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Anna K. Harding

Benzene is a widespread urban pollutant and monitoring results show concentrations are particularly high in Portland, Oregon. Nationally, benzene air pollution is the largest contributor to total cancer risk from air pollutants. We used data from several data sets including: modeled benzene distribution at the census block group level from the Oregon Department of Environmental Quality, ten-year leukemia incidence from the Oregon State Cancer Registry, and demographic data from the U.S. Census to examine the correlation of benzene with acute myeloid leukemia (AML), total myeloid leukemia (TML) and total leukemia subgroups. Modeled benzene values were averaged to census tracts using GIS methods. We performed Poisson regression on data for all census tracts and also aggregated data to quartiles of benzene concentration and modeled exposure to determine incidence rate ratios (IRR). We mapped the distribution of benzene, and age-standardized leukemia rates to examine spatial patterns which may not be evident in statistical analysis.

Our regression results found no significant association between benzene and leukemia at the census tract level. AML IRR was slightly elevated for females at the second, but not the third and fourth quartiles of benzene modeled exposure. We found non-significant elevations in AML IRR for those less than 19 years of age at the second and fourth, but

not the third quartiles of benzene modeled exposure. We did not observe a monotonically increasing trend toward higher incidence of leukemia with higher modeled benzene exposure. Nor did we see a tendency toward a stronger association in the myeloid types of leukemia. Similar modeling results were produced for perchloroethylene, a co-occurring air toxin that is not considered a leukemiagen. Although the general spatial pattern of leukemia incidence does not appear visually similar to the benzene distribution, some census tracts near point source emissions of benzene had AML rates in the highest bracket. There were some census tracts with elevated TML in the under 19 year old age group near major highways.

Our overall result shows no association between benzene and leukemia at the census tract level. Census tract level ambient air pollution data such as ours is homogenous within census tract measurement units. Most census tracts in our study area are between one and seven miles across so variability of ambient exposure within a few hundred yards of major roads was not captured in our air pollution data. This misclassification of exposure, along with misclassification of case residence in time and place limits the utility of an ecologic design such as ours to detect small changes in disease incidence. The magnitude of cancer risk from ambient benzene is very small, so any misclassifications of exposure or case residence may render even large datasets incapable of detecting elevated incidence rates. Future efforts to investigate health effects of ambient benzene or other mobile source pollutants could incorporate road and residence location as well as modeled air pollution data at the census tract level to achieve more definitive results.

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Leukemia Incidence and Benzene Air Pollution in Portland Oregon

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Robert W. Voss

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APPROVED:

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I understand that my thesis will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my thesis to any reader upon request.

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Robert W. Voss, Author

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CONTRIBUTION OF AUTHORS

Voss – Assembled data sets, performed GIS and statistical analysis, and authored the text.

Dr. Harding – Assisted in data acquisition, provided extensive review of drafts of all chapters and assisted with the preparation of the manuscript and thesis.

Dr. Lambert – Assisted with the study design, data acquisition and provided assistance in refining the analysis and presentation of results.

Dr. Morton – Discovered the air pollution data and conceived of the project, performed initial analysis with ZIP code level data sets, assisted with study design, and provided medical review of the methodology.

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My parents, for instilling in me an appreciation for environment and justice.

My sister Anna, for being a big rebel.

Leukemia Incidence and Benzene Air Pollution in Portland Oregon

CHAPTER 1 – INTRODUCTION

Air pollution has contributed to health problems throughout history. The 1990 Clean Air Act (CAA) states in part:

> "…that the growth in the amount and complexity of air pollution brought about by urbanization, industrial development, and the increasing use of motor vehicles, has resulted in mounting dangers to the public health and welfare…" (Clean Air Act Amendments 1990).

While air quality has improved under the CAA, many components of air pollution continue to cause concern on a national or local level. There are 188 toxic substances which the US Environmental Protection Agency (EPA) classifies as hazardous air pollutants or HAPs (EPA 1990). Among these regulated HAPs, benzene causes some of the greatest concern. It is widespread, being emitted by many industrial sources as well as all internal combustion engines, and it is a known carcinogen (ATSDR 1997a, IRIS. 2007). In the 1999 National Air Toxics Assessment (NATA), the EPA estimated cancer risk contributions by county in the United States for 85 components of air pollution (EPA 2006a). Benzene contributed the single largest cancer risk nationwide and in Oregon. Additionally, for cancer risk due to ambient benzene, Oregon ranked third among the 50 states behind New York and California (New Jersey and Washington State rounded out the top five). The three counties comprising metropolitan Portland Oregon (Multnomah, Washington and Clackamas) were ranked in the 6th, 33rd and 42nd respectively out of 3276 counties in the nation for benzene related cancer risk (EPA 2006a).

One of the primary pieces of supporting evidence leading to the designation of benzene as a known carcinogen has been the association of benzene inhalation in occupational settings with leukemia (ATSDR 1997a, Bayliss et al. 1998). Leukemia, an uncontrolled growth of abnormal blood cells, is described according to the type of cell which is affected and the rapidity of disease onset (Steen 1993). Both chronic and acute forms of myeloid (granulocytic, myelogenous) leukemia originate in the bone marrow

and result in uncontrolled proliferation of blood cells primarily involved in the immune system response. Lymphocytic (lymphoid, lymphatic) leukemias are also classified as acute and chronic forms and affect cells of the lymph system. Leukemias are typically identified as one of four types; acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), and chronic lymphocytic leukemia (CLL). The term acute non-lympatic leukemia (ANLL) is sometimes used and refers to a category only slightly different from AML.

The disease most consistently associated with benzene exposure in occupational settings is AML (Goldstein 1988; Hayes et al. 1997; Snider et al. 1993, Bayliss et al. 1998). Studies of workers in the 1970s in tanneries and footwear manufacturing facilities found elevated incidence of all leukemias at airborne concentrations in the 100 ppm range (ATSDR 1997a). Further studies of workers in the petroleum and chemical industries suggested elevated risk ratios at airborne concentrations of approximately 10 ppm (Hayes et al. 1997) and perhaps as low as 0.2 ppm, with an odds ratio of 3.84 (Glass et al. 2005). Although 0.2 ppm is still two orders of magnitude higher than typical (high) ambient concentrations in the United States, ambient concentrations potentially expose a greater number of people for longer durations than do occupational exposures. Glass et al. (2005) also found an odds ratio of 2.89 for cumulative exposure in the range of 2-4 ppm-years. The existence of a safe lower threshold of exposure for benzene has not been definitively established. The EPA Integrated Risk Assessment System’s support document for benzene carcinogenicity explains that there is uncertainty about population variations in the lowest dose which can cause harm (Bayliss et al. 1998). Although these findings do not demonstrate a clear association between leukemia and benzene at typical ambient concentrations, the trend toward positive associations at lower concentrations reinforces concerns about health effects from chronic exposure to ambient benzene pollution.

A recent review of literature concerning air pollution and childhood cancer found that four of fifteen studies supported an association between traffic-related air pollution and cancer (Raaschou-Nielsen and Reynolds 2006). An additional nine studies in this same review had non-significantly elevated risk ratios for leukemia (of studies reviewed and reporting risk ratios for multiple diseases, five of eight reported the leukemia risk ratio as highest) (Raaschou-Nielsen and Reynolds 2006). Though the authors concluded that only four of fifteen reviewed studies strongly supported an association between traffic related air pollution and childhood cancer, an alternate interpretation of this review study might conclude that thirteen of fifteen studies at least suggested a concern of elevated risk of childhood leukemia arising from air pollution. A California study (Reynolds et al. 2003) used EPA modeled hazardous air pollutant (HAP) concentration data at the census tract level to compute aggregate cancer exposure scores for all carcinogenic pollutants. They found modestly elevated but not statistically significant risk ratios for childhood acute non-lymphocytic leukemia (ANLL), linked to point source emissions dominated by benzene and perchloroethylene (PERC). This study used census tract level data but examined the contribution to total cancer risk from combined HAPs as a predictor variable. Because the cancer most consistently associated with occupational benzene exposure is AML, assessing the correlation of AML with benzene, specifically, might be a more advantageous design than examining the correlation of AML incidence and combined HAP concentration.

Assessing the influence of ambient pollution levels on the health of the general population is a difficult task, and is hampered by difficulties in properly assessing actual exposure concentration, time, and place as well as ascertaining information on a sufficient number of cases to conduct a meaningful study. Because monitoring pollution levels is expensive, analytic measurement data are usually sparse in time and place. Often just a few monitoring sites are located in a large city and data are available for only a year or two at a particular site. This decreases the accuracy of direct monitoring data as a proxy exposure assessment in epidemiologic studies. For any population large

enough to be useful in an epidemiological study there may only be one or two air pollution monitoring sites with available data. This means it is not possible to adequately characterize variability of exposure across a city sized population using monitoring data from just a few sites. To circumvent this limitation, investigations have used methods other than monitoring to assess the population level exposure to air pollutants. Traffic density, road density, distance to roads and vehicle ownership density have been used as proxies for ambient benzene exposure in epidemiological studies (Bayer-Oglesby et al. 2006; Carr et al. 2002; Crosignani et al. 2004; Raaschou-Nielsen et al. 2000; Raaschou-Nielsen et al. 2001). One problem with these approaches is they do not account for variations in emissions from sources other than on-road mobile ones. Distance to a source has been used as a proxy for exposure to both industrial mixed pollutant point sources (Walker et al. January 2007 unpublished draft) and to mobile sources (Pearson et al. 2000). These studies found elevated associations with childhood leukemia (Pearson et al. 2000; Walker et al. January 2007 unpublished draft). Studies using this design, however, fail to account for all source classes and also fail to differentiate contributions from relevant pollutants, making it difficult to distinguish which substance contributes most to the risk of disease.

Given the occupational evidence supporting a link between benzene and AML at concentrations in the part-per-million range and the widespread presence of benzene in urban pollution, research is needed to investigate the association of leukemia with ambient benzene levels. A 2004 study of pollution levels at the county level, suggested that the concentration of benzene is high enough to warrant health assessments in Portland using more accurate methods (Tam and Neumann 2004). Existing data sources on benzene ambient concentration and leukemia incidence, both available at the census tract level in Portland Oregon, presented a potentially useful opportunity for investigation. Modeled airborne benzene concentrations and exposure data were reported in the 1999 Portland Air Toxics Assessment (DEQ 2006b). We used this census tract level modeled HAP data as a proxy for personal exposure of incident cases

of leukemia in the same census tracts. This model accounts for vehicular as well as industrial and residential contributions to air pollution and provides a proxy measure of exposure across a broad metropolitan area.

Purpose of Study

To our knowledge, no previous studies have been conducted specifically investigating ambient benzene concentrations and acute myeloid leukemia incidence at the census tract level of analysis. Benzene is a ubiquitous component of air pollution and, among all air pollution constituents, is the largest contributor to total cancer risk (EPA 2006a). Oregon, and Portland in particular, have some of the highest ambient benzene concentrations in the country (EPA 2006a). Knowledge of the carcinogenicity of benzene is derived from studies of occupational exposures but studies of ambient exposures are needed. Existing data sources on disease incidence and air pollution can be used to economically investigate pressing public health concerns. Understanding how these data sources are and are not useful in epidemiological investigations might give researchers potentially valuable insights into how best to design future studies. To achieve the strongest possible design, our study used specific estimates of benzene as opposed to mixed HAPs. We also examined AML as a specific disease outcome, and used exposure and leukemia incidence data at the census tract level. The specific research question asked in this study was whether the incidence of acute myeloid leukemia at the census tract level, during the period 1995-2004 in Portland Oregon varies with ambient airborne benzene. There were additional objectives of this study beyond the main research question. Exploration of the utility and feasibility of using existing data sets from Oregon Department of Environmental Quality and the Oregon State Cancer Registry in epidemiologic research may help future researchers understand these data sources. Finally, using Geographic Information Systems (GIS) technology to organize the data gathered for this study offers an easy method of averaging benzene

measurements to the census tract level, as well as a way of assessing the spatial variability of leukemia and benzene in Portland.

Limitiations

Several limitations were inherent in the design of this study. This research uses an ecologic study design. Because group level data were used as a proxy for individual exposure, the results cannot be used to make inferences about individual disease cases within the study area.

Average exposures at the census tract level were used as a proxy for specific, individual exposure experienced by cases of disease. Cases were assumed to have been exposed to the ambient concentration in the census tract of their residence. Area level concentrations, therefore, may not be representative of individual level exposures for many reasons, including but not limited to: (1) differences in time spent in the home census tract; (2) other areas where significant time is spent; (3) occupational exposure differences: (4) temporal variability in activity patterns; and (5) local variability of benzene concentration.

Environmental exposures to other toxins from either air or other sources may be correlated with benzene exposures. This research assessed only benzene and PERC, so possible correlations with other toxins cannot be quantified or ruled out.

Case migration in or out of a study area will influence accurate assessment of exposure and incidence. Benzene concentrations estimated for 1999 may or may not represent the actual exposures in years relevant for initiation of disease cases.

The study assumed that community HAP concentrations and residence remain stable. Ambient benzene trend in Portland was assessed using monitoring data from

DEQ and residential stability was assessed using U.S. Census data to understand the validity of these assumptions.

While this study was limited to Portland Oregon and might be generalizable to other locations only if they can be demonstrated to be equivalent with respect to all major influencing variables, the method used here could be extended to other locations. Other U.S. cities have high ambient benzene levels and similar methods could be used to assess the presence of elevated leukemia rates in those locations. Given our inconclusive results, any extension of these methods might best be attempted in areas where either better residential history, an assessment of within census tract exposure variability, or larger exposed population is available for analysis.

Definition of Terms

Age Adjusted: Method for weighting local, age specific disease rates by population distribution of another, generally larger population. Removes influence of local population structure from disease rates.

Ambient Air Concentration: Level of a toxic substance present in ambient air

Census: United States decennial census

Census Block Group: Smallest population grouping used by US Census

Census Tract: Population group used by US Census. May contain several Census Block Groups.

Centroid: Geographic center of an irregular land area.

Directly Standardized Disease Rate: Method of weighting age specific disease rates in a study area by the age distribution in a standard population. This removes any disease rate effects which are the result of the unique age distribution of the study area.

Dispersion Modeling: Computer model which uses emission locations, terrain description, and meteorological data to determine the distribution of air pollutants across a region. The PATA used CALPUF algorithm to model dispersion of HAPs. Results are modeled concentration values.

Education- Percent Less than High School: A measure of the SES of a census tract. Computed by US Census as the percent of census tract population over age 25 who have less than high school equivalent education. Variable "education" in present study.

Exposure Levels: Quartiles of census tract level average HAP measures (modeled exposure or ambient concentration). Census tracts and incident cases are grouped by exposure levels to compare disease rates of larger population groups than in census tracts.

Exposure Modeling: Method of modifying ambient concentration data from a dispersion model to estimate "apparent" personal exposure. Uses ambient concentration, estimated activity patterns, commuting patterns, time spent indoors, indoor/outdoor concentration relationships, and microenvironment factors to estimate a range of likely "apparent" exposures for a population. The PATA used HAPEM5 algorithm to calculate modeled exposure. Results are modeled exposure.

Geographic Information System: Computer system for organizing, analyzing, and visualizing information which has a geographic distribution.

Goodness of Fit: Assessment of the appropriateness of a particular regression model (such as linear, Poisson, or negative binomial) to a given set of data. An acceptable GOF suggests it is appropriate to attempt to fit a particular regression model to a given set of data. Data may have an acceptable GOF and a strong, weak or non-existent relationship between independent and dependent variables.

Hazardous Air Pollutant: Designation by USEPA for 188 chemicals which are toxic to humans and may be constituents of air pollution.

Household Income: Measure of SES for a population. In present study, defined as weighted average of total number of persons with various household incomes in a census tract. Variable name "Income".

Incidence Rate: Rate of incidence of new cases of disease. In present study, calculated using ten-year case counts and denominator of 10*Year2000 population in each census tract. Scaled to reportable yearly rate per 100,000 persons.

Incidence Rate Ratio: Ratio of incidence rate at high exposure level (quartile) to reference exposure level (first quartile).

Income: See Household Income

Median Year Moved into Residence: Measure of length of time residents have lived in their current (at time of census) home. A median value for all residents in census tract. In present study, abbreviated as MYMI or sometimes referred to as, "Residential Duration."

Modeled Exposure: See Exposure Modeling.

Monitoring: Directly measuring concentrations of HAPs. Expensive and therefore usually limited assessment of the concentrations of air pollutants

Negative Binomial Regression: Variation of Poisson regression used when data are overdispersed or underdispersed. For a negative binomial distribution, the variance exceeds the mean.

Occupational Setting: Place of employment. Exposures in the occupational setting which can be much higher than ambient exposures but occur only during work hours and for the duration of employment.

Poisson Regression: Regression model used when data follows a Poisson distribution. For a Poisson distribution, the variance is equal to the mean. An appropriate distribution for modeling the frequency of independent events.

Risk Assessment: Numerical estimation of chances of an adverse health event. Calculated using measured or estimated concentration of toxic substance and estimated risk per unit of toxic substance.

Spatial: Considers the geographic relationship between variables or the geographic distribution of variables.

Total Leukemia: The sum of acute and chronic myeloid and acute and chronic lymphatic leukemia cases. Abbreviated TML in the present study.

Total Myeloid Leukemia: The sum of acute myeloid leukemia and chronic myeloid leukemia cases. Abbreviated TML in present study.

Unit Risk: Theoretical risk due to exposure to one unit of a toxic substance. Calculated from animal toxicology studies or epidemiological studies, usually with added safety factors to account for uncertainty regarding the actual effects in humans.

Abbreviations and Acronyms

ALL:	Acute lymphatic leukemia
AML:	Acute myeloid leukemia
AMLb:	Acute myeloid leukemia, both genders. Trailing "m" denotes male. Trailing "f" denotes female.
ANLL:	Acute non-lymphatic leukemia
CALPUFF:	A non-steady state Gaussian puff model for estimating the dispersion of atmospheric pollutants. Uses source, meteorological and topographic data to estimate dispersion over a grid.
CML:	Chronic myeloid leukemia
DEQ:	Oregon Department of Environmental Quality
EPA:	U.S. Environmental Protection Agency
GIS:	Geographic Information System
GOF:	Goodness of Fit
HAP:	Hazardous Air Pollutant
HAPEM5:	EPA Hazardous Air Pollution Exposure Model, version 5. Calculates average long-term inhalation exposures. Uses demographic data, micro-environment data, activity patterns, commuting patterns and air quality data to calculate probable personal exposures to ambient HAPs.
IQR	Inter quartile range. Interval between the 25^{th} and the 75^{th} percentiles of a variable.
IRR:	Incidence Rate Ratio
LASAR:	Laboratory Analytical Storage and Retrieval system (air monitoring data source)
NATA:	National Air Toxics Assessment

NEI:	National Emission Inventory
OSCaR:	Oregon State Cancer Registry
PATA:	Portland Air Toxics Assessment
PERC:	Perchlorethylene (aka. Tetrachloroehtylene)
SES:	Socio-Economic Status
TMLb:	Total myeloid leukemia (AML and CML). Trailing “m” denotes male. Trailing “f” denotes female.
TOLb:	Total leukemia (AML, CML, ALL, and CLL). Trailing “m” denotes male. Trailing “f” denotes female.
UTM:	Universal Transverse Mercator (a coordinate system for designating physical location)

CHAPTER 2 - LITERATURE REVIEW

Leukemia Disease Description

Hematopoietic malignancies are cancers that affect the blood forming tissues (Gunz and Henderson 1983; Steen 1993). They include lymphomas, myelomas and both chronic and acute leukemias. Lymphomas and myelomas form solid tumors early in the disease process while leukemias remain essentially liquid, affecting a great number of circulating blood cells. Leukemias may form solid tumors late in the disease process. An uncontrolled growth of abnormal blood cells, leukemias are named according to the type of cell which is affected and the rapidity of disease onset. Myeloid (granulocytic, myelogenous) leukemias, both chronic and acute forms, originate in the bone marrow and result from uncontrolled proliferation of blood cells primarily involved in the immune system response. Lymphocytic (lymphoid, lymphatic) leukemias are also broken into acute and chronic types and affect cells of the lymph system. Leukemias are typically classified into four major types: acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), and chronic lymphocytic leukemia. These diseases have different epidemiologic profiles and etiologies. All have been studied in relation to benzene exposure with varying results and consistency. Some studies use the term acute non-lymphocytic leukemia (ANLL) which is similar to AML, although slightly broader in scope.

Leukemia is a fatal disease if left untreated. Successful treatments exist, however, so it is important to include incidence as well as mortality data in any study investigating the disease. Comparing national data from 2003 for both mortality and incidence, mortality from AML is 70-80% of incidence while mortality from all leukemias is roughly 60% of the magnitude of incidence (USDHHS 2006). Oregon data for 2003 shows mortality is roughly 80% of incidence (Riddell and Pliska 2006). National and Oregon leukemia incidence rates by gender and race are presented in

Table 1. Nationally and in Oregon, rates of combined and acute myeloid leukemias are higher for males than for females. For AML, rates are comparable between genders until around age 50, at which time incidence increases for males (Morgan and Alvares 2005). AML incidence is low for those under 10 years old and increases among both genders after age 40 (Steen 1993). Leukemia rates are highest among the white racial group and lowest among Asian/Pacific Islander group for all leukemias, as well as for ALL and AML separately, with rates for African American and Hispanic groups falling between these values (USDHHS 2006). Computation of separate rates for racial groups in Oregon is difficult as Oregon's population is predominantly white and has low proportions of other races (Riddell and Pliska 2006). The incidence of AML is low up to age 10, moderate from age 20 to 40 and increases sharply after this, becoming the second most prevalent type of leukemia above age 60. Leukemia incidence peaks at age 70. The highest incidence of other types of leukemias is at different ages; five years of age for ALL, above 50 years of age for CLL, and about 60 years of age for CML (Steen 1993).

Benzene Toxicity

Once benzene enters the body, it is metabolized in the liver and bone marrow. These metabolites are believed to be responsible for benzene's toxicity (ATSDR 1997a). Metabolites may have different actions that damage marrow and contribute to "preleukemic" conditions such as aplastic anemia and myelodysplastic syndrome (Snyder and Hedli 1996). It is possible that the genesis of the disease could be with a single metabolite acting on a single cell type (Goldstein 1985).

In order for the disease to progress, a malformed cell must be able to survive and copy itself, creating other similarly malformed cells. The survival of a malignant cell depends on its not being destroyed by the immune system, so an under-functioning immune system may contribute to the survival and proliferation of malignant cells in

the early stages of leukemia. Benzene causes bone marrow suppression which leads to decreased immune system functionality. A dose-response relationship for this effect has been found in animal studies (Goldstein 1988). Because aplastic anemia can result from bone marrow damage and be a risk factor for AML, this is a mechanism by which benzene might influence leukemia occurrence (Goldstein 1988; Snyder and Hedli 1996). Leukemia can begin from a single malformed cell if it is allowed to reproduce in sufficient numbers (Gunz and Henderson 1983). It has also been noted that AML has never been known to result from a single chromosome damaging exposure and thus it is supposed that the development of AML is a multi-step process (Bird et al. 2005). Studies of benzene poisoning cases suggest that chromosomal damaged cells develop after a period of dysplasia, or cell disfigurement (Bird et al. 2005).

Benzene may be capable of providing two of the requirements for leukemiogenisis: initial stem cell mutation and reduced immune system capacity to recognize and eliminate the mutated cell before it reproduces. The environment of the bone marrow during the development of the disease process is also characterized by a general reduction of properly functioning stem cells. Any small dose theoretically could initiate a mutation and start the disease process, so the existence of a threshold below which exposures are safe is not certain (Goldstein 1985). The EPA Integrated Risk Assessment System's support document for benzene carcinogenicity explains that there is uncertainty about population variations in the lowest dose which can cause harm (Bayliss et al. 1998).

Latency Period

Leukemias are thought to develop only after some period of time, the lag-time or latency period, has elapsed after exposure to an agent such as benzene (Snyder and Hedli 1996). Following the atomic bomb blasts in World War II the incidence of leukemia peaked in 5-7 years (Steen 1993). Among malignant diseases which rose in

incidence after exposure to ionizing radiation during World War II, the peak in leukemia incidence was highest, suggesting that the hemopoitic cells are easily injured by radiation (Steen 1993). It is interesting to consider whether this same sensitivity exists for exposures to chemical agents such as benzene. Chemotherapy for cancer treatment can induce AML (t-AML) and the incidence of this disease falls off after 8-10 years (Bird et al. 2005). The cause of this lag-time and the biological actions during this time are not well understood for leukemia.

For AML, the disease most often associated with purported benzene exposure, studies have suggested a latency period of less than ten years and perhaps as little as four months (Hayes et al. 1997; Morgan and Alvares 2005). Non-Hodgskin's lymphoma (NHL) has been found to be more strongly associated with exposures greater than ten years in the past (Hayes et al. 1997). Some studies have found leukemia risk more associated with recent exposures (Bird et al. 2005; Hayes et al. 1997).

In addition to the dose response influence of benzene on disease incidence, there can be a dose response influence on the latency period of a disease. At occupational exposure levels to benzene, no dose response influence on the latency period for AML has been found (ATSDR 1997a). This suggests that latency periods typical in occupationally exposed groups (one to ten years as referenced previously) may also be applicable to community exposures at ambient concentrations.

Epidemiological Studies of Benzene Inhalation and Disease

An association between elevated benzene concentrations in air and AML has been noted in case reports for more than 70 years (Goldstein 1988). In the 1970s researchers began to find associations among occupationally exposed groups. Early industrial studies and findings included elevated crude leukemia incidence in Turkish tannery workers (Alskoy 1974) and elevated acute leukemia in Italy among shoe

workers (Vigliani et al. 1976). Airborne concentration levels of benzene were in the 10^2ppm range for these studies.

