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Characterization of Risk From Airborne Benzene Exposure in the State of Florida

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by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
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DEDICATION

To my loving wife, whose support, professional competence, and persistent nagging greatly facilitated the completion of this dissertation.

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LIST OF ACRONYMS AND ABBREVIATIONS

Acute Myelogenous Leukemia	AML
Arithmetic mean	AM
Florida Department of Environmental Protection	FLDEP
Inhalation Unit Risk	IUR
Integrated Risk Information System	IRIS
Method detection limit	MDL
Parts per billion	ppb
Parts per million	ppm
United States Environmental Protection Agency	USEPA
Upper confidence limit	UCL

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ABSTRACT

Environmental airborne benzene is a ubiquitous hazardous air pollutant whose emissions are generated from multiple sources, including industrial emissions, fuel station emissions, and automobile emissions. Chronic occupational exposures to elevated levels of benzene are known to be associated with leukemic cancers, in particular, acute myeloid leukemia (AML), though epidemiological evidence regarding environmental exposures and subsequent AML developmentis lacking. This investigation uses historical airborne monitoring data from six counties in the State of Florida to characterize the environmental cancer risk from airborne benzene concentrations using current Federal and State regulatory analysis methodology, and a comparative analysis based on occupational epidemiological evidence. Airborne benzene concentrations were collected from 24 air toxics monitoring stations in Broward, Duval, Orange, Miami-Dade, Hillsborough, and Pinellas counties. From the years 2003 – 2006, 3,794 air samples were collected using 8, 12, and 24 hr samples with sub-ambient pressure canister collectors consistent with EPA benzene methodological protocols 101 and 176. Mean benzene concentrations, by site, ranged from 0.18 – 3.58 ppb. Using risk analysis methodology consistent with the EPA and the Florida Department of Environmental Protection (FLDEP) the resulting cancer risk estimates ranged from 4.37×10^{-6} to 8.56×10^{-5}, exceeding the FLDEP's

acceptable cancer risk level, 1 x 10^{-6} for all monitoring sites. The cumulative lifetime exposures were calculated in ppm-years by site, ranging from 0.036 – 0.702 ppm-years. A comparative analysis with available epidemiological literature revealed that associations between benzene exposure and cancer outcomes were related to cumulative lifetime exposures in great excess of 1 ppm-years. The results of this investigation indicate that it is not reasonable to expect additional cancer outcomes in Florida residents as a result of airborne benzene exposures consistent with measured concentrations, despite the fact that all regulatory risk calculations exceed acceptable cancer risk levels in the State of Florida.

Chapter 1.0: Introduction

1.1 Overview of Benzene Related Health Research

Concern over the health hazards of benzene exposure has existed since the early 20th century. Researchers began reporting acute toxicities from extremely high exposures (3,000 to 20,000 ppm) such as anesthesia, confusion, and death in the 1920's (1-3). Chronic toxicities began to be reported soon after, with hematologic toxicity being most noted in the suppression of red and white blood cells, exhibiting as pancytopenia and aplastic anemia (1-6). One of the first cases of leukemia reported to be associated with benzene exposure occurred in 1928, though the link between benzene exposure and leukemia was not firmly established until several decades later (7). The carcinogenic nature of benzene began to come into focus in the 1970s, when larger groups of exposed workers started to see inordinate numbers of leukemia cases (8-13). Goguel et al. 1967, Girard and Revol 1970, and Aksoy et al. 1972 reviewed several of the first case series that seemed to indicate a more specific relationship between excessive benzene exposures and acute myelogenous leukemia (AML) (14-16). Vigliani et al. 1964 and Askoy et al. 1974 made the first attempts to characterize the risk of benzene exposure and leukemia, but unfortunately lacked a sufficient exposure assessment to produce any reliable estimates (17-18). In the 1980s and 1990s, the attention focused on exposure to petroleum and chemical workers to more clearly assess specific levels of benzene exposure and the risk of leukemogenesis (7). As well, non-occupational exposures began to be explored in this time period,

focusing on indoor air, tobacco usage, and self-service gasoline station benzene exposures (19-20). The focus of research in the 21st century undoubtedly lies in the pursuit of establishing a clear dose-response relationship between low level benzene exposures and leukemogenesis, in both occupational and environmental settings, in order to ascertain a level benzene exposure that will ensure the safety of workers, as well as the safety of the general population.

