Cross-Sectional Exposure Assessment of Environmental Contaminants in Churchill County, Nevada

Final Report

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EXECUTIVE SUMMARY

Background

As part of its response to the elevated number of children in Churchill County in whom acute lymphocytic leukemia (ALL) had been diagnosed, the Nevada State Health Division (NSHD) requested technical assistance from the Centers for Disease Control and Prevention (CDC). The purpose of the subsequent collaborative investigation was to conduct a cross-sectional exposure assessment to identify contaminants unique to the Churchill County community. We examined exposures to certain chemical contaminants known or suspected to cause cancer in humans, associated previously with clusters of childhood leukemia, thought to be present in the local environment, or because we had the analytic capacity to do so.

Methods

We conducted a cross-sectional exposure assessment that included the families of children already enrolled in an NSHD leukemia investigation and comparison families that we identified through random digit dialing. The study population included 14 ill children who resided in Churchill County before diagnosis of their ALL or acute myelocytic leukemia. Case families included parents and siblings, as well as other care-taking adults in the home. Each case child was matched with four comparison children by sex and age; the matched comparison parents also were enrolled. A total of 205 participants visited a CDC clinic site in Fallon, Nevada. Clinic staff collected extensive questionnaire information and biologic samples (i.e., blood, urine, and cheek swab samples). Environmental samples (i.e., indoor air, play yard soil, household dust, and tap water) were collected from current homes and previous homes for all case families. Environmental samples were also collected from current homes for comparison families and previous homes for one randomly selected matched comparison family for each case family. Biologic and environmental samples were tested for heavy metals, persistent and nonpersistent pesticides, polychlorinated biphenyls (PCBs), and volatile organic compounds (VOCs). We also tested the biologic samples for evidence of previous viral infections. We also tested environmental samples for radon and radionuclides.

Considerable efforts were taken to ensure the quality of the analyses we conducted. We convened statistical and genetic advisory groups to provide external peer review and comment. In addition, a multi-agency panel was formed to review all environmental results using a secure electronic site for data presentation. We also hosted dedicated weekly conference calls to facilitate communication among state and federal partners.

In our cross-sectional analysis, we compared our laboratory results with levels associated with adverse health effects in previous research. When no such levels were available, we compared our results with the geometric mean and 95th percentile levels from the *Second National Report on Human Exposure to Environmental Chemicals (National Exposure Report),* which provides population-based reference ranges. The environmental sample results were compared with published standards that are identified for each chemical.

Appropriate statistical procedures such as cross-sectional descriptive analysis, spatial analysis, and conditional logistic regression assessed the probability that any elevated exposures could have resulted by chance. During our case-comparison analysis, we initially considered the 13 out of 14 case children who had submitted biologic samples. We then repeated the analysis using the nine children who had the most similar disease profiles. The second analysis was

limited to case children with precursor-B cell lymphocytic leukemia that was diagnosed before they were 6 years of age, and who lived in Churchill County for at least the 6 months before their diagnosis.

We further compared the infection status of all case children diagnosed with each of the following to their matched comparison controls: precursor-B or B-cell lymphocytic leukemia; precursor-B or B-cell lymphocytic leukemia diagnosed before 6 years of age; precursor-B or B-cell lymphocytic leukemia residing in Churchill County for at least 6 months before the leukemia diagnosis; and T-cell leukemia.

Results

We found community-wide exposure to the element tungsten (geometric mean=1.19 μg/L, 95% CI 0.89-1.59) compared with the *National Exposure Report* reference of 0.08 μg/L (95% CI 0.07-0.09). We also found levels of arsenic in urine samples ranging from nondetectable to 1180.40 μg/L. Normal urine levels of arsenic are lower than 50 μg/L; a level >200 μg/L is considered abnormal and may be associated with health effects. Both tungsten and arsenic were identified in tap water samples community-wide. Six additional metals (antimony, barium, cesium, cobalt, molybdenum and uranium) were either slightly elevated above the population geometric mean or else had more than 10% of their results above the 95th percentile level of the reference population or health-based value. Although individual homes had environmental samples with detectable levels of these metals, they were not elevated community-wide.

Our cross-sectional analysis also identified five nonpersistent pesticides (out of 31 nonpersistent pesticides or metabolites analyzed) that were each above their respective 95th percentile national reference value in more than 10% of the Churchill County urine samples. These pesticides include two organophosphate pesticide metabolites, two chlorinated phenol pesticides, and a fungicide. We also identified an aromatic hydrocarbon pesticide that was slightly higher than the reference. We did not find community-wide elevations of any of these nonpersistent pesticides in environmental samples.

Among 11 persistent pesticides analyzed, we found only DDE (geometric mean=447.07 ng/g of lipid, 95% CI 355.09-562.87) to be above the *National Exposure Report* reference of 260.00 ng/g of lipid (95% CI 234.0-289.0). We did not find elevated levels of DDT or DDE in environmental samples, but levels in humans can reflect historical exposure because these chemicals are stored in body fat. We also found a geometric mean level of 10.46 ng/g of lipid of hexachlorobenzene in our Churchill County study population compared with the national level of less than the detection limit. However, the *National Exposure Report* used an instrument detection limit of 60.5 ng/g of lipid, which is substantially higher than our mean level. We found detectable levels in 18 of the 36 different PCBs that we analyzed; all were below the 95% percentile of the *National Exposure Report*.

VOCs were not included in the *National Exposure Report* so we used population reference levels from the third National Health and Nutrition Examination Survey (1988-1994). We compared arithmetic means and 95% CIs and found no community-wide elevated VOCs. Levels were similar among case and comparison families. VOCs were not elevated in air samples.

In this study, testing for multiple viruses could not definitively relate viral infection to the childhood leukemias in Churchill County.

We used conditional logistic regression to look for a relation between any of the exposures and leukemia status. An odds ratio (OR) greater than 1.00 suggests increased risk, and an OR equal to or less than 1.00 suggests no risk or decreased risk. A p-value less than 0.05 suggests that chance alone is unlikely to explain the deviation from 1.00. Tungsten (OR 0.78, p-value 0.57), arsenic (OR 0.60 p=0.22) and the rest of the metals did not suggest increased risk. One of the PCB congeners had an OR greater than 1.00 (p=0.01), while another congener had an OR less than 1.00 (p=0.02). One VOC (ethylbenzene) suggested increased risk (p-value 0.04) while another (tetrachloroethylene) suggested decreased risk (p=0.004). From the interview information, we identified an increased risk with older paternal age (OR 1.14, p=0.03). We found a decreased risk among children in whom allergic rashes were diagnosed (OR 0.7, p=0.01).

Conclusions and Recommendations

This investigation identified an ongoing environmental exposure of concern among Churchill County residents. We confirmed that many people living in Churchill County still receive significant arsenic exposure, despite the general knowledge that Churchill County water exceeds recommended levels of arsenic in drinking water. We recommend that community members take advantage of alternative water sources until the new water treatment facility is completed.

Biologic results also identified tungsten as a potentially unique exposure within Churchill County. We are working with NSHD to further define tungsten exposure in Nevada and to evaluate potential routes of exposure. Because of our study findings, the National Institutes of Health is considering tungsten as a priority chemical for toxicologic research.

Although biologic results demonstrated a limited degree of elevated pesticide exposure in the community, environmental testing did not identify any sources of ongoing exposure. We recommend conservative use of personal household pesticides and recommend that state public health officials increase public education efforts about safe use of pesticides.

Having found elevated levels of several chemicals, we now plan, with the input of the Children's Oncology Group and other experts, to conduct genetic testing to try to determine whether differences exist between case families and comparison families in genes that are responsible for the way these environmental chemicals are metabolized.

All participants have been given their personal results, as well as information about how to minimize their environmental exposures. We encourage participants to share elevated findings with their personal health care providers.

BACKGROUND

In February 2001, the Nevada State Health Officer convened an Expert Panel to review existing evidence regarding an increase in the number of children living in Churchill County, Nevada in whom acute lymphoblastic leukemia (ALL) had been diagnosed (Appendix A). The Expert Panel was familiar with previous investigations of ALL clusters and recognized that all such investigations had failed to identify a cause or an explanation for these excesses. However, because so many cases had been identified in such a small population during such a short time, the Expert Panel recommended that the State of Nevada formally request assistance from the Centers for Disease Control and Prevention (CDC) and the Agency for Toxic Substances and Disease Registry (ATSDR) to evaluate environmental exposures potentially associated with disease occurrence. The Expert Panel recommended that the Nevada State Health Division (NSHD) take six follow-up steps in the investigation of the excess occurrence of ALL in Fallon, Nevada (Appendix B). The panel recommended that a multi-agency investigation identify potential excess environmental exposures unique to the community by a cross-sectional exposure assessment of selective contaminants and an examination of contaminant releases into the local environment with assessment of completed pathways for the case families and recommended "collecting and banking biologic specimens for future scientific investigations". CDC's National Center for Environmental Health (NCEH) was asked to design and conduct a cross-sectional exposure assessment of selected contaminants in Churchill County. This report describes the methods and the results of the CDC investigation.

METHODS

CDC collaborated with state and federal agencies to design a cross-sectional exposure assessment protocol (Appendix C). We invited families of the 14 case children who were already enrolled in the NSHD leukemia investigation to participate (see Table 1). We defined a case family as the case child and everyone else living in the child's current home (i.e., all siblings, parents, guardians, and other adults). The siblings were enrolled as possible surrogates for case children whose leukemia status and current medications could influence biologic sampling results. The case family also included any biologic parents who were not living full time in the case family home but for whom contact information was available.

We simultaneously enrolled comparison families from Churchill County (with a goal of four comparison families for each case family) using random digit dialing to contact the comparison families. Case children and families were matched with comparison children and families according to the birth year (+/-2 years) of the case child, sex of the case child, and noncancer-diagnosed status of the comparison child at the date of the case child's leukemia diagnosis. We defined a comparison family as the matched comparison child and that child's parents, guardians, or other care-taking adults living full time in the comparison family home.

All participants were invited to visit a CDC-staffed clinic site in Fallon from August 20 through October 31, 2001. During that visit we collected extensive questionnaire information about recent and historical exposures and medical history and also collected biologic samples (blood, urine, and cheek swab samples). Biologic samples were tested at CDC laboratories for heavy metals, persistent and nonpersistent pesticides, polychlorinated biphenyls (PCBs), and volatile organic compounds (VOCs), as well as for infectious disease markers of past infection, such as Epstein-Barr virus and human T-cell leukemia virus. During the clinic visit we also arranged appointments for environmental sampling in participant homes. Laboratory methods are

referenced or described in Appendix D. DNA was extracted from blood and cheek cells and stored by CDC for future study of candidate genes involved in metabolizing carcinogens and in DNA repair from damage by environmental exposures.

A 15th case child was identified and invited to enroll in December 2001. Biologic and questionnaire data collection was completed in February 2002. Total study enrollment comprised 205 participants from 14 case families and 55 comparison families. One case child died before any biologic samples were collected from the child; however the child's family and four matched comparison families were included in the analysis. Although one case family declined participation, we had already enrolled four matched comparison families for that family and we included their information in the cross-sectional analysis but not in the case-comparison analysis. We enrolled all 15 of the eligible case siblings (age range:1-30 years) who were living in the case families' homes.

Genetic Information

In collaboration with NSHD, we requested cytogenic test results of samples collected from case children before their treatment began and analyses that were performed as part of their treatment protocol. We obtained results for 13 of the 14 case children who consented to participate. We obtained information about the type of leukemia (T-cell or precursor-B ALL) for all 13 case children and information about the types of chromosomal abnormalities found in three case children. For four case children, specimens were stored for later analyses. The reason for the small number of case children who had results for translocations and for which residual specimens were stored is that this information and specimen storage were assured only for the children who were entered into a Children's Oncology Group protocol that specifically requested storage of specimens and provided for testing for specific translocations. Similarly, the complement of diagnostic, pre-treatment specimens was not available for infectious agent testing.

Environmental Sampling

Using standardized protocols (Appendix E), the Nevada Department of Environmental Protection (NDEP) collected environmental samples, including indoor air, play yard soil, and household dust from case families' current and previous residences within Churchill County, current residences of all comparison families, and previous Churchill County residences of one out of four comparison families. Tap water samples were collected by the United States Geological Survey (USGS). We sampled all current residences of those case families still living in Churchill County at date of enrollment (n=11), all previous homes in which case families had lived since 1 year before the date of birth of the case child (n=8), all current (at date of enrollment) comparison families' homes (n=55), and the previous homes of one randomly chosen comparison child for each case child (n=6). Among the 36 eligible previous residences, eight case homes, and 14 comparison homes were not available for sampling. Current and previous residences outside of Churchill County were not sampled. Environmental sample collection, excluding tap water samples, was completed in March 2002. Tap water sample collection was completed in September 2002. Household samples were tested for heavy metals, persistent and nonpersistent pesticides, PCBs, VOCs, radon, and radionuclides. Environmental samples were analyzed by USGS, the U.S. Environmental Protection Agency (EPA) Region IX, the Nevada Department of Agriculture, and several contract laboratories (Appendix E).

