Analysis of the Spatial Proximity of Childhood Leukemia to High Traffic Roads in Utah

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Prepared by:

Environmental Epidemiology Program
Office of Epidemiology
Utah Department of Health
PO Box 142104
Salt Lake City, Utah 84114-2104
(801) 538-6191

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SUMMARY

Leukemias are malignant neoplasms of hematopoietic stem cells. Childhood leukemias are the most common cancers affecting children. Animal and occupational exposure studies implicate benzene as a causal risk factor for leukemia. Children are exposed to benzene in ambient indoor and outdoor air. Automotive combustion is a major contributor to outdoor ambient air concentrations of benzene. This study explores the spatial association of children residing in four Utah urban counties who have developed leukemia between 1973 and 2001. Of 465 geocodeable cases of children diagnosed with leukemia in four urban counties; 372 were acute lymphocytic cases, 56 acute myeloid cases, 6 chronic myeloid and the rest other acute forms. Cases were geocoded to the 2000 census blocks that they lived in at the time of diagnosis. Census blocks were classified as close or distant based on spatial proximity to major roads. Census block child populations were assigned to proximity exposure zones and dispersion modeled air concentration exposure zones either by an area intersect method or by the area centroid point using geographic information system technology. Proximity exposure zones were in 30 meter increments to 300 meters. Modeled exposure zones were in 1.0 $\mu g/m^3$ modeled concentration levels (0.01 - 1.0 to >5 $\mu g/m^3$). The comparison population for computing the relative risk (RR) for each exposure zone was those children living more than 300 meters from any major road way (for proximity zones) or those children living in areas with < 0.01 $\mu g/m^3$ modeled benzene air levels (for modeled exposure zones). The RR and 95% confidence limits (CL) of the cumulative childhood population living in each exposure. Children living in close proximity to roads (< 150 meters) appear to have an increased risk for all types of childhood leukemia and for myelogenous leukemia. Significant risk was also found for some modeled air concentration exposure zones. These findings suggest an association between increased incidences of childhood leukemia and living in close proximity to high-density traffic roadways. However, this study does not account for some spatially associated potential confounding factors. Additional study of measures of childhood exposure to ambient air levels of benzene through ambient air benzene monitoring and biomonitoring is needed.

BACKGROUND

Childhood Leukemia

Childhood leukemias are the most common cancer affecting children under the age of 15. Approximately 2,300 children and adolescents younger than 15 years of age are diagnosed with leukemia each year in the U.S. (Buffler et. al. 2005). Acute forms (lymphocytic and myeloid) of

leukemia account for nearly all childhood leukemia cases. In the United States, the incidence trend for childhood acute lymphocytic leukemia (ALL, also known as acute lymphoblastic leukemia) has been increasing over the past 20 years with an estimated annual percentage change of 0.9% and account for between 75% and 80% of childhood leukemia cases. Acute myelogenous leukemia (AML, also known as acute myeloid leukemia or acute nonlymphocytic leukemia or ANLL) incidence trend has remained the same for the past 20 years and account for 15% to 20% of childhood leukemia cases (Smith 1996, Smith & Zhang 1998, Reis et. al. 1999, Bauer et. al. 2003, Lamb 2004).

Benzene has been implicated in development of childhood leukemia. Animal toxicology and occupational cohort studies have linked benzene exposure to development of leukemia (IARC 1982, IARC 1987, IARC 1989, ATSDR 1997, EPA 1998, ATSDR 2000, EPA 2000). Children may develop leukemia as a result of exposure to benzene through several exposure pathways including childhood exposure to environmental benzene in the air or water and trans-placental maternal exposure (Dowty et. al. 1976, Ghantous & Danielsson 1986).

Sources of Benzene in the Environment

Benzene is a natural component of crude and refined petroleum and has been one of the world's major commodity chemicals. The industrial uses and subsequent occupational exposures for benzene have been well documented (Wallace 1989, Wallace 1996, ATSDR 1997, ATSDR 2000, EPA 2000). Indoor air concentrations are derived from infiltration of outdoor air, use of benzene containing products in the home, and smoke from tobacco products. Cigarette smoke represents about half of the benzene to which the general population is exposed. Levels may be increased in homes with attached garages. Seasonal variations occur with higher levels found in the fall and winter when buildings are less well ventilated (ATSDR 2000).

Mobile sources (vehicles) are a major contributor to outdoor ambient air concentrations of benzene (Wallace 1989, Wallace 1996, Weisel et. al. 1996, Barbieri et. al. 2002). Other sources for outdoor airborne benzene include combustion of fossil fuels small gasoline engines, discharges from petroleum processing and manufacturing facilities, and discharges from chemical and chemical product manufacturing facilities (Wallace et. al. 1987, Wallace 1996, Barbieri et. al. 2002). Close proximity to hazardous waste sites, land fills, petroleum-refining operations, petrochemical manufacturing sites, gas stations or leaking underground storage tanks contribute to increased outdoor and indoor air concentrations (ATSDR 2000).

The global average outdoor air concentration of benzene is 6 $\mu g/m^3$ (1.8 parts per billion, ppb) (range 2-9 $\mu g/m^3$ or 0.6 - 2.8 ppb) (ATSDR 2000). Ambient air sampling in thirty-nine cities in the United States by the U.S. Environmental Protection Agency, in the morning hours (6-9 A.M.), during the summer months (June-September), during 1984, 1985 and 1986, found the median ambient air concentrations to be 12.6 ppb (range of measures was 1.0 - 273 ppb). The

median concentration for any one of the forty-four sites ranged from 4.8 to 35.0 ppb (EPA 1987). The national ambient air benzene concentration for the U.S. is thought to average about 2.8 parts per billion (ppb) (EPA 1987, Egeghy et. al. 2000).

Previous studies of the association of childhood leukemia incidence to exposure of ambient air concentration of benzene from mobile sources have not been conclusive (Savitz & Feingold 1989, Nordlinder & Jarvholm 1997, Feychting et. al. 1998, Harrison et. al. 1999, Pearson et. al. 2000, Raaschou-Nielsen et. al. 2001, Reynolds et. al. 2001, Barbieri et. al. 2002, Langholz et. al. 2002, Reynolds et. al. 2002, Mc Nally et. al. 2003, Reynolds et. al. 2003, Crosignani et. al. 2004, Reynolds et. al. 2004 and Steffen et. al. 2004). All but the study by Barbieri (Barbieri et. al. 2002) used a modeled metric for exposure. The metric chosen included proximity to sources, density of sources, measured or modeled indicator contaminates of pollution levels and modeled diffusion of contaminates from sources.

