ENVIRONMENTAL AND REPRODUCTIVE HEALTH: A SPATIAL ANALYSIS OF ADVERSE BIRTH OUTCOMES AND ENVIRONMENTAL CONTAMINANTS IN BRITISH COLUMBIA

by

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Abstract

Exposure to contaminants during pregnancy is associated with certain adverse birth outcomes that require further investigation. Community reproductive and environmental health risk maps were produced utilizing birth data obtained from the B.C. Perinatal Health Program and environmental contaminant data from the National Pollutant Release Inventory and other national and provincial sources. Geographical information systems (GIS) were utilized to spatially relate perinatal and environmental hazard data, and the risk of adverse birth outcomes was tested using watersheds as the ecological aggregation unit adjusting for individual-level risk factors. The perinatal data included birth outcomes (low birth weight, prematurity, inter-uterine growth restriction, congenital anomalies, stillbirths) and numerous maternal and antenatal risk factor data for all singleton births in B.C from 2001 – 2006. Small but significant increased risks of adverse birth outcomes were found in high and intermediate hazard watersheds compared to low hazard watersheds. This suggests a possible environmental effect on these reproductive outcomes, however, further studies are needed to corroborate these results.

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Abbreviations Used

BC – British Columbia
Cr – Chromium
CSD – Census Subdivision
DF - Dioxins and Furans
GIS – Geographic Information System(s)
IUGR – Inter-Uterine Growth Restriction
HA – Health Authority
IR – Incidence Rate
LBW – Low Birth Weight
LGA – Large for Gestational Age
Mt - Metals
OR – Odds Ratio
PAH - Polycyclic Aromatic Hydrocarbons
$PM_{2.5}$ - Particulate Matter less than 2.5 microns in diameter
PTD – Pre-Term Delivery
RR – Risk Ratio
SES – Socioeconomic Status
SGA – Small for Gestational Age
VOC - Volatile Organic Compounds
WS1 – Local Watershed Boundary

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Introduction

Identifying the health impact of exposures to environmental pollutants on susceptible sub-populations is an important public health issue. Exposure to certain pollutants during pregnancy has been linked to increased risks of several adverse birth outcomes which are associated with infant mortality and chronic morbidities throughout childhood and into adulthood. Whereas exposures such as smoking and alcohol use have a pronounced effect on a small and specific population, exposure to environmental contaminants have a subtle effect on a large population and presumably have a larger population impact. Morbidity and pregnancy loss due to contaminant exposure should be preventable; however, further evidence is needed that supports an exposure-effect relationship in order to influence policy change.

The purpose of this Masters Thesis has five principle objectives, and will be completed in three parts:

1) Identify watersheds/communities in BC that have a high risk of exposure to contaminants from past and present industrial land use.
2) Identify watershed/communities in BC with an elevated risk of adverse birth outcomes.
3) Determine the appropriateness of using small-area (local) watersheds as the spatial aggregation unit to analyze birth outcomes in relation to environmental hazards.
4) Determine the association of risk of adverse birth outcomes in relation to environmental hazards.
5) Determine which if any adverse birth outcomes can be used as potential surrogates to assess the environmental health of a watershed/community.

Chapter 1 is an extensive literature review providing a state of the current knowledge around environmental exposures *in-utero*, the associated adverse birth outcomes and the various methodologies used to study health and disease as they relate to the environment. The literature review is organized into two main parts. In the

first part, the environmental epidemiological literature is reviewed to give background on which outcomes and pollutants have been the most extensively studied and the methods used. This is followed by a review of the biomedical and clinical epidemiological literature to gain insight into the various confounding, covariate and risk modifying variables that influence reproductive health. This is further supported by reviewing the toxicological literature to provide an in-depth understanding into the modes of actions and the affected biological pathways of various contaminants on human reproductive health. The first part concludes by listing which adverse birth outcomes are the best understood and most sensitive and accessible in terms of epidemiological research.

Part two of the literature review delves into the (relatively) new and emerging field of spatial epidemiology, spatial statistics and the role of GIS in spatial health analysis. The term and concept around GIS is introduced within the broader discipline of geography and spatial analysis. This is followed by a discussion into the potential and, more importantly, the pitfalls of spatial analysis as it pertains to health data. Finally, a review into the methods and applications of spatial epidemiology and spatial statistics is provided along with several great resources and tools available on-line.

Chapter 2 examines the feasibility of using a watershed approach in the analysis of environmental contaminants and reproductive health in British Columbia, Canada. Point-source pollution data and adverse perinatal outcome data were mapped using watersheds and compared to those obtained using administrative census boundaries. Different stressors occur simultaneously and/or episodically over time and space and

have diverse impacts on numerous biological systems, making them difficult to quantify and interpret. A watershed approach is able to accommodate a multi-stressor environment as it focuses on hydrologically-defined geographic regions rather than on a single discharger or specific media (e.g. air, water). It is hypothesized that both hazard and perinatal data can be classified using small-area local watersheds, and that the watershed approach can provide more relevant information in the identification of exposure-effect relationships.

Chapter 3 builds on the knowledge gained from the first two chapters in order to conduct an epidemiological analysis of adverse birth outcomes and environmental contaminants. The use of adverse birth outcomes as proxies of community environmental health are useful as they reflect a relatively short exposure window, the data are of reliable quality and access is non-invasive through birth registries which often have historical depth. Birth data is also collected at the individual-level often represented by the mother's residential street address or postal code. Therefore, it is possible to explore both spatial and temporal outcome patterns at the community-scale while still protecting the privacy of individual cases. This study is the first step in producing a model capable of analyzing birth outcomes in relation to environmental contaminants particularly attuned for rural, remote and Indigenous populations where the risk of environmental exposures is high and population density is low, and provide information on where to focus on-going environmental epidemiological investigations in British Columbia, Canada.

CHAPTER 1

Relating Adverse Birth Outcomes and Environmental Health Risks for Surveillance Purposes: A Review of the Evidence and Spatial Epidemiological Applications

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Abstract

Exposure to toxic substances *in-utero* is associated with adverse birth outcomes that have implications on learning disabilities and chronic diseases manifesting in adolescence and adulthood. There is a need to further understand these environmental-reproductive health relationships, while at the same time to identify at-risk populations for intervention and monitoring. The methods through which these relationships are analyzed are moving towards incorporating spatial statistical techniques and epidemiological methods with the aid of geographical information systems (GIS). This paper discusses the concept of integrating environmental monitoring data with birth outcome data as one potential facet of an environmental health surveillance system. Various techniques are presented as means of increasing the signal-to-noise ratio in environmental exposure and epidemiological studies. Examples are given to illustrate the potential of the techniques to generate hypotheses and describe the exposure-disease relationship.

Introduction

The significance of the environment in relation to human health is increasingly being realized, particularly with respect to children [1] and fetuses [2]. Reviews of the literature support a weak but significant positive association between adverse birth outcomes and exposure to environmental contaminants [3-5]. The findings are further supported by the toxicological evidence that reveal the negative impact of xenobiotics on various biological systems in relation to reproduction such as endocrine and transplacental oxygen and nutrient transport [6,7]. A cocktail of contaminants have been found in the cord blood [8] and meconium [9] of newborns, including known neurotoxins, immunosuppressants and carcinogens. The fetal origins of disease, or "Baker Hypothesis", postulates that perturbation of the early nutritional environment has long-term structural, physiological and neurological impacts on newborns that predispose them to chronic diseases in adulthood including type 2 diabetes, hypertension, coronary heart disease and obesity [10]. Other studies have shown that adolescents born severely underweight (very low birth weight (VLBW) < 1,500g) have impaired visual [11], motor [12], cognitive [13,14] and behavioural skills such as attention-deficit and anxiety compared to controls [15]. Early developmental exposures around mid-gestation may elicit epigenetic modifications such as DNA methylation, which could have transgenerational effects [16,17].

In Canada and the United States the proportion of infants born with low-birth weight (LBW < 2,500g) is six and eight percent respectively [18]. This corresponds to approximately 25,000 and 320,000 infants affected annually (derived from national vital statistics data on live births for 2006). For Canada, between two and ten percent can be

directly attributable to environmental contaminants excluding tobacco, alcohol and illicit drug use [19]. The environmental burden of disease of LBW in Canada amounts to $1.5 million in direct and indirect costs each year [19]. However, this figure does not capture the cost of latent ill-health effects associated with LBW in adolescents and adults, nor does it quantify the disproportionate costs bestowed upon low socio-economic status (SES) households [20]. Morbidity and mortality due to contaminant exposure are largely preventable; and therefore is a public health issue regarding environmental justice and the disproportionate risk of exposure among sub-populations.

Despite the ubiquity of toxins in the environment, individual exposure is not homogenous across populations. Some sub-populations are more susceptible to environmental pollutants (e.g. occupational exposures, Indigenous communities, low-income and non-white neighbourhoods) [21-23], while others are more sensitive (e.g. children, fetuses and the elderly). To address the environmental health risks to populations, there is a need for a systematic approach to investigate the relationships between environmental factors and health outcomes. An environmental health surveillance system would be able to detect, describe and monitor sentinel health events over space and time at various scales, classify cases for epidemiologic and cohort studies, identify sources and potential routes of exposure, and estimate ambient and personal exposure levels of target contaminants. Geographical information systems (GIS) could be used as the backbone of such a surveillance system because it can integrate various data sources, apply spatial analytical techniques, incorporate spatial models, and visually represent this information cartographically [24].

The purpose of this paper is to discuss how birth outcome and environmental monitoring data can be incorporated as one potential facet of an environmental health surveillance system. Epidemiological and toxicological evidence will be presented to justify the choice of using particular birth outcomes and to discuss their advantages and limitations as proxies for environmental health. Focus will then turn to the spatial epidemiological methods and the role of GIS to effectively analyze, interpret and visually represent disease events across the landscape and how they relate to putative pollution sources.

Adverse Birth Outcomes & Environmental Contaminants

A number of studies have indicated significant increased risks of adverse perinatal outcomes linked to maternal exposure to environmental contaminants such as particulate and gaseous air pollution [25], drinking water contaminants [26,27], perfluorinated compounds [28], bisphenol A [29,30], pesticides [31,32] and proximity to landfills, hazardous waste sites and industrial activities [3,33-35]. Consistent among these studies is the elevated risk of negative pregnancy endpoints such as LBW, preterm delivery, pre-clinical and/or recurrent miscarriage, stillbirth, small-for-gestational age (SGA), intra-uterine growth restriction (IUGR), and infant death less than one year.

A post World War II decline in male-to-female birth ratio observed in many industrialized countries is a debated sentinel birth outcome used to infer potential parental exposure [36,37]. Positive associations have been found specific to paternal exposure to dioxin or pesticides [38,39] and maternal exposure to PCBs [40]. However, results are inconsistent, with sample size and the temporal scale driving the analysis [41-43].

Studies investigating the relationship between birth defects/congenital anomalies

and environmental contaminants are mixed [44]. Increasing rates of hypospadias and cryptorchidism have been observed in some northern countries [45,46], although results are difficult to interpret due to large variability of case ascertainment between and within health regions [47,48]. In general however, weak positive associations have been found, requiring further controlled investigations [49-52].

Covariates and Confounders of Adverse Birth Outcomes

One of the many challenges of environmental epidemiological studies is the availability of covariate data as confounding and effect modifier variables, particularly at the individual-level. Because the potential exposure effect will be small, a high signal to noise ratio is required (i.e. low missing data rate of covariates). This is particularly important for rural or small population health studies which tend to have a high degree of variability. Very few birth registries collect sufficient data on maternal risk factors to adequately assess true differences of birth outcomes over space and time. While external data linkages are possible, the application process is often costly and time consuming. The British Columbia Reproductive Care Program's Perinatal Database Registry is an exceptional model that could easily be implemented in other regions [53]. In addition to general reproductive health status, maternal risk factors such as smoking status, drug/alcohol flag and educational attainment, are collected. Maternal place of residence is represented geographically by her postal code, although community name would be helpful in rural areas as would indication of any change in residence during the pregnancy. Other data that would be helpful include maternal and paternal occupation, nutritional status, paternal smoking status and exposure to environmental tobacco smoke.

In Canada, two important determinants of health not typically collected by birth registries are SES and race. Despite having a universal Health Care program, low SES and Aboriginal status are important predictors of negative birth outcomes [20]. However, these associations could be confounded as both variables are often correlated with inadequate prenatal care and other risk factors [54,55]. There tends to be a clear gradient of median birth weight and SGA by income quintile for term births (between 37-42 weeks), with lowest weights in the poorest quintile and highest weights in the richest quintile [20]. Similarly, maternal and paternal education are found to be strong predictors of negative birth outcomes and thus appropriate covariates to control for SES at the individual-level [56,57].

For status First Nations people in BC, median and mean birth weights tend to be significantly higher at all gestations compared to all births in BC [20]. Conversely, Chinese and South Asian descent infants born in BC have significantly lower birth weights than European descent infants [58]. The adoption of ethnic-specific fetal growth charts may be warranted in order to prevent the potential misclassification of newborns as SGA or LGA. Such misclassifications could have serious implications on follow-up care. For example, where as false-positives may result in unnecessary monitoring and parental anxiety, false-negatives could result in the neglect of health risks faced by small babies misclassified as normal growth [58].

Another variable often overlooked but shown to be both a confounder and effect modifier is maternal nutritional status [59]. The collection of nutritional status is not straight forward, and would require direct measurement via plasma assays [60], dietary

questionnaires or anthropometric measurements [61]. Indirectly, SES could be used as a predictor for nutritional risk factors. The role of low SES on food security often limits ones "choice" to calorie-dense nutritionally-poor foods and suboptimal fruit and vegetable intake. At the same time, rural and remote communities are constrained by the availability and cost of fresh produce, while foods with long shelf-lives are affordable but nutritionally poor [62,63].

The Affected Biological Pathways

The biological mechanisms whereby environmental pollutants influence reproductive outcomes remain to be fully elucidated. The majority of our understanding of the toxicological mechanisms affecting the reproductive system in both men and women has largely been generated using animal models in laboratory settings [64]. However, major differences in placental morphogenesis and endocrine function exist between rodent and human models [65,66]. The extrapolation between these two models is thus limited with respect to reproductive complications of placental origin such as preeclampsia and IUGR.

Current evidence suggests that the mechanisms may involve hormonal and/or immune disruption, DNA adduct formation, altered cellular proliferation, or inappropriate cellular death [67]. The specific biological pathway affected depends on the type of exposure (chemical makeup), exposure route (ingested/inhaled/absorbed) and duration. The endocrine system presents a number of target sites for the induction of adverse effects by environmental agents that can mimic or antagonize hormone signalling pathways [6]. Similarly, transplacental oxygen and nutrient transport may be the crucial biological pathway affected in maternal exposure to airborne particulate matter and adverse perinatal

outcomes [7].

Advances in molecular epidemiology have helped bridge the gap between laboratory and population-based studies. The identification of biomarkers has allowed for the characterization of the internal effective dose of toxicants that lead to early biological or preclinical effects; and as a result, has been instrumental in refining regulatory exposure guidelines for occupational and domestic settings [68]. Given an interest in disease-exposure relationships, placenta cord-blood and/or breast milk could be analyzed for contaminant levels and related to the pregnancy outcome [8,69]. Such biological samples would also serve to validate/refine any individual or group-level estimate of exposure. Likewise, biomarkers in sentinel wildlife species would be a valuable tool for environmental health surveillance and validation of fate modelling of contaminants released in the environment [70].

Sentinel Birth Outcomes

Because the reproductive system often fails before other systems, birth outcomes such as birth weight, IUGR, gestational age and infant mortality can act as sentinel indicators of environmental insults [24,71]. Birth outcomes are well suited as proxies for ecological studies of community health as they are sensitive to many environmental and socio-economic influences [1]. Here, congenital anomalies are not considered a sentinel indicator due to the potential inconsistency of diagnosis and misclassification within a surveillance system [47]. Assuming that prenatal exposure commences shortly before conception, the exposure window is relatively acute, as opposed to using cancer as an end-point which has a very long latency period. Furthermore, birth outcome data are collected

at the individual or postal code level, are of reliable quality, access is non-invasive and birth registries have historical depth (i.e. available over numerous years). Therefore, it is possible to explore both a spatial and temporal disease pattern that can be revisited periodically to track changes in distribution. This by itself is a useful tool in public health monitoring and surveillance; however, it is a model that can also incorporate additional covariate data in order to relate any observed changes to shifting demographics or other social and environmental factors [72-74].

Spatial Analysis, GIS & Health

The previous section reviewed the epidemiologic and biological mechanisms of adverse birth outcomes in relation to environmental contaminants and, as a consequence, their appropriateness as indicators of environmental health. Regardless of any causal association, negative birth outcomes, like most disease events, have an intrinsic spatial component. Whether that information is used to test a pollution-linked hypothesis or identify areas with high incidence for resource allocation, the importance of spatial health data are increasingly being recognized. The following section will discuss how adding spatial dimensions to health data creates new opportunities to explore, analyze and disseminate health and disease information.

GIS & Exploratory Spatial Data Analysis

Traditionally developed for natural resource management and land-use planning, GIS has become a powerful tool in public and environmental health [75]. GIS as a technology is similar to any information management system capable of integrating, storing, editing, analyzing, and sharing data. The distinguishing asset is its ability to capture,

link and visually display geographically-referenced (georeferenced) information as a means to model and analyze spatial patterns and relationships [76]. The process is similar to intersection and union operations from Venn diagrams overlaying multiple datasets. For example, one could explore the links between land-use, household exposure to traffic-related air pollution, socio-demographic factors and prevalence of low-birth weights at term [77]. This requires merging several distinct datasets from various sources into one *geo*database and visually displaying the results. Thus, the contemporary GIS research environment enables the scientific visualization of spatial relationships among several variables [78]. Here, thematic maps are produced as intermediate products for exploratory (spatial) data analysis and hypothesis building rather than for the final presentation of results. Although the act of display is itself an analytical strategy, to draw conclusions from such a map without appropriate statistical analysis would be flawed [78]. "An observed map pattern is [just] *one of the possible patterns that might have been generated by a hypothesized process*" [79]. Spatial analysis and statistics are required to determine if the observed pattern is significant or simply a spurious spatial correlation.

Often confused as one and the same, a distinction must be made between spatial analysis, spatial statistics and the role of GIS within an epidemiological context. *Spatial analysis* is the quantitative study of phenomena that are spatially-referenced. However, it is not only the analysis of objects/events located in space that is relevant, but also their spatial configuration or relative location to each other [80]. *Spatial statistics* is the collection of statistical methods that give prominence to the spatial arrangement of the objects/events being analyzed. Data that are close together in space (and time) are often

more alike than those that are far apart (Tobler's 1st Law of Geography). A spatial statistical model incorporates this spatial variation into the stochastic model-generating mechanism [79]. *Spatial epidemiology* is the study of spatial variation of disease risk. The development of methods in spatial epidemiology has gained interest, particularly among statisticians, over the past two decades [81-84].