External Peer Review

To further enhance the strength of this investigation, CDC convened several advisory groups to provide external peer review and comment. We established a statistical advisory group that wrote a statistical plan and met regularly to review questionnaire and biologic results. We convened a genetic advisory group that included representatives from Children's Oncology Group. We also formed a multi-agency Data Interpretation Group to review all environmental results using a secure electronic site for data presentation (Appendix F). CDC also hosted dedicated weekly conference calls to facilitate communication among state and federal partners. To further enhance communication with NSHD, CDC contracted to place a communication liaison in Carson City for 15 months and contracted a specialist to prepare a communication plan for NSHD.

Cross-sectional Analysis Methods

The cross-sectional analysis included all study participants. We used descriptive and spatial analysis to compare our biologic and environmental sampling results with a reference standard. Map 1 shows the geographic location of study households. We used the geometric means and 95% confidence intervals (CIs) under the assumption that the data approximates a log-normal distribution. The estimate of the geometric mean and CI is based on a statistical model that controls for the possible correlation of observations within a family (i.e., a variance components model), when appropriate. Statistical methods are further described in Appendix G.

For biologic samples, we compared our results to a reference level known to be associated with adverse health effects (e.g., blood lead levels or urine arsenic levels) when such levels are known. When no health-effect-based reference level was available, we compared the Churchill County geometric mean value to the geometric mean from the *Second National Report on Human Exposure to Environmental Chemicals* (*National Exposure Report*) (http://www.cdc.gov/exposurereport), which is based on population data collected as part of the National Health and Nutrition Examination Survey (NHANES) (http://www.cdc.gov/nchs/nhanes.htm). If the lower boundary of the Churchill County CI was higher than the upper boundary of the *National Exposure Report* CI, then we considered that chemical to be elevated in our study population. This is designated as "H" on tables that report cross-sectional results. If the Churchill County CI overlapped that in the *National Exposure Report*, then we considered the chemical to be consistent with national estimates. If the upper boundary of the Churchill County CI was below the lower boundary of the *National Exposure Report* CI, then we considered the chemical to be low in our study population; we designated this by an "L" on the tables that report cross-sectional results. We made this comparison as a conservative first step in evaluating our study results. We also looked at the percentage of study participants that exceeded the 95th percentile level of that chemical in the *National Exposure Report*. If more than 10% of our study population exceeded the 95th percentile from the *National Exposure Report*, we classified that chemical as "H" in our study population. Chemical results that do not have a health-based reference value, and were not measured in the *National Exposure Report*, were compared with reference levels found in the peer-reviewed literature—such references were available. The source of the reference for each individual chemical is provided on the results tables in this report.

For environmental samples, the Data Interpretation Group reviewed summary reports prepared by ATSDR's Federal Facilities Information Management System (FFIMS) for each site tested and summary data for each chemical. These reports were posted in a secure web-based

meeting space for review. Comments posted from agency representatives included a vote about whether the data set included any chemical levels of concern. We determined this by comparing the concentration of contaminants detected in air, water, or soil against ATSDR's health-based values. These values often are based on animal studies because relevant human data are lacking and they are designed to be orders of magnitude lower than levels known to produce adverse health effects. Chemical levels that were above the reference level were reviewed in detail. Site summaries written at the time samples were collected often provided information that would explain the elevated chemical levels, such as recent spraying of pesticides. Members of the Data Interpretation Group often consulted relevant scientific literature to determine whether comparison values were up to date and whether site-specific exposures could pose a hazard to public health.

If no ATSDR comparison value was available, FFIMS provided, in a hierarchical fashion, comparison levels from EPA Region IX, EPA Region III, or EPA Region VI. If available, levels from EPA Region IX were used first because it is the region in which Nevada is located, and these levels represent the level at which chemicals would most likely be found. If neither ATSDR nor EPA Region IX had levels for a given chemical, values from EPA Region III were used. EPA Region III was selected because of that region's strict regulations. Finally, if comparison levels were not available from any of these sources, levels from EPA Region VI were used. This region was selected because it is the most geologically similar to Region IX. If no comparison level of any kind was available for a chemical, the members of the Data Interpretation Group who had expertise with that chemical would make a determination based on the result, site summaries, known adverse health effects, and professional expertise.

Case-comparison Analysis Methods

Our case-comparison analysis included 14 case families and their 51 matched comparison families. Siblings were included in portions of the case-comparison analysis. Results excluding siblings are so labeled. We used conditional logistic regression to compare exposure between case and comparison families. Conditional logistic regression was performed for quantitative variables assuming a log-linear relation between the variable and the odds of disease. We standardized each independent variable by dividing each value by the standard deviation of that variable calculated using the entire Churchill County study population. As a result, odds ratios (ORs) for quantitative variables correspond to an increase in dose corresponding to one standard deviation in the study population. When 40% or more of the study participants had levels below the limit of detection for any quantitative variable, we grouped the variables into two categories: at or below the limit of detection and above the limit of detection. For these variables, ORs measure the association between case and comparison status and the presence of having detectable levels of the chemical of interest.

Conditional logistic regression models were used to model the probability of experiencing an exposure while conditioning on the matching strata that are apparent in the data. The resulting ORs provide a means of exploring the relation between disease and exposure. An OR of 1.0 indicates no differences between the two groups with respect to the exposure variable. ORs that are statistically significantly different from 1.0 (as assessed by a p-value) indicate that one group has higher (or lower) odds of having been exposed. In this study, small p-values (e.g., p-values < 0.01) indicate statistically significant differences in the exposure variable between the case and comparison groups. An OR also is considered statistically significant when the CI

around that point estimate does not include the number one. LogXact software from Cytel Corporation was used to fit the conditional logistic regression models (LogXact 4, 1996-2000).

During our analysis, we initially considered all 13 case children with biologic samples. We then repeated the analysis using the nine children who had the most similar disease profiles. The second analysis (referred to in the Results section as the restricted case definition) was limited to case children with pre-B-cell lymphocytic leukemia diagnosed before they were 6 years of age and who had lived in Churchill County for at least the 6 months before their diagnosis. Six months of exposure to a carcinogen before a cancer diagnosis is considered a conservative latency period for a pediatric cancer (Ford 1993). Restricted case definition analysis included only 34 comparison children matched to the nine case children.

Individual results of biologic and environmental sample analysis were reported back to each study participant before release of aggregate results.

RESULTS

On August 20, 2002, CDC released preliminary results of heavy metal analysis on blood and urine samples. Although the remaining biologic sample analyses had not been completed, the metals results were released to participants and to the community because arsenic and tungsten levels were markedly above reference levels. The median tungsten level in the study population was 0.97 µg/L compared with 0.10 µg/L in the 1999 NHANES, which was the most current population reference available in August 2002. Levels among case and comparison children and families were similar (case children median = 1.94 µg/L; comparison children median = 2.36 µg/L, and case family median =1.00 µg/L; comparison family median = 0.97µg/L). Almost 80% of the Churchill County participants had tungsten levels above the NHANES 90th percentile (0.32 µg/L). Upon receiving the biologic results, CDC contracted with USGS to collect and measure tungsten in tap water samples from participants' homes, and petitioned the National Toxicology Program of the National Institutes of Health to prioritize research regarding the health effects of tungsten exposure.

We also informed the Churchill County community that arsenic levels in the study participants ranged from less than the limit of detection to 1180.40 µg/L, with a median level of 37.40 µg/L; normal urine levels of arsenic are lower than 50 µg/L; levels >200 µg/L are potentially associated with adverse health effects (Haddad 1998). Individual participants were advised to limit their exposure to water containing arsenic.

By December 2002, CDC had received results of all the biologic and environmental samples that the many state and federal laboratories had analyzed, except for speciated arsenic results for biologic samples. The results are presented below divided into chemical categories (i.e., metals, nonpersistent pesticides, persistent pesticides, PCBs and VOCs) and infectious disease categories. Within each category, results of the cross-sectional analysis and the case-comparison analysis are presented separately.

We reviewed the results as both creatinine corrected and noncreatinine corrected, as well as lipid adjusted and lipid unadjusted. In this report, we present noncreatinine corrected results for metal and nonpersistent pesticide levels in urine samples, lipid-adjusted results for persistent pesticide and PCB levels in serum samples, and results not adjusted for lipids for VOCs analyzed in blood samples.

Metals

Cross-sectional Analysis

Table 2 shows the geometric mean level in biologic samples for the 16 metals we analyzed in the Churchill County study participants. Three of these metals (cadmium, lead, and mercury) were analyzed in both blood and urine samples; 12 other metals were analyzed in urine samples; selenium was analyzed in serum samples. We used health-based reference levels to determine excess exposure to cadmium (Lauwerys 2001), lead (Lauwerys 2001, Goldfrank 2002), mercury (Goldfrank 2002), arsenic (Haddad 1998, Goldfrank 2002), selenium (Hogberg 1986), and nickel (White 1998). For eight of the metals, the geometric mean and the 95th percentile reference level are available from the *National Exposure Report*. Chromium and manganese do not have any available reference levels for comparison.

Eight of the metals (antimony, arsenic, barium, cesium, cobalt, molybdenum, tungsten and uranium) measured in urine are classified as "H" (Table 2). Six of these metals (antimony, barium, cesium, cobalt, molybdenum and tungsten) are classified as high because the lower boundary of our study geometric mean is higher than the upper boundary around the confidence interval for the geometric mean of the *National Exposure Report*. For three of these metals (barium, cesium, and tungsten) more than 10% of the levels also are above the 95th percentile in the *National Exposure Report*: barium, 14% above; cesium, 12% above; and tungsten, 68% above. The study geometric mean for uranium is actually lower than the *National Exposure Report* geometric mean. However, uranium is classified as "H" on Table 2 because 25% of the Churchill County levels are above the 95th percentile level in the *National Exposure Report*. Similarly, arsenic is classified as "H" because 34% of our study participants are above the health-based reference level, although the geometric mean level of our study participants is below the health based reference level. Although eight metals are classified as high, only tungsten has a study population geometric mean that exceeds the 95th percentile level in the *National Exposure Report*. The following results further describe tungsten, arsenic, and uranium exposure in the cross-sectional analysis.

Tungsten was detected in 98.5% of our study population samples; the geometric mean was 1.17 µg/L (95%CI 0.93-1.46). In comparison, tungsten was detected in 76% of the participants sampled for the *National Exposure Report*, where the geometric mean was 0.09 µg/L (95%CI 0.09-0.1). Map 2 shows the distribution of household geometric mean tungsten levels according to residence at time of study enrollment. Results of tap water sampling from 76 residences ranged from 0 to 217.3 ppb; no reference level is available for tungsten in drinking water. Map 3 shows the distribution of tap water results at each study participant's current residence. Individual levels of urinary tungsten and tungsten levels in tap water samples were not correlated (Spearman correlation coefficient=0.09, p=0.18), even when stratified by source (well or public) and by treatment (reverse osmosis treatment, yes or no). Our questionnaire did not collect individual information about amount of drinking water consumed or the variety of potential drinking water sources (e.g., home, school, workplace) for a person accessing drinking water.

Naturally occurring **uranium** was detected in 86.7 % of our study population urine samples; the geometric mean was 0.02 µg/L (95% CI 0.02-0.03). In comparison, uranium was detected in 72.0% of the participants sampled for the *National Exposure Report*, where the geometric mean was 0.048 µg/L (95% CI 0.04-0.06). Uranium levels in tap water samples ranged from 0.004 µg/L to 290 µg/L; the National Drinking Water Standard for uranium will be

30 µg/L as of 12/08/03 (http://www.epa.gov/ogwdw/mcl.html). Individual levels of uranium in urine samples were slightly correlated (Spearman correlation coefficient=0.36, p=0.0001) with uranium levels in residential tap water.

We detected **arsenic** in 99.5% of our study participants' urine samples. Arsenic levels are not included in the *National Exposure Report*. Arsenic levels in the study population ranged from less than the limit of detection to 1180.40 µg/L, with a median level of 37.40 µg/L. The geometric mean was 34.61 µg/L (95% CI 28.07-42.68). Arsenic levels varied among family members within a single household. Map 4 shows the distribution of household geometric mean level of arsenic in urine samples. Tap water levels of arsenic varied from 2.0 to 874 µg/L; the National Drinking Water Standard for arsenic is 50 µg/L (http://www.epa.gov/ogwdw/mcl.html). Individual levels of arsenic in urine samples were only slightly correlated with residential tap water levels (Spearman correlation coefficient=.21, p=0.007).

