contrast with studies that reported a higher incidence of ABO in rural Canada. For example, Auger and collaborators[19] reported higher rates of SGA, PTB and LBW in the rural locations of Quebec, associated with low education level and after excluding aboriginal population. Luo and collaborators[49] reported higher rates of SGA in rural places in Quebec, associated with the degree of rural isolation where the access to optimal neonatal care could be

scarce. These contradictory findings support the multifactorial nature of ABO and reinforce the need to evaluate populations within distinct geographical boundaries.

The maternal risk factors and low area-level socioeconomic status for spontaneous-PTB, induced-PTB, SGA and LBWT identified in this study, are consistent with findings from other studies.[13,15,16,50-52] For example, smoking during pregnancy and low socioeconomic status have been reported as important contributors to the three studied ABO by their prevalence and associated risk (or odds) ratios, while other factors (e.g., past-SGA, bleeding after the 20th week) that have an high-risk ratio are, generally, less prevalent in the population. Thus, the prevalence of smoking during pregnancy, that was estimated at 16%, keeps this factor as an important contributor to ABO, even though its prevalence has reduced over time when compared to the 26% reported in 1994 to 1996.[29] It is important to note that in addition to lifestyle factors and socioeconomic status, the prevalence of pregnant women aged 35 or older (≈15%) has increased with respect to the 11.8% reported in Alberta in 1994 to1996,[29] but its contribution to ABOs cases was unnoticeable. Another maternal factor that deserves mention by its prevalence is gestational hypertension. This factor has remained relatively stable (5 to 6%) over time in Alberta as reported for the Calgary Health Region from 1994 to 2005.[53]

With respect to PTB, the high number of maternal risk factors significantly affecting PTB emphasizes the differing nature of the pathological processes involved in spontaneous and induced PTB.[2,13] For example, proteinuria was a significant risk factor only for induced-PTB; on the contrary, smoking and substance use during pregnancy, bleeding after the 20th week and gestational diabetes were relevant risk factors for spontaneous PTB.

In the case of SGA, two interesting patterns were observed. The first was related to the high prevalence of smoking and substance use during pregnancy in the *low*-ratio areas, where the prevalence of young mothers (<20 years old), and maternal pre-pregnancy weight >91 kg in low

SES-index were 12% and 13%, respectively (data not shown in the results), and above the corresponding averages (4.5% and 9.2% respectively). Although a global reduction in tobacco use by women in high-income countries from 2007 to 2013 has been reported by the World Health Organization,[54] an increment of smoking during pregnancy in young girls has been observed in low and medium-high income countries.[55] On the other hand, the protective effect of having an excess of pre-pregnancy weight in combination with excessive gestational weight gain on having small for gestational age babies in non-Hispanic women has been reported elsewhere.[56] However, a high prevalence of maternal pre-pregnancy weight > 91 kg, which has been previously reported in rural areas across Canada,[66] in combination with gestational diabetes are associated with large-for-gestational-age (weights at or above the 90th percentile of a reference according to gender and gestational age). Unfortunately, we did not include large-for-gestational-age in this study despite its known associated increased risk of intrauterine death or developing obesity, diabetes and other diseases (i.e., cancer) later in life.[67] These results suggest that the interplay among maternal age, weight, and smoking and socioeconomic status must be further studied in conjunction with other factors such as diet and ethnicity. The second pattern relates to the high ratios for SGA exclusively observed in five metropolitan areas including Calgary and Edmonton. The concentration of elevated SGA occurrence in the main census metropolitan areas of Alberta may be related to other unmeasured factors that may deserves attention. For example, demographical factors such as immigrant populations continuously arrive to Alberta. Immigration has been growing in Alberta for the last decade (between 2000 and 2007, Alberta received 7% of the total immigrants to Canada who have concentrated mainly in Calgary and Edmonton).[57] The concentration of South Asian and Chinese populations had considerable growth in Calgary and Edmonton from 2006 to 2011 according to researchers[58,59] who have analyzed the geographic changes of ethnic enclaves in Canadian cities over time. In

this regard, one potential explanation about having small babies from recent immigrants relies on the intergenerational influences of a small maternal structure with intrauterine and infant growth failure after adjusting for socioeconomic status.[60,61]

In the case of LBWT, the low rates we are reporting (<2%) are due to focusing on LBW at term to avoid the inclusion of PTB cases with LBW. Despite the low number of LBWT cases analyzed, it is important to highlight the co-occurrence of significant higher prevalence of mothers' weight <45 kg in combination with low socioeconomic status in the *high*-ratio areas, which may suggest that the interaction between these conditions deserve further exploration.

Finally, it is important to note that single maternal risk factors explored occurred in, at most, 18.5% of cases in the exposed group. For the area-level socioeconomic status, at most 12% of cases in the exposed group occurred in the lowest status. By considering that all the maternal and area-level risk factors did no act independently, and that other aspects affected the estimates of AF values (e.g., other non-accounted sources of bias), it may be incorrect to sum their AF values to estimate to what extent the complete set of those risk factors account for the ABO cases. Currently, attributable fractions estimation is an issue of considerable attention by theoretical epidemiologists and cautions must be taken in using AFs and in interpreting the resulted values.[65] However, it is apparent that they would not explain the totality of the ABO cases in the exposed group. It is probable that other unmeasured factors (e.g., diet, immigration status, air pollution) and their interactions may play a relevant role, which need to be elucidated to better understand the ABO occurrence in the province.

2.6. Strengths and limitations

A significant strength of this study is the use of the birth registry of the Alberta Perinatal Health Program, which covers the entire population of births in Alberta, whether in hospital or

planned home births with a registered midwife, and its quality in registering relevant mother's information about the past obstetrical history, pre-existing medical conditions and pregnancy-related health events. Additionally, the use of the Dissemination Areas for aggregating cases may ensure future comparability with other related research since they are stable geographical units. Besides, these areas are the smallest standard geographic boundaries in Canada for which all census data are disseminated, which could facilitate to combine health data with socioeconomic information when geographical analysis is required. However, it is important to emphasize that estimations of rates (e.g., SPR) are affected by the size and shape of the geographical units chosen for aggregating the data[63] and by the size of populations within the areas.[64] In this regard, the use of smoothing methods of the age-standardized prevalence ratio may produce more precise estimates of occurrence.[39]

Limitations of this study are related to (i) the absence of data about other important maternal risk factors for ABOs such as nutritional habits, and ethnicity; (ii) potentially inaccurate data provided by the mothers in their historical data; (iii) probable underestimation of smoking and substance use during pregnancy due to these information is self-reported at the time of labour and delivery, being probable that some mothers do not admit to smoking and/or substance use because of social pressures; (iv) over-representation of new and second generation Canadians in certain DAs who may have higher rates of SGA using standardized Canadian charts[62]; (v) misclassification bias in urban/rural locations of the mothers' postal codes having babies after 2006, since we based our geocoding on the 2006 geographical framework when the SES-index was created; and (vi) probable overestimation of the prevalence of maternal risk factors related to the past-obstetrical history (e.g., past-PTB) and pre-medical conditions (e.g., pre-diabetes) - affecting the estimation of their corresponding related odds ratios- since I was unable to identified mothers having more than one baby during the study period by using de-identified

maternal data. These limitations must be considered for future studies aimed to configuring target interventions.

2.7. Conclusions

Our study indicated that the areas with high occurrence in SGA, PTB, and LBWT in Alberta were predominantly urban. Low area-level socioeconomic status, smoking during pregnancy, and gestational hypertension are relevant conditions for the ABO occurrence in the province. The high prevalence of smoking and substance use during pregnancy observed in the low-ratio areas of SGA may indicate that the solely prevalence of these factors is not enough to explain the potential occurrence of SGA. Additionally, the attributable fractions of the maternal risk factors explored and area-level SES index, suggests that other unmeasured factors (e.g. diet, ethnicity, air pollutants) and risk factor interactions could be investigated for better understanding the occurrence of adverse birth outcomes in Alberta.

2.8. Acknowledgments

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Table 2.1 Prevalence (%) of the variables included in the study. Alberta, 2006-2012**.**

Category	Subcategory/variable	n	%[1]
Type of location			
	Urban	292,357	88.34
	Rural	38,600	11.66
	Province	330,957	100.00
Age groups			
	< 20	15,079	4.56
	20 - 34	263,218	79.53
	35 - 39	43,976	13.29
	≥ 40	8,684	2.62
SES-index quintiles			
	1 (most disadvantaged)	52,379	15.83
	2	59,385	17.94
	3	61,548	18.60
	4	74,700	22.57
	5 (most advantaged)	82,945	25.06
Current pregnancy			
	Smoker	53,174	16.20
	Gestational hypertension	17,242	5.25
	Bleeding before the 20th week	16,617	5.06
	Gestational diabetes	16,507	5.03
	Bleeding after the 20th week	10,700	3.26
	Substance use	10,746	3.25
	Proteinuria	6,520	1.99
	Anemia	2,422	0.74
	Blood antibodies	1,102	0.34
Pre-pregnancy			
	Mothers' weight > 91kg	30,235	9.21
	Pre-existing other medical disorders	23,982	7.25
	Pre-existing diabetes	3,199	1.00
	Pre-existing hypertension	2,775	0.84
	Mothers' weight < 45kg	2,041	0.60
Past obstetrical history			
	Past preterm	14,626	4.46
	Past abortions	13,779	4.20
	Past stillbirths	3,182	0.97
	Past SGA	2,268	0.69
	Neonatal deaths	1,784	0.54

[1]Most percentages are based in N =330,957, but denominator could vary for some variables with missing values.

Table 2.2 Prevalence (%) of preterm birth (PTB). Alberta, 2006-2012.

Category	subcategory/variable	cases (#)	(%)	95%CI
by Type of area				
	Province	22,560	6.82	[6.49, 7.15]
	Urban	19,924	6.81	[6.46, 7.16]
	Rural	2,636	6.83	[5.87, 7.79]
by PTB-type				
	Spontaneous	12,374	6.27	[5.84, 6.69]
	Induced	5,909	6.59	[5.96, 7.22]
by Age groups				
	< 20	1,187	7.87	[6.33, 9.40]
	20 - 34	17,215	6.54	[6.17, 6.91]
	35- 39	3,381	7.69	[6.79, 8.59]
	≥ 40	777	**8.95**[1]	[6.94, 10.96]
by SES-index				
	1 (most disadvantaged)	4,191	**8.00**[2]	[7.77, 8.23]
	2	4,186	**7.05**[2]	[6.84, 7.26]
	3	4,245	**6.91**[2]	[6.71, 7.11]
	4	4,862	6.51	[6.33, 6.69]
	5 (most advantaged)	5,067	6.11	[5.95, 6.27]
by PTB-ratio areas				
	Low [SPR = 0.88]	1,381	4.44	[3.35, 5.53]
	Middle [SPR = 1.00]	18,519	6.72	[6.36, 7.08]
	High [SPR = 1.13]	2,660	10.95	[9.76, 12.13]
The *high*-ratio areas predominantly occurred in the following CMAs[3]				
	Lethbridge	19	16.96	[10.01, 23.92]
	Wood Buffalo	16	14.29	[7.80, 20.77]
	Edmonton	901	12.55	[11.78, 13.31]
	Canmore	14	12.28	[6.26, 18.31]
	Grande Prairie	33	11.19	[7.59, 14.78]
	Brooks	22	10.95	[6.63, 15.26]
	Calgary	919	10.30	[9.67, 10.93]
	Okotoks	36	9.47	[6.53, 12.41]
	Wetaskiwin	30	9.35	[6.16, 12.53]
	Red Deer	52	8.97	[6,64, 11.29]

[1] significant higher vs. the 20-34 age category ($p<0.0167$ after Bonferroni's correction).
[2] significant higher vs. the highest SES-index quintile ($p<0.0125$ after Bonferroni's correction).
[3] exclusively the high-ratio areas with more than 5 cases were reported because of confidentiality issues

Table 2.3 Prevalence (%) of the positively associated maternal variables with spontaneous- or induced-PTB, and proportion of cases by SES-quintiles and age groups, in the *low*-, *middle*-, and *high*-PTB ratio areas. Maternal variables ordered by the prevalence in the *middle*-ratio areas of spontaneous cases within maternal-categories. Alberta, 2006-2012.

	Spontaneous PTB (12,374)			Induced PTB (5,909)		
	low (761)	middle (10,126)	high (1,487)	low (342)	middle (4,890)	high (677)
Category subcategory/variable	%	%	%	%	%	%
Current pregnancy						
Smoking during pregnancy	**14.6**	24.2	**36.9**	**14.4**	19.1	**25.9**
Bleeding after the 20th week	14.3	13.3	12.9	5.6	6.7	6.8
Bleeding before the 20th week	10.6	9.8	**6.2**	8.5	7.6	6.2
Gestational diabetes	6.6	6.6	6.9	8.8	9.9	10.8
Substance use during pregnancy	**3.3**	6.3	**11.4**	2.6	3.5	**6.1**
Gestational hypertension	2.9	3.2	**2.2**	24.9	27.6	28.5
Proteinuria	1.7	1.2	0.5	15.5	13.7	15.4
Anemia	0.6	1	**1.7**	2.1	1.3	1.2
Blood antibodies	0.8	0.4	0.5	1.5	1	1.3
Pre-pregnancy						
Pre-existing other medical disorders	8.9	8.9	8.8	14.9	13.3	11.2
Pre-existing diabetes	2.1	1.9	2.4	2.9	3	3.8
Mothers' weight < 45kg	0.4	1.1	1.4	0.6	1	1.6
Pre-existing hypertension	0.5	0.9	0.7	4.7	4	2.8
Past obstetrical history						
Past-preterm	17.8	18.2	**20.8**	13.5	11.7	**14.6**
Past-abortions	4.4	5.9	**7.6**	4.7	4.8	5.3
Past-stillbirths	2	2.1	**2.9**	2.1	2.4	3.4
Neonatal deaths	1.9	1.4	1.6	1.2	0.9	**1.6**
Past-SGA	1.1	0.8	0.9	2.4	1.7	1.3
SES-index quintiles						
1 (most disadvantaged)	3.2	17.6	**39.3**	4.7	16	**36.3**
2	10.1	19.6	14.1	9.9	20	16
3	19.2	18.6	19.0	17.8	19	16.4
4	21.6	22.2	18.8	23.4	21.5	21.1
5 (most advantaged: reference)	46.0	22.0	8.7	44.2	23.5	10.2
Age group (in years)						
< 20	5.4	6.3	**8.7**	5.3	4.3	**6.8**
20 - 34	80.8	77.6	77.7	77.2	77.7	77.8
35 - 39	11.3	13.6	10.9	13.7	14.8	10.8
≥ 40	2.5	2.6	2.7	3.8	3.2	4.6

In parentheses, the number of cases by area of occurrence. In green, the percentages significantly lower; in yellow, the percentages significantly higher. Both vs. the corresponding proportions in the middle-ratio areas (Level of significance was 0.003 after Bonferroni's correction). The distribution of PTB cases across the SES-index categories was not homogenous (Chi-square test of homogeneity: $p < 0.001$). The distribution of PTB cases across the age categories was not homogenous (Chi-square test of homogeneity: $p = 0.001$).

Table 2.4 Total attributable fractions (AF in %) for variables positively associated with the adverse birth outcomes. Alberta, 2006-2012.

Category	Risk factors	S-PTB[1]	I-PTB[2]	SGA	LBWT
Current Pregnancy	Smoking during pregnancy	**14.7**	5.8	5.7	**9.7**
	Bleeding after the 20th week	**10.9**	4		
	Substance use during pregnancy	4.5	0.3	0.3	1.4
	Gestational diabetes	4.2	1.9		1
	Bleeding before the 20th week	3.4	2		0.5
	Gestational hypertension	1.1	**18.5**	3.9	**7.2**
	Anemia	0.5	0.5		
	Blood antibodies	0.3	0.8		0.24
	Proteinuria	NA	**10.2**	0.72	1.1
Pre-pregnancy	Pre-existing other medical disorders	3.3	4.1	1.1	3.2
	Pre-existing diabetes	1.8	2.2		
	Mothers weight < 45kg	0.5	0.7	1.8	2.9
	Pre-existing hypertension	0.5	1.8	0.3	0.6
Past-obstetrical history	Past preterm	**17.6**	**11.6**	0.7	2.9
	Past abortions	**2.8**			
	Past stillbirths	**2.0**	**1.8**	1.2	0.63
	Neonatal deaths	**1.1**	**0.9**	0.5	0.2
	Past-SGA	0.3	0.7	2.8	4.8
SES-index quintiles	SES-index 1 (most disadvantaged)	**9.3**	3.9	**11.6**	**9.7**
	2	**1.7**		2.8	5.9
	3	**2.0**		1.8	1.6
	4	**1.6**		1.6	
	5 (most advantaged: reference)				
Age group (in years)	< 20	2.3		0.3	
	20-34 (reference)				
	35- 39	1.5	1.41		
	≥ 40	0.8	0.86	0.1	0.6

Empty cells = not applicable because OR is < 1.0 or because it is a reference condition

[1] S-PTB = Spontaneous-PTB

[2] I-PTB = Induced-PTB

Table 2.5 Prevalence (%) of small for gestational age in Alberta, 2006-2012.

Category	n (# cases)	%	95%CI
by Type of area			
Province	29,509	8.92	[8.59, 9.25]
Urban	26,893	9.20	[8.85, 9.55]
Rural	2,616	6.78	[5.82, 7.77]
by Age groups			
< 20	1,453	9.64	[8.12, 11.16]
20 - 34	23,364	8.88	[8.52, 9.24]
35 - 39	3,854	8.76	[7.87, 9.65]
≥ 40	838	9.65	[7.65, 11.65]
by SES-index			
1 (most disadvantaged)	5,530	**10.56**[1]	[10.30, 10.82]
2	5,638	**9.49**[1]	[9.25, 9.73]
3	5,492	**8.92**[1]	[8.70, 9.15]
4	6,399	**8.57**[1]	[8.37, 8.77
5 (most advantaged)	6,450	7.78	[7.60, 7.96]
by SGA-ratio areas			
Low [SPR = 0.78]	1,703	5.44	[4.36, 6.52]
Middle [SPR = 1.01]	24,458	8.81	[8.45, 9.17]
High [SPR = 1.28]	3,348	15.23	[14.01, 16.45]
The *high-ratio* areas predominantly occurred in the following CMAs:[2]			
Edmonton	430	17.15	[15.67, 18.62]
Red Deer	19	17.12	[10.11, 24.12]
Brooks	26	15.85	[10.26, 21.44]
Wood Buffalo	16	15.24	[8.36, 22.11]
Calgary	2,691	14.91	[14.39, 15.43]
Overall	3,182		

[1] significant higher vs. the highest SES-index quintile ($p<0.0125$ after Bonferroni's correction).

[2] exclusively the high-ratio areas with more than 5 cases were reported because of confidentiality issues

Table 2.6 Prevalence (%) of the positively associated maternal variables with SGA, and proportion of cases by SES-quintiles and age groups, in the *low*-, *middle*-, and *high*-SGA ratio areas. Maternal variables ordered by the prevalence in the *middle*-ratio areas within maternal-categories. Alberta, 2006-2012.

Category	variable/subcategory	Low (1,703) %	Middle (24,458) %	High (3,348) %
Current pregnancy				
	Smoking during pregnancy	**34.45**	23.27	**14.27**
	Substance use during pregnancy	**10.39**	4.33	**2.27**
	Proteinuria	**4.47**	3.53	**2.20**
	Gestational hypertension	8.46	8.23	9.24
Pre-pregnancy				
	Pre-existing other medical disorders	8.04	8.38	7.41
	Pre-existing hypertension	1.53	1.10	0.96
	Mothers' weight < 45Kg	1.31	1.73	**2.59**
Past obstetrical history				
	Past preterm	**5.24**	4.31	4.00
	Past-SGA	2.68	2.60	3.28
	Past stillbirths	1.25	0.91	1.02
	Neonatal deaths	0.66	0.52	0.54
SES-index quintiles				
	1 (most disadvantaged)	20.14	14.96	**45.67**
	2	13.45	19.82	16.79
	3	17.67	18.99	16.31
	4	14.21	22.81	17.23
	5 (most advantaged: reference)	**34.53**	23.42	4.00
Age group (in years)				
	< 20	**8.40**	4.91	3.26
	20 - 34	79.74	78.95	80.56
	35- 39	9.86	13.23	13.47
	≥ 40	2.00	2.92	2.72

In parentheses, the number of cases by area of occurrence. In green, the percentages significantly lower; in yellow, the percentages significantly higher. Both vs. the corresponding proportions in the middle-ratio areas (Level of significance was 0.003 after Bonferroni's correction). The distribution of SGA cases across the SES-index groups was not homogenous (Chi-square test of homogeneity: $p < 0.001$). The distribution of SGA cases across the age groups was not homogenous (Chi-square test of homogeneity: $p < 0.001$).

Table 2.7 Prevalence (%) of low birth weight at term. Alberta, 2006-2012.

Category	n (cases)	%	95%CI
by Type of area			
Province	5,453	1.65	[1.31, 1.99]
Urban	4,989	1.71	[1.35, 2.07]
Rural	464	1.20	[0.21, 2.19]
by Age groups			
< 20	267	1.77	[0.19, 3.35]
20 - 34	4,239	1.61	[1.23, 1.99]
35- 39	745	1.69	[0.76, 2.62]
≥ 40	202	2.33	[0.25, 4.41]
by SES-index			
1 (most disadvantaged)	1,110	**2.12**[1]	[1.99, 2.24]
2	1,084	**1.83**[1]	[1.72, 1.94]
3	979	**1.59**[1]	[1.49, 1.69]
4	1,116	1.49	[1.40, 1.58]
5 (most advantaged)	1,164	1.40	[1.32, 1.48]
by LBWT-ratio areas			
Low [SPR = 0.86]	195	0.76	[-0.46, 1.98]
Middle [SPR = 1.00]	4,169	1.51	[1.14, 1.88]
High [SPR = 1.17]	1,089	3.77	[2.64, 4.90]
The *high-ratio* areas predominantly occurred in the following CMAs[2]			
Lethbridge	28	6.19	[3.97, 8.42]
Medicine Hat	8	5.59	[1.83, 9.36]
Wood Buffalo	7	5.19	[1.44, 8.93]
Calgary	556	3.92	[3.60, 4.24]
Red Deer	31	3.66	[2.39, 4.92]
Edmonton	248	3.64	[3.20, 4.09]
Grande Prairie	30	2.98	[1.93, 4.03]
Lloydminster	7	2.69	[0.72, 4.66]
Overall	915		

[1] significant higher vs. the highest SES-index quintile ($p<0.0125$ after Bonferroni's correction).

[2] exclusively the *high-ratio* areas with more than 5 cases were reported because of confidentiality issues

Table 2.8 Prevalence (%) of the positively associated maternal variables with LBWT, and proportion of cases by SES-quintiles and age groups, in the low-, middle-, and high-LBWT ratio areas. Maternal variables ordered by the prevalence in the middle-ratio areas within maternal-categories. Alberta, 2006-2012.

Maternal variable	LBWT-ratio areas			
	Low (195)*	Middle (4,169)*	High (1,089)*	
	%	%	%	AF (%)
Current pregnancy				
Smoking during pregnancy	23.32	26.89	**22.05**	9.73
Gestational hypertension	13.99	12.29	11.8	7.21
Gestational diabetes	5.70	6.47	5.54	1.04
Substance use during pregnancy	6.15	5.88	5.05	1.39
Bleeding before the 20th-week	5.70	5.84	4.80	0.51
Proteinuria	5.70	4.63	3.97	1.13
Blood antibodies	0.52	0.48	0.65	0.24
Pre-pregnancy				
Pre-existing other medical disorders	8.21	10.79	9.55	3.18
Mothers' weight < 45kg	0.52	2.58	3.69	2.86
Pre-existing hypertension	2.56	1.54	1.29	0.59
Past obstetrical history				
Past-preterm	8.29	6.73	6.46	2.93
Past-SGA	3.63	5.04	5.35	4.78
Past-stillbirths	1.55	1.35	1.48	0.63
Neonatal deaths	1.04	0.58	0.74	0.22
SES-index quantiles				
1 (most disadvantaged)	7.69	17.85	**32.23**	9.69
2	12.31	17.99	28.47	5.87
3	12.31	17.77	19.65	1.62
4	13.85	23.55	9.83	NA
5 (most advantaged: reference)	**53.85**	22.84	9.83	NA
Age group (years)				
> 20	5.64	4.97	4.50	
20 - 34	77.95	76.88	80.99	
35 - 39	11.79	14.03	12.58	
≥ 40	4.62	4.13	1.93	

In parentheses, the number of cases by area of occurrence. In green, the percentages significantly lower; in yellow, the percentages significantly higher. Both vs. the corresponding proportions in the middle-ratio areas (Level of significance was 0.003 after Bonferroni's correction). The distribution of LBWT cases across the SES-index groups was not homogenous (Chi-square test of homogeneity: $p < 0.001$). The distribution of LBWT cases across the age groups was not homogenous (Chi-square test of homogeneity: $p = 0.01$).

Figure 2.1 Flow diagram for obtaining the study population.

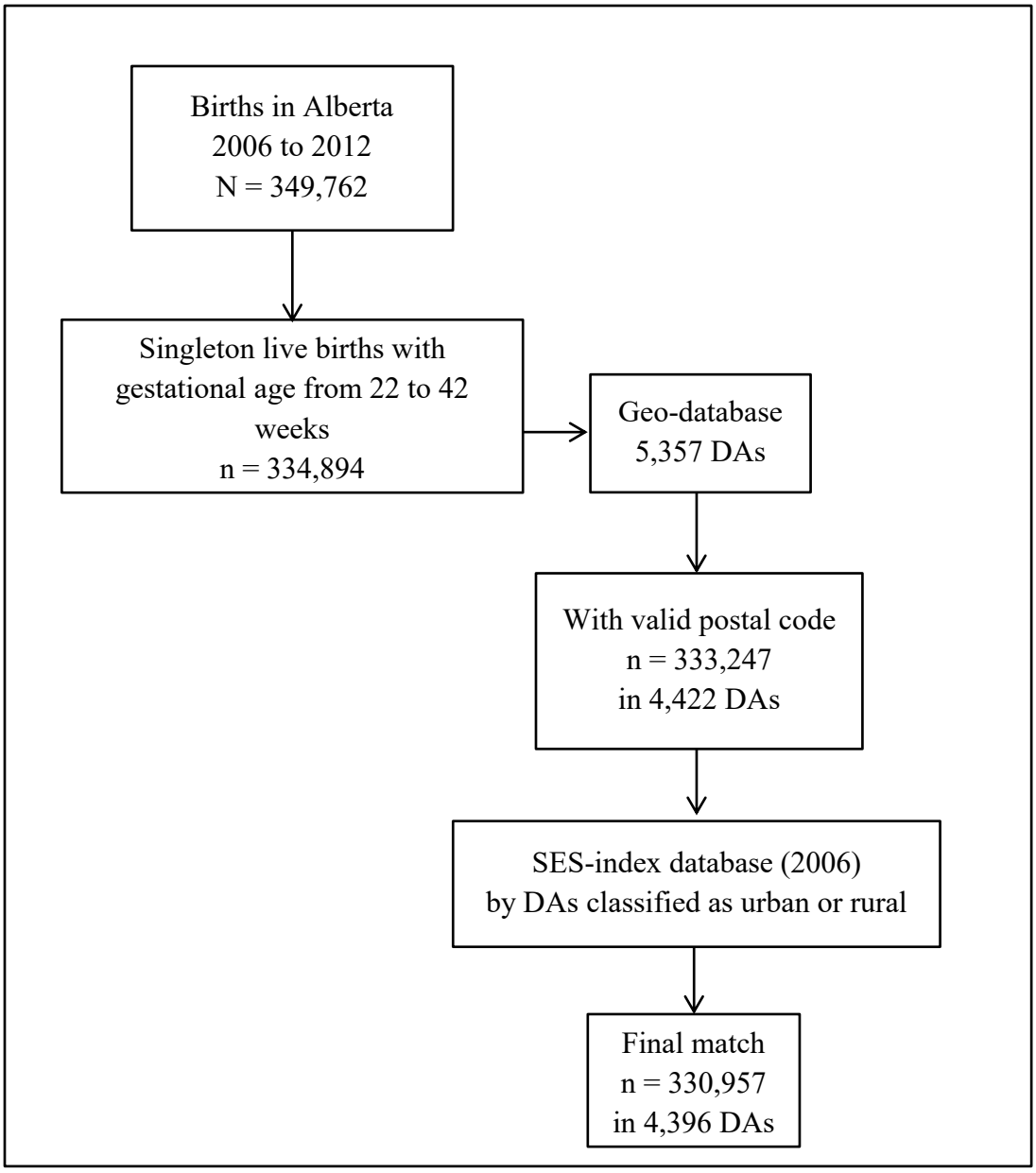


Figure 2.2 *Low*-, *middle*- and *high*-ratio areas for Preterm Birth in Alberta, 2006 to 2012. Standardized prevalence ratios (SPR) are values after smoothing.

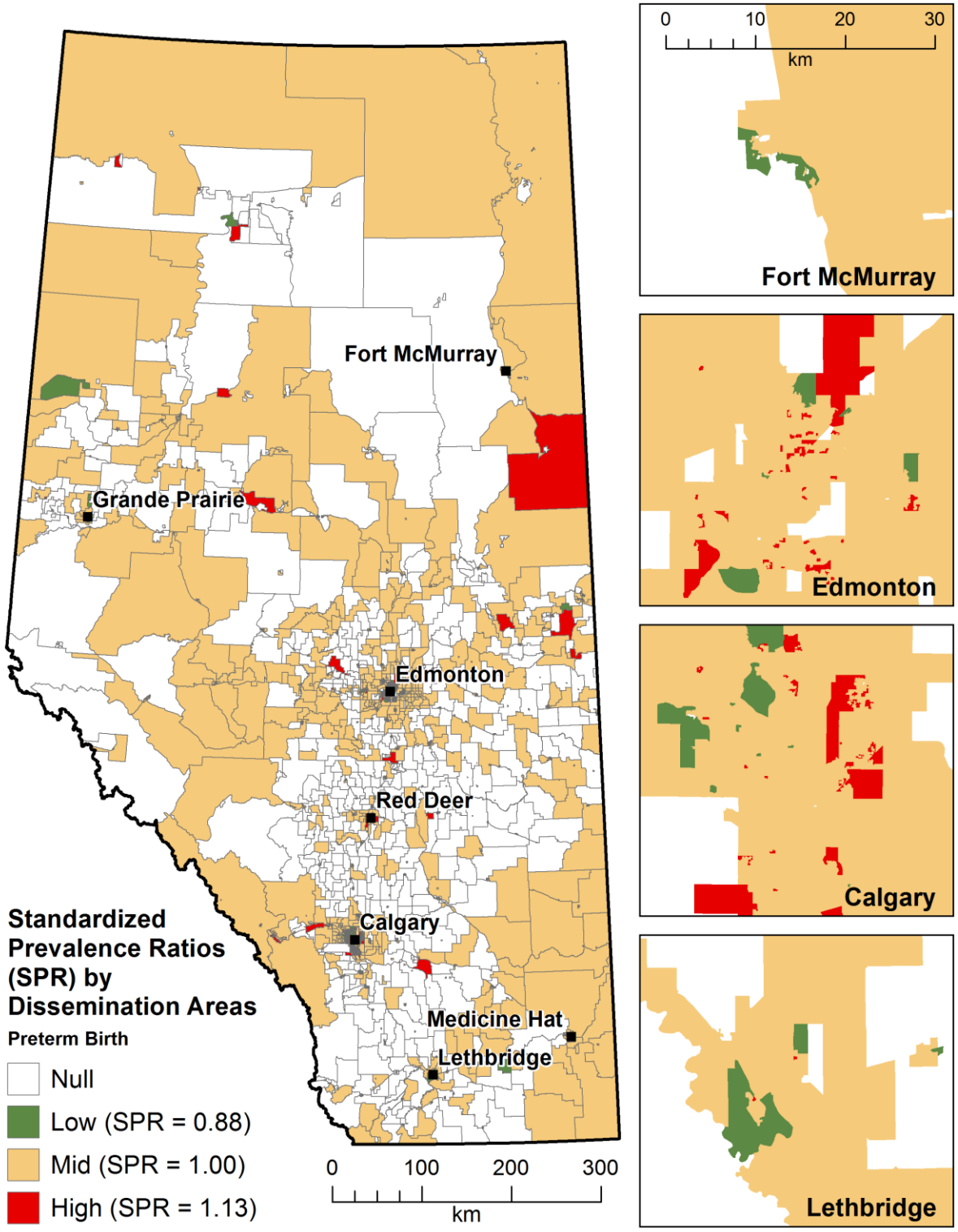


Figure 2.3 *Low*-, *middle*- and *high*-ratio areas for Small for Gestational Age in Alberta, 2006 to 2012. Standardized prevalence ratios (SPR) are values after smoothing.