To date, GIS software is generally lacking in spatial statistical capabilities, and until recently has been generally ill-equipped to manage higher order spatial analyses. There has been a great amount of development in the programming of spatial analytical software as either a stand-alone product or coupled with statistical software packages, for example: SPLANCS [85], SpatStat [86], GeoDa [87], DMAP [88], SaTScan [89] and WinBUGS [90].

The Potential and Pitfalls of Spatial Health Data

Patterns provide clues to a possible causal process, and a spatial process is a description of how a spatial pattern might be generated [79]. The geospatial relationships that exist among and between events provide new ways of looking at data (e.g. distance, adjacency, intersection, neighbourhoods). Because of these relationships, events have characteristic distances at which they are correlated with themselves [79]. Termed *spatial autocorrelation*, the upshot is that samples are not truly random or independent, a violation of the two principle assumptions in classical inferential statistics. First, events are dependent on variation in the underlying environment, be it population heterogeneity, access to health care or exposure to an environmental pollutant; therefore, the assumption of equal probability of each area receiving an event is violated. Second, the assumption that event placements are independent of each other is violated since interaction between

events can occur (e.g. infectious diseases) [79,91]. The issue of spatial autocorrelation is closely related to cluster analysis, and tests for spatial randomness exist to determine if the observed spatial point pattern is generated by chance or by some unobserved explanatory variable(s). These tests are often a launching point in any exploratory spatial data analysis and are reviewed by Kulldorff [92] as well as discussed in detail by O'Sullivan and Unwin [79].

The routine practice of aggregating health data into arbitrarily defined administrative areas, such as health regions or census tracts, elicits two common pitfalls that beleaguer spatial health studies: the *ecological fallacy* and the *modifiable aerial unit problem* (MAUP). The former arises from the loss of information from aggregated data in which incorrect individual-level inference is drawn from group (ecologic) level data [93]. The resulting bias is referred to as *ecological or cross-level bias*, which Wakefield (2008) specifies as "the inability of ecologic data to characterize within-area variability in exposures and confounders." Alternatively, when data collected from an individual is used to assign average characteristics for a population group, this is referred to as the *atomistic fallacy* [83].

MAUP [94] concerns the ability of statistical relationships to change at different levels of aggregation. Aggregation often strengthens the regression relationships, and the choice of spatial reference frame significantly dictates both the statistical and visual patterns observed. The implications of MAUP are immense since policy addressing a set of issues for a region might look very different if the administrative boundaries are rearranged [79]. The gerrymandering of electoral districts to achieve favourable majorities in each

riding is a classic example of MAUP. *Edge effects* are also a product of arbitrarily defined boundaries that can produce artificial asymmetry in the study region. This is due to the likelihood of events at the edge having fewer neighbours than those near the centre of the study region [79,95]. The take home message is that the geographical scale at which a phenomenon is examined should always be considered prior to any spatial investigation.

The increasing availability of georeferenced health data has been met with ethical concerns over data privacy and confidentiality, and rightly so. Similar to using a name or birth date, geocoded point locations displayed on a map can be used to identify patients [96]. Data aggregation is the common method used to protect sensitive individual-level data; however, this often impedes or destroys the information needed for geographic analysis of health events and still may not protect individuals in low populated areas [97]. The resolution of case-event data is often required to adequately analyze relationships between health outcomes and the environment. *Data masking* is a technique that preserves the confidentiality of individual health records while maintaining the high resolution needed for geographical analysis [98]. Rate smoothing (discussed later) is also capable of ensuring privacy by transforming point data into area-level rates thus facilitating interpretation by laypersons, clinicians and policy makers [99]. A review of methods that reduce the probability of disclosure of the individual are discussed by Kamel Boulos et al. [100].

As is true of all good research, study designs for spatial health research need to be carefully devised with particular attention paid to the quality of the data. For example, birth registries are typically of the best quality and reliability, but are designed to serve the

purposes of state governments, not epidemiological research. On the other hand, disease registries that rely on diagnosis or referrals, such as those for congenital anomaly surveillance, can suffer from mis/undiagnosed cases or changes to disease classification. This results in a false variation of the spatial coverage and a tendency of rural areas to be under represented [47,101,102]. Another potential source of high quality health data are administrative databases for medical visits and services maintained by the government and/or health insurance authorities. For example, Peace and Mazumder [103] used medical billing and fee-for-services data to track long-term patterns of enteric illness at the community-level. In most cases, data quality and accessibility are the primary limiting factors in health research.

Methods & Applications in Spatial Epidemiology

The discipline of spatial epidemiology has developed considerably in recent years with advancements in GIS, computer processing speeds and spatial statistical techniques. Spatial epidemiology can be categorized into four broad classes: disease mapping, cluster detection, ecological (geographical correlation) studies and exposure assessment [82]. While not entirely mutually exclusive, their differing aims distinguish them from being purely descriptive and exploratory to analytical studies building and testing hypotheses of aetiological significance. The type of study will depend on the quality and geographical resolution of the data; that is, the complete enumeration of the disease event and the spatial unit to which the cases have been collected, aggregated and stored.

There are two spatial unit realizations that demarcate the approach taken in spatial epidemiology: case (point) data and count (area) data [104]. Case event data is usually

represented by a residential street address or postal code, however, time spent in other exposure fields such as work or school should also be considered [105]. The location of each case is *geocoded* based on its latitude-longitude coordinates. The use of postal codes in rural areas becomes problematic since a single postal code can represent a large area encompassing several small towns or villages. In this case, the geocoded value may be the geographic center of the area or the location of the nearest post office. The accuracy of postal codes has been evaluated by Bow et al. [106], Siffel et al. [107], Zimmerman et al. [108] and Mazumdar [109]. Count data on the other hand is essentially the aggregation of all cases within some spatially defined area such as a census tract or health region. The typical objective with either case or count data is to derive a summary measure of relative risk; specifically, the ratio of observed incidence to the expected rate based on the background or '*at-risk*' population [83]. To legitimately compare relative risk rates between areas, however, certain methods are favoured over others.

Disease Mapping & Rate Smoothing

With any set of newly acquired data, it is important to explore the data by producing and inspecting graphs. This is analogous to what is termed *disease mapping* in spatial epidemiology: an exploratory analysis used to get an impression of the geographical distribution of disease or the corresponding risk [82]. However, like any other graphical display, a map can both inform and mislead. Choropleth maps (common in disease atlases) for instance, hardly embody a true realization of disease rates of an area with their "checkerboard" pattern of rates that change suddenly along administrative borders [110]. Alternatively, *density estimation* methods [111] produce maps where disease rates vary

continuously across the study area and have grown in popularity over the years [112,113].

Common throughout Canada, the 'small-number problem' often leads to extreme rates in sparsely populated areas sensitive to the addition or removal of a single case. Maps displaying direct age-standardized rates can be unreliable due to the instability of the estimator in low populated areas or when the age distribution of an area differs greatly from the standard population [84,114]. Indirect standardization addresses the 'small-number problem' by using estimates for the age-specific risk from a reference population [115]. The age-standardized ratio of observed to expected events yields the standardized mortality/morbidity ratio (SMR), essentially a relative risk based on age-specific reference rates. Confidence intervals are also obtainable, allowing one to only display areas of significant high or low risk on a map. While suitable for mapping and GIS analysis, indirect age-standardized rates assume independent age and area effects on the estimate of risk and therefore tend not to be comparable across highly variable areas [84,115].

Another solution to the 'small-number problem' is called *spatial smoothing*, where areas with low numbers "borrow" information or strength from neighbouring areas to produce a more stable risk estimate [84]. Density estimation is but one method of spatial smoothing among many that vary in complexity [116]. The two main advantages of smoothing are that: 1) it stabilizes the rate based on small numbers without having to aggregate to a larger region, and 2) it increases the ability to discern spatial pattern in the underlying risk by reducing the noise caused by different population sizes [84]. The trade-off is the potential introduction of autocorrelation and the inability to detect outliers; however, it is still strongly favoured over the mapping of raw rates.

There are numerous approaches to spatial smoothing using both parametric and non-parametric techniques and interested readers should refer to Anselin et al. [115] and Waller and Gotway (2004. pp.86-98) [84] for detailed descriptions. The most important property of smoothers is accuracy. The ability to quantify uncertainty and obtain standard errors and confidence intervals is an important criterion when selecting a smoother. If quick exploration is the goal for the disease mapping exercise, then ease of use and integration into a GIS should be considered [117]. To go from descriptive to inferential statistics, empirical Bayes smoothers use Bayesian principles to adjust for confounding and unmeasured/latent spatial random effects, but the model is considerably more complex [118,119]. Without getting into the technical details, the overarching goal is to develop a statistically reliable model that can be easily adopted into health surveillance systems to identify small-area variations of disease risk [120-122]. In the end, these risk maps offer ways of sound interpretation that are easily communicable to lay map users such as government and community health organizations [123].

Cluster Analysis

The analysis of disease clusters is an important tool in spatial epidemiology and public health surveillance. Even after the 'at-risk' population effects are accounted for, there are many situations where diseases seem to cluster despite the supported aetiology [124]. The purpose of cluster analysis is to determine if a spatial point pattern was produced by random chance or by some underlying environmental factor such as in "hot-spot analysis". For any test of spatial randomness the null hypothesis is: 1) a constant relative risk throughout the study region, and 2) that cases occur independent of each other [79].

Different test statistics are useful for different purposes, and Kulldorff [92] distinguishes between four different tests in terms of their mathematical approach. *Tests for global clustering* are concerned with the presence of clustering throughout the study region in general. *Cluster detection tests* are used to detect cluster location and assess their significance. *Focused cluster tests* look for excess risk near a pre-defined geographic feature such as a smelter or toxic waste dump; and finally, *multi-focused cluster tests* are useful to test multiple locations for disease clusters around putative focus points.

The performance of different test statistics to detect clusters of various shapes and sizes can be evaluated in terms of their sensitivity, specificity, and percentage correctly classified for each cluster. Aamodt et al. [125] and Puett et al. [126] state that magnitude/scale and cluster shape should be considered when choosing the appropriate method. Similarly, Lawson [127] and Hossain and Lawson [128] assess the degree to which differing clustering methods recover the true clustering behaviour of small area data and promote the appropriate use of Bayesian local likelihood models.

Ecological Studies

The focus of ecological studies is the association between measured covariables and disease incidence at some spatial scale [83]. Also referred to as *geographical correlations studies*, the objective is to model the interrelationships of health outcomes, lifestyle factors and environmental exposure variables based on grouped (ecologic) data that often correspond to defined geographic areas [82]. In terms of an environmental health surveillance framework, ecological studies can be viewed as the progression from an exploratory disease mapping exercise to the building or testing an aetiological hypothesis.

The statistical models are similar for the two types of studies; however, ecological studies are often interested in transferring the inference of exposure effects from the group-level down to the individual-level. Thus, ecological bias must be guarded against [93]. It is generally agreed upon that data containing variables measured at individual and aggregate levels should be analyzed using hierarchical models. Lawson (ch.8) [83], Richardson and Monfort [129] and Banerjee et al. [130] cover a variety of statistical methods appropriate for the analysis of multilevel data.

A prevalent challenge in ecologic studies is the control for known confounders of the disease/exposure under investigation. Lifestyle risk factors are typically not available at the individual-level and the attempt to control for these variables using area-level measures of SES may introduce ecological bias since they are insensitive to within-area variability [93]. *Semi-ecologic studies* may be less susceptible to ecological bias since they include individual-level data on outcome and confounders with exposure data at the ecologic-level. However, two possible sources of bias remain; first, within-area variability of exposure is not accounted for and second, exposure is not stratified by confounder strata within areas so within-area confounding is not controlled for. If within-area variability of exposures and confounders are small, then ecological bias will be minimal and results can be cautiously interpreted and compared with other studies to augment the evidence for an aetiological hypothesis [93].

Exposure Assessment

Among the difficulties of conducting environmental epidemiological studies are problems related to estimating exposure to individuals and detecting small effects. As

discussed in the previous section, exposure data are rarely available at the individual-level and thus some form of extrapolation is required to estimate personal exposure from available data sources. Exposure assessment can vary significantly in its degree of sophistication, from basic distance-to-source analysis to complex modelling of chemicals as they travel, transform and absorb in different media (air, water, soil, food, and biota). There is no single or optimal method of defining and assessing exposures, and the choice of methodology is driven by the cost, time and scope of the study [131]. The objective for environmental health surveillance is to provide early warnings of potential health effects as a basis for policy-targeting and priority-setting; thus, presenting a more basic 'quick and dirty' approach to exposure assessment is the focus here. Informative reviews on the topic of geographic modelling and GIS for exposure assessment in environmental epidemiology are provided by Bayea and Hatch [132], Nuckols et al. [133] and Briggs [134]. Thacker et al. [135] presents a useful environmental public health surveillance framework and review of the "hazard-exposure-outcome" axis. Those interested in complex pollution models are referred to the U.S. Environmental Protection Agency's Center for Exposure Assessment Modeling (http://www.epa.gov/ceampubl/).

To date, many environmental epidemiologic studies have relied on proximity-based assessment techniques such as buffer and weighted-distance functions as a surrogate for exposure. The ease of calculation and application makes 'proximity' attractive, and 'exposure' can come to describe not only emitted chemicals but other undesirable effects such as lower land value, industrial zoning and noise [136]. In most cases however, proximity is a poor exposure surrogate that can lead to non-differential misclassification of

exposure driving the effect estimate toward the null [24]. In other words, the within-area variability of exposure is poorly characterized which in turn inflates the error term and washes out any observed effect. To compensate, a more stringent alpha level of $p<0.01$ can be used to reduce potential type-1 errors [50]. However, the indiscriminate use of fixed circular buffers around different point pollution sources does not account for the amount or type of pollutant being released. Treating all point sources equally in multi-site studies ignores the spatial and biological variability of risk between facilities with different eco-toxicological footprints on the landscape.

Differences in chemical toxicity, persistence, bioavailability and bioaccumulative properties require the normalization of contaminant release data to arrive at a relative measure of harm. Hertwich et al. (2001) have calculated Human Toxicity Potentials (HTP) for 330 compounds that reflect the potential harm per unit of chemical released into the environment based on its toxic potency, persistence and potential dose via multiple exposure routes. The HTPs are calculated using CalTOX, a comprehensive environmental fate and exposure pathway model, thereby significantly enhancing the risk assessment without requiring site-specific input data (e.g. soil permeability, runoff rates, plume dispersion modelling). For the assessment of risk around multiple point sources of exposure, relative toxicity scores can be calculated for each polluting facility based on its potential impact on surrounding populations. Cutter et al. (2002) developed a Relative Potential Risk Score (RPRS) to characterize releases from individual facilities. By assigning an RPRS attribute to individual facilities, the spatial and biological variation of hazard is taken into account when assigning exposed and unexposed populations.

Rather than using administrative boundaries in ecologic health studies, watershed basins may serve well as a scale of analysis since they represent the topographical extent of an area, thus simulating the "catchment area" of contaminants. Depending on the scale of the watershed boundary layer, a community and its encompassing watershed can systematically be ranked as high, intermediate or low risk for exposure based on available environmental data. The ordinal ranking of watersheds allows for a comparative analysis of health outcomes between the watersheds after controlling for potential covariate heterogeneity. A specific example of this method could not be found in the published literature; however, Gilbreath and Kass [33] estimate exposure at the community-level using a hazard ranking of dumpsites in which significant positive associations of adverse birth outcomes were found for Alaskan Native villages. A review of the use of GIS in health research including watershed mapping and hazard assessment is provided by Cromley [137].

The past two decades have seen the rapid increase in availability of geo-referenced data from health outcomes, point sources of pollution and physical landscape data that can be readily incorporated into GIS mapping programs. In North America, the location of point releases of contaminants into the environment by large industrial facilities can be obtained from Environment Canada's *National Pollutant Release Inventory* (NPRI, http://www.ec.gc.ca/pdb/npri/npri_home_e.cfm), the U.S. EPA's *Toxics Release Inventory* (TRI, http://www.epa.gov/tri/), and Mexico's *Registro de Emisionnes y Transferencia* (RETC, http://www.semarnat.gob.mx/). The purpose of these release inventory databases are to collect data on substances of concern, and to provide citizen/environmental watchdog

groups with information on pollutants being released in their communities. Some environmental groups have created their own websites building on the government release registries by providing additional features such as ranking the facility by health threat (carcinogenic, reproductive, developmental. respiratory, etc.). These include: Canada Pollutionwatch (http://www.pollutionwatch.org), U.S. Scorecard (http://www.scorecard.org), and U.S. Right-to-Know Network (http://www.rtknet.org).

Conclusions

There is overwhelming evidence that even low-level environmental pollution has a negative effect on birth outcomes. Low birth weight, preterm delivery and intra-uterine growth restriction are significantly associated with infant mortality and morbidities ranging from pulmonary to neurological outcomes. Moreover, these perinatal pathologies may have latent or undiagnosed health effects on the child that continue into adolescence and adulthood including behavioural and cardiovascular disorders. It is therefore imperative that the surveillance of health outcomes be performed around sites or in communities where hazardous materials are being released into the environment. The integration of an environmental health surveillance system using reproductive outcomes with GIS has great potential for addressing this problem. Reproductive outcomes can act as sentinel health indicators as they are shown to be sensitive to multiple different environmental exposures to either parent. Over the past decade, methodology-technology based modelling procedures have been developed that combine spatial statistical techniques with GIS applications to produce statistically reliable risk estimates and disease maps. The creation of small-area risk maps would be useful in health impact assessments, community health

planning and disease prevention by defining baseline exposure measurements and spatial disease patterns that could be reassessed over time. The integration of these models into an environmental health surveillance system would be a cost effective and efficient tool to facilitate the translation of readily collected data from multiple sources (vital statistics, environmental monitoring data, land-use activities, etc.) into usable information for health policy and regional planning deliberations.

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CHAPTER 2

A feasibility study mapping environmental hazards and perinatal outcomes using a watershed approach

Table of Contents:

Abstract:

Environmental contaminants linked to increased risks of adverse perinatal outcomes are varied and numerous. The watershed approach framework is able to accommodate a multi-stressor environment as it focuses on hydrologically-defined geographic regions rather than on a single discharger or specific media (e.g. air, water). This paper examines the feasibility of using a watershed approach in the analysis of environmental contaminants and reproductive health in British Columbia, Canada. Point-source pollution data and adverse perinatal outcome data were mapped using two similar sized but vastly different spatial tessellations of local watershed areas and administrative census subdivision areas. Unlike administrative census boundaries, watershed areas are independent of population size and therefore were more appropriate to model the environmental hazard data particularly for rural and remote areas with low population densities. With respect to health outcomes, both tessellations were able to pick up many of the same community-level risk estimates thus confirming and often spatially refining the found result. Due to their slightly larger size, the watershed areas produced more stable risk ratios with less variability when sensitivity analyses were performed (70% vs. 50% of areas remaining significant after sensitivity analysis). For these reasons, the watershed defines an appropriate unit in which to investigate the cumulative impact of multiple physical, chemical, and biological stressors on human populations.