Case-comparison Analysis

Table 3 shows the OR and p-values for logistic regression models comparing case children and case families with their matched controls. Using conditional logistic regression and limiting our analysis of **tungsten** exposure to case families, excluding siblings, and their matched comparison families, we found no relation between leukemia and tungsten exposure (OR 0.96, 95% CI 0.77-1.24, p=0.85). For case parents and comparison parents the OR was 1.06 (95% CI 0.66-1.70, p=0.82); for case children and comparison children the OR 0.78 (95% CI 0.33-1.86, p=0.57). Results were similar (OR 1.16, 95% CI 0.59-2.03, p=0.78) when using the restricted case definition children only.

For **uranium**, we found no difference in exposure among case families, excluding siblings, and comparison families (OR 1.06, 95% CI 0.77-1.44, p=0.76), nor among case versus comparison restricted definition study children (OR 1.24, 95% CI 0.63-2.45, p=0.09). We identified a slightly increased risk for exposure among restricted case definition case families, excluding siblings, and comparison families (OR 1.91, 95% CI 1.11-3.28, p=0.002).

Arsenic exposure was somewhat lower among case families (geometric mean 26.24 µg/L (95% CI 18.59-37.02) than comparison families (38.12 µg/L (95% CI 31.23-46.53). Case families, excluding siblings, were less likely to be exposed to arsenic (OR 0.64, 95% CI 0.47-0.98, p=0.03) than were their matched comparison families. When using the restricted case definition the exposure among case children remained lower than among comparison children, but the difference was not statistically significant.

Nonpersistent Pesticides

Cross-sectional Analysis

Table 4 shows the geometric mean levels of 31 nonpersistent pesticides and pesticide metabolites analyzed in urine samples collected from the Churchill County study population. Nineteen of the metabolites relate to exposure to cholinesterase-inhibiting pesticides (e.g., organophosphate and carbamate pesticides), four metabolites originate from chlorinated phenol pesticides (e.g., hexachlorobenzene), three metabolites are specific to herbicides (e.g., atrazine), one metabolite is specific to pyrethroids, one compound is specific to a fungicide, and three compounds relate to exposure to insect repellents (e.g., DEET). Although 24 of the pesticide metabolites were analyzed for the *National Exposure Report*, only nine were detected in >60% of samples, which is the detection level necessary to calculate the geometric mean. Five of the

pesticides we measured (chlorpyrifos, diethylthiophosphate, 2,4,5-trichlorophenol [1TB], 2,4,6-trichlorophenol [3TB] and 2-naphthol) are above the reference geometric mean (Table 4). The compound specific to a fungicide (o-Phenylphenol) could not be compared to a reference geometric mean but 18% of the Churchill County participants were above the *National Exposure Report*. Four of the pesticides are below the national reference; most of the pesticides are similar to the national reference. Among the five pesticides with no available reference level, all Churchill County median levels were below the level of instrument detection. No results were reported for the metabolite alachor mercapturate. Map 5 shows the distribution of the household geometric mean of summed individual levels of organophosphate metabolites not adjusted for creatinine.

Two **chlorinated phenol** pesticides, 1TB and 3TB, were higher (median 5.87 µg/L and 4.78 µg/L, respectively) than levels in the *National Exposure Report* (median 0.80 µg/L and 2.45 µg/L, respectively). 1TB was detected in 71.3% of our study population samples; the overall geometric mean was 4.48 µg/L (95% CI 3.65-5.50). This compares with detection of 1TB in 88% of the participants sampled for the *National Exposure Report*, where the geometric mean was 1.19 µg/L (95% CI 1.00-1.41). 3TB was detected in 56.4% of our study population samples; the overall geometric mean was 4.58 µg/L (95% CI 3.69-5.69). This compares with detection of 3TB in 81% of the participants sampled for the *National Exposure Report*, where the geometric mean was 2.85 µg/L (95% CI 2.58-3.15).

Environmental sampling for nonpersistent pesticides included analysis for 1TB and 3TB in soil. Of 79 samples tested, two had minimally detectable levels of both 1TB and 3TB. We tested for 15 other chlorinated phenol compounds; low levels were detected in soil but all below reference levels.

Case-comparison Analysis

Table 5 shows the results of conditional logistic regression of the nonpersistent pesticides that had detectable percentages sufficient to calculate ORs and p-values.

For the chlorinated phenol **1TB**, the geometric mean for the case families was 4.08 µg/L (95% CI 2.68-6.21) and 4.63 µg/L (95% CI 3.61-5.94) for the comparison families (p=0.69). Exposure to 1TB was not associated with leukemia status (all study children OR 0.57, p=0.09). Restricted case definition comparison was similar.

For **3TB** the geometric mean for case families was 4.93 µg/L (95% CI 2.63-9.24) and for comparison families 4.31 µg/L (95% CI 3.22-5.77, p=0.23). Because more than 40% of the results for 3TB were below the limit of instrument detection, the OR and corresponding p-values could be calculated only for case children; results are similar to 1TB.

Persistent Organic Compound Results

Cross-sectional Analysis

Table 6a shows the geometric means of the 11 persistent pesticides, and Table 6b shows the geometric means of the 36 PCBs. Ten of the persistent pesticides have geometric mean and 95th percentile levels reported in the *National Exposure Report*. There is no reference level for dieldrin.

Nine of the persistent pesticides had geometric mean levels below the national geometric mean. Only 1,1-dichloro-2,2-bis(*p*-chlorophenyl)-ethylene (**DDE**), a breakdown product of 2,2-

bis(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT) was elevated (median 445.27 ng/gram lipid) in our study population, compared with the *National Exposure Report* (median 226.00 ng/g lipid).

We calculated medians and geometric means for subsets of the total study population according to potential sources of historical exposure (see Table 7).

Of the 36 PCBs, 22 have reference levels in the *National Exposure Report*; for the remaining PCB congeners, relevant reference levels are not available. Six of the 22 congeners (PCBs 28, 52, 66,101, 156, and 187) had geometric means that were above the *National Exposure Report* geometric mean levels. None of the PCB congeners exceeded the 95th percentile reference levels.

Persistent pesticides were analyzed in soil and dust samples. During review of the PCB mixture results in soil, the Data Investigation Group found that the analytical limit of detection for our levels were significantly higher than the available comparison values. The high detection limits probably resulted from matrix interference, commonly encountered in the analysis of soil and dust samples.

Data Investigation Group representatives from ATSDR took the lead in identifying an alternate comparison level that would allow PCB results to be more accurately interpreted. Using a conservative EPA clean-up goal value of 1.0 ppm, the detection limits for the seven aroclors for each household were summed. For most of the households, the summed detection limits were lower than the EPA value of 1.0 ppm. Four households, however, had summed detection limits higher than the comparison value, suggesting that the dust samples from these households had PCB levels approaching 9.0, 2.4, 2.4, and 2.1ppm. The Data Investigation Group reviewed PCB results in other environmental and biologic matrices. Summed detection limits for PCBs in soil did not exceed 1.0 ppm. Levels of PCB congeners in biologic samples collected from members of three of the households did not exceed comparison values. One member of the fourth household had slight elevations in three congeners, 146, 170, 180, but reported related occupational exposures. No members of the household with the highest summed detection limits had PCB levels above comparison levels. The Data Investigation Group determined resampling or reanalyzing dust samples from the four households whose summed detection limits for arochlor exceeded 1.0 ppm was not necessary.

One persistent pesticide (dieldrin) was elevated in environmental samples collected from residential play yard soil. The maximum result reported was 0.19 ppm. Although this level exceeds the ATSDR Cancer Risk Evaluation Guide (an estimated level of a chemical that is expected to cause no more than one excess cancer in a million people exposed over a lifetime) (0.04 ppm), it is within an acceptable risk range for long-term (chronic) exposures (ATSDR Public Health Guidance Manual). In addition, this level is less than the ATSDR chronic oral child Environmental Media Evaluation Guide (the concentration of a chemical in a particular medium e.g., air, water, soil that is calculated from ATSDR minimal risk levels for non-cancer health effects) (3 ppm) (ATSDR Public Health Guidance Manual).

Case-comparison Analysis

Table 8a and 8b show the results of conditional logistic regression of the three persistent pesticides that had detectable percentages sufficient to calculate ORs and p-values.

Geometric mean for DDE was 302.9 ng/g lipid (95% CI 125.43-731.45) for case families and 501.28 ng/gm lipid (95% CI 440.23-585.75) for their comparison families (p=0.08). Comparisons of all matched cases did not appear to associate DDE exposure with leukemia (OR 0.53, p=0.26).

Conditional logistic regression analysis identified seven PCB congener (# 18, 28, 52,101, 118, 196 and 206) with significant p-values (Table 8b).

Volatile Organic Compound Results

Cross-sectional Analysis

Table 9 shows the arithmetic mean levels of the 12 creatinine unadjusted VOCs analyzed in this study. Because VOCs were not included in the *National Exposure Report* reference levels are taken from population-based studies published in the peer-reviewed literature (Ashley 1994, Ashley 1996, and Churchill 2001). Two of the Churchill County levels (styrene and tetrachloroethylene) were slightly higher than the reference arithmetic mean but lower than the 95th percentile. Map 6 shows the distribution of household geometric mean levels of benzene in blood samples collected from Churchill County residents.

Air of 77 households was sampled for VOCs. None of the results suggested a community-wide exposure to any of the 61 VOC analytes we measured. The few VOC analytes detected in most of the households sampled were either common household VOCs (e.g., acetone, ethanol) or were lower than comparison levels. ATSDR screening levels and EPA regulatory or recommended levels were used as comparison values.

Two homes had elevated levels of tetrachloroethylene. The comparison value used to screen tetrachloroethylene was 3.3 $\mu g/m^3$ from EPA Region IX. The two homes had levels of 244 and 326 $\mu g/m^3$. In reviewing site summaries written at sample collection, we determined that dry-cleaned clothes had recently been brought into one house. The site summary for the other household did not indicate recent dry-cleaning. However, questionnaire data indicated that the father works as a mechanic and therefore would be likely to bring tetrachloroethylene residues into the house on his clothes.

Levels of all others VOCs were determined by the Data Investigation Group to be below a level of concern.

Case-comparison Analysis

Table 10 shows the results of conditional logistic regression of the nine VOCs that had detectable percentages sufficient to calculate ORs and p-values.

We found an OR of 0.35, p-value 0.004, when comparing tetrachloroethylene exposure among case and comparison families, excluding siblings. This suggestive protective effect did not remain statistically significant when we compared only study children, or restricted case definition children. An increased risk, but with wide CIs, associated with exposure to ethylbenzene was observed among case children matched to comparison children (OR 2.67, 95% CI 1.04-6.84, p-value 0.04).

Ethylbenzene was detected in 10 of 77 households, with a mean level of 8.36 ug/m^3. None of the households exceeded the EPA-recommended level of 1100 $\mu g/m^3$. The maximum level detected was 20 $\mu g/m^3$.

Questionnaire and Interview Results

Cross-sectional Analysis

We collected extensive information from all participants about residential, occupational, medical, and travel histories, including details of exposures from before pregnancy until

diagnosis. Case children (seven girls and seven boys) and matched comparison children ranged in age from 2 years to 19 years at diagnosis and from 3 years to 20 years at sample collection. At enrollment, case mothers were 24-50 years of age, and case fathers were 31-58 years; comparison mothers ranged in age from 22 to 57 years, and comparison fathers from 25 to 58 years. The complete questionnaire is included with the study protocol (Appendix C). Table 11 lists selected descriptive information collected from all study participants.

Case-comparison Analysis

Using conditional logistic regression to evaluate paternal age, we found an association between leukemia diagnosis and fathers being older at the time of the study child's birth (OR 1.14, 95% CI 1.01-1.29). This difference persisted for the restricted case definition group (OR 1.19, 95% CI 1.02-1.39). We found no association between case status and maternal age.

Case children were historically less likely to have been physician-diagnosed with an allergic skin rash (OR 0.067, 95% CI 0-0.46), although this estimate is considered unstable because no case children answered yes to the question. Several household recreational exposures occurred more frequently among comparison than case families. For example, comparison adults were more likely to use glues or adhesives daily (OR 0.74, 95% CI 0.18-2.7).

Infectious Disease Results

Because some studies suggest that certain viruses might influence the development of leukemias and other cancers (Greaves 2000, Smith 1997, CDC 1993, McNally 2000, Neglia 2000), we evaluated participants for evidence of certain infections. This evaluation included testing blood samples for the viruses described below, which are known or suspected to be associated with leukemia. The tests show whether a person was infected with the viruses at any time before blood was drawn. The tests cannot distinguish whether a person was infected before or after he/she developed leukemia.

Epstein-Barr Virus (EBV)

Blood samples from all community participants were tested for EBV. EBV is a common virus that infects most people before they reach middle age (Epstein 1996, Schooley 2000). In the United States, as many as 95% of adults aged 35-40 years have been infected. Risk of EBV infection increases with age. Most people infected with EBV have only mild symptoms or never get sick. Thus, many people never know they have been infected. Some EBV-infected people develop infectious mononucleosis or "mono". In the Churchill County study, some participants had evidence of past (more than three months before they gave blood for the study) or more recent (three months or less before they gave blood samples) EBV infection. Results for others suggested that they had never been infected with EBV. The age-related distribution of EBV serology among the study participants was not different than expected.