Reviews of benzene toxicity throughout the 1980s and early 1990s, continued to find associations with leukemias in cohorts occupationally exposed in the petrochemical and rubber industries (ATSDR 1997a; Rinsky et al. 1987). Notably, mortality due to leukemia was found to be proportional to duration of exposure for AML (Yin 1987, 1989) with no difference in mortality between genders (Li 1994). Studies of another occupational cohort in the 1980s indicated a dose-response relationship existed for concentrations between 40 and 400 ppm but no evidence of a dose response effect on the latency period was seen (Infante 1977, 1978; Rinsky 1981, 1987). In a large cohort study of benzene exposed workers in China, concentrations of 10ppm were associated with elevated risk ratios (RR) for ANLL (Hayes et al. 1997). This study noted a trend toward increased rates with higher concentrations. Studies often focus on occupational groups in industries such as chemical and petroleum manufacturing or leather or shoe production. Employment records have often been used in constructing exposure proxies in these studies (Glass et al. 2005; Hayes et al. 1997).

Reynolds et al. (2003) investigated benzene exposure but did not use an occupational cohort examined ambient HAPs and leukemias. This study examined childhood cancers and leukemias in relation to an aggregate of 25 ambient HAPs in California, including benzene, finding elevated RR for leukemia and ALL and a non-significantly elevated RR for AML (Reynolds et al. 2003). This study directly examines the health effects of HAPs at ambient concentrations which are in the range of a few micrograms per cubic meter or < 5 ppb. This study cites the importance of studying childhood cancers as the latency periods are necessarily short.

Walker et al. (unpublished) investigated spatial associations between leukemia and ambient concentrations of benzene and butadiene and found correlations between

proximity to benzene emission source and childhood ALL (Walker et al. 2007). The same study also found correlations between butadiene (but not benzene) concentration and ALL, AML and all leukemias in children. Problems with the study's design include poorly differentiated benzene and proximity groupings, a lack of meteorology or other dispersion modeling, use of self-reported toxic release inventory data to assess exposure and very sparse case numbers in upper exposure groups. These problems may limit the usefulness of the findings, but the study does suggest a need to undertake additional, carefully designed investigations using appropriate data sources and techniques to investigate ambient HAP concentrations and community health.

Although evidence has begun to show that benzene's carcinogenicity may extend to exposures at lower levels than previously thought (Glass et al. 2003), many recent studies are still limited to occupational groups so concentrations exceed ambient community levels, even for those living in high pollution locations (Bloemen 2004; Collins et al. 2003; Glass et al. 2005; Lan et al. 2004; Wong et al. 1999). There is disagreement and discussion about many aspects of a benzene-leukemia association including: (1) the accuracy of exposure characterization in previous studies; (2) how to extrapolate risk to low exposure groups; (3) the existence of a threshold below which no risk exists; and (4) determining which subtypes of leukemia or lymphomas are associated with benzene (Glass et al. 2003, Bayliss et al. 1998).

Airborne benzene concentrations associated with leukemia incidence have progressively decreased over the history of research on this topic. In the 1970's studies were of workers toiling in environments where concentrations were at the 10^2 ppm level (ATSDR 1997a). A 1987 study found elevated mortality at between 40 and 200 ppm with a strong dose response between benzene and leukemia. (Rinsky et al. 1987). In 1997 a study of over 100,000 employees in China found a risk ratio of 2.2 for exposures less than 10 ppm and 7.1 for exposures above 25 ppm (Hayes et al. 1997). An occupational study in 2005 found an odds ratio (OR) of 3.84 for all lympho-

hematopoietic cancers at a highest exposed job of 0.1-0.2 ppm and an OR of 7.79 for a cumulative exposure above 16 ppm-years (Glass et al. 2005). Glass et al. (2005) also found cumulative exposure of 2-4 ppm-years to have an OR of 2.89, though confidence intervals included unity (0.97- 8.52). Lower concentrations are being associated with leukemia in epidemiologic studies and cumulative exposures are appearing important. It is plausible that the limiting factor in finding the smallest benzene concentration that is associated with leukemia has been study design issues rather than a true threshold for disease causation.

While AML is most often associated with benzene exposure, other diseases have been investigated, with mixed results. Recent reviews and studies have reported tentative associations between benzene and CLL, with higher exposures or better exposure assessment being suggested as possible factors enhancing association (Bird et al. 2005; Glass et al. 2003; Schnatter et al. 2005).

An association between benzene and (ALL) was not able to be ruled out in the early 1990s (Snyder et al. 1993). Typically a disease of children and young adults, ALL was found to be correlated with combined HAPs in one study investigating childhood disease incidence in California (Reynolds et al. 2003). Even more recently, results have been characterized as still unclear, regarding this type of leukemia (Bird et al. 2005).

CML is the least common of the four main types of leukemia and its incidence is strongest in the elderly (Steen 1993). A recent review found CML morbidity and mortality to be “convincingly associated” with benzene (Mehlman 2006a). Other research found that a relationship between CML and benzene was possible, though not as clear as the AML relationshiop (Bird et al. 2005). Another review concluded the rarity of CML combined with the paucity of studies examining this disease specifically make clear conclusions regarding this leukemia type difficult (Schnatter et al. 2005).

Both multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL) may result, in part due to chronic stimulation of the immune system (Steen 1993). This, being one action of benzene on the body, may be a pathway through which benzene influences these diseases (ATSDR 1997a). Two studies have found no association between MM and benzene (Bezabeh et al. 1996; Glass et al. 2005), while three others have concluded that an association cannot be ruled out (Infante 2006; Snyder et al. 1993; Mehlman 2006b). Non-Hodgkin's lymphoma is a broad category of diseases consisting of many subtypes, and often classified according to the specific cell type which is affected (Steen 1993). If different cell types have different causes, it is possible that the practice of grouping all NHL cases together may have obscured associations with specific exposures in past epidemiological studies. Again, some studies have suggested a possible association between benzene and NHL, (Snyder et al. 1993) while others find no association (Glass et al. 2005; Rinsky 1981).

Benzene is known to have other, non-cancer effects on bone marrow and the immune system. Bone marrow depression is five times more common after benzene poisoning than leukemia (Gunz and Henderson 1983). Additionally, benzene acts to destroy bone marrow precursor cells possibly leading to aplastic anemia which may enhance risk of AML, regardless of cause (Goldstein 1988). Ideally, these outcomes would be included in population studies of the health effects of HAP concentrations in the ambient air. This is not always possible as cancer incidence statistics are usually compiled by state registries which have no access to other health data. Obtaining data on other disease incidence might be possible in case-control or cohort study designs investigating benzene exposure.

Some studies conclude that there is a high exposure threshold for influencing development of leukemia, including one study suggesting that risk occurs only at concentration levels above 100 ppm (Collins et al. 2003). This study examined a cohort of 4352 chemical plant workers and used mortality as their outcome variable. A case-

control study of refinery workers found no association between benzene exposure and mortality from AML or total leukemia (Wong et al. 1999). A cohort study of 594 chemical plant workers in Michigan found no mortalities attributable to benzene exposure (Ott et al. 1978).

Infante (2006) has criticized industrial groups for withholding from publication or regulatory review study results which have implicated benzene at low levels as a health threat, questioning the impartiality of a planned study funded and conducted by the American Petroleum Institute. The institute publicized the proposed study with the expected result that no effect will be found for levels of benzene typical of the general population.

Risk Estimates

AML is the only disease to be consistently associated with benzene (ATSDR 1997a; Bird et al. 2005; Schnatter et al. 2005). Alhough most studies have taken place in occupationally exposed populations and at airborne concentrations above 10 ppm, it has been suggested that benzene exposures at levels less than 1 ppm or cumulative exposures on the order of a few ppm-years may be associated with elevated odds ratios for leukemias (Glass et al. 2005). There is debate about the specifics of the leukemia disease process, the existence of a threshold dose below which no leukemia risk occurs or at what level that dose might be (Bayliss et al. 1998, Glass et al. 2005; Snyder et al. 1993). Given this uncertainty, regulatory agencies have adopted unit risk values several orders of magnitude less than the lowest levels implicated in occupational studies to date.

Using epidemiological studies and risk assessment methodology, the U.S. Environmental Protection Agency (EPA) determined exposure amounts it considers to be correlated with various excess cancer risks in populations. Called Unit risk estimates,

these estimates incorporate margins of safety to account for unknowns in the degree of similarity between animal and human responses to toxins as well as unknowns in the linearity of response between high and low exposures. Unit risks make assumptions about uniform lifespan (usually 70 years), weight and activity patterns, so they may not represent accurate assessments of sensitive populations. The EPA considers the potency of benzene as 0.04 ppb for a 10^{-6}, upper bound lifetime excess cancer risk (ATSDR 1997a, IRIS 2007). The Oregon DEQ, on the recommendation of the Oregon Air Toxics Scientific Advisory Committee, has adopted an ambient benchmark concentration of 0.13ug/m3, based on this EPA potency estimate (ATSAC 2006). This equates to a unit risk estimate of 7.69 $(ug/m^3)^{-1}$.These unit risk values are used to estimate the total excess cancer risk due to ambient concentrations of benzene or other HAPs (Davis and Klein 1996; Morris 1990).

Estimates of population risk can be calculated from the yearly fraction of individual risk, population size and duration of observation:

$$\text{Population Risk} = IR*(1/70)*P*D \qquad \text{Formula 2,}$$

where P is the size of the population group and D is the number of years of observation. Using Formula 2 to calculate a population risk assumes homogeneity of exposure over the population and even distribution of risk over a person's lifetime. Given these assumptions, any derivation of population risk is a crude estimate, but it can serve to give context to the magnitude of the effect which might be expected. This assumes there is a mechanistic link between exposure to a toxic substance and a disease outcome and that such a link is correctly estimated by the potency value on which the UR is based.

Few studies have been done investigating health effects from exposures of a few ppb, in spite of the large numbers of communities in the United States and around the world which have ambient benzene levels in this range.

Ambient Air Toxics

The EPA classifies certain airborne substances that are toxic to human health as hazardous air pollutants, or HAPs, for regulatory purposes (Godish 2004). While the concentrations of toxics in ambient air are generally less than in many occupational settings, they can still be significant. Cigarette smoking is the greatest non-occupational benzene exposure, but one urban study in Italy found ambient concentrations posed the second greatest risk to the general population (Carletti and Romano 2002). In the United States, the EPA regulates 188 HAPs, of which benzene causes the greatest cancer risk (Hope 2006). Sources for ambient benzene vary in importance by location. In Portland, mobile sources contribute the greatest percentage of benzene to the air, followed by area sources such as wood-burning stoves. (DEQ 2006)

The United States Clean Air Act (CAA) of 1970 mandated that the EPA study the human health effects of HAPs. Amendments to the CAA in 1987 required regulations to be based on human health data, rather than technical limitations, but in 1990 the EPA enacted interim guidelines for control of HAPs which were based on Maximum Achievable Control Technology (MACT). The MACT approach was intended to be a temporary strategy which implemented immediate reductions, but postponed final assessments which would ultimately be based on human health data. Currently EPA is conducting risk based analysis of individual emission sources of HAPs to determine the remaining human health risks and need for additional control measures (EPA 2007a). Epidemiological studies of the effects of ambient concentrations of HAPs would be useful in evaluating the EPA's risk analysis.

As previously discussed, EPA considers the potency of benzene as 0.04 ppb for a risk of one excess cancer case per 10^6 population for a 70 year average lifetime. Oregon's Air Toxics Scientific Advisory Committee (ATSAC) adopted the EPA value

in setting non-enforceable benchmark concentration of 0.13 ug/m^3 for ambient benzene in air (ATSAC 2006). The EPA unit risk value is accepted by the agency for use in calculating risk from exposures up to 100 ug/m^3 or 31 ppb (ATSDR 1997a). Because ambient levels are typically less than 5 ppb, the unit risk value is appropriate for calculating risk at exposures typical of ambient pollution levels. It is not appropriate for assessing risks in occupational settings where exposures are much higher. In particular, ambient benzene concentrations in Portland are below 10 ug/m^3, and therefore fall in the range in which EPA considers its potency value to accurately represent risk.

Assessment and Characterization of Hazardous Air Pollutants

There is limited ongoing monitoring of HAPs in Portland carried out by the Oregon Department of Environmental Quality (DEQ). This monitoring takes place at various sites in Portland and in other Northwest cities. Sites are usually sampled weekly and results are available as yearly averages for each site. Some sites have multi-year data. Direct monitoring is expensive to carry out and therefore limited in scope. Agencies such as DEQ or EPA instead rely on more extensive inventory and modeling strategies to produce detailed, broad area characterizations of HAP distribution. Monitoring serves to verify the model outcomes, which have a much more detailed resolution.

The National Emissions Inventory (NEI) is an air pollutant inventory program coordinated by EPA (EPA 2007). The program sets standards for data collection to guide states in achieving collection strategies which are as rigorous as possible and include quality assurance and quality control processes. While differences in collection methods used by different states make it difficult to make numerical comparisons of HAPs between states, the data have been reviewed and scrutinized for major methodological shortcomings. Because of the standardization in collection of data, NEI values represent a reliable assessment of HAP levels in the United States. It is an

improvement over self-reported Toxic Release Inventory (TRI) data which may be overestimated by some reporting entities and has limited quality control or oversight (B. Hope, personal communication, January 24, 2007).

In the Portland Air Toxics Assessment (PATA) the ODEQ has taken NEI data and used it as the inputs for extensive dispersion and exposure modeling, incorporating meteorological, geophysical and demographic data to model census tract concentration and exposure levels in the Portland metropolitan area (DEQ 2006). The PATA air toxics data reports concentrations for 12 air toxics which are present at concentrations high enough to be of local concern.

The PATA methodology combined data from the United States Environmental Protection Agencies' (EPA) 1999 National Emissions Inventory (NEI) and from DEQ-calculated inventories for the Portland Oregon metropolitan area. These inventories collected area, point and both non-road and on-road mobile sources. This inventory information then became inputs for dispersion modeling of distribution using the CALPUFF model. Major arterial and traffic analysis zone information was included in the modeling to accurately characterize mobile sources. Aircraft, marine and rail sources were allocated to their areas of operations. Dry cleaning businesses, an important point source for PERC were positioned according to their address of record in Oregon's waste reporting database. The PATA methodology assigned area source emissions, such as residential woodstoves, proportionally with population density distribution (DEQ 2006).

PATA Data Appropriateness for Epidemiologic Research

The PATA data is appropriate for a study of this type for several reasons: accurate and vetted inventory estimates are used, meteorological and geographic information on dispersion drivers is incorporated and it applies to a large exposed

population (~1.5 million), considerably more than most occupational cohorts. Concentrations range over an order of magnitude among the census tracts covered in the study, hopefully providing a statistically meaningful case occurrence over varied concentration levels.

There are limitations which must be accepted when pursuing any ecological study. Obtaining the best possible exposure information minimizes one inherent limitation of the ecologic design. Since actual personal exposure sampling is difficult and expensive, and must be carried out for years, studies of all types have historically relied on simplifying assumptions or other methods to quantify proxies of exposure. Industrial studies have reconstructed exposure histories from industrial hygiene and employment records (Glass et al. 2005; Hayes et al. 1997). Assessments of this type are specific in that occupational histories may be detailed for each participant, but exposure records have uncertainty and supposed average exposures may not apply to all workers uniformly.

Ambient Hazardous Air Pollutants in Portland

Benzene concentrations in the Portland area are high, compared to other cities nationally (EPA 2006a, b; Milstein 2006) (see Table 2). Factors contributing to these high levels include a growing population, frequent air stagnation, wood heating, and the high naturally occurring benzene levels in Alaskan crude oil (a primary source for fuels used in the Northwest region). Additionally, the EPA allowable levels for benzene have been higher in the Northwest than in other areas of the country. A rule change announced in February 2007 will reduce the allowable amount to a level similar to other areas of the country (EPA 2007b; Milstein 2007). The levels in the three counties which comprise the Portland metropolitan area are the highest in the state by a wide margin, averaging 2-3.3 ug/m^3 (EPA 2006a; Hope 2006). There is additional variability within counties and this is characterized at the census tract level in PATA. The range of

benzene levels in Portland census tracts covered by PATA is between 0.6 and 8.0 ug/m^3, so it offers an order of magnitude variation for the study of an association of ambient benzene with leukemia incidence.

Trends in Study Design

A report on benzene toxicity from the U.S. Agency for Toxic Substances and Disease Registry (ATSDR) reviews weaknesses in past studies of the health effects of benzene (ATSDR 1997a). These include poor sampling techniques, uncertain exposure determination, and doubt about the veracity of applying workplace exposure estimates to individual workers (ATSDR 1997a). Research investigating diseases possibly arising from environmental exposures should strive to obtain the best data inputs available and consider data quality carefully when making conclusions.

There are additional considerations when studying the association between benzene and leukemia. Not all leukemia types have shown the same association with benzene in past studies, yet studies often examine only all types, grouped together or do not examine AML separately. A review of epidemiologic studies of air pollution and childhood cancer lists fifteen studies, only one of which reports AML as an outcome (Raaschou-Nielsen and Reynolds 2006). However, given that leukemia types are differently influenced by benzene, grouping leukemias in this way may have limited the ability of past studies to detect a benzene AML association (Glass et al. 2003; Schnatter et al. 2005). Obtaining data that distinguishes the major types of leukemia is one factor that strengthens a study (Schnatter et al. 2005). It has even been suggested that distinguishing between specific cell types may be advantageous (Bird et al. 2005). For example, erythroleukemia, a specific cell subtype of AML, is rare but often reported in a benzene exposed workforce (Goldstein 1988). Patients undergoing radiation treatment for cancers may develop AML secondarily and these cases should be removed from studies investigating associations with environmental exposures (Bird et al. 2005;

Morgan and Alvares 2005). Accurate exposure assessment is crucial to building in validity to a study (Schnatter et al. 2005). Since ecological studies use area concentrations as a proxy for individual exposures, having a large range of concentrations in groups being compared is likely to improve upon studies that have relatively homogenous exposures. Reynolds et al. (2003) notes that children's diseases have shorter latency periods as well as possibly different etiologies, so retaining the ability to study children separately is important (Reynolds et al. 2003). Finally, leukemia has a case fatality rate between 60% and 80% so studies of mortality may underestimate cases in a population and therefore underestimate odds ratios or other measures of association.

Assessing the influence of ambient pollution levels on the health of the general population is a difficult task, and is hampered by difficulties in properly assessing actual exposure concentration, time, and place as well as ascertaining information on a sufficient number of cases to conduct a meaningful study. Because monitoring pollution levels is expensive, analytic measurement data are usually sparse in time and place, often just a few sites in a large city. This decreases the accuracy of direct monitoring data as a proxy exposure assessment for any population large enough to be useful in an epidemiological study. To get around this problem, investigations have used methods other than monitoring to assess the population level exposure to air pollutants. Traffic density, road density, distance to roads and vehicle ownership density have been used as proxies for ambient benzene exposure (Bayer-Oglesby et al. 2006; Carr et al. 2002; Crosignani et al. 2004; Raaschou-Nielsen et al. 2000; Raaschou-Nielsen et al. 2001). One problem with approaches such as these is they do not account for variations in emissions from sources other than on-road mobile ones. Using distance to a source as a proxy for exposure has been applied to both industrial mixed pollutant point sources (Walker et al. January 2007 unpublished draft) and to mobile sources (Pearson et al. 2000) finding elevated associations with childhood leukemia. Studies of this design fail to account for all source classes and also fail to differentiate contributions from relevant

pollutants, making it difficult to distinguish which substance contributes most to the risk of disease.

A recent review of literature concerning air pollution and childhood cancer found a minority of studies (4 of 15) supported an association between traffic related air pollution and cancer, though an additional nine had non-significantly elevated risk ratios for leukemia (of studies reviewed and reporting risk ratios for multiple diseases, five of eight reported the leukemia risk ratio as highest) (Raaschou-Nielsen and Reynolds 2006). An alternate interpretation of the results of this study might conclude that 13 of 15 studies at least suggested a concern of elevated risk of childhood leukemia arising from air pollution. A California study (Reynolds et al. 2003) used EPA modeled hazardous air pollutant (HAP) concentration data at the census tract level to compute aggregate cancer exposure scores for all carcinogenic pollutants. They found modestly elevated but not statistically significant risk ratios for childhood ANLL, linked to point source emissions dominated by benzene and perchloroehtylene (PERC). This study used census tract level data but examined the total cancer risk contribution from combined HAPs as a predictor variable.

Table 1. Leukemia Rates for Oregon and United States.

Incidence Rates of Leukemias by Race/Ethnicity for U.S. and Oregon

Type	All Races		White		African American		Asian/Pacific Islander		Hispanic	
	M	F	M	F	M	F	M	F	M	F
U.S. *										
All Leukemias	14.9	9.1	15.1	9.2	11.0	6.9	8.2	5.5	10.9	8.0
Acute Lymhpocytic	1.6	1.2	1.7	1.3	0.9	0.6	1.6	1.2	2.2	1.8
Acute Myeloid	4.4	3.0	4.5	3.1	3.4	2.6	3.1	2.4	3.5	2.9
Oregon										
All Leukemias	11.6* 14.1**	7.3* 9.1**	11.1*	7.1*	x	x	x	x	x	x

*- (USDHHS 2006)

**- 5- year rate ending 2003. (C Riddell and J Pliska 2006)

x- Rates not available. Not calculated when case counts in a category are <16.

Table 2. EPA Benzene Monitoring for Select US Cities

	Monitoring Years 1999-2000				Monitoring Years 2006-2007				
		Average of Site Yearly Means **				Average of Site Yearly Means **			
City	Count *	ppbC +	PpbV	ug/m3	Count *	ppbC +	ppbV	ug/m3	% change from 1999/2000 to 2006/2007
Boston	4	1.75	0.29	0.93	3	1.95	0.33	1.04	11.8
New York	9	2.15	0.36	1.15	13	2.29	0.38	1.22	6.3
Beaverton, OR	2	2.52	0.42	1.34	1	1.65	0.28	0.88	-34.5
Brattleboro, VT	4	2.57	0.43	1.37	~	~	~	~	
Minneapolis	6	2.78	0.46	1.48	16	1.44	0.24	0.76	-48.4
Chicago	3	3.17	0.53	1.69	3	1.00	0.17	0.53	-68.3
Washington	2	3.25	0.54	1.73	3	1.69	0.28	0.90	-48.2
Philadelphia	6	3.48	0.58	1.86	7	2.27	0.38	1.21	-34.9
San Francisco	2	3.50	0.58	1.87	2	2.17	0.36	1.16	-38.0
Baltimore	8	3.73	0.62	1.99	2	2.40	0.40	1.28	-35.7
Austin, TX	3	3.76	0.63	2.00	7	2.18	0.36	1.16	-42.1
Bakersfield, CA	4	4.01	0.67	2.13	4	2.56	0.43	1.37	-36.0
Seattle	2	4.09	0.68	2.18	2	2.41	0.40	1.28	-41.2
Portland	10	4.20	0.70	2.24	5	3.34	0.56	1.78	-20.5
San Jose, CA	2	4.27	0.71	2.27	2	3.01	0.50	1.60	-29.4
Cincinnati	4	4.37	0.73	2.33	~	~	~	~	
Houston	9	4.66	0.78	2.48	7	3.77	0.63	2.01	-19.2
Detroit	2	4.87	0.81	2.59	~	~	~	~	
Long Beach, CA	2	6.03	1.01	3.21	2	3.96	0.66	2.11	-34.4
Los Angeles	2	7.53	1.25	4.01	2	2.84	0.47	1.51	-62.3
West Valley, UT	6	7.63	1.27	4.06	~	~	~	~	
Burbank	3	8.19	1.37	4.36	3	4.88	0.81	2.60	-40.4
Cleveland	~	~	~	~	4	2.98	0.50	1.59	
Eugene, OR	~	~	~	~	1	1.94	0.32	1.03	
La Grande, OR	~	~	~	~	2	1.37	0.23	0.73	
Vancouver	~	~	~	~	1	2.46	0.41	1.31	

*Number of monitoring sites. May be two observations at same site. ** Average of site annual means for city.
+ ppbC = parts per billion carbon = 6 * ppbV ppbV = 0.313 * ug/m3

CHAPTER 3 – MANUSCRIPT

Leukemia Incidence and Benzene Air Pollution in Portland Oregon

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Introduction

The US Environmental Protection Agency (EPA) currently classifies 188 toxic substances as hazardous air pollutants or HAPs (EPA 1990) Among these regulated HAPs, benzene causes some of the greatest concern. It is widespread, being emitted by many industrial sources as well as all internal combustion engines and it is a known carcinogen (ATSDR 1997a, IRIS 2007). In the 1999 National Air Toxics Assessment (NATA), the EPA estimated cancer risk contributions by county in the United States for 85 components of air pollution (EPA 2006a). Benzene contributed the single largest cancer risk nationwide and in Oregon. Additionally, for cancer risk due to ambient benzene, Oregon ranked third among the 50 states behind New York and California (New Jersey and Washington State rounded out the top five). The three counties comprising metropolitan Portland Oregon (Multnomah, Washington and Clackamas) were ranked in the 6th, 33rd and 42nd respectively out of 3276 counties in the nation for benzene related cancer risk (EPA 2006a).

Benzene, a known carcinogen, has been associated with leukemia in occupational settings (ATSDR 1997a, IRIS 2007). Leukemia is typically categorized into four types, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), and chronic lymphocytic leukemia (CLL) (Steen 1993). The disease most consistently associated with benzene exposure is AML (ATSDR 1997a; Goldstein 1988; Hayes et al. 1997; Snider et al. 1993). Studies of workers in the 1970s in tanneries and footwear manufacturing facilities found elevated incidence of all leukemia at airborne concentrations in the 100 ppm range (ATSDR 1997a). Further studies of workers in the petroleum and chemical industries suggested elevated risk ratios at airborne concentrations of approximately 10 ppm (Hayes et al. 1997) and perhaps as low as 0.2 ppm (Glass et al. 2005). Although 0.2 ppm is still two orders of magnitude higher than typical (high) ambient concentrations in the United States, ambient concentrations potentially expose a greater number of people for longer

durations than do occupational exposures. A nested case-control study of Australian petroleum industry workers found an odds ratio of 2.89 for cumulative exposure in the range of 2-4 ppm years, suggesting that low levels can lead to disease, given enough time (Glass et al. 2005). The existence of a safe lower threshold of exposure for benzene has not been established, due to uncertainties in population susceptibility at low doses (Bayliss et al, 1998). Although these findings do not demonstrate an association between leukemia and benzene at typical ambient concentrations, the trend toward positive association at lower concentrations reinforces concern about health effects from chronic exposure to ambient benzene pollution.