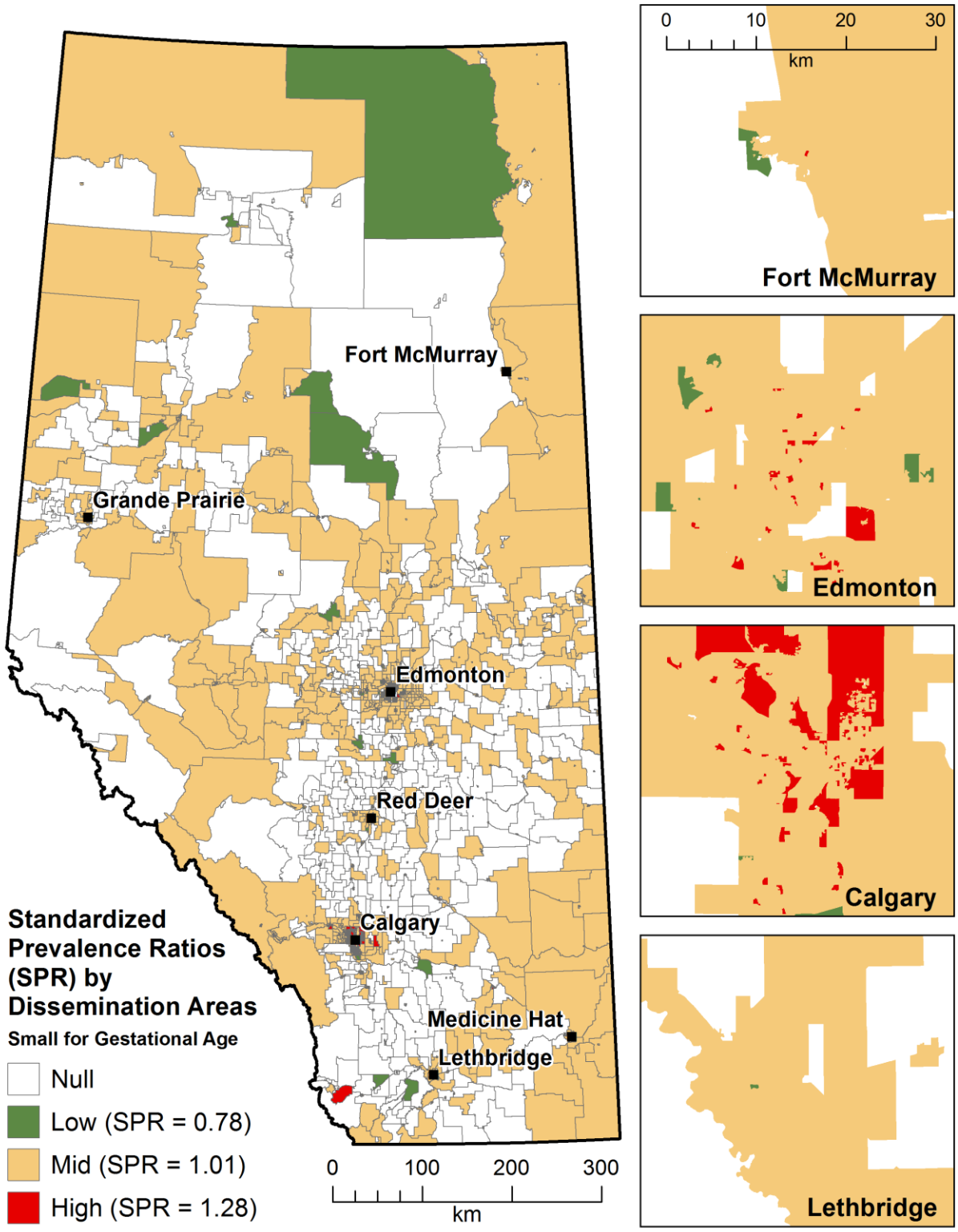
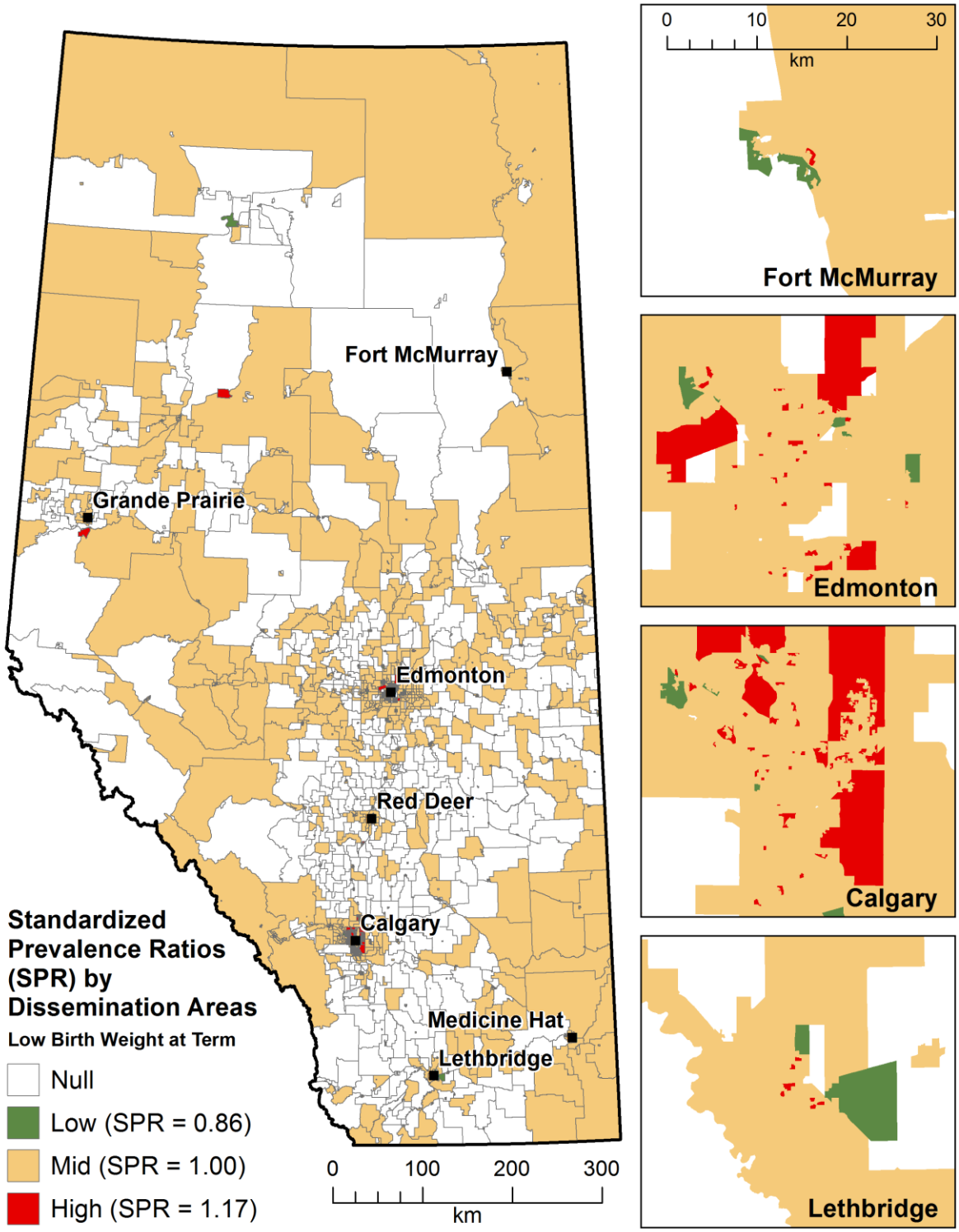


Figure 2.4 *Low*-, *middle*- and *high*-ratio areas for Low Birth Weight at Term in Alberta, 2006 to 2012. Standardized prevalence ratios (SPR) are values after smoothing.



Supplementary Table 2.1. Classification of the maternal variables evaluated.

Category	Variable	Definition
Current Pregnancy	Anemia	Anemia (HGB<100 gm/l)
	Blood antibodies	Blood antibodies (RH, Anti C, Anti K, etc.)
	Bleeding before the 20th-week	Bleeding < 20 weeks
	Bleeding after the 20th-week	Bleeding > 20 weeks
	Gestational hypertension	Pregnancy induced hypertension
	Gestational diabetes	Gestational diabetes
	Proteinuria	Proteinuria ≥ 1+
	Smoking	Smoker anytime during pregnancy
	Substance use during	Alcohol ≥ 3 drinks on any one occasion during pregnancy **OR** Alcohol ≥ 1 drink per day throughout pregnancy **OR** Drug dependent, inappropriate or excessive use of any substance which may adversely affect the outcome of the pregnancy.
Pre-pregnancy	Mothers' weight > 91kg	Weight > 91 kg
	Mothers' weight < 45kg	Weight < 45kg
	Pre-existing diabetes	Diabetes controlled by diet OR insulin dependent diabetes
	Pre-existing hypertension	Diagnosis of pre-pregnancy hypertension OR anti-hypertensive drugs used
	Pre-existing other medical disorders	Pre-existence of heart disease-symptomatic OR chronic renal disease OR other medical disorders (e.g. epilepsy, severe asthma, lupus, Crohns disease) OR acute medical disorder (acute Asthma, Thyrotoxicosis, UTI, etc.)
	Gravida	Total number of pregnancies, including the current pregnancy regardless of gestation or outcome.
Past obstetrical history	Neonatal deaths	Neonatal death(s)
	Parity	Total number of previous pregnancies that progressed beyond 20 weeks' gestation, regardless of outcome.
	Past-abortions	Abortion between 12 to 20 weeks and under 500 gr. birth weight
	Past-preterm	Delivery at 20- 37 weeks
	Past-SGA	Small for gestational age as recorded on antepartum risk assessment.
	Past-stillbirths	Stillbirth(s)

Supplementary Table 2.2 Association between maternal variables and SES-index with PTB (spontaneous and induced).

Maternal variable	Spontaneous -PTB OR[1]	95%CI	Induced-PTB OR[1]	95%CI	adjusted for[1]:
Current pregnancy					
Bleeding after the 20th wk.	**6.55**	[6.16, 6.96]	**2.41**	[2.15, 2.69]	
Gestational diabetes	**2.54**	[2.35, 2.74]	**1.22**	[1.11, 1.33]	Age
Bleeding before the 20th wk.	**2.21**	[2.07, 2.36]	**1.49**	[1.34, 1.65]	
Blood antibodies	**2.04**	[1.53, 2.72]	**2.64**	[2.01, 3.46]	
Gestational hypertension	**1.97**	[1.76, 2.20]	**2.85**	[2.68, 3.03]	Age
Smoking during pregnancy	**1.66**	[1.58, 1.74]	**1.29**	[1.20, 1.39]	Age, SES-index, substance use
Substance use during pregnancy	**1.65**	[1.53, 1.79]	**1.06**	[0.92, 1.24]	Age, smoking, SES-index
Anemia	**1.42**	[1.17, 1.72]	**1.68**	[1.32, 2.14]	Age, bleeding before & after 20th wk.
Proteinuria	0.93	[0.78, 1.11]	**2.99**	[2.71, 3.30]	Pre- and gestational diabetes & hypertension
Use of ACT	**0.88**	[0.85, 0.92]	1.01	[0.95, 1.06]	Age
Pre-pregnancy					
Pre-existing diabetes	**4.45**	[3.84, 5.16]	**2.34**	[1.99, 2.75]	Age
Pre-existing hypertension	**2.58**	[2.09, 3.19]	**2.90**	[2.51, 3.36]	Age, smoking, substance use, SES-index
Mothers' weight < 45kg	**1.66**	[1.38, 1.99]	**1.71**	[1.30, 2.24]	Age, SES-index, smoking, substance use
Pre-existing other medical disorders	**1.60**	[1.50, 1.71]	**1.58**	[1.46, 1.72]	Age
Mothers' weight > 91kg	1.03	[0.96, 1.11]	**0.85**	[0.78, 0.92]	Age
Past obstetrical history					
Past preterm	**6.69**	[6.33, 7.08]	**4.83**	[4.39, 5.31]	Age, parity
Past stillbirths	**3.21**	[2.80, 3.68]	**2.11**	[1.77, 2.54]	Age, parity
Neonatal deaths	**3.19**	[2.70, 3.79]	**2.29**	[1.72, 3.05]	Age, parity
Past abortions	**1.58**	[1.46, 1.71]	1.07	[0.95, 1.22]	Age
Past SGA	**1.57**	[1.28, 1.93]	**2.12**	[1.71, 2.62]	Age, parity
Gravida	**1.11**	[1.09, 1.12]	**1.05**	[1.04, 1.07]	Age
Parity	**1.06**	[1.04, 1.07]	1.01	[0.99, 1.03]	Age
SES-index quintiles					
1 (most disadvantaged)	**1.31**	[1.23, 1.38]	**1.12**	[1.03, 1.22]	Rural residence, age, smoking, substance use
2	**1.14**	[1.08, 1.21]	1.07	[0.99, 1.16]	
3	**1.12**	[1.06, 1.19]	1.05	[0.97, 1.14]	
4	**1.09**	[1.03, 1.15]	1.02	[0.94, 1.11]	
5 (most advantaged: reference)	1.00				

[1] Confounders for adjusting odds ratios per variables were selected as informed by direct acyclic graphs (DAG).
Bold indicates significant ORs (p-value < 0.05).

Supplementary table 2.3. Association between maternal variables and SES-index with SGA. Alberta (2006-2012).

Maternal variable	aOR[1]	95%CI	adjusted for[1]:
Current pregnancy			
Gestational hypertension	**1.75**	[1.67, 1.83]	Age
Smoking during pregnancy	**1.66**	[1.61, 1.71]	Age, SES-index, substance use
Proteinuria	**1.49**	[1.38, 1.61]	Pre-hypertension, gestational hypertension
Substance use during pregnancy	**1.17**	[1.09, 1.24]	Age, SES-index, smoking
Bleeding before the 20th-week	1.00	[0.94, 1.05]	
Use of ACT	1.00	[0.97, 1.02]	Age
Bleeding after the 20th-week	0.98	[0.92, 1.05]	
Anemia	0.91	[0.78, 1.05]	Age
Blood antibodies	0.91	[0.73, 1.13]	
Gestational diabetes	**0.91**	[0.85, 0.96]	Age
Pre-pregnancy			
Mothers' weight < 45kg	**3.42**	[3.09, 3.79]	Age, smoking, substance use, SES-index
Pre-existing hypertension	**1.41**	[1.26, 1.59]	Age, smoking, substance use, SES-index
Pre-existing other medical disorders	**1.17**	[1.12, 1.22]	Age
Pre-existing diabetes	**0.62**	[0.54, 0.75]	Age
Mothers' weight > 91kg	**0.49**	[0.47, 0.52]	Age
Past obstetrical history			
Past SGA	**6.40**	[5.84, 6.99]	Age, parity
Past stillbirths	**1.31**	[1.15, 1.49]	Age, parity
Neonatal deaths	**1.30**	[1.10, 1.55]	Age, parity
Past preterm	**1.22**	[1.14, 1.29]	Age, parity
Past abortions	1.02	[0.96, 1.08]	Age, parity
Gravida	**0.89**	[0.88, 0.90]	Age
Parity	**0.80**	[0.79, 0.81]	Age
SES-index quintile			
1 (most disadvantaged)	**1.34**	[1.29, 1.39]	Rural residence, age, smoking, substance use
2	**1.20**	[1.16, 1.25]	
3	**1.12**	[1.08, 1.16]	
4	**1.10**	[1.06, 1.14]	
5 (most advantaged: reference)	1.00		

[1] Confounders for adjusting odds ratios per variables were selected as informed by direct acyclic graphs (DAG). **Bold** indicates significant ORs (p-value < 0.05).

Supplementary table 2.4 Association between maternal variables and SES-index with LBWT. Alberta, 2006 to 2012.

Maternal variable	OR[1]	95%CI	Adjusted[2] for:
Current pregnancy			
Gestational hypertension	**2.57**	[2.36, 2.79]	Age
Smoking during pregnancy	**1.79**	[1.67, 1.91]	Age, SES-index, substance use
Blood antibodies	**1.57**	[1.07, 2.29]	
Proteinuria	**1.40**	[1.21, 1.61]	Pre- and gestational hypertension, gestational diabetes
Substance use during pregnancy	**1.38**	[1.22, 1.56]	Age, SES-index, smoking
Bleeding after the 20th week	**1.28**	[1.12, 1.46]	
Gestational diabetes	**1.23**	[1.10, 1.37]	Age
Bleeding before the 20th week	1.12	[1.00, 1.26]	
Anemia	0.84	[0.60, 1.19]	Bleeding before and after the 20th week
Pre-pregnancy			
Mothers' weight < 45kg	**4.47**	[3.76, 5.32]	Age, smoking, SES-index, substance use
Pre-existing hypertension	**1.83**	[1.47, 2.28]	Age, smoking, substance use, SES-index
Pre-existing other medical disorders	**1.50**	[1.37, 1.64]	Age
Pre-existing diabetes	0.91	[0.68, 1.21]	Age
Mothers' weight > 91kg	**0.53**	[0.46, 0.59]	Age
Past obstetrical history			
Past SGA	**9.45**	[8.29, 10.78]	Age, parity
Past preterm	**1.83**	[1.64, 2.05]	Age, parity
Past stillbirths	**1.75**	[1.38, 2.21]	Age, parity
Neonatal deaths	**1.43**	[1.02, 2.02]	Age, parity
Past abortions	1.14	[1.00, 1.30]	Age, parity
Gravida	**0.94**	[0.92, 0.96]	Age
Parity	**0.87**	[0.84, 0.89]	Age
SES-index quintiles			
1 (most disadvantaged)	**1.43**	[1.31, 1.56]	Rural residence, age, smoking, substance use
2	**1.26**	[1.16, 1.37]	
3	**1.09**	[1.00, 1.19]	
4	1.05	[0.97, 1.15]	
5 (most advantaged: reference)			
Age groups (20-34: reference)			
< 20	1.10	[0.97, 1.25]	
35 - 39	1.05	[0.97, 1.14]	
≥ 40	**1.45**	[1.26, 1.68]	

[1] Confounders for adjusting odds ratios per variables were selected as informed by direct acyclic graphs (DAG). **Bold** indicates significant ORs (p-value < 0.05).

Chapter 3

3. Associations between maternal residential proximity to air-pollutant mixtures from industrial sources and preterm birth and small for gestational age

3.1. Abstract

Background. The effect of mixtures of chemicals released into the air from industrial sources on adverse birth outcomes has been barely studied. The objectives of this study were (i) to characterize mixtures of chemicals released into the air by industrial facilities in Alberta during 2006 to 2012; (ii) to estimate their associations with small for gestational (SGA) spontaneous preterm birth (sPTB), and induced preterm birth (iPTB) for informing future research.

Methods: I used data from the Canadian National Pollutant Released Inventory. I grouped 133 chemicals released to the air by industrial facilities into ten broader chemical classes (NO_2, SO_2, *CO*, *PM*, *VOCs*, *PAHs*, *metals*, *other inorganics*, *nitrosamines/ethers/alcohols*, and *other organics*). I applied cluster analysis based on proportions of the ten chemical classes in the annual emissions per facility to profile the *mixtures*. Birth data were based on 330,257 singletons live births registered in the province. We used maternal residential proximity (10-km buffer) to assign exposure to the sources of the *mixtures* and multivariable logistic regression for estimating the associations of the *group of mixtures* with SGA, sPTB and iPTB in three areas of occurrence (low-, medium, and high-ratio), adjusted for the relevant maternal covariates and area-level socioeconomic status previously identified (chapter 2).

Results: A total of 6,259 facilities overall emitting 133 chemicals were classified into 52 *mixtures.* These mixtures were subsequently grouped into nine *groups of mixtures* based on the predominant chemical class (the chemical class with ≥ 60% of the proportional content) in the emissions. The *groups of mixtures* were: *NO_2-mixtures*, *CO-mixtures*, *SO_2-mixtures*, *PM-*

mixtures, *VOCs-mixtures*, *Metals-mixtures*, *Other inorganics-mixtures*, *Other organics-mixtures*, and *Heterogeneous-mixtures*. Results showed that mixtures containing a high proportion (≥60%) of NO_2, or PM, or CO were the most common (83% of the facilities) and represented 33% of the emissions. They were densely present across the province and were emitted mainly from the oil- and energy-related sectors. *Mixtures* having a high proportional content of *VOCs*, *metals*, *other organic*s and *other inorganic* chemicals, were scarce (they represented 0.24% of the total emissions) and mainly emitted in the major cities and not linked to the oil- and energy-related sectors. The V*OCs-mixtures* were associated with a 37% (95% CI: 11-69%) increase in the odds of SGA. *Metals-mixtures*, *other inorganic-mixtures*, and *other organic-mixtures* were associated with a 17% (95% CI: 5-30%), 17% (95% CI: 6-28%), and 24% (95% CI: 9-41%), respectively, increase in the odds of iPTB. *PM-mixtures* were positively associated with SGA (OR=1.08; 95%CI [1.02, 1.13]). *Heterogeneous-mixtures* were positively associated with spontaneous PTB (OR=1.36; 95%CI [1.13, 1.63]).

Conclusion: In summary, over one hundred of chemicals were released into the air by industrial facilities. Gases (NO_2, CO, SO_2) and PM were the main components in the mixtures. *Groups of mixtures* with high proportional content of *VOCs*, *metals*, *other organics*, and *other inorganic* substances were sparse, but were associated with SGA the first one, and with iPTB the rest. *Heterogeneous-mixtures* were positively associated with sPTP and *PM-mixtures* were positively associated with SGA. These results may motivate and justify further research for studying associations between mixtures of hazardous chemicals released into the air from industrial sources and adverse birth outcomes.

3.2. Introduction

The associations of mixtures of hazardous chemicals released into the air by industrial facilities on adverse birth outcomes (ABOs) such as preterm term birth (PTB) and small for gestational age (SGA) have been barely studied.[1-4] The research in air pollution and perinatal epidemiology has tended to focus on exploring the associations of criteria air pollutants such as ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2), sulphur dioxide (SO_2), and particulate matter (PM) with ABOs.[5,11] Recently, associations of mixtures of air pollutants with ABOs have been reported.[5] Such multipollutant approaches assume a more realistic pattern of environmental exposure[12] and hypothesize that the chemical composition of a mixture of air pollutants may alter the toxic behaviour of the single air pollutants that compose the mixture.[13] A mixture of pollutants may present additive, synergistic, potentiation, inhibition, or antagonistic effects on the human body[13] and, consequently, on the fetal development.[2] That means: the toxicity of a mixture of air pollutants may not be the sum of the toxicities of their components. In fact, multi-pollutant approaches have reported contrasting results. For example, a study, including data from Edmonton, Calgary and Montreal reported individual associations of CO, NO_2 and $PM_{2.5}$ on intrauterine growth restriction, while an association only persisted for CO when all pollutants were combined in the same model.[14] In contrast, a study in Detroit found positive associations of CO, SO_2, NO_2 and PM_{10} with SGA in both individual and multi-pollutant models.[15]

However, current single or multi-pollutant approaches have generally focused on evaluating criteria air pollutants since data are easily available from air monitoring stations, most of them located in urban settings.[2] As a result, a knowledge gap exists about the contribution of other hazardous chemicals to air pollution and their effects on pregnancy outcomes.[1] According to data reported by industries to national pollutant inventories (where they exist), hundreds of hazardous

chemicals that are not routinely measured by air monitoring stations are released into the atmosphere in considerable amounts.[1,16] Some of them are either recognized or suspected as developmental toxicants (agents that impact the quality of the fetal development and cause adverse effects such as death, structural and functional abnormalities, alteration of fetal growth, and preterm birth[17]). Compilations of toxic chemicals evaluated by environmental health hazard assessment's offices include a list of more than 500 chemicals recognized, and 200 chemicals suspected to be developmental toxicants.[18] Although the list of hazardous toxicants is ample, few studies have characterized their contribution to air pollution and measured their associations on pregnant women and newborns.[17,19] Some examples include: (i) polycyclic aromatic hydrocarbons (PAHs), that have been positively and negatively related to PTB in different pregnancy periods;[20] (ii) incremental exposure to total airborne PAHs during the first trimester of pregnancy has been associated with a decrement in the foetal growth ratio and an elevation of the cephalization index;[21] (iii) exposure to NO_2 combined with high levels of benzene (> 2.7 $\mu g/m^3$) were linked with an increased risk of PTB in pregnant women in a cohort of 785 women in Valencia, Spain.[22] The association of exposure to air pollutant mixtures from point industrial sources on ABOs is less clear. Recently, a cross-sectional study in Alabama[23] indicated that proximity (≤ 5 km) to coke production and steel manufacturing facilities emitting mixtures of volatile organic compounds and metals increased the odds of LBW and PTB, respectively.[23] Accordingly, there is a need to estimate the health risks related to the exposure to many, proven and suspected, developmental toxicants acting individually or as a chemical mixture that are released into the air by industrial sources.[24-26]

In parallel, interest exists in implementing interdisciplinary approaches to evaluate the environmental risk and the toxicity of complex air pollutant mixtures since the detailed biological mechanisms implicated have not been completely elucidated.[27,28] There is evidence

that air pollutants induce oxidative stress in cells, triggering a series of reactions that include the release of inflammatory mediators and apoptosis.[29-32] Some toxicological *in vitro* studies have shown that biological endpoints do not always follow a dose-response relationship specific to air pollutants mass. For example, changes in the chemical composition of PM may play a role in altering cell responses.[33] This, in turn, adds complexity to understanding the mechanistic relationships between cells and air pollutants. At the individual level, possible effects of air pollutants in the mothers include changes in blood viscosity, hypertension, genetic or epigenetic changes in germ cells, and endocrine disruption. All of them could relate to SGA or prematurity.[2]

The main goal of this study was to conduct an initial assessment of the potential association of mixtures of air pollutant emitted from industrial and commercial sources with PTB and SGA in Alberta, Canada. Alberta is a highly-industrialized province, where hundreds of hazardous chemicals are continuously released into the air by industrial facilities densely present across the province[34] **(**Figures 3.1 and 3.2). In 2014, Alberta had the highest emissions of SO_2, NO_2, volatile organic compounds (VOCs), ammonia (NH_3), and fine particulate matter ($PM_{2.5}$) in Canada[35]. The large amount of reported emissions and the high number of chemicals released into the air represent a challenge to understand and study the local effects of air pollution on adverse birth outcomes, especially within a multipollutant context. Additionally, the 2006-2010 crude rates of PTB and SGA in Alberta were reported above the national average.[36] Consequently, interest exist in characterizing the local constellation of the potential individual, social and environmental risk factors on ABOs in Alberta.

This study continues the previous work presented in Chapter 2, in which areas of *low*-, *medium*-, and *high*-ratio of PTB and SGA in Alberta were identified, as well as their corresponding prevalence profiles of known maternal risk factors and area-level socioeconomic status. Briefly, in the *high* ratio areas the key risk factors were: (i) for spontaneous PTB: past-

preterm, smoking during pregnancy, bleeding after the 20th week and low SES-index; (ii) for induced PTB: gestational hypertension, past preterm, and proteinuria; and (iii) for SGA: low SES-index, smoking during pregnancy and gestational hypertension. Now, the turn is to explore the potential participation of air pollutant mixtures from industrial sources in those areas of occurrence to better describe the network of the risk factors impacting the ABOs' occurrence in the province.

This work is part of an interdisciplinary exploratory study aimed to identify potential relationships between ABOs and air chemical emissions from industrial sources in Canada, by using complementary methodological approaches (i.e., spatial data mining, integrative geographical analysis and epidemiological analysis) as a foundation for future research.[37] This paper aims: (1) To characterize mixtures of air pollutants released by industrial facilities in Alberta during 2006 to 2012; and, (2) To estimate the association of the characterized industrial air-pollutant mixtures with preterm birth and small for gestational age.

3.3. Methods

3.3.1 Brief description of methods published in chapter 2

3.3.1.1 Study population

This study focuses on the births and industrial emissions data from the province of Alberta, Canada, between 2006 and 2012. All singletons live births with a gestational age between 22 and 42 completed weeks were considered. Birth records were provided by the Alberta Perinatal Health Program that covers the entire population of births in Alberta (whether in a hospital or planned home births with a registered midwife). It includes the six-character postal code of maternal residence at birth and an extensive list of maternal covariates (21 variables).

3.3.1.2 Health outcomes definition

Small for gestational age was defined as those newborns with weighs below the tenth percentile according to sex- and age of the Canadian population;[38] whereas preterm birth was defined as those newborns with less than 37 weeks and zero days of gestational age.[39] The gestational age at delivery in completed weeks was available in the APHP registry as well the type of labor: Spontaneous (sPTB) or Induced (iPTB).

3.3.1.3 Geocoding of health outcomes

The geographical latitude and longitude of the centroids for the six-character postal codes of the mothers' residences were obtained from the 2006 geographical framework[40] and assigned to the corresponding dissemination area (DA). DAs are census geographic areas with a population of 400 to 700 persons.[41] I used the DAs to estimate the area-level occurrence of PTB and SGA and to use an area-level socioeconomic status as covariate (see area-level covariates section). Because the Statistic Canada Postal Code Conversion File for 2006 did not include all postal codes instituted after 2006, a vector overlay of the postal code locations[42] with the DA boundary file[43] was performed to capture all postal codes in each one of the DAs included in the study period.

3.3.1.4 Areas of low-, medium- and high-ratio of PTB and SGA

I estimated the DA-level smoothed age-adjusted standardized prevalence ratios (SPR) of PTB and SGA to identify DAs with *low*-, *medium*-, and *high*-ratio of PTB and SGA. The detailed methods and results of the prevalence of ABOs' related maternal risk factors and area-level socioeconomic status were presented previously (see Chapter 2). Briefly, the area-level smoothed age-adjusted standardized prevalence ratios (SPR) of PTB and SGA were based on an empirical Bayes approach.[44] The *low*-ratio and the *high*-ratio areas were defined as the ones

located two or more standard deviations (SD), respectively below or above of the average age-adjusted SPR (≈1) after smoothing. The *medium*-ratio areas were the ones located between +/-2SD. The prevalence of maternal risk factors and the proportion of cases (PTB, SGA) by area-level SES-status quintiles were estimated by those area-level of occurrence. I used these areas of occurrence as strata for logistic regression (see following sections) to integrate the environmental component (exposure to the resulted mixtures) with the corresponding profiles of individual and social risk factors previously identified.

3.3.2 Characterization of the industrial air pollutant mixtures

I used data of chemical emissions by industrial and commercial facilities into the environment from the Environment and Climate Change Canada's National Pollutant Release Inventory (NPRI)[45]. Those emissions are reported annually. Data files were available from the NPRI website[45]. The database included, among other information: (i) the releases of 342 chemicals to media (air, water, land) in different units (e.g., *tonnes*, *kg*, *g*) above specific-chemical thresholds; (ii) the standard codes of single chemicals from the Chemical Abstracts Service,[46] and non-standard codes for other groups of chemicals aggregated specifically for reporting into the NPRI (i.e., arsenic and its compounds); (iii) the geo-location of the facilities (latitude/longitude); (iv) the industrial sector associated with the activity of each facility reporting emissions, and; (v) the changes in reporting requirements and thresholds, chemicals that have been added/removed, changes in the industry sectors, and substances reported both individually as a part of a group of chemicals (i.e., anthracene is reported individually and included in PAHs) to avoid double counting.[47]

I extracted the chemicals released into the air from the NPRI. The emissions reported in kilograms (kg) and grams (g) were converted to *tonnes.* I used the 19-key industry sectors for

reporting results used by the NPRI for disseminating results[48] (supplemental table S3.1). I conducted cluster analysis to statistically typify the air pollutant *mixtures* from industrial sources in Alberta by following the next steps and delimitations:

1) The individual chemicals reported by facilities were aggregated into chemical classes, or families of chemicals according to their chemical structure and properties (i.e., polycyclic aromatic hydrocarbons, volatile organic compounds). I followed the chemical classifications of the Agency for Toxic Substances and Disease Registry[49] for forming the chemical classes.

2) The defined chemical classes (*in italics*) were: (a) *SO_2*; (b) *NO_2*; (c) *CO*; (d) *PM* (grouped all types of reported particles regardless of its diameter: $PM_{2.5}$, PM_{10} or total PM); (e) *VOCs* (including 50 chemicals); (f) *PAHs* (including 32 chemicals), (g) *metals* (including 14 chemicals); (h) *other inorganics* (including 18 chemicals); (i) *nitrosamines/ethers/alcohols* (including 6 chemicals); and, (j) *other organics* (including 9 chemicals). The chemicals included in each chemical class category are listed in the supplemental table S3.2.

3) The emissions of SO_2, NO_2, and CO were kept as corresponding individual classes due to their large air emissions from industrial facilities in Alberta.

4) It is important to mention that industrial facilities do not report the detailed constituents of PM (such as metals, VOCs or PAHs) to the NPRI. Thus, particles (PM) are reported as an individual pollutant and it was considered as an independent pollutant in this analysis.

5) I calculated the facility-specific proportion of each chemical in a class as reported (annual tonnes).

6) I performed a cluster analysis on the facilities emitting two or more chemical classes to form groups of facilities emitting similar proportions of chemical classes. Accordingly, I defined *mixture* as a combination of the chemical classes based on their proportional amounts emitted. For example, a combination of two chemical classes SO_2:*VOC*s in the following proportions [0.8**:**0.2], [0.2**:**0.8], or [0.5:0.5] could potentially be considered as different *mixtures* by the cluster analysis. The rationale supporting this argument is based on recent evidence from *in vitro* toxicological studies suggesting that not only the types of chemicals that compose the air pollution in any given sample, but their proportional content play an important role in producing different biological responses[33,50]. Consequently, the type of chemical and its proportions in a mixture may alter the relationships between air pollutants and health outcomes. Cluster analysis was performed in STATA v.13[51] by choosing the Euclidean distance as a measure of resemblance or proximity among facilities, and the Ward's hierarchical agglomerative method (or Ward's minimum variance method)[52,53] to classify them in collective categories called *mixtures*. The Ward's method tends to produce compact clusters[54] and it has been used in characterizing multi-pollutant environments elsewhere.[54,55,56] The initial number of clusters for further analysis was determined by observing the pseudo-F stopping rule index[57] (see Appendix 2**)**.