Introduction:

The significance of the environment in relation to human health is increasingly being realized, particularly with respect to children [1] and fetuses [2]. Associations between exposure to environmental contaminants and adverse birth outcomes are well documented in the epidemiological literature [3-5]. Negative pregnancy endpoints such as low birth weight (LBW < 2,500g), preterm delivery (< 37 weeks gestation), small-for-gestational age (SGA), intra-uterine growth restriction (IUGR), stillbirth and infant death (< 1 year) have been identified as key perinatal outcomes that can be affected [4]. The findings are supported by toxicological evidences that reveal negative impacts of contaminants on biological systems related to reproduction [6,7]. Environmental contaminants linked to increased risks of adverse perinatal outcomes are varied and numerous, including: air pollutants [8] drinking water contaminants [9,10], perfluorinated compounds [11], metals and other hazardous materials from landfills, hazardous waste sites and industrial activities [12-14].

The availability of environmental contaminant data has greatly increased over the past two decades. Public campaigns have pressured governments to collect and disseminate information regarding harmful pollutants being released into the environment and communities. In Canada, major point sources of pollutants are spatially documented by the National Pollutant Release Inventory (NPRI), and made available on the Environment Canada website (www.ec.gc.ca/pdb/npri). Similarly, geospatial resource, infrastructure and land-use data are also made available by federal and provincial agencies (www.geobase.ca,

www.lrdw.bc.gov.ca) and formatted to be readily imported into geographical information systems (GIS). The use of GIS has become a powerful tool in epidemiologic and public health research as it is capable of integrating, storing, editing, analyzing, sharing and visualizing spatial relationships among multiple (seemingly unrelated) datasets [15]. By mapping potential sources of exposure along with birth outcome data, opportunities to investigate environment-health relationships arise and act as an initial exploratory step to identify "hotspot" areas suitable for more rigorous investigations, such as case-control and cohort studies [16,17].

The use of existing medical registries to identify environment-health relationships is a useful tool in public health monitoring and surveillance research and has been in practice for decades in Scandinavian countries [18-20]. The use of adverse birth outcomes as proxies of environmental-community health are useful as they reflect a relatively short exposure window, the data are of reliable quality, and access is non-invasive through birth registries which often have historical depth. Birth data is also collected at the individual level usually represented by the mother's residential postal code, and often with additional maternal/infant covariables such as reproductive history, procedures, interventions, morbidities (e.g. diabetes, hypertension), and risk factors like smoking status, education and level of prenatal care. Therefore, it is possible to explore both spatial and temporal outcome patterns at the community level and relate any observed changes to risk factors such as exposure to environmental contaminants.

Multiple physical, chemical, and biological stressors due to human activity combine with varied environmental conditions that may have diverse impacts on numerous biological systems [21]. Different stressors that may occur simultaneously and/or episodically vary over time and space, making them difficult to quantify and interpret. Thus, an analysis framework that is able to accommodate a multi-stressor environment is needed [22,23]. The Watershed Approach Framework [24], focuses on hydrologically-defined geographic regions rather than on a single discharger or specific media (e.g. air, water). Substances in the environment respect few boundaries, and are more likely to obey hydrologic or chemical processes than administrative delineations. Furthermore, watersheds and river basins often coincide with settlements of human populations. For these reasons, the watershed defines an appropriate unit in which to investigate the cumulative impact of multiple physical, chemical, and biological stressors on human populations.

The purpose of this paper is to assess the feasibility of using a watershed approach in the analysis of potential relationships between environmental hazards and reproductive health in British Columbia (BC) Canada. BC is the third largest province in Canada with a population of 4.5 million, and is situated between the Pacific Ocean and Rocky Mountains. This study will be accomplished by mapping environmental hazard data and adverse perinatal outcome data using a standard administrative boundary approach compared to a watershed boundary approach. We compare the sample size and rate variability using the two approaches and visually compare their geographic specificity in mapping hazard data and health outcomes. It is hypothesized that both hazard and perinatal data can be

classified within the geographical boundaries of local watersheds in the province of British Columbia, and that the watershed approach can provide relevant information in the identification of exposure-effect relationships.

Materials and Methods:

a) Data Sources:

1. National Pollutant Release Inventory (NPRI)

   The NPRI was established in 1992 and is the only legislated, nationwide, publicly-accessible inventory of its kind in Canada. The purpose of the NPRI is to collect data on substances of concern to provide Canadians with information on pollutants being released in their communities. The NPRI database is published annually by Environment Canada, and is made public on their website at http://www.ec.gc.ca/pdb/npri. Not all activities/facilities are required to report to the NPRI, and in general, facilities must meet three reporting criteria to be eligible: (1) an annual 20,000-hour employee threshold, (2) a 10-tonne release threshold, and (3) substance released at a concentration of 1% or greater by weight, unless produced as a by-product which are reported at any concentration [25]. Since 2000, lower reporting thresholds have been implemented for substances deemed to pose a serious risk to human health or the environment in relatively low quantities. This includes substances containing mercury, lead, arsenic, cadmium, chromium, polycyclic aromatic hydrocarbons (PAH), volatile organic compounds (VOC), particulate matter (PM), and dioxins-furans (DF). Other recent amendments include oil and gas sector activities, excluding exploration and

drilling (2003), and primary extraction mining activities (2006) [25]. However, the reporting data of millions of tonnes of hazardous mine tailings and waste rock from mining operations has been withheld by the federal government prompting a recent (April, 2009) Federal Court of Canada Order demanding the immediate publication of mining pollution data from 2006 onward to the NPRI [26].

2. The BC Mineral and Mining Inventory (MinFile)

   MinFile is a relational database containing geological, location and economic information on over 12,300 metallic, industrial mineral and coal mines, deposits and occurrences in BC. MinFile is made available through the Mining and Minerals Division in the BC Ministry of Energy, Mines & Petroleum Resources [27].

3. BC Perinatal Database Registry

   The British Columbia Perinatal Health Program (BCPHP) Registry is a comprehensive, province-wide perinatal database collected for the purpose of evaluating perinatal outcomes, care processes and resources, ultimately improving maternal, fetal, and newborn care. The Registry accounts for 99% of births in BC collected from facilities throughout the province on a voluntary basis. Data collected includes: antenatal, intrapartum and postpartum maternal and infant care and outcomes, as well as neonatal follow-up and outcomes including linking to BC Vital Stats to provide infant death data. Data quality is addressed by validation edits, errors and warnings as part of the data entry software program, and period end checks and reports. Third party data access is provided by a Partnership Accord/Memorandum of Agreement between all BC Health Authorities and the BCPHP through the *Freedom of Information and Privacy*

Protection Act. Data release applications are reviewed by the Research Review Committee with representation from health care providers, health authorities, and academic organizations [28].

4. The Postal Code Conversion File (PCCF)

The PCCF is a digital file created as a correspondence between the Canada Post six-character postal code and Statistics Canada's standard geographic areas [29]. The geographic coordinates attached to each postal code in the PCCF provides the ability to map the *approximate* distribution of data that may be attached to a postal code for spatial analytical purposes [30,31]. The PCCF's ability to provide the physical location of postal codes varies significantly between urban and rural areas. The latitude and longitude (lat/long) coordinate associated with a postal code does not always accurately represent the dwellings served by that postal code. Rural postal codes generally refer to a post office or postal station, including general deliveries, post office boxes and suburban services. As a consequence, rural postal codes cannot georeference a physical location of residence as precisely as urban postal codes. The reference date for the PCCF used is September 2007, and the postal codes are linked to the geographic areas used in the 2006 Census of Population. This includes the administrative boundary used in this analysis, the census subdivision (CSD). The CSD is the general term for municipalities (as determined by provincial/territorial legislation) or areas treated as municipal equivalents for statistical purposes (e.g. Indian reserves and unorganized areas) [29].

5. The BC Water Atlas

The 1:50,000 British Columbia Watershed Atlas is a topologically structured digital representation of all aquatic-related features (streams, lakes, wetlands, obstructions, dams, etc.). The data set includes boundaries for all third-order and greater watersheds, stream network connectivity, stream route systems, and a hierarchical watershed code associated with all bodies of water [32]. This analysis used the smallest watershed boundary areas available in the Atlas (1:20,000 streams), hereafter termed 'WS1' or 'local watershed area'. They are generally community specific, but their physical size ranges substantially with an average area of 250 km^2 and median area of 114 km^2.

b) Hazard characterization using administrative & watershed areas

Population exposure risk was estimated using hazard data from two sources: the National Pollutant Release Inventory (NPRI) and the BC Mineral and Mining Inventory (MinFile). To conduct this feasibility study, two different boundary tessellations with similar spatial support (or scale) were used to model the hazard data. One was a local watershed boundary area (WS1), and the other was a census subdivision administrative boundary area (CSD). Five substances shown to have negative effects on reproductive health were selected from the NPRI to be analyzed. They include sources of arsenic (As), cadmium (Cd), chromium (Cr), mercury (Hg) and lead (Pb). Their annual releases per facility were averaged over the number of reports filed to the NPRI for the six years of the study (2001 to 2006) and summed to created a single 'metals' variable. Acid rock drainage from active and abandoned mines is also a potential source toxic metal exposure, particularly arsenic, and

their presence in the watershed and CSD areas was added into the model.

The data from the point-source releases were integrated into the corresponding watershed and administration boundary areas using a *point-in-polygon spatial join* procedure in *ArcGIS 9.2* [33]. The spatial join had a 'one-to-many' relationship in which each point within an area retains its attribute data and is appended as a new row in the boundary tessellation table. Metal releases from multiple point-sources within the same area were summed to give an overall ecologic measure of hazard. Alternatively, the spatial join procedure for the MinFile data had a 'one-to-one' relationship in which each point within a given area is aggregated as a count and appended as a new column in the data table. The end result was the creation of two new variables (average annual metal release and number of acid rock drainage sites) quantifying the cumulative impact from multiple stressors for defined WS1 and CSD areas. Environmental hazards maps were created using the quartiles of the amount released in a particular area and presence of acid rock drainage sites.

c) Health outcome parameters by watersheds and administrative boundaries

The BC Perinatal Database Registry was used to establish a cohort of singleton births between January 1, 2001 and December 31, 2006 (N=237,470). The dataset included 54 independent, dependent and confounding variables. The dependent perinatal variables of concern include low birth weight (LBW <2,500g), preterm birth (between 20-37 weeks of gestation), intra-uterine growth restriction (IUGR), stillbirth (> 20 weeks gestation or > 500g), and congenital anomalies (International Classification of Disease 9 (ICD-9) 7400 to 7599 or ICD10 Q00 to Q99). Out-of-province records (n=926) and records missing geographic data on maternal area of residence (n=129) were excluded. Covariate

information obtained from the Registry included: sex, maternal age, parity, gravidity, smoking status, drug and alcohol flag, number of prenatal care visits, diabetes (prior diagnosis and gestational onset), hypertension during pregnancy, education and marital status.

The spatial location of each birth record was geocoded based on the latitude/longitude coordinate of the mother's residential postal code at the time of delivery. Postal code lat/long coordinates are obtained from a Postal Code Conversion File (PCCF) available through the University of Toronto's CHASS Census Analyzer website http://dc1.chass.utoronto.ca/census/ index.html. Further dataset clean-up and manipulation included creating new binary 1/0 data from continuous variables based on the parameters listed above. For example, records with a birth weight less than 2,500 grams were classified as 'LBW' and thus tagged as 1 (case) and births over 2,500 grams were tagged as 0 (non-case). Variables were reviewed for completeness and checked for illogical data entries; for instance, live births weighing 1 gram, and ensuring mutual exclusiveness between outcomes like stillbirths and LBW or preterm birth.

The birth records were appended to the hazard data by performing the same point-in-polygon spatial join procedure in *ArcGIS 9.2*. Birth records were geocoded based on maternal residential postal code lat/long coordinates derived from the PCCF and mapped using the 1983 North American Datum Geographic Coordinate System (GCS NAD83). Each birth record was imprinted with the corresponding WS1 and CSD area in which they resided along with the two hazard variables for that area.

Population-at-risk (PAR) and incidence rates (IR) for the five perinatal outcomes of

concern were calculated for the two different geographic tessellations (WS1 and CSD), as well as for the five Health Authorities in BC. The following formula was used, $\mathbf{IR_{ij}=(O_{ij}/PAR_j)}$; where IR_{ij} is the 6-year (2001-2006) incidence rate of outcome *i* in area *j*, O_{ij} is the observed number of cases of outcome *i* in area *j*, and PAR_j is the total number of birth in area *j*.

Risk Ratios (RR) were calculated using the incidence-proportion ratio between the IR for each CSD and WS1 geographic area divided by the IR of the corresponding Health Authority. Health Authority IRs were used instead of the BC-wide IR as a way to internally standardize the rates. It is assumed that the regional heterogeneity in socio-demographic and economic characteristics, risk behaviours, health care delivery and perinatal services of the five Health Authorities will be somewhat adjusted for (Refer to Appendix 2 to see the regional differences in confounding and covariate risk factors). Poisson confidence intervals (CI = 95%) were computed for the RRs using *STATA 10.0 [34]*. Sensitivity analyses were conducted to filter out unstable rates and determine the population size needed to support an epidemiological study of perinatal outcomes. A stable rate was defined as a rate which does not change its statistical significance when a case was removed from the count.

Results:

a) Hazard characterization using administrative & watershed areas

Figures 2.1 and 2.2 show the combined average annual release of arsenic, cadmium, chromium, lead, and mercury emitted into the air, water and soil by industrial facilities as reported in the NPRI for the years 2001 to 2006. The maps also identify additional potential sources of metal exposure via acid rock drainage from past and current mining operations.

Figure 2.1 uses the administrative boundaries to model environmental hazards. Because CSDs in BC are based on municipal boundaries and Regional District Electoral Areas for "unorganized areas" outside municipal centres, the boundary delineations are arbitrary and vary greatly in size between urban and rural areas (Figure 2.1). This can result in diffuse and misclassification of hazard risk. For example, while Area A in Figure 2.1 and Figure 2.2 are similar in both size and hazard level (50-75th percentile), Area B in Figure 2.1 covers a much larger area compared to Area B in Figure 2.2 and the geographical specificity of the hazard level is therefore decreased. Area C in Figure 2.1 covers a larger area and thus has an aggregated increased hazard level (50-75th percentile) compared to the several smaller watersheds in Area C in Figure 2.2 (bottom 25th percentile).

Table 2.2.1 lists the watersheds in the top 75th percentile of metal contaminant releases in BC along with the population-at-risk (i.e. the number of births from 2001 to 2006) and total population estimated from health authority wide birth rates. All but three watersheds with high metal pollution are populated (i.e. PAR > zero). The purpose of Table 2.2.1 was to show how pollutant releases typically were distributed with sufficient population across a gradient of hazard levels allowing for comparison.

b) Health outcome parameters by watersheds and administrative boundaries

Between 2001 and 2006, there were 236,417 singleton births ≥ 500 grams or over 27 weeks gestation with available geographic information to map and link to environmental hazards in BC. Small-area risk ratios (RR) of intra-uterine growth restriction were calculated and mapped using the two different tessellations CSD and WS1 (Figure 2.3). The RR map displays

areas with significantly high and low rates of IUGR in BC. Additional RR maps showing the other adverse birth outcomes are available in Appendix 1. The RRs have been internally standardized to their corresponding Health Authority rate in order to control for inter-regional variability. The displayed RRs have also undergone sensitivity analyses to filter out areas with unstable or highly variable rates. For privacy reasons, no area having less than 5 cases were shown on the maps.

In Figure 2.3 and Appendix 1, the shaded areas depict CSDs of varying risk and the areas with patterns (cross-hatching, etc.) depict the local watersheds (WS1). For nearly every significant RR that was detected using the CSD boundary, it was also identified using the WS1 boundary with the same level of effect. For example, an RR of 1.5 – 2.0 was consistently found for the same community area regardless of using a CSD or WS1 boundary (Prince George and Williams Lake). However, some significant RRs were only detected using one of the two boundary tessellations (e.g. the CSD of Vernon and the WS1 Mclennan Creek in Abbotsford or Trent Creek near Cumberland). In general, the CSD areas were smaller than the WS1 areas and were therefore able to focus the found effect more precisely to a given community with the exception in rural areas. For instance, WS1 area of Lake Okanagan is large and encompasses many of the lakeside communities including Kelowna and Vernon. Thus, this aggregation of several Lake Okanagan communities washed out any underlying signal for the WS1 area while the smaller CSD areas of Kelowna and Vernon were picked up having a significantly low and high RR for IUGR respectively. However, because of their smaller size, the CSD rates were highly variable to fluctuations with only 52 percent of areas remaining significant after the sensitivity analysis. In contrast, 70 percent of WS1 areas remained significant after the sensitivity analysis.

This finding is consistent with the expectation that larger areas with more population will have less variable rates.

To further evaluate between using watershed and administrative boundaries, Figure 2.4 displays the point-sources of metal pollutants in proximity to the communities of Trail, Warfield and Rossland. The map shows both WS1 and CSD tessellation areas for these communities and how the hazards and birth data are modelled using the different boundary tessellations. Table 2.2 shows the population counts, incidence rates and risk ratios of the adverse birth outcomes for the areas that make up this region. Two relevant observations should be noted: 1) ancillary hazard data provides a more complete estimate of potential contaminant exposure by including historical land-use (e.g. past producing gold mines and acid rock drainage sites provided by the BC MinFile; and 2) the significantly high risks of IUGR and LBW independent of environmental or covariate risk factors were found using both the CSD and WS1 tessellations from mainly non-overlapping populations. For example, the WS1 area of Trail Creek covers Rossland and Warfield whereas the CSD areas of Trail and Castlegar are mostly encompassed by the WS1 area of the Columbia River with very little overlap with Trail Creek. However, Trail Creek and the CSD of Trail both had significantly higher risks of IUGR and LBW compared the Interior Health Authority as the reference population. With the exception of the community of Warfield (RR for IUGR = 3.41, 95% CI 1.91-5.87), the other areas that make up this region suggested trends for increased risk for LBW and IUGR but were not statistically significant likely due to insufficient population size. Comparatively, Castlegar, a community of similar size and demographics as Trail and 150 km upstream on the Columbia River watershed has no increased risk to any adverse birth outcome.