Assessing the influence of ambient pollution levels on health is a difficult task. Because monitoring pollution levels is expensive, it is usually limited to a few sites in a large city, so concentration variability may not be captured. Investigations have used methods other than monitoring, such as traffic density, road density, distance to roads and vehicle ownership density as proxies to assess population level exposure to air pollutants (Bayer-Oglesby et al. 2006; Carr et al. 2002; Crosignani et al. 2004; Raaschou-Nielsen et al. 2000; Raaschou-Nielsen et al. 2001). These proxies do not account for contributions from sources other than on-road mobile ones. Distance to a source has been used as a proxy for exposure to both industrial mixed pollutant point sources (Walker et al. January 2007 unpublished draft) and to mobile sources (Pearson et al. 2000). These studies found elevated associations with childhood leukemia (Pearson et al. 2000; Walker et al. January 2007 unpublished draft). Studies which do not account for all source classes of pollutants, do not separately account for individual pollutants, or do not capture concentration variations in a study area make it difficult to distinguish which substances contribute most to disease risk.

A recent review of literature concerning air pollution and childhood cancer found that four of fifteen studies supported an association between traffic-related air pollution and cancer (Raaschou-Nielsen and Reynolds 2006). An additional nine studies

in this same review had non-significantly elevated risk ratios for leukemia (of studies reviewed and reporting risk ratios for multiple diseases, five of eight reported the leukemia risk ratio as highest) (Raaschou-Nielsen and Reynolds 2006). Though the authors concluded that only four of fifteen reviewed studies strongly supported an association between traffic related air pollution and childhood cancer, an alternate interpretation of this review study might conclude that thirteen of fifteen studies at least suggested a concern of elevated risk of childhood leukemia arising from traffic related air pollution. Benzene is a major component of traffic related air pollution (EPA 2005). A California study used EPA modeled data for combined HAPs at the census tract level to compute aggregate cancer risk scores due to all carcinogenic pollutants as a predictor variable, finding modestly elevated but not statistically significant risk ratios for childhood, acute non-lymphocitic leukemia (ANLL), linked to point source emissions dominated by benzene and perchloroehtylene (PERC) (Reynolds et al. 2003).

Given the occupational evidence supporting a link between benzene and AML, and the widespread presence of benzene in urban air pollution, research is needed to investigate the association of leukemia with ambient concentrations of benzene. Existing data sources on ambient benzene levels and leukemia incidence, both available at the census tract level in Portland Oregon, presented an opportunity for investigation. Modeled airborne benzene concentrations and exposure data were reported in the 1999 Portland Air Toxics Assessment (PATA) (DEQ 2006). We used this census tract level modeled HAP data as a proxy for personal exposure of incident cases of leukemia in the same census tracts. A 2004 study of pollution levels at the county level suggested that the concentration of benzene is high enough to warrant health assessments in Portland using more accurate methods (B Tam and C Neumann 2004).

The purpose of this study was to determine if the incidence of acute myeloid leukemia at the census tract level, during the period 1995-2004 in Portland Oregon varies with ambient airborne benzene. To achieve the strongest possible design, our

study used specific estimates of benzene as opposed to a combined measure of mixed HAPs. We also examined AML as a specific disease outcome and used exposure and leukemia incidence data at the census tract level. To our knowledge, no previous studies have been conducted specifically investigating ambient benzene concentrations and leukemia incidence at the census tract level of analysis.

Materials and Methods

We used three sets of secondary data in our main analysis: modeled air pollutant data from the Oregon Department of Environmental Quality (DEQ), ten year leukemia incidence from the Oregon State Cancer Registry (OSCaR), and population and demographic data from the United States Census for year 2000. Additional data on air pollutant monitoring results and point source locations contributed secondary roles in this study. We also used geographic data on census tract boundaries and highway locations in the analysis.

Ambient air concentrations of benzene

Ambient air modeled concentrations and exposure values were available from the DEQ's Portland Air Toxics Assessment (PATA). A comprehensive dispersion modeling project, PATA, characterized the prevalence and distribution of twelve HAPs known to be above levels of concern in the area (DEQ 2006). The geographic extent of the PATA study was a rectangular region containing the Portland metropolitan area and including census tracts in Multnomah, Clackamas, and Washington Counties. The dimensions of the domain are 50 x 60 kilometers beginning at UTM coordinate 495000 east and 5015000 north in Zone 10.

The PATA compiled modeled ambient concentration as well as modeled personal exposure estimates at census block group centroids for each HAP studied. Values for ambient concentration were calculated by DEQ using the CALPUFF model which incorporates information on meteorology and terrain as well as emission source locations and amounts for mobile, point and area sources (DEQ 2006; USEPA 2007). Personal exposure values reported in PATA were estimated by DEQ using the US Environmental Protection Agencies (EPA's) Hazardous Air Pollution Exposure Model version 5 (HAPEM5), which modifies the modeled concentration values using census tract level data on demographics, microenvironment, personal activity, and commuting patterns to estimate individual level inhalation exposure (Rosenbaum 2005). The HAPEM5 modeled exposure values in PATA present an estimate of personal exposure and thus provide a better proxy of personal exposure than concentration values. The PATA values for HAP concentration and exposure represent estimates for 1999, which is near the midpoint of the interval (1996-2005) for which we have leukemia incidence data.

We used average benzene modeled exposure at the census tract level from the PATA as a proxy for individual exposure. Although a proxy and therefore not an exact measure of individual exposure, these data are, as discussed above, a rigorously constructed measure of community HAP concentrations, and represent a level of detail not previously investigated for correlation with leukemia. We used data on benzene and perchlorethylene (PERC) in our study. PERC served as a negative control substance because it has not been strongly linked to AML (ATSDR 1997b). Results of epidemiological studies of PERC are inconsistent, with esophageal and bladder cancer as the most common outcomes, although these results are confounded by the frequency of co-exposure to other solvents.

We obtained two additional types of data from DEQ; benzene air monitoring data for several sites in Portland and five other cities in Oregon and Washington, and

point source emissions data for Portland. These data were available from DEQ's Laboratory Analytical Storage and Retrieval (LASAR) website (DEQ 2007) and consisted of measurements taken on a weekly or bi-weekly basis over the course of one to six years. The sampling years, dates and intervals were not identical at each of the monitoring sites for which DEQ recorded analytic samples, but there were between 20 and 60 measurements at each site in the years we examined. For each site, we averaged all measurements by year. We used monitoring data to assess the trend in airborne benzene concentrations over time in Portland, to compare Portland to other cities in the region, and to compare with PATA modeled data. Point source emission data included locations and amounts for all benzene and PERC point sources used in calculating the PATA model results. We incorporated point source data into maps for comparison with leukemia rates and PATA modeling results.

Census Tract Population and Demographic Data

We used year 2000 population and demographic data including household income, years of education completed and median year moved into residence from the United States Census Bureau's internet public data website (US Census Bureau2000). We used these data to assess the co-variability of socio-economic status (SES) with disease rates and HAP measures. We used population weighted average household income (Income) and percent of those over 25 years old having less than high school education (Education) as measures of SES

Because accurate yearly population values were not available for each census tract, we multiplied year 2000 census tract populations by ten to obtain our denominator when calculating rates and conducting regression analysis. Our incidence data were collected for the period (1996-2005) so this represents a scaled midpoint population for each census tract in our study area. The actual population trend during the study period in Portland is shown in Table 3, with county level data. Scaling up the year 2000 census

values underestimates total population in the three counties comprising Portland by less than 1%, although some census tract discrepancies may exceed this because population growth is unlikely to be homogenous in all census tracts.

The U.S. Census compiles a value for median year moved into residence (MYMI) for all those living in a census tract. While this is an aggregate value computed for each census tract, we used it to assess the general stability of the population in each census tract. Comparing to the census year 2000 yields a general idea of the length of time residents have been in their current home and thus, theoretically subject to the HAP concentration average for this census tract. The average value for MYMI over all census tracts used in this investigation was 1995, yielding a theoretical four year average time an incident case was subject to census tract average HAP values used as a proxy for actual personal exposure in this study. This hypothetical four year exposure time is within the latency period for leukemia due to environmental benzene exposure, which has been estimated as between four months and ten years (Morgan and Alvares 2005). A large cohort study of benzene exposed factory workers found the ANLL RR was higher among those exposed more recently than ten years than for those whose exposure occurred more than ten years in the past (Hayes et al. 1997).

Leukemia Data

The Oregon State Cancer Registry (OSCaR) provided case counts of incident leukemia for the period 1996-2005 (Riddell and Pliska 2006). The counts covered census tracts in the three counties (Multnomah, Clackamas, and Washington) which comprise metropolitan Portland Oregon and were stratified by gender and the ten age groups shown in Table 4. Total counts and study area population as well as raw incidence rates are presented in Table 5. We considered case count data by census tracts to be confidential as some census tracts had only one case. For this reason rates rather than count data are presented. Counts of incident cases were separated into three types

by OSCaR; acute myeloid leukemia (AML), combined or “total” myeloid leukemia (TML), and all leukemia types combined, “total leukemia” (TOL).

We were primarily interested in analyzing adult leukemia, as childhood only analysis reduced the available cases in our study area. We did analyze childhood leukemia separately for those under 19 years of age as children can be generally more sensitive to environmental contamination. Previous studies of childhood leukemia and ambient HAP levels found increased leukemia incidence in children under 15 years of age associated with higher combined HAP levels (Reynolds et al. 2003). Because case count data were available for the age groups 0-4, 5-9 and 10-19, it was necessary to make our cutoff at age 19. Separate analysis for children was limited because the myeloid leukemia types most associated with inhalation of benzene are less prevalent in children and we had relatively few cases to analyze.

We computed raw rates for AML, TML and TOL for each census tract in the PATA study area using 1996-2005 incidence counts from OSCaR and year 2000 U.S. Census data. These rates were directly age-standardized to the overall United States population using the U.S. Census year 2000 national population structure (Kahn and Sempos 1989). Standardized rates were computed for separate and combined genders. Rates for those under 19 years of age were calculated as well as rates for all ages combined. We used these incidence rates in mapping and exploratory data analysis but used case counts in regression and risk ratio analyses. Our study was approved by the Oregon State University Institutional Review Board for the protection of human subjects. Additional review and approval was provided by the OSCaR Advisory Board.

Geographic Data

We used Geographic Information System (GIS) to examine the spatial distribution of air pollution, disease rates and demographic data (ESRI, Inc. 2005). GIS

was also used to calculate census tract averages for benzene and PERC measures, using all PATA model receptor values falling within the boundaries of each census tract. We obtained shape files for census tracts in Portland from the Oregon Geospatial Enterprise Office (OGEO 2007). The HAP data produced by DEQ for the PATA study consisted of average ambient concentrations and modeled 50^{th} percentile exposures for over 900 receptor points, located by universal transverse mercator (UTM) coordinates. Most of the receptor points were located at census block group centroids with three to five block groups in most census tracts.

Statistical Analysis

We conducted univariate and bivariate analysis on standardized rates, HAP measures and SES indicators (Pagano and Gauvreau 2000; SPSS 2004). Benzene concentration and modeled exposure as well as SES indicators of income and education were normally distributed. Measures of PERC concentration were not normally distributed as the variability of this HAP was most pronounced in a few census tracts around two point sources. The distributions of all standardized disease rates were influenced by a large number of census tracts having zero cases. As a result these were also non-parametric variables. Various transformations failed to achieve a normal distribution for disease rates. Compared to the AML rate distribution, the number of tracts having zero cases decreased for TML and again for TOL. Each leukemia type did have numerous tracts with no cases.

Poisson Regression Analysis

We conducted Poisson regressions on ten-year disease counts and population data, utilizing STATA procedure “glm” and adjusted for overdispersion in the data using the STATA option “irls scale(dev)” (StataCorp 2007). For each major category of leukemia we conducted an analysis for male, female and combined gender groups as

well as for those less than 19 years of age. We repeated this analysis using ambient concentration and modeled exposure values for both benzene and PERC including income and education in each regression. Census tract population was included as an offset variable in each regression. The values for Goodness of Fit (GOF) measures df/deviance and df/Pearson were generally less than 1.3 with a few in the range of 1.3-1.5. The regressions for the under 19 age group had very low or disparate GOF statistics, indicating that they were not well fit by Poisson regression.

Incidence Rate Ratio Analysis

We categorized census tracts into groups at quartiles of average benzene or PERC modeled concentration and exposure. We aggregated case data for census tracts into these exposure levels to compare incidence rate ratios (IRR). We examined IRRs for AML male, female, and combined genders, AML for those less than 19 years old, and TML and TOL for combined genders. We used the lowest quartile of either modeled exposure or ambient concentration as a reference level. No statistically significant correlations or Poisson coefficients emerged for any of the measures of SES we used, so, these variables were dropped from the rate ratio analysis. We used linear regression of incidence rate ratio on the midpoint values of exposure quartiles to evaluate the presence of a trend.

Results

Raw Incidence Rates in Portland

Separate and combined gender, overall incidence rates (using all of our data for Portland) for the three main leukemia types are presented in Table 5 for select age groupings. For all age AML and TOL, the raw rates for males in Portland are less than

the national average (Portland AML= $3.5*10^{-5}$, TOL=$11.6*10^{-5}$, national AML= $4.4*10^{-5}$, TOL=$14.9*10^{-5}$) while the rates for females appear similar (Portland AML= $3.2*10^{-5}$, TOL=$9.9*10^{-5}$, national AML= $3.0*10^{-5}$, TOL=$9.1*10^{-5}$) (compare to Table 1). Examining overall Portland rates for those under five and nineteen years of age shows low AML and high TOL, consistent with what is known about the incidence of these diseases among young people (Steen 1993). Overall Portland rates of AML and TML are lower in both youth age groups than among adults in our study.

Univariate Analyses

Univariate statistics for census tract level variables used in our analysis are presented in Table 6. Distributions of census tract average modeled benzene concentration and benzene exposure show exposure values are roughly half of concentration at all percentiles. The mean value of 3.85 ug/m^3 for modeled benzene concentration is considerably higher than any of the monitoring site results for 1999, the same year as the inventory data on which the model is based (see Figure 1). These results are consistent with the PATA, which assessed the distribution of values at modeling receptors within a four kilometer radius of monitoring sites. In the PATA analysis, modeled estimates were 1.5 to 4.0 times higher than monitored values, a difference attributed mostly to the overestimation residential wood smoke (DEQ 2006).

Monitoring results show a steady reduction in ambient benzene, consistent across several regional cities (see Figure 1). Ambient concentrations were 10-20 times above the benchmark value in 1999 and this decreased roughly by half in 2005.Trend lines are included for some sites with more than one year of data. Several patterns appear to exist on a regional scale. There was a downward trend in ambient benzene concentration between 1999 and 2005. The year 2004 is notable in that all sites seem to have higher measured concentration averages than the previous year. Similarly, 2005 all sites seem to have lower averages than the previous year.

The percentile scores in Table 6 give some idea of the frequency of census tracts having zero cases of the various leukemia types. Among the rates for both genders combined, the highest percentile having a rate of zero is 25th for AML, 10th for TML, and less than 5th for TOL. The more specific the leukemia classification, the more census tracts have rates of zero. Not surprisingly, this is accentuated in the single gender rates where, for example, the female only AML rate is zero at the 50th percentile, indicating that over half the census tracts have rates of zero. Means of census tract rates for AML (male 3.99, female 3.69) and TOL (male 14.32, female 10.74) are similar to national values for both males and females (AML: male 4.4, female 3.0; TOL male 14.9, female 9.1). Though similar to national averages, the rates for both AML and TOL in males are a bit lower than national rates, while the rates for females are a bit above national rates for both these disease types. This same pattern was seen in the raw rates using our entire study population and aggregate leukemia counts.

Spatial Distributions

We mapped original PATA receptor values of modeled benzene exposure for comparison with point source emissions and major highways in the study area (see Figure 2). Modeled exposure visually appears to increase with proximity to the city center and proximity to major highways. The modeled values do not appear to be visually correlated to known point source emissions located along the Columbia and Willamette rivers. For comparison, the average census tract values for benzene modeled exposure and concentration are mapped, along with known point sources in Figures 3and 4. The spatial distributions of these two aggregate measures appear visually very similar and still more heavily associated with population density (assuming population density generally increases with proximity to city center) and major highways than with the point sources. That PATA modeled exposure and concentration values for benzene showed a tendency toward higher values nearer the city center and in proximity to the major freeways which ring the city is not a surprise. This is consistent with PATA

findings that mobile sources in Portland contribute the greatest percentage of benzene to the air, followed by area sources such as wood-burning stoves (DEQ 2006). Population density was used as a proxy for area source benzene emissions in PATA (DEQ 2006). For PERC the distribution of census tract average modeled exposure and point sources are shown in Figure 5. Distribution of PERC is strongly correlated to two locations and these all reach their highest outside the downtown city core.

We mapped the distribution of standardized leukemia rates in the Portland area. The spatial distributions of the three major classifications of leukemia, AML, TML, and TOL for combined genders are shown in Figures 6-8. Tracts with zero cases are evident throughout the study area, including near the city center for all three types. We categorized rates in order to show variation in rates including very high rates and rates of zero. Tracts with rates of zero were distributed throughout the study area for all three disease types. There is no dominant pattern apparent in the visual distribution of any of the three main types of disease.

Correlations

We used spearman rank correlation coefficients to assess co-variability of all variables (see Appendix Table 11). Disease rates were most correlated with each other and not with the SES indicators. For both benzene and PERC, exposure and concentration values are highly correlated (0.95, $p<0.05$). This means that, even with the alterations for activity and lifestyle, the HAPEM5 model results in a linear adjustment to the concentration values, at least in the PATA study area and for these two HAPs. Benzene exposure is correlated weakly with population (-0.161), median year moved into residence (MYMI) (0.201), and household income (-0.362) all at $p<0,05$. The population correlation likely reflects the apportionment of area benzene sources by population density in the original PATA inventory. The income and MYMI results suggest that those living in poorer census tracts having higher turnover in

residents may be at higher risk of exposure from ambient benzene sources. For all combined gender disease rates, the correlations with benzene modeled exposure were negative; AML= -0.163, $p<0.05$; TML= -0.091, $p>0.05$; and TOL = -0.054, $p>0.05$.

We divided census tracts in our study area into two groups based on the median year moved into residence of before of after 1995. We calculated bivariate Spearman correlations separately for each group. Correlations for separate and combined gender groups of the three types of leukemia all increase in the longer duration residence group (Appendix Table 9). While all correlations of leukemia types by gender with benzene modeled exposure were negative in our overall analysis, correlations for all but combined gender AML were positive in the long duration residence group. Even though the combined gender AML correlation was still negative in the long duration group, it changed the most among the groups analyzed.

Poisson Regression

Poisson regression results showed no consistent trend for any of the HAP measures and none of the coefficients approached statistical significance (Table 7). Betas vacillated about zero for both modeled exposure and ambient concentration measures of benzene. The magnitude of the betas was greater for PERC, but the direction of the predicted change vacillated as with benzene. The resulting changes in AML incidence predicted by the Poisson regression model for a one unit increase in benzene modeled exposure were a decrease of 14% for males and an increase of 2% for females (changes for TOL were a 2% decrease for males and a 12% increase for females). Results of the model show a small, non-significant increase in leukemia with income (increases of 2.6% for TOL and 1.2% for TML and 0.4% for AML associated with a $10,000 increase in average household income). Increases of 2.7%, 1.9%, and 1.3% in combined gender AML, TML, and TOL, respectively are predicted for a 10%

increase in the percentage of persons over age 25 having less than a high school education though, again, these are statistically non-significant findings.

Incidence Rate Ratios

Incidence rate ratios are shown in Table 8. For AML among females, we found a statistically significant increase in incidence for the second quartile of benzene modeled exposure and non-significantly elevated incidence at the third and fourth quartiles. ALM for those less than 19 years old had non-significantly elevated incidence at the second and fourth quartiles but lowered incidence at the third quartile of benzene modeled exposure. This same pattern of non-significant elevations at quartiles of benzene modeled exposure existed, to a lesser degree for TML. A fairly uniform 5% increase in incidence with benzene modeled exposure occurs in quartiles two through four of TOL, again without being statistically significant. Results for PERC shows a statistically significant trend for female only AML, as well as a general trend toward higher IRRs and significant trend as leukemia class broadens. This effect is most pronounced using the modeled exposure measure.

Mapping Leukemia Rates and Pollution Together

We mapped the original PATA modeling receptor values for modeled exposure along with leukemia rates and DEQ known point source emission locations. Figure 9 shows incidence rates for combined gender AML along with PATA receptor values for modeled benzene exposure, categorized at two levels. No overall relationship between leukemia rates and modeled benzene is apparent. The AML rate is presented with DEQ point source emissions, categorized at two levels, in Figure 10. Examining AML rate with point source benzene emission locations suggests areas of concern, particularly along the lower Willamette River. In this area there is a concentration of point source

emissions (particularly at the largest point source category) and several census tracts at the highest incidence rates of AML.

Because we had few cases of childhood leukemia for statistical analysis, we created maps as an alternative method of assessing for spatial relationships between childhood leukemia incidence and benzene measures. We mapped the benzene point sources, PATA receptor values for modeled benzene exposure, and incidence of the three major leukemia types for those less than 5 and less than 19 years of age (see Figures 11-16). These maps show some census tracts with elevated youth AML and TML near major highways. These maps reveal several tracts with occurrences of TML but not AML, indicating cases of CML contribute to these elevated rates. Additional tracts along both the Willamette and Columbia rivers are close to known benzene point sources and have high incidence of TML. This effect can also be seen when comparing the TML and AML maps for those under 5 years old. While many of the census tracts with high TML in young people appear to be located near major highways or point sources, many have modeled benzene exposure at the lowest level (see Figures 9, 13 and 14). These patterns exist in spite of the overall finding of a non-correlation between leukemia incidence and ambient benzene at the census tract level.

Because Total Leukemia was the leukemia type with the strongest correlation to PERC in both correlation and incidence rate ratio analysis, we mapped total leukemia incidence with PERC point sources and PATA receptor values for PERC modeled exposure (Figure 17).The modeling receptor distribution for PERC is strongly weighted by a peak in the east-central study area and a smaller peak in the west. A relationship between high incidence of combined leukemia and modeled PERC or point source PERC emissions is not suggested by these maps.

Post Hoc Analysis of Statistical Power

Risk assessment is a process of numerically estimating the contribution of specific toxins to total disease risk. Available toxicology and epidemiology results are used to derive a unit risk estimate (URE) or amount of toxin which is thought to cause an increase in probability of one case per million over a 70 year lifetime (BK Davis and AK Klein 1996; SC Morris 1990). For benzene, the URE is $7.8*10^{-6}$ (ATSDR 1997a, IRIS 2007). The unit risk value is used to calculate excess cancer risk attributable to an environmental toxin using the formula:

$$\text{Cancer Risk} = \text{Concentration} * \text{URE} \qquad \text{Formula 1}$$

where the concentration is assumed to occur over a 70-year lifetime. Based on this unit risk estimate, Oregon has adopted a benchmark value of $0.13 ug/m^3$ as an ambient benzene goal. Monitored concentrations in Portland exceeded this value by a factor of between 10 and 20 in 1999 and approximately half of this in 2005.

Using the PATA benzene exposure estimates, theoretical risk attributable to various increases in benzene exposure may be calculated. Since our incidence rate ratio analysis examined changes in rates at quartiles of modeled exposure, the attributable risk derived from the interquartile range (IQR) of modeled benzene exposure is relevant. The IQR for benzene modeled exposure in our study is ($0.83 ug/m^3$). The calculated yearly increase in cancer risk due to an increase of $0.83 ug/m^3$ is $9.1*10^{-8}$ and is roughly 0.3% of the incidence rate for both gender AML ($3.35*10^{-5}$) in the study area. Using the average concentration of benzene in Portland ($2.4 ug/m^3$ as recorded by EPA monitoring) the predicted excess cancer incidence in the city over a ten year period is 3.6 excess cases. Excesses of this magnitude would be difficult to detect using ecologic methods, especially given uncertainties in exposure and accuracy of residential designation.

Using the raw AML incidence rate for both genders in Portland ($3.35*10^{-5}$) as a baseline and adding the theoretical cancer risk attributable to benzene exposure at the IQR yields a theoretical AML rate of $3.36*10^{-6}$ for those exposed at the highest quartile. Using these incidence rate estimates to calculate lambda1 and lambda0 for Poisson distributions of 295 census tracts of 4500 persons, we calculated statistical power to be 0.043 at alpha=0.05..

Discussion

We found no evidence consistently supporting an association between ambient benzene and AML incidence in our study area. Both benzene and PERC modeled concentration clearly increase with proximity to the center of the city. For benzene there is a strong, secondary effect with proximity to major highways (see Figures 2 and 3). For PERC there are two distinct peaks in concentration in the study area (see Figures 5 and 17). Distribution of both of these HAPs is not clearly correlated with leukemia incidence at the city level. Regression results were non-significant and we saw no monotonic increase with benzene modeled exposure. Correlation results between modeled benzene exposure and the three main leukemia types were negative, with a more pronounced effect as leukemia type becomes more specific. A previous study also used census tract level analysis but combined HAPs as a predictor variable, finding elevated childhood leukemia for census tracts with high HAPs from combined sources (Reynolds et al. 2003). We found slight, non-significant elevations in AML IRRs for those less than 19 years of age but not in a consistent pattern of increasing risk with exposure level. The 2003 Reynolds et al. study took place in California, so it had significantly more population and census tract numbers, likely making it more robust even though our study focused on only one pollutant. For the three types of leukemia we found non-significant elevations at some quartiles of exposure but these increases

were not consistent with exposure level or larger effect for myeloid types. The largest increase of seven percent was for the Total Leukemia type. Occupational studies have shown that increases in leukemia rates are most often evident for AML (ATSDR 1997a; Goldstein 1988).