3.3.3 Assessment of the association of the industrial air pollutant mixtures on adverse birth outcomes

I applied multiple logistic regressions to examine the association between the health outcomes and the industrial air pollutant mixtures according to the following criteria:

a) Dependent variables. sPTB, iPTB, and SGA, measured individually as yes/no.

b) Exposure assignment. I used the presence (yes/no) of an emitting facility emitting a *mixture* in a 10-km buffer from the mother's postal code at birth as a proxy for environmental exposure. The distances were calculated by using the latitude and longitude of the centroids of the mother's postal codes at birth and the latitude and longitude of the facilities per year and for each postal code using ArcGIS software.[58] The geographical coordinates of the facilities are provided by the NPRI. Since pollution data is reported annually, we considered only births occurred from April to December to ensure potential exposure to *mixtures* at least during the last three months of the gestational period. Thus, the main explanatory variables were the *mixtures* in the 10 km buffer for each birth.

c) Individual covariates. I used as individual covariates the maternal risk factors previously identified as relevant for sPTB, iPTB, and SGA (see Chapter 2). For example, for sPTB we used as covariates: past-preterm, pre-existing diabetes, pre-existing hypertension, pre-existing other medical disorders, bleeding before the 20th-week, bleeding after the 20th-week, gestational hypertension, gestational diabetes, smoking during pregnancy, substance use during pregnancy, pre-pregnancy mothers' weight >

91kg, pre-pregnancy mothers' weight < 45kg, having more than 1 child, category of the mothers' age (<20, 20-34, 35-39, ≥ 40), and SES-index quintile. All covariates are mentioned in the corresponding tables of results.

d) Area-level covariates. I used the Canadian socioeconomic status index (SES-index) developed by Chan *et al*.[59] as a proxy for neighborhood-level socioeconomic status since no individual socioeconomic data were available for our study. This index incorporated data from the 2006 National Census in the dimensions related to (i) deprivation (e.g., educational certificate, employment status, income, marital status, owning a home or renting, transport mode), (ii) the potential existence of indoor environmental pollutants related to health outcomes (e.g., year of home-construction), and (iii) cultural identities (the aboriginal status or human development index of the individuals' country-origin). The SES-index was previously found to perform well in capturing gradients of the prevalence of adverse pregnancy outcomes.[59]

e) Strata. Our main interest in using the previously identified areas with *low*-, *medium*-, and *high*- ratio of PTB and SGA was to integrate a risk factor's profile of the individual, area-level socioeconomic status, and industrial air pollutant's mixtures by areas of occurrence. The profile of the prevalence of maternal risk factors (from a set of 21 maternal risk factors) and area-level socioeconomic status in the three ratio areas was previously integrated (see Chapter 2). To compensate for multiple tests, the significance level was adjusted by using the Bonferroni's correction. Thus, I interpreted only results with p-value < 0.006 as significant.

3.3.4 Ethics approval

The study received ethics approval from the University of Alberta Research Ethics Board and institutional approval from the Alberta Perinatal Health Program (APHP).

3.4. Results

3.4.1 Characterization of industrial air pollutant mixtures

Descriptive statistics of industrial air emissions. We extracted from the NPRI 62,641 entries of pollutants released to air in Alberta from 2006 to 2012. They include more than six thousand facilities (n=6,279) reporting more than seven million *tonnes* of 133 different chemicals releases to the air across Alberta (Supplemental Tables S3.3 and S3.4). Annual amounts showed a decreasing trend over time, being the total emissions in 2012 almost 17% lower than in 2006. The annual number of reported emitted chemicals varied from 114 to 103. After 2007, the number of chemicals was almost constant around 105 (Figure 3.3).

The emissions aggregated by chemical class indicated that SO_2, NO_2, *CO,* and *PM* accounted for approximately 97% of the total air pollutant emissions, and the remaining 3% is composed of *other inorganics* (≈1.4%), *VOCs* (≈1.3%), *other organics* (≈0.01%), *metals* (≈0.009%), *nitrosamines/ethers/alcohols* (≈0.004%), and *PAHs* (≈0.003%). The Table 3.1 shows the industrial emissions by year aggregated in the ten chemical classes.

Industrial facilities from the oil and energy sector (including *Conventional oil and gas extraction, Non-conventional oil and gas extraction*, *Electricity*, *Petroleum and coal product refining and manufacturing*, and *Oil and gas pipelines and storage*) were the major emitters of SO_2, NO_2, *CO*, *PM*, *VOC,* and *other inorganics*, contributing with approximately 88% of the pollutants released into the air during the study period. The *Wood products* sector accounted for 16% of the *CO* emissions, and 6% of both *PM* and *VOCs*' emissions. The emissions from the

Chemical industry generated approximately 70% of the *PAHs*, 47% *of other inorganics,* and 94% of *other organics*. *Metals* were released from a variety of industrial activities: 88% of the total metal-related releases were originated by the *Other Manufacturing* (≈28%), *Pulp and Paper* (≈21%), *Non-conventional oil and gas extraction* (≈16%), *Electricity* (≈15%), and the *Iron & Steel* (≈8%) sectors. Finally, the activities related to the *Plastics and Rubber* sector generated the 93% of the *nitrosamines/ethers/alcohols* emitted to the air during the study period. See Figure 3.4 and Table 3.2 for the results presented in this section.

***Mixtures'* profiles**. From the 6,279 facilities, 51% (n=3,223) emitted two or more chemical classes contributing 97% of the emissions (6,802,407 *tonnes*); the remaining 49% of the facilities (n=3,056) emitted only one chemical class contributing 3% of the total emissions (220,617 *tonnes*). We initially classified the 6,279 facilities in 52 clusters based on statistical criteria (stopping rule) (Table 3.3). Subsequently, we grouped them into nine *groups of mixtures* to simplify the description of the *mixtures*. The characteristic that grouped those 52 *mixtures* into nine *groups of mixtures* was the dominance of one chemical class proportionally representing more than 60% of the emissions, or the absence of dominance of any particular chemical class. The tables 3.3, 3.4 and 3.5 present the results of this section. The nine *groups of mixtures* characterizing the mixtures of industrial emissions were (ordered by the number of facilities belonging to each group: largest to smallest):

1) The *NO_2-mixtures*: this group included 2,776 facilities (44% of the facilities) densely present across the province (Figure 3.5), whose emissions (1.6 million tonnes) had a high proportional content of NO_2 (≥ 60%). It included 15 of the 52 mixtures. The *Conventional oil and gas extraction* sector was the major contributor to this group (86% of the total emissions within this group).

2) The *CO-mixtures*: this group included 1,072 facilities (17% of the facilities) densely present across the province (Figure 3.6), whose emissions (733.8 thousand tonnes) had a high proportional content of CO (≥ 60%). It included 9 of the 52 mixtures. The sectors of *Conventional oil and gas extraction* and *Wood products* contributed with almost 87% of the total emissions within this group.

3) The *PM-mixtures*: this group included 1,403 facilities (22% of the facilities) densely present across the province (Figure 3.7), whose emissions (32.8 thousand tonnes) had a high proportional content of *PM* (≥ 60%). This group comprises only 3 of the 52 *mixtures*. Seven key industrial sectors contributed to 98% of the total emissions within this group (*Mining and quarrying*, *Other-except manufacturing-*, *Conventional oil and gas extraction*, *Petroleum and coal product refining and manufacturing*, *Oil and gas pipelines and storage*, *Other manufacturing*, and *Wood products*).

4) The *heterogeneous mixtures*: this group included 702 facilities (11% of the facilities) located across the province (Figure 3.8), whose emissions were the highest in terms of amounts (3.2 million *tonnes*). This group was characterized by a combination of two or three gases with individual proportions no major than 60% of the total content, in combination with many other chemical classes such as *PM*, *VOCs,* and *OI*. It included 11 of the original 52 *mixtures*. The *Electricity* sector was the main contributor to these mixtures (46% of the total emissions within this group) followed by *Conventional oil and gas extraction* and *Non-conventional oil and gas extraction* (contributing 21% and 18%,

respectively). This group included a subgroup of mixtures where the combined participation of NO_2 and *CO* was predominant (subsequently named sub-group NO_2-*CO*).

5) The SO_2-*mixtures*: this group included 161 facilities (2.6% of the facilities) located across the province **(**Figure 3.9**)**, whose emissions (1.4 million tonnes) had a high proportional content of SO2 (≥ 60%). It included 5 of the 52 mixtures. The *Non-conventional oil and gas extraction*, and *Conventional oil and gas extraction* sectors contributed to 55% and 42% of the total emissions in this group.

6) The *VOC*s-*mixtures*: this group included 124 facilities (2% of the facilities), mainly located in Edmonton, Calgary and Lethbridge (Figure 3.10), whose emissions (8.8 thousand tonnes) had a high proportional content of *VOC*s (≥ 60%). It included 4 of the 52 *mixtures*. The *Other Manufacturing* sector was the major contributor to this group (58% of the total emissions within this group).

7) The *Metals-mixtures*: this group included 22 facilities (0.4% of the facilities), mainly located in Edmonton, Calgary, Lethbridge and Medicine Hat (Figure 3.11), whose emissions (198 tonnes) had a high proportional content of *Metals* (≥ 60%). It contained 2 of the 52 mixtures. The *Other Manufacturing* sector was the major contributor to this group (95% of the total emissions within this group).

8) The *OI-mixtures*: this group included 18 facilities (0.3% of the facilities), mainly located in the areas of Edmonton, Calgary, Reed Deer and in the northwest of the province (Figure 3.12), whose emissions (7.8 thousand tonnes) had a high proportional

content of *other inorganics (≥ 60%)*. It comprises 2 of the 52 mixtures. The *Water and Waste Water Systems* sector was the major contributor to this group (79% of the total emissions within this group).

9) The *OO-mixture* was composed of one facility (0.016% of the facilities) from the *Plastics and Rubber* sector whose emissions (0.88 tonnes) had a high proportional content of *Other Organics* (≥ 60%), and it was located in the Calgary area (Figure 3.13).

Overall, the *PAH*s and *nitrosamines/ethers/alcohols* classes had a very low proportional participation in some of the 52 *mixtures. The PAHs* represented less than 0.021% of the *tonnes* reported by 15% of the facilities (n=969) and they were present in 17 of the 52 *mixtures.*

3.4.2 Associations of industrial air-pollutant mixtures with preterm birth and small for gestational age

The results for the corresponding estimated odds ratios per adverse birth outcome, strata (level of PTB or SGA occurrence) and the *group of mixtures* are shown in the Table 3.6. The following *groups of mixtures* showed statistically significant ($p<0.006$) associations with some adverse birth outcome:

a) *PM-mixtures* were positively associated with SGA (OR=1.08; 95%CI [1.02, 1.13]) in the *medium-ratio* areas;
b) *VOCs-mixtures* were positively associated with SGA (OR=1.37; 95%CI [1.11, 1.69]) in the *high-ratio* areas;
c) *Heterogeneous-mixtures* were positively associated with spontaneous PTB (OR=1.36; 95%CI [1.13, 1.63]) in the *high-ratio* areas;

d) *Metals-mixtures* were positively associated with induced PTB (OR= 1.17; 95%CI [1.05, 1.30]) in the medium-ratio areas;

e) *OI-mixtures* were positively associated with induced PTB (1.17; 95%CI [1.06, 1.28]) in the medium-ratio areas;

f) *OO-mixtures* were positively associated with induced PTB (OR=1.24; 95%CI [1.09, 1.41]) in the medium-ratio areas.

3.5. Discussion

In this study, we firstly characterized industrial emissions in Alberta as sources of potentially hazardous air pollutant *mixtures* for adverse birth outcomes. As far as I know, no previous reports have characterized facility-reported air emissions in Alberta by using an approach based on combined air pollutants (*mixtures*). To reach this purpose, I used the NPRI since many of the chemicals reported by the industry as discharged to air are not captured by the air monitoring stations.[60] The NPRI collects data over 340 substances, including carcinogens, some hydrocarbons, and toxic substances of concern, but does not collect pollutant information on pesticides, herbicides, and greenhouse gases. Despite this limitations, the NPRI is the most complete and reliable data source about toxic industrial emissions in Canada according to Environment and Climate Change Canada.[45] In other countries where national toxic inventories compile industrial emissions, those inventories have played a relevant role in tracking emissions of hazardous chemicals by industrial sources over time and in setting initial hypothesis for research in environmental-health.[61] For example, they have been used to assess the effects of toxic chemicals released into the air (mainly using proximity analysis) on: gestation and birth weight,[4] infant mortality,[1] preterm birth and small for gestational age,[62] leukemia morbidity and

mortality,[63,64] cancer rates.[65] Also, they have been used to estimate toxic releases density and environmental equity issues in New Jersey.[66]

The characterization of the *mixtures* from the industrial facilities across Alberta was complicated due to a large number of facilities (more than 6 thousand) and the number chemicals reported during the study period (more than one hundred). This resulted in many potential combinations of chemicals complicating the creation of a comprehensive characterization of the *mixtures*. Consequently, the aggregation of single chemicals into chemical classes allows us to create an initial framework to facilitate the identification of patterns in the *mixtures*. It would be ideal to aggregate single chemicals according to their toxicity or health effects. However, not all chemicals have a well-characterized toxic potential (known as human toxicity equivalency potential[67]) or a well-recognized health effect. For this reason, I decided to use chemical groups based on their chemical structure and properties. For example, chlorine dioxide and toluene diisocyanate (mixed isomers), that were released into the air during the study period, do not have yet an associated human toxicity equivalency potential.[18] Thus, we considered that the use of the ten chemical classes could provide some insights into the potential effects of *mixtures* based on their proportional content to inform future research. As we described in the introduction, potential interactions of co-pollutants (i.e., antagonisms, potentiation, synergism, etc.) is one of the issues of major concern in studying the health effects of the mixtures of pollutants[13,68] and toxicological studies may be guided by the results of observational studies, like this study. Few toxicological studies have approached effects of mixtures of pollutants, but they have suggested that the proportional participation of co-pollutants in a mixture (i.e., PM) trigger different biological endpoints[33] and that reductions in certain components may best protect human health.[50]

Another point that it is important to mention is with regard to the use of cluster techniques for characterizing the industrial emissions. The use of clustering methods does not guarantee a "unique solution" but they provide a useful description of a complex data structure to facilitate its understanding and the extraction of information for specific purposes.[52,53] In fact, cluster analysis has been widely used in the context of air pollutant mixtures. For example, for finding similarities among monitoring site characteristics with regard to nitrogen oxides and oxidative chemicals,[55] among Chinese cities based on groups of pollutants,[56] and for exploring spatial and temporal air pollutant pattern profiles in areas where air monitoring stations provide sufficient temporal and spatial air pollutant concentrations.[54] Thus, given that many hazardous chemicals from industrial sources are not captured by current air monitoring systems, a cluster approach based on data from national toxic inventories may be useful for having an initial framework of the air pollutant mixtures derived from industry.

After characterizing the *mixtures*, our exploratory analysis corroborated previously identified downtrend in the emissions of NO_2, SO_2, and PM and the large participation of the energy-related sectors (i.e., oil and gas extraction, power generation, petroleum and coal product refining, and manufacturing) during the study period.[69-71] It is well known that Alberta is a key driver of Canada's economy due to its rich natural deposits of oil and gas, and power generation.[72] This situation explains the high number of industrial facilities from those sectors operating across the province, and the consequent amount of chemicals released into the air. However, the downtrend in the emissions during the last 20 years, probably could be explained, in part, by the role of the Environmental Protection and Enhancement Act[73] aiming to protect the integrity of ecosystems and human health.

Additionally, and importantly, our characterization of the *mixtures* showed three important aspects. The first one reinforces the idea of studying mixtures of chemicals instead of single

chemicals to describe more realistic patterns of exposure to air pollutants. This is based on the fact that the major industrial emissions included two or more chemicals (single chemicals were emitted by many facilities, but in relatively smaller amounts: 3% of total emissions). The second one relates to the complexity of the type of mixtures observed. Most of the identified *mixtures* contained large proportions of gases (i.e., NO_2, SO_2, CO) and PM, and smaller proportions of *VOCs*, *PAHs*, *metals*, *other organics* and *other inorganics*. This underlines the potential complexity associated with the study of *mixtures* in epidemiological and toxicological research, when many hazardous chemicals are participating in very small proportions and their effects could be masked by other pollutants. Studies on the toxicity of traffic-related PM have shown that organic content (consisting of potentially many chemical substances) could be related to a higher PM toxicity,[28] but other inorganic elements such as arsenic-content in $PM_{2.5}$ have been associated with an elevated toxicity of this pollutant.[74] The last one underlines the mixtures emitted in –relatively- small amounts but with a high proportional content of toxic *VOCs*, *metals*, *other inorganics*, and *other organics* could potentially be hazardous for adverse birth outcomes and that their further investigation is needed to elucidate their health effects. It has been reported that excessive exposure to heavy metals has been associated with cellular and DNA damage and carcinogenicity[75]. Interestingly, our results showed that *mixtures* with a high proportional content of *VOCs, metals, other inorganics,* or *other organics* were statistically associated with the adverse birth outcomes.

The *VOC*s-*mixtures* showed a statistically significant positive association with SGA. These mixtures may contain chemicals such as benzene, carbon disulphide, toluene, and methanol (whose combined emissions comprised approximately 30 thousand tonnes during the study period; see Supplementary table 3.3). These four chemicals are classified as recognized developmental toxicants.[18] Additionally, they may contain acetaldehyde, ethylbenzene, styrene

and xylene, which were also important contributors to the *VOC*s' emissions into the air and are listed as suspected developmental toxicants. Studies on the relationship between benzene in outdoor air pollution and adverse birth outcomes are sparse, but positive associations have been reported. Benzene exposure during pregnancy has been related to a decrease of biparietal diameter growth,[76] a decrease in head circumference in the fetus,[77] and an increased risk of preterm birth.[22] Currie and Schmieder[4], who have investigated the effect of fetal exposure to toxic releases in the United States, reported positive associations of VOCs and metals with birth weight and gestation duration.

Interestingly, the *heterogeneous-mixtures* containing small proportional content of *VOCs, PM, metals, other inorganics, and other organics* (combined accounted for 2% or more of the individual emissions) showed a statistically significant association with sPTB which may indicate that combinations of high content of gases with other chemical species may exacerbate pro-inflammatory processes.

The *Metals-mixtures, OI-mixtures and OO-mixtures* were statistically associated with iPTB. Previous studies have reported associations among some metals and adverse birth outcomes. A cohort study across Canada[78] found positive associations between mercury in blood samples of pregnant women and SGA. Metals in blood samples may come from many different sources (food, water, soil, dust) and are hypothesized to induce growth restriction through oxidative stress pathways by damaging the vascular endothelium of the placenta causing an impaired nutrient transport[78]. Lead has been more consistently associated with PTB and there is not conclusive evidence about the effects of other metals on PTB.[19] The metals from industrial sources that were released into the air in Alberta during the study period included recognized developmental toxicants (cadmium and mercury) and suspected developmental toxics (cobalt,

and nickel). Metals such as cadmium, chromium, lead, and mercury may induce multiple organ damages, even at lower levels of exposure.[75]

In regard to the association of *OI-mixtures* with iPTB, some studies have related single chemicals included in this group, such as arsenic (recognized as developmental toxicant), chlorine dioxide, and hydrogen fluoride (suspected developmental toxicants) and that were highly emitted during the study period (more than12 thousand tonnes, see Supplementary table 3.3). For example, health-occupational studies in an aluminum smelter facility (that is an important source of hydrogen fluoride) found a higher risk of preterm birth in the spouses of the male production-workers.[79] A study in Huelva[74], that is located close to the largest copper smelter in Spain, demonstrated that some inorganic arsenic species (As III) tend to concentrate in $PM_{2.5}$ representing an added health risk for local populations. On the other hand, the *OO-mixtures* may include hexachlorobenzene, and toluenediisocyanate (mixed isomers), which are recognized developmental toxicants, and HCFC-22 (chlorodifluoromethane) as a suspected developmental toxicant. Hexachlorobenzene is a bioaccumulative, persistent, and toxic chemical released as a by-product/impurity in the manufacturing of chlorinated compounds,[80] whose association with adverse birth outcomes has not been evaluated when present in outdoor air pollution.

PM-mixtures showed positive associations with SGA, which is in line with reported findings elsewhere.[5]

These results are exploratory in nature and other limitations need to be considered. A problem when using the NPRI for estimating environmental exposure is that it provides annual data. That means, we only know the total emissions per year per facility. For this reason, I used proximity analysis and restricted the birth data from April to December to ensure a time window of at least three months of potential exposure. The use of the proximity to sources of *mixtures* as

a proxy of exposure is expected to introduce misclassification bias. Real exposure to *mixtures* depends on other unaccounted factors such as prevailing winds, atmospheric chemistry and secondary pollutant production, mobility and activity patterns of pregnant women, among others. Bell and Belanger[81] reported that: (i) the median of the percentage of pregnant women that changes residence during pregnancy has been estimated at 20% after reviewing fourteen studies in different countries, and that (ii) the median distance moved during pregnancy was < 10 km. I used a 10 km buffer zone around mothers' postal code since it is considered as representative of the scale between 0.2 and 20 km that is regularly used to study human exposure to vehicular-related pollutants (which considers potential travelling distances of some pollutants)[82]. Transport of gases and aerosols varies according to the chemical, but long-range (regional to global) transport of gases and aerosols is well documented.[83] Currie and Schmieder,[4] that aggregated industrial emissions at county level in a national-level study, reported positive associations of prenatal exposure to toluene and cadmium with birth weight and an increased probability of death. Thus, we considered that the 10-km buffer could potentially provide important insights for our initial exploratory study for informing future research.

Although it is possible to apply intensity-distance exposure models by using the annual emissions reported to the NPRI and the distances from sources of mixtures to the maternal postal codes, these models do not consider the potential toxicity associated to the mixture, which is the key issue in studying mixtures. It has been reported that large air-pollutant emissions do not necessarily translate into a higher health risk and that toxicity-weighted approaches provide a better estimation of the health risks associated with air toxic pollutants.[87] Toxicity-weighted approaches incorporate individual toxicity factors previously estimated for weighing the emissions (i.e. the Non-cancer risk score for NO_2 is 2.2 and for Benzene is 8.1 compared to toluene[18]). However, I did not follow a toxicity-weighted approach because the toxicity

equivalency potentials for many of the chemicals included in our study are still unknown (as I explained previously). Consequently, I decided to apply a distance-proximity model as the starting point for identifying potential hazardous mixtures. The identification of potential hazardous mixtures and their sources is just the first step in a chain of steps of risk characterization.[26] Following steps will require (1) measuring or modeling changes in atmospheric concentrations of air pollutants and their environmental deposition, (2) modeling time/activity patterns and measuring individual exposure, and (3) assessing changes in health effects based on dose-response relationships. Complementary *in vitro* and *in vivo* studies would be useful for understanding the interactive biological effects that complex mixtures produce. In this regard, new evidence suggests that the particle size -from coarse to ultrafine-, and the content of secondary inorganic aerosols, black, elemental and primary and secondary organic carbon, and transition metals in the mixtures should be considered to better understand the potential deleterious effects of the air pollutant mixtures.[50]

Other factors that would limit the interpretation of the results are related to the effect of other unmeasured confounders, such as ethnicity, nutrition, and medication during pregnancy. It is expected to reduce the bias associated with confounding variables by incorporating a large set of maternal variables previously identified as relevant for sPTB, iPTB or SGA and an area-level socioeconomic status. Additionally, the use of the three-level of occurrence areas (*low*-, *medium*-, *high*-) may help to control for effect modification effects related to demographic characteristics (i.e., ethnicity, migration status) in combination with exposure disparities, which may be related to adverse birth outcomes.[84,85] For example, the results indicated that most of the high-*ratio* areas of SGA located in urban settings where the affluence of immigrant populations have been considerable in Alberta for the last decade[86] and traffic-related pollution may be higher compared to rural settings. Additionally, the average number of *mixtures* in the 10-km buffer of

the *high*-ratio areas (10 *mixtures* in the *high*-SGA ratio areas and 8 *mixtures* in the high-PTB ratio areas) was higher than then average number of mixtures in the 10 km buffer of the *low*-ratio areas (4 *mixtures* in the *low*-SGA ratio areas and 5 *mixtures* in the low-PTB ratio areas) (data not shown).

Finally, it is important to mention that I tested the associations between the *groups of mixtures* and the adverse birth outcomes and not between the 52 *mixtures* and ABOs due to the problem of multiple comparisons that arose from testing 52 mixtures in the three adverse birth outcomes (i.e., to find significant associations that are falsely significant only by random chance). I estimated that for a significance level of 0.05, random chance would explain 39% of the significant associations. By aggregating the mixtures into the broader *groups of mixtures* the sample size by groups increased for statistical analysis and reduced the false positive rate to some extent.

3.6. Conclusion

In this study, I characterized air pollutant mixtures from industrial sources in Alberta from 2006 to 2012 and explored their associations with small for gestational age (SGA), spontaneous preterm birth (sPTB) and induced preterm birth (iPTB) for informing future research. Results showed that (i) more than one hundred of chemicals are released into the air by industrial facilities; (ii) gases (NO_2, CO, SO_2) and PM were the main components in the *mixtures*; (iii) however, groups of mixtures with high proportional content of *VOCs*, *Metals*, *other organics*, and *other inorganic* substances are sparse but that were associated to either SGA, iPTB or sPTP; (iv) *VOCs-mixt*ures were associated with increased odds of SGA; (v) *Metals-mixtures*, *Other-inorganics mixtures* and *Other-organics mixtures* were associated with increased odds of iPTB; (v) *Mixtures* with a high proportional content of gases and PM were associated with increased

odds of sPTB and SGA respectively. These results may motivate and justify further research aimed to elucidate associations between ambient mixtures of hazardous chemicals released into the air from industrial sources and adverse birth outcomes.

3.7. Acknowledgments

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Table 3.1. Annual emissions into the air by chemical-class. Alberta, 2006-2012.

Chemical-class	Total (tonnes)	%	2006 (tonnes)	2007 (tonnes)	2008 (tonnes)	2009 (tonnes)	2010 (tonnes)	2011 (tonnes)	2012 (tonnes)
Nitrogen oxides (expressed as NO_2)	2,658,483	37.916	434,844	427,978	391,984	377,302	353,277	344,574	328,524
Sulphur dioxide (SO_2)	2,478,493	35.349	405,614	386,363	363,210	357,698	339,932	320,732	304,945
Carbon monoxide (CO)	1,498,960	21.379	207,043	211,483	197,758	223,898	229,442	197,639	231,698
Particulate Matter (PM)*	183,524	2.617	28,044	28,192	26,950	26,269	26,799	23,747	23,522
Other inorganic	96,296	1.373	14,476	13,124	12,897	12,195	12,574	12,090	18,941
Volatile Organic Compounds (VOC)	93,892	1.339	12,678	12,101	16,053	16,059	16,245	10,838	9,918
Other organic	670	0.010	168	160	141	180	5	8	8
Metals	662	0.009	50	39	47	131	117	236	41
Nitrosamines/ethers/alcohols (N/E/A)	304	0.004	87	70	43	30	22	26	27
Polycyclic aromatic hydrocarbons (PAHs)	179	0.003	34	25	25	13	24	38	19
Totals	**7,011,463**	**100.0**	**1,103,038**	**1,079,534**	**1,009,107**	**1,013,776**	**978,438**	**909,929**	**917,642**

*Particulate Matter is represented by total particulate matter (TPM). Amounts of PM_{10} and $PM_{2.5}$ were not considered for this table (they jointly accounted for and additional 11,560.70 tonnes, for reaching a total of 7,023,023.82 tonnes).

Table 3.2. Releases of chemical-classes into the air by industrial sector. Alberta, 2006-2012.

Industrial Sector	Total (tonnes)	%	SO_2 (tonnes)	NO_2 (tonnes)	CO (tonnes)	PM* (tonnes)	VOC (tonnes)	PAHs (tonnes)	Metals (tonnes)	Other Inorganic (tonnes)	N/E/A** (tonnes)	Other Organic (tonnes)
Conventional Oil and Gas Extraction	3,046,739	43.454	661,787.10	1,527,762.94	824,864.05	5,866.31	21,526.21		2.54	4,928.07	1.58	
Electricity	1,568,759	22.374	840,627.73	560,101.36	100,001.66	51,082.29	28.30		98.82	16,818.64		0.01
Non-Conventional Oil Extraction (including Oil sands and Heavy Oil)	1,374,665	19.606	818,608.65	294,533.60	165,584.04	44,920.53	35,536.40	33.81	103.71	15,332.86	0.01	11.62
Wood Products	266,687	3.804	87.11	8,676.75	240,435.29	11,555.05	5,890.32	0.64	39.24	0.09		2.32
Chemicals	213,069	3.039	14,634.12	88,407.41	40,299.60	11,548.62	11,536.65	122.04	12.36	45,860.38	17.42	630.22
Pulp and Paper	130,512	1.861	33,467.27	29,063.77	47,224.77	8,079.64	8,855.99	5.58	135.92	3,679.52		0.00
Petroleum and Coal Product Refining and Mfg.	127,776	1.822	56,176.01	30,705.60	27,013.47	10,513.50	1,626.61	8.52	5.95	1,724.72	1.78	0.00
Cement, Lime and Other Non-Metallic Minerals	74,082	1.057	10,850.94	39,193.61	14,871.00	8,705.48	101.48	7.27	14.09	338.47		0.00
Oil & Gas Pipelines and Storage	65,905	0.940	2,391.56	43,206.15	16,953.52	1,814.73	1,460.37	0.04	0.00	78.49		
Aluminum	36,226	0.517	33,274.19	1,777.15	207.98	721.35	245.70		0.01			
Mining and Quarrying	33,986	0.485	517.18	11,120.99	6,857.28	15,486.44	3.53	0.14				
Other Manufacturing	22,050	0.314	2,945.54	3,528.13	4,045.74	4,760.89	5,793.16		186.55	708.06	81.74	
Metals (Except Aluminum and Iron and Steel)	18,643	0.266	1,238.69	13,502.69	1,293.37	740.46			2.01	1,866.01		
Other (Except Manufacturing)	18,246	0.260	163.88	5,954.82	4,819.88	6,737.24	507.90	0.23	6.72	53.63	0.84	0.97
Iron and Steel	6,468	0.092	443.42	823.34	4,124.64	975.98	26.99		50.87	22.38		0.00
Water and Wastewater Systems	6,156	0.088	1,279.69					0.24		4,876.21		
Plastics and Rubber	941	0.013					713.78		1.33		200.87	24.62
Waste Treatment and Disposal	553	0.008		124.44	363.95	15.47	38.88		2.14	8.50		0.00
Totals	**7,011,463**	**100.000**	**2,478,493.07**	**2,658,482.75**	**1,498,960.25**	**183,523.99**	**93,892.27**	**178.50**	**662.26**	**96,296.03**	**304.23**	**669.76**

* Particulate Matter is represented by total particulate matter (TPM). Amounts of PM_{10} and $PM_{2.5}$ were not considered for this table (they jointly accounted for and additional 11,560.70 tonnes, for reaching a total of 7,023,023.82 tonnes).

** N/E/A = Nitrosamines/ethers/alcohols

Table 3.3 Characterization of *mixtures* by the proportional content of the ten chemical classes. Number of facilities and total emissions by *mixtur*e. Alberta, 2006-2012.

Group of mixtures	*mixture*	*SO_2 (%)*	*NO_2 (%)*	*CO (%)*	*PM (%)*	*VOC (%)*	*PAHs (%)*	*Metals (%)*	*OI* (%)*	*N/E/A** (%)*	*OO*** (%)*	Fac. #	*tonnes*
Heterogeneous-mixtures	**1**	20.6	31.1	44.2	2.2	1.0	5.E-04	1.E-02	0.9			31	186,497
	2	39.8	23.8	34.4	0.9	0.9	1.E-04	3.E-04	0.3			26	81,335
	3	0.5	42.5	27.7	17.5	11.4	7.E-05	0.4	0.0		6.E-05	19	48,943
	4	6.0	14.3	41.7	27.2	9.8		5.E-02	0.9		2.E-02	15	19,708
	5	35.0	49.2	13.2	1.7	0.6	6.E-04	8.E-04	0.3		3.E-07	30	776,340
	6	56.7	30.2	9.5	2.0	1.1	1.E-03	1.E-03	0.4		8.E-08	**39**	**1,546,537**
	7	2.3	17.2	7.6	2.9	11.4		2.E-04	35.9	0.1	14.6	12	123,217
NO_2-CO	**8**		50.1	49.4	0.4			2.E-03				149	102,573
	9	4.E-02	54.8	44.8	0.3	1.E-02		5.E-07	0.0			160	129,706
	10		46.2	53.7	0.1	1.E-03						87	79,645
	11	2.E-02	42.4	57.4	0.2	1.E-02	2.E-06					134	123,490
NO_2-mixtures	**12**	0.6	60.0	38.0	0.3	0.1	3.E-05	4.E-05	4.E-02	1.2	1.E-02	245	265,024
	13	4.E-02	64.6	35.0	0.3	0.1	4.E-05	3.E-06	3.E-03			150	107,140
	14	2.E-02	69.5	30.2	0.2							153	141,124
	15	0.1	74.1	25.3	0.5	1.E-03						102	109,247
	16	13.9	67.1	18.2	0.4	0.2			0.2			21	49,107
	17	17.6	81.3	0.9	0.3							16	8,416
	18	8.E-03	75.3	1.6	22.5	0.2	5.E-05	2.E-05	0.4	5.9	1.E-05	17	35,259
	19		78.9	20.8	0.2	1.E-03		6.E-09				137	123,112
	20	0.8	82.2	16.4	0.3	0.2	2.E-02		4.E-02			95	151,290
	21	4.E-02	86.2	13.5	0.2	0.0			3.E-03			122	147,090
	22		89.7	10.1	0.3							74	63,771
	23	1.E-02	99.5	0.0	0.5							202	80,363
	24		95.6		4.4			3.E-03	8.E-03		5.E-05	41	3,720
	25	4.E-02	94.7	5.1	0.1	3.E-02			5.E-04			151	112,938
	26		100.0									1250	179,087
SO_2-mixtures	**27**	66.3	9.1	17.8	1.4	4.4			1.1			21	124,009
	28	83.5	7.2	4.0	4.3	0.7	1.E-05	0.1	0.2			41	489,691
	29	96.8	0.1	0.2	2.8	3.E-02			1.E-02			86	113,832
	30	73.6	13.9	6.5	3.6	1.0	1.E-04	1.E-02	1.4		2.E-03	1	716,437
	31	100.0										12	1,010
CO-mixtures	**32**	5.E-05	39.3	60.6	0.1	1.E-03						199	81,580
	33	0.2	36.8	62.4	0.5	0.0		3.E-05	4.E-02			214	158,100
	34		33.1	66.7	0.1	3.E-02			1.E-03			61	37,148

Group of mixtures	*mixture*	*SO_2 (%)*	*NO_2 (%)*	*CO (%)*	*PM (%)*	*VOC (%)*	*PAHs (%)*	*Metals (%)*	*OI* (%)*	*N/E/A** (%)*	*OO*** (%)*	Fac. #	*tonnes*
	35		16.6	83.3	0.1	1.E-03						44	42,079
	36	0.1	26.7	73.0	0.2	0.0						96	47,502
	37	3.E-03	0.7	97.5	1.7	3.E-03	6.E-05	7.E-03	1.E-03			53	275,669
	38	0.6	2.7	84.6	10.6	1.5	3.E-05	2.E-05	0.1		5.E-04	22	46,408
	39	0.3	4.3	65.2	29.3	0.8		2.E-02	0.1		3.E-07	35	22,152
	40			100.0								348	23,172
PM-mixtures	**41**	1.E-02	8.2	3.5	74.2	5.5	5.E-05	3.3	5.3			30	15,083
	42				99.5	0.1		0.1	0.3		4.E-02	24	2,930
	43				100.0							1349	14,763
VOCs-mixtures	**44**				1.9	95.5	1.E-02	4.E-02	2.5			23	1,340
	45	7.E-03	2.4	2.4	4.2	74.0		3.4	9.2		3.5	19	3,898
	46	2.E-03	0.3	0.3	38.7	60.7						8	1,051
	47					100.0						74	2,499
OI-mixtures	**48**	7.0			2.2	0.6	7.E-04	0.9	89.2			13	7,712
	49								100.0			5	80
Metal-mixtures	**50**				10.4			89.5	0.1			5	194
	51							100.0				17	4
OO-mixtures	**52**										100.0	1	1

* *OI* = other inorganics
** *N/E/A* = Nitrosamines/ethers/alcohols
*** *OO* = other organics

Table 3.4. Groups of mixtures. Number of facilities and total emissions. Alberta, 2006-2012.