Case-Comparison Analysis: EBV

Using conditional logistic regression, this study further compared the results of EBV testing for all 13 case children submitting blood samples and their 47 matched controls. (Table 12). The analysis could not definitively relate EBV infection to the childhood leukemias in Churchill County (OR 0.41), 95% CI (0.07-1.92). EBV infection seemed to occur less frequently among the children with leukemia than among the comparison children. However, the study

could not conclude that EBV infection either protected against or increased the risk for the childhood leukemias.

Other Viruses

The study also examined blood samples for a group of viruses called "retroviruses". Samples from all children diagnosed with childhood leukemia were tested. For each of these children, samples from two comparison children also were tested to help interpret the results. The study employed a research test (ampRT) that screens for a number of retroviruses. Samples also were analyzed by other laboratory methods, including research tests, for these retroviruses: human T-lymphotropic virus type 1 (HTLV-1); human T lymphotropic virus type 2 (HTLV-2); feline leukemia virus (FeLV); avian leukosis virus (ALV). HTLV-1 is associated with a rare form of leukemia, adult T-cell lymphoblastic leukemia/lymphoma. HTLV-2 is a related virus. However, both HTLV-1 and HTLV-2 infections are uncommon in the United States. FeLV is found in cats with leukemia but has not been reported in humans with leukemias. ALV is a bird virus that has not been reported to infect humans. However, because humans have contact with birds, the study also tested blood samples for ALV. We found no evidence of any of these viruses or of viral activity in any of the participants.

Other Possible Markers of Infection

We analyzed certain interview and questionnaire items that might suggest exposure to infections. However, those analyses did not identify any specific infectious risks for childhood leukemia in the study population.

DISCUSSION

This report describes the methods and results of a multi-agency state-of-the-art investigation to determine whether environmental exposures in Churchill County, Nevada posed a risk to human health. CDC led a cross-sectional study to determine whether unrecognized chemicals were present in the community, and whether any associations existed between environmental exposures and the cluster of children with leukemia that had been identified in Churchill County. Before this investigation, the community was aware that water from municipal and private wells contained excess amounts of arsenic. The community also was concerned about potential exposures to VOCs because of their proximity to the Fallon Naval Air Station. In addition, the community voiced concerns about underground nuclear testing that had historically taken place in Nevada.

Our study found that most chemicals measured in biologic and environmental samples were comparable with reference levels. This investigation also identified that the elements tungsten and arsenic, two chlorophenol pesticides, two organophosphate metabolites and the persistent pesticide metabolite DDE were elevated above reference levels in the biologic samples. Tungsten and arsenic also were elevated in tap water samples; pesticides were not elevated in any of the environmental samples.

Neither tungsten nor arsenic has been previously associated with ALL. Within our study population, levels were not higher among case families than among comparison families, although people may react differently to excess exposures based on their own genetic make-up. We found a strong correlation (Spearman correlation coefficient=0.67, p-value < 0.0001) between tungsten and arsenic levels in urine samples and between tungsten and arsenic levels in

tap water samples (0.83, p-value <0.0001). However, we found only a slight correlation (p=0.21) between urine arsenic and tap water arsenic and no correlation (p=0.18) between urine tungsten and tap water tungsten. Water treatment processes that remove arsenic from drinking water are assumed to be equally effective for removing tungsten. Reverse osmosis and ion exchange treatment systems are effective for removing arsenic V (98-99%) and, to a lesser extent, arsenic III (46-75%). Based on its relation to chromium on the periodic chart, tungsten probably reacts similarly to treatment as chromium. Cr(III) and Cr(VI) are both well removed by reverse osmosis treatment and ion exchange, removals range from 96%-99% (Faust 1998).

Our cross-sectional study also identified increased levels of two chlorophenol pesticides that may be associated with exposure to hexachlorobenzene, or pentachlorophenol, or the pesticide lindane, which is dispensed by prescription to treat head lice and scabies. Although these levels were above our reference level, these levels have not been associated with adverse health effects. Once again, levels were similar among case and comparison participants. We did not find these pesticides elevated in environmental samples, and we have no evidence that exposure is from a common environmental source.

Similarly, we found DDE in biologic samples but have no evidence of an ongoing source of exposure to DDT or DDE. DDT is a chlorinated organic pesticide that was banned from most use in the United States in 1972 but continues to be used internationally for mosquito control. These chemicals persist in the environment and may accumulate in adipose tissue, with levels persisting for decades. DDT and DDE are reasonably expected to be human carcinogens based upon evidence from animal studies; however, human studies are mixed and inconclusive with regard to an association between DDT and DDE exposure and breast cancer and leukemia. (Longnecker 1997). Groups at increased risk for exposure to DDT and DDE include adults and children who have lived in countries where DDT is still used or have eaten food (including breast milk) that contains DDE. Our results suggest that the increased exposure in our study population may be at least partially attributed to historical exposures. Although we found lower exposure levels among our case population than among our comparison participants, we recognize that people may respond differently to defined exposures.

The cause or causes of leukemia in children are not known. Environmental contaminants that have been at least theoretically linked with some form of cancer include metals (e.g., arsenic), VOCs (e.g., benzene), nonpersistent pesticides (e.g., organophosphates), persistent pesticides (e.g., DDT), and radiation. Among these, only benzene has been clearly implicated as a cause of leukemia (Irons 1999). Nonetheless, we evaluated all of these chemicals in biologic and environmental samples. As described above, we found no evidence of ongoing human exposure to benzene or other VOCs.

We also attempted to collect information that would benefit researchers who are evaluating the population-mixing theory as a risk scenario for cancer clusters. This theory originated among European scientists, who noticed that leukemia often clustered in isolated rural communities after a sudden influx of people into the community. The scientists speculated that the immigrants could be introducing a variety of different infectious agents into a susceptible rural community that could trigger an unusual and rare reaction among a very small number of children within the susceptible population (Kinlen 1990 and 1993). We evaluated this possibility, but did not find any difference in markers of infectious disease between case children and comparison children.

Limitations

Several limitations should be considered in interpreting the national and county level data. First, the comparison results from the *National Exposure Report* represent the U.S. population as a whole, not the people living in Churchill County, Nevada. People included in the *National Exposure Report* were mostly people living in the eastern and western suburban and urban regions of the United States. People in Churchill County live in a rural area, rich in agriculture and mining. This difference may account for the higher levels of some metals and pesticides in blood and urine of Churchill County residents than in the general U.S. population. In addition, the volume of blood available for analysis in the *National Exposure Report* was significantly lower than the amount collected in Churchill County; this resulted in a lower limit of detection and increased sensitivity to detect chemicals in the blood of Churchill County residents than people in the *National Exposure Report*. The detection limits for PCBs and persistent pesticides were substantially lower for Churchill County than for people in the *National Exposure Report*. Finally, levels of metals, pesticides and other substances detected in blood and urine do not necessarily indicate a health risk. Blood and urine levels of most of these chemicals have not been associated with health problems.

The case and control comparisons have at least three limitations: the small number of case children, the cross-sectional nature of the measurements taken, and the multiple comparisons that were examined. In most etiologic studies of ALL, proper study design would call for more than 100 case children to provide study power sufficient to detect a significant difference in risk for exposure between cases and comparisons. The best studies enroll several hundred case-patients. In a study of a cluster, however, the investigation is limited to the children in the cluster itself. Unless some risk factor is particularly unique to the children in the cluster, it will be very difficult to identify. All of the chemicals measured in blood and urine and those measured in the soil, air, water, and dust of the homes came from samples collected after the cancer diagnosis. If a chemical caused the child's cancer, the exposure would have to have occurred several months, and possibly years, before the child's diagnosis. The Churchill County results may (or may not) represent earlier exposures. Nonetheless, the results provide reassuring information about the status of environmental exposures in Churchill County.

Because the study collected information on 108 biologic measurements, 207 environmental measurements, and 6 infectious diseases and analyzed these using different case definitions, thousands of comparisons were made. As a result, we would expect to find several statistically significant results due to chance alone. Thus, each significant finding should be interpreted with an appreciation for biologic plausibility and pre-existing hypotheses. Simply reporting a statistically significant result is not sufficient to establish a cause and effect relation between exposure and disease.

CONCLUSIONS AND RECOMMENDATIONS

This investigation identified an ongoing environmental exposure of concern among Churchill County residents. We confirmed that many people living in Churchill County still receive significant arsenic exposure, despite the general knowledge that Churchill County water exceeded recommended levels of arsenic in drinking water (http://www.cityoffallon.com/). New water treatment facilities will increase the availability of arsenic-free drinking water in this community. Until these new facilities are finished, we recommend that the City of Fallon continue to educate the community about alternative sources of drinking water.

Biologic results also identified tungsten as a potentially unique exposure within Churchill County. Efforts are under way to further define tungsten exposure in Nevada and to evaluate potential routes of exposure. The results of this continued tungsten investigation will be shared with the Churchill County community. Tungsten also is being considered by the National Institutes of Health as a priority chemical for toxicologic research.

Although biologic results demonstrated a limited degree of elevated pesticide exposure in the community, environmental testing did not identify any sources of ongoing exposure. We recommend conservative use of personal household pesticides and recommend that state public health officials increase public education efforts about safe use of pesticides.

With the input of the Children's Oncology Group and other experts, we plan to conduct genetic testing to try to determine whether differences exist between case families and comparison families in genes that are responsible for the way the elevated levels of environmental chemicals we found are metabolized or the way environmental chemicals may affect the products of genes. This means that we will look at normal genetic variation among people that may make some people slightly more susceptible than others to exposures. Little is known about genetic variation among people at this time, and we do not expect the Fallon study alone to provide definitive evidence. However, we believe that, over time, this information will help us to understand how genes and the environment act together to cause disease. The results of these analyses will not predict sensitivity or vulnerability in an individual child, but they will help us generate hypotheses about genetic differences in individual responses to environmental contaminants.

All participants have been given their personal results and information about how to minimize their environmental exposures. We encourage participants to share any elevated findings with their personal healthcare providers.

When we began this investigation, we recognized that our findings about the relation between environmental exposures and cancer occurrence would be limited by the small number of case reports, and we shared this limitation with the Churchill County community. Nonetheless, we launched and completed a multi-agency investigation that collected extensive lifestyle information and used state-of-the-art laboratory analysis for biomarkers of exposure. The data were carefully collected and analyzed. Even though we did not discover an environmental exposure that explains the cluster of leukemia in children in Churchill County, we collected information and laboratory samples with rigor, and we envision that our analytic results and stored biologic samples may be useful in any future aggregation of data among similar occurrences of leukemia. CDC is working with state health departments to review existing cancer cluster investigation plans, as well as reviewing benefits and limitations of conducting investigations. The results of the Churchill County investigation will be used to identify ways we can collaborate to increase our knowledge about environmental exposures and cancer occurrence.

Table 1. Participants Enrolled in the Churchill County Study of Environmental Chemicals

Participants	#	Urine sample	Blood sample	% Female
Case children alive at time of study enrollment (Note: 1 case child was deceased at time of case family enrollment. Study includes 14 case families.)	13	12	13	54%
Siblings of case children	15	15	14	34%
Case parents and guardians	24	24	24	50%
Other adults living with the case family	1	1	1	100%
Comparison children who had a matched case child	47	46	47	40%
Comparison children with no matched case child	8	8	8	50%
Comparison parents and guardians	92	92	92	55%
Other adults living with the comparison family	5	5	5	60%
Total study population	205	203	204	54%

Table 2. Levels of Metals [a] (µg/L)[b] in Urine and Blood of People Living in the United States and People Living in Churchill County, Nevada