Our exposure proxy, modeled ambient benzene at the census tract level, had a mean concentration of approximately 1ppbV. It was approximately 2ppbV at the 90th percentile. HAPEM5 Modeled exposure values were approximately half of this. The CALPUFF model results are known to overestimate benzene in Portland (DEQ 2006). Adjusting these census tract concentration values for the overestimation by the CALPUFF model and the reduction by half in the HAPEM5 exposure model gives a theoretical human exposure represented by our proxy of approximately 0.25 ppb at the mean and 0.5 ppb at the 90th percentile. Our results suggest airborne benzene at this concentration, typical in Portland, is not associated with any increase in acute myeloid leukemia incidence at the census tract level.

Monitoring trend data suggests a general improvement in the levels of airborne benzene in the city and the region during the period 2000-2006 (DEQ 2007). A steady reduction in ambient benzene appears to occur during this period, consistent across several regional cities (see Figure 1). Annual averages for benzene concentration dropped from a range of 0.4-0.8 ppbV in 2000 to a range of 0.2-0.4 ppbV in 2006. Ambient concentrations were 10-20 times above the benchmark value in 1999 and this decreased roughly by half in 2005. Trend lines are included in Figure 1 for some sites with more than one year of data. Several patterns appear to be common to all sites. There is a downward trend in ambient benzene concentration. The year 2004 is notable in that all sites seem to have higher measured concentration averages than the previous year. Similarly, 2005 all sites seem to have lower averages than the previous year. The variations from the overall downward trend in the monitoring results could be due to differences in sample months in these years. If more samples were taken in the winter

when there was a general increase in ambient benzene due to home wood heating, then the yearly average may appear high. Alternately, unseasonably warm or cold winters could impact the use of home wood heating. The overall downward trend could be due to changes in motor fuel composition, more stringent home wood heating regulation or voluntary reductions in the use of wood heat on days with atmospheric conditions which trap pollutants. Monitored benzene values in Portland are decreasing for all sites in the city. Results from other cites, while sparse compared to the heavily sampled Portland metropolitan area, suggest that ambient benzene may be present in these cites at levels comparable to those in Portland.

Our study occurred during a period of population growth in the city, so it is possible that regulatory improvements have been the main influencing factor in the decrease which occurred during this time. This decrease may have begun at the turn of the century or be a continuation of a trend which existed in the 1990s. Assuming this decrease continued in a linear manner back into the 1990s, the average ambient benzene concentration associated with the earliest incident cases in our study would likely have been under 2ppbV. If the decrease began around 1999, when our monitoring data begins, then the ambient benzene concentrations associated with cases in our study would be less than 1 ppb, as are the monitoring results from 1999. The PATA modeled benzene concentrations are greater than these monitoring results by a factor of between two and three, so census tract values used in our study are likely higher than true values. This overestimation in the modeling data should be taken into account when considering the magnitude of exposures for which our results apply.

Occupational studies have found increased leukemia risk at concentrations possibly down to 0.2ppm (Glass et al. 2005). Our study had exposures two to three orders of magnitude less than those previously attributed to increased cancer risk. The 2000 monitoring results confirm the magnitude of actual census tract average concentration in our study as likely being between 0.5 and 2.0 ppb. Actual personal

exposures are likely half of these values, according to the trend in correlation between modeled concentration and HAPEM5 modeling results in PATA. Monitoring trend results suggest that actual risk is not increasing in Portland. We assume the variability between census tract benzene values in PATA is accurate, even if the actual values are overestimated by PATA.

Relevant variability of mobile source pollution is probably not captured at census tract level. Studies using traffic density or road proximity have found correlations with leukemia (Crosignani et al. 2004; Pearson et al. 2000) and these have important variations at distances of 50-300 meters (Carr et al. 2002). In our study area, most census tracts are from one to seven miles across, so census tract average HAP data cannot adequately account for variations in mobile source emissions.

The DEQ HAP data, modeled at the census tract level and available for Portland and other areas of the United States, is a valuable resource. It represents a refined estimate of total contributions from mobile, area and point sources, adjusted for meteorology and topography. Consideration of, and adjustment for within census tract variability, such as proximity to major highways or traffic density, would assure the most thorough and appropriate use of this data as an exposure proxy in future health related research. Having census tract level data allowed us to apportion cases to exposure levels more accurately than would have been possible with larger geographic unit of analysis. It also allowed for regression using US Census data on possible confounders at the census tract level of analysis.

If mobile sources play a dominant role in determining the ambient benzene concentrations to which residents are subjected, and the variability of mobile emissions is not captured at the census tract level, then our analysis may not properly classify those residents having the highest actual exposures from ambient sources; those living very near to major roadways. Rothman and Greenland (1998) describe how non-

differential exposure misclassification of a dichotomous exposure can produce bias toward the null and even reverse the direction of the association. Further, for exposures with more than two categories the bias may be away from the null as odds ratios at low exposures are raised (Rothman and Greenland 1998). Our study had negative bivariate correlations and elevated IRRs at the second quartile for several leukemia groupings. Exposure misclassification of cases exposed to high mobile source benzene could explain this.

Another misclassification may result from assuming that benzene concentration in the residence census tract is representative of actual daily exposure. Since more people, on average, work in the busier, urban census tracts, an individual's actual exposure may exceed the average concentration in the home area census tract. Daily air pollution levels may peak during the daylight hours, exacerbating this misclassification of exposure which, as discussed above, could result in higher IRRs for low exposure quartiles.

Migration bias could result from uncertainty in duration of residence, producing uncertainty in the relevance of the reported concentration to any given disease case. This might contribute to non-differential misclassification in our study, assuming: that no reason exists for cases to preferentially migrate in or out of our study area before diagnosis, migration is random with respect to benzene exposure, and disease data correctly attributes address at time of diagnosis. Migration bias would likely result in regression toward the null, or underestimating any benzene leukemia effect which was present in the data.

Geographic analysis can suggest insights which may not be apparent from a statistical viewpoint. We mapped modeled exposure of benzene along with known point sources and major highways in order to understand the exposure data we were using, finding that mobile and area sources were the most apparent correlation to the PATA

model data (see Figure 2). The model data did not appear to be strongly influenced by known point sources in major industrial areas but was concentrated around the downtown city core and areas of major highway corridors.

Some census tracts with elevated incidence of AML are near point source benzene emissions along the Columbia and Willamette rivers (see Figure 10). A previous study showed that the highest rates of childhood leukemia incidence were near point sources dominated by benzene emissions (Reynolds et al. 2003). In our study, these tracts are near an area of major industrial activity, have average household income levels and relatively long average duration of residence. Residential stability and incomes in the range of average for the city may indicate stable working class residents and the possibility of confounding occupational exposures among the populations in these areas. When we examine maps of TML for those less than 19 years of age, we see a tendency for rates to be elevated in some census tracts near major roads, in agreement with traffic studies suggesting variations of less than 300yds may influence benzene distribution (Carr et al. 2002) and leukemia incidence (Crosignani et al. 2004; Pearson et al. 2000) (see Figures 13 and 14). These maps reveal several tracts with occurrences of TML but not AML, indicating cases of CML contribute to these elevated rates. Since this disease is normally rare in young people, it is of interest that several of these tracts with elevated TML but not elevated AML are close to major highways or roads. We did observe AML IRRs greater than one for quartiles two and four only in the less than 19 year old group, though these were not statistically significant findings. The observation that TML in young people is elevated in several census tracts near highways may support the importance of proximity to traffic as an important factor in assessing the impact of ambient benzene on leukemia. Methods to augment census tract level benzene assessment may be needed to more accurately use census tract level data as a proxy for ambient benzene exposure in epidemiology studies.

These mapped observations may represent effects which deserve further investigation, even though the overall result of our analysis does not support an association between benzene and leukemia. Proximity to traffic may be a more important exposure risk for leukemia than modeled benzene exposure at the census tract level. If traffic related benzene were associated with higher TML in young people but was not adequately represented by census tract averages of pollution dispersion, then the combination of effects seen in the present study might result: We find a lack of an overall association between benzene distribution and leukemia incidence at the census tract level but observe a possible overabundance of cases in census tracts near high traffic density. An assessment of traffic density within census tracts would be needed to better understand this combination of findings and observations.

It is possible our study lacked sufficient or appropriately detailed data to allow a statistically significant result to emerge. This possibility is supported by the finding that correlations and IRRs increase when examining only census tracts having a longer average duration of residence. Though the correlations for the “Long Duration” group are close to zero, this shift from negative effect to a more positive one might suggest that the accuracy of census tract level data as a proxy improves with longer average residence duration in the census tract.

The increase in incidence rates with modeled PERC exposure was an unexpected finding, as PERC was intended to serve as a negative control substance. This result may be influenced by an association between PERC and an unknown confounding variable in the study area or by the same misclassification discussed for benzene. Census tract measures of PERC concentration and modeled exposure were non-normally distributed and this could have introduced bias in our analysis

This study was advantaged by several factors. We used data specific to benzene as opposed to aggregate carcinogens. Our outcome data was for a disease (AML)

specifically associated with benzene in occupational studies rather than more broad, combined diseases types. We used census tracts as a unit of analysis to achieve an improvement in exposure assessment over previous, county level analysis. The pollution data we used included point, area and mobile sources so it was not limited to a single source category.

Limitations

Our study was subject to a number of limitations. We averaged modeling data to the census tract level as a proxy for actual exposure and used aggregate leukemia incidence and demographic data. We have no specific information on actual case exposures from occupational, commuting, or prior residential sources such as smoking. We assumed distribution of HAPs was homogeneous within census tracts. We do not know precise location of cases within census tracts or their true duration of residence. We also assumed residence at the time of diagnosis was the same as the residence during the biologically relevant exposure window. Though this cannot be verified, census tract average duration of residence is five years, similar to suggested latency period for AML (Hayes et al. 1997; Morgan and Alvares 2005). The concentrations of ambient benzene present in the original modeling data varied over an order of magnitude, but this variation decreased to a factor of four when comparing the 5^{th} to the 95^{th} percentiles and less than a factor of two between the first and fourth quartiles of exposure. PATA modeling results were at census block group resolution, so we lost resolution in HAP data when we computed census tract averages for our analysis. This was necessary to match the resolution of our leukemia data but may have limited the sensitivity of our study because of possible variations in exposure close to major roads (Carr et al. 2002). We explored incidence and exposure source locations using maps which are subject to interpretation bias and should be viewed with caution. Given the size of our study area, benzene variation at the census tract level was not adequate to

provide sufficient statistical power to detect the difference in leukemia rates predicted by risk assessment.

Conclusions

We used available modeled data on benzene concentration at the census block group level. The original data had a range of between 0.56 and 10.03 ug/m^3. We aggregated this data to the census tract level for our analysis and the range of benzene concentration decreased to 0.7 to 8.6 ug.m^3. The inter-quartile range (IQR) of benzene concentration was between 3.0 and 4.7 ug/m^3 and the IQR of modeled benzene exposure, which we used as a proxy for actual exposure, was 1.5 to 2.4 ug/m^3. The original modeled benzene data varied over an order of magnitude, but this was substantially reduced when data were aggregated into quartiles for analysis. Given the small effects predicted by risk assessment, this variability is not adequate for detecting elevated incidence rates of leukemia, if they exist.

Overall, we found no association between AML and ambient airborne benzene at the census tract level of analysis. Both benzene and PERC concentrations have clear patterns of distribution at the census tract level, which are not mirrored in leukemia rate distribution. Our regression and rate ratio analysis did not find rates of myeloid leukemia to be more influenced by ambient benzene than overall leukemia. This result does not agree with occupational studies but exposure levels in our study were likely 2ppb at most and less than 1ppb on average. Low statistical power may have limited our analysis. A few elevated AML IRRs were noted for females and those under 19 years of age, though the elevations were not large, monotonic or statistically significant (except for female AML at the second quartile of benzene modeled exposure).

We did observe possible increased incidence near point sources for adult AML and near roads for TML in those under age 19. While this result is only an observation

derived from maps of disease incidence and source locations, given the statistical limitations of our overall design, it may represent a real effect which could not be detected in the regression or rate ratio analysis. The observation that census tracts with elevated TML incidence but not AML incidence in those under 19 years of age seem to be disproportionately near highways in of interest. While just an observation, this disease is rare in this age group so a tendency for cases to be near mobile sources of benzene might reflect high sensitivity among young people to benzene in air pollution.

While many of the census tracts with high TML in young people appear to be located near major highways or point sources, many have modeled benzene exposure at the lowest level. Proximity to traffic may be a better approximation of exposure risk for leukemia than modeled benzene exposure at the census tract level. This is suggested by the combination of our overall negative finding at the census tract level and the observation of increased childhood TML in some census tracts near major roadways in our study. Census tract size is generally much larger than the distance found in previous studies to be associated with increased traffic related pollution.

The US Census collects data on duration of residence at current home. We found correlations and incidence rate ratios to be different in a subgroup of census tracts with longer average duration of residence. This may reflect reduced misclassification of residence in this subgroup. This change would be consistent with an association between ambient benzene and leukemia when duration of residence is long. Census tract level HAP data may be improved as a proxy for actual exposure in census tracts with longer average duration of residence.

We used data specific to benzene, as opposed to only aggregate HAP measures. We also used data specific to AML along with more broad leukemia classes. Having specific toxin and outcome measures makes sense when there are known effects for the exposure substance of interest. If we had had only aggregate pollution or outcome

variables, our results would have been unable to assess the presence of the most obvious, expected outcome.

Recommendations

Future studies should seek methods to adjust census tract level modeling data to account for both the large contribution of major highways and arterial streets and the rapid decrease of this contribution as distance from roadways decreases. These dynamics may not be adequately represented by the census tract level data we used. A better approach might be to develop a method which used the modeling data at the census block group level as a sort of “high resolution background” measure of pollutants and combine this with some sort of traffic density variable which could be precisely geo-located to road segment location. It may be possible to “decouple” the original mobile source component from dispersion models to facilitate this type of analysis. This would be an ideal design, capturing the distribution of important point and area sources as well as on road mobile variability at important spatial scales not captured by block group geography.

Our research might be improved by obtaining leukemia case information geocoded by address of residence. This would allow more exact comparison of location of disease incidence to ambient HAP levels than census tract analysis. Geocoding specific address of case from registry records would allow use of GIS technology to build exposure level buffer zones around major sources, such as traffic corridors or point source locations and accurately apportion cases to the appropriate exposure zone or levels.

Further assessment of tracts along the Willamette River, which have low PATA modeled benzene levels but a high concentration of point sources and a tendency toward higher Leukemia rates may be warranted. These areas may represent a uniquely

exposed group. In addition, study of this area may reveal patterns of residence and pollution modeling which could assist the future use of census tract modeled air pollution in epidemiologic studies.

Investigating the influence of environmental toxins on rare diseases requires exposure and disease data covering a large population. Costs in obtaining such data along with the vast number of toxins and diseases which generate concern, make an ecologic analysis an attractive first choice to help refine further research. Our study offered improved exposure resolution over previous county level studies and targeted a specific HAP constituent, benzene. Use of census tract level data allows for more accurate assessment of exposure than a county level analysis. However, our ten year leukemia data at the census tract level provided only several hundred cases which, combined with exposure uncertainty at the census tract level may have rendered our study incapable of detecting any influence of benzene on leukemia incidence. Longer intervals or records of larger populations would be more useful in future studies of such rare diseases, ideally combined with improved exposure assessment in time and place. We used a readily obtainable census variable to separate out a subset of our population which may have a more stable residence pattern and thus be better represented by a geographic exposure proxy. Though still an aggregate measure, this may be useful for refining exposure in future ecologic studies. Specific information on duration of residence could be collected by disease registries and this would facilitate more accurate exposure assessment in future ecologic studies.

Wherever possible, the ability to study specific disease types known to be associated with particular pollutants should be retained in study design, rather than using only broad classes of disease. Where uncertainty exists in the disease outcomes of interest, using a broader approach makes sense but when specific diseases have a history of association with the exposure under study, retaining the option to study specific disease types is sensible.

Monitoring results show a steady reduction in ambient benzene, consistent across several regional cities (DEQ 2007). In particular, Portland values are decreasing for all sites in the city. Still, when compared to the benchmark value of 0.13ug/m^3, both modeled and monitoring data show that benzene values are high in Portland. This research used minimal resources in investigating the impact of a toxic air pollutant of concern in a major U.S. city. We assessed the influence of ambient airborne benzene on leukemia incidence using existing data sources and an ecologic design. Our analysis does not suggest a citywide increase in leukemia, though our study design is probably not capable of discerning the small, overall associations predicted by risk assessment. We found areas of possible concern in our mapping of leukemia incidence and both mobile and point source emission locations. Such areas may be good places to focus future research investigations, health promotion efforts or source reduction programs. A monitoring trend toward lower ambient benzene in the region, coupled with recent strengthening of regulations regarding benzene in fuels suggests future risks may be less than those assessed in this study.

Exposures possible from ambient sources are very low compared to occupational studies in which a modest association has been found with AML incidence. Though ambient benzene concentrations are high in Portland relative to other U.S. cities, they are small with respect to occupational exposures and, at the census tract level, vary little in our study area, so any influence on AML rates which exists may not have been discernable in our analysis. Detecting an influence of ambient benzene on leukemia incidence may require examining larger populations than were available to us, comparing populations for which the exposure variability is greater, or using more specific methods of exposure assessment. Available census tract level data may not represent mobile source pollution accurately enough to be useful in ecologic studies of leukemia.

Table 3. Portland Population Trend 1996-2005

Population by County during Study Period			
Year	Clackamas	Multnomah	Washington
1996	322,160	638,780	399,590
1997	328,680	646,260	412,650
1998	332,830	651,520	425,580
1999	336,050	656,810	437,790
2000	338,391	660,486	445,342
2001	345,150	666,350	455,800
2002	350,850	670,250	463,050
2003	353,450	677,850	472,600
2004	356,250	685,950	480,200
2005	361300	692825	489785
Percentage Change During Study Period			
1996 to 2005	12.1	8.5	22.6
Percentage Change From 2000 US Census			
1996	-4.8	-3.3	-10.3
2005	6.8	4.9	10.0
Underestimation using 10*year2000 as Person Year Estimate			
Total Person Years (actual)	3425111	6647081	4482387
Total Person Years (10x2000 Census)	3383910	6604860	4453420
Portland 3 County Totals			
Actual PY	14554579		
Computed PY (10x2000 Census)	14442190		
Percent Difference	-0.77		

Table 4. Oregon State Cancer Registry Age Brackets for Leukemia Case Counts

Age Groups	Ages Included
1	> 0 and <= 4
2	>= 5 and <= 9
3	>= 10 and <= 19
4	>= 20 and <= 29
5	>= 30 and <= 39
6	>= 40 and <= 49
7	>= 50 and <= 59
8	>= 60 and <= 69
9	>= 70 and <= 79
0	>= 80 and <= 110

Table 5. Summary of Case Count Data, Raw Incidence Rates and Population in Study Area by Age and Gender

	Study Area	Case Counts (1996-2005)			Raw Incidence Rates (yearly per 100,000 exposed population)		
	Population US 2000 Census	AML	TML	TOL	AML	TML	TOL
Male	667853	234	345	773	3.50	5.17	11.57
Female	680461	218	307	677	3.20	4.51	9.95
Both Genders	1348314	452	652	1450	3.35	4.84	10.75
Male < 19 y.o.	180998	22	27	88	1.22	1.49	4.86
Female < 19 y.o.	175813	9	12	74	0.51	0.68	4.21
Both Genders < 19 y.o.	356811	31	39	162	0.87	1.09	4.54
Male > 19 y.o.	481628	212	318	685	4.40	6.60	14.22
Female > 19 y.o.	504648	209	295	603	4.14	5.85	11.95
Both Genders > 19 y.o.	986276	421	613	1288	4.27	6.22	13.06
Male < 5 4 y.o.	47197	9	11	38	1.91	2.33	8.05
Female < 5 y.o.	44277	1	3	40	0.23	0.68	9.03
Both Genders < 5 y.o.	91474	10	14	78	1.09	1.53	8.53

Table 6. Descriptive Statistics

	Mean	Standard Deviation	95% CI	Median	Minimum	Maximum	Range	Int.er Quartile Range	Skew.	Kurtosis
HAP Measures										
Benzene Modeled Concentration	3.852	1.335	3.7 - 4.01	3.82	0.70	8.60	7.90	1.72	0.20	0.26
Benzene Modeled Exposure	1.967	0.675	1.89 - 2.04	1.97	0.47	4.72	4.25	0.83	0.51	1.22
PERC Modeled Concentration	0.201	0.059	0.194 - 0.208	0.19	0.14	0.80	0.66	0.03	6.44	54.36
PERC Modeled Exposure	0.081	0.024	0.078 - 0.083	0.080	0.060	0.310	0.250	0.020	6.13	49.87
Demographic Variables										
Household Income	57357	17770	55320 - 59393	53218.0	10412	122315	111903	24030	0.81	1.07
Education - % of > 25 y.o. Having < HS	12.9	7.87	11.96 - 13.76	11.80	1.10	43.00	41.90	11.70	0.78	0.29
Computed Composite SES Measure	110.9	27.8	107.7 - 114.1	111.3	27.9	214.6	186.7	36.1	0.13	0.63
Median Year Moved into Residence	1995.3	2.07	1995.1 - 1995.5	1996.0	1985	1999	14	3.00	-0.89	1.60
Census Tract Total Population	4570.6	1922	4350 - 4790	4508.0	136.0	11842.0	11706.0	2456	0.63	1.08
Leukemia Rates										
AML Male	3.99	5.43	3.37 - 4.61	1.88	0	31.40	31.40	6.56	1.78	3.88
AML Female	3.69	6.22	2.98 - 4.4	0.00	0	65.71	65.71	5.37	4.60	36.42
AML Both Genders	3.83	4.11	3.36 - 4.31	3.03	0	29.67	29.67	5.72	2.17	8.66
TML Male	5.89	6.82	5.11 - 6.68	3.75	0	50.32	50.32	9.49	1.85	6.20
TML Female	5.08	6.83	4.29 - 5.86	3.59	0	65.71	65.71	7.85	3.49	23.00
TML Both Genders	5.56	5.43	4.94 - 6.18	4.75	0	57.83	57.83	5.41	3.84	30.10
TOL Male	14.23	13.45	12.69 - 15.77	11.70	0	136.87	136.87	13.71	4.40	34.41
TOL Female	10.74	9.32	9.67 - 11.81	10.28	0	65.71	65.71	12.17	1.42	4.53
TOL Both Genders	12.57	8.49	11.6 - 13.55	12.00	0	74.00	74.00	9.00	2.68	13.87

Table 6. (continued) Descriptive Statistics - Percentiles

	5	10	25	50	75	90	95
HAP Measures							
Benzene Modeled Concentration	1.66	2.014	2.99	3.82	4.71	5.494	6.122
Benzene Modeled Exposure	0.856	1.088	1.52	1.97	2.35	2.76	3.222
PERC Modeled Concentration	0.15	0.16	0.18	0.19	0.21	0.24	0.25
PERC Modeled Exposure	0.06	0.06	0.07	0.08	0.09	0.09	0.1
Demographic Variables							
Household Income	33996	39365	44387	53218	68417	81660	89280.2
Education - % of > 25 y.o. Having < HS Education	2.66	3.92	6.2	11.8	17.9	23.74	27.4
Computed Composite SES Measure	65.98	75.99	91.42	111.27	127.47	144.12	159.34
Median Year Moved into Residence	1991	1992	1994	1996	1997	1998	1998
Census Tract Total Population	1704.2	2167.6	3257	4508	5713	6872.2	7831.4
Leukemia Rates							
AML Male	0	0.0	0.0	1.9	6.6	11.1	14.7
AML Female	0	0.0	0.0	0.0	5.4	10.0	14.3
AML Both Genders	0	0.0	0.0	3.0	5.7	8.7	10.9
TML Male	0	0.0	0.0	3.7	9.5	14.8	20.1
TML Female	0	0.0	0.0	3.6	7.8	12.9	15.5
TML Both Genders	0	0.0	2.4	4.8	7.8	11.0	13.9
TOL Male	0	2.3	6.1	11.7	19.8	27.7	31.9
TOL Female	0	0.0	3.4	10.3	15.5	21.9	26.4
TOL Both Genders	2	4.6	7.0	12.0	16.0	21.0	26.0

Table 7. Poisson Regression Results

					Examples:	e^(10*2.00E-03)	e^(-0.2)	e^(10000*2.70E-06)				
			Coefficients						RR Calculated fromPoisson Coefficients			
										*$10000	*10%	*100k pop.
HAP	DISEASE	Gender	HAP	p	95%CI	Income	Education	Const.	HAP	Income	Educ.	Const.
Benzene Modeled Exposure	AML	m	-0.2	0.215	-0.384 : 0.086	1.30E-06	2.40E-03	-10.09	0.86	1.01	1.02	4.15E-05
	AML	f	0.02	0.896	-0.235 : 0.269	-7.80E-07	2.60E-03	-10.37	1.02	0.99	1.03	3.14E-05
	AML	b	-0.1	0.451	-0.253 : 0.112	3.70E-07	2.70E-03	-10.23	0.93	1.00	1.03	3.61E-05
	TML	m	-0.1	0.617	-0.247 : 0.147	1.00E-06	2.00E-03	-9.81	0.95	1.01	1.02	5.49E-05
	TML	f	0.05	0.621	-0.160 : 0.268	1.40E-06	6.00E-03	-10.27	1.05	1.01	1.06	3.47E-05
	TML	b	0	0.978	-0.149 : 0.145	1.20E-06	1.90E-03	-10.03	1.00	1.01	1.02	4.41E-05
	TOL	m	-0	0.773	-0.153 : 0.114	2.50E-06	-4.80E-04	-9.17	0.98	1.03	1.00	1.04E-04
	TOL	f	0.11	0.19	-0.053 : 0.267	2.70E-06	3.00E-03	-9.62	1.12	1.03	1.03	6.64E-05
	TOL	b	0.04	0.479	-0.068 : 0.145	2.60E-06	1.30E-03	-9.38	1.04	1.03	1.01	8.44E-05
Benzene Ambient Concentration	AML	m	-0.1	0.292	-0.176 : 0.053	1.90E-06	3.70E-03	-10.19	0.94	1.02	1.04	3.75E-05
	AML	f	0.02	0.788	-0.106 : 0.140	-4.70E-07	2.90E-03	-10.42	1.02	1.00	1.03	2.98E-05
	AML	b	-0	0.592	-0.113 : 0.064	8.20E-07	3.50E-03	-10.31	0.98	1.01	1.04	3.33E-05
	TML	b	0.01	0.857	-0.065 : 0.078	1.50E-06	2.30E-03	-10.08	1.01	1.02	1.02	4.19E-05
	TOL	b	0.02	0.352	-0.027 : 0.076	2.80E-06	1.40E-03	-9.41	1.02	1.03	1.01	8.19E-05
PERC Modeled Exposure	AML	m	0.09	0.975	-5.594 : 5.778	4.30E-06	6.70E-03	-10.6	1.09	1.04	1.07	2.49E-05
	AML	f	-0.8	0.799	-7.076 : 5.449	-1.50E-06	1.90E-03	-10.22	0.44	0.99	1.02	3.64E-05
	AML	b	-0.4	0.878	-4.821 : 4.122	1.60E-06	4.50E-03	-10.43	0.70	1.02	1.05	2.95E-05
	TML	b	1.1	0.507	-2.148 : 4.347	1.80E-06	2.40E-03	-10.16	3.00	1.02	1.02	3.87E-05
	TOL	b	0.96	0.433	-1.435 : 3.346	2.30E-06	5.60E-04	-9.36	2.61	1.02	1.01	8.61E-05
PERC Ambient Concentration	AML	m	0.12	0.914	-2.128 : 2.378	4.40E-06	6.80E-03	-10.63	1.13	1.04	1.07	2.42E-05
	AML	f	-0.4	0.788	-2.890 : 2.191	-1.50E-06	1.80E-03	-10.21	0.70	0.99	1.02	3.68E-05
	AML	b	-0.1	0.911	-1.893 : 1.689	1.60E-06	4.60E-03	-10.44	0.90	1.02	1.05	2.92E-05
	TML	b	0.36	0.595	-0.964 : 1.683	1.70E-06	2.30E-03	-10.14	1.43	1.02	1.02	3.95E-05
	TOL	b	0.23	0.647	-0.758 : 1.220	2.10E-06	4.10E-04	-9.32	1.26	1.02	1.00	8.96E-05