Discussion:

The purpose of this paper was to assess the feasibility of using watersheds as the aggregation unit in an epidemiological analysis of environmental hazards and adverse reproductive outcomes in BC. Environmental hazards were modelled using two different spatial tessellations (CSD and WS1), and are shown in Figures 2.1 and 2.2 respectively. Despite mapping the same data, Figures 2.1 and 2.2 are drastically different looking maps. Referred to as the modifiable aerial unit problem (MAUP), the choice of spatial reference frame significantly dictates both the statistical and visual patterns observed [35]. CSD delineations are based on administrative-political boundaries that can change over time in accordance to population growth and land-use zoning. Alternatively, local watershed areas (WS1) are a reasonable and stable unit to model the exposure potential of environmental hazards as substances in the environment tend to obey hydrologic and geochemical processes [36,37]. For example, Reif et al. [38] modelled the hydraulic characteristics of a groundwater catchment area to assign individual level exposures within the study population.

The application of defining area-level estimates of hazard is used as an independent variable in the analysis of adverse birth outcomes while controlling for several key confounders at the individual-level. In a case-control study, the rate of adverse birth outcomes in the bottom quartile areas can be compared to the rates in the middle and top quartile areas. This could identify hotspot areas that warrant further investigation. Five different contaminants were initially chosen and modelled in addition to those for metals, including particulate matter, polycyclic aromatic hydrocarbons, volatile organic compounds and dioxins-furans. These substances can be analyzed individually, or modelled in a way to give an combined overall

hazard level. Much of the research in the field of environmental toxicology and risk assessment is concerned with exposure to a single chemical at a time. This approach is generally chosen due to the high degree of complexity involved in estimating the dose and health effects from mixtures of chemicals, and also due to the difficulty in regulating chemical mixtures. However, the cumulative health effects from exposure to environmental agents, including biological, chemical, physical, and psychosocial stressors, can contribute to vulnerabilities of human populations such as impaired immuno-response to viral or bacterial insults or aggravate respiratory ailments [21]. Tailings from historic and current gold mine operations, ore smelting and wood preservative facilities are the principle anthropogenic sources of environmental arsenic in BC; elevated concentrations have been reported for sites in proximity and downstream to those point sources (Wang, 2005). The mixtures of metals present in tailing leachate from mining waste have a high propensity to interact with other sources of metal contaminants, possibly affecting exposure by altering dose and absorption which may result in adverse developmental effects of the foetus and children.

The risk ratio maps in Figure 2.3 and Appendix 1 show that it is feasible to map small-area risk ratios of adverse perinatal outcomes while maintaining a high degree of privacy. In general, both spatial tessellations (WS1 and CSD) showed similar results thus confirming the findings. However, in some instances high risk areas were only picked up by one of the two tessellations. For example, in Figure 2.3 the CSD area of Penticton is highlighted as having an increased risk of preterm births (RR=1.28, Poisson Exact 95%CI=1.11 – 1.48). The WS1 tessellation did not reveal the same small but significant increased risk. This difference may be due to the larger watershed area encompassing neighbouring communities along Okanagan

Lake with normal or below normal risk of preterm birth, thereby diluting the small excess risk in Penticton. Similarly, an increased risk was detected for a small watershed near Kelowna (RR=1.54, Poisson Exact 95%CI=1.16 – 2.01) but not for the CSD of Kelowna itself.

The RR maps using both spatial tessellations provide a focussing of excess risk from large regions to, in many cases, community-specific areas across BC. This information is potentially very useful in determining candidate communities for further monitoring and possible intervention. Currently, the BCPHP produces incidence rates of various perinatal health indicators at the Health Service Delivery Area (HSDA) for its annual report [39]. The five large Health Authorities are divided into either three or four HSDAs, thus representing relatively large regions. This scale of spatial support is necessary in order to ascertain sufficient population to evaluate annual regional trends of perinatal outcomes and resources for the purpose of monitoring and improving perinatal care [39]. However, significant heterogeneity exists within the HSDA regions, and it is important to identify community-level rates of the same outcomes and care resources.

Areas with significantly low risk of adverse birth outcomes provide interesting opportunities in which to study further. These include the area of Golden and Peace River District (Fort St. John, Dawson Creek, Hudson Hope). This might be due to an under ascertainment in the BCPHP database. It's possible that high risk births receive care in the closer tertiary care centre of Calgary or Edmonton, rather than tertiary care centres in BC further away. Communities such as Chilliwack and Langley have lower rates of LBW compared

to the rest of the Fraser Health Authority. If confirmed, these communities could be explored as good models for the rest of the region.

In general, the CSD areas are effective in determining pregnancy outcome risks in defined urban/city centres, but not as effective in rural and remote populations where the boundaries are large and the populations sparse. Further, CSD boundaries are subject to change over the years as Statistics Canada re-configures boundaries in accordance with population dynamics and urban/rural development. This makes comparison across multiple years difficult. Watershed boundaries in contrast are more static as they are hydrographically defined and therefore not subject to administrative or population fluctuations. Furthermore, the WS1 areas were able to pick up many of the same significant risk ratios as the CSD areas confirming the strength of the findings. Combined they can provide insightful new evidence of small-area risk ratios in BC.

Limitation and Future Work:

Despite the technological advances over the past decade in GIS and environmental modelling, a major challenge in environmental epidemiology remains to be the quantification of exposure to a population or individual. This study uses an ecological design to assess exposure risk within defined geographic areas that contain multiple stressors using readily available hazard data. Here, hazards refer to the compulsory self-reported releases of pollutants by individual industrial facilities to the NPRI and the presence of mines with *identified* acid rock drainage concerns. Releases are estimated using a variety of methods, all of which have some degree of uncertainty. Further, minimum thresholds must be surpassed

before a facility is required to report the release of a specific substance. Therefore, small but chronic releases of a toxic substance can go unreported. Future work will focus on enumerating missing sources of potential exposure such as contaminated sites, landfills, hazardous waste sites, and transportation corridors including major highways and railroads.

The cumulative toxicity impacts from multiple sources of contaminants were not modeled and may disproportionately underestimate hazard assessment rankings. Human Toxicity Potentials (HTP) can be calculated to reflect the relative measure of harm per unit of chemical released into the environment based on its toxicity, persistence and potential dose via multiple exposure routes [40]. HTPs can then be used to calculate Relative Potential Risk Scores (RPRS) [41], used to weight the relative impact a particular polluting facility has on the surrounding environment. By assigning a RPRS to individual facilities, the spatial and biological variation of hazard is taken into account when assigning exposed and unexposed populations. Validation of the exposure estimates would be beneficial in order to assess the level of uncertainty in our model. For example, water quality [42] and biological sample [43] data exist for major confluence locations along the Fraser River in BC which may help in validating the estimated risk to upstream tributary watersheds. Ambient air quality data from stationary monitoring stations would also help validate estimated air contaminant data.

One specific limitation of using local watershed areas (WS1) is that occasionally a single community can be divided into two or more distinct areas at the confluence of two rivers. For example, the area of Trail/Rossland in Figure 2.4 is split into four watershed areas, each containing some percentage of the population which likely travels throughout the entire area

on a daily basis for work, school and recreation. Areas such as this, where a population's daily activity space includes multiple adjacent smaller areas, could be amalgamated and assessed as one area. Some form of sensitivity analysis could be performed to assess the degree of potential misclassification of one spatial configuration over another.

Conclusions:

The creation of small-area risk maps are valuable in health impact assessments, community health planning and disease prevention by defining baseline spatial disease patterns that can be reassessed over time. Using watersheds in environmental risk assessment carry several advantages over using administrative boundaries, and is a methodology that the US EPA has adopted over the past decade. The ability to map health outcomes by watersheds, such as adverse birth outcomes, allows for an insightful new analysis of environmental health relationships. The use of GIS technology is invaluable in modelling environmental hazards, and determining what populations could be included in case-control and cohort studies. The integration of these models into an environmental health surveillance system would be a cost effective and efficient tool to facilitate the translation of readily collected data from multiple sources (vital statistics, environmental monitoring data, land-use activities, etc.) into usable information for health policy and regional planning deliberations.

Legend of Figures & Tables

Figure 2.1: An Environmental hazard map showing the exposure risk to metals and to acid rock drainage contaminant sites by census subdivision areas (CSD) in BC, Canada

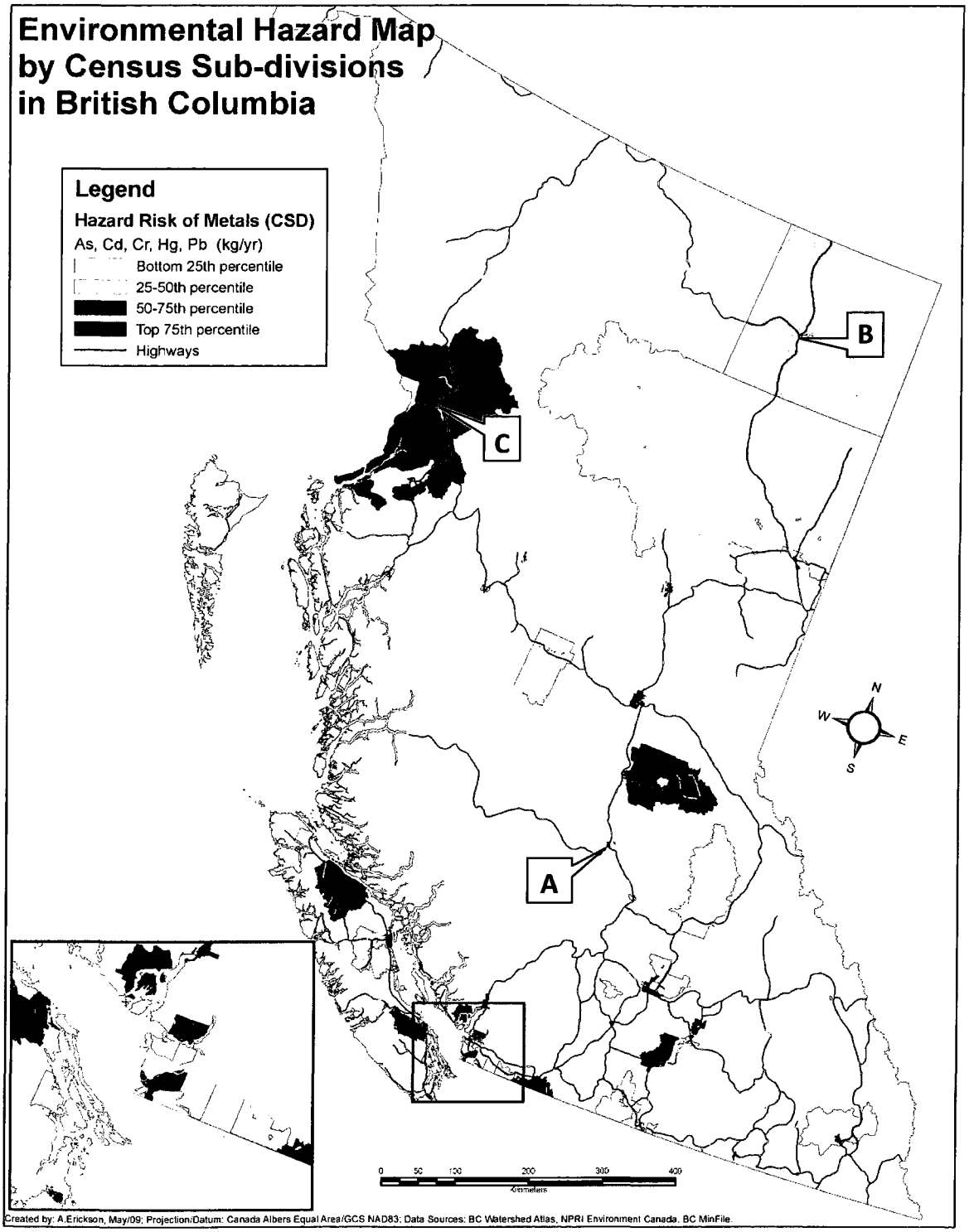

Figure 2.2: An Environmental hazard map showing the exposure risk to metals and to acid rock drainage contaminant sites by local watershed (WS1) in BC, Canada

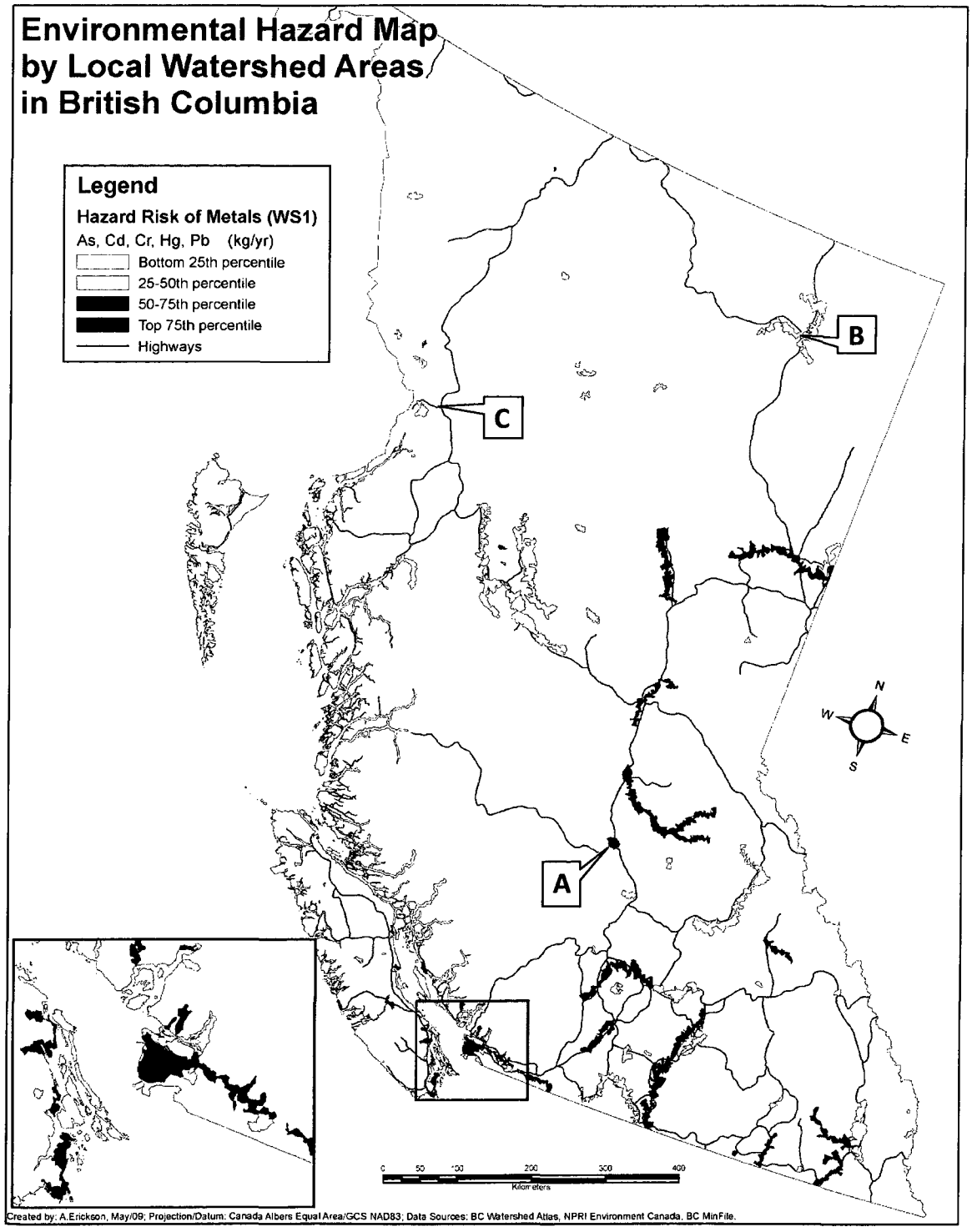

Figure 2.3: Risk Ratio map of IUGR in BC, Canada using a local watershed boundary (WS1) and a census subdivision boundary (CSD) for the years 2001-2006.

