Title: An investigation of the association between hazardous air pollutants and lymphohematopoietic cancer risk among residents of Harris County, Texas

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Abstract

While recent reports have commented on the elevated ambient levels of hazardous air pollutants (HAPs) in certain areas of Houston, relative to other cities, few studies have assessed the health effects of HAPs for Houstonians and none have evaluated the association between ambient levels of these pollutants and lymphohematopoietic cancer risk in this population. To begin to address this deficit in the literature, we conducted a population based analysis of ambient levels of HAPs and lymphohematopoietic cancer incidence in Harris County. Cancer cases were obtained from the Texas Cancer Registry (TCR), 1995-2003, and included adult and childhood cancers. We used existing monitoring data collected from 1992-2003 by the Texas Commission on Environmental Quality (TCEQ) to estimate ambient benzene and 1,3 butadiene levels for each census tract, which were then collapsed into 3 or 4 categories, respectively, in the analyses that were carried out. We also estimated risk of lymphohematopoietic cancer associated with residential proximity to the Houston Ship Channel (HSC) as another proxy (albeit a crude measure) of HAP exposure. Poisson regression was used to estimate rate ratios for increasing HAP levels and cancer rates, adjusting for gender, age, and a composite index for socioeconomic status and race / ethnicity. We observed an association among children living within two miles of the HSC and higher rates of acute lymphocytic leukemia (adjusted rate ratio [aRR] = 1.56; p=0.01) compared with those living greater than 10 miles from the HSC. Further, higher 1,3-butadiene levels ($\geq$1.15 parts per billion [ppbV] relative to <0.266 ppbV) were associated with acute lymphocytic leukemia, acute myeloid leukemia and all leukemias in children. While we did not observe statistically significant associations for the other two categories (i.e., 0.266 - 0.381 ppbV or 0.382 - 1.15 pbbV) as compared to the referent group of <0.226 ppbV, a trend of increasing 1,3-butadiene levels and increasing leukemia rates was noted for these cancers. Higher benzene levels were not associated with lymphohematopoietic cancer by types in children. Among adults, neither proximity to the HSC, nor ambient levels of benzene or 1,3-butadiene levels were associated with lymphohematopoietic cancers in a dose dependent manner for either males or females. Additional analyses using more sophisticated methods to assess exposure are planned to confirm our findings. Additionally, future analyses will address many of the limitations of the current analysis. However, observing a specific health effect of HAPs in light of recently documented elevated levels of two known carcinogens, benzene and 1,3 butadiene, in Houston,(1) suggests a need to explore this issue further and to potentially take action to limit potential exposure to HAPs.

Introduction

In 1997, Texas ranked among the top three states in the number of chemical and allied products manufacturing facilities and in the number of petroleum and coal products manufacturing facilities, with more facilities located in Harris County (Houston) than in any other Texas county. (2) In a recent report on the effects of air pollution, the Mayor's Task Force determined that ambient levels of both benzene and 1,3-butadiene pose a 'definite' cancer risk to Houstonians. (1) According to the International Agency for Research on Cancer (IARC), benzene is classified as a known human carcinogen and 1,3-butadiene is classified as a probable human carcinogen. (3) Few studies have assessed the health effects of hazardous air pollutants (HAP) for Houstonians and none have addressed ambient levels of these pollutants and risk of lymphohematopoietic cancer, which includes leukemia, lymphoma and myeloma.

The majority of studies that have examined the potential health effects of HAPs have been conducted in occupational workers. However, most have not directly measured individual exposures to pollutants. The HAPs of primary concern in Houston, benzene and 1,3-butadiene, are mainly produced by petrochemical and synthetic rubber and plastics manufacturers. Occupational studies conducted in these settings typically compare worker populations with the population at large and report lower cancer mortality and incidence rates, for all cancers combined. (4-23)

Four studies reported more deaths from lymphohematopoietic cancers than expected among refinery/petrochemical plant employees (10, 13) or those exposed to 1,3-butadiene (7) or benzene (24) while findings from eight studies do not support this association.(6, 16, 17, 19, 21, 25-27) When looking at risk of developing cancer, four worker based cohort studies found higher risk of leukemia associated with exposure to benzene, (28, 29) or 1,3-butadiene (5, 30) and ten studies did not find an association. (6, 8-10, 12, 13, 16, 19-21) A nested case-control study (31) reported a significant increased risk of leukemia associated with an average exposure to 1,3-butadiene at levels of 1 ppm and another study reported that workers exposed to benzene at levels below 1 ppm had significantly decreased levels of white blood cells compared with unexposed workers. (32)

Few studies have looked at HAPs and risk of cancer in community populations. In these studies, exposure to HAPs is usually measured with a proxy measure such as residential distance from a plant or spill. One study compared actual and expected number of cancers in an area affected by a gasoline spill as a measure of high exposure; residents' leukemia rates were 4.40 (95% CI: 1.09-10.24) higher than expected by chance. (33) Another study found no effect of proximity (three kilometer area radius) to a petrochemical plant on the risk for leukemia (standardized incidence ratio [SIR]=0.99, 95% CI: 0.66-1.51) yet they did note a significant increased risk of multiple myeloma (SIR=2.15, 95% CI: 1.25-3.67). (34) Three other studies found no increased risk of leukemia in areas thought to be affected by industrial pollution.(35-37) Five have found a significant association with residence near industrial facilities and specific lymphohematopoietic cancers (38-42) while three others have found no association (34, 42, 43)

Only a small number of studies have explored the potential association between HAPs and childhood cancers. In a large California based study including 7,143 childhood cancer cases, Reynolds et al. (15) found a slight but non significant increase in leukemias (aRR=1.15; 95% CI 0.97–1.37) and proximity to road ways; there was no evidence that cancer rates increase with increasing vehicle or road density. In a follow-up for this study, Reynolds et al. (14) used data from the same 7,143 cases but used a dispersion model developed by the EPA to assign census tract level exposure scores to 25 potentially carcinogenic HAPs. Exposure scores for individual HAPs were summed to create a combined HAP

exposure score. Reynolds et al. found a significant ($p<0.05$) trend of increasing childhood leukemia rates with increasing HAP exposure levels with a 21% (aRR = 1.21; 95% CI: 1.03-1.42) increased risk of childhood leukemia in census tracts with the highest combined exposure score. They further report a 32% increase in leukemia risk (aRR = 1.32; 95% CI: 1.11-1.57) associated with the highest levels of HAP exposure from point sources, compared with non-significant leukemia risks associated with the highest levels of HAP exposures from mobile (aRR=1.18) and area (aRR=1.16) sources. In the United Kingdom, Knox found correlations between residence at birth near geographically defined "hotspots" for several criteria pollutants as well as volatile organic compounds (VOCs), benzene, dioxins, 1,3-butadiene, and benz(a)pyrene and childhood leukemias. (11) Additional studies are needed to confirm the findings from these studies.