Table 8. Incidence Rate Ratios for Three Major Leukemia Types

		AML			Total Myeloid Leukemia			Total Leukemia		
HAP Measure	Census Tracts	Cases	IRR	[95% C.I.]	Cases	IRR	[95% C.I.]	Cases	IRR	[95% C.I.]
Benzene Ambient Concentration										
L1: <2.99 (ug/m^3)	73	120	Ref.	---	166	ref.	---	351	ref.	---
L2: 2.99-3.82	75	126	1.00	0.78-1.29	176	1.01	0.82-1.25	400	1.09	0.94-1.26
L3: 3.82-4.68	73	104	0.90	0.69-1.17	153	0.96	0.77-1.19	355	1.05	0.91-1.22
L4: >4.68	74	102	0.95	0.73-1.23	157	1.05	0.85-1.31	344	1.09	0.94-1.27
Benzene Modeled Exposure										
L1: <1.52 (ug/m^3)	74	121	Ref.	---	168	ref.	---	362	ref.	---
L2: 1.52-1.97	73	132	1.06	0.83-1.36	182	1.05	0.85-1.3	393	1.05	0.91-1.22
L3: 1.97-2.35	77	106	0.88	0.68-1.14	160	0.96	0.77-1.19	380	1.05	0.91-1.22
L4: >2.35	71	93	0.95	0.72-1.24	142	1.04	0.83-1.3	315	1.07	0.92-1.24
									(*)	
PERC Ambient Concentration										
L1: <0.175 (ug/m^3)	72	117	Ref.	---	165	ref.	---	349	ref.	---
L2: 0.175-0.190	87	131	0.94	0.73-1.21	183	0.93	0.76-1.15	454	1.10	0.95-1.26
L3: 0.190-0.213	66	107	1.15	0.89-1.5	159	1.22	0.98-1.51	327	1.18(+)	1.02-1.38
L4: >0.213	70	97	0.99	0.76-1.3	145	1.05	0.84-1.32	320	1.10	0.94-1.28
PERC Modeled Exposure										
L1: <0.069 (ug/m^3)	30	47	Ref.	---	59	ref.	---	124	ref.	---
L2: 0.069-0.077	92	150	0.99	0.71-1.37	211	1.11	0.83-1.48	465	1.16	0.95-1.41
L3: 0.077-0.086	93	137	0.99	0.71-1.38	205	1.18	0.88-1.58	478	1.31(+)	1.08-1.6
L4: >0.086	80	118	1.05	0.75-1.47	177	1.26	0.94-1.69	383	1.29(+)	1.06-1.58
			(*)			(*)				

(*)- Trend significant at p<0.10
(**)- Trend significant at p<0.05
(+)- Individual IRR significant at p<0.05

Table 8. (continued) Incidence Rate Ratios for AML Subgroups

	Census Tracts	AML			AML Male			AML Female			AML <19 y.o.		
		Cases	IRR	[95% C.I.]	Cases	IRR	[95% C.I.]	Cases	IRR	[95% C.I.]	Cases	IRR	[95% C.I.]
Benzene Ambient Concentration													
L1: <2.99 (ug/m^3)	73	120	ref.	---	71	ref.	---	49	ref.	---	8	ref.	---
L2: 2.99-3.82	75	126	1.00	0.78-1.29	54	0.74	0.52-1.06	72	1.37	0.96-1.98	8	1.06	0.4-2.81
L3: 3.82-4.68	73	104	0.90	0.69-1.17	57	0.85	0.6-1.2	47	0.98	0.66-1.46	9	1.31	0.5-3.39
L4: >4.68	74	102	0.95	0.73-1.23	52	0.82	0.58-1.18	50	1.13	0.76-1.67	6	1.02	0.35-2.94
									(*)				
Benzene Modeled Exposure													
L1: <1.52 (ug/m^3)	74	121	ref.	---	74	ref.	---	47	ref.	---	8	ref.	---
L2: 1.52-1.97	73	132	1.06	0.83-1.36	60	0.80	0.57-1.13	72	1.46(+)	1.01-2.11	10	1.32	0.52-3.35
L3: 1.97-2.35	77	106	0.88	0.68-1.14	52	0.72	0.51-1.03	54	1.13	0.76-1.66	6	0.86	0.3-2.48
L4: >2.35	71	93	0.95	0.72-1.24	48	0.80	0.56-1.15	45	1.17	0.78-1.77	7	1.37	0.5-3.79
PERC Ambient Concentration													
L1: <0.175 (ug/m^3)	72	117	ref.	---	70	ref.	---	47	ref.	---	11	ref.	---
L2: 0.175-0.190	87	131	0.94	0.73-1.21	60	0.73	0.52-1.03	71	1.26	0.87-1.82	8	0.62	0.25-1.54
L3: 0.190-0.213	66	107	1.15	0.89-1.5	55	1.01	0.71-1.44	52	1.37	0.92-2.03	8	1.08	0.43-2.67
L4: >0.213	70	97	0.99	0.76-1.3	49	0.86	0.6-1.24	48	1.20	0.8-1.79	4	0.53	0.17-1.65
PERC Modeled Exposure													
L1: <0.069 (ug/m^3)	30	47	ref.	---	27	ref.	---	20	ref.	---	4	ref.	---
L2: 0.069-0.077	92	150	0.99	0.71-1.37	78	0.91	0.59-1.42	72	1.09	0.66-1.79	11	0.87	0.28-2.72
L3: 0.077-0.086	93	137	0.99	0.71-1.38	74	0.96	0.62-1.49	63	1.04	0.63-1.72	11	1.07	0.34-3.36
L4: >0.086	80	118	1.05	0.75-1.47	55	0.88	0.56-1.4	63	1.27	0.77-2.1	5	0.64	0.17-2.38
			(*)						(**)				

(*)- Trend significant at p<0.10
(**)- Trend significant at p<0.05
(+)- Individual IRR significant at p<0.05

Figure 1. Monitoring Trend Results for Benzene

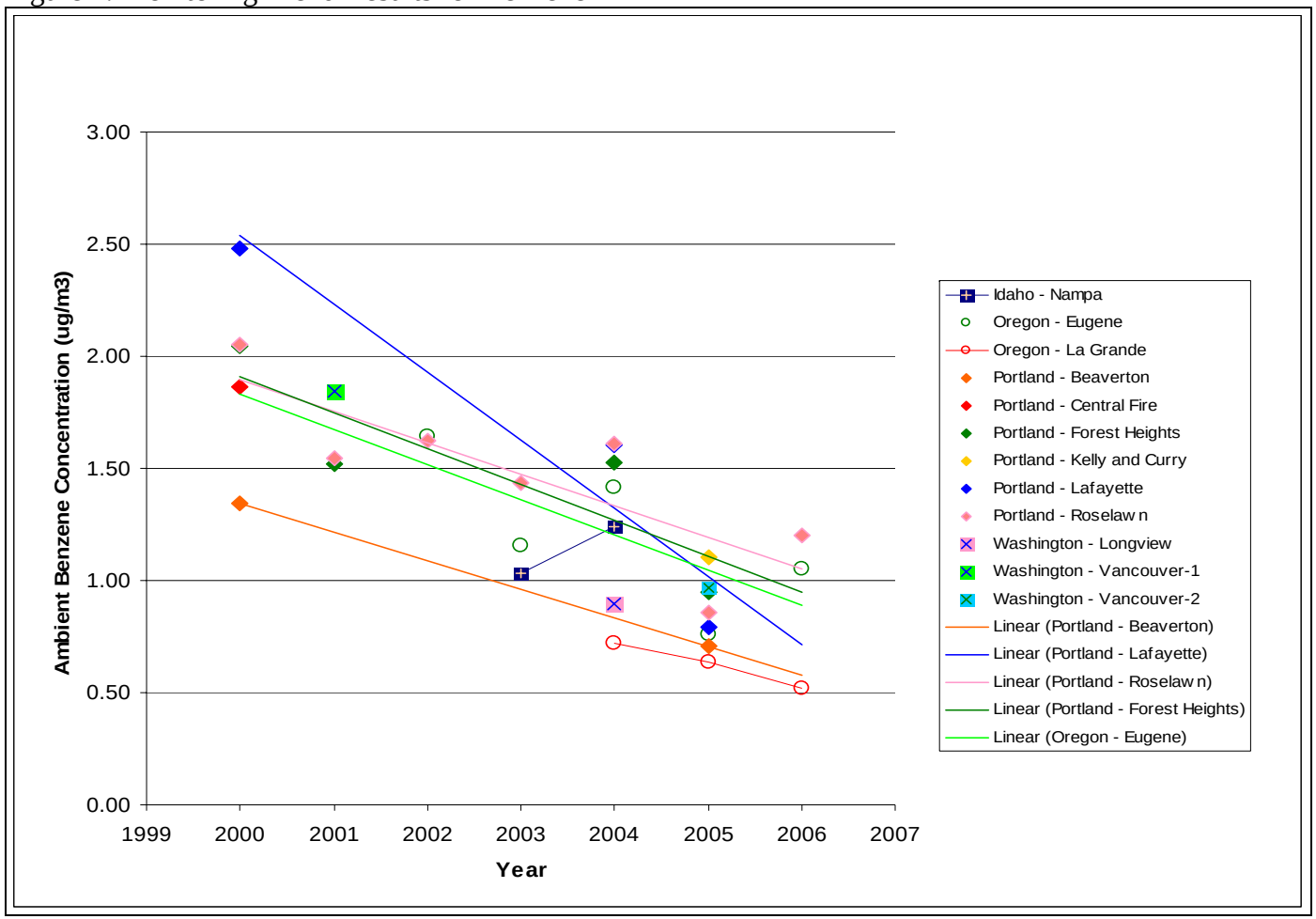


Figure 2. PATA Modeling Receptor Values of Benzene Exposure with Source Locations

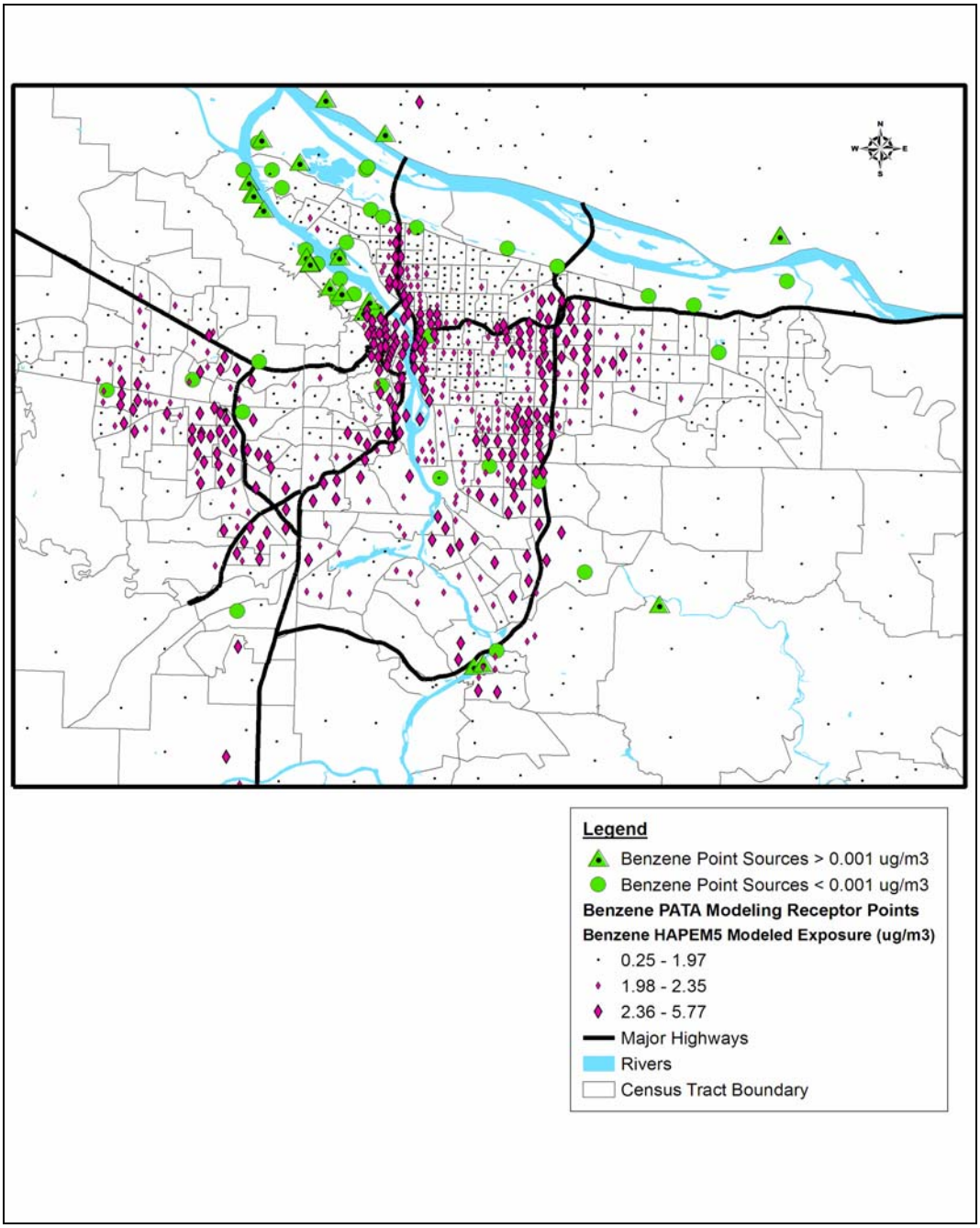


Figure 3. Census Tract Average Benzene Modeled Exposure and Source Locations

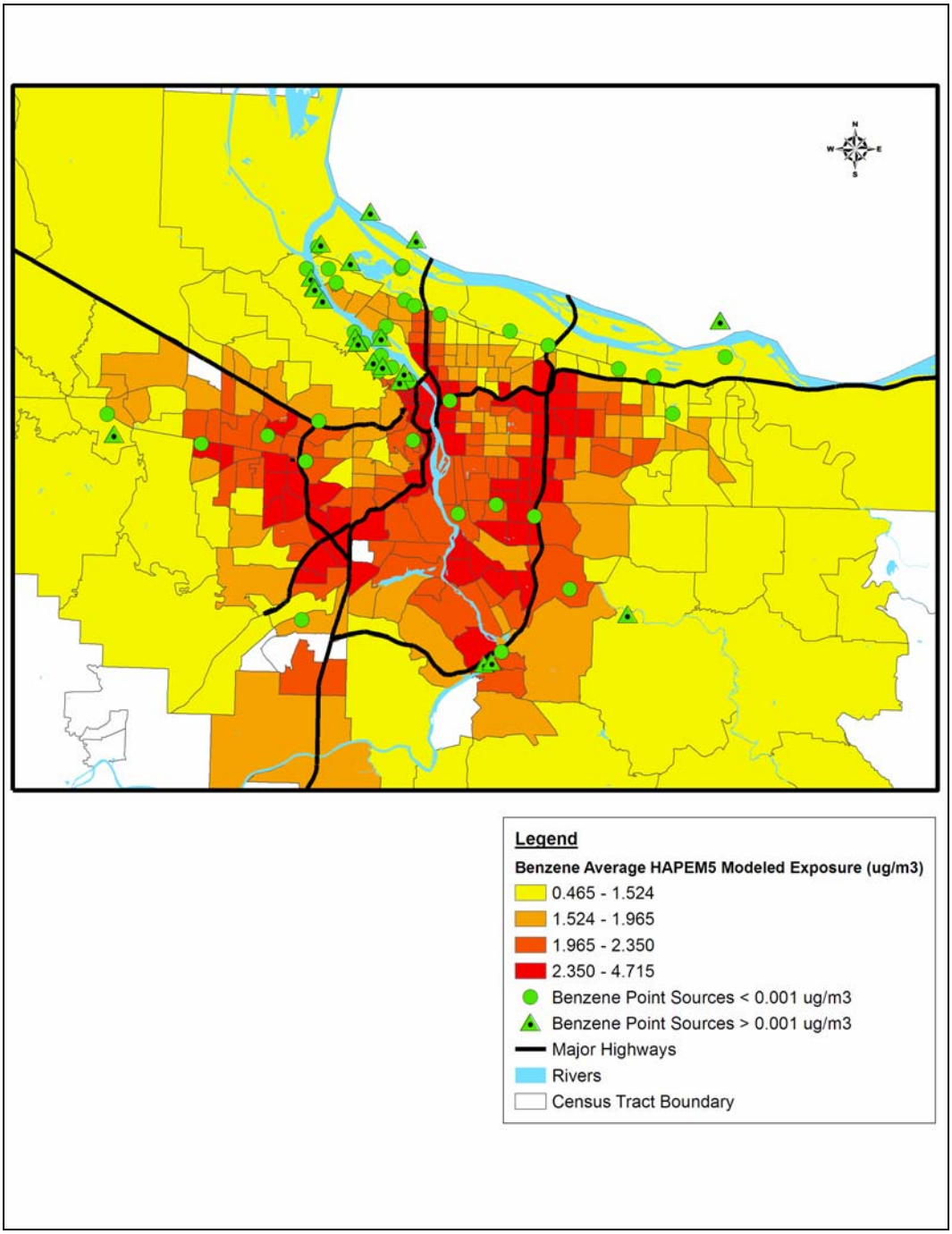


Figure 4. Census Tract Average Benzene Modeled Concentration and Source Locations