Metal	United States[c]		Churchill County		Comparison
	Geometric Mean (95% Confidence Interval)[d]	95th Percentile	Geometric Mean (95% Confidence Interval)	% > U.S. 95th or Health Value	
Antimony	0.11 (0.10–0.13)	0.41 (0.39–0.46)	0.15 (0.14–0.16)	4.0	H[e]
Arsenic	NA[f]	50.0[g]	34.61 (28.07–42.68)	34.0[g]	H
Barium	1.15 (0.96–1.38)	6.60 (6.0–8.30)	2.45 (2.10–2.85)	14.0	H
Cadmium (urine)	0.33 (0.31–0.35)	2.0[h]	0.31 (0.28–0.34)	0.0	—[i]
Cadmium (blood)	0.41 (0.39–0.44)	5.0[h]	NC[j]	0.0	L[k]
Cesium	4.34 (4.06–4.63)	11.40 (10.30–12.50)	5.98 (5.43–6.58)	12.0	H
Chromium	NA	NA	NC	NA	NA
Cobalt	0.37 (0.35–0.40)	1.32 (1.16–1.45)	0.56 (0.50–0.62)	7.0	H
Lead (urine)	0.76 (0.71–0.81)	25.0[h]	0.68 (0.61–0.76)	0.0	—
Lead (blood)	1.66 (1.58–1.73)	10.0[g]	1.11 (1.02–1.21)	0.0	L
Manganese	NA	NA	0.73 (0.67–0.80)	NA	NA
Mercury (urine)	0.72 (0.64–0.81)	20.0[g]	0.38 (0.32–0.44)	0.0	L
Mercury (blood)	0.34 (0.30–0.39) 1-5 yrs 1.02 (0.81–1.22) 16-49 yrs	10.0[g]	0.32 (0.22–0.45) 0.76 (0.65–0.88)	0.0 0.0	—
Molybdenum	34.3 (29.4–40.1)	174 (153– 201)	62.14 (53.52–72.15)	10.0	H
Nickel	NA	5.0[l]	NC	3.0	L
Selenium (serum)	NA	179.0[m]	121.02 (118.56–123.50)	0.0	L
Thallium	0.17 (0.16–0.18)	0.45 (0.42–0.47)	0.16 (0.15–0.18)	2.0	—
Tungsten	0.08 (0.07–0.09)	0.48 (0.41–0.55)	1.19 (0.89–1.59)	68.0	H
Uranium	0.007 (0.006–0.008)	0.05 (0.04–0.05)	0.02 (0.02–0.03)	25.0	H

a Urine levels are noncreatinine adjusted. Blood levels are not lipid-adjusted.
b Micrograms per liter
c U.S. values are from the *Second National Report on Human Exposure to Environmental Chemicals,* 2003.
d The interval of numbers in which we are 95% assured the value is contained.
e The lower boundary of the Churchill County confidence interval (CI) was higher than the upper boundary of the CI for the U.S. level or, b) more than 10% of the Churchill County participants had a value above the U.S. 95th percentile.
f Not available. This metal was not included in the *Second National Report on Human Exposure to Environmental Chemicals*, 2003.
g Goldfrank L. Goldfrank's Toxicologic Emergencies 7th ed. 2002. McGraw Hill; New York and Haddad L, Shannon M, Winchester J. Haddad's Clinical Management of Poisoning and Drug Overdose. 3rd ed. 1998. WB Saunders Company; Philadelphia.
h Lauwerys R, Hoet P. In Industrial Chemical Exposure: Guidelines for Biological Monitoring 3rd ed. 2001. Lewis Publishers; Boca Raton, Florida.
i The Churchill County geometric mean is consistent with national estimates.
j Not Calculated was used when less than 60% of the study population had detectable levels of this chemical.
k The upper boundary of the Churchill County CI was below the lower boundary of the CI for the U.S. level and b) less then 10% of the Churchill County participants had a value above the U.S. 95th percentile.
l White M, Sabbioni E. Trace element reference values in tissues from inhabitants of the European Union. Sci Total Environ 1998;216:253-70.
m Hogberg, J. Selenium. In Handbook on the Toxicology of Metals. 2nd ed.; 1986.

Table 3. Estimated Risk for Childhood Leukemia Associated with Urine and Blood Levels of Metals (µg/L)* for Case Children and Families Compared with Control Children and Families Living in Churchill County

	Case vs. Comparison (Child)		Case vs. Comparison (Families)†	
Metal	**Odds Ratio‡**	***P*-Value§**	**Odds Ratio**	***P*-Value**
Antimony	1.40	0.31	0.80	0.36
Arsenic	0.60	0.22	0.67	0.11
Barium	0.91	0.77	0.86	0.52
Cesium	0.64	0.25	0.74	0.20
Cobalt	0.84	0.68	1.18	0.45
Lead (urine) (µg/dL)‖	0.64	0.24	0.98	0.93
Lead (blood) (µg/dL)‖	0.33	0.002	1.24	0.36
Manganese	1.51	0.30	0.96	0.84
Mercury (urine)	0.84	0.66	0.89	1.03
Mercury (blood)	1.15	0.68	1.50	0.14
Molybdenum	0.82	0.64	0.77	0.27
Selenium (serum)	0.75	0.42	0.84	0.48
Thallium	0.68	0.35	0.80	0.34
Tungsten	0.78	0.57	1.06	0.82
Uranium	NC¶	NC	1.11	0.62

* Micrograms per liter

† Family members include parents/guardians only.

‡ The odds ratio is the estimated relative risk of leukemia associated with one standard error of the geometric mean increase in the blood or urine level of each chemical. Odds ratios are not reported if fewer than 60% of cases and controls had detectable levels of the chemical in their blood or urine.

§ The *P*-value is from likelihood ratio test. The *P*-value estimates the probability that the deviation of the odds ratio from 1.0 (no difference in risk) is due to chance. A *P*-value less than 0.05 suggests that chance is unlikely to explain the deviation.

‖ Micrograms per deciliter

¶ Not Calculated. Less than 60% of the study population had detectable levels of this metal.

Metals that were analyzed in the Churchill County investigation but that were detected in fewer than 60% of the participants were:

Cadmium
Nickel
Chromium

Table 4. Nonpersistent Pesticide Levels* (µg/L)† in Urine of People Living in the United States and People Living in Churchill County, Nevada

Nonpersistent Pesticide or Metabolite	United States		Churchill County		Comparison
	Geometric Mean (95% Confidence Interval)‡	95th Percentile	Geometric Mean (95% Confidence Interval)	% > U.S. 95th percentile	
1-Naphthol	1.70 (1.38–2.09)	12.0 (7.20–19.0)	NC§	9.0	L‖
Methyl parathion	NC	5.0 (3.30–9.0)	NC	10.0	—¶
Acephate	NA#	NA	NC	NC	NC
Azinophos	NA	NA	NC	NC	NC
Carbofuranphenol	NC	0.74 (NC–1.30)	NC	0.0	—
Chlorpyrifos	1.77 (1.56–2.01)	9.90 (7.60–14.0)	2.46 (1.93–3.14)	16.0	H**
Coumaphos	NA	NA	NC	NC	NC
Diazinon	NC	NC	NC	0.0	—
Diethyldithiophosphate	NC	0.87 (0.65–1.0)	NC	9.0	—
Diethylphosphate	1.03 (0.76–1.40)	13.0 (8.00–21.0)	NC	4.0	L
Diethylthiophosphate	NC	2.20 (1.70–2.80)	1.04 (0.81–1.33)	30.0	H
Dimethyldithiophosphate	NC	19.0 (17.0–37.0)	NC	4.0	—
Dimethylphosphate	NC	13.0 (9.50–21.0)	NC	8.0	—
Dimethylthiophosphate	1.82 (1.43–2.32)	46.0 (38.0–60.0)	NC	8.0	L
Isazophos	NA	NA	NC	NC	NC
Malathion	NC	NC	NC	0.0	—
Methamidophos	NA	NA	NC	NC	NC
Pirimiphos	NA	NA	NC	NC	NC
Propoxur	NC	NC	NC	0.0	—
2,4-Dichlorophenol	1.11 (0.88–1.40)	22.0 (17.0–31.0)	1.15 (0.91–1.46)	1.0	—
2,4,5-Trichlorophenol	NC	16.0 (4.30–39.0)	4.48 (3.64–5.53)	24.0	H
2,4,6-Trichlorophenol	2.85 (2.58–3.15)	25.0 (17.0–37.0)	NC	17.0	H
Pentachlorophenol	NC	1.30 (0.66–2.0)	NC	4.0	—
2,4-D	NC	NC	NC	9.0	—
2,4,5-T	NC	NC	NC	0.0	—
Atrazine	NC	NC	NC	0.0	—
3-Phenoxybenzoic acid	NA	NA	NC	0.0	NC
o-Phenylphenol	0.49 (0.41–0.59)	2.0 (1.60–2.50)	NC	18.0	H
DEET	NC	NC	NC	0.0	—
2,5-Dichlorophenol	6.01 (4.22–8.57)	440 (240–700)	NC	0.0	L
2-Naphthol	0.47 (0.33–0.68)	15.0 (9.90–19.3)	0.98 (0.73–1.32)	9.0	H

* Urine levels are noncreatinine adjusted. Blood levels are not lipid-adjusted.

† Micrograms per liter

‡ The interval of numbers in which we are 95% assured the value is contained.

§ Not Calculated was used when less than 60% of the study population had detectable levels of this chemical

‖ The upper boundary of the Churchill County CI was below the lower boundary of the CI for the U.S. level and b) less then 10% of the Churchill County participants had a value above the U.S. 95th percentile.

¶ The Churchill County geometric mean is consistent with national estimates.

\# Not available. This pesticide was not included in the *Second National Report on Human Exposure to Environmental Chemicals*, 2003.

** The lower boundary of the Churchill County confidence interval (CI) was higher than the upper boundary of the CI for the U.S. level or, b) more than 10% of the Churchill County participants had a value above the U.S. 95th percentile.

Table 5. The Estimated Risk of Childhood Leukemia Associated with Urine Levels of Nonpersistent Pesticides for Case Children and Families Compared with Control Children and Families Living in Churchill County

	Case vs. Comparison (Child)		Case vs. Comparison (Families)*	
Nonpersistent Pesticide or Metabolite †	**Odds Ratio**‡	***P*-Value** §	**Odds Ratio**	***P*-Value**
1-Naphthol	0.84	0.62	NC‖	NC
Chlorpyrifos	0.78	0.51	1.05	0.82
Diethylthiophosphate	0.91	0.79	0.88	0.59
2,4-Dichlorophenol	0.88	0.70	0.90	0.68
2,4,5-Trichlorophenol	0.57	0.09	1.31	0.24
2,4,6-Trichlorophenol	0.91	0.77	NC	NC
2-Naphthol	1.34	0.50	0.98	0.93

* Family members include parents/guardians only.

† A breakdown product of another chemical.

‡ The estimated relative risk of leukemia associated with one standard error of the geometric mean increase in the blood or urine level of each chemical. Odds ratios are not reported if fewer than 60% of cases and controls had detectable levels of the chemical in their blood or urine.

§ Estimates the probability that the deviation of the odds ratio from 1.0 (no difference in risk) is due to chance. A *P*-value less than 0.05 suggests that chance is unlikely to explain the deviation.

NC‖ Not Calculated was used when less than 60% of the study population had detectable levels of this chemical.

Nonpersistent pesticides that were analyzed in the Churchill County investigation but that were detected in fewer than 60% of the participants were:

2,4-D
2,5-Dichlorophenol
3-Phenoxybenzoic acid
Acephate
Atrazine
Azinophos
Carbofuranphenol
Dimethyldithiophosphate
2,4,5-T
o-Phenyl phenol
Parathion/methyl parathion
Methamidophos
Coumaphos
DEET
Diethylphosphate
Dimethylphosphate
Propoxur
Pentachlorophenol
Pirimiphos
Isazophos
Malathion
Diazinon
Diethyldithiophosphate
Dimethylthiophosphate

Table 6a. Persistent Pesticide Levels* (ng/g lipid)† in Blood of People Living in the United States and People Living in Churchill County, Nevada

Pesticide	United States		Churchill County		Comparison
	Geometric Mean *National Exposure Report* (Confidence Interval)‡	95th Percentile *National Exposure Report*	Geometric Mean Total Study Population (Confidence Interval)	% Above 95th Percentile	
DDE, p, p, -	260.0 (234–289.0)	1780 (1520–2230)	447.07 (355.09–562.87)	8.0	H§
DDT, o, p, -	NC‖	NC	NC	0.0	—¶
DDT, p, p, -	NC	27.0 (NC–34.0)	NC	3.0	—
Dieldrin	NA#	NA	NC	NA	—
Heptachlor epoxide	NC	24.1 (16.9–35.5)	NC	1.0	—
Hexachlorobenzene	NC	NC	10.46 (8.34–13.10)	0.0	—
Hexachloro-cyclohexane, beta	15.00 (NC-16.10)	111.0 (88.2–137.0)	NC	2.0	—
Hexachloro-cyclohexane,	NC	NC	NC	0.0	—
Mirex	NC	NC	NC	0.0	—
Oxychlordane	NC	44.8 (41.4–49.6)	NC	0.0	—
Transnonachlor	18.3 (16.9–19.7)	77.1 (65.9–84.6)	2.66 (1.65–4.29)	1.0	L**

* Levels have been lipid-adjusted.
† Nanograms per gram lipid
‡ The interval of numbers in which we are 95% assured the value is contained.
§ The lower boundary of the Churchill County confidence interval (CI) was higher than the upper boundary of the CI for the U.S. level or, b) more than 10% of the Churchill County participants had a value above the U.S. 95th percentile.
‖ Not Calculated was used when less than 60% of the study population had detectable levels of this chemical.
¶ The Churchill County geometric mean is consistent with national estimates.
\# Not available. This pesticide was not included in the *Second National Report on Human Exposure to Environmental Chemicals*, 2003.
** The upper boundary of the Churchill County CI was below the lower boundary of the CI for the U.S. level and b) less then 10% of the Churchill County participants had a value above the U.S. 95th percentile.