Because there have been few community level studies of HAP and cancer risk and because most of these studies have not utilized data on ambient levels of specific air pollutants, we have conducted a population based analysis of the association between HAPs and lymphohematopoietic cancer incidence in Harris County. We used existing monitoring data collected from 1992-2003 by the Texas Commission on Environmental Quality (TCEQ) to estimate census tract ambient levels of benzene and 1,3-butadiene. Cancer cases were obtained from the Texas Cancer Registry (TCR), 1995-2003, and included cases in adults and children.

Methods:

Overview and Study Population:

Two ecologic analyses utilizing existing data sources were performed to begin to address the question of whether air pollution is associated with increased rates of lymphohematopoietic cancer in Harris County, Texas. Our focus was on two specific hazardous air pollutants, benzene and 1,3-butadiene, identified as posing a 'definite' cancer risk in a recent report to the Houston Mayor's Office. (1) The two analyses presented in this report serve as preliminary results for a future planned study incorporating more complex methodology. In the first analysis, we assessed the association between distance from the Houston Ship Channel (HSC) and cancer rates. We then evaluated the association between cancer rates and ambient levels of benzene and 1,3-butadiene. Both analyses were performed at the census tract level.

Our study population included all residents of Harris County, Texas between 1995 and 2003. We identified cases of lymphohematopoietic cancer diagnosed and reported to the Texas Cancer Registry (TCR) during the same time period. All incident cases of lymphohematopoietic cancer, independent of age or stage of disease were eligible. The specific lymphohematopoietic cancers we examined include leukemia (ICD-10 codes C91-C95), myeloma (ICD10 codes C88, C90, C96), non-Hodgkin's lymphoma (ICD-10 codes C82-C85) and Hodgkin's disease (7.8% of total) (ICD-10 code C81). We excluded those cancer cases with a prior cancer diagnosis. No primary data were collected for this study and no patients, physicians or hospitals were contacted. Since only cancer registry data was used, no identifying information other than age, race/ethnicity and address at the time of diagnosis was available. Addresses were used solely for the purposes of assignment of cases to census tracts. At the census tract level, rates of cancer were calculated using the Census 2000 estimates for the population. All rate ratios were adjusted for census tract level age, gender, and socioeconomic status and race / ethnicity indicators.

Exposure Assessment:

Distance from Houston Ship Channel:

We evaluated distance of census tracts from the HSC using geographic information system (GIS) methodology. Using ArcGIS(44) we constructed a set of five mutually exclusive buffers two miles apart around the HSC (see figure 1). We then assigned census tracts to a particular buffer based on the buffer in which the centroid of the census tract fell. Consequently, there were five exposure groups corresponding to the five buffers that we will refer to as the following: : 0-2 miles, 2-4 miles, 4-6 miles, 6 -8 miles, 8-10 miles. Census tracts with centroids that fell outside all five buffers (i.e., > 10 miles) served as the referent group. We hypothesized that if distance from the Houston Ship Channel were correlated with and therefore a proxy for industrial air pollution levels and this proxy was related to lymphohematopoietic cancer risk, rates of cancer would be higher in those buffers closest to the HSC. We do recognize that distance from the Houston Ship Channel is only one proxy measure of industrial air pollution and that there are other industrial pollutants outside the HSC.

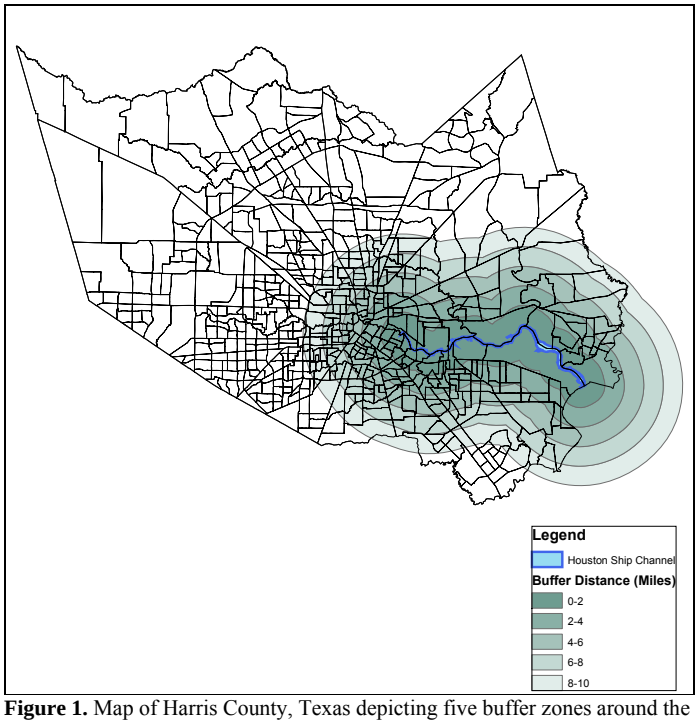

Figure 1. Map of Harris County, Texas depicting five buffer zones around the Houston Ship Channel

Compound-Specific Exposure:

Notwithstanding the limitations of using ambient air levels as a surrogate of personal exposure (45-47), we utilized data from the Texas Commission on Environmental Quality (TCEQ) to construct an assessment based on the potential for exposure to specific compounds. The TCEQ operates an extensive air monitoring network in the state of Texas, with Houston being one of the most monitored cities in the nation.(48) Although the TCEQ began monitoring air quality in the early 1970's, they did

not begin monitoring for HAPs until 1992. Between the years 1992 and 2005, 15 TCEQ monitoring sites were recording data on HAPs in Harris County. However, not all 15 sites were operable for the entire period. Because the cancer data obtained from the TCR extends only to 2003, we limited our use of the TCEQ data through this year as well. One monitoring site was not operable before 2005; therefore, the data used for this assessment comes from a total of 14 monitoring sites noted as red dots in Figure 2. As shown in the figure, these monitors are not geographically distributed throughout the Houston area as many are located within or near the Ship Channel, which poses difficulty in any assessment that attempts to utilize such data to estimate ambient levels at distances remote from the monitoring stations.