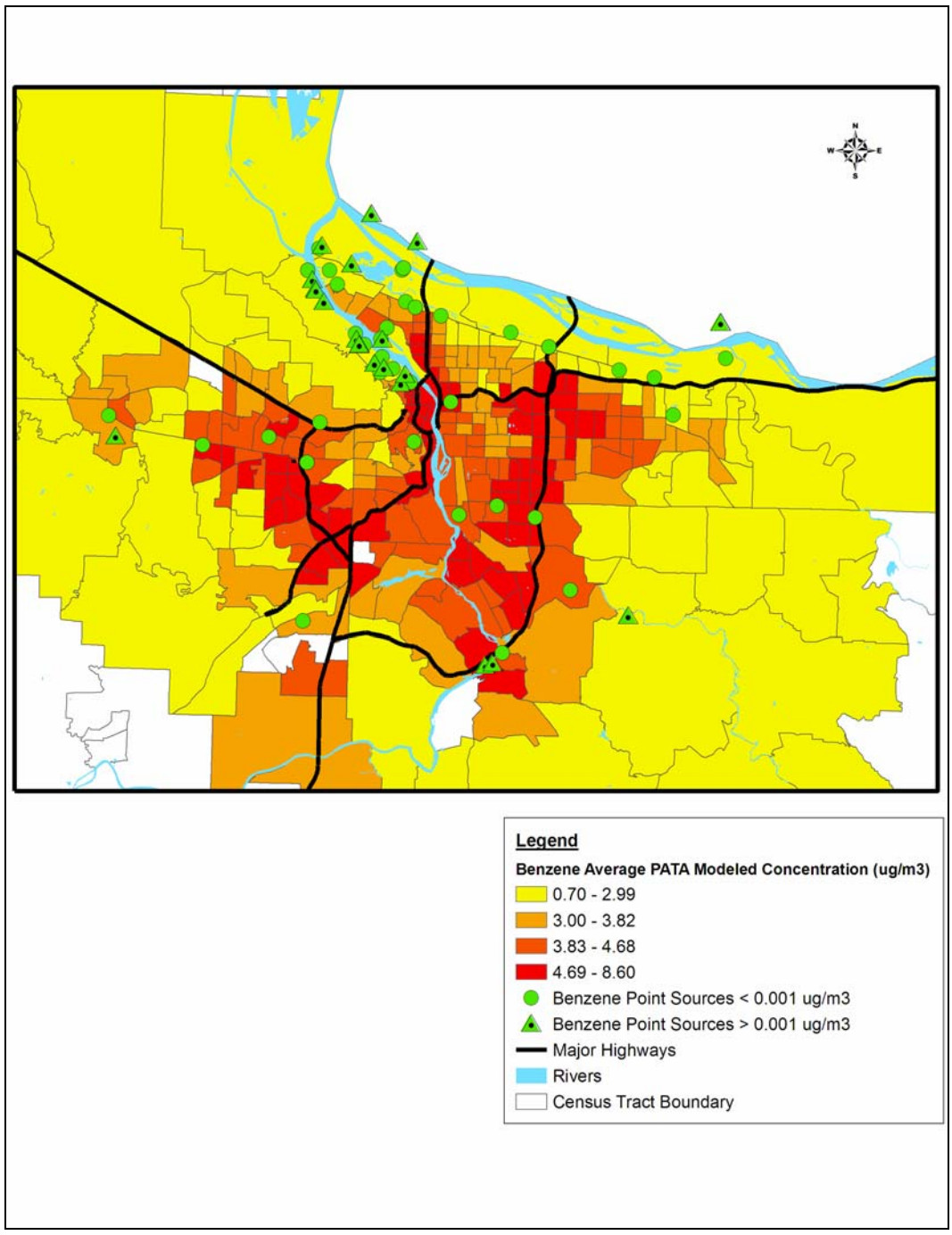


Figure 5. Census Tract Average Modeled PERC Exposure and Source Locations

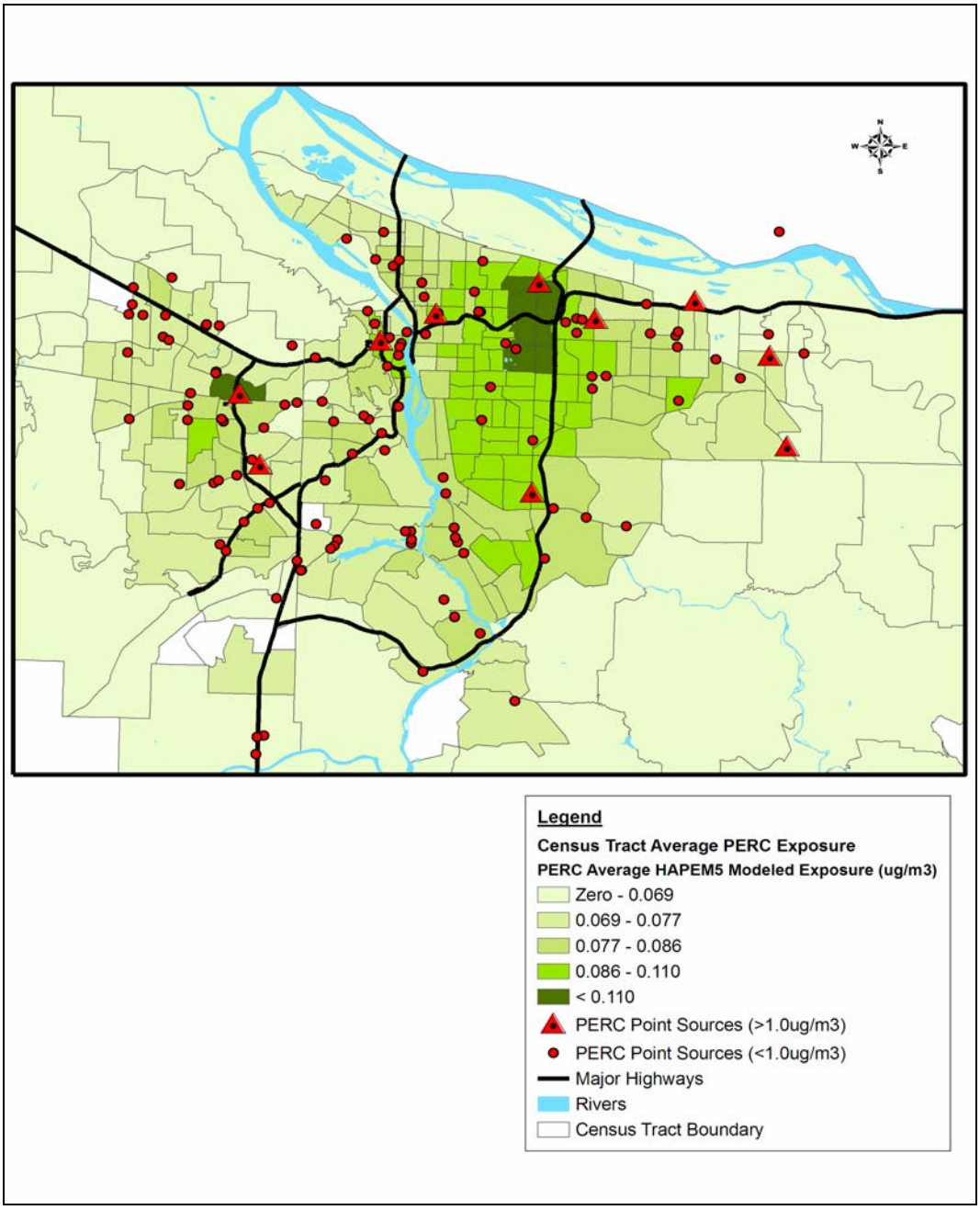


Figure 6. Standardized Acute Myeloid Leukemia Rates for Combined Genders

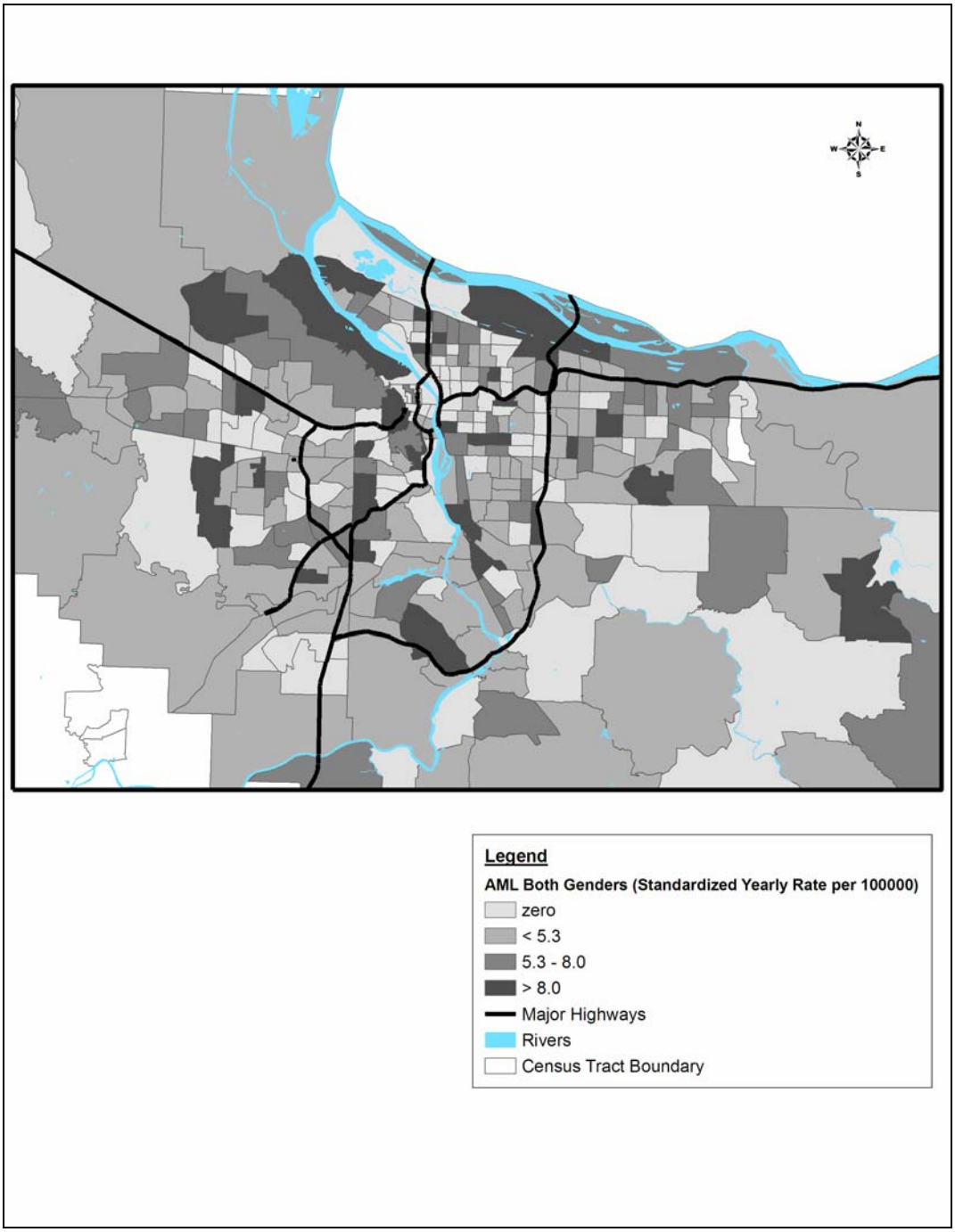


Figure 7. Standardized Total Myeloid Leukemia Rates for Combined Genders

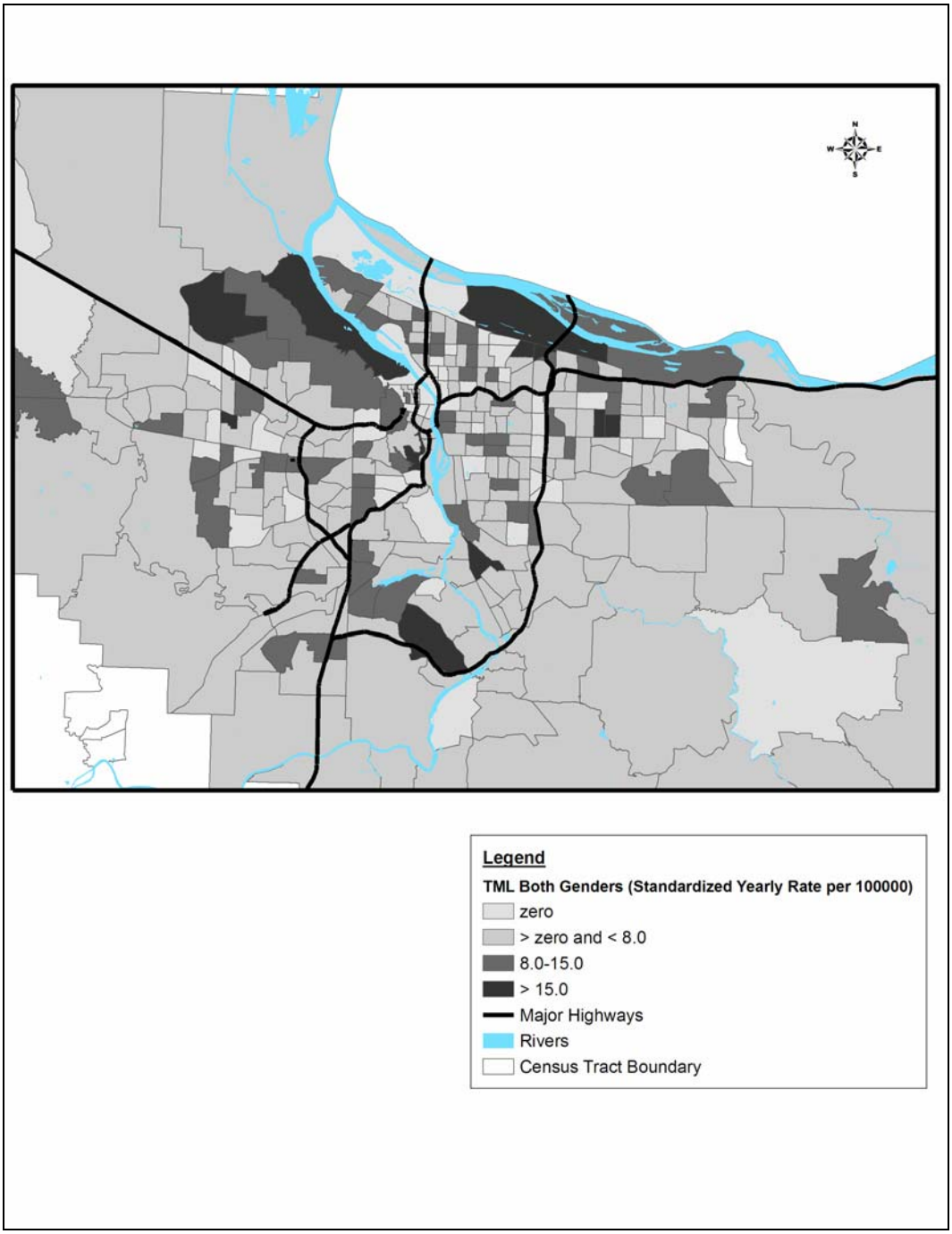


Figure 8. Standardized Total Leukemia Rates for Combined Genders

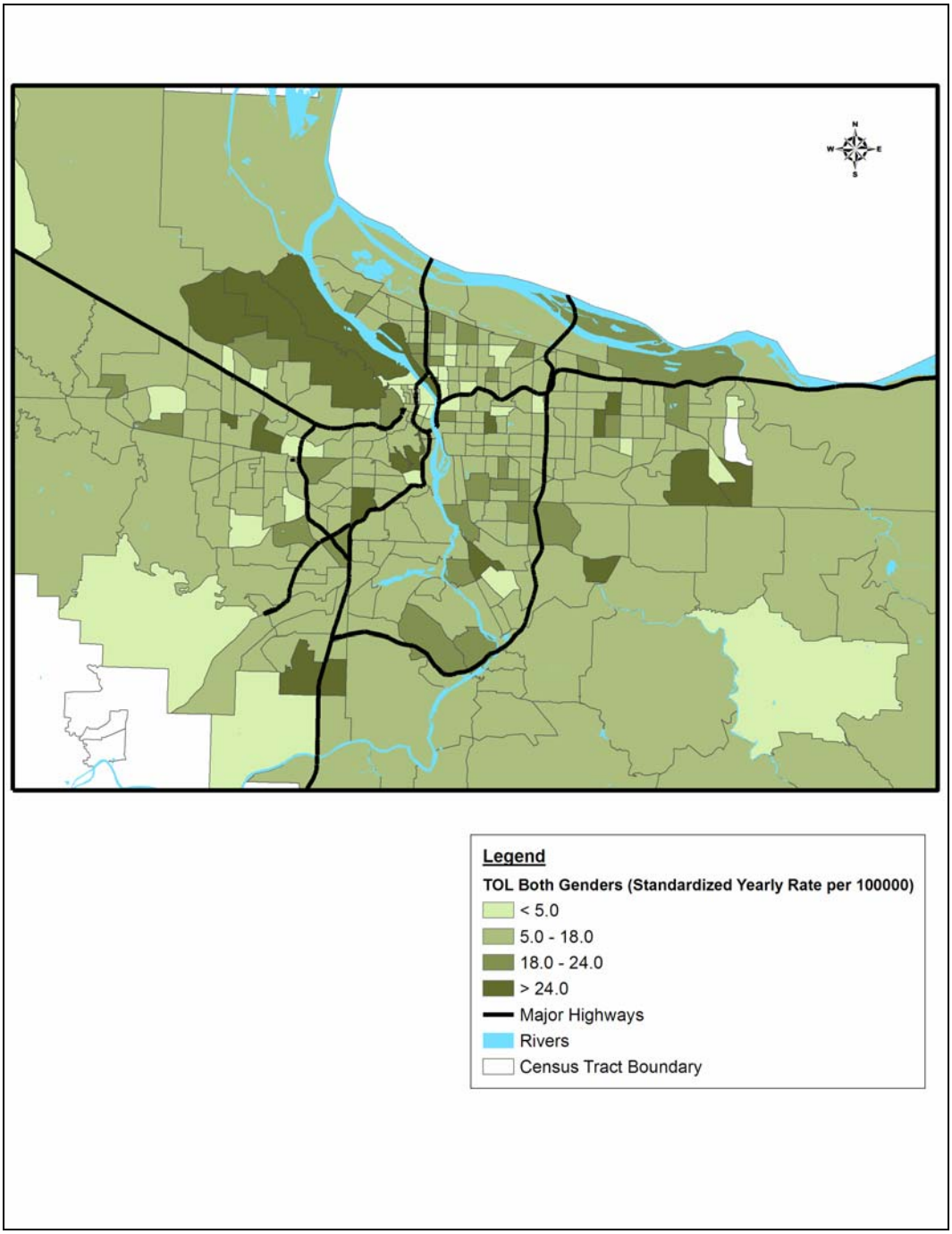


Figure 9. Acute Myeloid Leukemia Rates and PATA Receptor Values for Benzene Modeled Exposure.

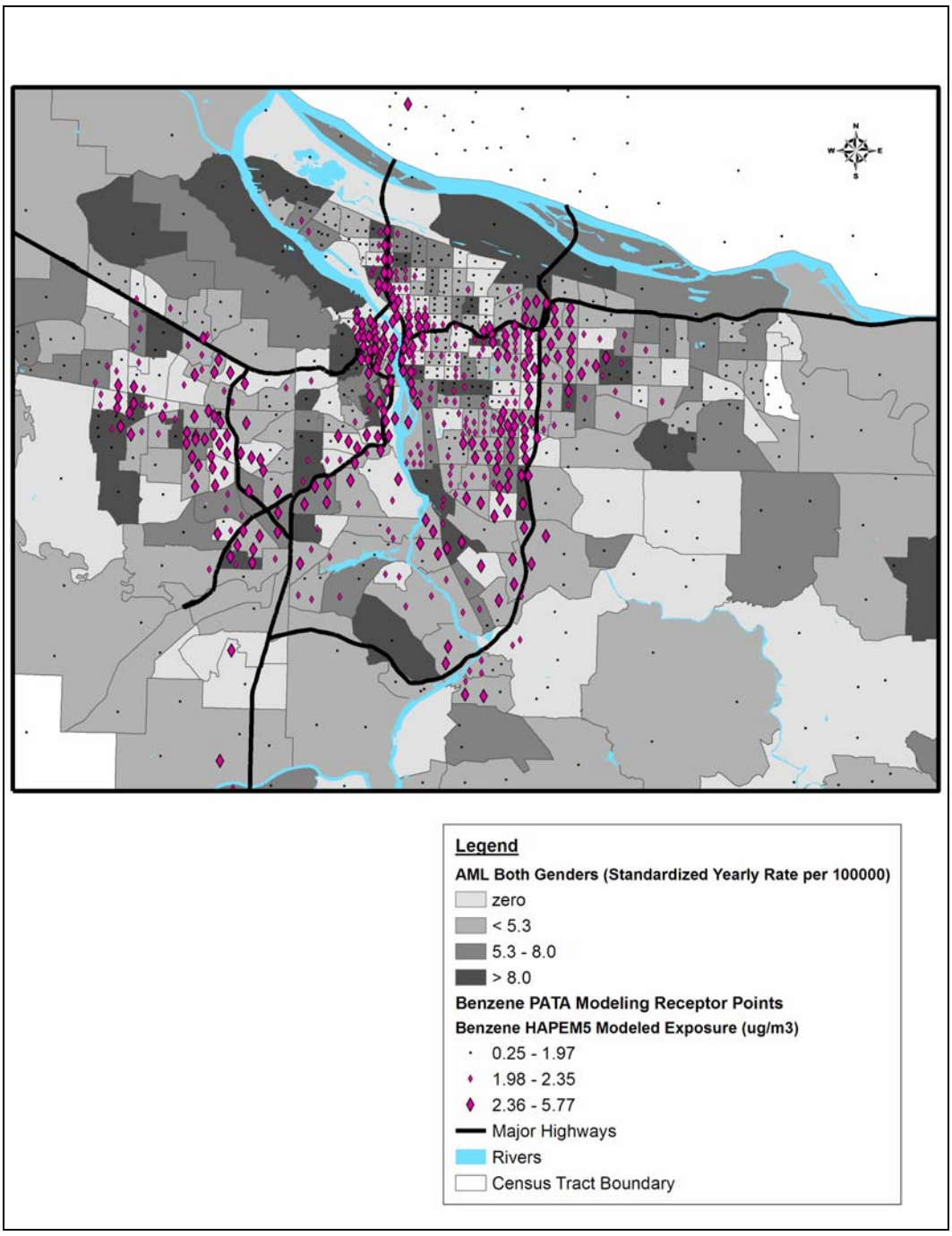


Figure 10. All Ages Acute Myeloid Leukemia Rates and Benzene Point Source Locations

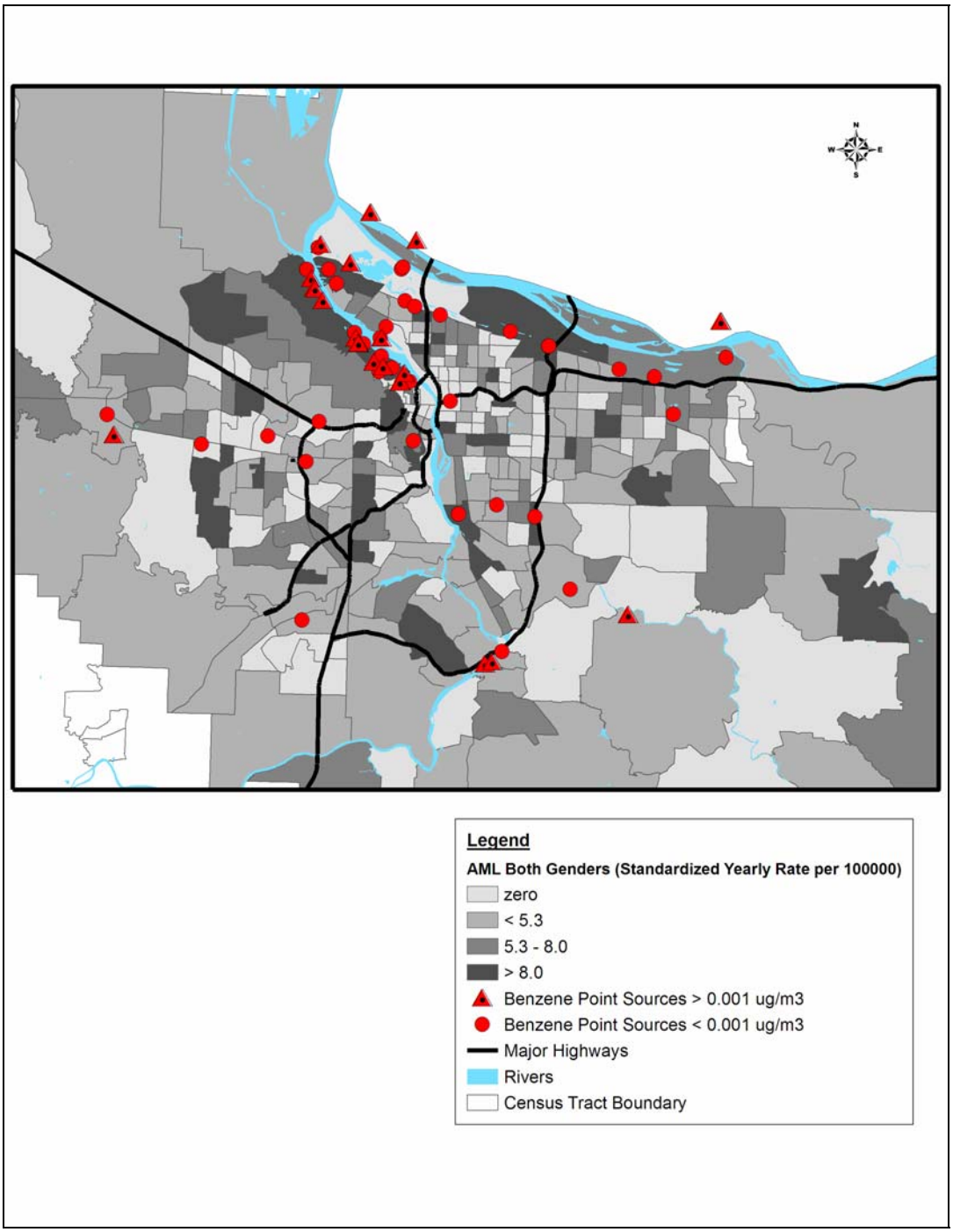


Figure 11. Acute Myeloid Leukemia for Under Five Years of Age with Benzene Modeling Receptor Values and Source Locations

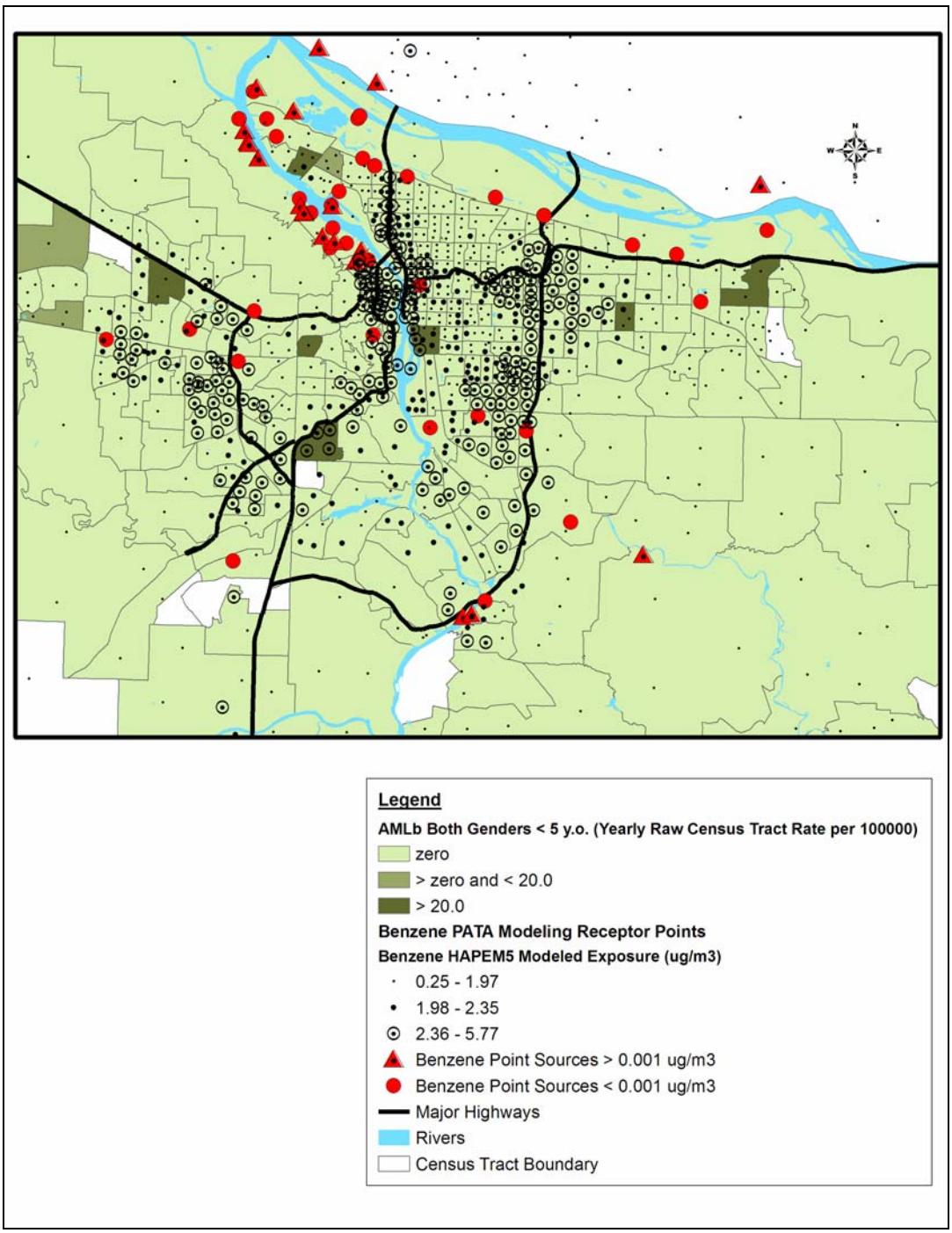


Figure 12. Acute Myeloid Leukemia for Under 19 Years of Age
with Benzene Modeling Receptor Values and Source Locations

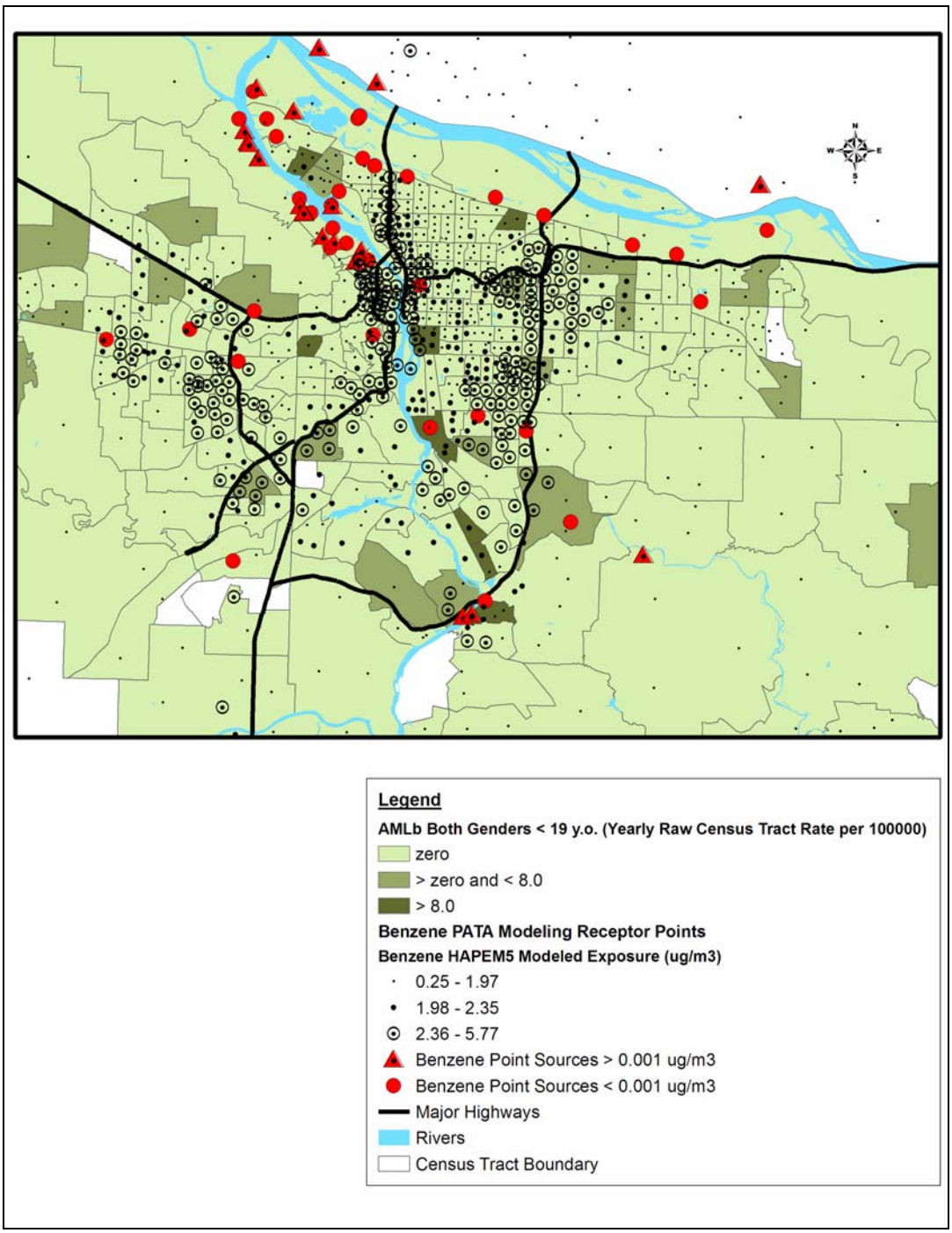


Figure 13. Total Myeloid Leukemia for Under Five Years of Age
with Benzene Modeling Receptor Values and Source Locations