Exposure Pathway and Metabolism of Benzene

Inhaled or ingested benzene is rapidly and extensively absorbed into the body. Absorption through the skin is also rapid but not extensive, as most of it evaporates before it can be absorbed. After a 4-hour exposure to approximately 50 ppm benzene in air, human volunteers absorbed about 50% of the amount inhaled (ATSDR 2000). Absorbed benzene preferentially distributes to the bone marrow and tissues with either high perfusion rates (e.g., kidney and liver) or high lipid content (e.g., adipose tissues and the brain), but can be found throughout the body. Approximately half of an inhaled dose is distributed to the liver and bone marrow (ATDSR 2000).

Absorbed benzene is metabolized by a pathway that leads to reactive ring-opened aldehyde metabolites or a pathway that leads to benzene quinones and semiquinones (Smith 1996, Weisel et. al. 1996, Witz et. al. 1996, Rothman et. al. 1998, Smith & Zhang 1998, Bauer et. al. 2003). Metabolism takes place primarily in the liver, with a small amount metabolized in the bone marrow (ATSDR 2000, Bauer et. al. 2003). Benzene metabolism initially involves oxidation, with phenol as the major metabolite. Further metabolic products formed by introduction of hydroxy groups on the aromatic ring include hydroquinione, catechol, and 1,2,4-trihydroxybenzene (Weisel et. al. 1996, Witz et. al. 1996, Rothman et. al. 1998, ATSDR 2000, Bauer et. al. 2003)

These hydroxylated metabolites can be further oxidize to their corresponding quinones or semiquinones (ATSDR 2000). Hydroquinone and catechol are converted by bone marrow myeloperoxidase to reactive 1,4-benzoquinone and 1,2-benzoquinone, which in turn can be detoxified back to hydroquinone and catechol by NADPH:quinone oxidoreductase-1 (Bauer et. al. 2003). Polymorphism of NADPH:quinone oxidoreductase-1 may result in loss of protein and enzyme activity and increased risk for the reactive toxicity of the benzoquinones. Polymorphism

varies among ethnic groups, for example, 4% of Caucasians present with NADPH:quinone oxidoreductase-1 polymorphism, whereas 22% of Chinese present with NADPH:quinone oxidoreductase-1 polymorphism (Bauer et. al. 2003).

Bone marrow contains the myeloperoxidase (MPO) enzymes that further metabolize benzene metabolites from the liver. The rate of benzene metabolism in the bone marrow is lower than in the liver. (Smith 1996, Witz et. al. 1996, Smith & Zhang 1998, Yoon et. al. 2002)

Toxic Effect of Benzene

Bone marrow is the main target organ of benzene toxicity. Adverse health effects include hematoxic, aneuploidigenic, clastogenic, genotoxic and carcinogenic effects (Rothman et. al. 1998, Bauer et. al. 2003). The exact metabolites responsible for each of those effects are not fully understood (Bauer et. al. 2003). Benzene toxicity is believed to involve biological interactions of multiple reactive metabolites which may alkylate or bind to critical cellular macromolecules (e.g., proteins, DNA, and RNA) causing disruption to cell growth and replication (Witz et. al. 1996). A synergy may exist between combinations of benzene metabolites (Bauer et. al. 2003). Damage to DNA appears to result from metabolites from the open ring pathway, where as benzene hematotoxicity seems to be a result of metabolites from the quinone/semiquinone pathway (Bauer et. al. 2003). The resulting adverse health effects include aplastic anemia and hypoplasia caused by resulting bone marrow failure; myelodyspastic syndrome; myelofibrosis; thrombocythemia; paroxysmal nocturnal hemoglobinuria; erthroleukemia and various forms of leukemia and lymphoma. The cancers include acute and chronic myelogenous (nonlymphocytic) leukemia, acute promyelocytic leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphoma and multiple myeloma (ATSDR 2000, Rothman et. al. 1998). The population rates of adverse health events follow a dose-response relationship for exposure to benzene (Rothman et. al. 1998).

Human data on the risk of leukemia due to low concentrations of benzene is sparse. The risk assessment process has generally relied on the extrapolation of observations made in highly exposed populations and occupational settings (Rothman et. al. 1998).

METHODS

Study Design

This study presents analysis of the spatial relationship of cases of childhood leukemia to high traffic density (multi-lane) roads in the four Utah urban counties (Davis, Salt Lake, Utah and Weber) during 1973 to 2001. The estimated childhood population for census block areas using the 2000 Census block geographic boundaries were tested for risk due to potential exposure to

automobile emissions originating from high traffic density roads. Spatial proximity for either any portion of a census block area or the centroid point of a census block area was used as one method to identify potentially exposed child populations. The other method used a simple line source air dispersion model to estimate the dispersion distance from a high traffic density road segment to achieve an exposure level. Census block child populations were considered potentially exposed if either any portion of the block area or the centroid point of the block area was within the modeled distance for the exposure level. The population outside of the proximity distance or outside of the exposure distance were used as the comparison population. Relative risk was used as the measure of risk (Van Atten et. al. 2005).

Data and Data Preparation

Software: ArcView (version 9.1) software developed by Environmental Systems Research Institute (ESRI) was used to link spatial data for this study and to conduct spatial analysis. ArcView supports Visual Basic for Applications (VBA) macro development and implementation. VBA macros were used to develop the exposure models for this study. Microsoft Excel (Version 2003 SP2) was used to conduct the statistical analysis.

Study Area: The four urban counties (Davis, Salt Lake, Utah, and Weber) of the State of Utah was used as the study area for this study. Figure 1 presents the study area. The U.S. 2000 Census Block areal units were selected as the subdivision unit for the study area (USCB 2004). Geographic information files (GIS feature layer file) for the Utah U.S. 2000 Census Block areas for the State of Utah was obtained from the Utah Automated Geographic Reference Center (AGRC) which is part of the Utah Department of Administrative Services (AGRC 2005). Geographic data for the study area was projected using the North American Datum (NAD) 1983 Universal Transmercator (UTM) Zone 12N. This data was indexed by a feature key which consisted of the state and county Federal Information Processing Standards (FIPS) codes and the U.S. 2000 census tract, census block group and census block enumeration codes (ITL 1990, USCB 2004). This composite key, known as the Standard Federal Identifier (STFID), is a unique standardized identification of census areas and was used to geographically link spatial data, population data and case data. A GIS feature layer of just the census blocks of the four urban counties within the study area was created from the state level census block feature layer. The study area consists of 28,279 distinct census block areas. Davis County has 3,611 census block areas, Salt Lake County has 12,456 census block areas, Utah County has 8,008 census block areas and Weber County has 4,204 census block areas. The median size for each census block area is 27,439 square meters (range = 8.75 - 452,249,394 square meters). The X- and Y-coordinates for the geographic centroid point of each census block were calculated.