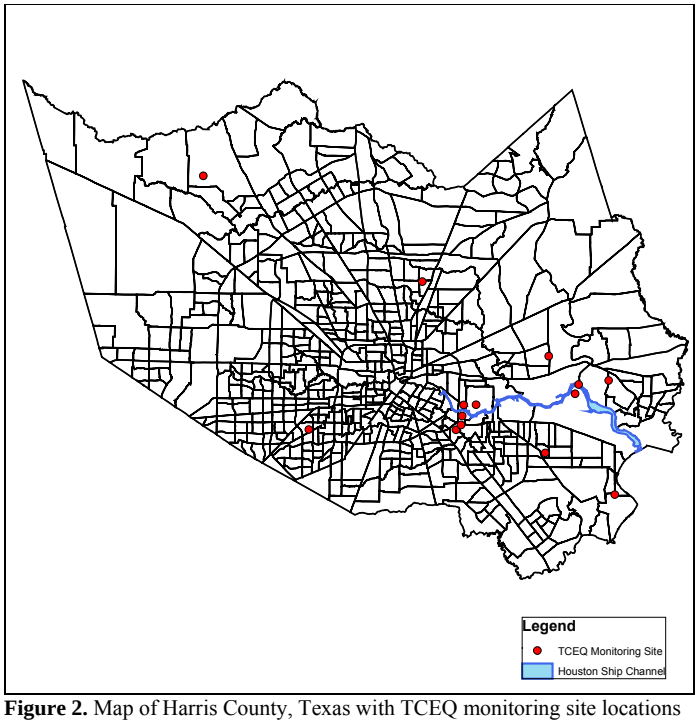

Figure 2. Map of Harris County, Texas with TCEQ monitoring site locations

In order to assess potential exposure to benzene and 1,3-butadiene, we developed a method to estimate ambient levels of these compounds for each census tract, based on the data obtained from the 14 monitoring sites without any adjustment for meteorological conditions (a limitation that we note later in the report). We first calculated the annual arithmetic mean concentrations of benzene and 1,3-butadiene for each monitoring location. We refer to this value as the site-specific annual mean. We then calculated the arithmetic mean concentrations for each of these two compounds over the entire period, 1992-2003, for each site. We refer to this value as the site-specific period mean. Because not all sites were active for all 12 years, we calculated the site-specific period mean as a weighted average of the annual means. Next, we determined, for each census tract, the distance of the centroid to each of the 14 monitoring sites, using ArcGIS(44)software. We were then able to assign each census tract an ambient value for benzene and for 1,3-butadiene based on the average of the site specific period means from the three closest monitoring sites. This value is the tract-specific mean.

The tract-specific means for benzene and 1,3-butadiene were categorized based on risk concentrations calculated using the California Office of Environmental Health Hazard Assessment (OEHHA) unit risk estimates (URE) as compiled by the Houston Mayor's Task Force on the Health Effects of Air Pollution. (1) These UREs reflect the excess cancer risk expected to occur as a result from lifetime exposure to 1 $\mu g/m^3$ of the chemical. (1) In order to calculate a risk concentration for a given lifetime cancer risk (1 in a million, for example), the lifetime cancer risk is divided by the URE. (1) Because the UREs are reported by the Task Force in units of $(\mu g/m^3)^{-1}$ and the TCEQ data is reported in units of ppbV, we first calculated the risk concentrations in units of $\mu g/m^3$ and then transformed them based on the following equation:

$$\mu g / m^3 = \frac{ppbV * MolecularWeight * 273K}{22.4 * 298K}$$

For example, given a unit risk estimate for benzene of 0.000029, the risk concentration based on 1 in a million risk is 0.034 $\mu g/m^3$ or 0.0107 ppbV. For 1,3-butadiene, the risk concentration based on 1 in a million risk is 0.00266 ppbV. Because the minimum site-specific period means for each benzene and 1,3-butadiene were greater than these concentrations, we chose to base our categorization of the tract-specific means on a lifetime risk of 1 in 10,000 rather than 1 in 1,000,000. The values corresponding to a 1 in 10,000 lifetime cancer risk for benzene and 1,3-butadiene were: 1.07 ppbV and 0.266 ppbV, respectively. For benzene, the tract-specific means were categorized into three groups, <1.07 ppbV, 1.07 - 1.19 ppbV and ≥1.20 ppbV with the referent group being those values below 1.07 ppbV. For 1,3-butadiene, the tract-specific means were categorized into four groups, with the referent group being those values below 0.266 ppbV. The remaining three categories were: 0.266 - 0.381, 0.382 - 1.14 and ≥1.15. The benzene categorization resulted in one less category than that for 1,3-butadiene because only 10% of census tracts had tract-specific means greater than 1.07 ppbV; therefore, more than three exposure categories would have resulted in very sparse numbers. We chose to categorize tract-specific means for benzene and 1,3-butadiene in this manner rather than by percentiles because we felt using the UREs to guide the categorization would result in more biologically meaningful categories. The use of UREs were chosen over reference exposure levels (REL) because, unlike the derivation of RELs, the approach to deriving UREs does not assume a threshold level.(49) Therefore, the URE is more appropriate when considering cancer risk.

Statistical Analyses:

Confounding Factors:

For all analyses, we considered age at diagnosis, race / ethnicity and socioeconomic status as potential confounders. Further, because the etiology of childhood cancers (age at diagnosis <20 years) is likely different than adult cancers (age at diagnosis ≥20 years), we analyzed these two groups separately. To further account for the potential influence of age at diagnosis on cancer incidence within these groups, we adjusted for age in 5 year intervals within the children and adult groups. Additionally, we stratified analyses of adult cancers by gender. For analyses of childhood cancers, we adjusted for gender. Because socioeconomic status is a complex term and involves such attributes as income, education level and household characteristics,(50) and because it is difficult to obtain individual measures of these attributes, we constructed a composite index of socioeconomic status based on census tract level data from the 2000 Census, using principal component analysis to identify the most relevant factors. This variable was then categorized into quartiles based on its distribution in the state of Texas. While we did not include race as an independent variable in the statistical models, we did include a factor representing the percent of the census tract population that is Hispanic and the percent

of the census tract population that is African-American in the composite socioeconomic status variable. Including race as an additional independent variable would have produced too fine a stratification for constructing census tract level case counts and population totals, resulting in a loss of power and potentially affecting the ability of the models to converge properly.