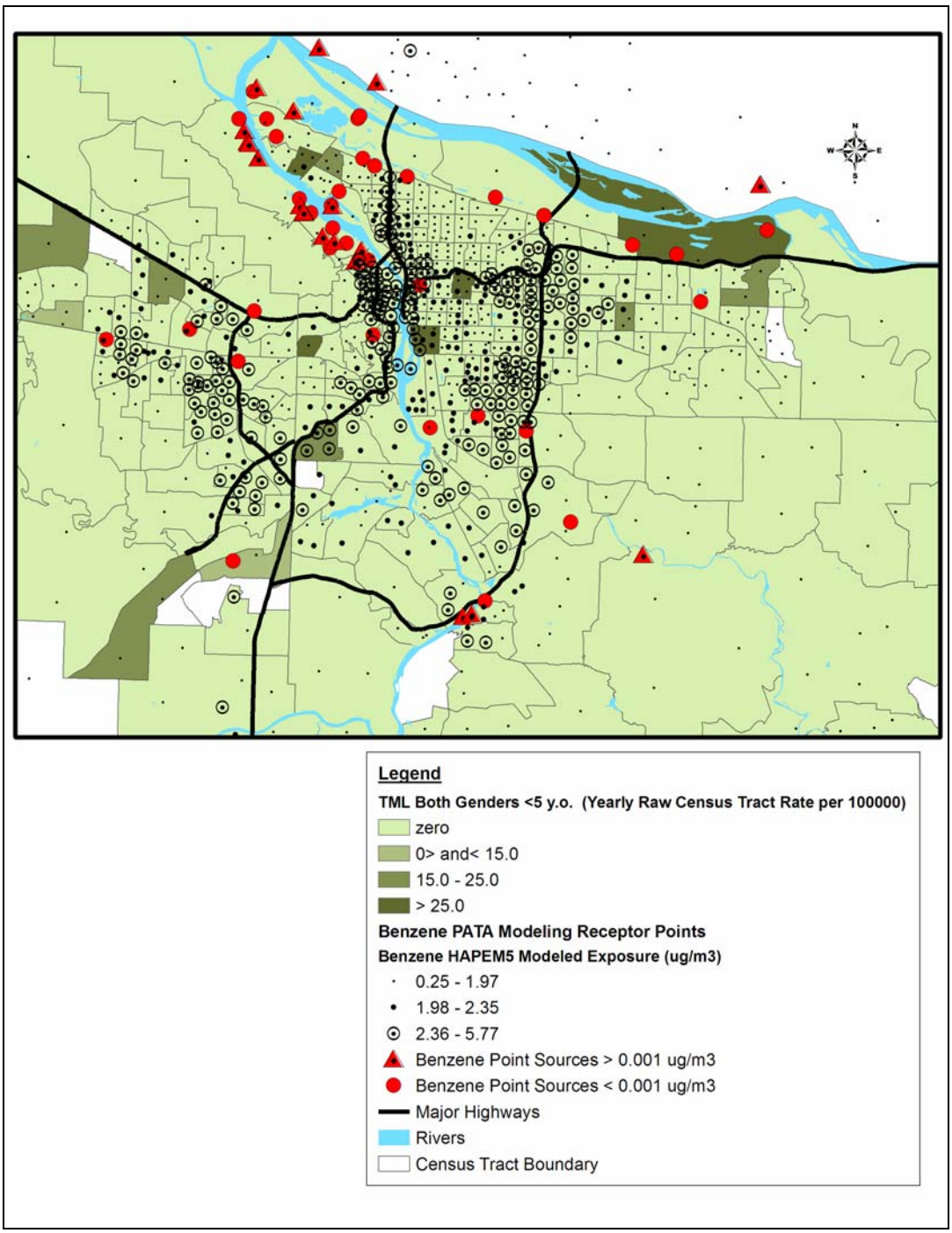


Figure 14. Under 19 Years of Age, Total Myeloid Leukemia with Benzene Modeling Receptor Values and Source Locations.

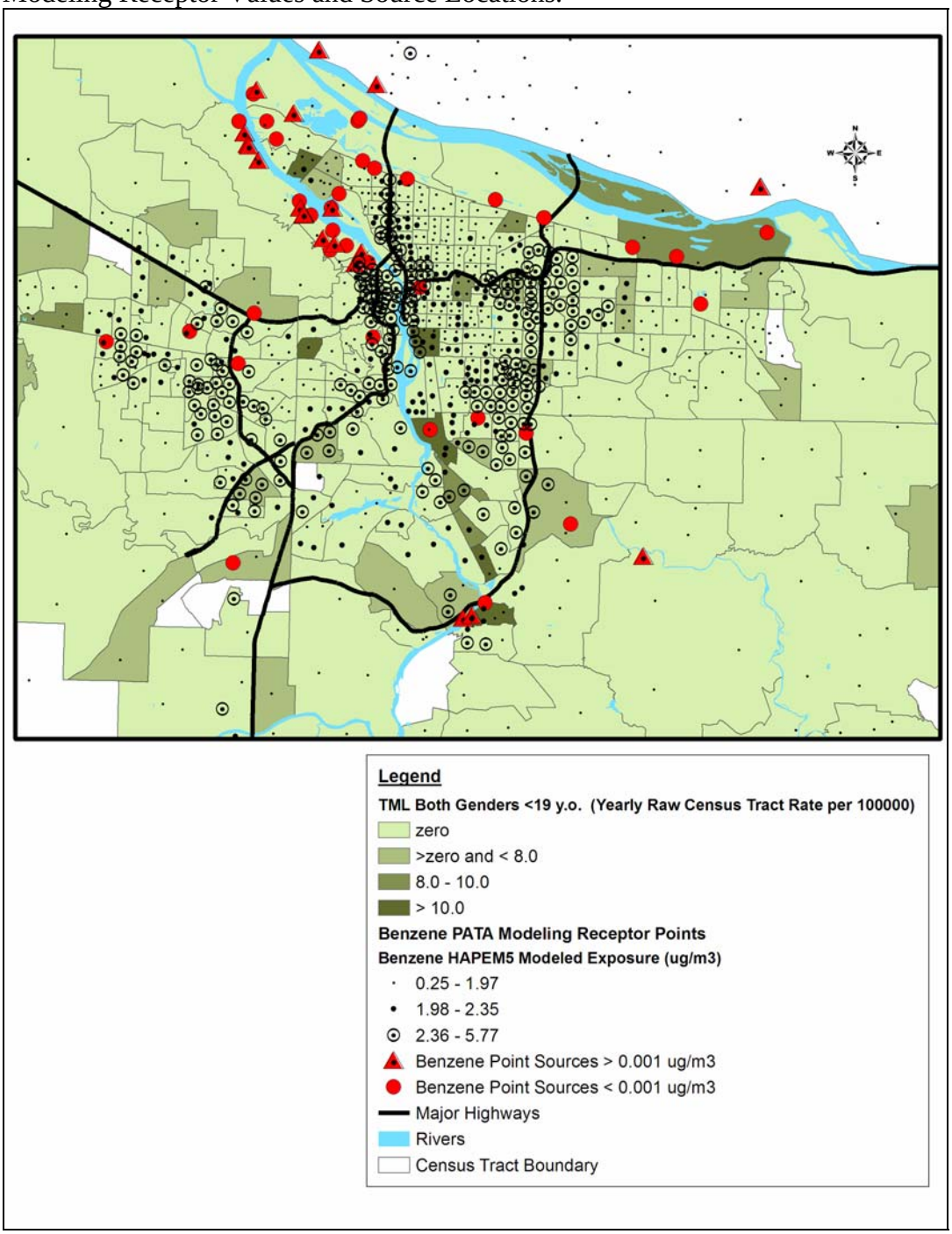


Figure 15. Total Leukemia for Under Five Years of Age With Benzene Modeling Receptor Values and Source Locations.

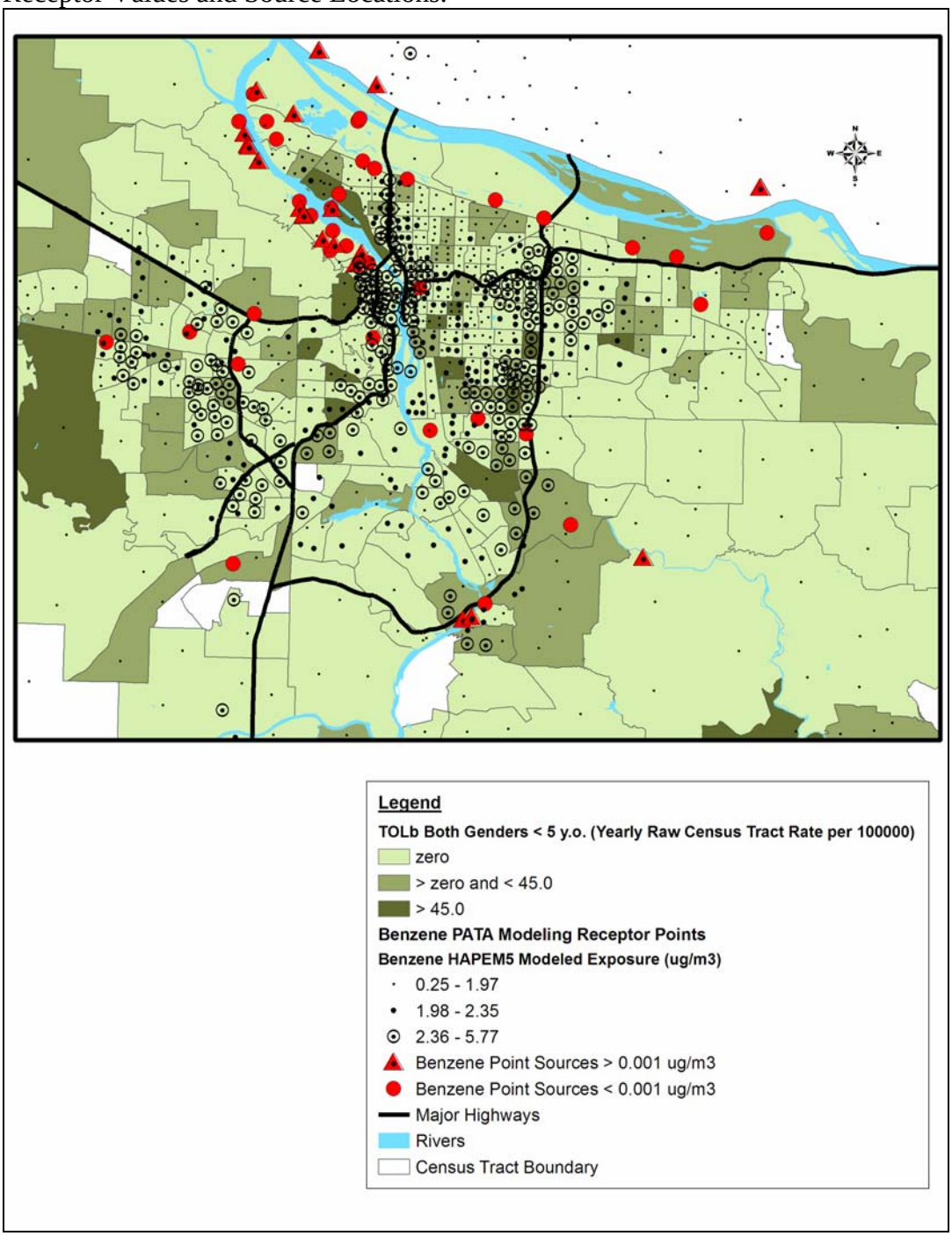


Figure 16. Total Leukemia for Under 19 Years of Age with Benzene Modeling Receptor Values and Source Locations

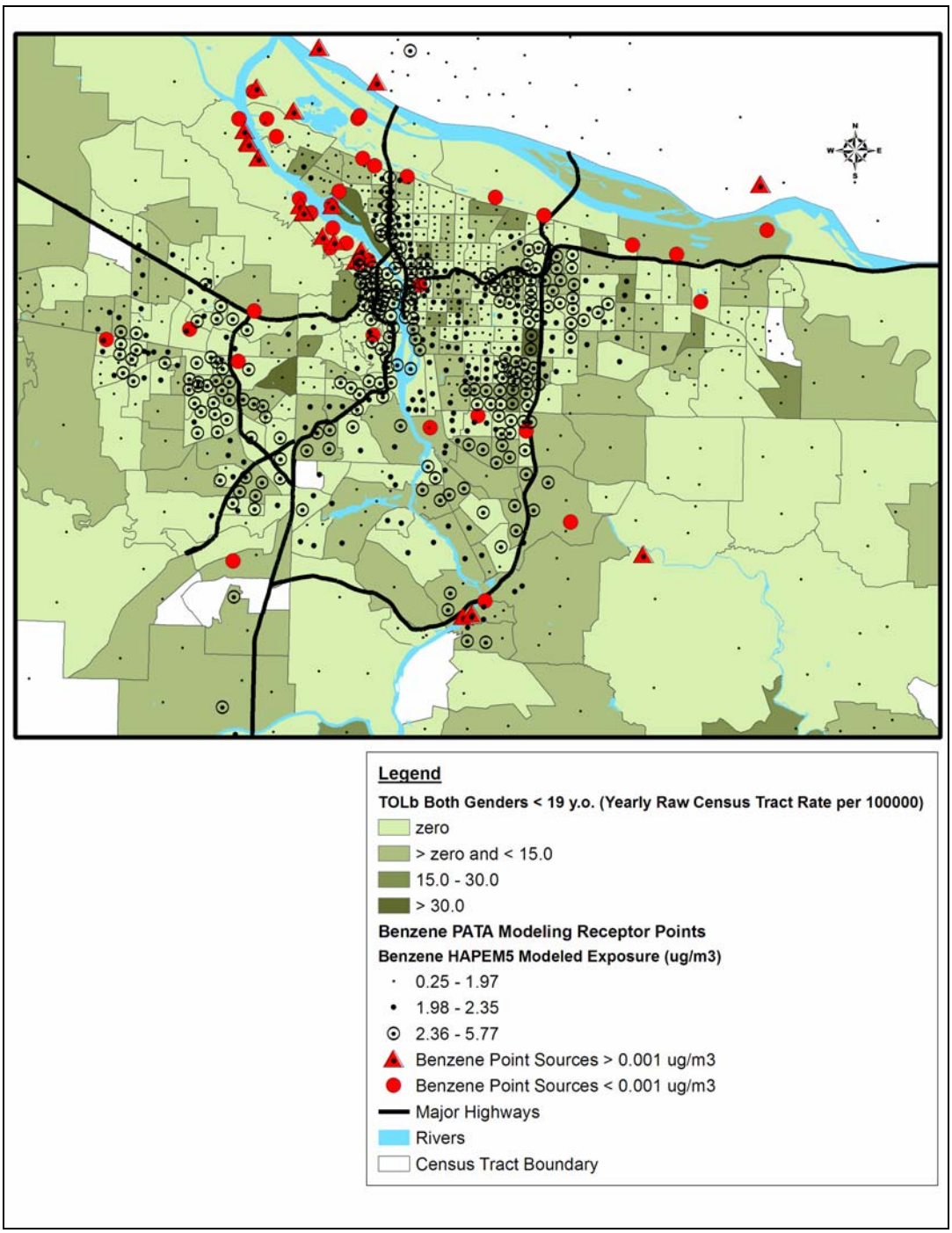
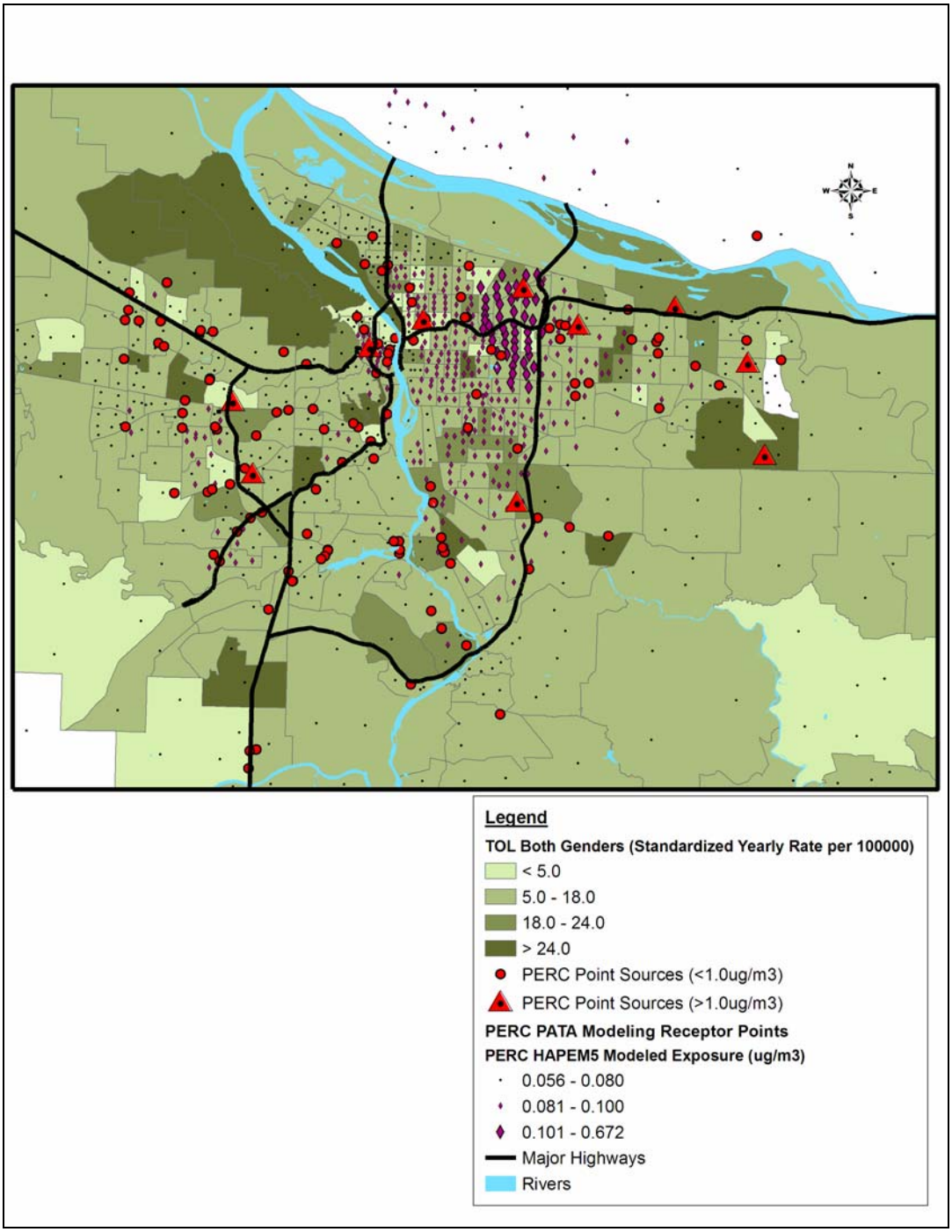


Figure 17. Total Leukemia Rates and PERC Modeled Exposure Receptor Values and Source Locations



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APPENDIX

APPENDIX

This chapter contains analysis and discussion not included in the manuscript, Chapter 3. It is arranged in the same order as the manuscript, with analogous sections. Tables and figures which could not be included in the manuscript are discussed and presented here. Material covered in Chapter 3 is not repeated here, so the most important results and conclusions are omitted from this chapter.

Materials and Methods (Additional Material)

Separate Analysis of Long Duration Residence Census Tracts

We separated census tracts into two groups; those having a median year moved into residence less than 1995 and greater than or equal to 1995 (Table 9). Census tracts in this "Long Duration Residence" group have a median duration of residence among their population of between six and fifteen years. The latency period for AML associated with benzene exposure has been characterized at less than ten years and perhaps less than one year by one study (Hayes et al. 1997; Morgan and Alvares 2005). We compared bivariate correlations of benzene modeled exposure and leukemia incidence for these two groups and calculated incidence rate ratios at exposure quartiles for the long duration residence group.

Oregon State Cancer Registry

We obtained only leukemia case counts by census tract, so the data were entirely de-identified and we did not contact or track any individual subjects during the course of this study. Because we used only de-identified data at the census tract level, our study met exempt criteria and we were not required to obtain written consent from case

subjects. Upon inclusion in the registry, OSCaR does inform newly diagnosed persons that their de-identified information may be used for research purposes (ODHS 2006).

Averaging Hazardous Air Pollutant Measurements in Census Tracts

Because the majority of the model receptor points in the PATA study are located at census block group centroids, we did not encounter model points that either straddled borders of census tracts or were located near edges of tracts. We used a geographic information system (ESRIinc. 2005), weighted all points within tracts equally, to calculate the census tract averages for benzene and PERC, exporting these for statistical analysis.

Results (Additional Material)

Goodness of Fit Results for Poisson Regression

Goodness of Fit statistics for Poisson regressions are reported in Table 10.

Bivariate Correlations

Correlation Statistics are shown in Table 11 for census tract average benzene and PERC measures, both gender leukemia rates and demographic variables. These are discussed in Chapter 3.

Mapping Demographic Variables

Figures 18 and 19 show the spatial distribution of household income and percent of population having less than high school education. They are in general agreement in

reflecting the spatial distribution of SES in the city. We divided the US Census variable "Median Year Moved Into Residence" (MYMI) into two groups of less than 1995 and 1995 or later (see Figure 20). Distribution of this variable has similarities to the income and educations variables, indicating that higher income tends to favor residential stability. However, there are also tracts with more stable population at middle category of income, perhaps indicating more stable but working class neighborhoods.

Mapping Leukemia and Mobile Source Locations

Several census tracts with high TML rates in the under 19 year old age group are near major highways (see Figure 14). In fact, additional tracts with high rates are located near major roads we were not able to include in our map (southwest and south middle of map). These roads and highways include the continuation of the Interstate 5 freeway, which ends abruptly on our map, and Milwaukie Boulevard which, while not a freeway, is a very busy expressway/major arterial street linking the east side of Portland and the Oregon City area.

Analysis for Longer Duration Residence Group

We divided census tracts in our study area into two groups based on the median year moved into residence and calculated bivariate Spearman correlations separately for each group. Correlations for leukemia on average modeled benzene exposure in the Long Duration Residence group are presented in Table 9. Correlations for separate and combined gender groups of the three types of leukemia types all increase in the longer duration residence group. Correlations for all but combined gender AML become positive and, even though it is still negative, the change in combined gender AML is the largest among the groups analyzed.

We computed incidence rate ratios at quartiles of benzene modeled exposure for census tracts having a median year moved into residence of 1994 or greater (see Table 12. Using the first quartile as a reference, the second quartile showed statistically significant elevations in incidence for the combined genders of AML, TML and TOL. The third and fourth quartiles for TML and TOL had non-significant elevations in IRR while only the third quartile of AML also had a non-significant IRR above unity. The female only AML rate at the second benzene exposure quartile also showed significantly elevated incidence.

Risk Assessment

Estimates of population risk can be calculated from the yearly fraction of individual risk, population size and duration of observation:

$$\text{Population Risk} = IR*(1/70)*P*D \qquad \text{Formula 2,}$$

where P is the size of the population group, D is the number of years of observation, and IR is the product of the unit risk value and a particular exposure concnetration. Using Formula 2 to calculate a population risk assumes homogeneity of exposure over the population and even distribution of risk over a person's lifetime. Given these assumptions, any derivation of population risk is a crude estimate, but it can serve to give context to the magnitude of the effect which might be expected. This assumes there is a mechanistic link between exposure to a toxic substance and a disease outcome and that such a link is correctly estimated by the potency value on which the UR is based.

Various ambient concentrations values are presented, along with attributable risk values for individuals and population groups in Table 13. All calculated risk values assume a linear causal relationship in excess cancer which is correctly estimated by the value of UR. The value for "Portland Excess" assumes Portland has an ambient benzene

concentration double a hypothetical national average and estimates the number of extra cases of cancer which would be induced by this “excess” benzene. The resulting excess for Portland over ten years is 1.8 cases of cancer. We use the same calculations to estimate the difference in ten year cancer incidence in an average census tract of approximately 4500 persons which would result from the “increase” in benzene between the 5^{th} and 95^{th} percentiles of modeled exposure and from the first to the fourth quartile of modeled exposure. These figures estimate the expected difference in incidence when comparing census tracts at these exposure levels. The expected increase from the 5^{th} to the 95^{th} percentiles of modeled exposure would be 0.012 cases in the average census tract in ten years. For quartiles of exposure, we calculate that the increase in modeled benzene exposure in the fourth quartile should be expected to induce 0.004 excess cases of cancer in the average census tract in ten years.

For comparison, a numerical approximation of the odds ratio function derived by Rinsky gives an OR of 1.0009 for a lifetime exposure to 1ppb ambient benzene and an OR of 1.00023 for the 0.25ppb difference between quartiles one and four of the PATA modeled exposure (Rinsky et al. 1987). Risk analysis suggests very small increases in leukemia incidence would result from an association with ambient benzene and these changes in incidence may not be detectable using ecologic methods (Duarte-Davidson et al. 2001).