Childhood Leukemia Cancer Data: All registered cases of childhood leukemia (622 records for children ages 0 to 14 years old) for the State of Utah for the period 1973 to 2001 were obtained from the Utah Cancer Registry (UCR, UCR 2004). Those data included the UCR reference

number, a sequence number indicating primary and secondary cancer reports, the cases age at diagnosis, sex, and address at diagnosis, as well as site, histology and behavior information.

All of the records with a geocodeable address were geocoded using the ArcView geocoding utility and the Dynamap/2000 (version 14.3) Street File Network for the State of Utah was obtained from Geographic Data Technology, Inc. (GDT 2004) for the address reference data. Geocode-able addresses were obtained for 535 (86.0%) of the 622 records for childhood leukemia for children ages 0-14 years old for the State of Utah. Within the four urban county study area, 465 (98.5%) of 472 cases of childhood leukemia residing within the study area at the time of diagnosis were geocoded to the house and street address. The types of childhood leukemia in the study area are as follows:

Type	State	Study Area	Study Area Geocoded
Lymphocytic Leukemia	496	379	373
Acute			*372*
Chronic			*0*
Other			*1*
Myelogenous Leukemia	89	68	67
Acute			*56*
Chronic			*6*
Other			*5*
Monocytic Leukemia	19	12	12
Acute			*11*
Chronic			*0*
Other			*1*
Other Leukemia	18	13	13
Acute			*7*
Other			*6*
TOTAL	622	472	465

The childhood leukemia case count for each census block were added to the census block feature layer's data (attribute) table. During the study period (1973-2001), 454 (of 28,279 or 1.6%) of the census block areas had the residential address at the time of diagnosis for one or more cases of childhood leukemia (children ages 0-14). Nine census block areas had at 2 cases and one area had 3 cases during the 29-year study period. Sixty-six (of 28,279 or 0.2%) of the census block areas had the residential address of children diagnosed with myelogenous leukemia. One census block area had 2 myelogenous leukemia cases and the remaining 65 areas had one case.

Population Data: Commercially available U.S. Census population data for the U.S. 1970, 1980, 1990 and 2000 censuses were obtained on computer optical data disks (CDs) from Geolytic, Inc. (Geolytic 2002 a-f). The population for each census period (1970, 1980, 1990, and 2000) were organized into sex specific five year age groups (0 to 4 year old, 5 to 9 year olds and 10 to 14 year olds) population counts for each census block group area in the study area counties. Stratified census data is not available for the census block area. However, the total number of persons residing in each census tract at the time of the 2000 census is available. The intercensal population counts for each one-year period from 1973 to 2001 were calculated for each sex-age group census count for each census tract in the study population by linear regression between corresponding previous and subsequent census data. The census block group age groups and sex specific population counts were totaled into a single childhood population for children (0-14 years old) living in the census tract during that year. The number of person-years for children ages 0-14 years in each census block group from 1973 through 2001 were computed by summation of the annual populations. The population was not stratified for race or ethnicity due to limitations in the data. The STFID key was used to link census block group level population data to the geographic feature in the GIS census block feature layer files. This index allowed the direct linkage of census data to the spatial representation fo the census block. The census block childhood person-years for children ages 0-14 from 1973 through 2001 were computed from the census block total population:

$$PY_b = PY_{bg} \frac{TP_b}{TP_{bg}}$$

where:
- PY is the number of child-person-years between 1973-2001 for children ages 0-14 per unit area;
- TP is the total persons residing within a unit area at the time of the 2000 census;
- b is the census block unit area; and
- bg is the census block-group unit area that includes the census block unit area.

Within the study period (1973-2001), the population of children 0 to 14 years old ranged from 294,858 children in 1973 to 455,861 children in 2001 (for Davis County the range was 42,297 to 69,408 children, for Salt Lake County the range was 161,252 to 227,793, for Utah County the range was 50,744 to 107,686 and for Weber County the range was 40,565 to 50,974 children). This resulted in 11,212,093 person-years for children ages 0-14 between 1973 and 2001. The average number of person-years per census block was 396.5 (range = 0.0 to 28,474.0, standard deviation = 617.8, and median = 233.0 person-years) Of the 28,279 census block areas, 20,943 (74.1%) census block areas had children living in them.

Traffic Density Data: Annual 24-hour average moving vehicle counts for 1,436 monitoring points in Salt Lake County were obtained from the Utah Department of Transportation (UDOT) for 2003. The UDOT monitors traffic density of multi-lane or high traffic density roads throughout the State of Utah and computes annual 24-hour average traffic density values for road segments. Those data provided the density on approximately 2,514 kilometers of multi-lane or high traffic density roads in the four urban counties (Davis, Salt Lake, Utah and Weber). Geographic information files (GIS feature layer file) for all roads in the State of Utah were obtained from the AGRC (AGRC 2005). The average length of each road segment was 1.75 kilometers (range = 0.06 to 58.07 kilometers, standard deviation = 2.96 kilometers, median = 2.96 kilometers). Geographic road data for the study area was projected in the same NAD 1983 UTM Zone 12N datum as the 2000 Census Block feature layer. Road types were identified by the Standard Feature Class Code (FCC). A GIS feature layer of just the census blocks of the four urban counties within the study area was created from the state level census block feature layer. Data from UDOT were added to this road feature layer. Using the ArcView software's feature edit functions, some road features were merged or split in order to have road segments matching the UDOT road segment data. All trail, off-road, unpaved, and neighborhood features were removed from the feature layer files, leaving only the multi-lane or primary traffic road network identified by UDOT for inclusion in the study. The average 24-hour car density was 21,858 cars/24-hour period (range = 245 to 286,490 cars/24-hour period, standard deviation = 27,454.9 cars/24-hour period, median = 14,728 cars/24-hour period). Figure 2 presents data on the distance by car density.

Eight thousand, one hundred and eighty-five (8,185) of 28,279 or (29%) of the census block areas were intersected by one or more of the selected high traffic density roads. Those census blocks included 224 cases of childhood leukemia and 4,549,563 person-years of child population during the study period. A distance of four meters was required before additional census blocks were intersected.