Analysis #1 – Distance from the Houston Ship Channel:
To test the association between distance from the HSC and lymphohematopoietic cancer incidence, we used poisson regression. The dependent variable in this regression was case count, indexed by census tract, gender and age group. The buffer zones indicating distance from the HSC was modeled as an ordinal variable with 6 levels, as previously discussed. Other independent variables included in the model were gender (childhood cancers only), age group, and race/ ethnicity and socioeconomic status. An offset equal to the log of the population total for each census tract, gender and age group combination was used to account for the different population sizes in each of these groups. Additionally, generalized estimating equations were used to account for clustering of incidence rates within census tracts.

Because the etiology of lymphohematopoietic cancer differs by cancer subtypes, analyses were conducted separately for adult and childhood cancers as well as by the following cancer types: Hodgkin's lymphoma, non-Hodgkin's lymphoma, Myeloma, all leukemias, acute lymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, and chronic myeloid leukemia.

Analysis #2 – Compound-Specific Exposure:
We conducted a second poisson regression analysis to test the association between lymphohematopoietic cancer incidence and ambient levels of benzene and 1,3-butadiene, separately. As in the previous regression, the dependent variable for this second analysis was case count, indexed by census tract, gender and age group. The independent variables were gender, age group, socioeconomic status and the tract-specific mean for either benzene or 1,3-butadiene, categorized as already discussed. An offset equal to the log of the population total for each census tract, gender and age group combination was used to account for the different population sizes in each of these groups. Generalized estimating equations were also used to account for clustering of incidence rates within census tracts.

This analysis was conducted separately for adult and childhood cancers as well as by the following cancer types: Hodgkin's lymphoma, non-Hodgkin's lymphoma, myeloma, all leukemias, acute lymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, and chronic myeloid leukemia

Results

Analysis among children, adjusting for gender, age, and socio-economic status:
Based on the buffer analysis (table 1), no trend toward increasing risk of any lymphohematopoietic cancer by distance from the HSC in 2 mile intervals was noted. However, rates of acute lymphocytic leukemia were significantly higher for those living 0-2 miles from the HSC (aRR = 1.56; p=0.0105) compared with those living greater than 10 miles from the HSC. Additionally, higher 1,3-butadiene levels ($\geq$1.15 ppbV relative to <0.266 ppbV) were associated with acute lymphocytic leukemia (p=0.05), acute myeloid leukemia (p 0.03) and all leukemias (p = 0.02) and a trend of increasing 1,3-butadiene levels and increasing leukemia rates was noted for these cancers (table 2). Higher benzene

levels (1.07-1.19 ppbV or ≥1.20 ppbV relative to <1.07 ppbV) were not associated with any lymphohematopoietic cancer in children (table 3).

Analysis among adults, stratifying by gender and adjusting for age and socio-economic status: No significant trends of increasing lymphohematopoietic cancer risk with increasing proximity to the HSC was observed for men or women for any specific cancer type (table 4). Although we did observe several significant associations between Hodgkin's disease, non-Hodgkin's Lymphoma and myeloma and specific distances from the HSC, no consistent pattern of risk emerged for either gender (table 4). Finding an association for both genders would provide greater support for an environmental versus an occupational route of exposure. Among male adults, higher 1,3-butadiene levels were associated with non-Hodgkin's lymphoma and a significant trend was also noted (p=0.010) (table 5). A similar pattern was not observed for females. Although we also found a 57% increased risk of Hodgkin's disease among females associated with 1,3-butadiene levels of 0.382 - 1.14 ppbV relative to the lowest level of <0.226 ppbV, there was not a significant increasing trend (table 5). We did also observe an increased risk of chronic myeloid leukemia in men associated with benzene levels between 1.07 -1.19 ppbV (table 6). However, higher benzene levels were not associated with a significant trend toward increasing lymphohematopoietic cancer rates for men or women for any specific cancer type (table 6).

Discussion

Our findings and methods are similar to those reported by Reynolds et al. (14); they report a 21% increase in childhood leukemia associated with those census tracts with higher modeled ambient levels of HAPs. On the basis of our assessment using residential proximity to the HSC, those living within 2 miles had a 56% higher childhood lymphocytic leukemia rate than did those living greater than 10 miles from the HSC (p=0.01). When we evaluated risks using monitored ambient levels of specific HAPs, those living in areas with the highest estimated 1,3-butadiene levels had significantly higher childhood acute lymphocytic leukemia, acute myeloid leukemia and all leukemias. Neither proximity to the HSC nor levels of benzene or 1,3-butadiene were associated with adult lymphohematopoietic cancer. Our finding that higher 1,3-butadiene levels were associated with higher non-Hodgkin's lymphoma rates (among adult males only) may be due to an occupational exposure confounding the association. Had we found that non-Hodgkin's lymphoma rates were associated with higher 1,3-butadiene levels in both males and females, we would have better evidence of an unconfounded association.

Our team has taken the following efforts to limit bias and improve study validity. We limited selection bias by using population based TCR data. To the extent that TCR is complete and accurate for lymphohematopoietic cancer from years 1995-2003, we have included all cases in the population. We used Census 2000 as the data source for the denominator at the census tract level which is the smallest unit of analysis possible for rare cancers while maintaining sufficient study power. One limitation of ecologic studies is that we do not have individual data on exposure, disease, and confounding factors. Because we used the smallest geographic unit possible, census tracts, we got closer to having individual level data and therefore have reduced the impact of ecological misclassification bias on study findings. Our use of census data to additionally control for important confounders including age, gender and socioeconomic status also limits confounding bias common in ecological studies. Because cancer rates vary by age and socioeconomic status and because there is considerable variation in the distributions of these factors within census tracts across Houston, we adjusted our analyses for both factors. Smoking may also confound the putative association between exposure to ambient benzene and 1,3-butadiene since smoking may provide another source of exposure to these chemicals. It has

been shown in numerous studies that aggregate measures of socioeconomic status may be viewed as a proxy for individual level smoking status. (51-54) By adjusting rate ratios for socioeconomic status we are also attempting to control for confounding due to occupational exposures, although residual confounding is likely still present. We attempted to address this residual confounding in adults through stratification by gender, as males are more likely to be affected by this type of exposure.