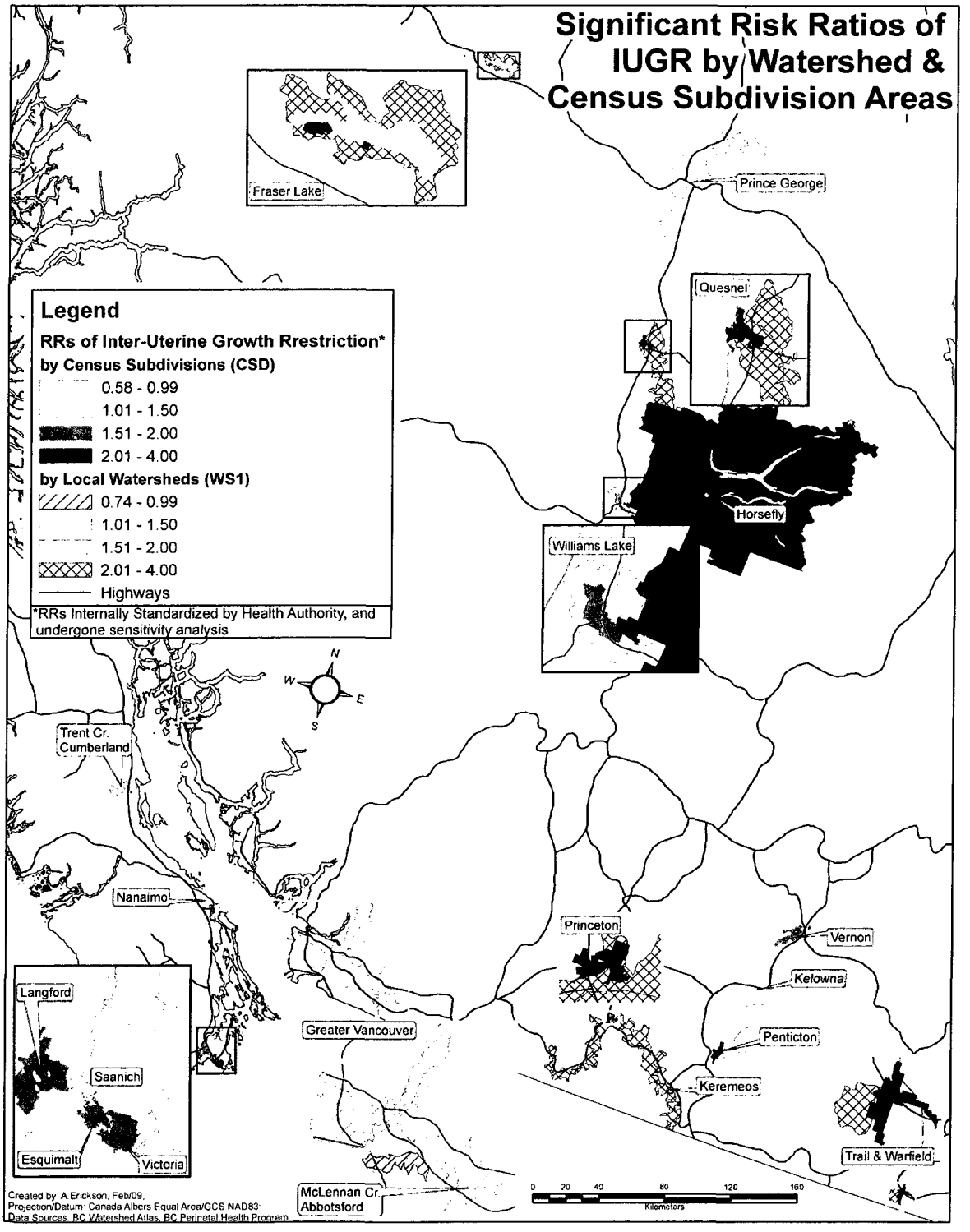

Figure 2.4: Environmental hazard map showing the difference between using watersheds and administrative boundaries to model exposure risk of metal releases from the Inco smelter, upstream historic mining activity and acid rock drainage sites around Trail BC, Canada

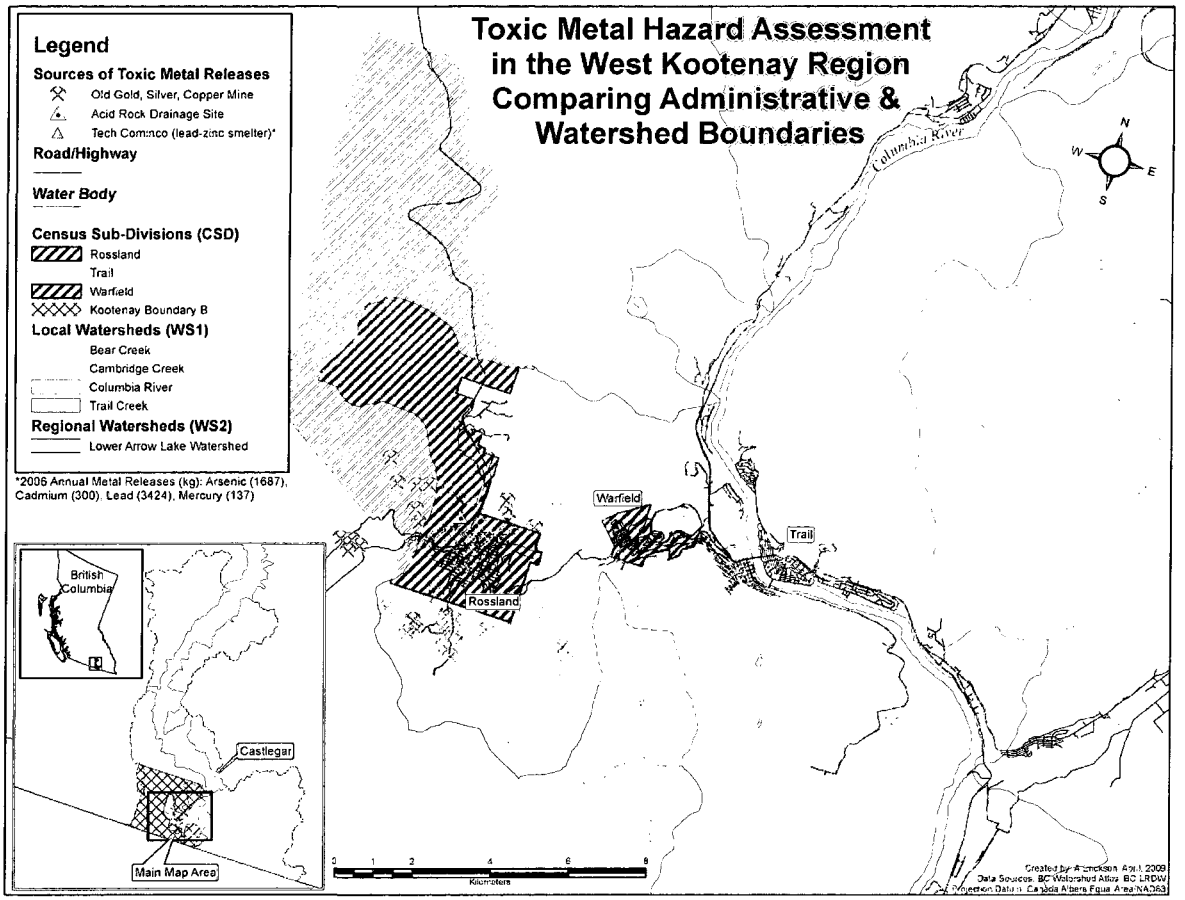

Table 2.1: Top 75th percentile of local watersheds in BC ranked by total metal release and listing population size, population-at-risk (number of birth) and number of acid rock drainage sites

Watershed Name (WS1)	Community	Pop'n	PAR	Total kg/yr	ARD mine
Trail Creek	Rossland/Trail	5,521	318	7,047	1
MacKay Creek	N. Vancouver	14,730	928	2,405	--
Fraser Delta	Lower Mainland	570,651	35951	2,347	--
Vedder River	Chilliwack	6,551	511	1,007	--
Peace River	Ft. St. John/Taylor	24,410	1,904	586	--
N. Fraser River	Prince George	31,628	2467	517	--
Deep Creek	Armstrong	7,535	434	496	--
Thompson River	Kamloops	32,691	1883	425	--
Bush Creek	Nanaimo	9,116	536	399	--
Selkirk Inlet	Victoria	29,983	1763	360	--
Chase Creek	Namaimo	11,548	679	335	--
Rainy River	Gibsons	0	0	300	--
Okanagan River	Kelowna	83,819	4828	316	--
St. Mary's River	Kimberley	1,823	105	285	--
Casey Creek	Campbell River	884	52	276	--
Coldwater River	Merritt	1,319	76	221	--
Ketchum Creek	Stewart	0	0	228	1
Squamish River	Squamish	0	0	204	--
Victoria Harbour	Victoria/Esquimalt	137,840	8105	190	--
Williams Lake R.	Williams Lake	14,962	1167	185	--
Quesnel River	Quesnel	9,000	702	165	--
Lynn Creek	N. Vancouver	25,540	1609	153	--
Myrtle Creek	Powell River	9,302	586	146	--
Maple Bay	Crofton	357	21	132	--
Somass River	Port Alberni	6,480	381	126	--

Pop'n: estimated total population using health authority birth rates;
PAR: Population-at-risk (# births 2001 – 2006); ARD: Acid Rock Drainage

Table 2.2: Birth Outcomes for select communities within the Interior Health Authority by census subdivisions and watershed boundaries as depicted in Figure 2.4

Boundary Name	PAR	LBW Risk Ratio	Preterm Risk Ratio	IUGR Risk Ratio	CA Risk Ratio
Census Subdivisions	**950**				
Castlegar	346	0.74	0.85	0.85	0.46
Trail	290	2.04*	1.29	2.53*	0.66
Rossland	199	1.42	1.14	1.84	1.28
Warfield	86	1.20	1.55	3.41*	0.37
Kootenay Boundary B	29	1.78	1.38	2.53	2.20
Watersheds	**977**				
Columbia River	650	1.07	0.82	1.58	0.78
Trail Creek	318	1.70*	1.38^	2.54*	1.00
Bear Creek	5	0.00	0	0.00	12.74
Cambridge Creek	< 5	6.44	3.33	0.00	0.00

*Significant result using 95% Poisson Confidence Intervals and sensitivity analysis
^ Significant result using 95% Poisson Confidence Intervals but not with the sensitivity analysis
Perinatal Outcomes: LBW-Low Birth Weight, PT-Preterm, IUGR-Inter Uterine Growth Restriction, CA-Congenital Anomaly

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CHAPTER 3

Adverse Perinatal Outcomes and

Environmental Hazards using a Watershed Approach

Table of Contents

Abstract:

Exposure to contaminants during pregnancy is associated with certain adverse birth outcomes that require further investigation. This study builds on a well established methodology of using adverse birth outcomes as proxies for environmental threats to assess the environmental-reproductive health in British Columbia, Canada. Geographical information systems (GIS) were utilized to spatially relate perinatal and environmental hazard data, and the risk of adverse birth outcomes was tested using watersheds as the ecological aggregation unit adjusting for individual-level risk factors. Small but significant increased risks of adverse birth outcomes were found in high and intermediate hazard watersheds compared to low hazard watersheds. Metals and polycyclic aromatic hydrocarbons (PAHs) were the contaminants that produced the strongest significant risk estimates (mean odds ratio: 1.63 and 1.59 respectively). For birth outcomes, intra-uterine growth restriction (IUGR) and congenital anomalies had the most pronounced significant risk estimates with adjusted odds ratios ranging between 1.34 and 2.17 (mean odds ratio: 1.92 and 1.67 respectively). This suggests a possible environmental effect on these reproductive outcomes; however, further studies are needed to corroborate these results.

Introduction:

Identifying the health impact of exposures to environmental pollutants on susceptible sub-populations is an important public health issue. For example, between 2 and 10 percent of low birth weight (LBW) births per year in Canada (up to 2,500 births) are directly attributable to environmental contaminants (*excluding* tobacco, alcohol and illicit drug use) amounting to some $1.5 million in direct and indirect annual costs [1]. However, this estimate does not consider the contribution of LBW to the burden of chronic disease among adolescents and adults including behavioural and learning disorders, type 2 diabetes, obesity, hypertension and cardiovascular disease [2-4]. Associations between exposure to environmental contaminants and adverse birth outcomes are well documented in the epidemiological literature [5-7], and the findings are supported by toxicological evidence [8,9]. Adverse pregnancy endpoints such as low birth weight (LBW < 2,500g), preterm delivery (< 37 weeks gestation), small-for-gestational age (SGA) or intra-uterine growth restriction (IUGR), stillbirth and infant death (< 1 year) have been identified as the key perinatal outcomes that can be affected [6]. These perinatal pathologies are significantly associated with infant mortality and morbidities affecting multiple biological systems ranging from pulmonary to neurological [10,11].

Because the potential health risk of exposures on the fetus within maternal control is so high (alcohol, tobacco etc), the consequence is that environmental exposure outside of maternal control could be neglected from a public health perspective. However, whereas exposures such as smoking and alcohol use have a pronounced effect on a small and specific population, exposure to environmental contaminants have a subtle effect on a large

population and presumably have a larger population impact. Morbidity and pregnancy loss due to contaminant exposure should be preventable; however, further evidence is needed that clearly supports an exposure-effect relationship in order to influence policy change.

Geographical information systems (GIS) has become a powerful tool in epidemiologic and public health research [12]. By mapping potential sources of exposure along with birth outcome data, opportunities to investigate environment-health relationships arise and act as an initial exploratory step to identify "hotspot" areas suitable for more rigorous investigations, such as case-control and cohort studies. The use of adverse birth outcomes as proxies of community environmental health are useful as they reflect a relatively short exposure window, the data are of reliable quality and access is non-invasive through birth registries which often have historical depth. Birth data is also collected at the individual-level often represented by the mother's residential street address or postal code. Therefore, it is possible to explore both spatial and temporal outcome patterns at the community-scale while still protecting the privacy of individual cases. This methodology is a useful tool in public health monitoring and surveillance which has been in practice for decades in Scandinavian countries [13-15]. It is also a model that can incorporate additional covariate data to relate any observed changes to shifting demographics or other social and environmental factors.

A common challenge in ecologic studies is the control for known confounders of the disease/exposure under investigation. Lifestyle risk factors are typically not available at the individual-level and the attempt to control for these variables using area-level measures of socio-economic status (SES) may introduce ecological bias since they are insensitive to

within-area variability. *Semi-ecologic studies* may be less susceptible to ecological bias since they include individual-level data on outcome and confounders with exposure data at the ecologic-level [16]. Medical birth registries often have additional individual-level maternal/infant covariables such as reproductive history, procedures, interventions, morbidities (e.g. diabetes, hypertension), and other risk factors like smoking status, education and level of prenatal care. Although some possible sources of bias still remain; if within-area variability of exposures and confounders are small, then ecological bias will be minimal and results can be interpreted cautiously and compared with other studies to augment the evidence for an aetiological hypothesis [16].

The spatial support, or geographic scale, used in spatial epidemiological studies is critical to the design and ultimately the outcomes of the study. Substances in the environment respect few boundaries, and are more likely to obey hydrologic processes than administrative delineations. The Watershed Approach Framework [17], focuses on hydrologically-defined geographic regions rather than on a single discharger or specific media (e.g. air, water). Multiple physical, chemical, and biological stressors due to human activity combine with varied environmental conditions that may have diverse impacts on numerous biological systems. The watershed defines an appropriate unit in which to investigate the cumulative impact of a multi-stressor environment on human populations [18]. Erickson et al. in the last chapter establish the feasibility of using such a watershed approach to map environmental contaminants and relative risks of adverse birth outcomes in British Columbia, Canada.

The purpose of this paper is to conduct a semi-ecological study relating the risk of

adverse birth outcomes in British Columbia, Canada to environmental contaminants using the watershed approach developed by Erickson et al. This will be accomplished by identifying low, intermediate and high hazard watersheds for several environmental contaminants and determining the associated risk of adverse birth outcomes after controlling for important confounding variables. It is hypothesized that high hazard watersheds will have a slight increase in risk of one or more adverse birth outcome compared to low hazard watersheds. This study is the first step in producing a model capable of analyzing birth outcomes in relation to environmental contaminants particularly attuned for rural, remote and Indigenous populations where the risk of environmental exposures is high and population density is low. This study will also provide information on where to focus on-going environmental epidemiological investigations in British Columbia, Canada.

Materials and Methods:

This was a population-based semi-ecological study that utilized a retrospective cohort design for the years 2001-2006 in British Columbia (BC), Canada. BC is the third largest province in Canada with a population of 4,420,000 and an average annual birth rate of 10.3 per 1,000 population [19]. Health care services are delivered by five geographically-based regional Health Authorities (HAs) that vary inversely between population and area. The Fraser HA in the southwest is the most populated and fastest growing HA with 1.5 million people covering an area of 16,000 km^2; contrast that to the Northern HA which is 608,000 km^2 but has only 350,000 people. A sixth health authority, the Provincial Health Services Authority, is responsible for coordinating the network of high-quality specialized

health care services such as BC Children's Hospital, BC Transplant, BC Cancer Agency and the Perinatal Health Program.

Birth records were obtained from the British Columbia Perinatal Health Program (BCPHP) Registry. The Registry accounts for 99 percent of births in BC and collects data on: antenatal, intrapartum and postpartum maternal and infant care and outcomes, as well as neonatal follow-up and outcomes [20]. Eligible pregnancies were those coded as singleton births from January 01, 2001 to December 31, 2006 (N=237,470). Additionally, birth records required the maternal residential postal code in order to geocode the birth record to the appropriate watershed.

The dataset included 54 independent, dependent and confounding variables. The dependent perinatal variables of concern included low birth weight (LBW <2,500g), preterm birth (between 20-37 weeks gestation), intra-uterine growth restriction (IUGR – physician identified during the antenatal period using ultrasound imaging), stillbirth (> 20 weeks gestation or > 500g), and congenital anomalies (International Classification of Disease 9 (ICD-9) 7400 to 7599 or ICD10 Q00 to Q99). Out-of-province records (n=926) and records missing geographic data on maternal area of residence (n=129) were excluded. Covariate information obtained from the Registry included: sex, maternal age, parity, gravidity, smoking status, drug flag, alcohol flag, number of prenatal care visits, diabetes (prior diagnosis and gestational onset), hypertension during pregnancy, education level and marital status.

Population "exposure" was estimated using hazard data from the National Pollutant Release Inventory (NPRI) published annually by Environment Canada [21]. Nine substances

shown to have negative effects on reproductive health were selected from the NPRI to be analyzed. They include sources of polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs), particulate matter less than 2.5 microns in diameter ($PM_{2.5}$), dioxins and furans (DF), and chromium (Cr). The release of arsenic, cadmium, mercury and lead were highly correlated (R>0.70) and grouped together as a single 'metals' variable. Each of these substances' annual release per facility was averaged over the number of reports filed to the NPRI for the years 2001 to 2006. The data from the point-source releases were integrated into the corresponding watershed areas using a *point-in-polygon spatial join* procedure in *ArcGIS 9.2* [22]. The spatial join had a 'one-to-many' relationship in which each point within an area retains its attribute data and is appended as a new row in the watershed data table. Similar substances released from multiple point-sources within the same area were summed to give an overall ecologic (area-level) measure of exposure hazard to the selected pollutants.

The distribution of hazards by watershed across BC were not normally distributed, but rather followed a steep exponential curve with large outliers. To reduce the effect of outliers, logarithm transformations were performed for all hazard data variables. Three ordinal rankings of hazard were then created for each pollutant: 'no (low) hazard', 'intermediate hazard' and 'high hazard'. The majority of the population for each pollutant fell into the 'no hazard' category, and the remaining population was deliberately divided as equally as possible into the remaining two categories (Refer to Tables 3.1 – 3.4).

Watershed data came from the 1:50,000 BC Watershed Atlas, a topologically structured digital representation of all aquatic-related features in BC (streams, lakes,

wetlands, obstructions, dams, etc.). The data set includes boundaries for all third-order and greater watersheds, stream network connectivity, stream route systems, and a hierarchical watershed code associated with all bodies of water [23]. This analysis used the smallest watershed tessellation areas available in the Atlas (1:20,000 streams), hereafter termed 'WS1' or 'local watershed area'. A total of 547 local watersheds were identified in BC in which there was at least one birth recorded over the study period (2001-2006). They are generally community specific, but their size ranges substantially with an average area of 250 km^2 and median area of 114 km^2, and a range in population from 10 to 350,000 people.

The spatial location of each birth record was geocoded based on the latitude/longitude coordinate of the mother's residential postal code at the time of delivery. Postal code lat/long coordinates were obtained from a Postal Code Conversion File (PCCF) [24] available through the University of Toronto's CHASS Canadian Census Analyzer [25]. Birth records were imprinted with their corresponding local watershed (WS1) area including the six ecologic hazard variables for each watershed area by performing point-in-polygon spatial join procedures in *ArcGIS 9.2*. Further dataset clean-up and manipulation included transforming yes/no variables into binary 1/0 data, and creating new binary variables from continuous variables based on defined parameters. For example, records with a birth weight less than 2,500 grams were classified as 'LBW' and thus tagged as 1 (case) and births over 2,500 grams were tagged as 0 (non-case). Variables were reviewed for completeness and checked for illogical data entries. For example, live births weighing 1 gram and ensuring mutual exclusiveness between certain outcomes like stillbirths and LBW or preterm birth.