Table 6b. Polychlorinated Biphenyl* Levels (ng/g lipid)† in Blood of People Living in the United States and People Living in Churchill County, Nevada

PCB	United States		Churchill County		Comparison
	Geometric Mean *National Exposure Report* (Confidence Interval)‡	95th Percentile from *National Exposure Report*	Geometric Mean Total Study Population (Confidence Interval)	% above 95th Percentile	
18	NC§	NC	NC	0.0	–‖
28	NC	NC	0.03 (0.03–0.04)	0.0	–
44	NC	NC	0.006 (0.005–0.007)	0.0	–
49	NC	NC	0.009 (0.008–0.01)	0.0	–
52	NC	NC	0.012 (0.01–0.013)	0.0	–
66	NC	NC	0.007 (0.007–0.008)	0.0	–
74	NC	29.0 (25.0–32.1)	0.024 (0.021–0.026)	0.0	–
87	NC	NC	NC	0.0	–
99	NC	18.6 (15.5–21.1)	0.015 (0.014–0.017)	0.0	–
101	NC	NC	0.008 (0.008–0.009)	0.0	–
105	NC	NC	NC	0.0	–
110	NC	NC	0.006 (0.006–0.007)	0.0	–
118	NC	42.4 (33.0–52.0)	0.023 (0.021–0.025)	0.0	–
128	NC	NC	NC	0.0	–
138	NC	70.5 (59.3–83.4)	0.027 (0.023–0.031)	0.0	–
146	NC	13.1 (NC–14.9)	NC	1.0	–
149	NC	NC	0.006 (0.006–0.007)	0.0	–
151	NC	NC	NC	0.0	–
153	NC	111 (92.0–127)	0.071 (0.062–0.082)	0.0	–
156	NC	16.5 (15.2–18.7)	0.009 (0.008–0.011)	0.0	–
157	NC	NC	NC	0.0	–
167	NC	NC	NC	0.0	–
170	NC	30.8 (26.4–36.5)	0.018 (0.015–0.021)	0.0	–
172	NC	NC	NC	0.0	–
177	NC	NC	NC	0.0	–
178	NC	NC	NC	0.0	–
180	NC	79.0 (70.9–91.4)	0.047 (0.039–0.056)	2.0	–
183	NC	NC	NC	0.0	–
187	NC	24.3 (21.8–26.5)	0.015 (0.013–.018)	1.0	–
189	NC	NC	NC	0.0	–
194	NC	NC	NC	0.0	–
195	NC	NC	NC	0.0	–
196	NC	NC	NC	0.0	–
201	NC	NC	0.011	0.0	–
206	NC	NC	NC	0.0	–

* Polychlorinated Biphenyl (PCB)
† Nanograms per gram lipid
‡ The interval of numbers in which we are 95% assured the value is contained.
§ Not Calculated was used when less than 60% of the study population had detectable levels of this chemical.
‖ The Churchill County geometric mean is consistent with national estimates.

Table 7. Risk Factors Potentially Associated with Exposure to DDT and DDE (ng/g lipid)

Risk Factor	Median	Geometric mean (95% CI)	p-value
Child born or resided outside of U.S. (n=5)	345.86	274.73 (137.33-549.55)	0.63
Child born or living only in U.S. (n=59)	279.14	329.24 (265.36-408.5)	
Child breast fed by mothers born outside of U.S. (n=6)	541.78	1055.0 (275.56-4039.19)	0.06
Child not breast fed or breast fed by mothers born in U.S. (n=50)	274.45	296.43 (245.28-358.2)	
Mother born outside U.S. (n=4)	2687.29	1889.56 (298.96-11941.80)	0.10
Mother born in U.S. (n=48)	506.93	419.31 (253.03-694.92)	
Father born outside U.S. (n=6)	974.59	888.03 (439.71-2254.76)	0.59
Father born in U.S. (n=42)	624.65	739.96 (583.65-938.14)	

Table 8a. The Estimated Risk of Childhood Leukemia Associated with Blood Levels of Persistent Pesticide Levels (ng/g lipid)* for Cases Compared with Controls Living in Churchill County

	Case vs. Comparison (Child)		Case vs. Comparison (Families)†	
Persistent Pesticide	**Odds Ratio ‡**	***P*-Value§**	**Odds Ratio**	***P*-Value**
DDE, p,p,-	0.53	0.26	0.79	0.25
Hexachlorobenzene	0.70	0.06	1.35	0.52
Transnonachlor	NC‖	NC	1.40	0.41
Hexachloro-cyclohexane, beta	NC	NC	1.27	0.32
Oxychlordane	NC	NC	1.24	0.40

* Nanogram per gram lipid

† Family members include parents/guardians only.

‡ The odds ratio is the estimated relative risk of leukemia associated with one standard error of the geometric mean increase in the blood or urine level of each chemical. Odds ratios are not reported if fewer than 60% of cases and controls had detectable levels of the chemical in their blood or urine.

§ The *P*-value estimates the probability that the deviation of the odds ratio from 1.0 (no difference in risk) is due to chance. A *P*-value less than 0.05 suggests that chance is unlikely to explain the deviation.

‖ Not calculated. Less than 60% of the study population had detectable levels of this chemical.

Persistent pesticides that were analyzed in the Churchill County investigation but that were detected in fewer than 60% of the participants were:

DDT, o,p,-
DDT, p,p,-
Dieldrin
Mirex
Heptachlor epoxide
Hexachloro-cyclohexane, gamma

Table 8b. The Estimated Risk of Childhood Leukemia Associated with Blood Levels of Polychlorinated Biphenyls (ng/g lipid)* for Case Children and Families Compared with Control Children and Families Living in Churchill County

	Case vs. Comparison (Child)		Case vs. Comparison (Families)[†]	
PCB[‡]	**Odds Ratio**[§]	***P*-Value**[‖]	**Odds Ratio**	***P*-Value**
18	9.1	0.002	2.98	0.02
28	4.0	0.001	1.41	0.17
44	NC[**]	NC	1.33	0.25
49	70.96	0	1.59	0.13
52	3.25	0.002	1.60	0.05
66	1.30	0.46	1.37	0.22
74	0.88	0.66	0.70	0.07
99	0.73	0.09	1.99	1.7
101	15.32	0.01	1.09	0.69
110	0.73	0.28	0.84	0.34
118	0.59	0.02	0.78	0.11
138	0.76	0.21	0.82	0.25
149	1.24	0.51	0.70	0.11
153	0.73	0.17	0.15	0.23
156	NC	NC	1.12	0.73
180	0.94	0.78	0.98	0.96
183	NC	NC	0.99	0.96
187	NC	NC	0.87	0.70
194	NC	NC	1.45	0.23
196	NC	NC	2.11	0.04
201	NC	NC	1.59	0.20
206	NC	NC	2.04	0.05

* Nanogram per gram lipid

† Family members include parents/guardians only.

‡ Polychlorinated biphenyls

§ The estimated relative risk of leukemia associated with one standard error of the geometric mean increase in the blood or urine level of each chemical. Odds ratios are not reported if fewer than 60% of cases and controls had detectable levels of the chemical in their blood or urine.

‖ The *P*-value estimates the probability that the deviation of the odds ratio from 1.0 (no difference in risk) is due to chance. A *P*-value less than 0.05 suggests that chance is unlikely to explain the deviation.

** Not calculated

The PCBs that were analyzed in the Churchill County investigation but that were detected in fewer than 60% of the participants are as follows:

87	157	178
105	167	189
128	170	195
146	172	209
151	177	

Table 9. Volatile Organic Compounds (µg/L)* in the Blood of the People Living in the United States and People Living in Churchill County, Nevada

VOCs)†	United States		Churchill County	
	Arithmetic Mean from NHANES III‡	95th Percentile	Arithmetic Mean of Total Study Population	% > U.S. 95th percentile
1,1,1-Trichloroethane	0.34	0.8	0.04	0.0
1,4-Dichlorobenzene	1.9	9.2	0.2	0.0
2,5-Dimethylfuran	Smokers = 0.14 Nonsmokers = 0.024	NA§	Smokers = 0.1 Nonsmokers = 0.02	Could not calculate
Benzene	0.13	0.48	0.11	1.0
Carbon tetrachloride	NC‖	NC	NC	0.0
Ethylbenzene	0.11	0.25	0.07	2.0
m-/p-Xylene	0.37	0.78	0.32	2.0
o-Xylene	0.14	0.28	0.08	2.0
Styrene	0.074	0.18	0.1	8.0
Tetrachloroethylene	0.19	0.62	0.3	4.0
Toluene	0.52	1.5	0.33	1.0
Trichloroethylene	0.017	0.021	0.01	5.0

* Micrograms per liter
† Volatile Organic Compounds.
‡ VOC data were not reported in the *Second National Report on Human Exposure to Environmental Chemicals,* 2003.
§ Not available. The 95th percentile for this VOC was not reported in the study we used as a reference.
‖ Not Calculated was used when less than 60% of the study population had detectable levels of this chemical.

Table 10. The Estimated Risk of Childhood Leukemia Associated with Blood Levels of Volatile Organic Compounds (µg/L)* for Case Children and Families Compared with Control Children and Families Living in Churchill County

	Case vs. Comparison (Child)		Case vs. Comparison (Families)†	
VOC ‡	**Odds Ratio§**	***P*-Value‖**	**Odds Ratio§**	***P*-Value‖**
1,4-Dichlorobenzene	NC¶	NC	1.26	0.21
Ethylbenzene	2.67	0.04	1.34	0.16
m-/p-Xylene	0.80	0.74	0.84	0.49
O-Xylene	1.45	0.47	1.05	0.81
Styrene	1.21	0.62	1.22	0.29
Tetrachloroethylene	0.32	0.19	0.35	0.004
Toluene	0.77	0.70	0.98	0.92

* Nanogram per gram lipid
† Family members include children and their parents/guardians.
‡ Volatile organic compounds
§ The estimated relative risk of leukemia associated with one standard error of the geometric mean increase in the blood or urine level of each chemical. Odds ratios are not reported if fewer than 60% of cases and controls had detectable levels of the chemical in their blood or urine.
‖ The *P*-value estimates the probability that the deviation of the odds ratio from 1.0 (no difference in risk) is due to chance. A *P*-value less than 0.05 suggests that chance is unlikely to explain the deviation.
¶ Not calculated. Less than 60% of the study population had detectable levels of this chemical.

The VOCs that were analyzed in the Churchill County investigation but that were detected in fewer than 60% of the participants were:

Trichloroethylene
Benzene
Carbon tetrachloride
1,1,1-Trichloroethane
2,5-Dimethylfuran

Table 11. Selected Exposure Information Collected Through Questionnaire and Interview from the Churchill County Study Population

Exposure	Total study population	Case children	Comparison children	p-value*
Number of years living in Churchill County before diagnosis 0 yrs >0–5 yrs 5–10 yrs >10	 15.94 % 57.97 % 13.04 % 13.04 %	 14.29 % 71.43 % 7.14 % 7.14 %	 16.36 % 54.55 % 14.55 % 14.55 %	0.41
Maternal age at child's birth	26.31 yrs	27.93 yrs	25.89 yrs	0.17
Paternal age at child's birth	29.19 yrs	32.36 yrs	28.36 yrs	0.03
Mean birth weight of study child	119.32 oz	119.85 oz	119.19 oz	0.63
Mothers born outside U.S.	10.29 %	21.43 %	7.41 %	0.36
Fathers born outside U.S.	13.24 %	28.57 %	9.26%	0.09
Hispanic Ethnicity White, non-Hispanic White, Hispanic	14.71% 52 7	28.57% 10 2	11.11% 42 5	0.63 0.25
Adult military service during pregnancy	22.60%	35.71%	18.52%	0.10
Currently own cat	33.82 %	14.29 %	38.89 %	0.18
International birth of study child	5.88 %	7.14 %	5.56 %	1.00

* p-value for overall significance of variables in a conditional logistic regression model.

Table 12. Measure of Association with Infection Status Among Case and Comparison Subjects*

	Number of Case Subjects		Number of Comparison Subjects				
Population of Interest	**Positive for EBV**	**Negative for EBV**	**Positive for EBV**	**Negative for EBV**	**Odds Ratio (Positive vs. Negative)**	**95% CI**	**P-value**
Children	5	8	27	20	0.41	(0.07-1.92)	0.32

* The results of all other viral testing were negative. Therefore statistical analysis could only be using EBV serology results.

References

Agency for Toxic Substances and Disease Registry. Public Health Guidance Manual. Chelsea, Michigan:Lewis Publishers:1992.

Ashley DL, Bonin M, Cardinali F, McCraw J, Wooten J. Blood concentrations of volatile organic compounds in a nonoccupationally exposed U.S. population and in groups with suspected exposure. Clin Chem 1994;40:1401-4.

Ashley DL, Bonin M, Hamar B, McGeehin M. Using the blood concentration of 2,5-dimethylfuran as a marker for smoking. Int Arch Occup Environ Health 1996;68:183-7.