At the suggestion of several environmental scientists, we repeated our analyses for childhood leukemias using the USEPA's 1999 National Air Toxics Assessment (NATA) modeled ambient 1,3-butadiene and benzene levels at the census tract level. In general we saw a similar pattern to that reported in table 2 based on our TCEQ estimates of ambient levels. From table 2, for all leukemias in children, the rate ratio for comparing the highest grouped ambient level to the lowest was 1.40 and the p-value was 0.02. Using the NATA data for childhood leukemias, again comparing the highest with the lowest 1,3-butadiene levels, this rate ratio was 1.32 (p=0.09). The latter was of borderline statistical significance. Note however that the actual levels of 1,3-butadiene differ for the two analyses yet the relative grouping based on quartiles are similar. Further and more sophisticated analyses are planned to compare the NATA modeled estimates with the actual TCEQ monitoring data to determine reliability of our categorizations and the extent of exposure misclassification. Additionally, techniques known as kriging will be used to better estimate ambient benzene and 1,3-butadiene levels by census tracts based on TCEQ monitoring data.

This is the one of the first health effects studies to use monitoring data as a measure of ambient air levels of HAPs in Houston. However, there are challenges to using these data. The strategy that we used to estimate ambient levels for each census tract was limited by several factors. First, the TCEQ monitoring sites are not distributed randomly across Houston and not all monitors have been active over the entire period of interest (1995-2003). This presented a particular challenge for those census tracts in the presumed low exposed area where few monitors exist (see Figure 2). The distribution of monitors raises a question related to the appropriateness of using monitoring data collected for one purpose (i.e., assessing compliance) for another (i.e., assessing an exposure-response relationship). Note however that these data are the only existing source of potential ambient HAP exposures collected over time. Secondly, the methods used in this analysis to estimate ambient levels of pollutants for each census tract did not account for meteorological conditions, which affect the transport and fate of air pollutants. Analyses are planned that will improve upon the methods used to estimate ambient levels by census tract and thereby limit the biases that may have been introduced in the current investigation. Finally, we opted to estimate ambient levels for each census tract in this investigation by averaging data collected over the entire period (along with cancer incidence). While long-term HAP exposures are more likely to be etiologically related to cancer development, this approach raises questions regarding temporality of the potential exposure-disease relationship. We did exclude those cancers that occurred prior to the recorded years of HAP monitoring data reported by TCEQ as a means to address this issue of temporal sequence. In subsequent analyses we will attempt a more comprehensive assessment of lagged exposures relative to cancer incidence. However, these analyses will be limited by study power as the annual number of cancer cases are relatively small. We opted to explore HAP ambient levels with these specific cancers because of the relatively short latency period from exposure to cancer development. Because the TCEQ monitoring data and the TCR cancer data have only been collecting data over the past decade, this preliminary report represents the first opportunity to correlate ambient HAP levels with those cancers for which we might expect to see an association given the shorter latency periods. Additionally, because the California OEHHA unit risk estimates (URE) are not the same as URE obtained from other sources, such as the United States Environment Protection Agency, had we used another source, our resulting classification would have been different which could then have affected our final results.

We used distance of census tracts from the HSC as a crude surrogate for proximity to higher ambient levels of air pollutants given the concentration of petroleum and chemical manufacturing facilities in the HSC. However, we recognize that there is variability in ambient air levels within the HSC, that there may be industrial facilities that emit benzene and 1,3-butadiene located outside the HSC, and that mobile sources contribute to air pollution as well. Nonetheless, our preliminary results of an association between childhood leukemia rates and both proximity to industrial sources (defined as distance from the HSC) and ambient levels of HAPs, derived from TCEQ monitoring data, suggest that a true association may exist. Given the increased sensitivity of children to environmental toxicants including carcinogens(55) and that children metabolize toxins differently than adults with behaviors which present a unique opportunity for exposure(56), it is plausible that we might observe an association between HAPs and lymphohematopoietic cancer in children but not adults. Other than the increased sensitivity of children, studying childhood cancer development presents advantages over that of adults since there are few known risk factors for childhood cancer and because the latency of childhood cancers is much shorter. Additional studies in child and adult populations will be necessary to allow for more definitive statements to be made regarding whether increased cancer risk is associated with ambient air pollution.

In conclusion, the primary limitation of this study lies in the 'exposure assessment' and the potential for biases that may have affected study validity. In fact, we do not have individual exposure data nor were we able to assess the validity of using monitoring data as a surrogate measure for personal exposure. Thus, the results presented here should be viewed as preliminary. Nonetheless, additional analytic studies with more refined methodology are warranted to further evaluate the association between increased lymphohematopoietic cancer risk and ambient levels of hazardous air pollutants, the results of which might inform policies intended to mitigate health risks of Houstonians in the future.

Table 1. Crude annual incidence rates and adjusted rate ratios for association between distance from the Houston Ship Channel (HSC) and lymphohematopoietic cancer incidence among children (aged <20)

Cancer Type	Distance from HSC (Miles)	# Census Tracts	# Cases	Crude Annual Incidence Rate (per 100,000)	Rate Ratio*	p-value	p-value for trend
Hodgkin's Disease	>10	344	64	1.168	1.00		
	8-10	60	10	1.444	1.17	0.6169	
	6-8	62	9	1.452	1.15	0.6917	
	4-6	71	11	1.348	1.06	0.8794	
	2-4	77	7	0.609	0.47	0.0995	
	0-2	35	4	0.867	0.61	0.3708	0.1522
non-Hodgkin's Lymphoma	>10	344	46	0.839	1.00		
	8-10	60	7	1.011	1.28	0.5825	
	6-8	62	5	0.807	1.05	0.9076	
	4-6	71	8	0.981	1.30	0.4597	
	2-4	77	10	0.870	1.14	0.7044	
	0-2	35	3	0.650	0.91	0.8947	0.7031
All Leukemia	>10	344	274	5.000	1.00		
	8-10	60	38	5.487	1.09	0.6412	
	6-8	62	36	5.809	1.17	0.4335	
	4-6	71	44	5.393	1.11	0.5282	
	2-4	77	55	4.783	0.96	0.8322	
	0-2	35	29	6.285	1.22	0.2688	0.6189
Acute Lymphocytic Leukemia	>10	344	207	3.777	1.00		
	8-10	60	32	4.620	1.21	0.2974	
	6-8	62	23	3.712	0.98	0.9917	
	4-6	71	34	4.167	1.16	0.4405	
	2-4	77	40	3.479	0.96	0.8280	
	0-2	35	27	5.852	**1.56**	**0.0105**	0.3274
Acute Myeloid Leukemia	>10	344	40	0.730	1.00		
	8-10	60	4	0.578	0.71	0.5215	
	6-8	62	8	1.291	1.58	0.3301	
	4-6	71	5	0.613	0.74	0.5577	
	2-4	77	9	0.783	0.87	0.7434	
	0-2	35	1	0.217	0.20	0.1290	0.3470