Data Analysis

Benzene Concentration Model: The average benzene emission rate from vehicles ranges from 24.20 mg/mile (median = 16 mg/mile, range = 0.30 - 133.62 mg/mile) in the winter to 47.97 mg/mil (median 21.72 mg/mile, range 0.85 - 290.94 mg/mile) in the summer (Knapp et. al. 2000). The average benzene flux rate for dispersion modeling was estimated as follows:

$$Q = A \times ER \times k$$

where: Q is the emissions flux rate (mg/sec•m);
A is the average number of vehicles (vehicle/day);
ER is the emissions rate (35 mg/vehicle•mile);

k =(1,000 mg/g × 86,400 sec/day × 1,609.35 meters/mile)$^{-1}$
= 7.19177 x 10^{-12} g·day·mile/mg·sec·m

The continuous emitting infinite line source with migration perpendicular to the line and no effective plume height was calculated using the methodology described in Turner (1994). A neutral stability class (stability class 4 or D) and a migration speed of 1 meter per second was used to estimate the concentration at distances away from a road segment.

$$\chi(x) = \frac{2Q}{(2\pi)^{0.5}\sigma\mu}$$

where:
- $\chi(x)$ is the air concentration (g / m^3) at a distance x (m) from the road segment.
- μ is the contaminate migration speed (1 m/s)
- σ is the Briggs Urban Dispersion Parameter for neutral meteorological stability (class 4 or D)
  = 0.14 x (1 + 0.0003 x)$^{-0.5}$ which at close distances
  = 0.1357 x + 0.1591 (Turner 1994).

This can be rearranged to get the distance from a road segment at which a specified modeled air concentration occurs as:

$$x = \left(\frac{2Q}{\chi(x) \cdot (2\pi)^{0.5}\mu} - 0.1591 \right) \Big/ 01357$$

The model also was limited to dispersion distance not to exceed 300 meters (Zhu et. al. 2002, Gilbert et. al. 2003, Levy et al 2003, Gilbert et. al. 2005). Table 1 presents modeled concentrations at selected distances from the source for varying car density values. Table 2 presents the behavior of modeled distances for designated concentrations for the high traffic density roads in the study area.

Exposure Zones: Two methods were used to map exposure zones around each leg segment. Proximity exposure zones were uniform in size for all road segments. Uniform zone distances from 30 meters to 300 meters in 30 meter intervals were used to map proximity bands around roads with a 24-hour average traffic density greater than or equal to 5,000 cars. Modeled exposure zones were dependent on the modeled exposure distance from each road segment at which a concentration limit was achieved. Modeled zone distances for concentration limits from 0.01 µg/m^3 to 5.0 µg/m^3 in 1.0 µg/m^3 intervals (0.01 - 1.0, 1.0 - 2.0 ... 4.0 - 5.0, and ≥5.0 µg/m^3)

were used to map proximity bands around roads for which the modeled distance as greater than or equal to 10 meters. The buffer distances were constrained to 300 meters. This constraint functionally applied only to the 0.01 and 1.0 $\mu g/m^3$ concentration limits and to road segments with a car density greater than 1,785 cars for the 0.01 $\mu g/m^3$ or 178,500 cars for 1.0 $\mu g/m^3$.

Assignment to Exposure Zones: Two methods were used to assign census block populations to mapped exposure zones. The intersect method assigned census blocks to the exposure zone if any portion of census block area was contained within the exposure zone area. Census block areas crossing the buffer zone boundary were assigned to the closer exposure zone, regardless of the proportion of census block area within the closer or farther exposure zone. Alternatively, a census block population was assigned to the exposure zone in which the census block centroid point was located.

Comparison Population: The comparison population for proximity exposure zones were the cumulative population of census blocks more than 300 meters from any road with an average traffic density greater than or equal to 5,000 cars in a 24-hour period. The comparison population for modeled exposure zones were the cumulative population of census blocks with less than 0.01 $\mu g/m^3$ exposure levels.

Relative Risk: Relative risk and 95% confidence limits for the cumulative census block populations for each exposure zone (proximity or modeled concentration) for each assignment method (area intersection or area centroid point) computed for all types of childhood leukemia combined and for myelogenous leukemia. The method described by the SAS Institute Inc. (SAS 1998) was used:

$$RR = \frac{\left(C_Z / P_Z\right)}{\left(C_{NE} / P_{NE}\right)}$$

$$\overline{\underline{RR}} = RR \times \exp\left(\pm z\sqrt{v}\right) = RR \times \exp\left(\pm 1.96 \times \sqrt{\left(1 - \frac{\left[C_Z / P_Z\right]}{C_Z}\right) + \left(1 - \frac{\left[C_{NE} / P_{NE}\right]}{C_{NE}}\right)}\right)$$

where:
- C_Z is the number of cases in the exposure zone
- P_Z is the child-years in the exposure zone
- C_{NE} is the number of cases in the comparison population

P_{NE} is the child-years in the comparison population

RESULTS

Tables 3 and 4 presents the relative risks for populations of children living within iterative 30-meter wide proximity bands. Table 3 presents data for populations assigned to proximity exposure zones by the intersect method and Table 4 presents data for populations assigned by the centroid method. Ideally, the level risk would be inversely proportional to increasing distance from high traffic density roads. However, measured risk is subject to the heterogeneous distribution of populations. The population within the areas of three proximity exposure zones (0-30, 90-120 and 120-150 meters) when assigned by the intersect method had significantly increased risks for all types of childhood leukemia. The population within the areas of two proximity exposure zones (0-30 and 90-120 meters) had significantly increased risks for mylogenous leukemia. Assignment by the intersect method can result in census blocks being assigned to closer proximity zones when the greater proportion of the census block area may be in one or several further zones, or may be in the unexposed population. Assignment by the centroid method was found to be more conservative and resulted in smaller populations in each exposure zone. Using the centroid method, the closest proximity exposure zone (0-30 meters) population had a significantly increased risk for myelogenous leukemia. A higher but not significant risk was also found for all childhood leukemia types.

Tables 5 and 6 presents the relative risks for populations of children living within increasing modeled exposure zones from 0.1 $\mu g/m^3$ to 0.5 $\mu g/m^3$ in 1.0 $\mu g/m^3$ increments. Table 5 presents data for populations assigned to proximity exposure zones by the intersect method and Table 6 presents data for populations assigned by the centroid method. Significantly increased relative risks were found for all childhood leukemia types for children residing in two exposure zones (1.0 - 2.0 and 3.0 - 4.0 $\mu g/m^3$) for populations assigned to exposure zones by the intersection method. Other zones were also elevated but not significant. The population in three exposure zones (1.0 - 2.0 and 3.0 - 4.0 and 4.0 - 5.0 $\mu g/m^3$) were found to be significant for myelogenous leukemia. Using the centroid assignment method, populations in one zone (1.0 - 2.0 $\mu g/m^3$) were found to have a significant increased risk for myelogenous leukemia. In the ideal situation, a strong positive correlation between exposure level and risk would demonstrate a dose-response relationship. This study did not find a linear dose-response relationship.