Both CALPUFF modeled ambient concentration and HAPEM5 modeled personal exposure values for benzene were available to us in the PATA data we received. To understand the relationship between these two variables, we plotted them together (Figure 21). Census tracts are sorted into three groups, based on AML rates of zero, less than six per 100,000, or greater than six per 100,000 persons. In our data set for benzene, the HAPEM5 modeled exposure values are very linearly related to the modeled concentration at the census tract level. Modeled exposure is approximately half

of concentration. This relationship does not appear to differ between the three AML rate groups we examined.

Discussion (Additional Material)

Benzene values in PATA are an average taken at the centroids of census tracts. For some residents this will overestimate actual exposure, for others it will be and underestimate (those living close to major roads for instance). Studies have shown that benzene exposure falls off rapidly with distance from roadways (Carr et al. 2002).Some census tracts located near major roads and freeways show some of the highest benzene levels in the PATA study area, so this effect may be partially captured, at least on the scale of major highways. Busy surface streets may contribute the same effect on a smaller scale and this will not be discernable with the PATA data. If benzene from traffic were a contributing factor in AML (and thus more cases occurred near busy roads), using average values from census tracts would result in cases being assigned an erroneously low exposure level and this study would underestimate the magnitude of the association between benzene concentration and disease. It is possible that this misclassification can result in elevated IRRs at low exposure quartiles, even to the point of low quartiles having higher IRRs than high quartiles (Rothman and Greenland 1998). The IRR results for the longer duration residence group, described above, would appear consistent with better exposure classification with respect to migration and a continued, unaccounted for misclassification due to location in which true exposure (and thus IRRs) is higher than recorded in low quartiles.

Geographic analysis can suggest insights which may not be apparent from a statistical viewpoint. We mapped modeled exposure of benzene along with known point sources and major highways in order to understand the exposure data we were using,

finding that mobile and area sources were the most apparent correlation to the PATA model data (see Figure 2). The model data did not appear to be strongly influenced by known point sources in major industrial areas but was concentrated around the downtown city core and areas of major highway corridors and interchanges. We have no reason to doubt the accuracy of the modeling work, in fact mobile and area sources may be greater than these point sources and thus it may be totally accurate that there is a less obvious contribution from point sources when they are mapped together. However, incidence of leukemia seems to increase in some census tracts near certain point and mobile sources in the PATA study area and it is important to examine this effect. Adult AML is high in some census tracts near major point source congregations near the Willamette river while childhood TML seems high near major roadways in our study area (see Figures 10, 13 and 14). If an ambient benzene influence on leukemia exists and census tract level benzene data does not represent an accurate proxy of true ambient exposures, then census tract level analysis would not be able to detect such an effect.

The long duration residence group may have more consistently lived in the census tract of current residence than the shorter duration residence group. If this is true, the long duration residence group may have actual ambient exposures which are more accurately represented by census tract averages. Essentially, the migration misclassification may be reduced in this group, though other misclassifications due to daily activity, commuting, and occupational exposures would still be unknown.

Table 9 Benzene and Leukemia Analysis - Split on Census Tract Variable

Median Year Moved Into Residence (MYMI)

Tracts Grouped by MYMI	Short Duration	Long Duration
Minimum MYMI	1995	1985
Maximum MYMI	1999	1994
Range MYMI	1995-1999	1985-1994
Mean Income	53984	66423
Mean Education (%<HS)	14	10
Mean CT Population	4672	4298
Census Tract Count	214	79

Increase in Spearman Correlation Coefficient of Leukemia Rate and Benzene Exposure
Comparing Long Duration Group to Short Duration Group

	r - Short Duration	r - Long Duration	r - INCREASE
AMLm	-0.192**	0.009	0.201
AMLf	-0.135*	0.041	0.176
AMLb	-0.224**	-0.020	0.204
TMLm	-0.116	0.048	0.164
TMLf	-0.087	0.057	0.144
TMLb	-0.124	0.010	0.134
TOLm	-0.061	0.098	0.159
TOLf	-0.038	0.083	0.121
TOLb	-0.091	0.043	0.134

** p< 0.01

* p < 0.05

Frequency of Census Tracts
For Values of Census Variable "MYMI"

MYMI (Year)	Count of Tracts
1985	1
1990	4
1991	11
1992	17
1993	23
1994	24
1995	56
1996	79
1997	45
1998	26
1999	9

Table 10. Poisson Regression, Goodness of Fit Statistics

HAP	DISEASE	Gender	HAP	Household Income	Percent of Population with < high school Education	CONSTANT	1/deviance	1/Pearson
Benzene Modeled Exposure	AML	m	-0.15	1.3E-06	2.4E-03	-10.09	1.09	1.00
	AML	f	0.02	-7.8E-07	2.6E-03	-10.37	1.15	1.19
	AML	both	-0.07	3.7E-07	2.7E-03	-10.23	1.26	1.16
	TML	m	-0.05	1.0E-06	2.0E-03	-9.81	1.14	1.00
	TML	f	0.05	1.4E-06	6.0E-03	-10.27	1.17	1.12
	TML	both	0	1.2E-06	1.9E-03	-10.03	1.19	1.09
	TOL	m	-0.02	2.5E-06	-4.8E-04	-9.17	1.18	1.17
	TOL	f	0.11	2.7E-06	3.0E-03	-9.62	1.46	1.31
	TOL	both	0.04	2.6E-06	1.3E-03	-9.38	1.39	1.38
Benzene Ambient Concentration	AML	m	-0.06	1.9E-06	3.7E-03	-10.19	1.09	1.00
	AML	f	0.02	-4.7E-07	2.9E-03	-10.42	1.15	1.19
	AML	both	-0.02	8.2E-07	3.5E-03	-10.31	1.26	1.16
	TML	both	0.01	1.5E-06	2.3E-03	-10.08	1.19	1.08
	TOL	both	0.02	2.8E-06	1.4E-03	-9.41	1.39	1.38
PERC Modeled Exposure	AML	m	0.09	4.3E-06	6.7E-03	-10.60	1.09	1.00
	AML	f	-0.81	-1.5E-06	1.9E-03	-10.22	1.15	1.19
	AML	both	-0.35	1.6E-06	4.5E-03	-10.43	1.26	1.15
	TML	both	1.1	1.8E-06	2.4E-03	-10.16	1.19	1.08
	TOL	both	0.96	2.3E-06	5.6E-04	-9.36	1.39	1.39
PERC Ambient Concentration	AML	m	0.12	4.4E-06	6.8E-03	-10.63	1.09	1.00
	AML	f	-0.35	-1.5E-06	1.8E-03	-10.21	1.15	1.19
	AML	both	-0.1	1.6E-06	4.6E-03	-10.44	1.26	1.15
	TML	both	0.36	1.7E-06	2.3E-03	-10.14	1.19	1.08
	TOL	both	0.23	2.1E-06	4.1E-04	-9.32	1.40	1.39

Table 11. Bivariate Correlations – Spearman's rho

		B. M. E.	P. M. C.	B.M.C	P.M.C	AMLb	TMLb	TOLb	Income	MYMI	Educ.	Population
Benzene Modeled Exposure	Correlation Coeffi.	1	0.604**	0.988**	0.647**	-0.163**	-0.091	-0.054	-0.362**	0.201**	0.061	-0.161**
	Sig. (2-tailed)	.	0.000	0.000	0.000	0.005	0.120	0.353	0.000	0.001	0.295	0.005
PERC Modeled Exposure	Correlation Coeffi.	0.604**	1	0.619**	0.954**	-0.062	0.002	0.014	-0.382**	0.011	0.168**	-0.146*
	Sig. (2-tailed)	0.000	.	0.000	0.000	0.285	0.966	0.812	0.000	0.854	0.004	0.012
Benzene Modeled Concentration	Correlation Coeffi.	0.988**	0.619**	1	0.662**	-0.145*	-0.075	-0.041	-0.391**	0.192**	0.118*	-0.115*
	Sig. (2-tailed)	0.000	0.000	.	0.000	0.013	0.202	0.486	0.000	0.001	0.043	0.049
PERC Modeled Concentration	Correlation Coeffi.	0.647**	0.954**	0.662**	1	-0.042	0.009	-0.013	-0.436**	0.033	0.203**	-0.156**
	Sig. (2-tailed)	0.000	0.000	0.000	.	0.470	0.884	0.820	0.000	0.568	0.000	0.007
AML both genders	Correlation Coeffi.	-0.163**	-0.062	-0.145*	-0.042	1	0.819**	0.48**	0.051	-0.059	0.031	0.144*
	Sig. (2-tailed)	0.005	0.285	0.013	0.470	.	0.000	0.000	0.382	0.313	0.594	0.013
TML both genders	Correlation Coeffi.	-0.091	0.002	-0.075	0.009	0.819**	1	0.624**	0.052	-0.052	0.001	0.096
	Sig. (2-tailed)	0.120	0.966	0.202	0.884	0.000	.	0.000	0.378	0.375	0.993	0.100
TOL both genders	Correlation Coeffi.	-0.054	0.014	-0.041	-0.013	0.48**	0.624**	1	0.069	-0.066	-0.015	0.03
	Sig. (2-tailed)	0.353	0.812	0.486	0.820	0.000	0.000	.	0.239	0.256	0.800	0.613
Income	Correlation Coeffi.	-0.362**	-0.382**	-0.391**	-0.436**	0.051	0.052	0.069	1	-0.441**	-0.779	0.179**
	Sig. (2-tailed)	0.000	0.000	0.000	0.000	0.382	0.378	0.239	.	0.000	0.000	0.002
MYMI	Correlation Coeffi.	0.201**	0.011	0.192**	0.033	-0.059	-0.052	-0.066	-0.441**	1	0.192**	0.049
	Sig. (2-tailed)	0.001	0.854	0.001	0.568	0.313	0.375	0.256	0.000	.	0.001	0.400
Education	Correlation Coeffi.	0.061	0.168**	0.118*	0.203**	0.031	0.001	-0.015	-0.779**	0.192**	1	0.006
	Sig. (2-tailed)	0.295	0.004	0.043	0.000	0.594	0.993	0.800	0.000	0.001	.	0.920
Census Tract Population	Correlation Coeffi.	-0.161**	-0.146*	-0.115*	-0.156**	0.144**	0.096	0.03	0.179**	0.049	0.006	1
	Sig. (2-tailed)	0.005	0.012	0.049	0.007	0.013	0.100	0.613	0.002	0.400	0.920	.

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Table 12. Incidence Rate Ratios for Benzene Modeled Exposure in Long Duration Residence Group

		AML					TML					TOL				
Benzene Modeled Exposure (ug/m3)	Census Tracts	Cases	Person Years	IRR	p	95% CI	Cases	Person Years	IRR	p	95% CI	Cases	Person Years	IRR	p	95% CI
L1: <1.52	24	24	967670	ref	~	~	35	967670	ref	~	~	87	967670	ref	~	~
L2: 1.52-1.97	26	47	1116020	1.78	0.035	1.04 - 2.78	72	1116020	1.78	0.005	1.19 - 2.67	148	1116020	1.48	0.004	1.13 - 1.92
L3: 1.97-2.35	18	25	868310	1.16	0.602	0.66 - 2.03	43	868310	1.37	0.168	0.88 - 2.14	103	868310	1.32	0.057	0.99 - 1.76
L4: >2.35	12	12	486250	1.00	0.989	0.5 - 1.99	21	486250	1.19	0.521	0.7 - 2.05	61	486250	1.40	0.046	1.01 - 1.94

		AML Male					AML Female					AML < 19				
Benzene Modeled Exposure (ug/m3)	Census Tracts	Cases	Person Years	IRR	p	95% CI	Cases	Person Years	IRR	p	95% CI	Cases	Person Years	IRR	p	95% CI
L1: <1.52	24	15	490080	ref	~	~	9	477590	ref	~	~	1	270390	ref	~	~
L2: 1.52-1.97	26	23	543470	1.38	0.329	0.72 - 2.65	24	572550	2.21	0.041	1.03 - 4.79	3	312670	2.59	0.409	0.27 - 24.94
L3: 1.97-2.35	18	12	421900	0.93	0.853	0.43 - 1.99	13	446410	1.56	0.316	0.66 - 3.62	0	223550	0.00	~	~
L4: >2.35	12	6	237960	0.82	0.688	0.32 - 2.12	6	248290	1.28	0.637	0.46 - 3.6	1	170900	1.58	0.745	0.1 - 25.3

Table 13. Risk Assessment Calculations

Definitions

UR=estimate of lifetime P(cancer) for individual from continuous exposure to Benzene at 1ug/m3. (UR has units of m^3/ug)
EC = Ambient Exposure Concentration (EC has units of ug/m^3)
Benchmark Concentration = ambient concentration for which Risk = $1*10^{-6}$ per 70yr lifetime. BC is a specific EC.
Attributable Risk=UR*Concentration (Excess Cancer Risk from given concentration)
Attributable Risk(yearly, individual)=ARy=AR/70
Lifetime defined as 70 years
AR=Attributable Risk (per person per lifetime)
ARy=Attributable Risk (per person per year)
ARCity10=Attributable Risk (city wide 10 year)
ARCT10=Attributable Risk (avg. census tract 10 year)

Formulas

AR=Attributable Cancer Risk = EC*URE
ppb=0.313*ug/m3
Attributable Risk (group) = ARy *(Group Population)*(Study Duration)

Givens

Portland Population 2000 = 1444219	1444219
Average Census Tract Population = 4508	4508
Oregon Ambient Benchmark Concentration for Benzene (ug/m3)	0.13
URE (units of m3/ug)	7.69E-06

Benzene Level Definition	Ambient Benzene Concentration (ug/m3)	AR	ARy	ARCity10	ARCT10
Portland Average (EPA Monitoring)	2.24	1.7E-05	2.5E-07	3.6	1.1E-02
Half of Portland Average (Hypothetical "Less Exposed" City	1.12	8.6E-06	1.2E-07	1.8	5.5E-03
Portland Excess	1.12	8.6E-06	1.2E-07	1.8	5.5E-03
PATA 5th Percentile (Modeled Exposure)	0.856	6.6E-06	9.4E-08	1.4	4.2E-03
PATA 95th Percentile	3.22	2.5E-05	3.5E-07	5.1	1.6E-02
PATA delta 5th to 95th percentiles	2.36	1.8E-05	2.6E-07	3.7	1.2E-02
PATA Q1 (modeled exposure)	1.52	1.2E-05	1.7E-07	2.4	7.5E-03
PATA Q4 (modeled exposure)	2.35	1.8E-05	2.6E-07	3.7	1.2E-02
PATA delta Q1 TO Q4 (modeled exposure)	0.83	6.4E-06	9.1E-08	1.3	4.1E-03

Figure 18. Census Tract Average Household Income

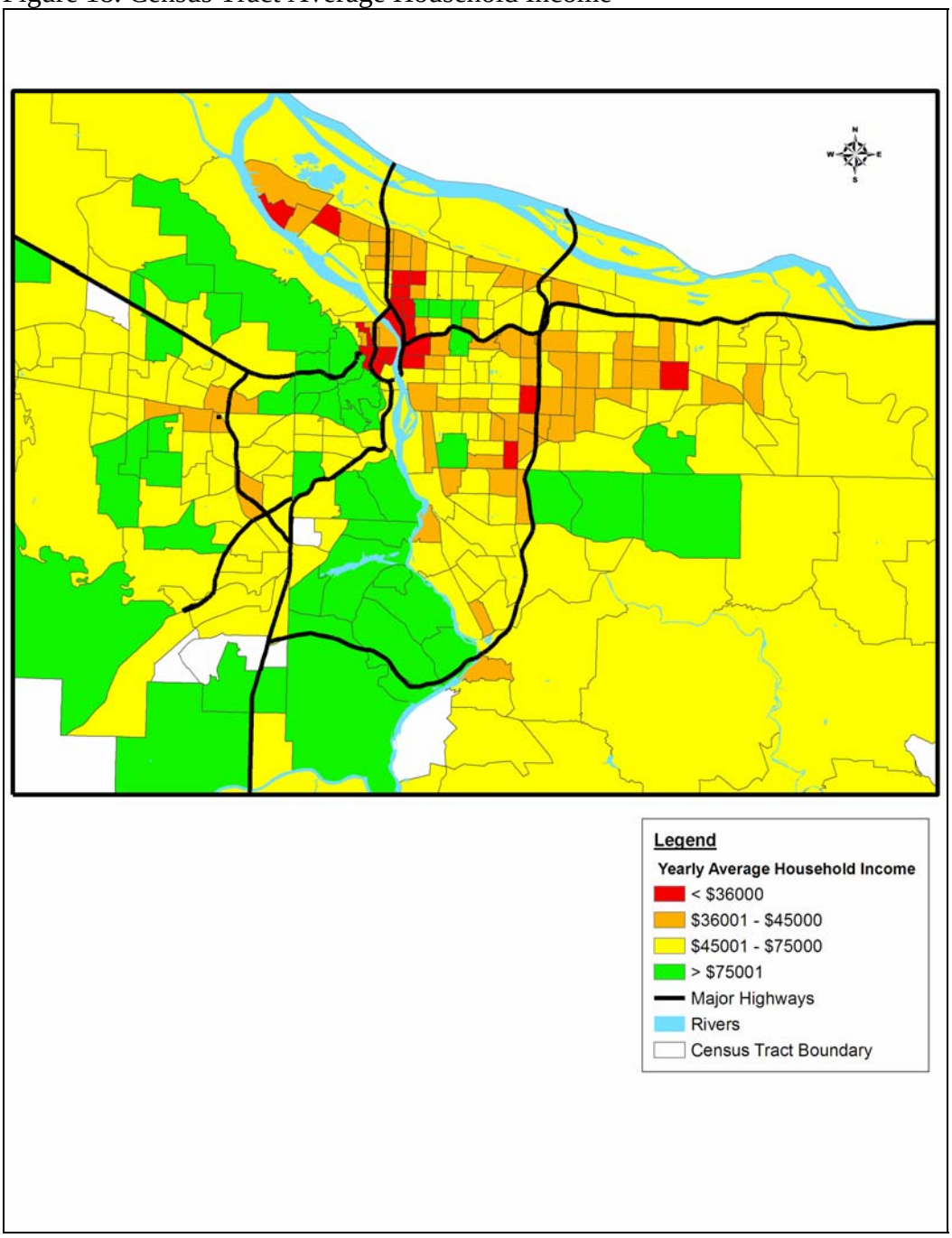

Figure 19. Census Tract Average Percent Population Over Age 25 with Less than High School Education

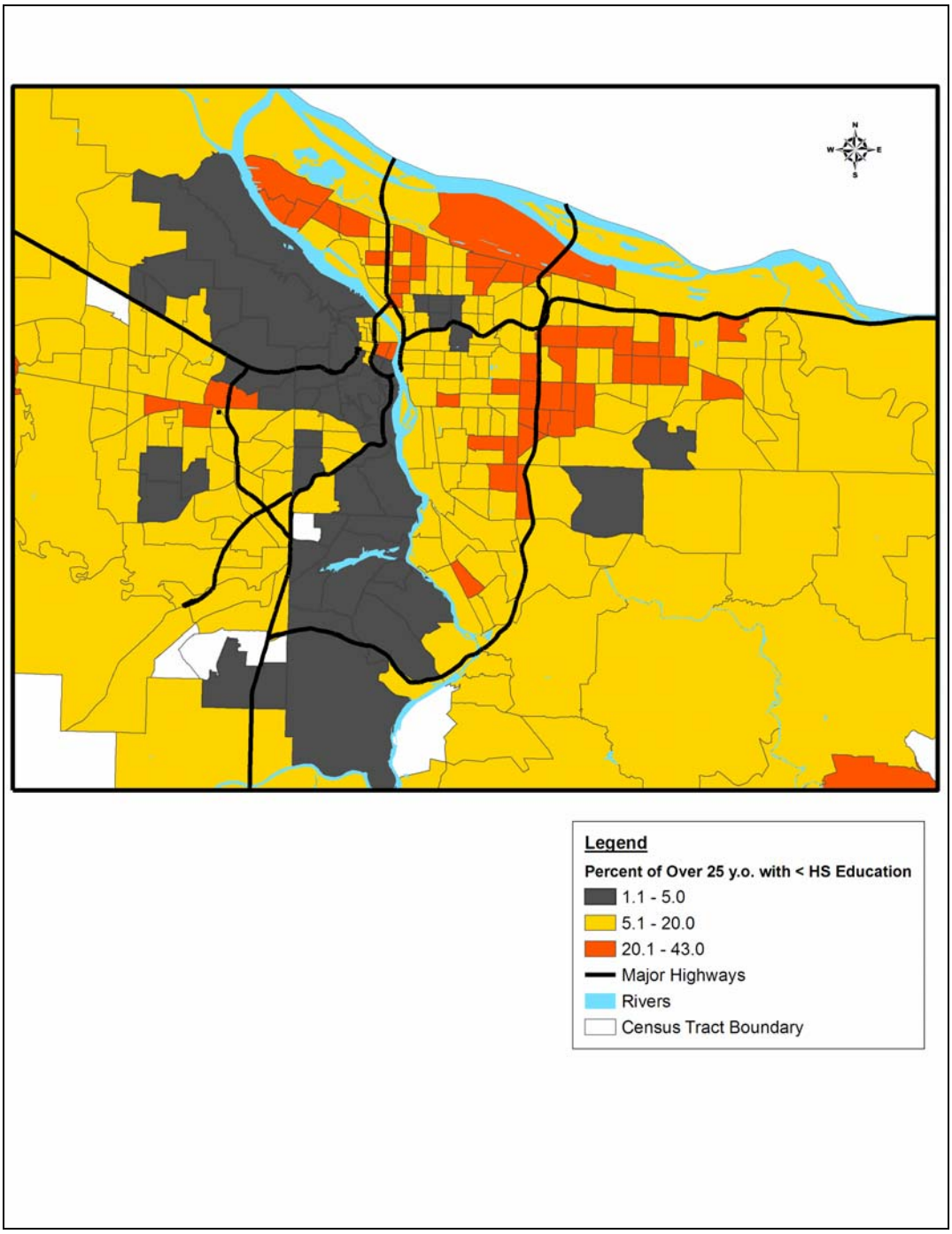

Figure 20. Census Tract Median Year Moved Into Residence

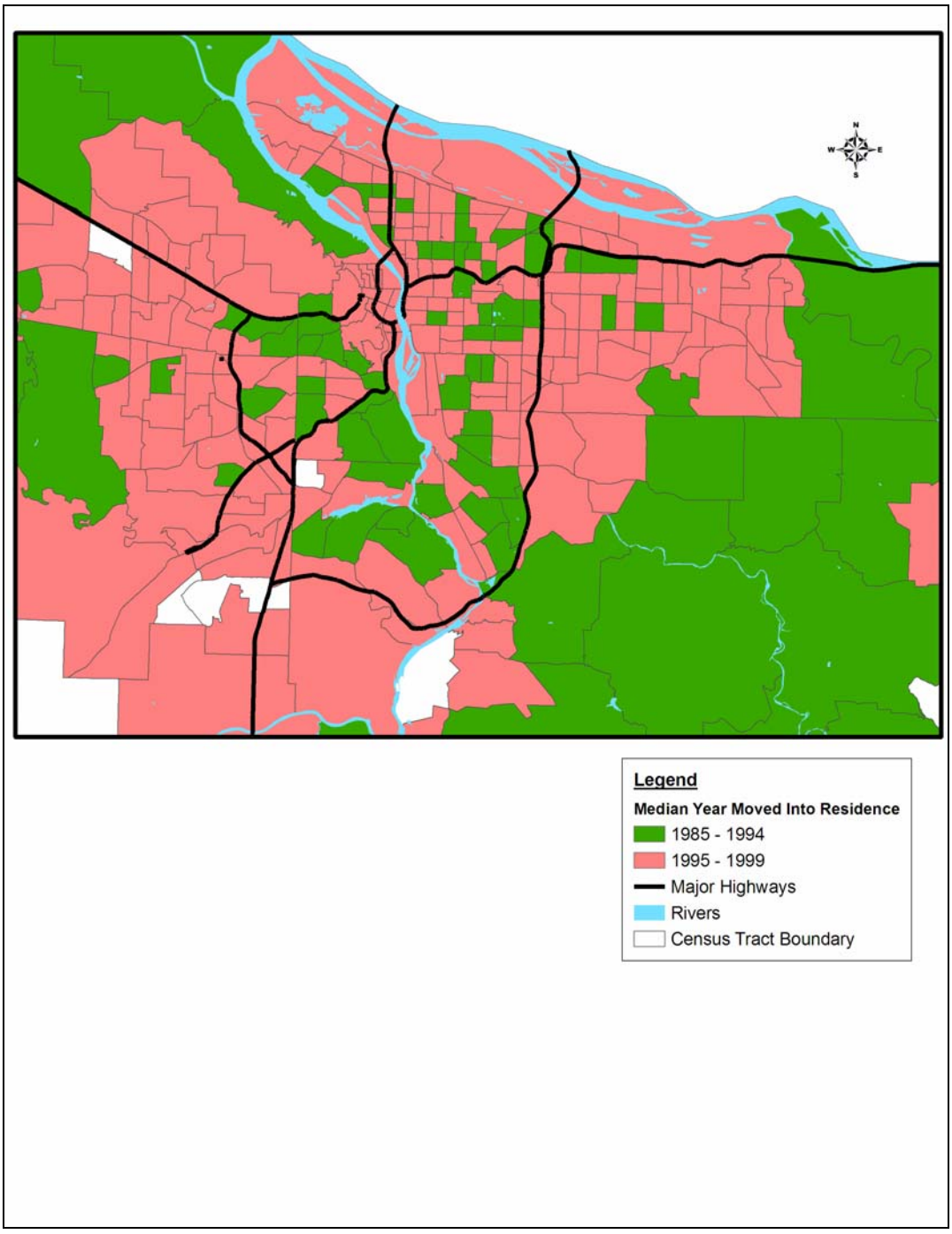

Figure 21. Benzene PATA Modeled Exposure vs Modeled Concentration by AML Rate Grouping