*Rate Ratios Adjusted for Age, Gender, Ethnicity, and Socioeconomic Status

Note: There were no childhood Myeloma cases; Results are not shown for chronic lymphocytic leukemia or chronic myeloid leukemia due to small numbers (4 and 16 total cases, respectively)

Table 2. Crude annual incidence rates and adjusted rate ratios for association between ambient 1,3-Butadiene levels and cancer Incidence among children aged 0-19

Cancer Type	1,3-Butadiene Level*	# Census Tracts	# Cases	Crude Annual Incidence Rate (per 100,000)	Rate Ratio**	p-value	p-value for trend
Hodgkin's Disease	1	148	22	0.86	1.00		
	2	158	25	1.21	1.53	0.171	
	3	137	22	1.23	1.67	0.152	
	4	206	36	1.29	1.80	0.071	0.099
non-Hodgkin's Lymphoma	1	148	20	0.78	1.00		
	2	158	20	0.96	1.44	0.264	
	3	137	18	1.01	1.73	0.128	
	4	206	21	0.75	1.25	0.510	0.559
All Leukemia	1	148	116	4.51	1.00		
	2	158	99	4.77	1.10	0.530	
	3	137	93	5.21	1.19	0.292	
	4	206	168	6.02	**1.40**	**0.024**	**0.017**
Acute Lymphocytic Leukamia	1	148	89	3.46	1.00		
	2	158	76	3.67	1.09	0.629	
	3	137	68	3.81	1.11	0.528	
	4	206	130	4.66	**1.38**	**0.051**	**0.041**
Acute Myeloid Leukemia	1	148	12	0.47	1.00		
	2	158	13	0.63	1.50	0.359	
	3	137	14	0.78	1.79	0.217	
	4	206	28	1.00	**2.53**	**0.033**	**0.026**

*1,3-Butadiene levels correspond to: level 1 =<0.266 ppbV; level 2 = 0.266 - 0.381 ppbV; level 3 = 0.382-1.14 ppbV; and level 4 = ≥1.15 ppbV

**Rate Ratios Adjusted for Age, Gender, Ethnicity and Socioeconomic Status

Note: There were no childhood Myeloma cases; Results are not shown for chronic lymphocytic leukemia or chronic myeloid leukemia due to small numbers (4 and 16 total cases, respectively)

Table 3. Crude annual incidence rates and adjusted rate ratios for association between ambient Benzene levels and cancer Incidence among children aged 0-19

Cancer Type	Benzene Level*	# Census Tracts	# Cases	Crude Annual Incidence Rate (per 100,000)	Rate Ratio**	p-value	p-value for trend
Hodgkin's Disease	1	543	85	1.11	1.00		
	2	79	14	1.27	1.14	0.721	
	3	27	6	1.27	1.16	0.745	0.673
non-Hodgkin's Lymphoma	1	543	66	0.86	1.00		
	2	79	8	0.73	0.98	0.965	
	3	27	5	1.06	1.36	0.487	0.587
All Leukemia	1	543	399	5.22	1.00		
	2	79	62	5.63	1.01	0.943	
	3	27	15	3.17	0.60	0.078	0.164
Acute Lymphoctyic Leukemia	1	543	308	4.03	1.00		
	2	79	42	3.81	0.86	0.450	
	3	27	13	2.75	0.66	0.183	0.147
Acute Myeloid Leukamia	1	543	55	0.72	1.00		
	2	79	11	1.00	1.17	0.733	
	3	27	1	0.21	0.27	0.186	0.372

*Benzene Levels correspond to: level 1 = <1.07 ppbV; level 2 = 1.07 - 1.19 ppbV; and level 3= ≥1.20 ppbV

**Rate Ratios Adjusted for Age, Gender, Ethncity, and Socioeconomic Status

Note: There were no childhood Myeloma cases; Results are not shown for chronic lymphocytic leukemia or chronic myeloid leukemia due to small numbers (4 and 16 total cases, respectively)

Table 4. Crude annual incidence rates and adjusted rate ratios for association between distance from the Houston Ship Channel (HSC) and lymphohematopoietic cancer incidence among adults (aged ≥20)