DISCUSSION

Protection of human health against disease and injury caused by toxic chemicals in the environment is the ultimate goal of risk assessment and risk management. Children today are at risk of disease caused by environmental hazards not encountered by previous generations. The

reported incidence of childhood cancer has increased substantially in the Unites States in the past two decades (Landrigan et. al. 2004).

Benzene is recognized as an occupational health risk. Chronic exposure to benzene in an occupational setting has been shown to cause hematological, mutagenic and carcinogenic effects (ATSDR 1997, ATSDR 2000, Duarte-Davidson et. al. 2001). The estimated lowest observed adverse effect level (LOAEL) for adult carcinogenic effects is 32-80 mg/m^3 after years of chronic occupational exposure (ATSDR 1997, EPA 1998, EPA 1999, Duarte-Davidson et. al. 2001). This level is four to six orders of magnitude higher than the modeled ambient air exposures levels (0.01 to 5.0 $\mu g/m^3$). The modeled levels in this report are consistent with levels found by air monitoring in other urban environments (EPA 1987, Duarte-Davidson et. al. 2001, Payne-Sturges et. al. 2004). Crosignani (et. al. 2003) found an elevated but not significant risk (RR = 1.51, 95% CI = 0.91 - 2.51) for exposures to 0.1 - 10 $\mu g/m^3$ benzene in the air and a significant risk (RR = 3.91 95% CI = 1.36 - 11.27) for exposures to > 10 $\mu g/m^3$ benzene in the air in a smaller study. Concentrations of benzene in fresh vehicular exhaust are high near roadways but decline markedly within 150-300 meters (Zhu et. al. 2002, Gilbert et. al. 2003, Levy et.al. 2003, Gilbert et. al. 2005).

In this study, two methods were used to assign populations of children to zones of decreasing exposure levels. Uniform depth proximity zones are easy to generate and in some cases more readily applied to available data (i.e., locations of cases and populations). An increased risk associated with proximity to major roadways may be more easily explained to policy makers and to the general public (McConnell et. al. 2006).

Modeled air concentration using the simplest continuous line source air dispersion model also was used to assign populations of children to zones of decreasing exposure levels. The model did not account for a variety of meteorological or topographical conditions that effect the dispersion of air contaminates released from automobile traffic. Further, the model design did not have that complexity to account for traffic events such as intersections with stopped traffic, or for other potential sources of benzene exposure. More robust line dispersion models are available but are not easily implemented within ArcView. Data prepared for geographic presentation within ArcView is not readily useable or appropriate for those models. Not withstanding these limitations, the model did provide a means for estimating a general exposure level for population sub units.

In this study, two methods were used to assign census block level populations of children to exposure zones. The intersect method assigns the whole census block population to the closest or highest exposure zone for which any portion of the census block area is contained in. This method has the effect of maximizing the exposure level for census block populations. In some cases, the larger portion of the census block is contained within the further exposure zone. Census blocks may also cross through several exposure zones including extending into the

comparison population. Assignment of those census blocks to the closer exposure zone when a small, potentially insignificant, amount of census block area is within that closer zone results in mis-classification of that census block population. An improvement is to use the centroid point of the census block to determine which exposure zone to assign the census block's population. This method affects assignment to the average exposure level for the census block population if the dispersion and depletion of air contaminates are uniform and linear. However, since this is not the case, the centroid method underestimates the exposure level depending on the orientation of the census block with respect to the road segment from which the dispersion model originates. Both methods maximized assignment to the closest road (in the case of proximity zones) or to highest concentration (in the case of modeled zones). Neither assignment method accounted for additional exposures derived from next nearest roads nor the additive modeled exposure levels from derived multiple road segments. It is conceivable that a population proximal to and surrounded by a number of road segments with lower traffic density may have an actual exposure level higher than a population proximal to a single higher traffic density road segment but would have been assigned to a lower exposure zone.

The results of this study suggest a higher risk for childhood leukemia associated to close proximity to high traffic density roads. In addition, to the likely increased exposure to ambient air concentrations of benzene, there are competing risk factors which were not accounted for in this study. Exposure to extremely low frequency magnetic fields (ELF-MF) generated along high voltage electrical power transmission lines is an environmental risk factor for childhood leukemia (Brain et. al. 2003, Buffler et. al. 2005). In the study area, 787.544 kilometers (31% of 2,514.384) of roads were within 300 meters of a power line. The traffic density for most of those roads segments close (within 300 meters) to power lines was low (mean = 19,253 based on 220 segments, range 500 - 143,076). Forty-seven cases of childhood leukemia including seven cases of myelogenous leukemia were within 300 meters of a power line. Exposure to vapors of other solvents (e.g., paint products), metal dust, and pesticides have also been shown to increase the risk for developing childhood leukemia (Shu et. al. 1999, Ma et. al. 2002, Buffler et. al. 2005). Information about the presence and concentrations of those chemical hazards are not available. However, manufacturing and other industrial uses of those kinds of chemicals are known to be concentrated along major road systems. In addition, the use of pesticides and herbicides as part of highway grooming may represent a source of those chemicals along major road networks. Socioeconomic factors such as diet, exposure to environmental tobacco smoke, and environmental residential contaminates resulting from parental occupational exposures are also risks for childhood leukemia (Robison et. al. 1995, Shu et. al. 1999, Buffler et. al. 2005). Data directly related to those risks are also not available, although they can be estimated from other socioeconomic status indicators. Those risks factors are likely positively correlated with proximity to high traffic density road systems and are likely confounding explanatory factors for some of the risk found for exposure ambient air benzene levels from traffic by proximity or modeled air level zones. Finally, there are known genetic susceptibilities for childhood leukemia

(Buffler et. al. 2005). Data about the genetic risk factors for the cases of childhood leukemia for this study were not available.

CONCLUSION AND RECOMMENDATIONS

The results of this study present evidence of increased risk for childhood leukemia among children living in close proximity to high traffic density roads. Exposure to benzene emissions as a component of automobile exhaust are thought to be a risk factor for childhood leukemia. In this study, exposure to benzene were estimated by proximity zones or by modeled air dispersion zones. Other risk factors for childhood leukemia may be positively correlated to proximity to high traffic density roads, so that it is not possible to conclusively state that the increased risk results from exposure to ambient air benzene levels. To complete the association of increased risk for childhood leukemia to exposure to benzene in the ambient air, it would be necessary to 1) validate the air dispersion model and population assignment methods through environmental sampling, 2) validate childhood exposure through the use of personal exposure monitoring or bio-monitoring, 3) quantify the risk contributed by other explanatory variables (i.e., ELF-MF, other environmental chemical contaminates, socioeconomically, residential and genetic risks) through environmental assessment and model those factors together.