Group of mixtures	Description	# mixtures included	Facilities (#)	Facilities (%)	*tonnes*	*tonnes* (%)
Heterogeneous	Any group is less that 60%	11	702	11.18	3,217,990.93	45.82
NO_2-mixtures	NO2 ≥ 60% of the emissions	15	2,776	44.21	1,576,689.49	22.45
SO_2-mixtures	SO2 ≥ 60% of the emissions	5	161	2.56	1,444,978.58	20.57
CO-mixtures	CO ≥ 60% of the emissions	9	1,072	17.07	733,809.27	10.45
*PM-mixtures**	PM ≥ 60% of the emissions	3	1,403	22.34	32,776.54	0.47
VOC-mixtures	VOC ≥ 60% of the emissions	4	124	1.97	8,787.81	0.13
*OI-mixtures***	OI ≥ 60% of the emissions	2	18	0.29	7,792.33	0.11
Metals-mixtures	Metals ≥ 60% of the emissions	2	22	0.35	197.88	2.82E-03
*OO-mixtures****	OO ≥ 60% of the emissions	1	1	0.02	1	1.42E-05
	TOTALS	**52**	**6,279**	**100**	**7,023,023.82**	**100.00**

* PM represent Total PM (TPM) when it is reported; $PM_{10,}$ when TPM is not reported; $PM_{2.5}$, when TPM and PM_{10} is not reported.
** *OI* = other inorganics;
*** *OO* = other organics

Table 3.5. Proportional contribution (%) of the 19 key industrial sectors to the *groups of mixtures*. Alberta, 2006-2012.

Sector*	*NO_2-mixtures*	*PM-mixtures*	*CO-mixtures*	*Heterogeneous mixture*	*SO_2-mixtures*	*VOCs mixtures*	*Metals mixtures*	*OI** mixtures*	*OO*** mixtures*
1	86.02	16.40	54.32	21.27	42.25	2.83	1.64		
2	1.99	0.03	6.10	46.40					
3	0.21	0.02	1.52	17.78	54.57	0.25			
4	0.02	6.19	33.20	0.64					
5	4.40	0.06	0.31	4.30	0.16	8.67	0.35		
6	0.03		1.07	3.80					
7	0.82	14.46	0.20	3.33	0.12				
8	1.57	1.77	0.51	1.40					
9	3.38	6.95	0.32	0.18	0.10	12.89			
10					2.49	2.79			
11	0.19	27.99	0.56	0.55					
12	0.10	6.44	0.70	0.12	0.31	58.31	95.37	2.55	
13	1.09							17.63	
14	0.18	19.59	0.25	0.22		5.45	0.95	0.35	
15			0.88			0.32			
16								79.43	
17						8.03	0.67		100
18		0.08				0.42	1.01	0.04	
19						0.03			
Totals	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**

* 1 (Conventional Oil and Gas Extraction); 2 (Electricity); 3 (Non-Conventional Oil Extraction, including Oil sands and Heavy Oil); 4 (Wood Products); 5(Chemicals); 6 (Pulp and Paper); 7 (Petroleum and Coal Product Refining and Mfg.); 8 (Cement, Lime and Other Non-Metallic Minerals); 9 (Oil & Gas Pipelines and Storage); 1 (Aluminum); 11 (Mining and Quarrying); 12 (Other Manufacturing); 13 (Metals, except Aluminum and Iron and Steel); 14 (Other, except Manufacturing); 15 (Iron and Steel); 16 (Water and Wastewater Systems); 17 (Plastics and Rubber); 18 (Waste Treatment and Disposal); 19 (Transportation Equipment Mfg.). White cells express values equal to zero or less than 1%.
** OI = other inorganics.
*** OO = other organics.

Table 3.6. Adjusted odds ratios (adj-OR) for groups of mixtures by ABO. Alberta, 2006-2012.

ABO	*Group of mixture*	low-ratio areas adj-OR	95%CI	medium-ratio areas adj-OR	95%CI	high-ratio areas adj-OR	95%CI
SGA[1]		(n=23,587)		(n=210,471)		(n=16,693)	
	Heterogenous	0.90	[0.75, 1.07]	0.97	[0.93, 1.01]	1.14	[0.98, 1.33]
	NO_2CO	1.03	[0.89, 1.19]	1.00	[0.96, 1.03]	0.97	[0.87, 1.07]
	NO_2	1.01	[0.88, 1.19]	1.03	[0.99, 1.08]	1.17	[0.88, 1.55]
	SO_2	0.91	[0.73, 1.14]	0.94	[0.90, 0.99]	0.93	[0.83, 1.03]
	CO	1.00	[0.87, 1.14]	1.04	[1.00, 1.09]	1.00	[0.76, 1.32]
	PM	1.08	[0.92, 1.26]	1.08	[1.02, 1.13][4]	0.73	[0.57, 0.93]
	VOC	0.98	[0.81, 1.21]	1.00	[0.95, 1.05]	1.37	[1.11, 1.69][4]
	OI	1.17	[0.95, 1.43]	0.99	[0.95, 1.04]	1.09	[0.94, 1.26]
	Metals	0.83	[0.64, 1.08]	1.05	[1.00, 1.10]	0.92	[0.74, 1.14]
	OO	omitted		1.05	[0.98, 1.11]	0.84	[0.72, 0.98]
sPTB[2]		**(n=14,125)**		**(n=124,665)**		**(n=10,930)**	
	Heterogenous	1.07	[0.81, 1.41]	0.96	[0.90, 1.02]	1.36	[1.13, 1.63][4]
	NO_2CO	1.00	[0.81, 1.23]	1.00	[0.94, 1.05]	0.92	[0.78, 1.09]
	NO_2	0.85	[0.69, 1.04]	1.00	[0.93, 1.06]	0.96	[0.78, 1.20]
	SO_2	1.18	[0.87, 1.60]	1.07	[1.01, 1.15]	0.96	[0.79, 1.15]
	CO	1.01	[0.90, 1.34]	0.98	[0.91, 1.05]	1.06	[0.86, 1.30]
	PM	0.87	[0.68, 1.09]	1.01	[0.93, 1.09]	0.81	[0.66, 1.01]
	VOC	0.89	[0.67, 1.18]	1.07	[0.99, 1.15]	1.08	[0.84, 1.39]
	OI	0.86	[0.61, 1.21]	1.08	[1.01, 1.15]	0.98	[0.82, 1.18]
	Metals	1.10	[0.83, 1.47]	0.96	[0.89, 1.03]	1.22	[0.98, 1.52]
	OO	omitted		0.97	[0.87, 1.07]	0.89	[0.64, 1.25]
iPTB[3]		**(n=6,265)**		**(n=56,216)**		**(n=5,161)**	
	Heterogenous	0.93	[0.61, 1.41]	0.89	[0.81, 0.98]	1.00	[0.74, 1.32]
	NO_2CO	1.16	[0.85, 1.58]	1.03	[0.96, 1.12]	0.96	[0.75, 1.23]
	NO_2	1.13	[0.84, 1.53]	1.04	[0.94, 1.15]	1.20	[0.85, 1.68]
	SO_2	0.83	[0.52, 1.32]	0.91	[0.83, 1.01]	1.00	[0.76, 1.30]
	CO	0.96	[0.71, 1.29]	0.99	[0.90, 1.10]	0.90	[0.65, 1.23]
	PM	1.05	[0.74, 1.48]	0.99	[0.88, 1.11]	1.32	[0.95, 1.83]
	VOC	1.02	[0.65, 1.59]	0.97	[0.86, 1.01]	0.85	[0.60, 1.21]
	OI	1.53	[0.96, 2.44]	1.17	[1.06, 1.28][4]	1.11	[0.85, 1.45]
	Metals	0.96	[0.64, 1.45]	1.17	[1.05, 1.30][4]	1.25	[0.90, 1.73]
	OO	omitted		1.24	[1.09, 1.41][4]	1.36	[0.87, 2.12]

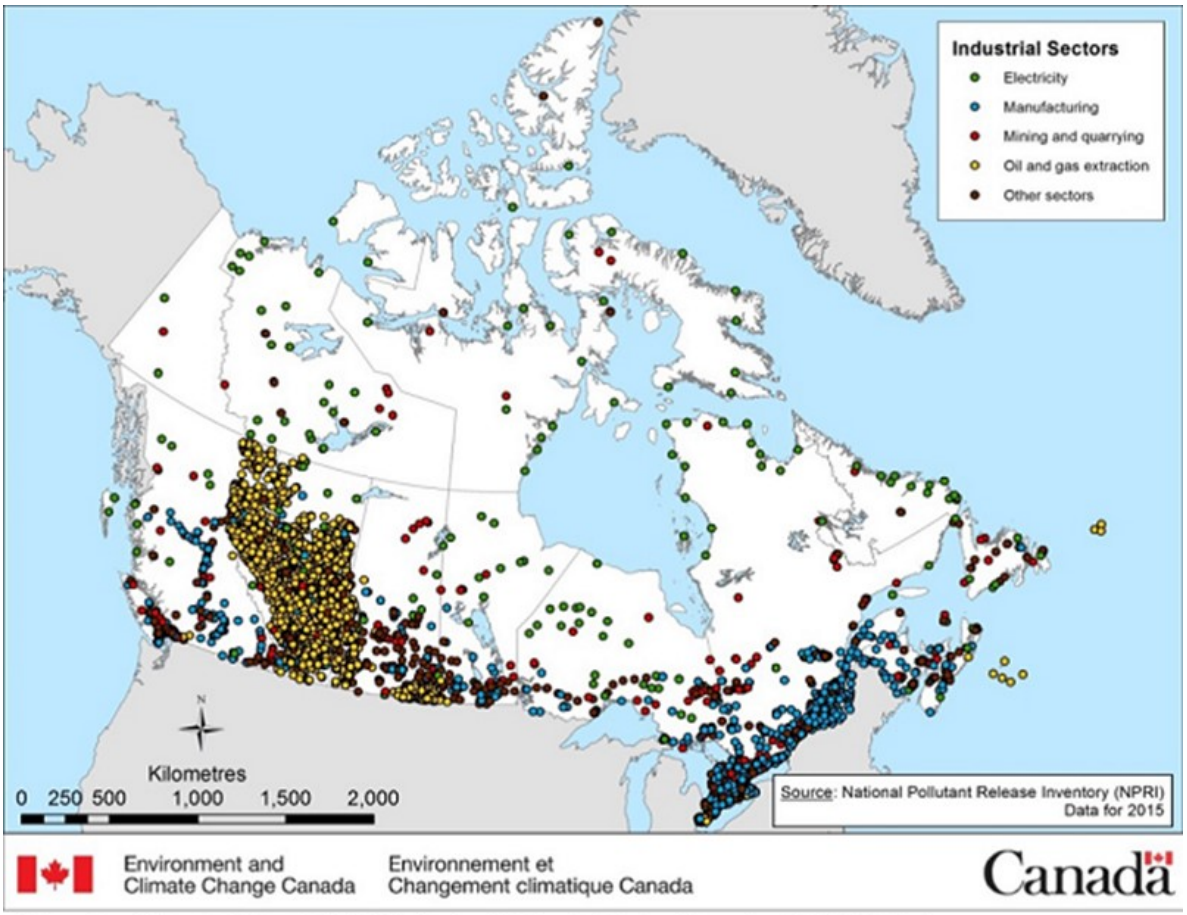
[1]adj-OR for SGA: Covariates: SES-index, age-category, more than one child in the past, smoking during pregnancy, substance use during pregnancy, past-SGA, pre-diabetes, pre-hypertension, gestational-diabetes, gestational-hypertension, pre-existing other medical disorders.

[2]adj-OR for sPTB: Covariates: SES-index, age-category, more than one child in the past, smoking during pregnancy, substance use during pregnancy, past-preterm, pre-diabetes, pre-hypertension, gestational-diabetes, gestational-hypertension, pre-existing other medical disorders, pre-pregnancy maternal weight < 45kg, pre-pregnancy maternal weight > 91 kg, bleeding during pregnancy.

[3]adj-OR for iPTB: Covariates: SES-index, age-category, more than one child in the past, smoking during pregnancy, substance use during pregnancy, past-preterm, pre-diabetes, pre-hypertension, gestational-diabetes, gestational-hypertension, pre-existing other medical disorders, bleeding during pregnancy, blood antibodies, proteinuria.

[4] Highlighted ORs indicates p-value < 0.006 (Level of significance was 0.0055 after Bonferroni's correction).

Figure 3.1. Map of facilities reporting direct releases to air in 2014, by sector, and reported total quantities of these releases.



Source: Environment and Climate Change Canada. Summary of Data Reported for 2015. National Pollutant Release Inventory (NPRI) Fact Sheet. [Internet]. [cited 2017 July 3]. Available from: http://www.ec.gc.ca/inrp-npri/default.asp?lang=En&n=D55C89B3-1

Figure 3.2. Map of facilities reporting direct releases to air. Alberta, 2006-2012.

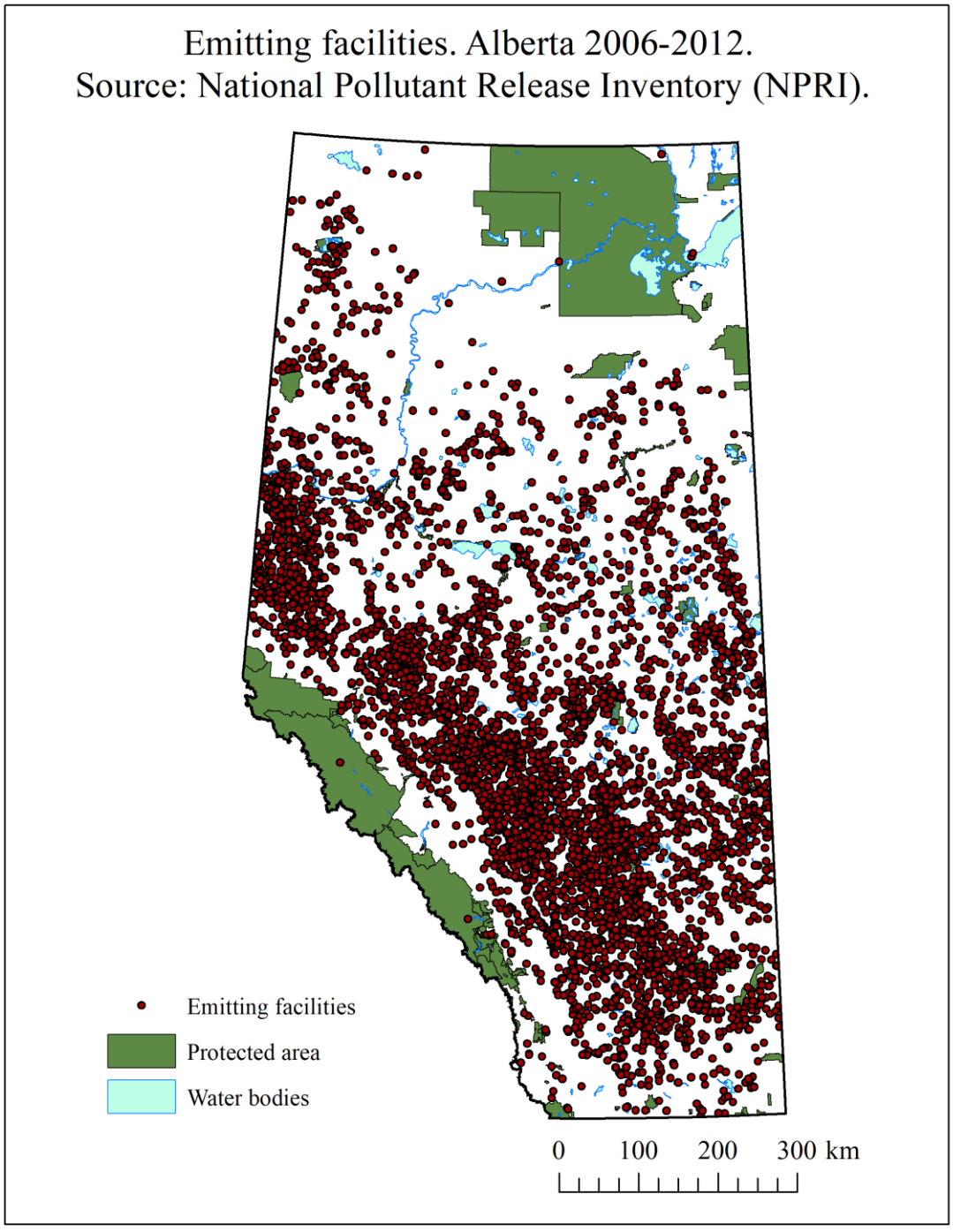


Figure 3.3 Total *tonnes* (left y-axis) of pollutant releases to the air and number of chemicals (right y-axis) reported. Alberta 2006-2012.

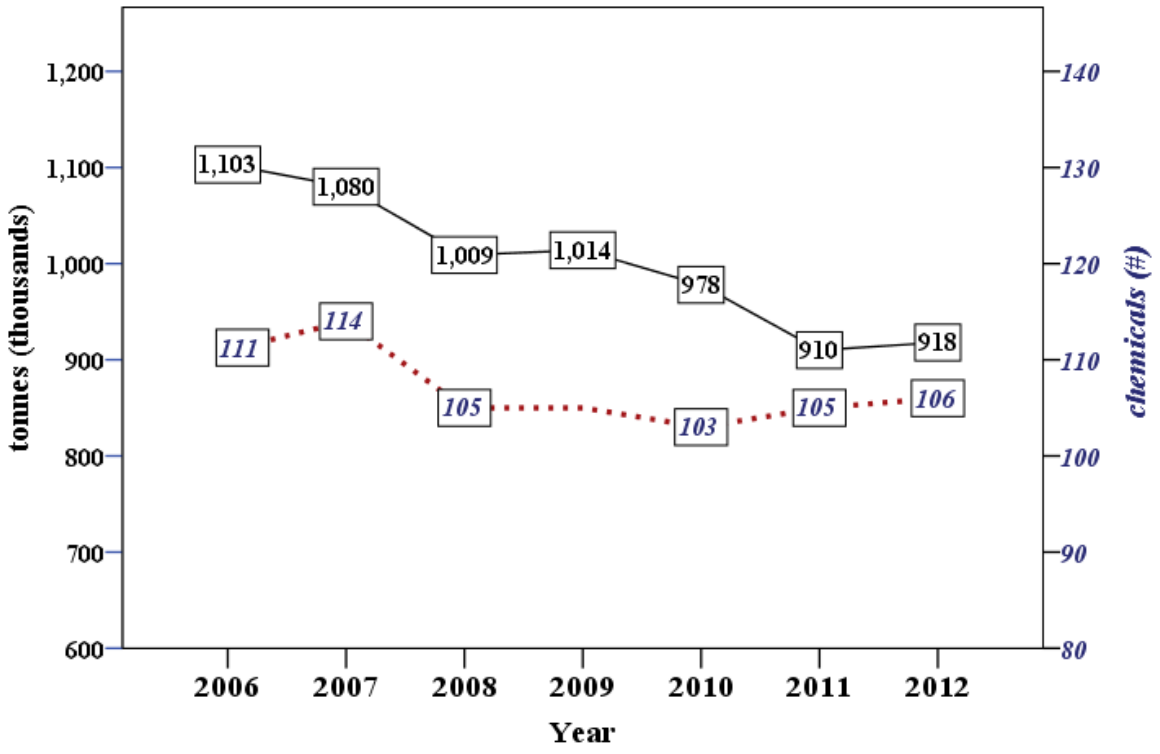


Figure 3.4 Percent distribution of the ten chemical-classes of pollutants released to the air in by the main industrial sectors. Alberta, 2006-2012.

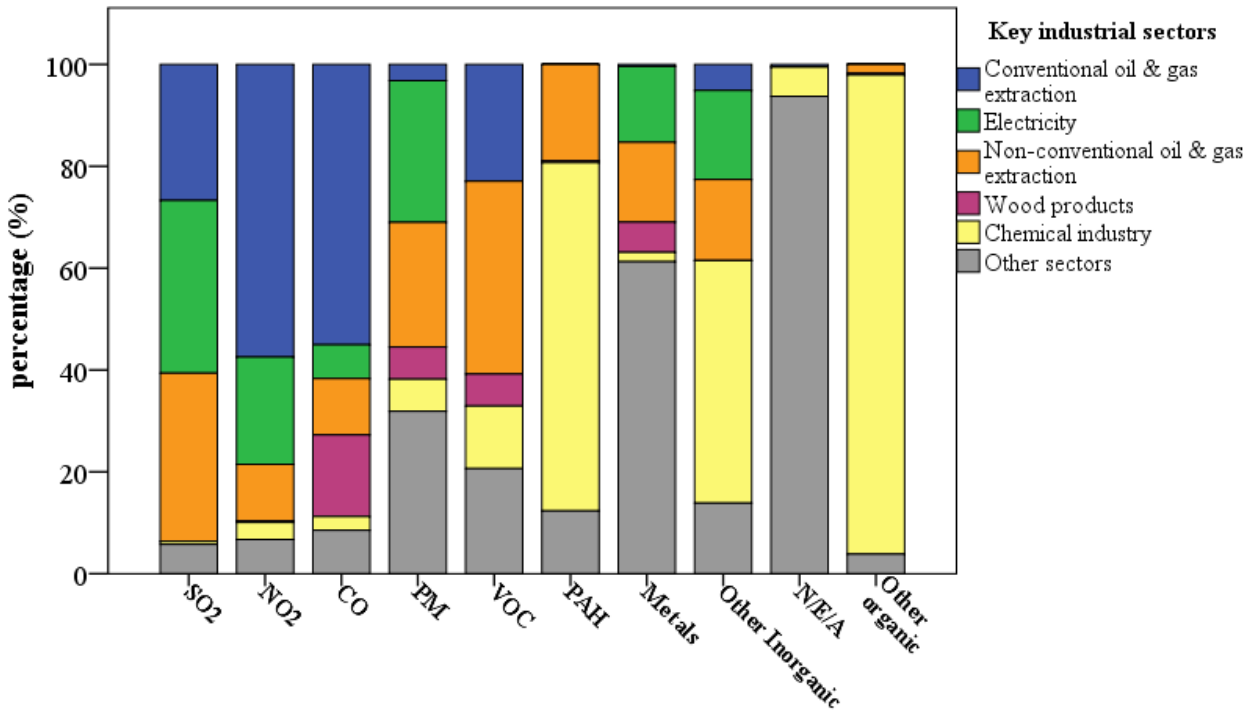


Figure 3.5. Facilities emitting mixtures with high proportional content (≥ 60%) of NO_2. Alberta, 2006-2012

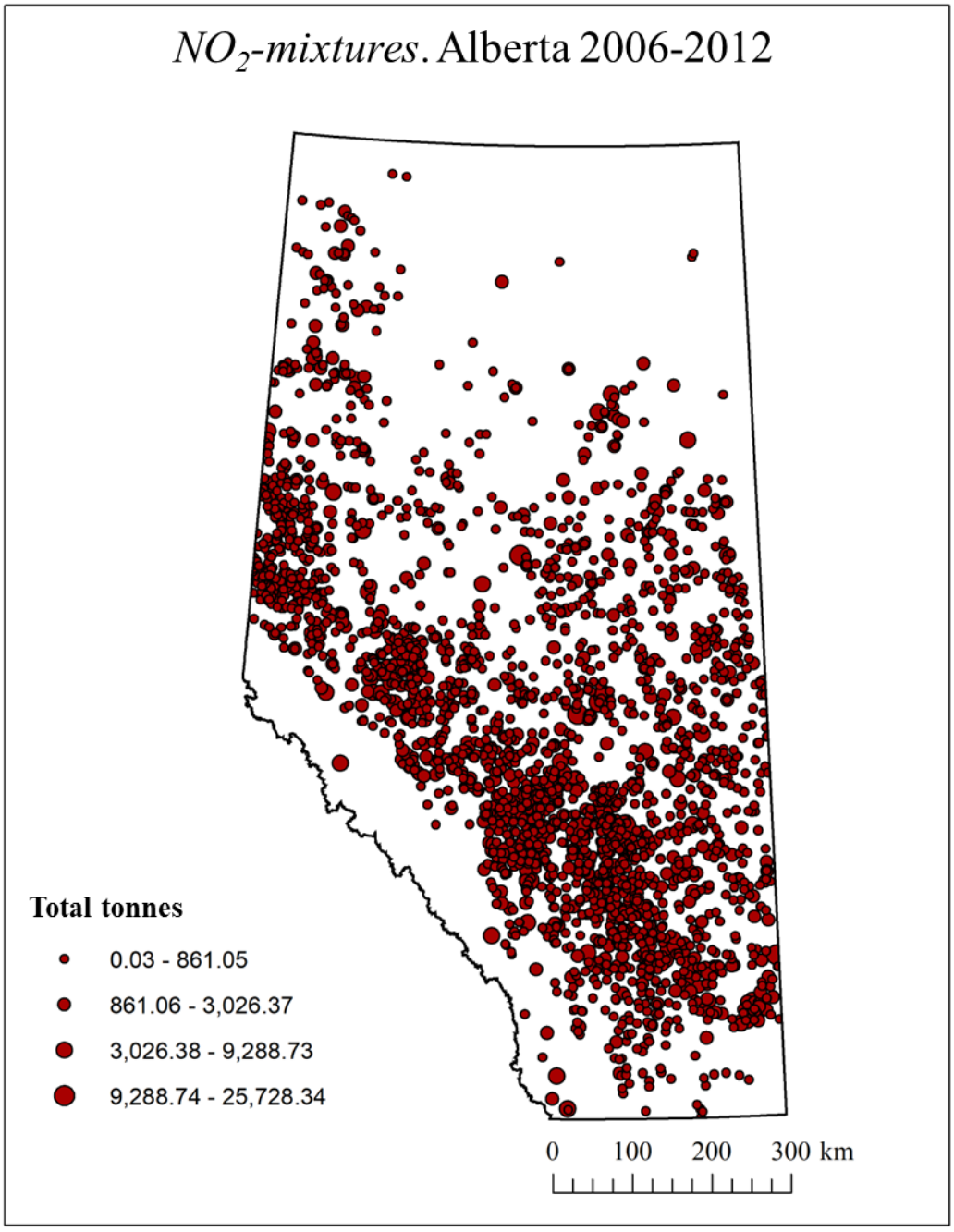


Figure 3.6. Facilities emitting mixtures with high proportional content (≥ 60%) of CO. Alberta, 2006-2012.

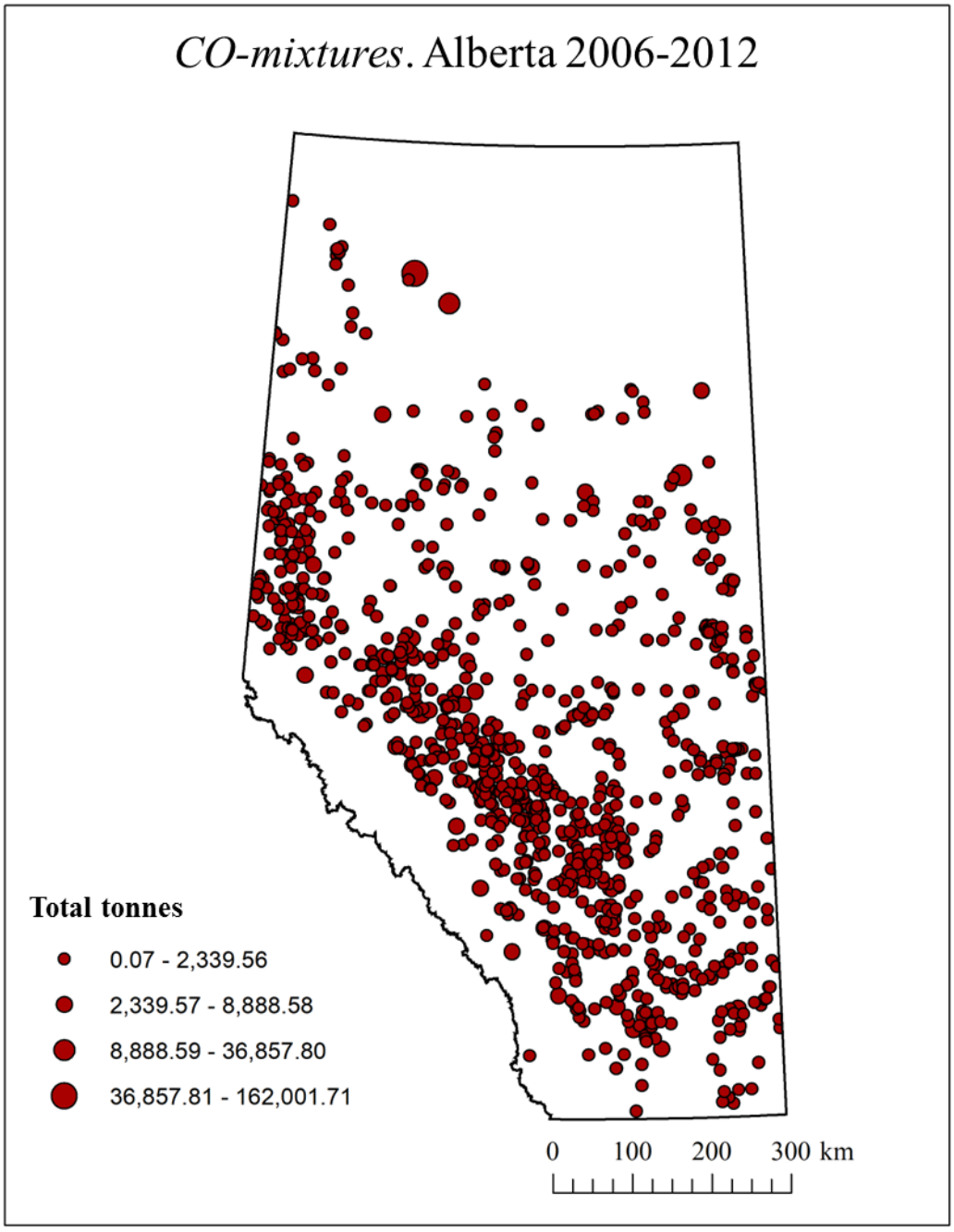


Figure 3.7. Facilities emitting mixtures with high proportional content (≥ 60%) of PM. Alberta, 2006-2012.