Cancer Type	Gender	Distance from HSC (Miles)	# Census Tracts	# Cases	Crude Annual Incidence (per 100,000)	Rate Ratio*	p-value	p-value for trend
Acute Myeloid Leukemia	Male	>10	344	169	2.79	1.00		
		8-10	60	37	4.38	1.37	0.1272	
		6-8	62	277	33.97	1.14	0.4942	
		4-6	71	37	3.84	1.34	0.0956	
		2-4	77	37	3.26	1.25	0.2300	
		0-2	35	16	3.78	1.49	0.1376	0.052
	Female	>10	344	188	2.94	1.00		
		8-10	60	27	3.02	0.89	0.5832	
		6-8	62	31	3.66	1.19	0.3712	
		4-6	71	37	3.77	1.22	0.2758	
		2-4	77	34	3.00	1.07	0.7170	
		0-2	35	11	2.71	1.00	0.9966	0.431
Chronic Lymphocytic Leukemia	Male	>10	344	233	3.85	1.00		
		8-10	60	37	4.38	0.92	0.6582	
		6-8	62	41	5.03	1.14	0.4452	
		4-6	71	45	4.67	1.04	0.8375	
		2-4	77	35	3.08	0.76	0.1467	
		0-2	35	15	3.54	0.82	0.4916	0.327
	Female	>10	344	162	2.53	1.00		
		8-10	60	31	3.47	1.07	0.7148	
		6-8	62	22	2.60	0.95	0.8166	
		4-6	71	36	3.67	1.29	0.1922	
		2-4	77	39	3.44	1.37	0.1091	
		0-2	35	7	1.72	0.69	0.3529	0.303
Chronic Myeloid Leukemia	Male	>10	344	106	1.75	1.00		
		8-10	60	18	2.13	1.04	0.8925	
		6-8	62	24	2.94	1.50	0.1996	
		4-6	71	20	2.08	1.04	0.8713	
		2-4	77	16	1.41	0.73	0.2530	
		0-2	35	8	1.89	0.88	0.7650	0.613
	Female	>10	344	87	1.36	1.00		
		8-10	60	9	1.01	0.65	0.1769	
		6-8	62	8	0.94	0.65	0.2090	
		4-6	71	19	1.94	1.25	0.3999	
		2-4	77	11	0.97	0.67	0.2202	
		0-2	35	6	1.48	1.03	0.9505	0.608
Myeloma	Male	>10	344	304	5.03	1.00		
		8-10	60	53	6.28	1.04	0.8132	
		6-8	62	62	7.60	1.29	0.0733	
		4-6	71	84	8.72	1.40	0.0105	
		2-4	77	69	6.08	1.07	0.6517	
		0-2	35	29	6.85	1.16	0.4786	0.111
	Female	>10	344	310	4.84	1.00		
		8-10	60	43	4.81	0.77	0.1122	
		6-8	62	58	6.85	1.09	0.5622	
		4-6	71	83	8.46	1.19	0.1884	
		2-4	77	66	5.83	0.89	0.4139	
		0-2	35	18	4.43	0.62	0.0608	0.483

Table 4. (cont.) Crude annual incidence rates and adjusted rate ratios for association between distance from the Houston Ship Channel (HSC) and lymphohematopoietic cancer incidence among adults (aged ≥20)

Cancer Type	Gender	Distance from HSC (Miles)	# Census Tracts	# Cases	Crude Annual Incidence (per 100,000)	Rate Ratio*	p-value	p-value for trend
Acute Myeloid Leukemia	Male	>10	344	169	2.79	1.00		
		8-10	60	37	4.38	1.37	0.1272	
		6-8	62	277	33.97	1.14	0.4942	
		4-6	71	37	3.84	1.34	0.0956	
		2-4	77	37	3.26	1.25	0.2300	
		0-2	35	16	3.78	1.49	0.1376	0.052
	Female	>10	344	188	2.94	1.00		
		8-10	60	27	3.02	0.89	0.5832	
		6-8	62	31	3.66	1.19	0.3712	
		4-6	71	37	3.77	1.22	0.2758	
		2-4	77	34	3.00	1.07	0.7170	
		0-2	35	11	2.71	1.00	0.9966	0.431
Chronic Lymphocytic Leukemia	Male	>10	344	233	3.85	1.00		
		8-10	60	37	4.38	0.92	0.6582	
		6-8	62	41	5.03	1.14	0.4452	
		4-6	71	45	4.67	1.04	0.8375	
		2-4	77	35	3.08	0.76	0.1467	
		0-2	35	15	3.54	0.82	0.4916	0.327
	Female	>10	344	162	2.53	1.00		
		8-10	60	31	3.47	1.07	0.7148	
		6-8	62	22	2.60	0.95	0.8166	
		4-6	71	36	3.67	1.29	0.1922	
		2-4	77	39	3.44	1.37	0.1091	
		0-2	35	7	1.72	0.69	0.3529	0.303
Chronic Myeloid Leukemia	Male	>10	344	106	1.75	1.00		
		8-10	60	18	2.13	1.04	0.8925	
		6-8	62	24	2.94	1.50	0.1996	
		4-6	71	20	2.08	1.04	0.8713	
		2-4	77	16	1.41	0.73	0.2530	
		0-2	35	8	1.89	0.88	0.7650	0.613
	Female	>10	344	87	1.36	1.00		
		8-10	60	9	1.01	0.65	0.1769	
		6-8	62	8	0.94	0.65	0.2090	
		4-6	71	19	1.94	1.25	0.3999	
		2-4	77	11	0.97	0.67	0.2202	
		0-2	35	6	1.48	1.03	0.9505	0.608
Myeloma	Male	>10	344	304	5.03	1.00		
		8-10	60	53	6.28	1.04	0.8132	
		6-8	62	62	7.60	1.29	0.0733	
		4-6	71	84	8.72	**1.40**	**0.0105**	
		2-4	77	69	6.08	1.07	0.6517	
		0-2	35	29	6.85	1.16	0.4786	0.111
	Female	>10	344	310	4.84	1.00		
		8-10	60	43	4.81	0.77	0.1122	
		6-8	62	58	6.85	1.09	0.5622	
		4-6	71	83	8.46	1.19	0.1884	
		2-4	77	66	5.83	0.89	0.4139	
		0-2	35	18	4.43	0.62	0.0608	0.483

*Rate Ratios adjusted for age, ethnicity, and socioeconomic status

Table 5. Crude annual incidence rates and adjusted rate ratios for association between ambient 1,3-Butadiene levels and cancer incidence among adults (aged ≥20)

Cancer Type	Gender	1,3-Butadiene Level*	# Census Tracts	# Cases	Crude IR (per 100,000)	Rate Ratio**	p-value	p-value for trend
Hodgkin's Disease	Male	1	148	89	3.31	1.00		
		2	158	81	3.52	1.12	0.475	
		3	137	64	3.12	1.06	0.741	
		4	206	81	2.54	0.84	0.307	0.222
	Female	1	148	55	1.92	1.00		
		2	158	48	1.95	1.04	0.842	
		3	137	53	2.67	**1.57**	**0.025**	
		4	206	75	2.23	1.19	0.369	0.238
non-Hodgkin's Lymphoma	Male	1	148	487	18.11	1.00		
		2	158	464	20.14	1.08	0.250	
		3	137	413	20.14	**1.29**	**0.015**	
		4	206	618	19.41	**1.20**	**0.014**	**0.010**
	Female	1	148	444	15.54	1.00		
		2	158	435	17.71	0.97	0.645	
		3	137	364	18.36	1.09	0.327	
		4	206	508	15.10	0.91	0.168	0.226
All Leukemia	Male	1	148	312	11.60	1.00		
		2	158	303	13.15	0.97	0.702	
		3	137	248	12.09	0.96	0.669	
		4	206	360	11.31	0.91	0.296	0.296
	Female	1	148	236	8.26	1.00		
		2	158	254	10.34	1.06	0.583	
		3	137	212	10.70	1.21	0.112	
		4	206	320	9.51	1.09	0.400	0.358
Acute Lymphocytic Leukemia	Male	1	148	23	0.86	1.00		
		2	158	19	0.82	0.88	0.662	
		3	137	15	0.73	0.76	0.445	
		4	206	32	1.01	1.03	0.922	0.843
	Female	1	148	14	0.49	1.00		
		2	158	15	0.61	1.09	0.813	
		3	137	13	0.66	1.10	0.831	
		4	206	23	0.68	1.22	0.597	0.600