All statistical analysis was performed in *STATA 10.0* [26]. Independent odds ratio (OR)

tests and 95 percent confidence intervals (95%CI) were calculated for each covariate on each adverse birth outcome. Chi-square tests were used to determine if the distribution of covariates were homogeneous across exposure groups. Crude and adjusted ORs along with 95%CIs were calculated for the effect of hazard ranking on each adverse birth outcome. The *tabodds adjust* command in *STATA 10.0* was used to tabulate the Mantel-Haenszel adjusted odds ratios. The effect of possible confounding was adjusted for by stratifying on these factors in the analysis, which included: maternal age, smoking status, drug flag, alcohol flag, number of prenatal care visits, diabetes (prior diagnosis and gestational onset), hypertension during pregnancy, education level and marital status. The inclusion of a covariate into the adjusted odds ratio tests depended on their demonstrated effect on the adverse birth outcome in question.

Results:

Between 2001 and 2006, there were 236,417 singleton births ≥ 500 grams or over 27 weeks gestation with available geographic information to map and link to environmental hazards in British Columbia. Independent odds ratio tests revealed the effects of several covariates on the dependent variables, and therefore were appropriately controlled for in the analysis (Figure 3.1). Chi-square tests showed that the distribution of sex and pre-existing diabetes were equally distributed across exposure levels. The level of prenatal care was also evenly distributed across exposure groups depending on exposure type; all other covariates were less evenly distributed across exposure levels.

<u>Intra-uterine Growth Restriction:</u>

Of the qualified births, 235,363 records had data for the IUGR variable. 4,309 (1.9

percent) of these infants were diagnosed as IUGR. All factors except education level were associated with a significant change in risk for IUGR births (Figure 3.1).

Crude odds ratios showed that mothers residing in watersheds with an intermediate hazard ranking for the contaminants VOCs, DFs, $PM_{2.5}$, and Cr had a moderate increase in risk (avg. increase 18 percent) for IUGR births compared to mothers residing in watersheds with a low hazard ranking. Mothers residing in watersheds with high hazard rankings for all selected contaminants except Cr had a moderate increase in risk (avg. increase 23 percent) for IUGR births compared with the referent group. After adjustment for known confounders, the risk estimate increased slightly from the unadjusted estimate for most contaminants for both intermediate and high hazard rankings (avg. increase 19 and 28 percent respectively).

Limiting the analysis to specific health authorities revealed a substantial increase in risk of IUGR in both intermediate and high hazard watersheds within the Northern Health Authority (Table2). The contaminants that showed a large increase in risk (avg. increase 85 percent) of IUGR compared to the reference group within the same HA were PAHs 2.05 (1.19-3.52) 1.77 (1.23-2.56), DFs 2.17 (1.11-4.24), Metals 1.57 (1.09-2.26), $PM_{2.5}$ 1.89 (1.24-2.89), and Cr 1.62 (1.13-2.33).

Low Birth Weight:

Among the 236,417 infants born between 2001 and 2006 and included in the analysis, 235,322 had complete birth weight information in their records. A total of 9,399 (3.99 percent) of these infants were low birth weight (Table 3.2). All risk factors were associated with a change in risk for LBW.

Crude estimates revealed that mothers residing in watersheds with high or intermediate hazard ranking for all contaminants modelled were at a mildly increased risk for LBW (smallest and largest effects: OR(95%CI) for $PM_{2.5}$ and DF = 1.09(1.04-1.15) to 1.17(1.11-1.24) respectively), compared with mothers residing in watersheds with low hazard rankings (Table 3.2). Adjusted estimates detected slightly higher increased risk for mothers residing in high and intermediate hazard risk watersheds compared with the referent category (OR (95%CI)) for $PM_{2.5}$ and DF = 1.17 (1.10-1.23) and 1.22 (1.15-1.29) respectively. After limiting the analysis to within specific HAs, risks estimates of LBW increased slightly for high and intermediate hazard watersheds only in the more populated HAs (Fraser and Vancouver Coastal). The risk estimates for the Northern, Interior and Vancouver Island HAs, ceased to be significant with the exception of mothers residing in intermediate risk watersheds within VIHA for $PM_{2.5}$ OR= 1.29 (1.08-1.54).

Preterm Birth:

Of the qualified births, 234,991 records had complete gestational information. A total of 17,453 (7.4 percent) of these infants were born premature (under 37 weeks). All factors were associated with a change in risk for preterm birth (Figure 3.1).

Crude odds ratios showed that mothers residing in watersheds with an intermediate hazard ranking for the contaminants PAHs and DFs had a slight increase in risk (avg. increase 8 percent) for preterm births compared to mothers residing in watersheds with a low hazard ranking. Mothers residing in watersheds with high hazard rankings for all selected contaminants except VOCs had a mild increase in risk (avg. increase 8 percent) for delivering premature compared with the referent group. After adjustment for known confounders, the

risk estimate increased slightly from the unadjusted estimate for all contaminants for both intermediate and high hazard rankings (Table 3.2).

Limiting the analysis to specific health authorities, risk estimates of preterm births increased for some contaminants in intermediate and high hazard ranked watersheds. For example, the analysis limited to mothers residing in Vancouver Island HA showed an increased risk of preterm births in watersheds ranked with an intermediate and high hazard for $PM_{2.5}$ 1.42 (1.25-1.61) 1.34 (1.01-1.77) respectively compared to the reference group within the same health authority (Table 3.2).

Congenital Anomalies:

Of the qualified births, 236,415 records had complete congenital anomaly data. These birth defects are collected passively from discharge summary records from the hospitalization at birth and all re-admissions until 28 days of age. A total of 8,237 (3.5 percent) of BC infants were diagnosed with one or more congenital anomalies. All factors except smoking and education level were associated with a significant change in risk for congenital anomalies (Figure 3.1).

Crude odds ratios showed that mothers residing in watersheds with an intermediate hazard ranking for all selected contaminants except VOCs and DFs had a moderate increase in risk (avg. increase 28 percent) of congenital anomalies compared to mothers residing in watersheds with a low hazard ranking. Mothers residing in watersheds with high hazard rankings for all selected contaminants had a moderate increase in risk (avg. increase 31 percent) for congenital anomalies compared with the referent group. The intermediate hazard ranking for VOCs became significant after adjustment for known confounders,

ORcrude= 1.03 (0.98-1.09) to ORadjust=1.07 (1.01-1.13), but in general adjustment made little difference in risk estimates.

After limiting the analysis to specific HAs, watersheds with either an intermediate or high hazard ranking for metal pollution showed increased risks for congenital anomalies across all HAs. Other contaminants such as PAHs, $PM_{2.5}$ and Cr also revealed similar trends (Table2). Mothers who resided in Northern HA watersheds ranked as high hazard for PAHs and Cr had nearly two times the risk of congenital anomalies compared to the reference group OR=1.98 (95%CI: 1.61-2.42) and OR=1.98 (95%CI: 1.61-2.42) respectively.

Stillbirths:

There were a total of 1,052 (0.4 percent) stillbirths in BC between 2001 and 2006. All factors except alcohol flag, education level and gestational diabetes were associated with a significant change in risk for stillbirths (Figure 3.1). Interestingly, the number of prenatal care visits showed a remarkable effect on the risk of stillbirth with over six-times the risk when the number of visits was less than four (OR = 6.58, 95%CI 5.46- 7.93). The risk mapping exercise revealed several rural and remote areas with an increase risk of stillbirths compared to neighbouring areas, including Bella Coola, Ucluelet and Port Alberni, Harrison Hot Springs, Clinton, Williams Lake and Fort St. John. Statistical test analysing the risk of stillbirths with regard to environmental contaminants showed no significant results.

Discussion:

This study detected small but significant increases in risk of four adverse birth outcomes to mothers who resided in intermediate and high hazard watersheds compared to mothers who resided in low hazard watersheds. Tests for linear trend were also significant

with increasing level of hazard. This apparent dose response effect was consistent for all pollutants across each outcome except for Cr with LBW and VOC with preterm births. Cross-level effects were examined by limiting the analysis to within specific health authorities (HAs), thus spatially determining where the effect was coming from. Although many of the significant risk estimates disappeared, particularly among the less populated HAs, some risk estimates increased for certain contaminants and outcomes. The HA specific analyses reduced the sample (population-at-risk) size disproportionately across the hazard levels, and as a result, increased the variability of the risk estimates. In some cases, hazard levels for certain outcomes and pollutants were eliminated altogether (represented by an 'n/a' in Tables 1 - 4).

Of the five adverse birth outcomes studied, the largest effects were seen with IUGR. Women from the intermediate hazard ranked watersheds for PAH and DF had over two-times the risk for IUGR than mothers from low hazard watersheds when the analysis was restricted to the Northern HA. Additionally, three of the remaining four pollutants produced risk estimates greater than 50 percent for women residing in the high hazard watersheds compared to the reference group in the Northern HA. High risk estimates of over 50 percent were also produced within the Vancouver Coastal HA for every contaminant except DF. IUGR may be one of the more sensitive birth outcomes utilized in this study based on physician identified diagnoses of restricted fetal growth measured around the 30^{th} week gestation. However, the diagnosis is liable to be highly subjective and may only capture the more extreme cases while moderately restricted fetal growth remained undetected. The outcome small-for-gestational age may be more appropriate outcome to use as it is based on sex-

standardized weight-versus-gestational age plots, and newborns that fall below the tenth or third percentiles are identified.

Small but significant increases in risk of LBW were detected across all hazard levels for each pollutant; however, the HA-specific analysis revealed only significant risk estimates in the two most populated health authorities Fraser and Vancouver-Coastal. LBW is comprised of two overlapping etiologies, IUGR and prematurity; and therefore may be the least informative outcome of the three. Furthermore, rates may also reflect ethic differences in size, and the use of LBW as a binomial variable may have unintended implications in ethnically diverse populations such as in BC. For instance, status First Nations people in B.C. tend to have significantly higher median and mean birth weights at all gestations compared to all births in B.C. [10]. Conversely, Chinese and South Asian descent infants born in B.C. have significantly lower birth weights than European descent infants [27]. This might explain the absence of association in the Northern HA where the highest proportion of First Nations people reside in BC, compared to the lower mainland which have a high Chinese and South Asian population. The analysis of birth weight as a continuous variable may offer additional and complimentary results to that seen using the binary LBW variable.

This study also detected small excess risk of preterm births to mothers residing in intermediate and high hazard watersheds compared to with low hazard watersheds; however, the risk of preterm births were smaller and not as constant as those for LBW. Preterm birth as an outcome is considerably more complex than birth weight, and is influenced by several other risk factors that were not controlled for including: infection,

birthing method (e.g. spontaneous vs. induced, vaginal vs. caesarean), oligohydramnios and/or placental abnormalities. Further, information about gestation could be subject to reporting errors. Gestational age of the child is calculated based on the availability of four data elements with varying degrees of completeness: by earliest ultrasound, by last normal menstrual period, by newborn exam, by maternal chart.

The risk of congenital anomalies was also remarkably elevated in high and intermediate hazard watersheds compared to low hazard watersheds. Metals in particular showed a consistent significant effect across all health authorities except the Interior HA. Large effects were also found particularly in the Northern HA, with nearly two times the excess in risk. The congenital anomaly data in this data set is limited, reflecting passively collected information from discharge summaries. Although it is interesting that an association seems present in the intermediate and high hazard areas, these data might underestimate the true impact. The current data collection is only to age 28 days, precluding congenital anomalies not requiring hospital admission before that time, and may under-report non-life threatening anomalies such as some brain anomalies, heart defects, and genital defects. Alternately, artificial clusters may arise due to a more concerted effort or different skill sets of physicians and may reflect regional differences. For example, the likelihood of birth defects being documented in the first month of life may reflect the availability of tertiary level care. Finally, for this study all congenital anomalies were grouped into one variable which also may have influenced the observed results. Future studies will assess specific anomalies known to be effected by environmental influences, such as congenital heart malformations and male genital abnormalities.

Despite no significant effects of watershed hazard levels on rates of stillbirth an important covariate result is worth commenting on. The independent odds ratio for stillbirth and the number of prenatal care visits exhibited an excess of over six-times the risk, even greater than for prematurity and low birth weight which demonstrated 3 and 4 times the risk respectively. Our risk mapping exercise revealed several rural and remote areas with an increase risk of stillbirths compared to neighbouring areas, including Bella Coola, Ucluelet and Port Alberni, Harrison Hot Springs, Clinton, Williams Lake and Fort St. John. Barriers to health care, whether geographic or other are worth pursuing further. The analysis did reveal some increased risk of stillbirths with certain contaminants, but were either insignificant or failed to remain significant after adjustment of confounders. The presence of wide confidence intervals suggested that the analysis was either underpowered, and/or there was a large amount of error. Future considerations will likely require increasing the temporal window to ten years, spatial aggregation, and/or perform a smoothing function that would "borrow" cases from neighbouring areas to help increase the sample size and stabilize the rates.

Polycyclic aromatic hydrocarbons, chromium and the metals variable were among the environmental contaminants that produced the largest significant effects on the selected birth outcomes, particularly IUGR and congenital anomalies (Table 3.5). Further, their odds ratios increased after limiting the analysis to within individual health authorities; none more stark than in the Northern HA with nearly a two-times the risk in intermediate or high hazard watersheds for PAHs, Metals, and Cr. [OR (95%CI) IUGR = 2.05 (1.19-3.52), 1.57 (1.09-2.26), 1.62 (1.13-2.33) respectively; and OR(95%CI) Congenital Anomalies = 1.98 (1.61-

2.42), 1.78 (1.44-2.19), 1.98 (1.61-2.42) respectively. The local watersheds of concern within the NHA with high levels of these specific contaminants include Fraser River (Prince George), Peace River (Fort St. John and Taylor), Quesnel River (Quesnel). Ketchum Creek near Smithers and Moore Creek near Kitamat would also be considered high hazard for these contaminants, but no birth data were recorded for those areas.

There are several limitations to this study, the foremost being the assumption that women living in high or intermediate hazard watersheds were all exposed equally and that women living in low hazard watersheds are less exposed to these teratogenic substances. Misclassification errors are inherent in ecological studies which utilize area-level estimates of exposure, and may drive the observed ORs towards the null if the misclassification is purely non-differential (i.e. independent of outcome status) and independent from other error [28]. In case-control studies with three exposure levels the direction of bias is also dependent on the risk level, misclassification rates, and exposure distributions [29]. Furthermore, other biases such as confounding, selection bias, and mismeasurement of covariates can cause the total bias to be away from the null [28]. Despite watersheds being community specific in general, some larger towns and cities were comprised of two or more watersheds and daily inter-watershed movement is a hazard classification concern. It is not know what proportion of their pregnancies women spent in their corresponding watershed, nor is it known whether women permanently relocated during pregnancy either across town or across the province. There is conflicting evidence on the importance of timing of exposure, whether it's in the first trimester or later in the pregnancy [30]. Further, covariates

were not homogeneously distributed across exposure levels, and occupational exposure data were not available for the analysis.

A statistical concern arises when attempting to compare between hazard groups. Unequal population sizes occur as a result of categorizing the hazard data into quartiles based on release amounts. The use of generalized additive models (GAMs) to describe the relationship between outcome and predictors would help resolve this issue by allowing for smoothing of the case-control binary outcomes evenly across the hazard groups while adjusting for covariates [31]. This would also increases the ability to discern spatial pattern in the underlying risk by reducing the noise caused by different population sizes [32].

Future studies will need to focus on enumerating missing sources of potential exposure such as provincial contaminated sites, historic and current mining activity, landfills and hazardous waste sites, and transportation corridors such as major highways and railroads. Validation of the exposure estimate is would be beneficial, and could be achieved using existing water quality [33] and biological sample [34] data for major confluence locations along the Fraser River. Ambient air quality data from stationary monitoring stations would also help validate estimated air contaminant data. Human Toxicity Potentials (HTP) can be calculated to reflect the relative measure of harm per unit of chemical released into the environment based on contaminant differences in toxicity, persistence and potential dose via multiple exposure routes [35]. HTPs can then be used to calculate Relative Potential Risk Scores (RPRS) [36] used to weight the relative impact a particular polluting facility has on the surrounding environment. By assigning RPRS to individual facilities, the spatial and

biological variation of hazard is taken into account when assigning exposed and unexposed populations.

Conclusions:

Reproductive outcomes can act as sensitive proxies to environmental threats, since the effect is demonstrated in a relatively short time frame compared to other outcomes, such as chronic disease or cancer. This study uses a novel methodology to ascribe exposure by using watersheds as the ecological aggregation unit as opposed to some arbitrary administrative boundary. Small but significant increased risks were consistently found for the adverse birth outcomes when comparing mothers who resided in high and intermediate hazard watersheds to mothers who lived in low hazard watersheds. This suggests a possible environmental effect on these reproductive outcomes, however, further studies, such as large scale cohort studies will be needed to explore the implications more precisely to corroborate these results.