Authors

R. Wayne Ball, Ph.D., M.P.H., D.A.B.T.
Toxicologist / Program Manager
Environmental Epidemiology Program
Office of Epidemiology
Utah Department of Health

Samuel D. LeFevre
Research Consultant / Project Manager
Environmental Epidemiology Program
Office of Epidemiology
Utah Department of Health

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FIGURES AND TABLES

Figure 1. Four Utah Urban Counties (Weber, Davis, Salt Lake and Utah) in the Study Area for Analysis of the Spatial Proximity of Childhood Leukemia to High Traffic Roads from 1973 to 2001.

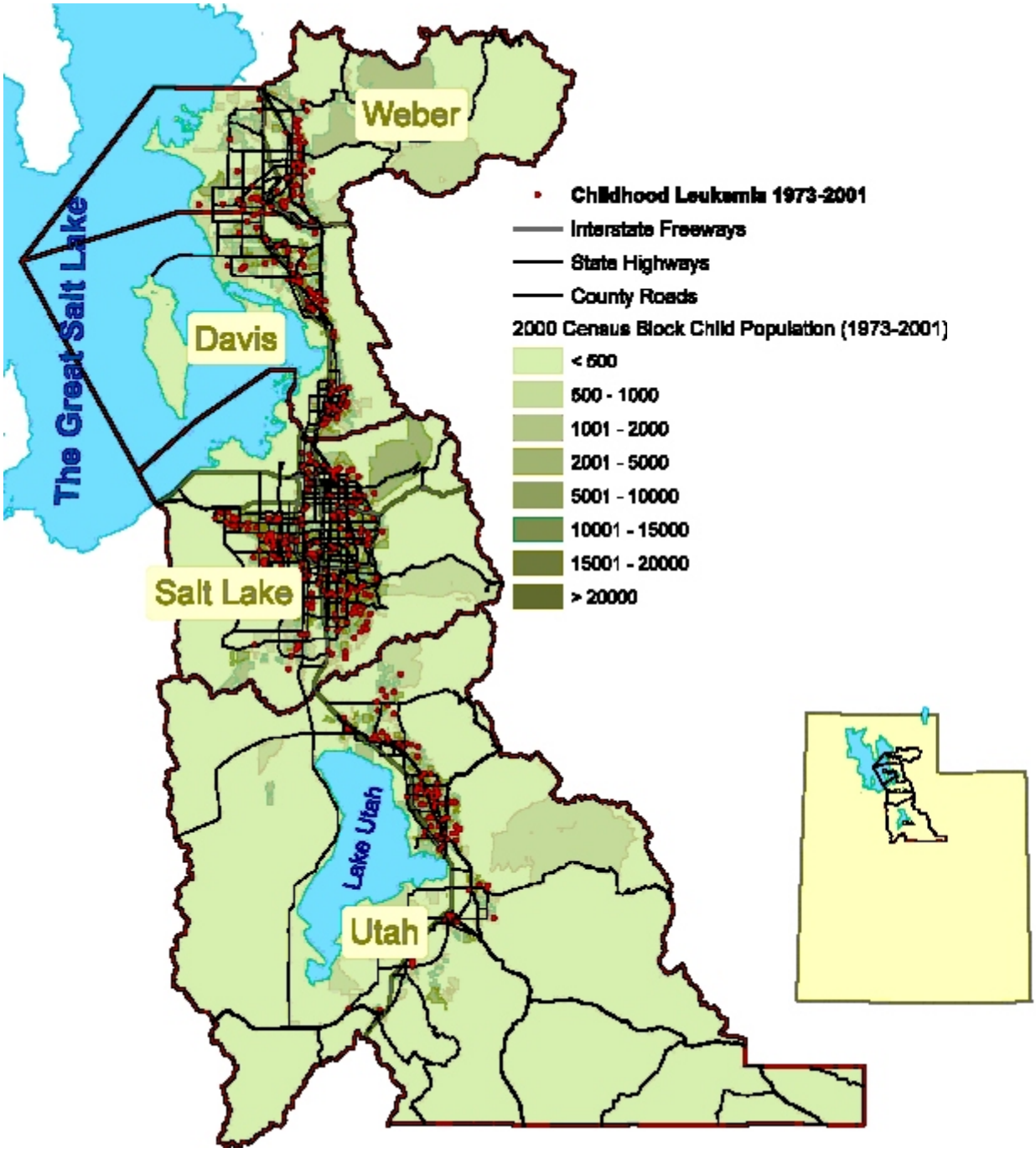

Figure 2. Distribution of Kilometers or High Traffic Density Roads in Four Utah Urban Counties (Davis, Salt Lake, Utah, and Weber) by Car Density Levels as of 2002. Includes Only Roads that Annual 24-Hour Traffic Density Measures are made by the Utah Department of Transportation.