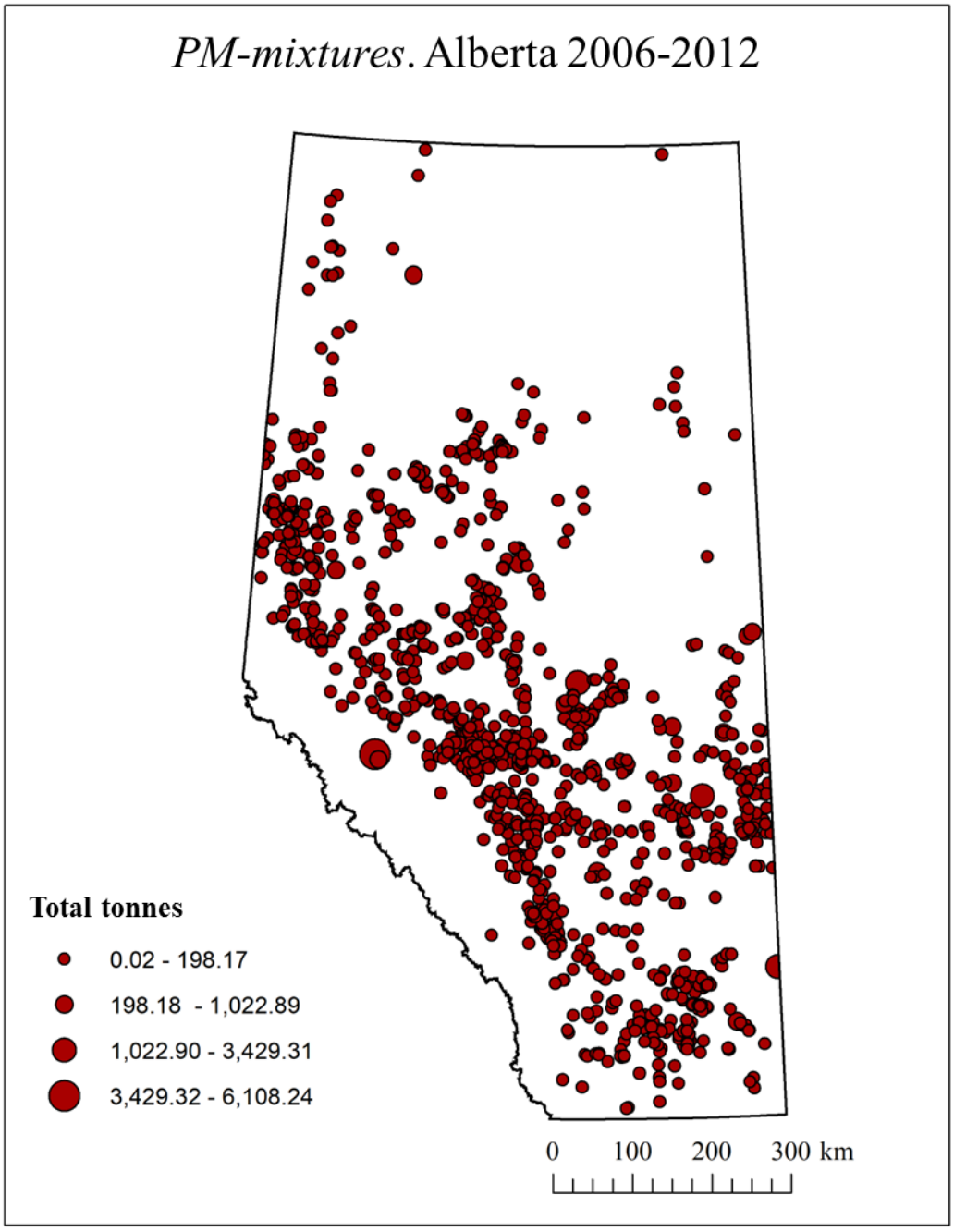


Figure 3.8 Facilities emitting mixtures with no dominance (≥ 60%) of some chemical class. Alberta, 2006-2012.

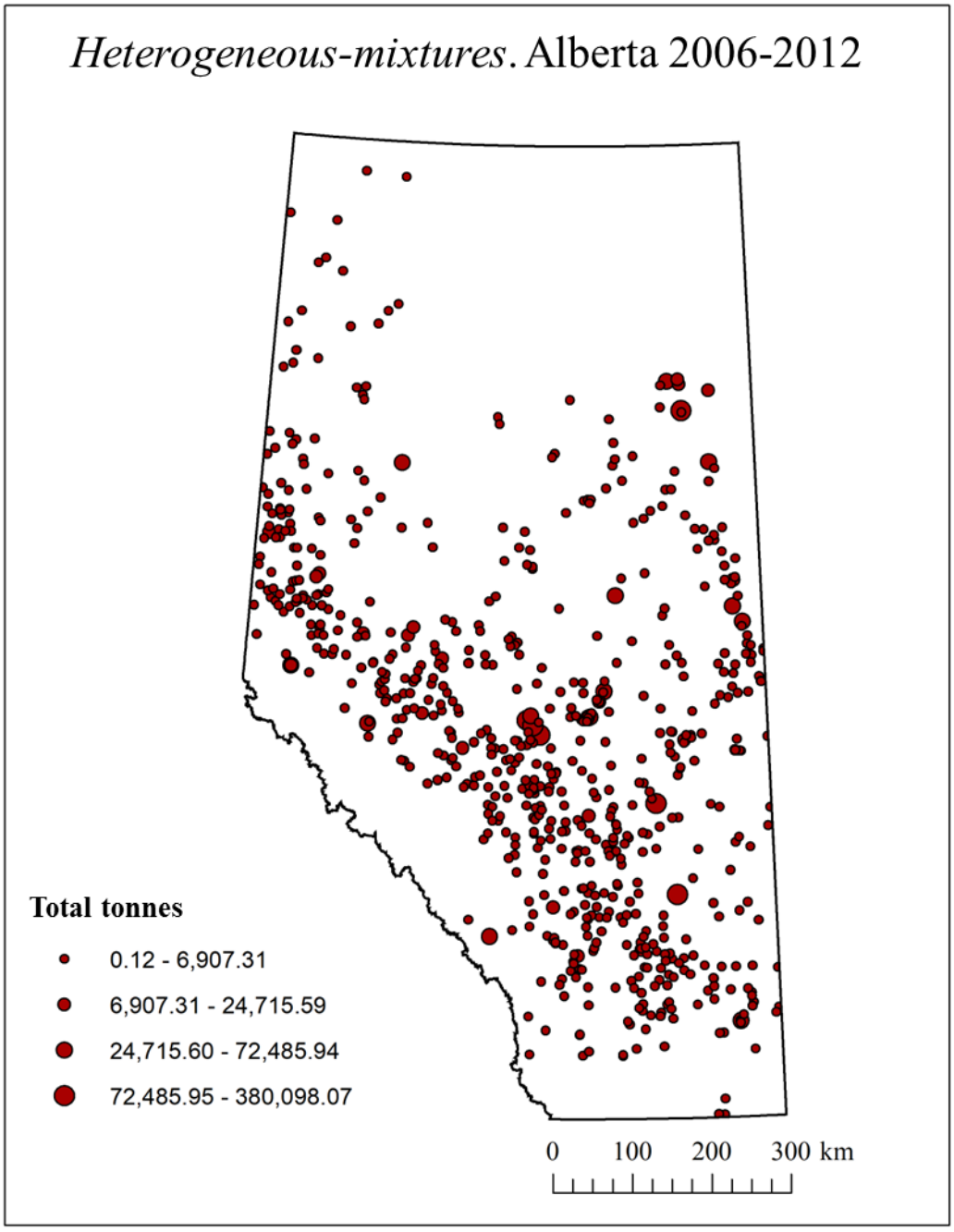


Figure 3.9. Facilities emitting mixtures with high proportional content (≥ 60%) of SO_2. Alberta, 2006-2012.

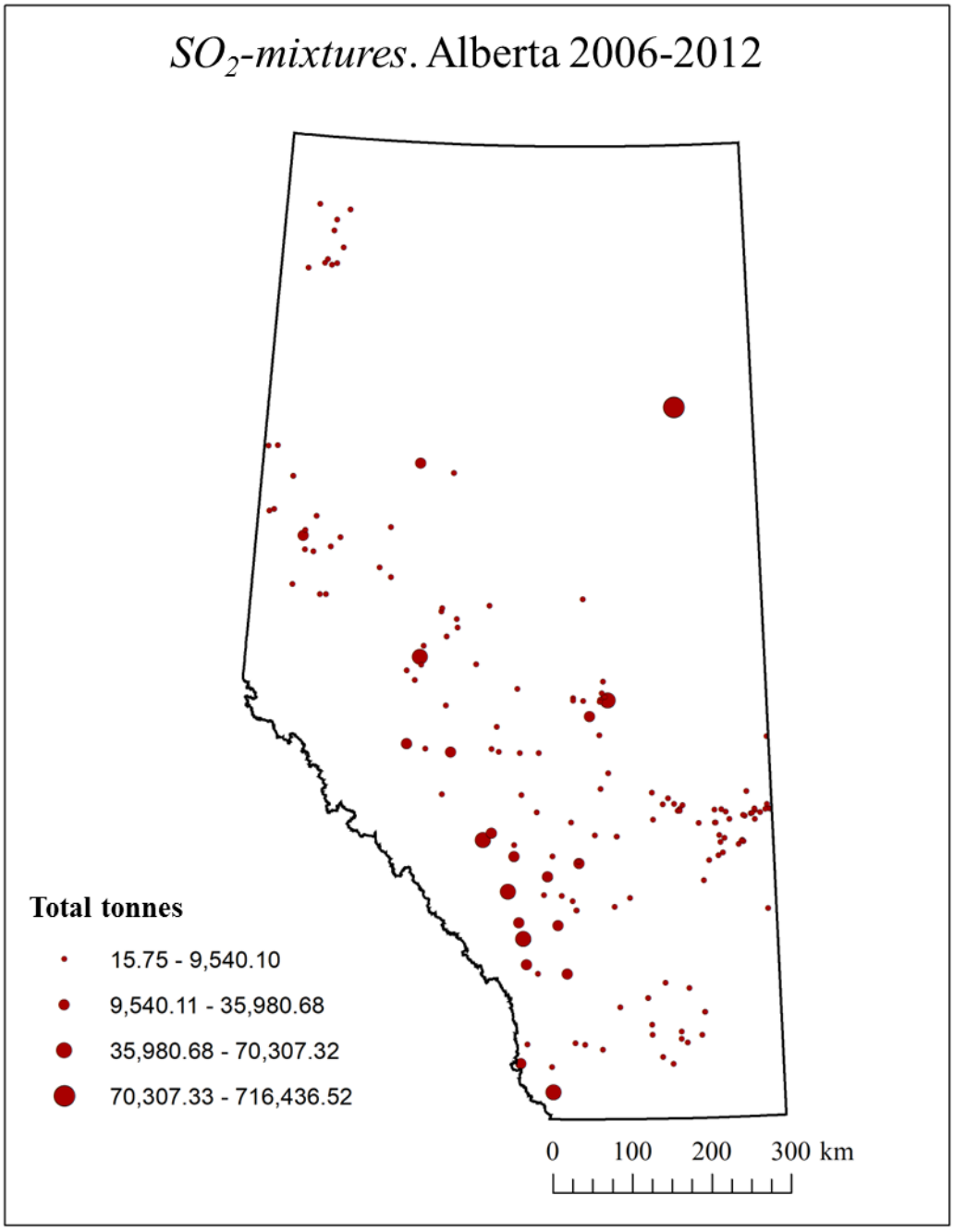


Figure 3.10 Facilities emitting mixtures with high proportional content (≥ 60%) of *VOCs*. Alberta, 2006-2012.

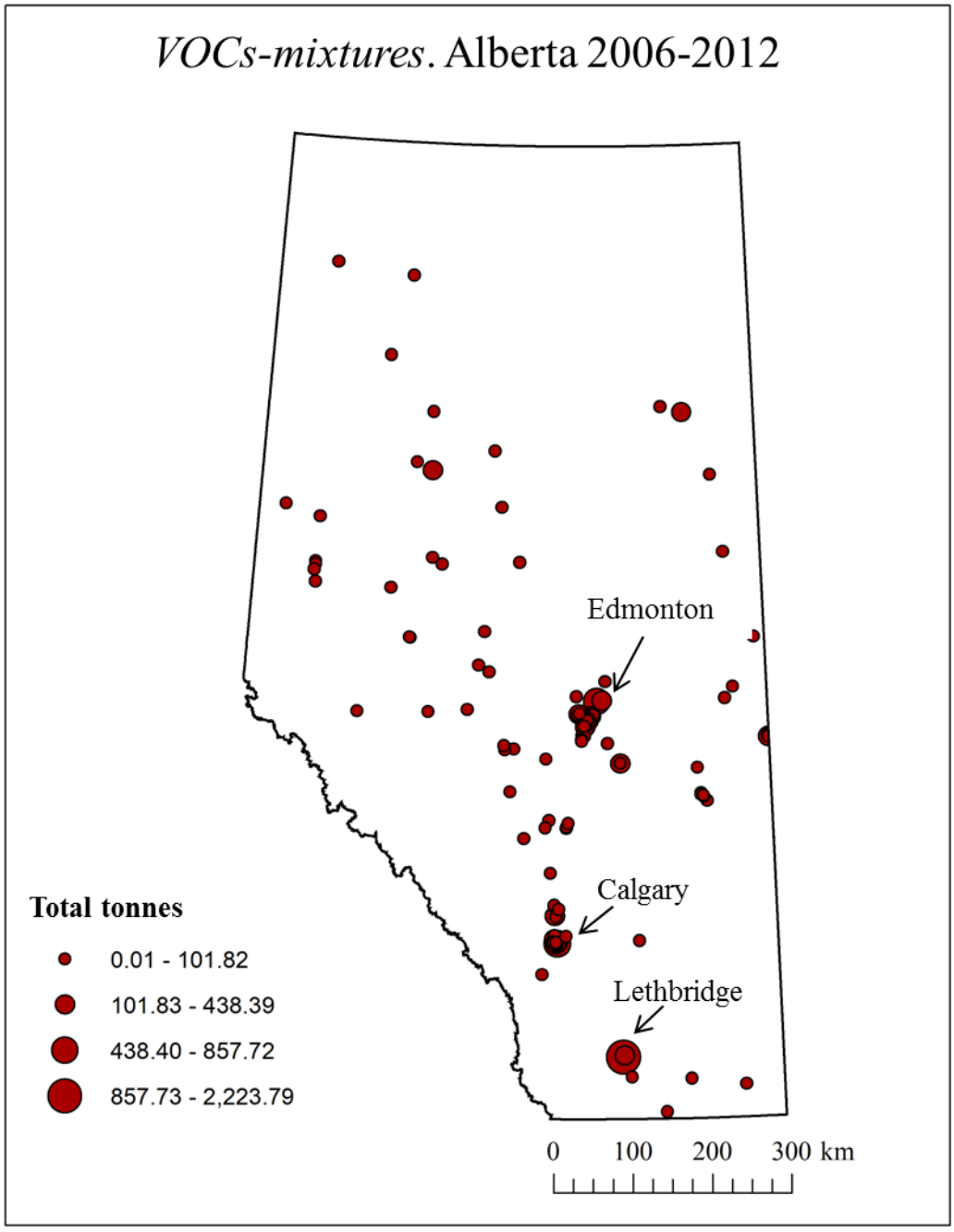


Figure 3.11 Facilities emitting mixtures with high proportional content (≥ 60%) of *Metals*. Alberta, 2006-2012.

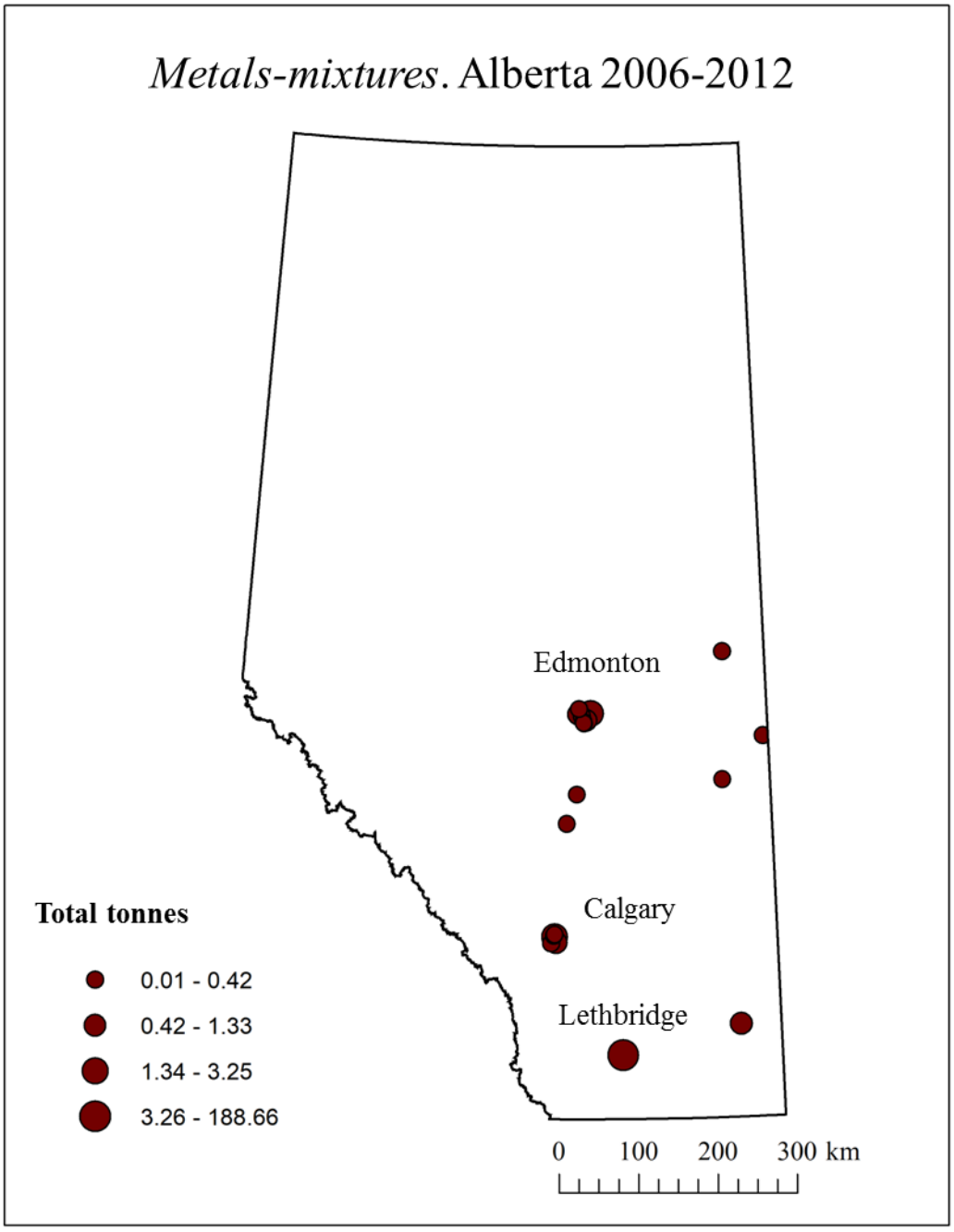


Figure 3.12 Facilities emitting mixtures with high proportional content (≥ 60%) of *Other-inorganics*. Alberta, 2006-2012.

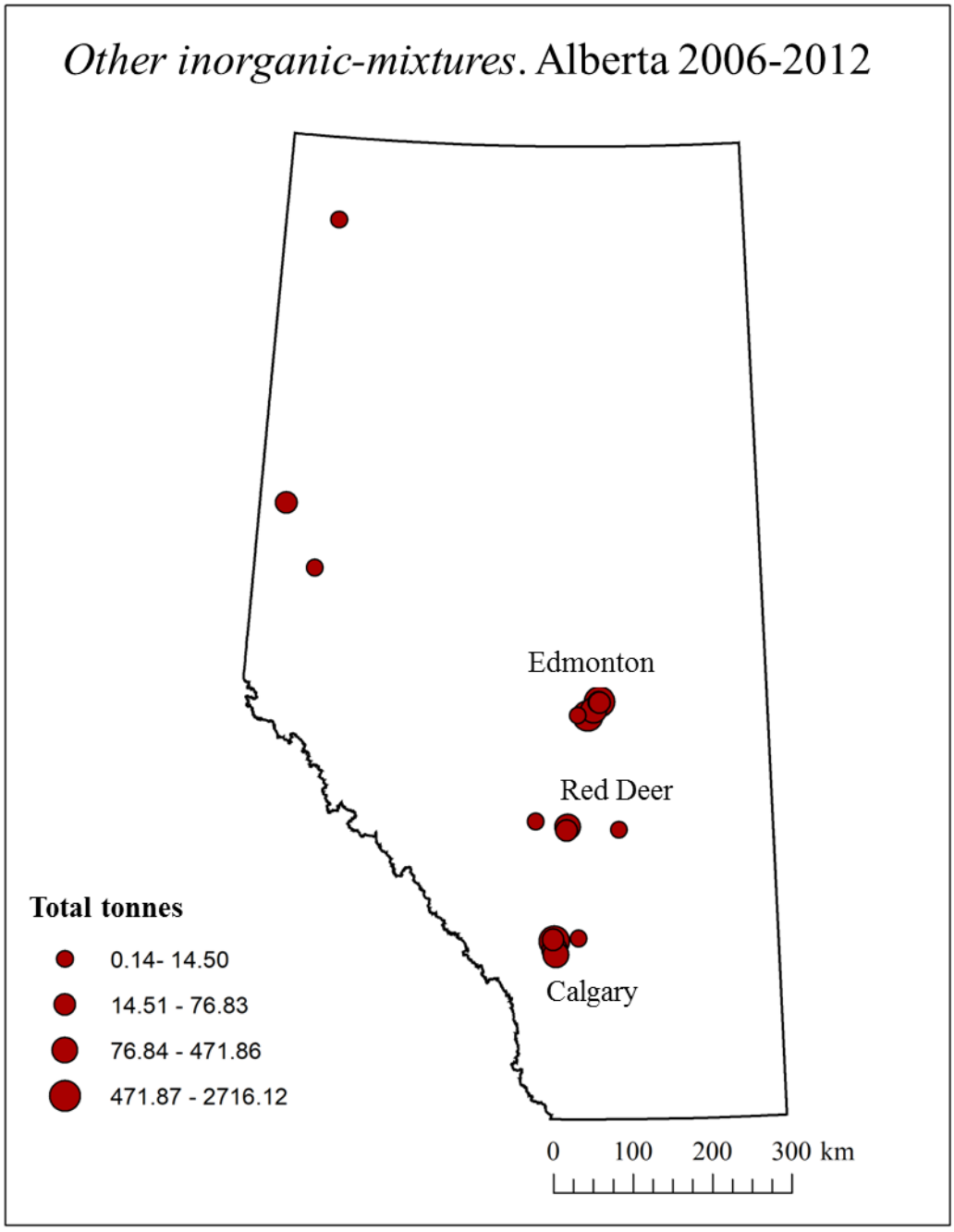
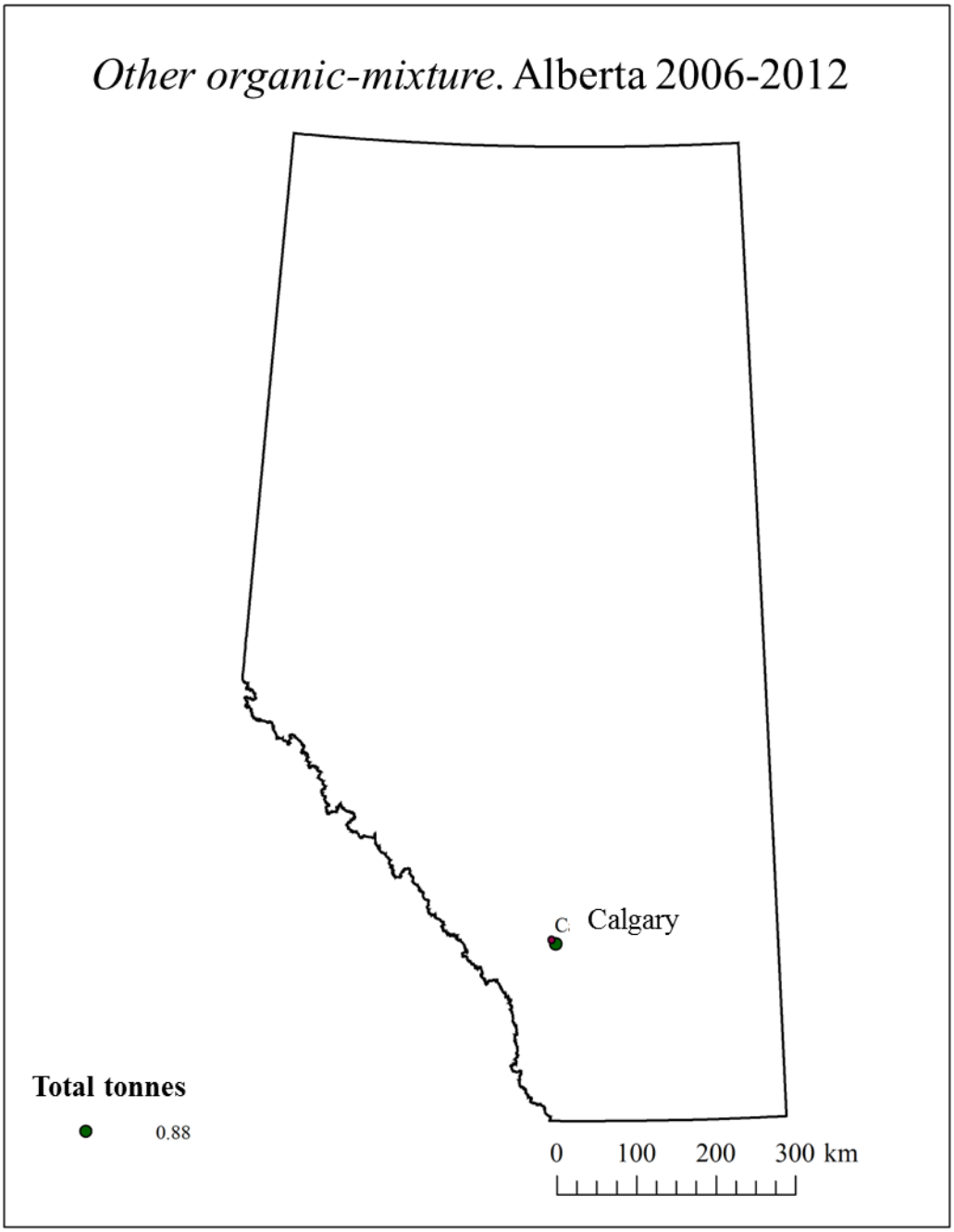


Figure 3.13 Facilities emitting mixtures with high proportional content (≥ 60%) of *Other-organics*. Alberta, 2006-2012.



Supplemental table 3.1. List of the 19 key industrial sectors used by the NPRI for reporting pollutant releases (to air, water and land).

Key industrial sectors
Conventional Oil and Gas Extraction
Non-Conventional Oil Extraction (including Oilsands and Heavy Oil)
Electricity
Wood Products
Chemicals
Pulp and Paper
Petroleum and Coal Product Refining and Mfg.
Oil & Gas Pipelines and Storage
Cement, Lime and Other Non-Metallic Minerals
Other Manufacturing
Mining and Quarrying
Aluminum
Other (Except Manufacturing)
Metals (Except Aluminum and Iron and Steel)
Iron and Steel
Water and Wastewater Systems
Plastics and Rubber
Waste Treatment and Disposal
Transportation Equipment Mfg.

Source: Statistic Canada 2016. Industry classifications. [Internet]. [cited 2016 Sep 23].

Available from: http://www.statcan.gc.ca/eng/concepts/industry

Supplemental Table 3.2. Classification of chemicals into chemical classes.

Category	Chemical-class	Chemical name	CAS_Number
1	Sulphur dioxide	Sulphur dioxide	7446- 9-5
2	Nitrogen oxides	Nitrogen oxides (expressed as NO2)	111 4-93-1
3	Carbon monoxide	Carbon monoxide	63 - 8-
4	Particulate Matter	PM2.5 - Particulate Matter <= 2.5 Microns	NA - M1
		PM1 - Particulate Matter <= 1 Microns	NA - M 9
		PM - Total Particulate Matter	NA - M 8
5	Volatile Organic	1,1,2,2-Tetrachloroethane	79-34-5
	Compounds	1,1,2-Trichloroethane	79- -5
	(non-PAHs)	1,2,4-Trimethylbenzene	95-63-6
		1,2-Dichloroethane	1 7- 6-2
		1,3-Butadiene	1 6-99-
		1,4-Dioxane	123-91-1
		2-Butoxyethanol	111-76-2
		Acetaldehyde	75- 7-
		Acetonitrile	75- 5-8
		Acrolein	1 7- 2-8
		Aniline (and its salts)	62-53-3
		Benzene	71-43-2
		Biphenyl	92-52-4
		Carbon disulphide	75-15-
		Carbon tetrachloride	56-23-5
		Carbonyl sulphide	463-58-1
		Chloroform	67-66-3
		Cresol (all isomers and their salts)	1319-77-3
		Cumene	98-82-8
		Cyclohexane	11 -82-7
		Dicyclopentadiene	77-73-6
		Ethylbenzene	1 -41-4
		Ethylene	74-85-1
		Ethylene glycol	1 7-21-1
		Ethylene oxide	75-21-8
		Formaldehyde	5 - -
		Formic acid	64-18-6
		Isoprene	78-79-5
		Isopropyl alcohol	67-63-
		Methanol	67-56-1
		Methyl ethyl ketone	78-93-3
		Methyl isobutyl ketone	1 8-1 -1
		Methyl tert-butyl ether	1634- 4-4
		Methylenebis(phenylisocyanate)	1 1-68-8
		n,n-Dimethylformamide	68-12-2
		n-Butyl alcohol	71-36-3
		n-Hexane	11 -54-3
		N-Methyl-2-pyrrolidone	872-5 -4

Category	Chemical-class	Chemical name	CAS_Number
5	Volatile Organic	Phenol (and its salts)	1 8-95-2
	Compounds	Propylene	115- 7-1
	(non-PAHs)	Quinoline (and its salts)	91-22-5
		Styrene	1 -42-5
		tert-Butyl alcohol	75-65-
		Toluene	1 8-88-3
		Toluene-2,6-diisocyanate	91- 8-7
		Trichloroethylene	79- 1-6
		Triethylamine	121-44-8
		Vinyl acetate	1 8- 5-4
		Vinyl chloride	75- 1-4
		Xylene (mixed isomers)	133 -2 -7
6	Polycyclic aromatic	1-Nitropyrene - PAH	5522-43-
	Hydrocarbons (PAHs)	3-Methylcholanthrene - PAH	56-49-5
		5-Methylchrysene - PAH	3697-24-3
		7,12-Dimethylbenz(a)anthracene - PAH	57-97-6
		7H-Dibenzo(c,g)carbazole - PAH	194-59-2
		Acenaphthene - PAH	83-32-9
		Acenaphthylene - PAH	2 8-96-8
		Anthracene	12 -12-7
		Benzo(a)anthracene - PAH	56-55-3
		Benzo(a)phenanthrene - PAH	218- 1-9
		Benzo(a)pyrene - PAH	5 -32-8
		Benzo(b)fluoranthene - PAH	2 5-99-2
		Benzo(e)pyrene - PAH	192-97-2
		Benzo(g,h,i)perylene - PAH	191-24-2
		Benzo(j)fluoranthene - PAH	2 5-82-3
		Benzo(k)fluoranthene - PAH	2 7- 8-9
		Dibenz(a,h)acridine - PAH	226-36-8
		Dibenz(a,j)acridine - PAH	224-42-
		Dibenzo(a,e)fluoranthene - PAH	5385-75-1
		Dibenzo(a,e)pyrene - PAH	192-65-4
		Dibenzo(a,h)anthracene - PAH	53-7 -3
		Dibenzo(a,h)pyrene - PAH	189-64-
		Dibenzo(a,i)pyrene - PAH	189-55-9
		Dibenzo(a,l)pyrene - PAH	191-3 -
		Fluoranthene - PAH	2 6-44-
		Fluorene - PAH	86-73-7
		Indeno(1,2,3-c,d)pyrene - PAH	193-39-5
		Naphthalene	91-2 -3
		PAHs, total unspeciated	NA - P/H
		Perylene - PAH	198-55-
		Phenanthrene - PAH	85- 1-8
		Pyrene - PAH	129- -
7	Metals	Aluminum (fume or dust)	7429-9 -5
		Aluminum oxide (fibrous forms)	1344-28-1

Category	Chemical-class	Chemical name	CAS Number
7	Metals	Cadmium (and its compounds)	NA - 3
		Chromium (and its compounds)	NA - 4
		Cobalt (and its compounds)	NA - 5
		Copper (and its compounds)	NA - 6
		Hexavalent chromium (and its compounds)	NA - 19
		Lead (and its compounds)	NA - 8
		Manganese (and its compounds)	NA - 9
		Mercury (and its compounds)	NA - 1
		Nickel (and its compounds)	NA - 11
		Silver (and its compounds)	NA - 13
		Vanadium (except when in an alloy) and its compounds	744 -62-2
		Zinc (and its compounds)	NA - 14
8	Other inorganics	Ammonia (total)	NA - 16
		Antimony (and its compounds)	NA - 1
		Arsenic (and its compounds)	NA - 2
		Asbestos (friable form)	1332-21-4
		Calcium fluoride	7789-75-5
		Chlorine	7782-5 -5
		Chlorine dioxide	1 49- 4-4
		Hydrochloric acid	7647- 1-
		Hydrogen fluoride	7664-39-3
		Hydrogen sulphide	7783- 6-4
		Molybdenum trioxide	1313-27-5
		Nitrate ion in solution at pH ≥ 6.	NA - 17
		Nitric acid	7697-37-2
		Phosphorus (total)	NA - 22
		Phosphorus (yellow or white)	7723-14-
		Selenium (and its compounds)	NA - 12
		Sulphuric acid	7664-93-9
		Titanium tetrachloride	755 -45-
9	Nitrosamines/ethers/ alcohols	2-Ethoxyethanol	11 -8 -5
		Chloroethane	75- -3
		Diethanolamine (and its salts)	111-42-2
		i-Butyl alcohol	78-83-1
		Pentachloroethane	76- 1-7
		Tetrachloroethylene	127-18-4
10	Other organics	Dichloromethane	75- 9-2
		HCFC-142b	75-68-3
		HCFC-22	75-45-6
		Hexachlorobenzene	118-74-1
		Nitrilotriacetic acid (and its salts)	139-13-9
		Polymeric diphenylmethane diisocyanate	9 16-87-9
		p-Phenylenediamine (and its salts)	1 6-5 -3
		Toluene-2,4-diisocyanate	584-84-9
		Toluenediisocyanate (mixed isomers)	26471-62-5

Supplemental Table 3.3. List of the 133 chemicals and releases reported to the air. Alberta, 2006-2012.
Note the change in the format of reporting tonnes in scientific notation when tonnes < 0.01.