Legend of Figures & Tables

Figure 3.1: Independent Odds Ratios of Covariate Risk Factors for all Singleton Births in B.C. 2001-2006

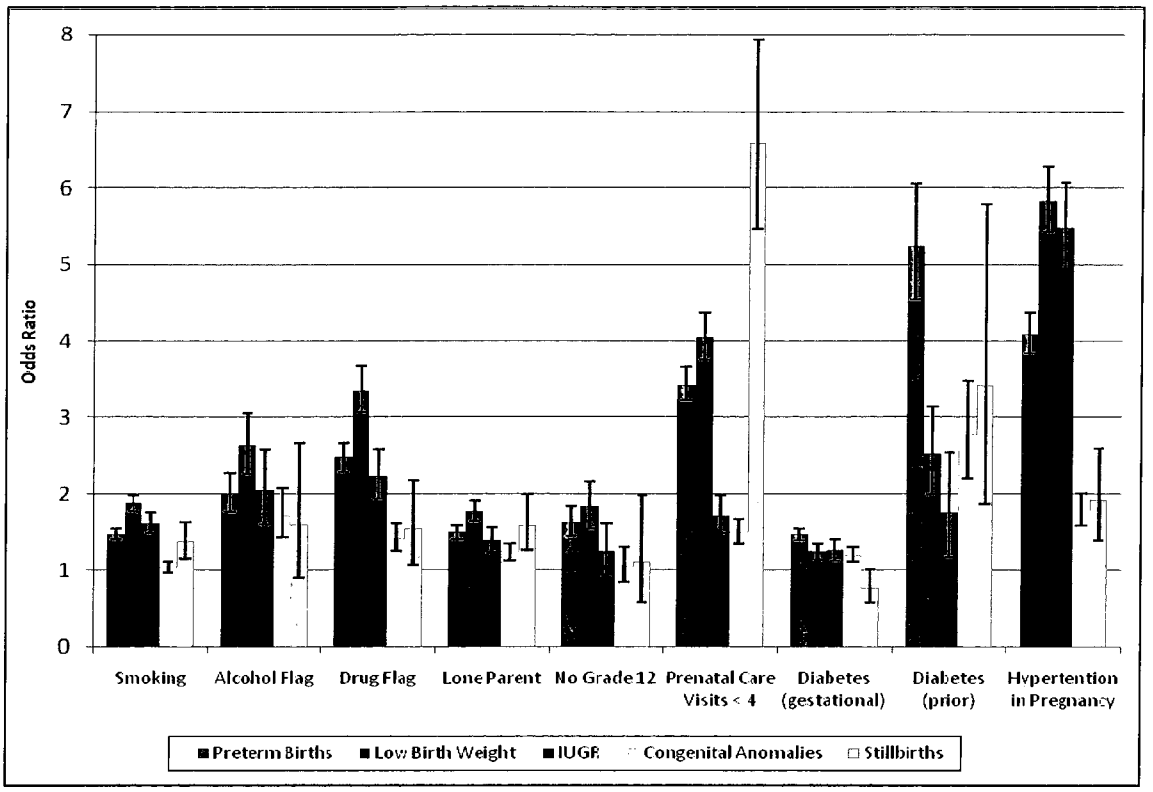

Table 3.1: Odds Ratios of Intra-uterine Growth Restriction and Hazard Ranked Watersheds Pooled for all BC and by Health Authority

IUGR	Outcome not present n = 231,054	Outcome present n = 4,309	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Interior OR (95% CI)	Fraser OR (95% CI)	Van. Coast OR (95% CI)	Van. Isle OR (95% CI)	Northern OR (95% CI)
PAH	164,780	2,940							
PAH - low	28,897	503	0.98 (0.89-1.07)	0.99 (0.90-1.10)	0.75 (0.52-1.08)	1.13 (0.89-1.43)	1.23 (1.04-1.46)*	0.60 (0.32-1.14)	2.05 (1.19-3.52)*
PAH - high	37,377	866	1.30 (1.20-1.40)*	1.35 (1.24-1.46)*	n/a	1.12 (1.00-1.25)*	1.59 (1.34-1.88)*	n/a	1.77 (1.23-2.56)*
VOC	81,215	1,404							
VOC - low	78,241	1,492	1.10 (1.02-1.19)*	1.10 (1.02-1.19)*	0.89 (0.72-1.10)	0.98 (0.88-1.10)	1.81 (1.40-2.35)*	0.70 (0.55-0.89)	1.10 (0.71-1.72)
VOC - high	71,598	1,413	1.14 (1.06-1.23)*	1.17 (1.08-1.26)*	0.90 (0.66-1.24)	1.12 (0.99-1.27)	1.87 (1.52-2.30)*	n/a	1.24 (0.89-1.74)
DF	171,093	2,970							
DF - low	22,212	472	1.22 (1.11-1.35)*	1.18 (1.06-1.31)*	1.14 (0.93-1.40)	1.24 (1.08-1.42)*	n/a	n/a	2.17 (1.11-4.24)*
DF - high	37,749	867	1.32 (1.23-1.43)*	1.37 (1.26-1.49)*	0.42 (0.11-1.69)	1.15 (1.03-1.29)*	1.39 (1.21-1.60)*	0.89 (0.60-1.33)	n/a
$PM_{2.5}$	96,284	2,074							
$PM_{2.5}$ - low	62,005	961	1.08 (1.01-1.17)*	1.11 (1.02-1.20)*	0.84 (0.61-1.14)	1.02 (0.92-1.14)	1.45 (1.11-1.90)*	0.70 (0.51-0.98)	1.11 (0.80-1.53)
$PM_{2.5}$- high	72,765	1,274	1.16 (1.08-1.25)*	1.20 (1.12-1.30)*	1.07 (0.86-1.32)	1.16 (1.03-1.31)*	1.73 (1.38-2.16)*	0.30 (0.10-0.94)	1.89 (1.24-2.89)*
Metal (Mt)	118,151	2,074							
Mt – low	54,343	961	1.01 (0.93-1.09)	1.04 (0.97-1.15)	1.29 (0.95-1.76)	0.94 (0.83-1.07)	1.51 (1.22-1.86)*	1.04 (0.72-1.50)	0.77 (0.52-1.15)
Mt – high	58,560	1,274	1.24 (1.16-1.33)*	1.29 (1.19-1.39)*	1.11 (0.88-1.39)	1.08 (0.97-1.21)	1.89 (1.52-2.35)*	1.66 (1.40-1.98)*	1.57 (1.09-2.26)*
Cr	159,274	2,805							
Cr - low	39,530	919	1.32 (1.22-1.42)*	1.37 (1.26-1.48)*	n/a	1.05 (0.95-1.17)	1.59 (1.34-1.88)*	n/a	n/a
Cr - high	32,250	585	1.03 (0.94-1.13)	1.05 (0.96-1.16)	1.10 (0.84-1.45)	1.10 (0.91-1.33)	1.24 (1.04-1.47)*	n/a	1.62 (1.13-2.33)*

Table 3.2: Odds Ratios of Low Birth Weight and Hazard Ranked Watersheds Pooled for all BC and by Health Authority

Low Birth Weight	Outcome not present n = 225,923	Outcome present n = 9,399	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Interior OR (95% CI)	Fraser OR (95% CI)	Van. Coast OR (95% CI)	Van. Isle OR (95% CI)	Northern OR (95% CI)
PAH	161,199	6,499							
PAH - low	28,200	1,189	1.05 (0.98-1.11)	1.08 (1.01-1.16)*	1.15 (0.95-1.39)	0.90 (0.72-1.11)	1.05 (0.94-1.17)	1.12 (0.81-1.55)	1.22 (0.85-1.75)
PAH - high	36,524	1,711	1.16 (1.10-1.23)*	1.20 (1.13-1.27)*	n/a	1.17 (1.07-1.28)*	1.20 (1.07-1.35)*	n/a	0.99 (0.77-1.26)
VOC	79,518	3,085							
VOC - low	76,484	3,241	1.09 (1.04-1.15)*	1.12 (1.06-1.18)*	0.95 (0.83-1.09)	1.08 (0.99-1.19)	1.56 (1.32-1.85)*	1.08 (0.93-1.25)	1.17 (0.93-1.48)
VOC - high	69,921	3,073	1.13 (1.08-1.19)*	1.18 (1.11-1.24)*	1.13 (0.94-1.38)	1.20 (1.08-1.33)*	1.39 (1.22-1.59)*	1.07 (0.34-3.33)	1.01 (0.84-1.22)
DF	167,351	6,682							
DF - low	21,692	989	1.14 (1.06-1.22)*	1.12 (1.04-1.21)*	1.04 (0.91-1.18)	1.22 (1.09-1.37)*	n/a	1.67 (0.23-12.33)	1.11 (0.66-1.85)
DF - high	36,880	1,728	1.17 (1.11-1.24)*	1.22 (1.15-1.29)*	1.00 (0.56-1.79)	1.21 (1.11-1.32)*	1.14 (1.03-1.26)*	1.18 (0.93-1.51)	n/a
$PM_{2.5}$	94,124	3,813							
$PM_{2.5}$ - low	60,723	2,444	0.99 (0.94-1.05)	1.07 (1.01-1.13)*	0.91 (0.76-1.10)	1.00 (0.91-1.09)	1.37 (1.15-1.62)*	1.29 (1.08-1.54)*	1.09 (0.92-1.29)
$PM_{2.5}$ - high	71,076	3,142	1.09 (1.04-1.15)*	1.17 (1.10-1.23)*	1.00 (0.87-1.14)	1.13 (1.03-1.25)*	1.36 (1.18-1.56)*	0.99 (0.64-1.54)	1.08 (0.83-1.40)
Metal (Mt)	115,595	4,614							
Mt – low	53,082	2,212	1.04 (0.99-1.10)	1.13 (1.07-1.20)*	1.09 (0.89-1.34)	1.06 (0.96-1.17)	1.40 (1.22-1.61)*	1.06 (0.84-1.33)	0.96 (0.79-1.18)
Mt – high	57,246	2,573	1.13 (1.07-1.18)*	1.18 (1.12-1.25)*	1.07 (0.93-1.23)	1.17 (1.07-1.28)*	1.50 (1.30-1.73)*	1.13 (1.00-1.29)*	0.93 (0.73-1.19)
Cr	155,697	6,357							
Cr – low	38,683	1,758	1.11 (1.05-1.17)*	1.16 (1.09-1.23)*	0.53 (0.13-2.11)	1.07 (0.98-1.16)	1.22 (1.08-1.37)*	n/a	n/a
Cr – high	31,543	1,284	1.00 (0.94-1.06)	1.03 (0.96-1.10)	0.92 (0.77-1.11)	0.91 (0.77-1.07)	1.07 (0.96-1.20)	n/a	0.97 (0.76-1.24)

Table 3.3: Odds Ratios of Preterm Births and Hazard Ranked Watersheds Pooled for all BC and by Health Authority

Preterm Births	Outcome not present n = 217,538	Outcome present n = 17,453	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Interior OR (95% CI)	Fraser OR (95% CI)	Van. Coast OR (95% CI)	Van. Isle OR (95% CI)	Northern OR (95%CI)
PAH	155,219	12,220							
PAH - low	27,081	2,272	1.07 (1.02-1.12)*	1.09 (1.04-1.15)*	1.15 (1.01-1.32)*	1.07 (0.92-1.23)	1.04 (0.95-1.12)	1.23 (0.98-1.54)	1.15 (0.87-1.52)
PAH - high	35,238	2,961	1.07 (1.02-1.11)*	1.06 (1.02-1.11)*	n/a	1.11 (1.04-1.19)*	1.07 (0.98-1.16)	n/a	1.06 (0.89-1.26)
VOC	76,430	6,053							
VOC - low	73,715	5,888	1.01 (0.97-1.05)	1.02 (0.98-1.06)	1.09 (0.99-1.20)	0.99 (0.93-1.06)	1.10 (0.97-1.24)	1.15 (1.04-1.27)*	1.02 (0.86-1.20)
VOC - high	67,393	5,512	1.03 (0.99-1.07)	1.04 (1.00-1.09)*	1.30 (1.13-1.50)*	1.10 (1.02-1.19)*	1.11 (1.02-1.22)*	0.35 (0.09-1.42)	0.84 (0.74-0.97)
DF	161,093	12,667							
DF - low	20,892	1,763	1.07 (1.02-1.13)*	1.07 (1.01-1.13)*	1.19 (1.09-1.31)*	1.00 (0.91-1.09)	n/a	0.69 (0.09-5.15)	1.04 (0.71-1.51)
DF - high	35,553	3,023	1.08 (1.04-1.13)*	1.09 (1.04-1.14)*	0.87 (0.57-1.38)	1.11 (1.04-1.19)*	1.03 (0.96-1.11)	1.29 (1.09-1.53)*	n/a
$PM_{2.5}$	90,642	7,157							
$PM_{2.5}$ - low	58,520	4,530	0.98 (0.94-1.02)	1.02 (0.98-1.06)	0.95 (0.83-1.08)	1.06 (0.99-1.13)	1.05 (0.93-1.18)	1.42 (1.25-1.61)*	0.94 (0.83-1.07)
$PM_{2.5}$- high	68,376	5,766	1.07 (1.03-1.11)*	1.10 (1.06-1.14)*	1.16 (1.06-1.28)*	1.13 (1.05-1.21)*	1.10 (1.00-1.21)*	1.34 (1.01-1.77)*	0.92 (0.75-1.11)
Metal (Mt)	111,296	8,716							
Mt – low	51,214	4,014	1.00 (0.96-1.04)	1.04 (0.99-1.08)	1.10 (0.95-1.28)	1.01 (0.94-1.09)	1.10 (1.00-1.21)*	0.99 (0.85-1.17)	0.87 (0.75-1.01)
Mt – high	55,028	4,723	1.10 (1.06-1.14)*	1.11 (1.06-1.15)*	1.28 (1.16-1.41)*	1.10 (1.03-1.18)*	1.12 (1.02-1.24)*	1.00 (0.91-1.09)	1.01 (0.85-1.20)
Cr	155,697	6,357							
Cr – low	38,683	1,758	1.11 (1.05-1.17)*	1.16 (1.09-1.23)*	0.53 (0.13-2.11)	1.07 (0.98-1.16)	1.22 (1.08-1.37)*	n/a	n/a
Cr – high	31,543	1,284	1.00 (0.94-1.06)	1.03 (0.96-1.10)	0.92 (0.77-1.11)	0.91 (0.77-1.07)	1.07 (0.96-1.20)	n/a	0.97 (0.76-1.24)

Table 3.4: Odds Ratios of Congenital Anomalies and Hazard Ranked Watersheds Pooled for all BC and by Health Authority

Congenital Anomalies	Outcome not present n = 228,178	Outcome present n = 8,237	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Interior OR (95% CI)	Fraser OR (95% CI)	Van. Coast OR (95% CI)	Van. Isle OR (95% CI)	Northern OR (95% CI)
PAH	163,181	5,294							
			1.49	1.46	1.20	1.10	1.27	0.93	1.14
PAH - low	28,161	1,361	(1.40-1.58)*	(1.37-1.55)*	(0.98-1.46)	(0.90-1.34)	(1.15-1.41)*	(0.62-1.39)	(0.76-1.70)
			1.32	1.30	n/a	1.15	1.09	n/a	1.98
PAH - high	36,836	1,582	(1.25-1.40)*	(1.23-1.38)*		(1.05-1.27)*	(0.98-1.22)		(1.61-2.42)*
VOC	80,409	2,576							
			1.03	1.07	1.00	1.08	1.13	1.02	0.90
VOC - low	77,524	2,567	(0.98-1.09)	(1.01-1.13)*	(0.87-1.15)	(0.99-1.19)	(0.97-1.32)	(0.87-1.21)	(0.69-1.18)
			1.37	1.37	1.09	1.21	1.29	1.13	1.30
VOC - high	70,245	3,094	(1.30-1.45)*	(1.30-1.45)*	(0.89-1.34)	(1.08-1.34)*	(1.15-1.45)*	(0.28-4.60)	(1.07-1.56)*
DF	168,750	6,069							
			0.80	0.82	0.91	0.79	n/a	n/a	1.09
DF - low	22,171	634	(0.73-0.86)	(0.75-0.89)	(0.79-1.04)	(0.69-0.91)			(0.66-1.81)
			1.14	1.13	1.59	1.12	0.93	1.11	n/a
DF - high	37,257	1,534	(1.08-1.21)*	(1.06-1.20)*	(1.00-2.54)*	(1.02-1.22)*	(0.84-1.01)	(0.84-1.46)	
$PM_{2.5}$	95,361	3,040							
			1.08	1.09	1.03	1.18	1.01	1.04	0.77
$PM_{2.5}$ - low	61,341	2,117	(1.02-1.15)*	(1.02-1.15)*	(0.86-1.24)	(1.08-1.30)*	(0.87-1.18)	(0.84-1.29)	(0.63-0.93)
			1.35	1.34	0.91	1.26	1.24	0.77	1.32
$PM_{2.5}$- high	71,476	3,080	(1.28-1.42)*	(1.27-1.41)*	(0.79-1.05)	(1.14-1.40)*	(1.09-1.39)*	(0.44-1.33)	(1.05-1.68)*
Metal (Mt)	117,157	3,624							
			1.43	1.40	1.63	1.21	1.37	0.97	0.84
Mt - low	53,192	2,350	(1.35-1.51)*	(1.33-1.48)*	(1.35-1.97)*	(1.10-1.34)*	(1.22-1.54)*	(0.74-1.26)	(0.67-1.05)
			1.27	1.24	1.05	1.21	1.16	1.15	1.78
Mt - high	57,829	2,263	(1.20-1.33)*	(1.18-1.32)*	(0.91-1.22)	(1.10-1.33)*	(1.02-1.32)*	(1.01-1.33)*	(1.44-2.19)*
Cr	157,674	5,146							
			1.23	1.22	0.97	1.09	1.11	n/a	n/a
Cr - low	39,061	1,566	(1.16-1.30)*	(1.14-1.29)*	(0.30-3.06)	(1.00-1.19)*	(0.99-1.24)		
			1.49	1.46	0.93	1.10	1.32	n/a	1.98
Cr – high	31,443	1,525	(1.40-1.58)*	(1.37-1.55)*	(0.77-1.12)	(0.93-1.29)	(1.20-1.47)*		(1.61-2.42)*

Table 3.5: Environmental Pollutants Ranked by Observed Effect on Selected Adverse Birth Outcomes

Environmental Pollutant	IUGR Odds Ratio	CA Odds Ratio	LBW Odds Ratio	Preterm Odds Ratio	Mean Odds Ratio
Metals	1.89	1.78	1.50	1.28	**1.61**
Polycyclic Aromatic Hydrocarbons	2.05	1.98	1.20	1.15	**1.60**
Dioxin-Furans	2.17	1.59	1.22	1.29	**1.57**
Volatile Organic Compounds	1.87	1.37	1.56	1.30	**1.53**
Particulate Matter < 2.5	1.89	1.34	1.37	1.42	**1.51**
Chromium	1.62	1.98	1.22	1.17	**1.50**
Mean Odds Ratio	**1.92**	**1.67**	**1.35**	**1.27**	

Perinatal Outcomes: LBW-Low Birth Weight, IUGR-Inter Uterine Growth Restriction, CA-Congenital Anomaly

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CHAPTER 4

Conclusions and Recommendations

Conclusions and Recommendations

Reproductive outcomes can act as sensitive proxies to environmental threats, and this study builds on this well established methodology to assess the environmental-reproductive health in British Columbia, Canada. The purpose of this Masters Thesis was five fold:

1) Identify watersheds/communities in BC that have a high risk of exposure to contaminants from past and present industrial land use.
2) Identify watershed/communities in BC with an elevated risk of adverse birth outcomes.
3) Determine the appropriateness of using small-area (local) watersheds as the spatial aggregation unit to analyze birth outcomes in relation to environmental hazards.
4) Determine the association of risk of adverse birth outcomes in relation to environmental hazards.
5) Determine which if any adverse birth outcomes can be used as potential surrogates to assess the environmental health of a watershed/community.

A series of reproductive and environmental health risk maps were produced utilizing birth data obtained from the B.C. Perinatal Health Program and environmental contaminant data from the National Pollutant Release Inventory and BC Mineral Exploration Database (BC MinFile). Local (1:20,000) watershed boundaries and similar sized administrative census subdivision (CSD) areas were used as the spatial reference frame to assess environmental and reproductive health at the community/local watershed scale. These community risk maps may serve to focus the allocation of program funding to higher risk communities in order to minimize environmental health risks through intervention and enhanced monitoring.