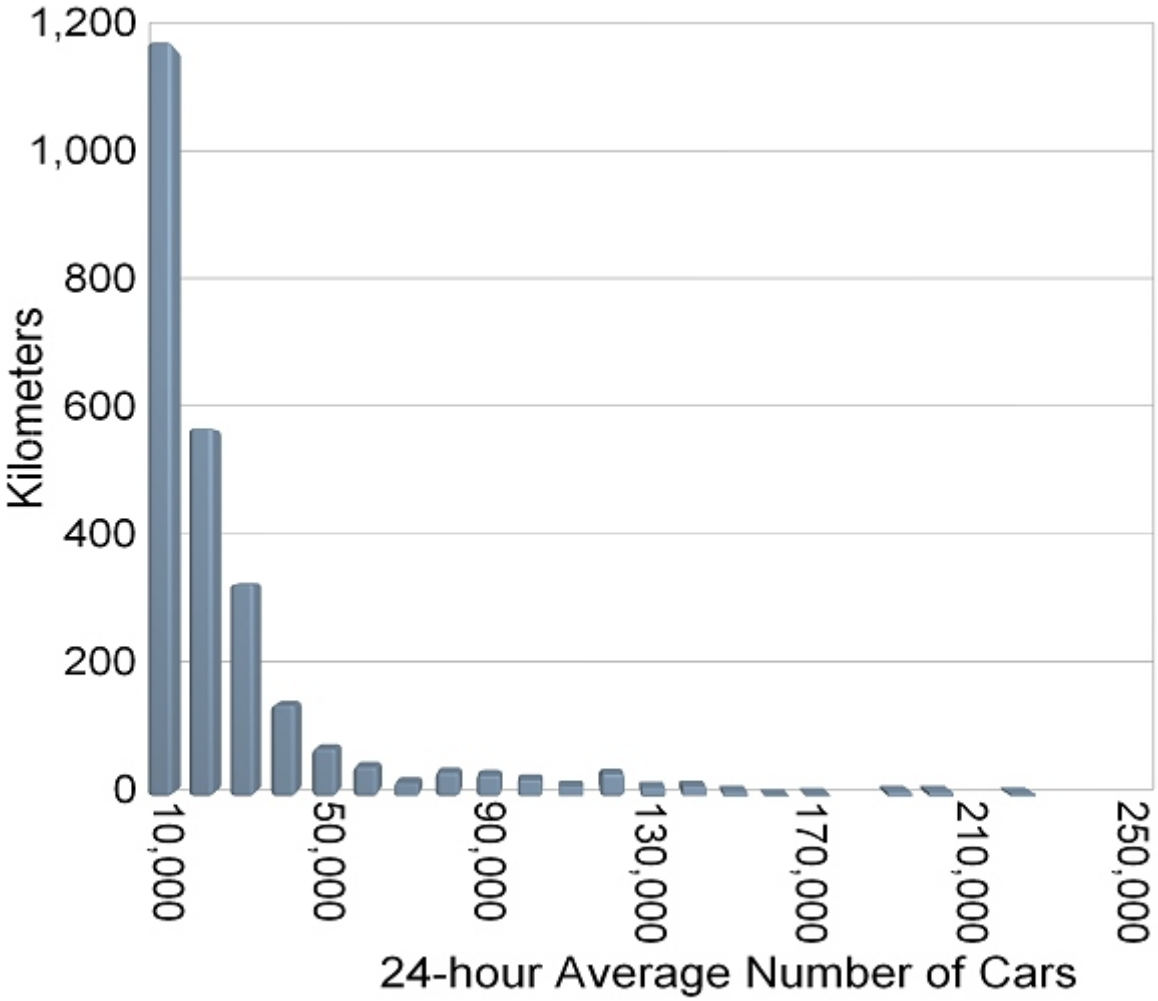

Table 1. Modeled Concentrations of Benzene in the Ambient Air from Automobile Emissions at Varying Distances from a Road Segment using a Simple Line Dispersion Model (Turner 1994) for Different Levels of 24-Hour Average Car Density.

24-hour Average Car Density	Distance (m)										
	5	10	20	50	100	125	150	175	200	250	300
	Concentration ($\mu g/m^3$)										
500	0.13	0.08	0.04	0.02	0.01						
1,000	0.27	0.15	0.08	0.03	0.02	0.01					
2,000	0.55	0.30	0.16	0.07	0.03	0.03	0.02	0.02	0.02	0.01	
5,000	1.37	0.76	0.40	0.17	0.08	0.07	0.06	0.05	0.04	0.03	0.03
10,000	2.74	1.51	0.80	0.33	0.17	0.13	0.11	0.10	0.08	0.07	0.06
20,000	5.48	3.03	1.60	0.66	0.33	0.27	0.22	0.19	0.17	0.13	0.11
50,000	13.70	7.57	3.99	1.65	0.84	0.67	0.56	0.48	0.42	0.34	0.28
100,000	27.40	15.14	7.99	3.31	1.67	1.34	1.12	0.96	0.84	0.67	0.56
200,000	54.86	30.28	15.98	6.61	3.34	2.68	2.24	1.92	1.68	1.35	1.12
300,000	82.21	45.42	23.97	9.92	5.02	4.02	3.36	2.88	2.52	2.02	1.68

Model based on 35 mg benzene emitted per vehicle mile. Average 24-hour vehicle density per road segment ranges from 245 to 286,490 vehicles.

Table 2. Modeled Dispersion of Benzene from Vehicle Exhaust from high traffic density roads in Davis, Weber, Utah and Salt Lake Counties in Utah, based on the 2003 annual 24-hour traffic density per road segment.

Modeled Concentration ($\mu g/m^3$)	Road Segments (n = 1,436)	Mean Distance (m)	Standard Deviation (m)	Range Min (m)	Range Max (m)
0.1	1,436	368.56	464.38	2.97	4,846.32 *
0.5	1,433	72.77	92.88	0.00	968.33 *
1.0	1,356	35.82	42.20	0.00	483.58 *
1.5	1,352	23.51	30.93	0.00	321.99 *
2.0	1,343	17.36	23.19	0.00	241.20
2.5	1,333	13.67	18.54	0.00	192.73
3.0	1,318	11.21	15.44	0.00	160.41
3.5	1,306	9.45	13.22	0.00	137.33
4.0	1,292	8.14	11.56	0.00	120.01
4.5	1,282	7.12	10.26	0.00	106.55
5.0	1,260	6.30	9.23	0.00	95.78

Model based on 35 mg benzene emitted per vehicle mile. Average 24-hour vehicle density per road segment ranges from 245 to 286,490 vehicles.

* Distance constrained to 300 meters ((Zhu et. al. 2002, Gilbert et. al. 2003, Levy et al 2003, Gilbert et. al. 2005).

Table 3. Relative Risk for Childhood Leukemia (all types and myelogenous) among Children Living in Close Spatial Proximity to High Traffic Roads in Four Urban Utah Counties (Davis, Salt Lake, Utah and Weber) between 1973 and 2001. Populations of Children were Assigned to Proximity Exposure Zones by the Intersect Method (see text).