Chemical Name	Total (tonnes)	%	2006 (tonnes)	2007 (tonnes)	2008 (tonnes)	2009 (tonnes)	2010 (tonnes)	2011 (tonnes)	2012 (tonnes)
Nitrogen oxides (expressed as NO2)	2,658,482.75	37.92	434,843.88	427,978.41	391,983.52	377,302.11	353,276.51	344,574.24	328,524.07
Sulphur dioxide	2,478,493.07	35.35	405,614.17	386,362.78	363,209.69	357,698.11	339,931.87	320,731.87	304,944.59
Carbon monoxide	1,498,960.25	21.38	207,042.70	211,482.61	197,757.94	223,897.64	229,441.99	197,639.43	231,697.94
PM - Total Particulate Matter*	183,523.99	2.62	28,043.88	28,192.03	26,950.24	26,269.33	26,799.29	23,747.29	23,521.95
Ammonia (total)	63,827.27	0.91	10,512.57	9,285.10	8,902.46	8,128.63	8,709.99	8,933.31	9,355.22
Methanol	16,362.57	0.23	2,494.24	2,274.53	2,399.44	2,173.53	2,179.98	2,368.63	2,472.22
Xylene (mixed isomers)	13,338.14	0.19	1,174.58	1,062.02	3,328.10	3,122.29	3,379.16	694.92	577.08
n-Hexane	12,822.55	0.18	1,862.14	1,739.33	1,669.74	2,108.61	2,301.25	1,553.57	1,587.91
Hydrogen fluoride	12,585.72	0.18	1,170.44	1,159.89	974.31	947.02	907.11	814.58	6,612.37
Carbonyl sulphide	11,819.15	0.17	1,745.25	1,734.48	1,726.27	1,924.53	1,857.86	1,697.97	1,132.79
Hydrogen sulphide	8,202.13	0.12	943.70	988.08	1,534.63	1,558.15	1,537.73	856.45	783.38
Carbon disulphide	7,424.87	0.11	1,388.69	1,311.62	1,268.49	1,246.76	996.62	721.09	491.60
Toluene	7,421.27	0.11	733.59	597.22	1,741.52	1,680.46	1,817.94	436.47	414.07
Sulphuric acid	6,880.16	0.10	1,292.70	1,095.71	943.64	874.71	913.54	910.53	849.33
Ethylene	5,998.53	0.09	694.67	768.75	712.52	900.33	720.25	1,204.13	997.88
Hydrochloric acid	3,793.23	0.05	459.04	482.49	443.36	437.57	402.74	470.90	1,097.15
Ethylbenzene	2,516.89	0.04	183.49	173.77	618.88	612.43	657.85	134.41	136.08
Formaldehyde	2,325.49	0.03	507.16	423.86	268.91	250.42	243.66	341.59	289.89
Cyclohexane	2,297.72	0.03	357.47	324.50	374.19	343.39	274.68	263.44	360.06
1,2,4-Trimethylbenzene	2,271.89	0.03	139.06	132.69	575.89	547.28	635.75	127.75	113.47
Benzene	1,574.33	0.02	279.62	223.99	249.66	218.37	231.85	147.58	223.26
Acetaldehyde	1,335.09	0.02	212.27	279.87	232.30	201.42	137.69	131.20	140.35
Propylene	1,287.78	0.02	122.96	205.22	210.16	188.77	191.78	208.98	159.91
Vinyl acetate	1,254.92	0.02	101.60	113.07	92.70	79.53	116.45	378.88	372.69
Styrene	826.64	1.18E-02	168.47	182.96	124.97	65.52	68.56	61.80	154.38
Ethylene glycol	628.50	8.96E-03	148.55	126.81	89.61	125.57	62.93	43.14	31.89
HCFC-142b	595.36	8.49E-03	138.41	151.35	134.63	170.96			

Chemical Name	Total (tonnes)	%	2006 (tonnes)	2007 (tonnes)	2008 (tonnes)	2009 (tonnes)	2010 (tonnes)	2011 (tonnes)	2012 (tonnes)
2-Butoxyethanol	486.00	6.93E-03	72.08	87.82	65.07	54.58	72.01	70.61	63.81
Methyl ethyl ketone	458.79	6.54E-03	73.28	108.99	90.94	32.56	37.65	64.90	50.48
n-Butyl alcohol	448.54	6.40E-03	77.17	89.05	61.44	43.99	57.13	70.58	49.18
Phosphorus (total)	445.82	6.36E-03	43.65	47.07	38.39	185.81	26.64	34.01	70.26
Chlorine dioxide	289.43	4.13E-03	40.45	39.43	36.33	32.20	35.28	36.94	68.80
i-Butyl alcohol	283.39	4.04E-03	79.23	63.45	36.49	30.01	21.76	26.06	26.40
Zinc (and its compounds)	252.29	3.60E-03	14.66	8.86	12.32	61.56	12.10	133.06	9.73
Chlorine	218.20	3.11E-03	8.40	20.85	17.73	17.51	24.87	28.54	100.30
Acrolein	205.71	2.93E-03	20.45	34.61	32.50	36.55	26.52	27.12	27.97
Cumene	204.53	2.92E-03	11.15	11.23	58.67	54.14	57.69	5.67	5.97
Manganese (and its compounds)	183.41	2.62E-03	8.93	7.36	7.96	44.78	41.80	60.94	11.64
Isopropyl alcohol	120.24	1.71E-03	37.99	13.40	11.80	11.73	12.22	18.63	14.48
Methyl isobutyl ketone	94.57	1.35E-03	8.04	30.14	18.97	2.90	4.99	15.50	14.02
Acenaphthylene - PAH	84.16	1.20E-03	16.13	12.57	12.25	8.48	11.00	12.44	11.28
Formic acid	77.24	1.10E-03	1.55	0.02	0.07	0.05	68.64	6.62	0.30
Cresol (all isomers and their salts)	64.01	9.13E-04	0.07	0.08		18.17	17.89	17.02	10.77
1,4-Dioxane	63.89	9.11E-04	13.65	22.63	5.72	3.06	4.74	13.21	0.89
Naphthalene	57.76	8.24E-04	12.48	7.05	6.95	0.71	7.73	21.07	1.77
Dichloromethane	55.18	7.87E-04	26.41	6.83	2.41	7.06	3.67	4.18	4.62
Chromium (and its compounds)	54.93	7.83E-04	2.80	2.55	3.60	3.81	39.51	1.60	1.06
Phenol (and its salts)	54.79	7.81E-04	11.60	11.33	9.50	1.90	3.85	1.85	14.75
Vanadium and its compounds	51.40	7.33E-04	8.60	7.55	7.95	7.57	8.14	6.07	5.53
1,3-Butadiene	40.75	5.81E-04	9.33	10.43	5.41	4.31	2.65	4.36	4.26
Nickel (and its compounds)	39.43	5.62E-04	5.44	6.26	6.72	5.46	5.43	5.22	4.90
Copper (and its compounds)	34.32	4.89E-04	1.65	1.61	1.62	1.78	3.06	23.42	1.19
Lead (and its compounds)	25.65	3.66E-04	3.17	2.99	3.77	3.29	4.03	3.45	4.95
Calcium fluoride	21.78	3.11E-04	2.67	2.96	2.92	3.09	3.35	3.35	3.44
Diethanolamine (and its salts)	19.69	2.81E-04	7.24	5.76	5.82	0.33	0.32	0.21	0.01
Phenanthrene - PAH	18.16	2.59E-04	3.38	2.98	2.87	1.85	2.20	2.46	2.41
Nitrate ion in solution at pH $\geq$ 6.0	16.29	2.32E-04				8.14	8.15		

Chemical Name	Total (tonnes)	%	2006 (tonnes)	2007 (tonnes)	2008 (tonnes)	2009 (tonnes)	2010 (tonnes)	2011 (tonnes)	2012 (tonnes)
Trichloroethylene	14.03	2.00E-04	14.03						
Ethylene oxide	12.55	1.79E-04	5.11	1.57	1.11	1.24	1.32	1.00	1.20
HCFC-22	12.18	1.74E-04	3.23	1.95	1.72	1.17	1.10	1.66	1.35
Molybdenum trioxide	7.91	1.13E-04	1.40	1.41	2.34	1.53	1.23		
Methyl tert-butyl ether	6.72	9.59E-05	0.42	0.02	4.64	1.27	0.25	0.11	4.00E-03
PAHs, total unspeciated	6.44	9.19E-05	0.80	0.81	0.79	0.41	0.81	0.91	1.92
Dicyclopentadiene	6.37	9.09E-05	1.01	1.42	1.48	0.74	0.65	0.02	1.06
N-Methyl-2-pyrrolidone	5.75	8.20E-05		0.08		0.79	1.30	2.02	1.56
1,2-Dichloroethane	5.38	7.68E-05	3.98	0.55	0.55	0.09	0.12	0.07	0.03
Mercury (and its compounds)	4.97	7.09E-05	0.93	0.99	0.64	0.73	0.82	0.41	0.45
n,n-Dimethylformamide	4.80	6.84E-05	0.78	0.49		1.32	0.84	0.63	0.74
Cadmium (and its compounds)	4.26	6.07E-05	0.23	0.38	0.47	0.99	0.60	0.73	0.86
Acetonitrile	4.20	5.98E-05	1.20	0.80	0.03	0.01		1.39	0.78
Hexavalent chromium (and its compounds)	3.86	5.51E-05	0.66	0.58	0.57	0.54	0.55	0.46	0.50
Arsenic (and its compounds)	3.73	5.32E-05	0.66	0.54	0.63	0.61	0.43	0.44	0.42
Nitrilotriacetic acid (and its salts)	3.53	5.03E-05						1.69	1.84
Cobalt (and its compounds)	3.44	4.91E-05	0.70	0.25	0.24	0.34	1.04	0.59	0.29
Methylenebis(phenylisocyanate)	3.02	4.30E-05	0.30	1.04	1.57	0.05	0.05		
7H-Dibenzo(c,g)carbazole - PAH	2.91	4.15E-05	0.00	0.00	0.82	0.82	1.26		
Pyrene - PAH	2.78	3.97E-05	0.41	0.42	0.42	0.32	0.38	0.42	0.40
Asbestos (friable form)	2.65	3.78E-05					2.65		
Fluoranthene - PAH	2.57	3.67E-05	0.40	0.42	0.42	0.33	0.34	0.35	0.31
Aluminum oxide (fibrous forms)	2.45	3.49E-05	2.45						
Polymeric diphenylmethane diisocyanate	2.32	3.32E-05	0.06	0.20	1.61	0.10	0.12	0.12	0.12
Biphenyl	2.30	3.28E-05	0.09	0.07	0.09	0.49	0.55	0.55	0.45
Fluorene - PAH	1.84	2.62E-05	0.30	0.24	0.28	0.21	0.25	0.27	0.28
Aluminum (fume or dust)	1.58	2.26E-05		0.06	1.40	0.02	0.04	0.04	0.03
Toluenediisocyanate (mixed isomers)	1.13	1.61E-05	0.10	0.09	0.30	0.29	0.30		0.05
Selenium (and its compounds)	0.86	1.23E-05				0.09	0.10	0.35	0.33
Vinyl chloride	0.81	1.16E-05	0.81						

Chemical Name	Total (tonnes)	%	2006 (tonnes)	2007 (tonnes)	2008 (tonnes)	2009 (tonnes)	2010 (tonnes)	2011 (tonnes)	2012 (tonnes)
Tetrachloroethylene	0.80	1.14E-05	0.01	0.37	0.37	0.03	0.02		0.01
Acenaphthene - PAH	0.79	1.13E-05	0.17	0.12	0.14	0.08	0.09	0.10	0.09
Triethylamine	0.46	6.53E-06	0.15	0.08			0.00	0.18	0.05
Anthracene	0.40	5.70E-06	0.14	0.04	0.05	0.04	0.05	0.04	0.04
Phosphorus (yellow or white)	0.36	5.17E-06					0.00	0.25	0.11
Chloroethane	0.34	4.79E-06	0.06				0.07	0.12	0.09
Antimony (and its compounds)	0.32	4.54E-06	0.01	0.01				0.28	0.02
Silver (and its compounds)	0.27	3.86E-06			0.00	0.08	0.09	0.05	0.05
Chloroform	0.27	3.84E-06	0.14	0.13					
Benzo(a)phenanthrene - PAH	0.22	3.20E-06	0.04	0.04	0.03	0.03	0.02	0.03	0.03
Benzo(a)anthracene - PAH	0.19	2.72E-06	0.04	0.03	0.04	0.03	0.02	0.02	0.01
Nitric acid	0.15	2.17E-06	0.04	0.05	0.07				
1,1,2-Trichloroethane	0.11	1.55E-06	1.09E-01						
Benzo(e)pyrene - PAH	0.07	9.36E-07	1.23E-02	1.13E-02	1.12E-02	9.96E-03	7.43E-03	7.33E-03	6.02E-03
tert-Butyl alcohol	0.05	6.56E-07	4.60E-02						
Benzo(a)pyrene - PAH	0.04	6.08E-07	1.09E-02	1.05E-02	6.01E-03	5.44E-03	3.17E-03	3.15E-03	3.52E-03
Benzo(g,h,i)perylene - PAH	0.04	5.66E-07	6.44E-03	4.76E-03	7.26E-03	4.24E-03	3.65E-03	6.05E-03	7.32E-03
Toluene-2,4-diisocyanate	0.03	4.96E-07						3.48E-02	
Benzo(b)fluoranthene - PAH	0.03	4.58E-07	5.84E-03	4.48E-03	3.48E-03	3.89E-03	4.51E-03	4.73E-03	5.17E-03
Indeno(1,2,3-c,d)pyrene - PAH	0.02	3.50E-07	4.84E-03	3.66E-03	4.52E-03	2.82E-03	2.65E-03	2.37E-03	3.68E-03
1,1,2,2-Tetrachloroethane	0.02	3.00E-07	2.10E-02						
Benzo(k)fluoranthene - PAH	0.02	2.65E-07	4.14E-03	3.02E-03	3.16E-03	2.26E-03	1.12E-03	2.08E-03	2.80E-03
Hexachlorobenzene	0.02	2.43E-07	5.63E-03	2.60E-03	1.77E-03	1.80E-03	1.89E-03	2.13E-03	1.20E-03
Benzo(j)fluoranthene - PAH	0.01	1.89E-07	2.92E-03	2.42E-03	2.37E-03	1.48E-03		1.47E-03	2.57E-03
2-Ethoxyethanol	0.01	1.75E-07				1.00E-03	1.13E-02		
Titanium tetrachloride	0.01	1.71E-07	4.00E-03	8.00E-03					
Perylene - PAH	9.96E-03	1.42E-07	2.03E-03	1.35E-03	6.99E-04	1.02E-03	8.16E-04	2.01E-03	2.04E-03
Carbon tetrachloride	9.00E-03	1.28E-07	5.00E-03	4.00E-03					
p-Phenylenediamine (and its salts)	9.00E-03	1.28E-07	4.00E-03	5.00E-03					
Toluene-2,6-diisocyanate	8.70E-03	1.24E-07						8.70E-03	

Chemical Name	Total (tonnes)	%	2006 (tonnes)	2007 (tonnes)	2008 (tonnes)	2009 (tonnes)	2010 (tonnes)	2011 (tonnes)	2012 (tonnes)
Dibenzo(a,h)anthracene - PAH	6.55E-03	9.34E-08	1.11E-03	1.35E-03	1.07E-03	7.64E-04	8.19E-04	6.64E-04	7.71E-04
Quinoline (and its salts)	6.10E-03	8.70E-08					3.60E-03		2.50E-03
Isoprene	4.00E-03	5.70E-08	2.00E-03	2.00E-03					
Dibenz(a,j)acridine - PAH	3.20E-03	4.56E-08	8.62E-04	6.98E-04	6.22E-04	3.70E-04		3.23E-04	3.21E-04
Aniline (and its salts)	2.90E-03	4.14E-08					1.90E-03		1.00E-03
7,12-Dimethylbenz(a)anthracene - PAH	1.36E-03	1.93E-08		3.75E-04	3.50E-04	1.15E-04		1.30E-05	5.02E-04
3-Methylcholanthrene - PAH	1.31E-03	1.87E-08		5.63E-04	2.55E-04	5.00E-06		2.00E-06	4.89E-04
Dibenzo(a,i)pyrene - PAH	1.29E-03	1.84E-08	7.55E-04	2.50E-04	2.84E-04				
Pentachloroethane	1.00E-03	1.43E-08	1.00E-03						
Dibenzo(a,e)pyrene - PAH	8.19E-04	1.17E-08		2.50E-04	2.48E-04		2.12E-04	1.09E-04	
Dibenz(a,h)acridine - PAH	6.50E-04	9.27E-09		2.50E-04	2.48E-04	1.20E-04		1.50E-05	1.70E-05
1-Nitropyrene - PAH	5.34E-04	7.62E-09		2.50E-04	2.48E-04	2.00E-05		8.00E-06	8.00E-06
Dibenzo(a,l)pyrene - PAH	5.02E-04	7.16E-09		2.50E-04	2.48E-04	2.00E-06		1.00E-06	1.00E-06
5-Methylchrysene - PAH	4.98E-04	7.10E-09		2.50E-04	2.48E-04				
Dibenzo(a,e)fluoranthene - PAH	4.98E-04	7.10E-09		2.50E-04	2.48E-04				
Dibenzo(a,h)pyrene - PAH	4.98E-04	7.10E-09		2.50E-04	2.48E-04				
Totals	**7,011,463.12**	**100.00**	**1,103,038.06**	**1,079,534.26**	**1,009,106.82**	**1,013,775.55**	**978,437.59**	**909,928.60**	**917,642.23**

*Particulate Matter is represented by total particulate matter (TPM).

Amounts of PM_{10} and $PM_{2.5}$ were not considered for this table (they jointly accounted for and additional 11,560.70 tonnes) .

Supplemental Table 3.4. Pollutant releases to air by industrial sector. Alberta, 2006-2012

Industrial Sector	Total (tonnes)	%	2006 (tonnes)	2007 (tonnes)	2008 (tonnes)	2009 (tonnes)	2010 (tonnes)	2011 (tonnes)	2012 (tonnes)
Conventional Oil and Gas Extraction	3,046,739	43.45	528,010	502,555	458,206	430,847	393,119	378,586	355,416
Electricity	1,568,759	22.37	234,022	234,121	227,601	221,563	228,233	216,722	206,496
Non-Conventional Oil Extraction (including Oilsands and Heavy Oil)	1,374,665	19.61	189,675	198,750	191,122	214,666	200,333	186,065	194,053
Wood Products	266,687	3.80	37,482	37,508	24,879	44,288	51,114	18,372	53,043
Chemicals	213,069	3.04	30,877	29,593	30,181	29,894	30,299	31,317	30,907
Pulp and Paper	130,512	1.86	20,732	19,412	19,322	16,891	17,714	15,843	20,598
Petroleum and Coal Product Refining and Mfg.	127,776	1.82	18,180	17,348	19,892	18,878	17,202	18,957	17,319
Cement, Lime and Other Non-Metallic Minerals	74,082	1.06	11,894	12,057	11,679	8,683	9,842	9,846	10,083
Oil & Gas Pipelines and Storage	65,905	0.94	12,130	11,978	9,779	8,758	7,980	8,189	7,091
Aluminum	36,226	0.52	4,771	3,993	4,586	5,621	6,028	5,980	5,247
Mining and Quarrying	33,986	0.48	751	2,177	2,596	4,429	6,787	9,948	7,297
Other Manufacturing	22,050	0.31	3,680	3,075	2,574	2,993	3,206	3,250	3,273
Metals (Except Aluminum and Iron and Steel)	18,643	0.27	3,085	2,991	2,805	2,382	2,505	2,333	2,541
Other (Except Manufacturing)	18,246	0.26	5,854	1,893	1,891	1,950	2,056	2,477	2,125
Iron and Steel	6,468	0.09	807	975	958	927	932	929	940
Water and Wastewater Systems	6,156	0.09	881	912	855	835	861	903	910
Plastics and Rubber	941	0.01	194	191	152	89	82	74	159
Waste Treatment and Disposal	553	0.01	13	3	31	82	144	138	143
Totals*	**7,011,463**	**100.00**	**1,103,038**	**1,079,534**	**1,009,107**	**1,013,776**	**978,438**	**909,929**	**917,642**

*Based on table 3.3, in which Particulate Matter is represented by total particulate matter (TPM). Amounts of PM_{10} and $PM_{2.5}$ were not considered for this table (they jointly accounted for and additional 11,560.70 tonnes).

Chapter 4

4. Conclusions and final remarks

This thesis focused on providing a better understanding of the local factors impacting the occurrence of preterm birth and small for gestational age in Alberta. Also, in the identification of potentially hazardous mixtures of air pollutants from industrial sources associated with adverse birth outcomes (a significant knowledge gap in air pollution and perinatal epidemiology[1,2]). These two aspects represent initial steps for further generation of new hypotheses for the study of air pollution and perinatal epidemiology. A more extensive research project named DoMINO[3] established the research framework for this thesis study. It will be briefly commented on the research context section below. Afterward, this chapter summarizes the key findings of this thesis and their potential links with future research in public health.

4.1. The research context

DoMINO[3] was an interdisciplinary and collaborative research project in which knowledge users, researchers, and trainees from different disciplines (i.e., computer sciences, geography, epidemiology, and perinatology) examined co-location of sources of industrial emissions, socioeconomic index, maternal risk factors, and adverse birth outcomes in Canada. The project was exploratory considered as a foundation for future research. The project's strategy based on an integrated knowledge translation plan (iKT)[4,5] that, among other benefits, allowed knowledge users to be involved in focusing the research questions, and allowed trainees to develop skills in interdisciplinary collaboration.

Accordingly, some specific research questions emanating from DoMINO were integrated into the main topic of this thesis research. Those questions were: (i) Where did low and high

occurrence of ABO exists during the study period? (ii) Which maternal risk factors, among those routinely measured by health authorities in Alberta, could explain the ABO range of occurrence?

Within this context, the results of this thesis contributed to reaching the research goals by:

1. Identifying areas of low, moderate, and high occurrence of preterm birth and small for gestational age;
2. Comparing the distribution of the prevalence of risk factors in those areas, and identifying local key risk factors for spontaneous and induced preterm birth, and small for gestational age;
3. Estimating the effects of air pollutant mixtures from industrial sources on spontaneous and induced preterm birth, and small for gestational age.

Lastly, the DoMINO project was a great opportunity to learn how to work in an interdisciplinary environment towards the same goals.

4.2. Key findings

4.2.1. Areas of elevated occurrence of PTB and SGA: the urban imprint in Alberta

The results showed that the areas with a high occurrence of PTB and SGA were predominantly urban. This result may be associated, to a certain degree, with the urbanization and migration changes observed in the province during the study period. According to national statistics, Alberta has urbanized more rapidly than other provinces in Canada in the last five decades[6], and, currently, around 80% of its population lives in urban settlements.[7] In parallel, a high demographic flow of immigrant populations mainly to Calgary and Edmonton (the major cities in the province)[8,9] occurred since 2000s. Alberta has one the highest population growth rates in Canada: the national population growth rate was +5.3%, while in Alberta was +10.2%, between 2006 and 2012[10].

Consequently, it is probable that associated factors to a rapid urbanization process and demographic changes are playing a relevant role in the occurrence of PTB and SGA. Worldwide, it has been observed that urbanization processes are usually accompanied by an economic development and an increase in poverty in some population groups.[12] The economic development is accompanied by an increase of infrastructure (i.e., industrial facilities, roads, increased use of motor vehicles) that usually increase the level of air pollution and, consequently, the expected negatively impact human health[12]. In this regard, the data indicated that populations of mothers living in the areas of high occurrence were potentially exposed, on average, to more air pollutant mixtures from industrial sources compared to the mothers living in the areas with low occurrence (10 mixtures vs. 4 mixtures, respectively); although, the industrial emissions have reduced over the study period. The increase in poverty is linked to some population subgroups who fail to adapt and to align with the urban-style life and standards, suffering lack of opportunities and increasing the problems of psychological adaptation;[12] which may increase individual stress and impact negatively pregnant women. In this regard, the results indicated a higher proportion of PTB and SGA cases in areas with low socioeconomic index compared to the high socioeconomic index. Additionally, the intergenerational influences of a small maternal structure of South Asian and Chinese populations, which have increased their concentration in Calgary and Edmonton from 2006 to 2011[9] could be related to high rates of SGA[11]. The extent to which immigrant populations contribute to high rates of ABO in Alberta is an issue that deserves further research.

4.2.2. Risk factors impacting the occurrence of PTB and SGA in Alberta

To my knowledge, this is the first study identifying small areas of low and high occurrence of ABO in Alberta, and the distribution of risk factors across those areas. Traditionally,

observational epidemiological studies identify risk factors of diseases, or the effects of specific interactions (i.e., effect modification) of a small number of risk factors.[13] However, there is an increasing interest in identifying networks of already known risk factors acting at local/regional scale to understand how they distribute in subgroups of populations across different geographic settings. This approach, different from the classical risk factor epidemiology, may improve our understanding of the role of multiple risk factors in the causal pathway for ABO in different places and could result as highly informative for public health researchers and policy-makers.[13]

The results of the prevalence of risk factors participating in the high-occurrence areas *vs*. the low-occurrence areas, showed for:

a) **Spontaneous PTB**: A higher prevalence of smoking during pregnancy (+22%), substance use during pregnancy (+8%), and past abortions (+3%). There were 36% more cases in the lowest SES-index quintile and 3% more cases in the mothers less than 20 years of age.

b) **Induced PTB**: A higher prevalence of smoking during pregnancy (+12%), and substance use during pregnancy (+4%). There were 32% more cases in the lowest SES-index quintile and 2% more cases in the mothers less than 20 years of age.

c) **SGA**: A lower prevalence of smoking during pregnancy (-20%), substance use during pregnancy (-8%), and proteinuria (-2%). There were 5% fewer cases in the mothers less than 20 years of age and 26% more cases in the lowest SES-index quintile.

The higher prevalence of smoking and substance use during pregnancy in areas with a low occurrence of SGA was unexpected. These results motivated a subsequent analysis in urban and rural areas. That analysis showed a high prevalence of smoking and substance use during

pregnancy in very young women living in rural areas (results did not show in this study) that may explain these results.

Additionally, the corresponding attributable fractions of the measured risk factors of ABOs in the high-occurrence areas of Alberta provided an initial assessment of the key risk factors for ABOs. The key measured determinants were, for:

a) **Spontaneous PTB**: Past-preterm (AF=18%), smoking during pregnancy (AF=15%), bleeding after the 20th week (AF=11%), the lowest SES-index (AF=9%), substance use during pregnancy (AF=5%), and gestational diabetes (AF=4%).

b) **Induced PTB**: Gestational hypertension (AF=19%), past-preterm (AF=11%), proteinuria (AF=10%), and smoking during pregnancy (6%).

c) **SGA**: the lowest SES-index (AF=12%), smoking during pregnancy (AF=6%), gestational hypertension (AF=4%), and past-SGA (AF=3%).

These results showed that no one risk factor explained more than 19% of cases (in the high-occurrence areas), and that if it was possible to sum their AFs (which theoretically it is not always possible and cautions in its interpretation is needed) they would account, at most, for 62% of the spontaneous PTB cases, 46% of the induced PTB cases, and 25% of the SGA cases. In such case, the observed results of preterm birth are in line with other studies reporting that approximately 30% of the PTB cases are from unknown causes.[14]

Another important result was revealing the role of gestational diabetes, gestational hypertension, proteinuria, and bleeding after the 20th week (which were homogeneously distributed across the areas of occurrence) as important contributors to the ABO occurrence in Alberta. This underlines the importance of keeping a continuous surveillance of pregnant women and the need of understanding how susceptibility to exposure to air pollutants may be modified

by these factors. Recently, the presence of pregnancy comorbidities such as preeclampsia, chronic diabetes, and asthma status has been identified as effect modifiers of air pollutants on preterm birth.[15] Concomitantly, in this thesis, the finding that the lowest SES-index and smoking during pregnancy were common important factors for spontaneous PTB and SGA, are in line with two previous studies of predictors of PTB[16,17] and SGA[16] in Alberta. In parallel, and as it was previously mentioned, there is evidence on how urbanization processes may be associated with an increase of adverse social conditions despite the economic benefits accompanying urban development.[12]

All these results emphasize the importance of further research in public health for understanding how all these key factors may interact to impact the occurrence of adverse birth outcomes.

4.2.3. The characterization of mixtures of air pollutants from industrial sources

The characterization of mixtures of air pollutants is a building block in the multi-pollutant approach to understanding the human health risk they represent.[18] Studies on the adverse health effects of mixtures of air pollutants based on the commonly measured criteria air pollutants (i.e., NO_2, SO_2, CO, O_3, and PM) have increased over the last decade.[19] However, the content of other hazardous chemicals within those mixtures is practically unknown mainly because they are not measured by air monitoring systems. Operational issues (i.e., associated costs to identify small quantities of a variety of chemical substances in air samples), among other things, complicate initiatives to measure their concentrations in the air. Consequently, assessing their health impact is hard to achieve.

I used data from the National Pollutant Release Inventory (NPRI)[20] of Canada to characterize mixtures of chemicals released by industrial facilities into the air in Alberta. The NPRI is

publicly available, and their data-quality is certified by the environmental authorities in Canada. The NPRI tracks hundreds of chemicals considered as dangerous for human health, although do not track other important pollutants released to air. The NPRI, it collects and reports only annual emissions. The use of annual emissions is a limiting factor for estimating the level of exposure to hazardous chemicals during pregnancy in the nearby populations. Despite these limitations, the NPRI represents a valuable data source for building an initial framework to generate hypothesis about the potential effects air pollutant mixtures from industrial sources on adverse birth outcomes. Currently, it is the only source of information compiling a large set of chemicals emitted to the environment by industrial sources in Canada.

This study proposed an original approach for generating an initial view of the type of mixtures emitted from industrial sources in Alberta based on chemical groups and their proportional content in the emissions for each facility.

The main results showed that:

a) 97% of the total emissions were composed of two or more chemical groups.

b) Very complex mixtures containing many chemical classes, including a high proportion of gases, were the most relevant regarding the amounts released into the air: they represented 46% of the total emissions during the study period, were emitted by 11% of the facilities and were widely present across the province.

c) Mixtures containing a high proportion (≥60%) of NO_2, or PM, or CO were the most common (83% of the facilities) and represented 33% of the emissions. They were densely present across the province and were emitted mainly from the oil- and energy-related sectors.

d) Mixtures containing a high proportion (≥60%) of SO_2 were emitted by 3% of the facilities but represented 21% of the total emissions.

e) Mixtures having a high proportional content (≥60%) of volatile organic compounds, metals, other organic chemicals and other inorganic chemicals, were scarce (they represented 0.24% of the total emissions). They were principally emitted in the major cities and not linked to the oil- and energy-related sectors.

These results clearly show that a wide range of different mixtures is present in the ambient air of Alberta, and give empirical support to the use of multi-pollutant approaches for a better understanding of the impact of air pollution on health outcomes. Interestingly, the mixtures having a high proportional content of volatile organic compounds, metals, other organic chemicals, and other inorganic chemicals, were located mainly in urban areas, where we also observed a higher prevalence of adverse birth outcomes. Since these types of mixtures may be highly toxic for human populations, their geo-location is important for planning further studies about their health effects.

4.2.4. The associations of mixtures from industrial sources with adverse birth outcomes

The results indicated that not all mixtures were associated with spontaneous preterm birth, induced preterm birth or small for gestational age. The mixtures that increased the odds of the studied adverse birth outcomes were:

a) Mixtures with a significant proportion (≥60%) of volatile organic compounds increased odds of SGA by 37%;

b) Mixtures with a significant proportion (≥60%) of metals, or other organics, or other organics increased odds of induced PTB by 17%, 17% and 24%, respectively;

c) Mixtures heterogeneous with a major proportion of gases increased odds of spontaneous PTB by 36%, and;

d) Mixtures with a significant proportion (≥60%) of PM increased odds of SGA by 8%

A careful interpretation of results must be done since limitations exist. An important one is that the analysis was based on the presence (yes/no) of the mixtures emitted within a 10 km buffer around maternal postal codes. This is a weak method for correctly assigning exposure to women during pregnancy. However, I decided to use it since we were also limited by the annually reported emissions in the NPRI. Nevertheless, the use of important covariates (maternal risk factors, area-level socioeconomic index, and the presence of the other mixtures in the buffer zone) for adjusting their effects may reduce, to some extent, uncertainty. Additionally, the biologically plausible mechanisms already associated with individual chemicals in these groups may add some theoretical support to our results.[21,22]

Although substantial evidence exists about the toxicity of some individual volatile organic compounds (i.e., benzene, toluene) metals (i.e., lead, cadmium), arsenic, and other many chemicals[21,22] in the mixtures, the toxicity of mixtures of hazardous pollutants is a key question to be solved. One of the most significant challenges in a multi-pollutant approach is to understand the interactive patterns (i.e., potentiation, synergism, inhibition) of air pollutant mixtures on different health outcomes.[23] In multi-pollutant approaches, it is hypothesized that the mixture determines its toxicity and that this toxicity could be the results of the changes suffered during their transport in the atmosphere (during which photochemical reactions occurs to produce secondary pollutants) altering their physic-chemical properties (i.e., solubility, volatility, persistence). Consequently, different mixtures of the same chemicals could impact biological endpoints in different ways. One example was provided recently by an *in vitro* toxicological

study done by Manzano-Leon *et al*. (2016)[23], who observed that $PM_{2.5}$ samples from Mexico City showed pro-inflammatory effects, except when the proportional content of polycyclic aromatic hydrocarbons increased above 0.1% of the $PM_{2.5}$ mass. Their findings suggested the existence of inhibitory processes among chemical components that could be detected when the chemical content of the mixture changes.

Accordingly, the mixtures that were identified as having a significant proportion of volatile organic compounds, metals, and other inorganic chemicals may provide preliminary insights about the potential role of these groups of chemicals in increasing the toxicity of a mixture of air pollutants. Those identified mixtures were emitted in very small amounts in relation to the total emissions, but could be highly toxic. As far as I know no other studies have investigated the effects of mixtures of air pollutants from industrial sources on adverse birth outcomes. Thus, the identified mixtures associated with preterm birth and small for gestational age could be good candidates for further research aiming to assess their toxicity and health effects.