Watersheds were more appropriate to model the environmental hazard data in general but particularly for rural areas with low population densities. The use watersheds in ecological risk assessment carry several advantages over using administrative boundaries

including: watersheds are stable over time and are not subject to political-administrative boundary adjustments based on population growth and land-use zoning, they are independent of population size and therefore more useful in rural areas, they often coincide with settlements of human populations, substances in the environment are more likely to obey hydrologic geochemical processes than administrative delineations, and finally watersheds can accommodate a multi-stressor environment focused on hydrologically-defined geographic regions rather than on a single discharger or specific media (e.g. air, water). With respect to health outcomes, the watershed areas and CSD areas performed surprisingly similar, however, watersheds produced more stable risk ratios with less variability when sensitivity analyses were performed (70% vs. 50% of areas remaining significant after sensitivity analysis). For these reasons, the watershed defines an appropriate unit in which to investigate the cumulative impact of multiple physical, chemical, and biological stressors on human populations.

Using this watershed approach, small but significant increased risks were found for adverse birth outcomes when comparing mothers who resided in high and intermediate hazard watersheds to mothers who lived in low hazard watersheds. Metals and polycyclic aromatic hydrocarbons (PAHs) were the contaminants that produced the strongest risk estimates (mean odds ratio: 1.61 and 1.60 respectively). For birth outcomes, inter-uterine growth restriction (IUGR) and congenital anomalies were found to have the strongest effects with adjusted odds ratios ranging between 1.34 and 2.17 (mean odds ratio: 1.92 and 1.67 respectively). The findings suggest that certain reproductive outcomes can act as sensitive proxies to environmental threats, since the effect is demonstrated in a relatively

short time frame compared to other outcomes such as chronic disease or cancer. IUGR may be one of the more reliable birth outcome utilized in this study as its diagnosis is based on sex-specific weight-versus-gestational age plots.

This thesis was successfully able to demonstrate that using a watershed approach in an environmental epidemiological study is feasible and may produce stronger (less variable) effects by reducing the misclassification error of exposure risk to a population. The final epidemiological findings suggests a possible environmental effect on these reproductive outcomes, however, further studies such as large scale cohort studies will be needed to explore the implications more precisely to corroborate these results. Future work will focus on improving exposure risk estimates and building a robust statistical model able to produce reliable small-area risk estimates of specific birth outcomes particularly attuned for rural, remote and Indigenous populations where risk of environmental exposures are high and population densities are low.

APPENDIX 1

Community Reproductive Risk Maps

Figure A: Risk Ratio map of Low Birth Weight Births in BC, Canada using a local watershed boundary (WS1) and a census subdivision boundary (CSD) for the years 2001-2006.

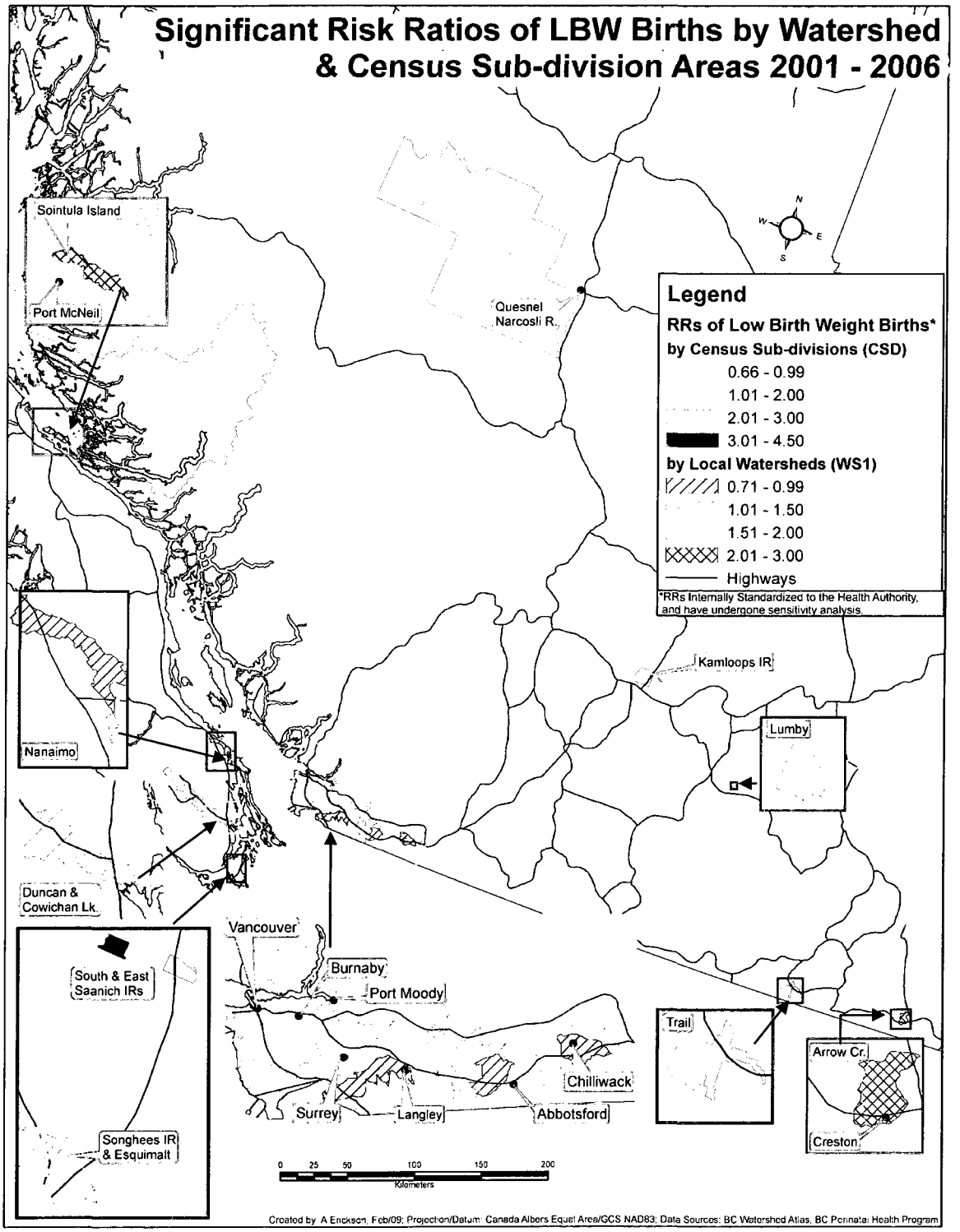


Figure B: Risk Ratio map of Preterm Births in BC, Canada using a local watershed boundary (WS1) and a census subdivision boundary (CSD) for the years 2001-2006.

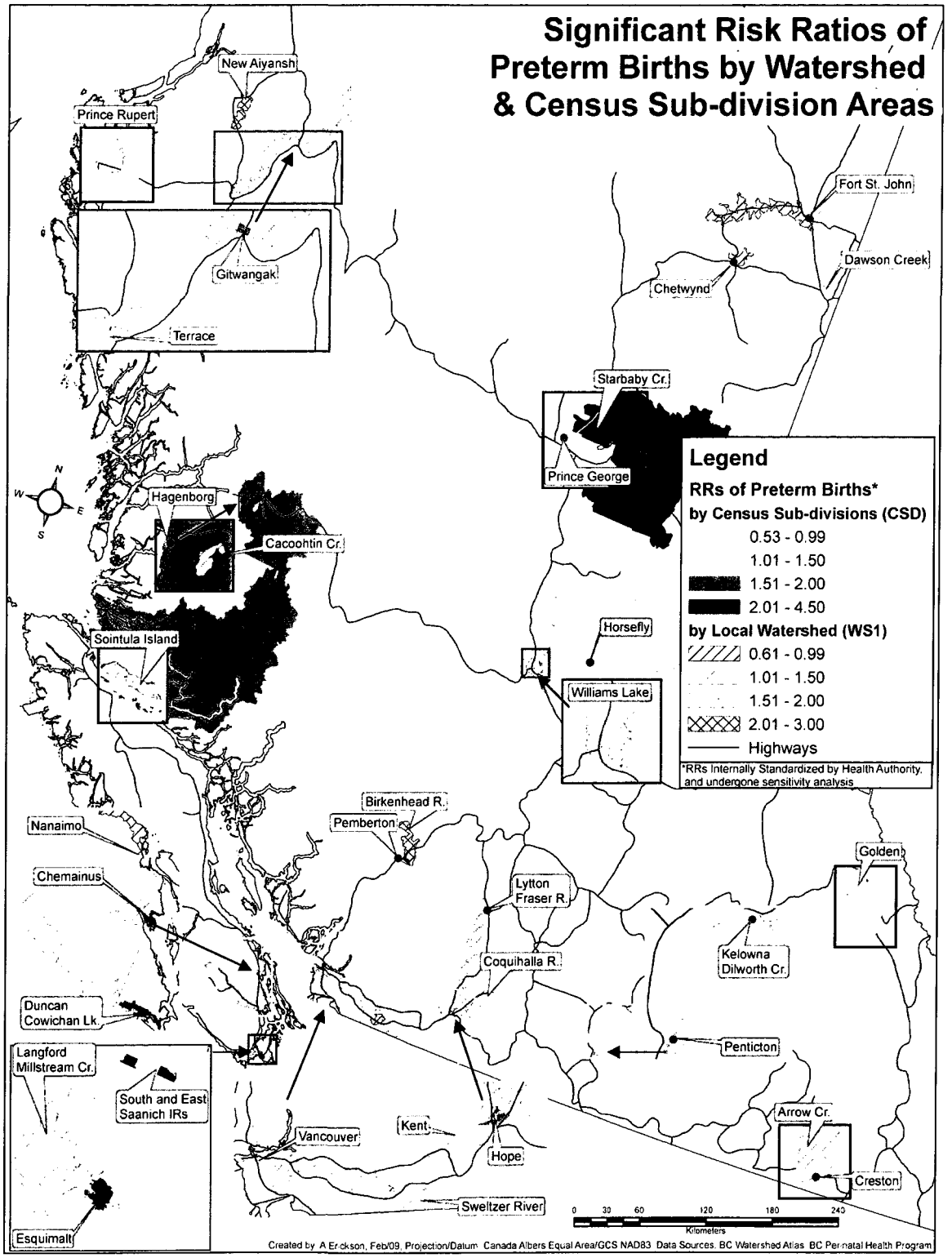
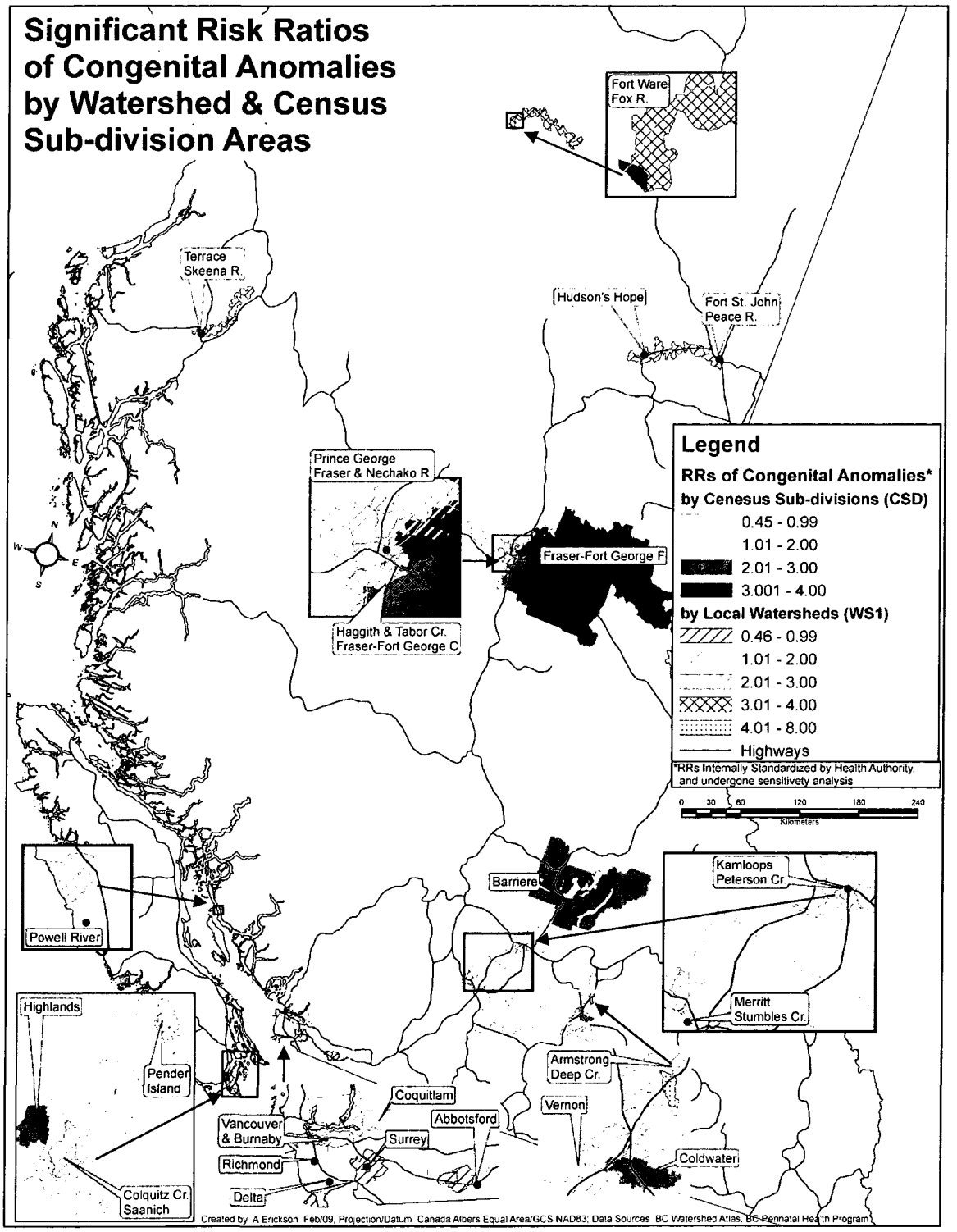


Figure C: Risk Ratio map of Congenital Anomalies in BC, Canada using a local watershed boundary (WS1) and a census subdivision boundary (CSD) for the years 2001-2006.

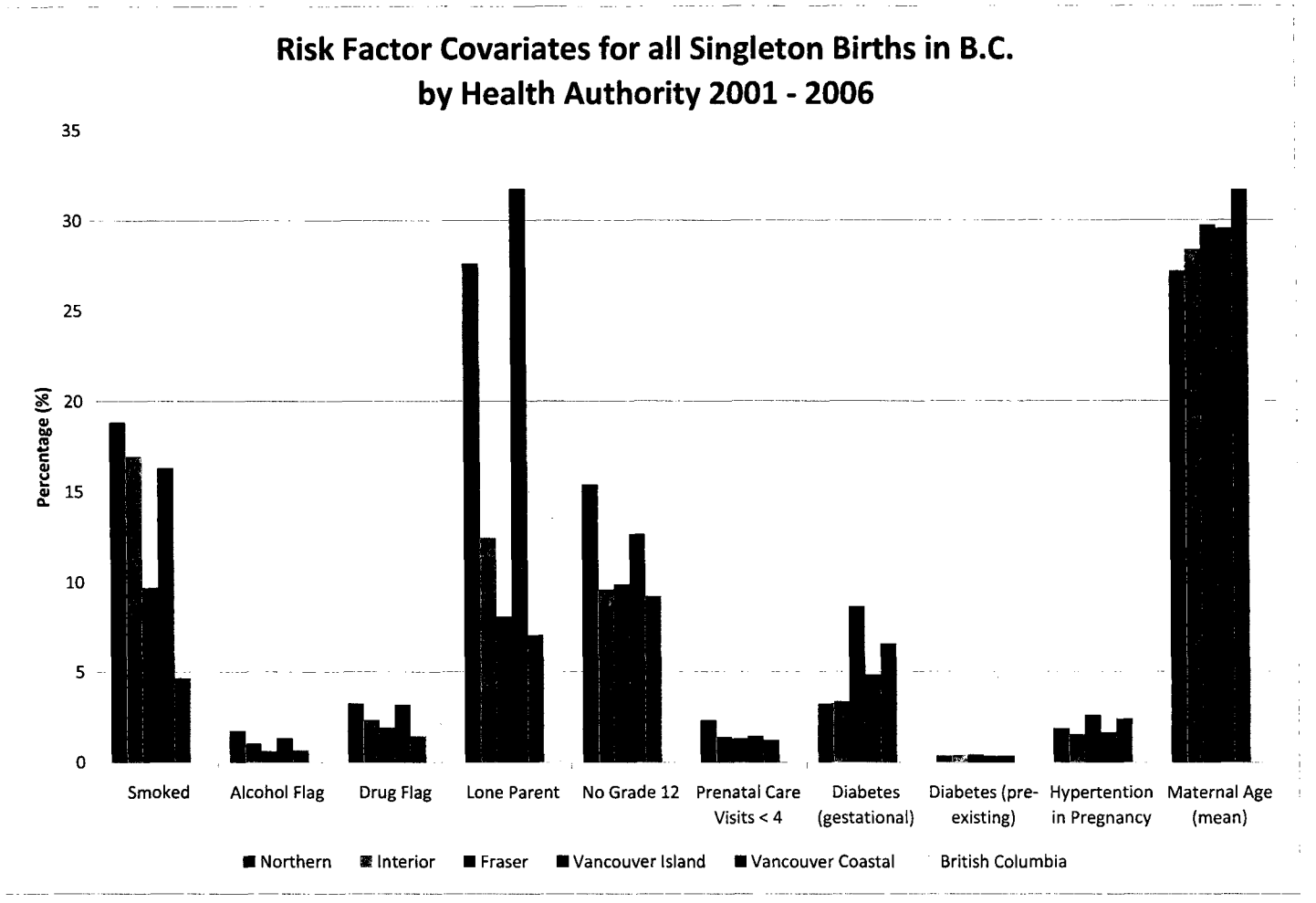


APPENDIX 2

Distribution of Covariate Risk Factors for all

Singleton Births in B.C. by Health Authority 2001-2006

Figure D:


Risk Factor Covariates for all Singleton Births in B.C.
by Health Authority 2001 - 2006
Percentage (%)
35
30
25
20
15
10
5
0
Smoked
Alcohol Flag
Drug Flag
Lone Parent
No Grade 12
Prenatal Care Visits < 4
Diabetes (gestational)
Diabetes (pre-existing)
Hypertention in Pregnancy
Maternal Age (mean)
Northern
Interior
Fraser
Vancouver Island
Vancouver Coastal
British Columbia