DISTANCE (meters)	CENSUS BLOCKS (count)	CASES (count)	POPULATION (p-y)	RELATIVE RISK	95%CONFIDENCE INTERVALS	
			All Childhood Leukemia			
All	28,279	465	11,212,093			
0- 30	7,735	200	4,351,416	1.38	1.08 - 1.77	*
30- 60	1,211	11	504,720	0.66	0.35 - 1.23	
60- 90	1,338	24	534,185	1.35	0.86 - 2.12	
90-120	1,329	34	560,713	1.83	1.23 - 2.71	*
120-150	1.117	26	497,227	1.58	1.02 - 2.43	*
150-180	983	17	425,241	1.20	0.72 - 2.02	
180-210	1,102	22	508,052	1.30	0.82 - 2.08	
210-240	957	19	440,263	1.30	0.79 - 2.13	
240-270	782	9	325,774	0.83	0.42 - 1.65	
270-300	626	10	263,173	1.14	0.60 - 2.20	
>300	11,153	93	2,801,329	1.00		
			Myelogenous Leukemia			
All	28,279	67	11,212,093			
0- 30	7,735	36	4,351,416	2.54	1.35 - 4.80	*
30- 60	1,211	1	504,720	0.61	0.08 - 4.66	
60- 90	1,338	4	534,185	2.30	0.75 - 7.06	
90-120	1,329	8	560,713	4.39	1.82 - 10.59	*
120-150	1.117	1	497,227	0.62	0.08 - 4.73	
150-180	983	3	425,241	2.17	0.62 - 7.61	
180-210	1,102	1	508,052	0.61	0.08 - 4.63	
210-240	957	2	440,263	1.40	0.32 - 6.19	
240-270	782	0	325,774			
270-300	626	0	263,173			
>300	11,153	13	3,998,324	1.00		

p-y = person years (1973-2001)
* statistically significant relative risk

Table 4. Relative Risk for Childhood Leukemia (all types and myelogenous) among Children Living in Close Spatial Proximity to High Traffic Roads in Four Urban Utah Counties (Davis, Salt Lake, Utah and Weber) between 1973 and 2001. Populations of Children were Assigned to Proximity Exposure Zones by the Centroid Point Method (see text).

DISTANCE (meters)	CENSUS BLOCKS (count)	CASES (count)	POPULATION (p-y)	RELATIVE RISK	95%CONFIDENCE INTERVALS	
			All Childhood Leukemia			
All	28,279	465	11,212,093			
0- 30	1,952	39	830,866	1.12	0.80 - 1.58	
30- 60	1,671	32	728,890	1.05	0.72 - 1.52	
60- 90	1,586	28	721,529	0.93	0.63 - 1.38	
90-120	1,480	22	664.270	0.79	0.51 - 1.23	
120-150	1,440	25	620,808	0.96	0.64 - 1.46	
150-180	1,274	18	552,207	0.78	0.48 - 1.26	
180-210	1,144	24	542,731	1.06	0.69 - 1.61	
210-240	1,079	18	468,694	0.92	0.57 - 1.49	
240-270	987	21	468,575	1.07	0.69 - 1.68	
270-300	971	25	515,364	1.16	0.77 - 1.76	
>300	14,695	213	5,098,159	1.00		
			Myelogenous Leukemia			
All	28,279	67	11,212,093			
0- 30	1,952	10	830,866	2.33	1.15 - 4.70	*
30- 60	1,671	4	728,890	1.06	0.38 - 2.98	
60- 90	1,586	5	721,529	1.61	0.68 - 3.82	
90-120	1,480	2	664.270	0.58	0.14 - 2.42	
120-150	1,440	3	620,808	0.93	0.29 - 3.04	
150-180	1,274	5	552,207	1.75	0.69 - 4.47	
180-210	1,144	2	542,731	0.71	0.17 - 2.96	
210-240	1,079	2	468,694	0.82	0.20 - 3.43	
240-270	987	4	468,575	1.65	0.59 - 4.64	
270-300	971	2	515,364	0.75	0.18 - 3.12	
>300	11,153	35	6,765,640	1.00		

p-y = person years (1973-2001)
* statistically significant relative risk

Table 5. Relative Risk for Childhood Leukemia (all types) among Children Living in Areas with Different Modeled Air Concentrations Levels of Benzene from High Traffic Roads in Four Urban Utah Counties (Davis, Salt Lake, Utah and Weber) between 1973 and 2001. Populations of Children were Assigned to Proximity Exposure Zones by the Intersect Method (see text).

Concentration ($\mu g/m^3$)	Census Blocks (count)	CASES (count)	POPULATION (p-y)	Relative Risk	95% Confidence Intervals	
			All Childhood Leukemia			
All	28,279	465	11,212,093			
≥5.0	1,803	27	911,957	0.86	0.57 - 1.30	
4.0-5.0	839	24	556,987	1.23	0.79 - 1.92	
3.0-4.0	1,061	33	595,758	1.59	1.08 - 2.34	*
2.0-3.0	1,702	41	908,601	1.29	0.90 - 1.85	
1.0-2.0	2,795	73	1,471,804	1.42	1.06 - 1.91	*
0.1-1.0	8,129	158	3,642,980	1.24	0.97 - 1.59	
un-exposed (<0.1)	11,950	109	3,124,006	1.00		
			Myelogenous Leukemia			
All	28,279	67	11,212,093			
≥5.0	1,803	4	911,957	1.52	0.47 - 0.49	
4.0-5.0	839	5	556,987	3.12	1.04 - 9.30	*
3.0-4.0	1,061	3	595,758	1.75	0.47 - 6.46	
2.0-3.0	1,702	9	908,601	3.44	1.36 - 8.66	*
1.0-2.0	2,795	16	1,471,804	3.77	1.67 - 8.54	*
0.1-1.0	8,129	21	3,642,980	2.00	0.92 - 4.37	
un-exposed (<0.1)	11,950	9	3,124,006	1.00		

p-y = person years (1973-2001)
* statistically significant relative risk

Table 6. Relative Risk for Childhood Leukemia (all types) among Children Living in Areas with Different Modeled Air Concentrations Levels of Benzene from High Traffic Roads in Four Urban Utah Counties (Davis, Salt Lake, Utah and Weber) between 1973 and 2001. Populations of Children were Assigned to Proximity Exposure Zones by the Centroid Point Method (see text).

Concentration ($\mu g/m^3$)	Census Blocks (count)	CASES (count)	POPULATION (p-y)	Relative Risk	95% Confidence Intervals	
			All Childhood Leukemia			
All	28,279	465	11,212,093			
≥3.0	758	4	263,719	0.35	0.13 - 0.95	
2.0-3.0	551	8	221,592	0.84	0.42 - 1.70	
1.0-2.0	1,510	33	614,936	1.25	0.87 - 1.80	
0.1-1.0	9,093	166	4,196,179	0.92	0.76 - 1.12	
un-exposed (<0.1)	16,367	254	5,915,667	1.00		
			Myelogenous Leukemia			
All	28,279	67	11,212,093			
≥2.0	1,309	2	485,311	0.76	0.18 - 3.18	
1.0-2.0	1,510	8	614,936	2.40	1.11 - 5.22	*
0.1-1.0	9,093	25	4,196,179	1.10	0.65 - 1.86	
un-exposed (<0.1)	16,367	32	5,915,667	1.00		

p-y = person years (1973-2001)
* statistically significant relative risk