Additionally, the results could provide practical knowledge applicable to environmental health policy. One is related to the importance of geographically locate hazardous mixtures released into the air from industrial sources to advise environmental authorities where and what chemicals should be monitored. Another relates to the increased scientific evidence about the long-term adverse health effects from being exposed to hazardous chemicals during fetal development and early life, such as Alzheimer's disease[24], or cancer diseases[25]. In this regard, the results of this thesis may inform public health authorities about potential long-term effects of hazardous mixtures on populations living in their proximity. In parallel, the results may motivate and inform future research to develop new methods for measuring the toxicity of hazardous mixtures in the ambient air (i.e., by measuring their oxidative burden[26]). Thus, the knowledge of

how mixtures of hazardous pollutants affect pregnancy outcomes and the future life of newborns should be a priority in environmental health epidemiology.

4.3. The inherent complexity of environmental-health research

The last reflection is about the complexity associated with the study of the risk factors for adverse birth outcomes. It is recognized that the relationships among individual (i.e., genetic, lifestyle, age), social (i.e., education, income, access to medical care), and environmental factors (i.e., exposure to toxicants in air, water, and food) with adverse birth outcomes are highly complex. Keune and collaborators[27] have postulated that environmental and health research is by "nature" complex and that some considerations should accompany this type of studies, for example: (i) some health outcomes are the result of multi-causal systems and that, in such systems, the search for a single or ultimate cause is fruitless; (ii) that ambiguity and controversies in the assessment of environmental health risks are expected due to the large uncertainties, knowledge gaps, and partial understanding of the disease-risk factors' relationships (for example, health effects from high doses for a number of toxicants are well established, but their effect of small doses over longer periods is unknown); and that (iii) all the related aspects to a specific environment and health issue cannot be investigated by only one research.

Finally, this thesis showed the complexity associated with the study of a wide range the risk factors for preterm birth and small for gestational age. It provided supporting knowledge about small areas in Alberta with an excess occurrence of adverse birth outcomes, the distribution of key maternal risk factors in the three areas of occurrence (low, moderate, high), and the key maternal risk factors impacting the occurrence of these health outcomes. It faced the complexity associated with exploring the effects of industrial emissions related to the heterogeneity in the industrial emissions into the air in Alberta. However, the characterization of the mixtures may be

used as an initial framework for suggesting new hypotheses about the role of specific potential hazardous mixtures on pregnancy outcomes. The results suggest that much more efforts are required to understand the effects of the air pollution on adverse birth outcomes.

References

Chapter 1

1. Osornio-Vargas A, Zaiane O, Wine O. Domino Project: Data Mining and Newborn Outcomes Exploring Environmental Variables. 26th Annual Conference of the International Society for Environmental Epidemiology; 2014 Aug 24-28; Seattle: Abstract Number: 2187 | ID: P3-607.

2. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. The lancet. 2008;371(9606):75–84.

3. World Health Organization. Media Centre. Preterm birth. Fact sheet # 363. [Internet]. 2016 [cited 2017 October 5]. Available from: http://www.who.int/mediacentre/factsheets/fs363/en/

4. Canadian Institute for Health Information, Too Early, Too Small: A Profile of Small Babies Across Canada.Ottawa, Ont.: CIHI, 2009.

5. Lim G, Tracey J, Boom N, Karmakar S, Wang J, Berthelot JM, Heick C. Hospital costs for preterm and small-for-gestational age babies in Canada. Healthcare quarterly. 2009;12(4):20-24.

6. Mangham LJ, Petrou S, Doyle LW, Draper ES, Marlow N. The cost of preterm birth throughout childhood in England and Wales. Pediatrics. 2009;123(2):12-27.

7. Johnston KM, Gooch K, Korol E, Vo P, Eyawo O, Bradt P, et al. The economic burden of prematurity in Canada. BMC pediatrics. 2014;14(93):1.

8. Stieb DM, Chen L, Eshoul M, Judek S. Ambient air pollution, birth weight and preterm birth: A systematic review and meta-analysis. Environmental Research. 2012;117:100–11.

9. Menon R. Oxidative Stress Damage as a Detrimental Factor in Preterm Birth Pathology. Frontiers in Immunology [Internet]. 2014 [cited 2017 Sep 15]. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2014.00567/full

10. March of Dimes, PMNCH, Save the Children, WHO. Born Too Soon: The Global Action Report on Preterm Birth. Eds CP Howson, MV Kinney, JE Lawn. World Health Organization. Geneva/ [Internet]. 2012 [cited 2017 June 17]. Available from: http://www.who.int/pmnch/media/news/2012/201204_borntoosoon-report.pdf

11. Public Health Agency of Canada. Canadian Perinatal Health Report, 2008 Edition. [Internet]. Ottawa 2008. [cited 2014 Apr 8]. Available from: http://www.phac-aspc.gc.ca/publicat/2008/cphr-rspc/pdf/cphr-rspc08-eng.pdf

12. Public Health Agency of Canada. Perinatal Health Indicators for Canada 2013: a Report of the Canadian Perinatal Surveillance System. Ottawa, 2013.

13. Canadian Institute for Health Information. Highlights of 2010–2011.Selected indicators describing the birthing process in Canada. 2012. [Internet]. [cited 2014 Sep 9]. Available from: https://secure.cihi.ca/free_products/Childbirth_Highlights_2010-11_EN.pdf

14. Heaman M, Kingston D, Chalmers B, Sauve R, Lee L, Young D. Risk Factors for Preterm Birth and Small-for-gestational-age Births among Canadian Women: Risk factors for PTB and SGA births. Paediatric and Perinatal Epidemiology. 2013;27(1):54–61.

15. Zeitlin JA, Ancel P-Y, Saurel-Cubizolles M-J, Papiernik E. Are risk factors the same for small for gestational age versus other preterm births? American Journal of Obstetrics and Gynecology. 2001;185(1):208–15.

16. Shah PS, Balkhair T. Air pollution and birth outcomes: A systematic review. Environment International. 2011;37(2):498–516.

17. Black RE. Global prevalence of small for gestational age births. In: Embleton ND, Katz J, Ziegler EE. (eds.) Low-Birthweight Baby: Born Too Soon or Too Small. Basel: Karger Publishers; 2015 [cited 2017 Jan 25]. p. 1–7. Available from: http://www.karger.com/Article/Abstract/365790

18. Harrison RM. Introduction. In: Harrison, RM. (ed.) An Introduction to Pollution Science. UK: Publishig, dorset; 2006. p 1-7.

19. Walker CH, Sibly RM, Hopkin SP, Peakall DB. Principles of Ecotoxicology. 4th ed. Florida: CRC Press; 2012.

20. Gaffney JS, Marley NA. Atmospheric Chemistry and Air Pollution. The Scientific World Journal. 2003;3:199–234.

21. Heal MR, Kumar P, Harrison RM. Particles, air quality, policy and health. Chemical Society Reviews. 2012;41(19):6606.

22. Fenger J. Air pollution in the last 50 years – From local to global. Atmospheric Environment. 2009;43(1):13–22.

23. Volkamer R, Jimenez JL, San Martini F, Dzepina K, Zhang Q, Salcedo D, et al. Secondary organic aerosol formation from anthropogenic air pollution: Rapid and higher than expected. Geophysical Research Letters [Internet]. 2006 [cited 2017 Jun 22];33(17). Available from: http://doi.wiley.com/10.1029/2006GL02689.

24. World Health Organization. Health effects of Particulate Matter. Policy implications for countries in eastern Europe, Caucasus and central Asia. [Internet]. 2013 [cited 2017 June

17]. Available from: http://www.euro.who.int/data/assets/pdf_file/0006/189051/Health-effects-of-particulate-matter-final-Eng.pdf

25. de Kok TMCM, Driece HAL, Hogervorst JGF, Bried JJ. Toxicological assessment of ambient and traffic-related particulate matter: A review of recent studies. Mutation Research/Reviews in Mutation Research. 2006;613(2-3):103–22.

26. Ha S, Hu H, Roussos-Ross D, Haidong K,.Roth J, Xu X. The effects of air pollution on adverse birth outcomes. Environ. Res. 2014;134:198–204.

27. World Health Organization. Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide. Global update 2005. Geneva, Switzerland. Available from: http://apps.who.int/iris/bitstream/10665/69477/1/WHO_SDE_PHE_OEH_06.02_eng.pdf

28. World Health Organization. Media centre 2014: 7 million premature deaths annually linked to air pollution. [Internet]. 2014 [cited 2017 June 17]. Available from: http://www.who.int/mediacentre/news/releases/2014/air-pollution/en/

29. Amann M, Cofala J, Schupp W, Dentener F. Future trends in air pollution. In: Sokhi R.S. ed. World Atlas of Atmospheric Pollution. New York: Anthem Press; 2008 p:95-102.

30. Stone R. Air pollution. Counting the cost of London's killer smog. Science 298. 2002:(5601);2106–2107

31. Anderson HR. Air pollution and mortality: A history. Atmospheric Environment. 2009;43(1):142–52.

32. Kim K-H, Kabir E, Kabir S. A review on the human health impact of airborne particulate matter. Environment International. 2015;74:136–43.

33. World Health Organization. Review of evidence on health aspects of air pollution. REVIHAAP Project. 2013. Copenhagen, Denmark. Available from: http://www.euro.who.int/__data/assets/pdf_file/0004/193108/REVIHAAP-Final-technical-report.pdf

34. World Health Organization. Public health, environmental and social determinants of health (PHE). Global Urban Ambient Air Pollution Database (update 2016). [Internet]. 2015 [cited 2017 October 5] Available from: http://www.who.int/phe/health_topics/outdoorair/databases/cities/en/

35. United States Environmental Protection Agency (EPA). Clean Air Act Overview. Air Pollution: Current and Future Challenges. [Internet] [cited 2017 June 17]. Available from: http://www.epa.gov/clean-air-act-overview/air-pollution-current-and-future-challenges

36. Dominici F, Peng RD, Barr CD, Bell ML. Protecting Human Health From Air Pollution: Shifting From a Single-pollutant to a Multipollutant Approach. Epidemiology. 2010;21(2):187–94.

37. Vedal S, Kaufnam, J. What does multi-pollutant air pollution research mean? American Journal of Respiratory and Critical Care Medicine. 2011;183(1):4-6.

38. Greenbaum D, Shaikh R. First Steps Toward Multipollutant Science for Air Quality Decisions: Epidemiology. 2010;21(2):195–7.

39. Davalos AD, Luben TJ, Herring AH, Sacks JD. Current approaches used in epidemiologic studies to examine short-term multipollutant air pollution exposures. Annals of Epidemiology. 2017;27(2):145–53.e1.

40. Oakes M, Baxter L, Long TC. Evaluating the application of multipollutant exposure metrics in air pollution health studies. Environment International. 2014;69:90–9

41. Austin E, Coull B, Thomas D, Koutrakis P. A framework for identifying distinct multipollutant profiles in air pollution data. Environment International. 2012;45:112–21.

42. Hidy GM, Pennell WT. Multipollutant Air Quality Management. Journal of the Air & Waste Management Association. 2010;60(6):645–74.

43. Samet JM. Some current challenges in research on air pollution and health. Salud Pública de México. 2014;56(4):379–85.

44. Mauderly JL, Burnett RT, Castillejos M, Özkaynak H, Samet JM, Stieb DM, et al. Is the air pollution health research community prepared to support a multipollutant air quality management framework? Inhalation Toxicology. 2010;22(S1):1–19.

45. Coull BA, Bobb JF, Wellenius GA, Kioumourtzoglou M-A, Mittleman MA, Koutrakis P, Godleski JJ. Statistical Learning Methods for the Effects of Multiple Air Pollution ConstituentsNumber 183 Parts 1 June 2015. 2015 [cited 2017 Jun 22]; Available from: https://www.healtheffects.org/system/files/Coull-Park-RR183-Parts1-2.pdf

46. Molitor J, Coker E, Jerrett M, Ritz B, Li A. Part 3. Modeling of Multipollutant Profiles and Spatially Varying Health Effects with Applications to Indicators of Adverse Birth Outcomes. In: Development of Statistical Methods for Multipollutant Research. 2016. Research Report 183. Boston, MA:Health Effects Institute.

47. King LE, Weber RJ. Development and testing of an online method to measure ambient fine particulate reactive oxygen species (ROS) based on the 2',7'-dichlorofluorescin (DCFH) assay. Atmospheric Measurement Techniques. 2013;6(7):1647–58.

48. Zanobetti A, Austin E, Coull BA, Schwartz J, Koutrakis P. Health effects of multi-pollutant profiles. Environment International. 2014;71:13–9.

49. Czarnota J, Gennings C, Colt JS, De Roos AJ, Cerhan JR, Severson RK, et al. Analysis of Environmental Chemical Mixtures and Non-Hodgkin Lymphoma Risk in the NCI-SEER NHL Study. Environmental Health Perspectives [Internet]. 2015 Mar 6 [cited 2015 Mar 9]; Available from: http://ehp.niehs.nih.gov/1408630.

50. Coker E, Liverani S, Ghosh JK, Jerrett M, Beckerman B, Li A, et al. Multi-pollutant exposure profiles associated with term low birth weight in Los Angeles County. Environment International. 2016;91:1–13.

51. Crouse DL, Peters PA, Hystad P, Brook JR, van Donkelaar A, Martin RV, et al. Ambient PM 2.5 , O 3 , and NO 2 Exposures and Associations with Mortality over 16 Years of Follow-Up in the Canadian Census Health and Environment Cohort (CanCHEC). Environmental Health Perspectives. 2015;123(11). Available from: http://ehp.niehs.nih.gov/14-09276

52. Lodovici M, Bigagli E. Oxidative Stress and Air Pollution Exposure. Journal of Toxicology. 2011;2011:1–9.

53. Vadillo-Ortega F, Osornio-Vargas A, Buxton MA, Sánchez BN, Rojas-Bracho L, Viveros-Alcaráz M, et al. Air pollution, inflammation and preterm birth: A potential mechanistic link. Medical Hypotheses. 2014;82(2):219–24.

54. Manzano-Leon N, Serrano-Lomelin J, Sanchez BN, Quintana-Belmares R, Vega E, Vazquez-Lapez I, et al. TNF-alpha and IL-6 Responses to Particulate Matter in Vitro: Variation According to PM Size, Season, and Polycyclic Aromatic Hydrocarbon and Soil Content. Environmental Health Perspectives. 2015;124(4). Available from: http://ehp.niehs.nih.gov/1409287

55. Johns DO, Stanek LW, Walker K, Benromdhane S, Hubbell B, Ross M, et al. Practical Advancement of Multipollutant Scientific and Risk Assessment Approaches for Ambient Air Pollution. Environmental Health Perspectives. 2012;120(9):1238–42.

56. Agarwal N, Banternghansa C, Bui LTM. Toxic exposure in America: Estimating fetal and infant health outcomes from 14 years of TRI reporting. Journal of Health Economics. 2010;29(4):557–74.

57. Cucurachi S, Sala S, Laurent A, Heijungs R. Building and Characterizing Regional and Global Emission Inventories of Toxic Pollutants. Environmental Science & Technology. 2014;48(10):5674–82.

58. Wine O, Hackett C, Campbell S, Cabrera-Rivera O, Buka I, Zaiane O, et al. Using pollutant release and transfer register data in human health research: a scoping review. Environmental Reviews. 2014;22(1):51–65.

59. Environment and Climate Change Canada. Canadian Environmental Protection Act, 1999 (CEPA 1999). [Internet]. [cited 2017 June 17]. Available from: https://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&n=26A03BFA-1

60. Environment and Climate Change Canada. The National Pollutant Release Inventory. [Internet]. [cited 2016 October 14]. Available from: https://www.ec.gc.ca/inrp-npri/

61. Environment Canada. National Pollutant Release Inventory. Pollution Data and Reports: [Internet] 2014. [cited 2014 Apr 5] Available from: https://www.ec.gc.ca/inrp-npri/default.asp?lang=En&n=B85A1846-1

62. Simpson IJ, Marrero JE, Batterman S, Meinardi S, Barletta B, Blake DR. Air quality in the Industrial Heartland of Alberta, Canada and potential impacts on human health. Atmospheric Environment. 2013;81:702–709.

63. O´Neill MS, Osornio-Vargas A, Buxton MA, Sánchez BN, Rojas-Bracho L, Castillo-Castrejon M, et al. Air pollution, inflammation and preterm birth in Mexico City: Study design and methods. Science of The Total Environment. 2013;448:79–83.

Chapter 2

1. Black RE. Global prevalence of small for gestational age births. In: Embleton ND, Katz J, Ziegler EE. (eds.) Low-Birthweight Baby: Born Too Soon or Too Small. Basel: Karger Publishers; 2015 [cited 2017 Jan 25]. p. 1–7. Available from: http://www.karger.com/Article/Abstract/365790

2. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller A-B, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health. 2013;10(Suppl 1):S2.

3. Cosmi E, Fanelli T, Visentin S, Trevisanuto D, Zanardo V. Consequences in Infants That Were Intrauterine Growth Restricted. Journal of Pregnancy. 2011;2011:1–6.

4. Katz J, Lee AC, Kozuki N, Lawn JE, Cousens S, Blencowe H, et al. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. The Lancet. 2013;382(9890):417–25.

5. Luu TM, Katz SL, Leeson P, Thébaud B, Nuyt A-M. Preterm birth: risk factor for early-onset chronic diseases. Canadian Medical Association Journal. 2016;188(10):736.

6. Johnston KM, Gooch K, Korol E, Vo P, Eyawo O, Bradt P, Levy A. The economic burden of prematurity in Canada. BMC Pediatrics. 2014; 5:14:93

7. Johnson RC, Schoeni RF. The Influence of Early-Life Events on Human Capital, Health Status, and Labor Market Outcomes Over the Life Course. The BE Journal of Economic Analysis & Policy [Internet]. 2011 Jan 6 [cited 2017 Jan 26];11(3). Available from: http://www.degruyter.com/view/j/bejeap.2011.11.issue-3/bejeap.2011.11.3.2521/bejeap.2011.11.3.2521.xml

8. World Health Organization, others. WHO recommendations on interventions to improve preterm birth outcomes. [Internet]. 2015 [cited 2017 Feb 3]; Available from: http://apps.who.int/iris/handle/10665/183037

9. Critchley H, Bennett P, Thornton S. (eds.) Preterm Birth. London: RCOG Press; 2004.

10. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. The Lancet. 2012;379(9832):2162–72.

11. Smith R, Mesiano S, Nicholson R, Zakar T, Chan E-C, Bisits A, et al. Control of the length of gestation: lessons from women. In: Critchley H, Bennett P, Thornton S (eds.). Preterm Birth. London: RCOG Press; 2004.p.13–27.

12. Kim D, Saada A. The Social Determinants of Infant Mortality and Birth Outcomes in Western Developed Nations: A Cross-Country Systematic Review. International Journal of Environmental Research and Public Health. 2013;10(6):2296–335.

13. Räisänen S, Gissler M, Saari J, Kramer M, Heinonen S. Contribution of Risk Factors to Extremely, Very and Moderately Preterm Births – Register-Based Analysis of 1,390,742 Singleton Births. Dastgiri S.(ed.) PLoS ONE. 2013;8(4):e60660.

14. Sapkota A, Chelikowsky AP, Nachman KE, Cohen AJ, Ritz B. Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis. Air Quality, Atmosphere & Health. 2012;5(4):369–81.

15. Behrman RE, Butler AS. Preterm birth causes, consequences, and prevention. Washington DC; National Academies Press; 2007.

16. Zeitlin JA, Ancel P-Y, Saurel-Cubizolles M-J, Papiernik E. Are risk factors the same for small for gestational age versus other preterm births? American Journal of Obstetrics and Gynecology. 2001;185(1):208–15.

17. Luo Z-C, Kierans WJ, Wilkins R, Liston RM, Mohamed J, Kramer MS. Disparities in Birth Outcomes by Neighborhood Income: Temporal Trends in Rural and Urban Areas, British Columbia. Epidemiology. 2004;15(6):679–86.

18. Taylor CA. Associations between measures of SES and low birth weight among black mothers and white mothers in Michigan. Michigan Sociological Review. 2010;56–73.

19. Auger N, Authier M-A, Martinez J, Daniel M. The Association Between Rural-Urban Continuum, Maternal Education and Adverse Birth Outcomes in Québec, Canada. The Journal of Rural Health. 2009;25(4):342–51.

20. Bertin M, Viel J-F, Monfort C, Cordier S, Chevrier C. Socioeconomic Disparities in Adverse Birth Outcomes in Urban and Rural Contexts: a French Mother-Child Cohort: Socioeconomic disparities in adverse birth outcomes. Paediatric and Perinatal Epidemiology. 2015;29(5):426–35.

21. DeFranco E, Moravec W, Xu F, Hall E, Hossain M, Haynes EN, et al. Exposure to airborne particulate matter during pregnancy is associated with preterm birth: a population-based cohort study. Environmental Health [Internet]. 2016 Dec [cited 2016 Apr 19];15(1). Available from: http://www.ehjournal.net/content/15/1/6.

22. Stieb DM, Chen L, Beckerman BS, Jerrett M, Crouse DL, Omariba DWR, et al. Associations of Pregnancy Outcomes and PM2.5 in a National Canadian Study. Environmental Health Perspectives [Internet]. 2015 Jun 19 [cited 2016 Apr 19];124(2). Available from: http://ehp.niehs.nih.gov/1408995

23. Parker JD, Rich DQ, Glinianaia SV, Leem JH, Wartenberg D, Bell ML, et al. The International Collaboration on Air Pollution and Pregnancy Outcomes: Initial Results. Environmental Health Perspectives. 2011;119(7):1023–8.

24. Keyes KM, Galea S. Commentary: The Limits of Risk Factors Revisited. Epidemiology. 2017;28(1):1–5.

25. South AP, Jones DE, Hall ES, Huo S, Meinzen-Derr J, Liu L, et al. Spatial Analysis of Preterm Birth Demonstrates Opportunities for Targeted Intervention. Maternal and Child Health Journal. 2012;16(2):470–8.

26. Public Health Agency of Canada. Perinatal Health Indicators for Canada 2011. Ottawa, 2012.

27. Public Health Agency of Canada. Perinatal Health Indicators for Canada 2013: A Report of the Canadian Perinatal Surveillance System. Ottawa, 2013.

28. Canadian Institute for Health Information. Highlights of 2010–2011. Selected Indicators Describing the Birthing Process in Canada, ON. CIHI. 2012.

29. Tough SC, Svenson LW, Johnston DW, Schopflocher D. Characteristics of preterm delivery and low birth weight among 113,994 infants in Alberta:1994-1996. Canadian Journal of Public Health, 2001;92(4):276-80.

30. Twilley L, Wang FL. Predictors of Preterm and Small for Gestatonal Age Birth in Alberta. Edmonton, AB: Alberta Health and Wellness; 2006.

31. Osornio-Vargas A, Zaiane O, Wine O. Domino Project: Data Mining and Newborn Outcomes Exploring Environmental Variables. 26th Annual Conference of the International Society for Environmental Epidemiology; 2014 Aug 24-28; Seattle: Abstract Number: 2187 | ID: P3-607.

32. Kramer MS, Platt RW, Wen SW, Joseph KS, Allen A, Abrahamowicz M, et al. A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics. 2001;108(2):e35–e35.

33. Chan E, Serrano J, Chen L, Stieb DM, Jerrett M, Osornio-Vargas A. Development of a Canadian socioeconomic status index for the study of health outcomes related to environmental pollution. BMC Public Health [Internet]. 2015 Dec [cited 2016 Apr 19];15(1). Available from: http://www.biomedcentral.com/1471-2458/15/714.

34. Statistics Canada. 2006 Census Dictionary. Statistics Canada Catalogue no. 92-566-XWE. Ottawa, Ontario. February 2008.

35. DMTI Spatial. Platinum Postal Suite: CanMap Multiple Enhanced Postal Code Geography 2001-2013. [computer file]. Markham, Ontario: DMTI Spatial Inc. 2014.

36. Statistics Canada. 2006 Census - Boundary files: Reference Guide. Statistics Canada Catalogue no. gda_000b06a_e.zip. Ottawa, Ontario. 2007. Available from: http://www12.statcan.ca/census-recensement/2011/geo/bound-limit/bound-limit-2006-eng.cfm.

37. Statistics Canada. GeoSuite, 2006 Census Geographic Data Products. Statistics Canada Catalogue no. 92F0150XCB. Ottawa, Ontario. March 2007. 2007.

38. Canadian Institute for Health Information. In Due Time: Why Maternal Age Matters. Ottawa. [Internet]. 2011 [cited 2017 February 9]. Available from : https://secure.cihi.ca/free_products/AIB_InDueTime_WhyMaternalAgeMatters_E.pdf.

39. Rabe-Hesketh S, Skrondal A. Multilevel and longitudinal modeling using Stata. 2nd ed. Stata Press, USA. 2008.

40. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. American journal of public health. 1998;88(1):15–9.

41. Rothman KJ. Epidemiology: An Introduction. USA: Oxford University Press; 2012.

42. Dallolio L, Bellocco R, Richiardi L, Fantini MP. Using directed acyclic graphs to understand confounding in observational studies. Biomedical Statistics and Clinical Epidemiology. 2009;3(2):89-96.

43. StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.

44. IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.

45. ESRI 2011. ArcGIS Desktop: Release 10. Redlands, CA: Environmental Systems Research Institute.

46. Agrawal S. Urban, Suburban, Regional and Wet Growth in Alberta. Alberta Land Institute. University of Alberta. [Internet] 2007 [cited 2017 April 11]. Available from: www.albertalandinstitute.ca/public/download/documents/34087

47. Statistics Canada. Population, urban and rural, by province and territory (Alberta). [Internet] [cited 2017 April 11]. Available from: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo62j-eng.htm

48. Canadian Institute for Health Information (CIHI). Too Early, Too Small: A Profile of Small Babies Across Canada.Ottawa, Ont.: CIHI, 2009.

49. Luo Z-C, Wilkins R. Degree of rural isolation and birth outcomes. Paediatric and Perinatal Epidemiology. 2008;22(4):341–9.

50. Murphy DJ. Epidemiology and environmental factors in preterm labour. Best Practice & Research Clinical Obstetrics & Gynaecology. 2007;21(5):773–89.

51. Farley TA, Mason K, Rice J, Habel JD, Scribner R, Cohen DA. The relationship between the neighbourhood environment and adverse birth outcomes. Paediatr Perinat Epidemiol 2006; 20:188–200.

52. Rahman LA, Hairi NN, Salleh N. Association Between Pregnancy Induced Hypertension and Low Birth Weight; A Population Based Case-Control Study. Asia-Pacific Journal of Public Health. 2008;20(2):152–8.

53. Walker RL, Hemmelgarn B, Quan H. Incidence of gestational hypertension in the Calgary health Region from 1995 to 2004. Can J Cardiol 2009;25(8):e284-e287.

54. World Health Organization. WHO report on the global tobacco epidemic, 2015: raising taxes on tobacco. World Health Organization 2015. ISBN 978 92 4 069460 6 (PDF)

55. Tolosa JE, Echavarría-Restrepo LG, Agudelo B. Smoking during pregnancy: a preventable silent epidemic in Colombia. Revista Colombiana de Obstetricia y Ginecología. 2011;62(2):123-126.

56. Hunt KJ, Alanis MC, Johnson ER, Mayorga ME, Korte JE. Maternal Pre-Pregnancy Weight and Gestational Weight Gain and Their Association with Birthweight with a Focus on Racial Differences. Maternal and Child Health Journal. 2013 Jan;17(1):85–94.

57. Government of Alberta. International Migration. Demographic Spotlight. Treasury Board and Finance. Report December 2009. [Internet]. 2009 [cited 2017 April 11]. Available from: http://www.finance.alberta.ca/aboutalberta/osi/demographics/Analysis-and-Reports/2009/2009_1221_International_Migration_Spotlight_Final.pdf

58. Qadeer M, Kumar S. Ethnic enclaves and social cohesion. Canadian Journal of Urban Research. 2006;15(2):1–17.

59. Qadeer M, Agrawal SK, Lovell A. Evolution of Ethnic Enclaves in the Toronto Metropolitan Area, 2001–2006. Journal of International Migration and Integration / Revue de l'integration et de la migration internationale. 2010;11(3):315–39.

60. Martorell R, Zongrone A. Intergenerational Influences on Child Growth and Undernutrition: Intergenerational influences. Paediatric and Perinatal Epidemiology. 2012; 26:302–14.

61. Heaman M, Kingston D, Chalmers B, Sauve R, Lee L, Young D. Risk Factors for Preterm Birth and Small-for-gestational-age Births among Canadian Women: Risk factors for PTB and SGA births. Paediatric and Perinatal Epidemiology. 2013;27(1):54–61.

62. Urquia and Ray, 2012. Seven caveats on the use of low birth weight and related indicators in health research. J Epidemiol Community Health. 2012;66(11):971-5.

63. Arsenault J, Michel P, Berke O, Ravel A, Gosselin P. How to choose geographical units in ecological studies: Proposal and application to campylobacteriosis. Spatial and Spatio-temporal Epidemiology. 2013;7:11–24.

64. Clayton D, Kaldor J. 1987. Empirical Bayes estimates of age-standardized relative risks for use in disease mapping. Biometrics 1987;43:671–681.

65. Greenland S. Concepts and pitfalls in measuring and interpreting attributable fractions, prevented fractions, and causation probabilities. Annals of Epidemiology. 2015 Mar;25(3):155–6

66 Lisonkova S, Haslam MD, Dahlgren L, Chen I, Synnes AR, Lim KI. Maternal morbidity and perinatal outcomes among women in rural versus urban areas. Canadian Medical Association Journal. 2016;188(17–18):E456–E465.

67. Kim SY, Sharma AJ, Sappenfield W, Wilson HG, Salihu HM. Association of maternal body mass index, excessive weight gain, and gestational diabetes mellitus with large-for-gestational-age births. Obstet Gynecol. 2014;(4):737-44

Chapter 3

1. Agarwal N, Banternghansa C, Bui LTM. Toxic exposure in America: Estimating fetal and infant health outcomes from 14 years of TRI reporting. Journal of Health Economics. 2010;29(4):557–74.

2. Slama R, Darrow L, Parker J, Woodruff TJ, Strickland M, Nieuwenhuijsen M, et al. Meeting Report: Atmospheric Pollution and Human Reproduction. Environmental Health Perspectives. 2008;116(6):791–8.

3. Stillerman KP, Mattison DR, Giudice LC, Woodruff TJ. Environmental Exposures and Adverse Pregnancy Outcomes: A Review of the Science. Reproductive Sciences. 2008;15(7):631–50.

4. Currie J, Schmieder JF. Fetal exposure to toxic releases and infant health. National Bureau of Economic Research [Internet]. 2008 [cited 2017 Sep 17]. Available from: http://www.nber.org/papers/w14352.

5. Edwards S, Maxson P, Sandberg N, Miranda ML. Air Pollution and Pregnancy Outcomes. In: Nadadur SS, Hollingsworth JW (eds.) Air Pollution and Health Effects. London: Springer-Verlag; 2015. Chapter 3. pp.51-91.

6. Ha S, Hu H, Roussos-Ross D, Haidong K, Roth J, Xu X. The effects of air pollution on adverse birth outcomes. Environmental Research. 2014;134:198–204.

7. Stieb DM, Chen L, Eshoul M, Judek S. Ambient air pollution, birth weight and preterm birth: A systematic review and meta-analysis. Environmental Research. 2012;117:100.

8. Sapkota A, Chelikowsky AP, Nachman KE, Cohen AJ, Ritz B. Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis. Air Quality, Atmosphere & Health. 2012;5(4):369–81.

9. Shah PS, Balkhair T. Air pollution and birth outcomes: A systematic review. Environment International. 2011;37(2):498–516.

10. Ritz B, Wilhelm M. Ambient Air Pollution and Adverse Birth Outcomes: Methodologic Issues in an Emerging Field: Ambient air pollution and adverse birth outcomes. Basic & Clinical Pharmacology & Toxicology. 2008;102(2):182–90.

11. Seltenrich N. The Uncertain Relationship between Air Pollution and Risk of Preterm Birth: Does Spatial Variation Drive Disparate Findings? Environmental Health Perspectives [Internet]. 2016 [cited 2017 Oct 2];124(8). Available from: http://ehp.niehs.nih.gov/124-A147

12. Dominici F, Peng RD, Barr CD, Bell ML. Protecting Human Health From Air Pollution: Shifting From a Single-pollutant to a Multipollutant Approach. Epidemiology. 2010;21(2):187–94.

13. Mauderly JL, Burnett RT, Castillejos M, Özkaynak H, Samet JM, Stieb DM, et al. Is the air pollution health research community prepared to support a multipollutant air quality management framework? Inhalation Toxicology. 2010;22(S1):1–19.

14. Liu S, Krewski D, Shi Y, Chen Y, Burnett RT. Association between maternal exposure to ambient air pollutants during pregnancy and fetal growth restriction. Journal of Exposure Science and Environmental Epidemiology. 2007;17(5):426.

15. Le HQ, Batterman SA, Wirth JJ, Wahl RL, Hoggatt KJ, Sadeghnejad A, et al. Air pollutant exposure and preterm and term small-for-gestational-age births in Detroit, Michigan: Long-term trends and associations. Environment International. 2012;44:7–17.

16. Cucurachi S, Sala S, Laurent A, Heijungs R. Building and Characterizing Regional and Global Emission Inventories of Toxic Pollutants. Environmental Science & Technology. 2014;48(10):5674–82.

17. Mattison DR. Environmental exposures and development: Current Opinion in Pediatrics. 2010;22(2):208–18.

18. The air pollution information site. Scorecard. Health effects/developmental toxicants. [Internet]. [cited 2017 Sept 10]. Available from: http://scorecard.goodguide.com/health-effects/chemicals-2.tcl?short_hazard_name=devel&all_p=t

19. Ferguson KK, O'Neill MS, Meeker JD. Environmental Contaminant Exposures and Preterm Birth: A Comprehensive Review. Journal of Toxicology and Environmental Health, Part B. 2013;16(2):69–113.

20. Padula AM, Noth EM, Hammond SK, Lurmann FW, Yang W, Tager IB, et al. Exposure to airborne polycyclic aromatic hydrocarbons during pregnancy and risk of preterm birth. Environmental Research. 2014;135:221–6.