Centers for Disease Control and Prevention and the U.S.P.H.S. Working Group. Guidelines for counseling persons infected with human T-lymphotropic virus type I (HTLV-I) and type II (HTLV-II). Ann Intern Med 1993;118:448-54.

Churchill J, Ashley DL, Kaye W. Recent chemical exposures and blood volatile organic compound levels in a large population-based sample. Arch Environ Health 2001;56:157-66.

Epstein MA, Crawford DH. The Epstein-Barr virus. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. Oxford Textbook of Medicine, 3rd ed. Oxford, UK:Oxford Medical Publications, 1996;1:352.

Ford AM, Ridge ME, Cabrera H, Mahmoud C, Steel M, Chan LC, Greaves M. In utero rearrangements in the trithorax-related oncogene in infant leukaemias. Nature 1993;363:358-360.

Goldfrank L, Flomenbaum N, Lewin N, Howland MA, Hoffman R, Nelson L. In Goldfrank's Toxicologic Emergencies 7th ed. 2002. McGraw Hill, New York.

Greaves MF. Does childhood acute lymphoblastic leukemia have an infectious etiology? In: Goeddert JJ (ed). Infectious Causes of Cancer:Targets for Intervention. Towata, NJ, 2000; 25:451-60.

Haddad L, Shannon M, Winchester J. In Haddad's Clinical Management of Poisoning and Drug Overdose. 3rd ed. 1998. WB Saunders Company, Philadelphia, Pennsylvania.

Hogberg J. Selenium; In Handbook on the Toxicology of Metals. 2nd ed. 1986.

Irons R. Benzene and Other Hemotoxins. In: Sullivan J, Krieger G, eds. Hazardous Materials Toxicology: Clinical Principles of Environmental Health, 2nd ed. Baltimore, MD. Williams and Wilkens 1999:750-7.

Kinlen LJ, O'Brien F, Clarke K, Balkwill A, Matthews F. Rural population mixing and childhood leukaemia: effects of the North Sea oil industry in Scotland, including the area near Dounreay nuclear site. BMJ 1993;306:743-748.

Kinlen LJ. Evidence from population mixing in British new towns 1945-85 of an infective origin of childhood leukaemia. Lancet 1990;336:577-82.

Lauwerys R, Hoet P. In Industrial Chemical Exposure: Guidelines for Biological Monitoring 3rd edition, 2001. Lewis Publishers, Boca Raton, Florida.

LogXact 4 For Windows User Manual, Cytel Software Corporation, 1996-2000 Cambridge, MA

Longnecker M, Rogan W, Lucier G. The human health effects of DDT and PCBS and an overview of organochlorines in public health. Annu Rev Public Health 1997;18:211-44.

McNally RJQ, Birch JM, Taylor GM, Eden OB. Incidence of childhood precursor B-cell acute lymphoblastic leukaemia in north-west England. Lancet 2000;356:485-6.

Neglia JP, Linet MS, Shu XO, Severson RK, Potter JD, Mertens AC, et al. Patterns of infection and day care utilization and risk of childhood acute lymphoblastic leukaemia. Br J Cancer 2000;82:234-40.

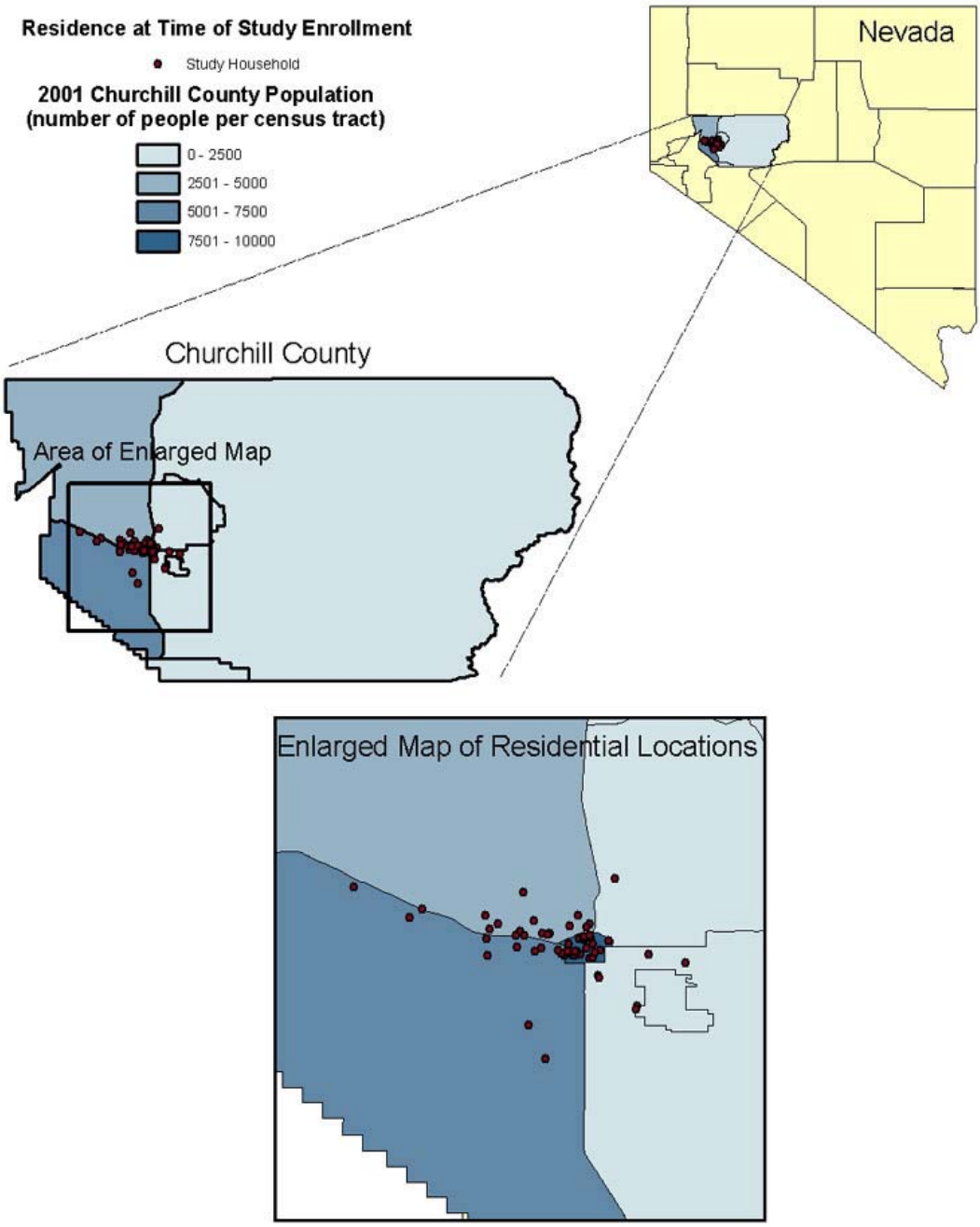
Schooley RT. Epstein-Barr virus. In: Mandell GL, Douglas JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 5th ed. Philadelphia, PA: Churchill Livingstone, 2000;2:1600-1601.

S.D. Faust and O.M. Aly. 1998. *Chemistry of Water Treatment, 2nd Edition*. Ann Arbor Press. Celsea, MI.

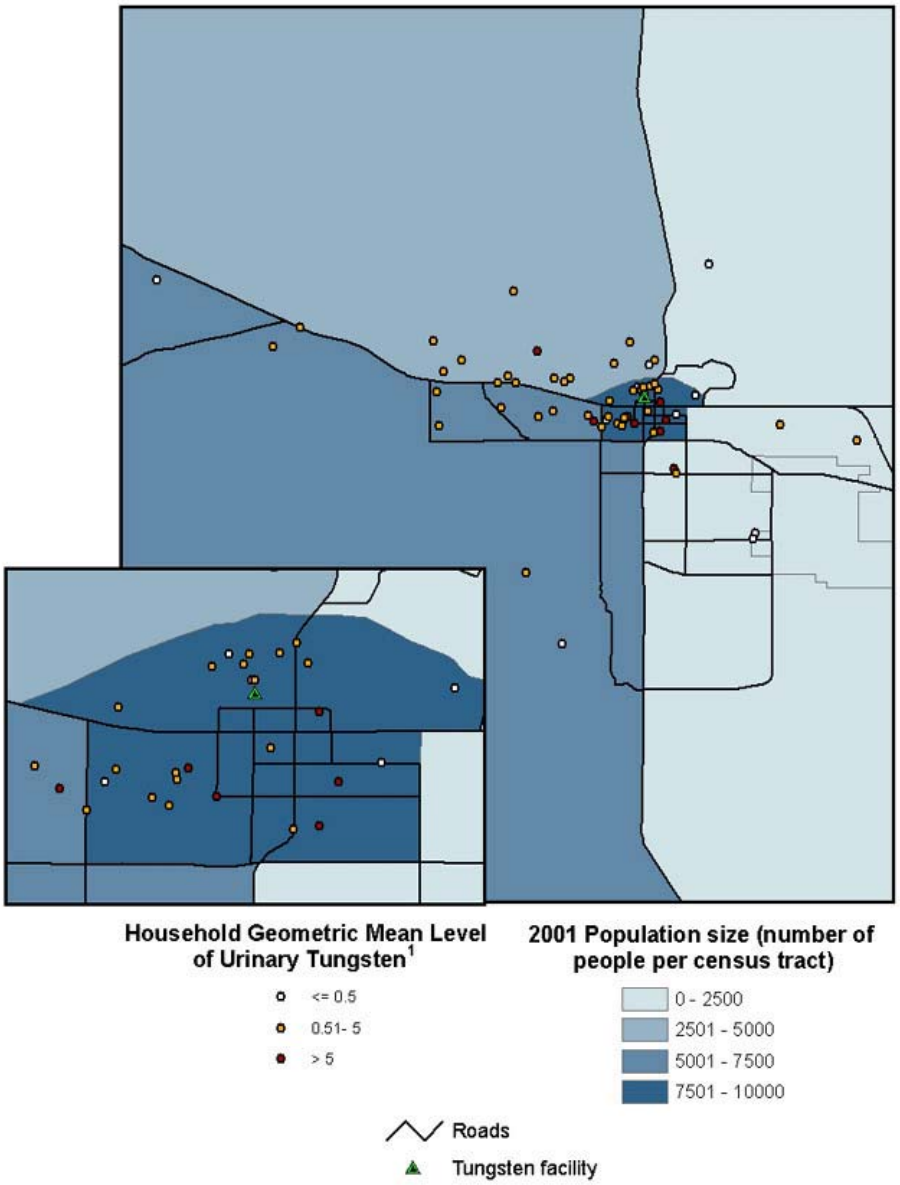
Smith M. Considerations on a possible viral etiology for B-precursor acute lymphoblastic leukaemia of childhood. J Immunol 1997;20:89-100.

White M, Sabbioni E. Trace element reference values in tissues from inhabitants of the European Union. Science of the Total Environment. 1998;216:253-270.

Map 1. Geographic Location of Study Households, Churchill County, Nevada.

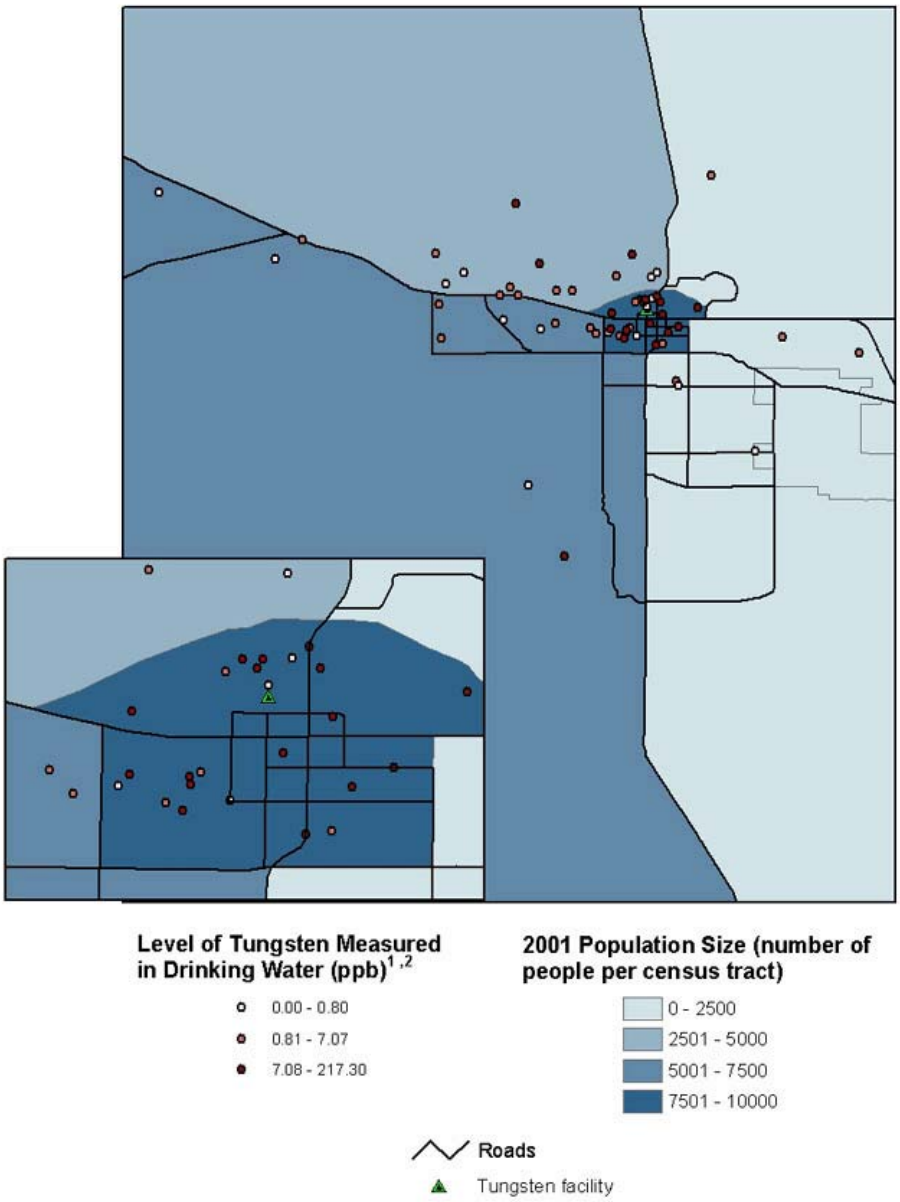


Map 2. Distribution of Urinary Tungsten Results Among Churchill County Residents at Time of Sample Collection, August 2001- February 2002.