Table 5. (cont.) Crude annual incidence rates and adjusted rate ratios for association between ambient 1,3-Butadiene levels and cancer incidence among adults (aged ≥20)

Cancer Type	Gender	1,3-Butadiene Level*	# Census Tracts	# Cases	Crude IR (per 100,000)	Rate Ratio**	p-value	p-value for trend
Acute Myeloid Leukemia	Male	1	148	74	2.75	1.00		
		2	158	89	3.86	1.24	0.143	
		3	137	54	2.63	0.92	0.670	
		4	206	106	3.33	1.20	0.240	0.470
	Female	1	148	81	2.83	1.00		
		2	158	81	3.30	1.03	0.849	
		3	137	68	3.43	1.23	0.243	
		4	206	98	2.91	1.01	0.955	0.884
Chronic Lymphocytic Leukemia	Male	1	148	105	3.90	1.00		
		2	158	110	4.77	1.01	0.962	
		3	137	85	4.15	0.95	0.754	
		4	206	106	3.33	0.79	0.119	0.085
	Female	1	148	61	2.13	1.00		
		2	158	78	3.17	1.24	0.214	
		3	137	63	3.18	1.47	0.054	
		4	206	95	2.82	1.31	0.117	0.136
Chronic Myeloid Leukemia	Male	1	148	53	1.97	1.00		
		2	158	34	1.48	0.68	0.093	
		3	137	48	2.34	1.07	0.791	
		4	206	57	1.79	0.88	0.601	0.956
	Female	1	148	39	1.36	1.00		
		2	158	34	1.38	0.90	0.650	
		3	137	28	1.41	0.99	0.983	
		4	206	39	1.16	0.83	0.410	0.458
Myeloma	Male	1	148	125	4.65	1.00		
		2	158	161	6.99	1.18	0.177	
		3	137	128	6.24	1.08	0.582	
		4	206	187	5.87	1.06	0.641	0.988
	Female	1	148	119	4.16	1.00		
		2	158	132	5.37	0.92	0.521	
		3	137	118	5.95	0.99	0.921	
		4	206	209	6.21	1.11	0.405	0.200

*1,3-Butadiene levels correspond to: level 1 = <0.266 ppbV; level 2 = 0.266 - 0.381 ppbV; level 3 = 0.382-1.14 ppbV; and level 4 ≥1.15 ppbV

**Rate Ratios Adjusted for Age, Ethnicity, and Socioeconomic Status

Table 6. Crude annual incidence rates and adjusted rate ratios for association between ambient Benzene levels and cancer Incidence among adults (aged ≥20)

Cancer Type	Gender	Benzene Level*	# Census Tracts	# Cases	Crude Incidence Rate (per 100,000)	Rate Ratio**	p-value	p-value for trend
Hodgkin's Disease	Male	1	543	280	3.20	1.00		
		2	79	25	2.41	0.85	0.518	
		3	27	10	2.33	0.81	0.492	0.392
	Female	1	543	199	2.17	1.00		
		2	79	21	2.01	1.05	0.841	
		3	27	11	2.47	1.22	0.551	0.560
non-Hodgkin's Lymphoma	Male	1	543	1728	19.73	1.00		
		2	79	185	17.80	0.98	0.826	
		3	27	69	16.04	0.93	0.588	0.585
	Female	1	543	1487	16.22	1.00		
		2	79	191	18.25	1.11	0.178	
		3	27	73	16.37	1.16	0.528	0.285
All Leukemia	Male	1	543	1038	11.85	1.00		
		2	79	137	13.18	1.05	0.665	
		3	27	48	11.16	1.00	1.000	0.861
	Female	1	543	884	9.64	1.00		
		2	79	102	9.75	0.98	0.871	
		3	27	36	8.07	0.92	0.566	0.609
Acute Lymphoctyic Leukemia	Male	1	543	75	0.86	1.00		
		2	79	12	1.15	1.34	0.454	
		3	27	2	0.47	0.51	0.284	0.650
	Female	1	543	55	0.60	1.00		
		2	79	8	0.76	1.02	0.957	
		3	27	2	0.45	0.66	0.566	0.658
Acute Myeloid Leukemia	Male	1	543	287	3.28	1.00		
		2	79	25	2.41	0.65	0.052	
		3	27	11	2.56	0.80	0.402	0.118
	Female	1	543	284	3.10	1.00		
		2	79	31	2.96	1.04	0.844	
		3	27	13	2.92	1.12	0.660	0.656
Chronic Lymphocytic Leukemia	Male	1	543	345	3.94	1.00		
		2	79	44	4.23	0.99	0.940	
		3	27	17	3.95	1.08	0.763	0.839
	Female	1	543	262	2.86	1.00		
		2	79	28	2.68	0.93	0.769	
		3	27	7	1.57	0.64	0.256	0.293
Chronic Myeloid Leukemia	Male	1	543	155	1.77	1.00		
		2	79	32	3.08	1.71	0.037	
		3	27	5	1.16	0.71	0.500	0.589
	Female	1	543	120	1.31	1.00		
		2	79	14	1.34	1.04	0.895	
		3	27	6	1.35	1.12	0.759	0.761
Myeloma	Male	1	543	501	5.72	1.00		
		2	79	70	6.73	0.91	0.516	
		3	27	30	6.98	1.11	0.595	0.908
	Female	1	543	483	5.27	1.00		
		2	79	71	6.78	0.94	0.675	
		3	27	24	5.38	0.89	0.584	0.525

*Benzene Levels correspond to: level 1 = <1.07 ppbV; level 2 = 1.07- 1.19 ppbV and level 3 = ≥1.20 ppbV

**Rate Ratios Adjusted for Age , Ethnicity, and Socioeconomic Status

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