21. Choi H, Wang L, Lin X, Spengler JD, Perera FP. Fetal Window of Vulnerability to Airborne Polycyclic Aromatic Hydrocarbons on Proportional Intrauterine Growth Restriction. Cook AR. (ed.) PLoS ONE. 2012 Apr 24;7(4):e35464.

22. Llop S, Ballester F, Estarlich M, Esplugues A, Rebagliato M, Iñiguez C. Preterm birth and exposure to air pollutants during pregnancy. Environmental Research. 2010;110(8):778–85.

23. Porter TR, Kent ST, Su W, Beck HM, Gohlke JM. Spatiotemporal association between birth outcomes and coke production and steel making facilities in Alabama, USA: a cross-sectional study. Environmental Health. 2014;13(1):85.

24. Sacks JD, Fann N, Owens EO, Costa DL. Using Science to Shape Policy. In: Air Pollution and Health Effects. Nadadur SS, Hollingsworth JW. editors. Springer-Verlag London 2015. Chapter 11. p403-436.

25. Samet JM. Some current challenges in research on air pollution and health. Salud Pública de México. 2014;56(4):379–385.

26. Hidy GM, Pennell WT. Multipollutant Air Quality Management. Journal of the Air & Waste Management Association. 2010;60(6):645–74.

27. O´Neill MS, Osornio-Vargas A, Buxton MA, Sánchez BN, Rojas-Bracho L, Castillo-Castrejon M, et al. Air pollution, inflammation and preterm birth in Mexico City: Study design and methods. Science of The Total Environment. 2013;448:79–83.

28. de Kok TMCM, Driece HAL, Hogervorst JGF, Briede JJ. Toxicological assessment of ambient and traffic-related particulate matter: A review of recent studies. Mutation Research/Reviews in Mutation Research. 2006;613(2–3):103–22.

29. Vadillo-Ortega F, Osornio-Vargas A, Buxton MA, Sánchez BN, Rojas-Bracho L, Viveros-Alcaráz M, et al. Air pollution, inflammation and preterm birth: A potential mechanistic link. Medical Hypotheses. 2014;82(2):219–24.

30. Menon R. Oxidative Stress Damage as a Detrimental Factor in Preterm Birth Pathology. Frontiers in Immunology [Internet]. 2014 Nov 12 [cited 2017 Sep 15];5. Available from: http://journal.frontiersin.org/article/10.3389/fimmu.2014.00567/abstract

31. Ghio AJ, Carraway MS, Madden MC. Composition of Air Pollution Particles and Oxidative Stress in Cells, Tissues, and Living Systems. Journal of Toxicology and Environmental Health, Part B. 2012;15(1):1–21.

32. Lodovici M, Bigagli E. Oxidative Stress and Air Pollution Exposure. Journal of Toxicology. 2011;2011:1–9.

33. Manzano-Leon N, Serrano-Lomelin J, Sanchez BN, Quintana-Belmares R, Vega E, Vazquez-Lapez I, et al. TNF-alpha and IL-6 Responses to Particulate Matter in Vitro: Variation According to PM Size, Season, and Polycyclic Aromatic Hydrocarbon and Soil Content. Environmental Health Perspectives [Internet]. 2015 Sep 15 [cited 2017 Jun 22];124(4). Available from: http://ehp.niehs.nih.gov/1409287

34. Environment and Climate Change Canada. Summary of Data Reported for 2015. National Pollutant Release Inventory (NPRI) Fact Sheet. [Internet]. [cited 2017 July 3]. Available from: http://www.ec.gc.ca/inrp-npri/default.asp?lang=En&n=D55C89B3-1

35. Environment and Climate Change Canada. Canadian Environmental Sustainability Indicators: Air Pollutant Emissions. [Internet]. 2016. [cited 2017 July 4]. Available at: http://www.ec.gc.ca/indicateurs-indicators/default.asp?lang=en&n=E79F4C12-

36. Public Health Agency of Canada. Perinatal Health Indicators for Canada 2013: A Report of the Canadian Perinatal Surveillance System. Ottawa, 2013.

37. Osornio-Vargas A, Zaiane O, Wine O. Domino Project: Data Mining and Newborn Outcomes Exploring Environmental Variables. 26th Annual Conference of the

International Society for Environmental Epidemiology; 2014 Aug 24-28; Seattle: Abstract Number: 2187 | ID: P3-607.

38. Kramer MS, Platt RW, Wen SW, Joseph KS, Allen A, Abrahamowicz M, et al. A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics. 2001;108(2):e35–e35.

39. Murphy DJ. Epidemiology and environmental factors in preterm labour. Best Practice & Research Clinical Obstetrics & Gynaecology. 2007;21(5):773–89.

40. Statistics Canada. 2006 Census - Boundary files: Reference Guide. Statistics Canada Catalogue no. gda_000b06a_e.zip. Ottawa, Ontario. 2007. [Internet] [retrieved 2014 March 20]. Available from: http://www12.statcan.ca/census-recensement/2011/geo/bound-limit/bound-limit-2006-eng.cfm

41. Statistics Canada. 2006 Census Dictionary. Statistics Canada Catalogue no. 92-566-XWE. Ottawa, Ontario. February 2008.

42. DMTI Spatial. Platinum Postal Suite: CanMap Multiple Enhanced Postal Code Geography 2001-2013. [computer file]. Markham, Ontario: DMTI Spatial Inc. 2014.

43. Statistics Canada. GeoSuite, 2006 Census Geographic Data Products. Statistics Canada Catalogue no. 92F0150XCB. Ottawa, Ontario. March 2007. 2007.

44. Rabe-Hesketh S, Skrondal A. Multilevel and longitudinal modeling using Stata. 2nd ed. USA: Stata Press; 2008.

45. Environment and Climate Change Canada. The National Pollutant Release Inventory. [Accessed 2016 October 14]. Available from: https://www.ec.gc.ca/inrp-npri/

46. Chemical Abstracts Service. CAS REGISTRY. The gold standard for chemical substance information. [Internet]. Available from: https://www.cas.org/content/chemical-substances

47. Environment and Climate Change Canada. Guide for Using and Interpreting National Pollutant Release Inventory (NPRI) Data. [Internet] [Last review 2016 Sep 23]. Available from: http://www.ec.gc.ca/inrp-npri/default.asp?lang=En&n=B5C1EAB8-1

48. Statistic Canada 2016. Industry classifications. [Internet]. [cited 2016 Sep 23]. Available from: http://www.statcan.gc.ca/eng/concepts/industry

49. Agency for Toxic Substances and Disease Registry (ATSDR). Toxic Substances Portal/ Chemical Classifications. [Internet]. Available from: https://www.atsdr.cdc.gov/substances/ToxChemicalClasses.asp.

50. Cassee FR, Héroux M-E, Gerlofs-Nijland ME, Kelly FJ. Particulate matter beyond mass: recent health evidence on the role of fractions, chemical constituents and sources of emission. Inhalation Toxicology. 2013;25(14):802–12.

51. StataCorp. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP, 2013.

52. Everitt BS, Landau S, Leese M, Stahl D. Cluster Analysis. 5th ed. Great Britain: John Wiley & Sons Ltd; 2011.

53. Legendre and Legendre. Numerical Ecology. Amsterdam: Elsevier; 2012.

54. Austin E, Coull B, Thomas D, Koutrakis P. A framework for identifying distinct multipollutant profiles in air pollution data. Environment International. 2012;45:112–21.

55. Iizuka A, Shirato S, Mizukoshi A, Noguchi M, Yamasaki A, Yanagisawa Y. A Cluster Analysis of Constant Ambient Air Monitoring Data from the Kanto Region of Japan. International Journal of Environmental Research and Public Health. 2014;11(7):6844–55.

56. Zhang J, Zhang L, Du M, Zhang W, Huang X, Zhang Y, et al. Indentifying the major air pollutants base on factor and cluster analysis, a case study in 74 Chinese cities. Atmospheric Environment. 2016;144:37–46.

57. StataCorp. Stata Statistical Software: Release 8.0. Stata Cluster Analysis. College Station, TX: Stata Corporation; 2003.

58. ESRI 2011. ArcGIS Desktop: Release 10. Redlands, CA: Environmental Systems Research Institute.

59. Chan E, Serrano J, Chen L, Stieb DM, Jerrett M, Osornio-Vargas A. Development of a Canadian socioeconomic status index for the study of health outcomes related to environmental pollution. BMC Public Health [Internet]. 2015 Dec [cited 2016 Apr 19];15(1). Available from: http://www.biomedcentral.com/1471-2458/15/714

60. Alberta Environment. Air Management in Alberta. 2009. ISBN No. 978-0-7785-8088-1 Available from: http://www.environment.alberta.ca/

61. Wine O, Hackett C, Campbell S, Cabrera-Rivera O, Buka I, Zaiane O, et al. Using pollutant release and transfer register data in human health research: a scoping review. Environmental Reviews. 2014;22(1):51–65.

62. Castelló A, Río I, García-Pérez J, Fernández-Navarro P, Waller LA, Clennon JA, et al. Adverse birth outcomes in the vicinity of industrial installations in Spain 2004–2008. Environmental Science and Pollution Research. 2013;20(7):4933–46.

63. García-Pérez J, López-Abente G, Gómez-Barroso D, Morales-Piga A, Pardo Romaguera E, Tamayo I, et al. Childhood leukemia and residential proximity to industrial and urban sites. Environmental Research. 2015;140:542–53.

64. García-Pérez J, López-Cima MF, Boldo E, Fernández-Navarro P, Aragonés N, Pollán M, et al. Leukemia-related mortality in towns lying in the vicinity of metal production and processing installations. Environment International. 2010;36(7):746–53.

65. Conley JF. Estimation of exposure to toxic releases using spatial interaction modeling. International journal of health geographics. 2011;10(1):20.

66. Mennis JL, Jordan L. The Distribution of Environmental Equity: Exploring Spatial Nonstationarity in Multivariate Models of Air Toxic Releases. Annals of the Association of American Geographers, 95(2), 2005, p249–268.

67. Hertwich EG, Mateles SF, Pease WS, McKone TE. Human toxicity potentials for life-cycle assessment and toxics release inventory risk screening. Environmental Toxicology and Chemistry 2001;20(4):928-939.

68. Woodruff TJ, Parker JD, Darrow LA, Slama R, Bell ML, Choi H, et al. Methodological issues in studies of air pollution and reproductive health. Environmental Research. 2009;109(3):311–20.

69. Environment and Climate Change Canada. Canadian Environmental Sustainability Indicators: Air Pollutant Emissions 2016. [Internet] [cited 2017 July 4]. Available from: http://www.ec.gc.ca/indicateurs-indicators/default.asp?lang=en&n=E79F4C12-

70. Environment and Climate Change Canada. Canada's Emissions Trends 2013. [Internet]. [cited 2017 July 5]. Available from: https://ec.gc.ca/ges-ghg/default.asp?lang=En&n=985F05FB-1

71. Environment and Climate Change Canada. Air Pollutant Emissions from the Oil and Gas Sector. [Internet]. [cited 2017 July 5]. Available from: https://www.ec.gc.ca/indicateurs-indicators/default.asp?lang=en&n=117ECDEC-1

72. Government of Alberta. Alberta Industry/ Oil and Gas. [Internet]. [cited 2017 July 5]. Available from: http://www.albertacanada.com/business/industries/oil-and-gas.aspx

73. Government of Alberta. Environmental Protection and Enhancement Act. [Internet]. [cited 2017 July 5]. Available from: www.qp.alberta.ca

74. Sanchez-Rodas D, Sanchez de la Campa A, Oliveira V, de la Rosa J. Health implications of the distribution of arsenic species in airborne particulate matter. Journal of Inorganic Biochemistry. 2012;108:112–4.

75. Tchounwou PB, Yedjou CG, Patlolla AK, Sutton DJ. Heavy Metal Toxicity and the Environment. In: Luch A. (ed.). Molecular, Clinical and Environmental Toxicology [Internet]. Basel: Springer; 2012 [cited 2017 Sep 23]. p. 133–64. Available from: http://www.springerlink.com/index/10.1007/978-3-7643-8340-4_6

76. Protano C, Scalise T, Orsi GB, Vitali M.A systematic review of benzene exposure during pregnancy and adverse outcomes on intrauterine development and birth: still far from scientific evidence.Ann Ig. 2012;24(6):451-63.

77. Slama R, Thiebaugeorges O, Goua V, Aussel L, Sacco P, Bohet A, et al. Maternal Personal Exposure to Airborne Benzene and Intrauterine Growth. Environmental Health Perspectives. 2009;117(8):1313–21.

78. Thomas S, Arbuckle TE, Fisher M, Fraser WD, Ettinger A, King W. Metals exposure and risk of small-for-gestational age birth in a Canadian birth cohort: The MIREC study. Environmental Research. 2015;140:430–9.

79. Sakr CJ, Taiwo OA, Galusha DH, Slade MD, Fiellin MG, Bayer F, et al. Reproductive Outcomes Among Male and Female Workers at an Aluminum Smelter: Journal of Occupational and Environmental Medicine. 2010;52(2):137–43.

80. Reed L, Buchner V, Tchounwou PB. Environmental toxicology and health effects associated with hexachlorobenzene exposure. Rev Environ Health. 2007; 22(3):213-43.

81. Bell ML, Belanger K. Review of research on residential mobility during pregnancy: consequences for assessment of prenatal environmental exposures. Journal of Exposure Science and Environmental Epidemiology. 2012;22(5):429–38.

82. Samson PJ. Atmospheric transport and dispersion of air pollutants associated with vehicular emissions. In: Watson AY, Bates RR, Kennedy D (eds.). Air Pollution, the automobile, and Public Health. The Health Effects Institute. 1998. p77-98.

83. Gaffney JS, Marley NA. Atmospheric Chemistry and Air Pollution. The Scientific World Journal. 2003;3:199–234.

84. Geer LA. Identifying exposure disparities in air pollution epidemiology specific to adverse birth outcomes. Environmental Research Letters. 2014;9(10):101001.

85. Smith TJ, Krieber D. A biologic approach to environmental assessment and epidemiology. New York: Oxford University Press; 2010.

86. Government of Alberta 2009. International Migration. Demographic Spotlight. Treasury Board and Finance. Report December 2009. [Internet]. [cited 2017 April 11]. Available from http://www.finance.alberta.ca/aboutalberta/osi/demographics/Analysis-and Reports/2009/2009_1221_International_Migration_Spotlight_Final.pdf

87. Oommen R, Hauser J, Dayton D, Swift J. Identifying Priority Hazardous Air Pollutants of Potential Concern: A Comparison of Toxicity-Weighted Emissions and Ambient Risk Screening Results. [Internet] [cited 2017 Dec 10]. Available from: https://www3.epa.gov/ttnchie1/conference/ei17/session7/oommen1.pdf

Chapter 4

1. Slama R, Darrow L, Parker J, Woodruff TJ, Strickland M, Nieuwenhuijsen M, et al. Meeting Report: Atmospheric Pollution and Human Reproduction. Environmental Health Perspectives. 2008;116(6):791–8.

2. Ritz B, Wilhelm M. Ambient Air Pollution and Adverse Birth Outcomes: Methodologic Issues in an Emerging Field: Ambient air pollution and adverse birth outcomes. Basic & Clinical Pharmacology & Toxicology. 2008;102(2):182–90.

3. Osornio-Vargas A, Zaiane O, Wine O. Domino Project: Data Mining and Newborn Outcomes Exploring Environmental Variables. 26th Annual Conference of the International Society for Environmental Epidemiology; 2014 Aug 24-28; Seattle: Abstract Number: 2187 | ID: P3-607.

4. Canadian Institute of Health Research. Guide to Knowledge Translation Planning at CIHR: Integrated and End-of-Grant Approaches. 2012. [cited 2012, Sep 13]. Available from: http://www.cihr-irsc.gc.ca/e/45321.html.

5. Bowen S, Martens PJ. The Need to Know Team. Demystifying knowledge translation. Learning from the community. Journal of Health Research and Policy. 2005;10(4):203-211.

6. Agrawal S. Urban, Suburban, Regional and Wet Growth in Alberta. Alberta Land Institute. University of Alberta. 2007. [Internet] [cited 2017 April 11]. Available from: www.albertalandinstitute.ca/public/download/documents/34087

7. Statistics Canada. Population, urban and rural, by province and territory (Alberta). [Internet]. [cited 2017 April 11]. Available from: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo62j-eng.htm

8. Government of Alberta. International Migration. Demographic Spotlight. Treasury Board and Finance. Report December 2009. [Internet]. [cited 2017 April 11]. Available from: http://www.finance.alberta.ca/aboutalberta/osi/demographics/Analysis-and-Reports/2009/2009_1221_International_Migration_Spotlight_Final.pdf

9. Qadeer M, Kumar S. Ethnic enclaves and social cohesion. Canadian Journal of Urban Research. 2006;15(2):1–17.

10. Statistics Canada. Annual demographic estimates: Canada, Provinces and Territories. Section1: Total demographic estimates. [Internet]. [cited 2017 August 12]. Available from: http://www.statcan.gc.ca/pub/91-215-x/2013002/part-partie1-eng.htm.

11. Martorell R, Zongrone A. Intergenerational Influences on Child Growth and Undernutrition: Intergenerational influences. Paediatric and Perinatal Epidemiology. 2012; 26:302–14.

12. Dociu M, Dunarintu A. The socio-economic impact of urbanization. International Journal of Academic Research in Accounting, Finance and Management Sciences. 2012;2(1):47–52.

13. Keyes KM, Galea S. Commentary: The Limits of Risk Factors Revisited: Is It Time for a Causal Architecture Approach? Epidemiology 2017;28(1):1-5.

14. Smid M, Stringer E, Stringer J. A Worldwide Epidemic: The Problem and Challenges of Preterm Birth in Low- and Middle-Income Countries. American Journal of Perinatology. 2016;33(03):276–89.

15. Lavigne E, Yasseen AS, Stieb DM, Hystad P, van Donkelaar A, Martin RV, et al. Ambient air pollution and adverse birth outcomes: Differences by maternal comorbidities. Environmental Research. 2016;148:457–66.

16. Twilley L, Wang FL. Predictors of Preterm and Small for GestatonalGestational Age Birth in Alberta. Edmonton, AB: Alberta Health and Wellness; 2006.

17. Wood S, McNeil D, Yee W, Siever J, Rose S. Neighbourhood socio-economic status and spontaneous premature birth in Alberta. Can J Public Health. 2014;105(5):e383–8.

18. Hidy GM, Pennell WT. Multipollutant Air Quality Management. Journal of the Air & Waste Management Association. 2010;60(6):645–74.

19. Edwards S, Maxson P, Sandberg N, Miranda ML. Air Pollution and Pregnancy Outcomes. In: Nadadur SS, Hollingsworth JW. (eds.). Air Pollution and Health Effects. London: Springer-Verlag; 2015. Chapter 3. p51-91.

20. Environment and Climate Change Canada. The National Pollutant Release Inventory. [Internet]. [cited 2016 October 14]. Available from: https://www.ec.gc.ca/inrp-npri/

21. Christopher JR. editor. Toxicology of the human environment: the critical role of free radicals. New York: Taylor & Francis Limited; 2000.

22. Hubbs-Tait L, Nation JR, Krebs NF, Bellinger DC. Neurotoxicants, micronutrients, and social environment. Individual and combined effects on Children's Development. Psychol Sci Public Interest. 2005;6(3):57-121.

23. Mauderly JL, Burnett RT, Castillejos M, Özkaynak H, Samet JM, Stieb DM, et al. Is the air pollution health research community prepared to support a multipollutant air quality management framework? Inhalation Toxicology. 2010;22(S1):1–19.

23. Manzano-Leon N, Serrano-Lomelin J, Sanchez BN, Quintana-Belmares R, Vega E, Vazquez-Lapez I, et al. TNF-alpha and IL-6 Responses to Particulate Matter in Vitro: Variation According to PM Size, Season, and Polycyclic Aromatic Hydrocarbon and Soil Content. Environmental Health Perspectives [Internet]. 2015 Sep 15 [cited 2017 Jun 22];124(4). Available from: http://ehp.niehs.nih.gov/1409287

24. Lahiri DK, Maloney B, Basha RM, Bailey JA, Ray B, Zawia NH. Early-life events trigger latent biochemical pathways for late disorders. In: Reddy GR, Flora SJS, Basha R. (eds.). Environmental Pollution: ecology and human health. New Delhi, India: Narosa Publishing House; 2012. p1-10.

25. Sankap U, Kaja S, Rahim A, Patel PP, Abdelrahim M, Basha R. Role of the environment in Human Cancers. In: Reddy GR, Flora SJS, Basha R. (eds.). Environmental Pollution: ecology and human health. New Delhi, India: Narosa Publishing House; 2012. p136-147.

26. Weichenthal S, Crouse DL, Pinault L, Godri-Pollitt K, Lavigne E, Evans G, et al. Oxidative burden of fine particulate air pollution and risk of cause-specific mortality in the Canadian Census Health and Environment Cohort (CanCHEC). Environmental Research. 2016;146:92–9.

27 Keune H, Morren B, Loot I. Natural scientific complexity from social scientific perspective: environment and health research and policymaking in Flanders (Belgium). Int. J. Risk Assessment and Management. 2009;13(3-4):242-258.

Appendix 1 – Age-adjusted Standardize Prevalence Ratios and Smoothing

1) Standardization of prevalence proportions (Age-adjusted).

We used the indirect method for calculating Standardized Proportions Ratios (SPR). The expected number of ABOs cases were based on the age-specific PTB/SGA/LBWT proportions for the age distribution of the whole province and the age distribution in the Dissemination Areas (DAs)

The age-categories were chosen from the Canadian Institute of Health Information ( ):

Category 1 (k=1): less than 20 years' old

Category 2 (k=2): between 20 and 34 years' old

Category 3 (k=3): between 35 and 39 years' old

Category 4 (k=4): 40 years old and older

The age-adjusted SPR for the i^{th} DA is (Gerstman 2003):

$SPR_i = o_i / e_{i\bullet}$ where:

o_i = observed number of cases in the Dissemination Area *i*

$e_{i\bullet} = \sum_{k=1}^{4} P_k n_{ki}$ it represents the age-adjusted expected number of cases in the Dissemination Area *i*

P_k = proportion of adverse birth outcomes in the k^{th} age-category of the reference population

n_{ki} = number of livebirths in the k^{th} age-category in the i^{th} DA

Age-category proportions of Preterm Birth in the Province (reference population)

Age-category proportions of small for gestational age in the province (reference population)

Age-category proportions of low birth weight at term in the province (reference population)

2) Smoothing of SPR based on a Bayesian model.

We used the Rabe-Hesketh and Skrondal (2008) program developed for *stata*-Software for predicting SPR using empirical Bayes. The model specification is based on a random-intercept Poisson model for the number of cases by DA.

Model specification:

$$\ln(\mu_i) = \ln(e_i) + \beta_1 + \zeta_i$$

where:

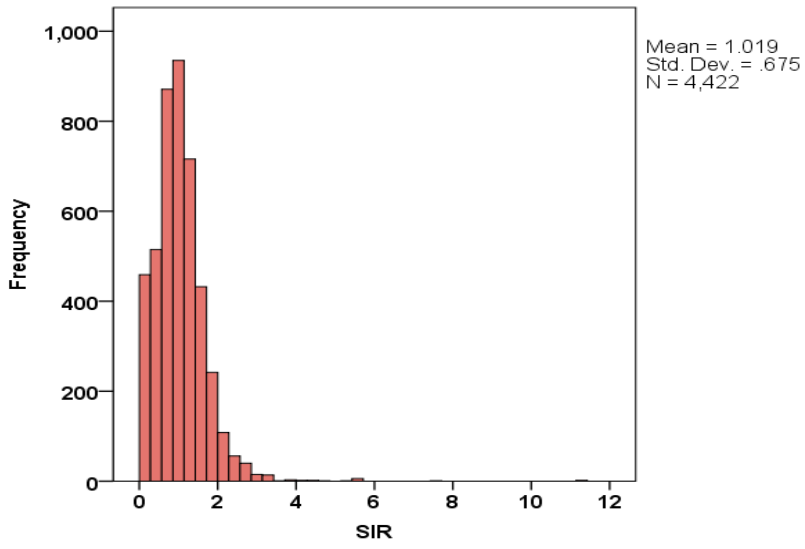
$\ln(e_i)$ is an offset to ensure that $\beta_1 + \zeta_i$ can be interpreted as a model-based DA-specific log of SPR.

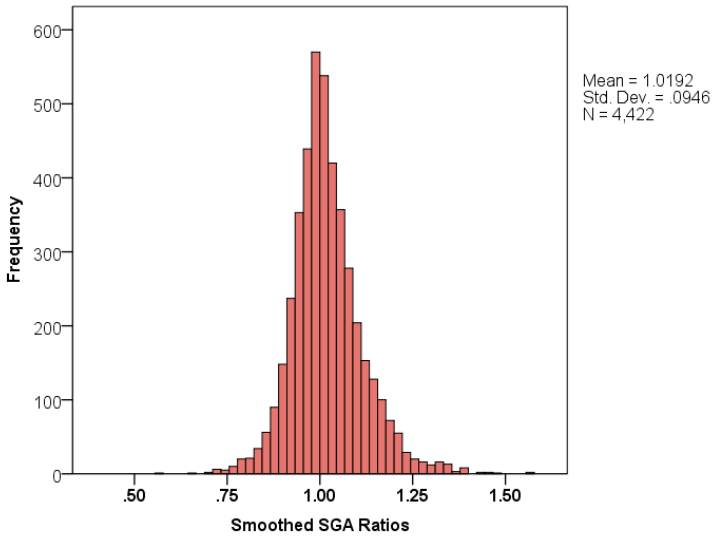
$\zeta_i \sim N(0, \psi)$ is a random intercept representing unobserved heterogeneity between DAs.

The commands are (using PB_cases variable as an example):

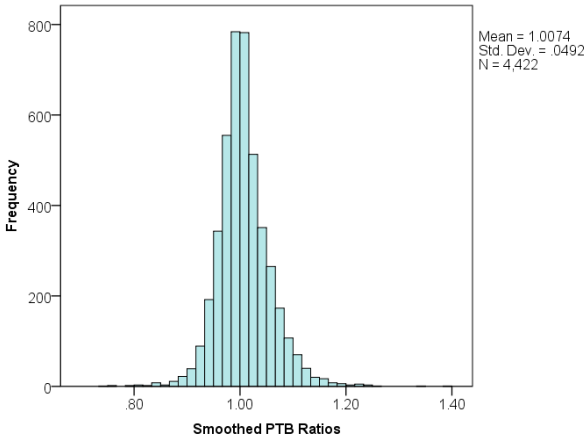
```
gllamm PB_cases , i( DA) offset ( lnexpected ) family(poisson) link(log) adapt

gllapred mu, mu nooffset
```

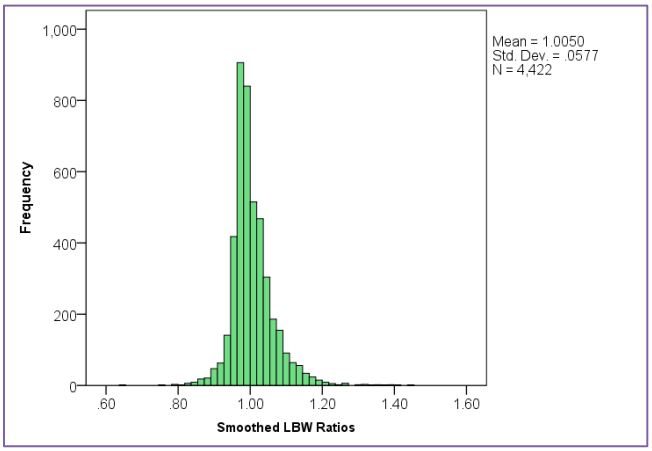
The following graphs show the histograms for age-adj. SPR of SGA and the smoothed age-adj. SRP of SGA as an example.





The following graphs shows the final histogram for the smoothed age-Adj.SPR of PTB and LBWT.





Appendix 2 - Cluster Analysis

We followed the steps suggested by Everitt et al (2 11: p. 261) to do cluster analysis.

1) Define objects to cluster. *The objects should be representative of the cluster structure believed to be present.* Industry and commercial facilities are the emitters of pollutants into the air, water and land. Facilities reporting to the NPRI are one of the most complete sources of information to characterize air pollutants from industry and commerce. Although not all facilities report to the NPRI, they represent the fraction of the industry and commercial activities that release important quantities of pollutants to the media (thresholds are defined by law).

2) Variables to be used. *Variables should only be included only if there is good reason to think they will define the clusters*. We assumed that the knowledge of the mixtures of pollutants emitted by industry and commercial facilities can be approached by aggregating the chemicals released to the air in Alberta (n=135) into ten broader classes. These ten classes of chemicals are based on the chemical structure and nature of the 135 chemicals released in the province during the study period. Our objective was to gain knowledge about mixtures of chemicals released by industry. Besides, working with classes of chemicals avoids managing a lot of ZERO values in the data matrix (see next point), since it is no expected that all facilities (n=6,279) release all chemicals (n=133).

3) Missing values. *It is desirable have a low proportion of missing values*. The aggregation of chemicals into classes resulted in lowering the number of missing and ZERO values. In our context, a missing value can be replaced as zero (that means that there are no emissions of the chemicals aggregated in a specific class or they are emitted in very small quantities

below of the standard-thresholds), since neither the informative meaning is altered nor mathematical calculations.

4) Variable standardization. *Standardization is not necessarily always indicated and can sometimes be misleading*. In our context, all descriptors were expressed with values between and 1 (proportions of the emissions by class of chemicals per facility) and no further standardization was needed.

5) Proximity measure. *Knowledge of the context and type of data may suggest suitable choices*. We chose Euclidean distances as proximity measurement between objects (facilities), which is a metric distance developed for quantitative descriptors. The Euclidean distance is defined as (Legendre and Legendre, 2 11):

$$D_1(\mathbf{x}_1, \mathbf{x}_2) = \sqrt{\sum_{j=1}^{p} (y_{1j} - y_{2j})^2}$$

Where:

D_1 (x_1, x_2) = Distance between objects x_1, and x_2

$y_{1j} = j^{th}$ descriptor in object 1

$y_{2j} = j^{th}$ descriptor in object 2

The Euclidean distance do not have an upper limit (it increases with the number of descriptors) and produces an Euclidean dissimilarity matrix which is a desirable property for dissimilarity matrices (see Everitt et al, 2 11).

6) Clustering method. *Methods should be effective at recovering clusters and insensitive to error*. We used the Wards linkage agglomerative hierarchical method that works well for many situations and is reasonably robust.

7) Number of clusters. One of the most difficult decisions to make is the number of clusters to be considered for further analysis. We used the stopping rules criteria to determine the number of clusters. We calculated the Calinski & Harabaz pseudo-F provided by *stata* to select the number of clusters.

   Stata commands:

   For example:

   ```
   cluster wardslinkage Prop_G1 Prop_G2 Prop_G3 Prop_G4 Prop_G5 Prop_G6 Prop_G7 Prop_G8 Prop_G9
   Prop_G10, measure(L2) name(Ward_Link)

   cluster stop Ward_Link, rule(calinski) groups(2/100)

   cluster generate C_WardLink = groups (52), name( Ward_Link)
   ```

   The final table of clusters was:

```
. tabulate mixprof_C43WardLink
```

mixprof_C43 WardLink	Freq.	Percent	Cum.
1	31	0.49	0.49
2	26	0.41	0.91
3	19	0.30	1.21
4	15	0.24	1.45
5	5	0.08	1.53
6	30	0.48	2.01
7	39	0.62	2.63
8	12	0.19	2.82
9	13	0.21	3.03
10	23	0.37	3.39
11	19	0.30	3.69
12	8	0.13	3.82
13	30	0.48	4.30
14	24	0.38	4.68
15	21	0.33	5.02
16	41	0.65	5.67
17	86	1.37	7.04
18	245	3.90	10.94
19	150	2.39	13.33
20	149	2.37	15.70
21	160	2.55	18.25
22	199	3.17	21.42
23	214	3.41	24.83
24	61	0.97	25.80
25	87	1.39	27.19
26	134	2.13	29.32
27	44	0.70	30.02
28	96	1.53	31.55
29	53	0.84	32.39
30	22	0.35	32.74
31	35	0.56	33.30
32	153	2.44	35.74
33	102	1.62	37.36
34	21	0.33	37.70
35	16	0.25	37.95
36	17	0.27	38.22
37	137	2.18	40.40
38	95	1.51	41.92
39	122	1.94	43.86
40	74	1.18	45.04
41	202	3.22	48.26
42	41	0.65	48.91
43	151	2.40	51.31
44	1	0.02	51.33
45	12	0.19	51.52
46	1,250	19.91	71.43
47	348	5.54	76.97
48	1,349	21.48	98.46
49	74	1.18	99.63
50	17	0.27	99.90
51	5	0.08	99.98
52	1	0.02	100.00
Total	6,279	100.00	

8) Replication and testing. Cophenetic correlation for comparing dendograms. We compared the solution obtained by applying the average linkage and the Ward's method before selecting the final solution. Both solutions were similar.

9) Interpretation. We described the final selected categories (mixtures) based on the proportional content of the ten chemical classes.

Appendix 3 – Ethics Approval

From: hero@ualberta.ca
Subject: HERO: An Amendment or Renewal has been Approved Pro00039545_REN4
Date: June 19, 2017 at 16:00
To: osornio@ualberta.ca

UNIVERSITY OF ALBERTA

Amendment/Renewal to Study has been Approved

Amendment/Renewal ID:	Pro00039545_REN4
Study ID:	MS7_Pro00039545
Study Title:	Spatial data mining exploring co-location of adverse birth outcomes and environmental variables
Study Investigator:	Alvaro Osornio Vargas
Description:	The amendment/renewal to the above study has been approved. Click on the link(s) above to navigate to the HERO workspace. Please do not reply to this message. This is a system-generated email that cannot receive replies.

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