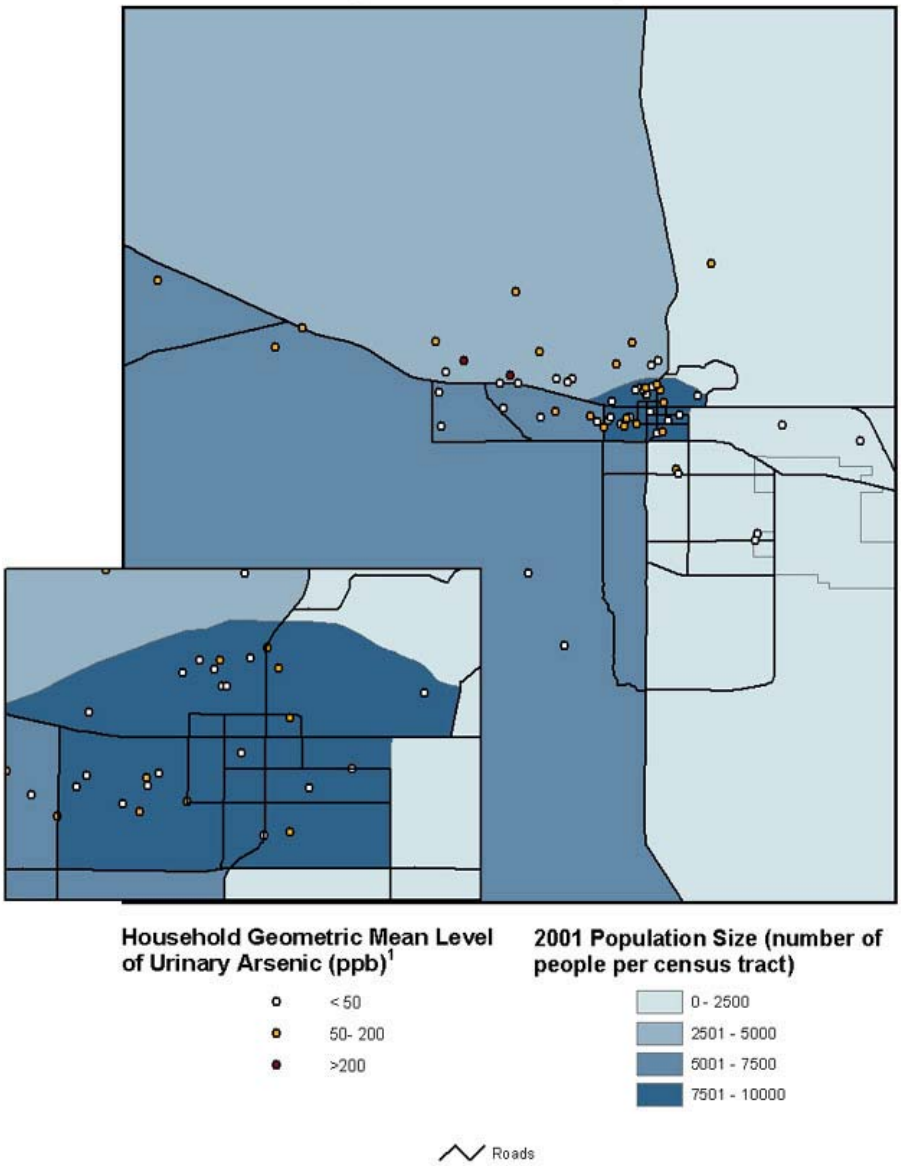
[1] 95% of the population in the 2nd National Report on Human Exposure to Environmental Chemicals 2003 had levels at or below 0.5.

Map 3. Distribution of Tungsten Measured in Drinking Water Samples Collected at Current Residence of Study Participant, August 2001- October 2002.



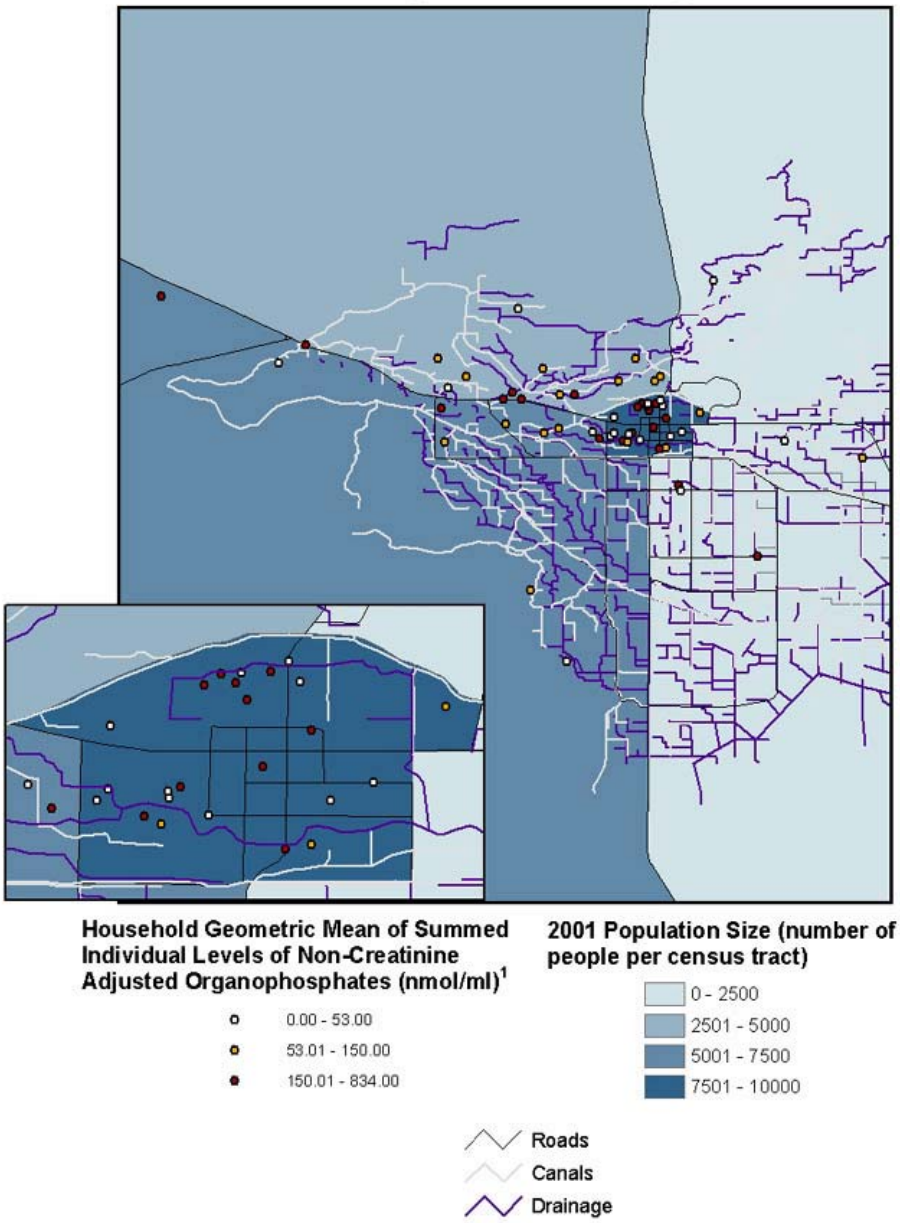
[1] Data is dislayed as tertiles.
[2] Health effects from exposure to any level of tungsten in drinking water has not been studied.

Map 4. Distribution of Urinary Arsenic Levels Among Churchill County Residents at Time of Sample Collection, August 2001- February 2002.



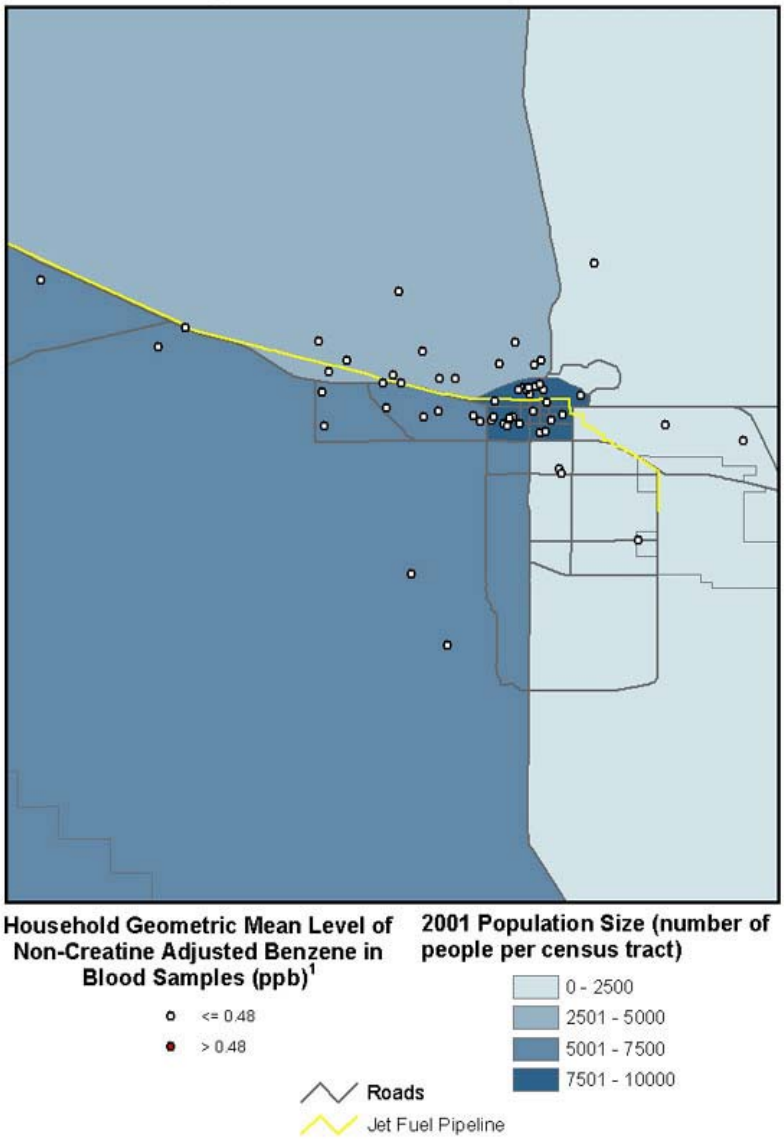
[1] Normal urine levels of arsenic are less than 50 ppb. A level between 50 and 200 ppb should be monitored by your physician but does not necessarily represent a health risk. A level over 200 ppb is considered abnormal and may require therapy if signs and symptoms consistent with arsenic poisoning are present. Haddad's Clinical Management of Poisoning and Drug Overdose, 3rd Edition.

Map 5. Distribution of Non-Persistent Pesticide Results Among Churchill County Residents at Time of Sample Collection, August 2001- February 2002.



[1] Tertiles represent summed organophosphate household levels including all tested parent compounds and metabolites.

Map 6. Distribution of Benzene Results Among Churchill County Residents at Time of Sample Collection, August 2001- February 2002.



[1] 95% of the population included in the following study had levels at or below 0.48: Churchill J et al. Recent chemical exposures and blood volatile organic compound levels in a large population-based sample. Archives of Environmental Heath 2001; 56: 157-166.