1.2.1 Acute Lethality

The inhalation LC50 value for rats has been determined to lie between 13,700 ppm and 16,000 ppm for a 4-hour exposure (21-22). Green et al. 1981 observed mice exposed by inhalation to doses of benzene up to 4,862 ppm, 6 hours/day for 5 days without lethality (23). Deaths in humans from acute benzene exposures are often poorly characterized, but it has been estimated that 5 to 10 minutes of exposure to 20,000 ppm is most likely fatal (24). The pathology in cases of lethal benzene exposures may be described by asphyxiation, respiratory arrest, central nervous system depression, suspected cardiac collapse, cyanosis, hemolysis, and congestion or hemorrhage of organs (25-28).

1.2.2 Respiratory Toxicity

Several adverse respiratory effects have been reported in humans after acute exposures to benzene vapors between 30 and 300 ppm for a period of several days or weeks in relatively higher exposures, or as long as a year for relatively lower exposures. These effects include mucous membrane irritation, dyspnea, nasal

irritation, and sore throat (25-30). In extremely high exposures that resulted in fatalities, pulmonary edema, acute granular tracheitis, laryngitis, bronchitis, and massive hemorrhaging have been observed (25-27).

1.2.3 Dermal Toxicity

Skin irritation has been noted at airborne occupational exposures of >60 ppm for up to 3 weeks as well as with extremely high acute exposures (25, 29).

1.2.4 Neurological Toxcity

At acute exposure levels between 300 and 3,000 ppm, neurological effects have been observed such as drowsiness, dizziness, headache, vertigo, tremor, delirium, and loss of consciousness (29, 31-33). There is some evidence of neurological toxicity from excessive chronic exposures (~200 ppm) in the form of global atrophy of lower extremities and distal neuropathy of upper extremities, though this is based on a limited number of cases and a crude estimation of exposure (34).

1.2.5 Reproductive Toxicity

There has been some suggestion that benzene exposure may lead to dysmenorrheal, disturbances in the menstrual cycle, and spontaneous abortion. Unfortunately, the research related to these possible effects does not have accurate exposure measurements and is plagued by confounding factors such as mixed chemical exposures (35-37).

1.2.6 Hematological Toxicity

Hematological effects from acute exposures have not been well established, but there is some evidence that indicates leukopenia, anemia, and thrombocytopenia may occur after more than 2 days of occupational exposure to more than 60 ppm benzene in a small portion of workers (29). Chronic exposures to benzene in excess of occupational regulatory levels (~ 10 ppm) for many years may result in pancytopenia, the reduction in the number of all three major types of blood cells: erythrocytes (red blood cells), thrombocytes (platelets), and leukocytes (white blood cells). Additionally, aplastic anemia may result, a more severe condition wherein the bone marrow ceases to function and the stem cells never reach maturity. Some research indicates that aplastic anemia may be a precursor to myelogenous leukemia (38-49).

There are several studies clearly indicating that high level chronic exposure is associated with hematological abnormalities. Askoy et al. 1971, 1972 found various increases in hematological abnormalities (leukopenia, thrombocytopenia, eosinophilia, pancytopenia, and hypoplastic, acellular, hyperplastic, or normoblastic bone marrow) with exposures estimated to be between 15 to >200 ppm (50-51). Dosemeci et al. 1996 found similar abnormalities when assessing rubber manufacturing workers with more accurately defined exposure estimates ranging from 5 to >40 ppm (52). At lower levels of chronic exposure (0.01 – 1.4 ppm), evidence indicates chronic benzene exposure does not produce hematological toxicity (53-55).

1.3 Benzene as a Carcinogen

As previously mentioned, benzene has been a suspected leukemogen, particularly the myeloid cell type, since the late 1920's, though the causal association between benzene and leukemia had not been confirmed until the 1970's. The carcinogenic nature of benzene, in terms of the specific mechanism of action has not been clearly established. An examination of benzene metabolism does provide some insight, however, for potential mechanisms by which the metabolites of benzene may function as carcinogens.

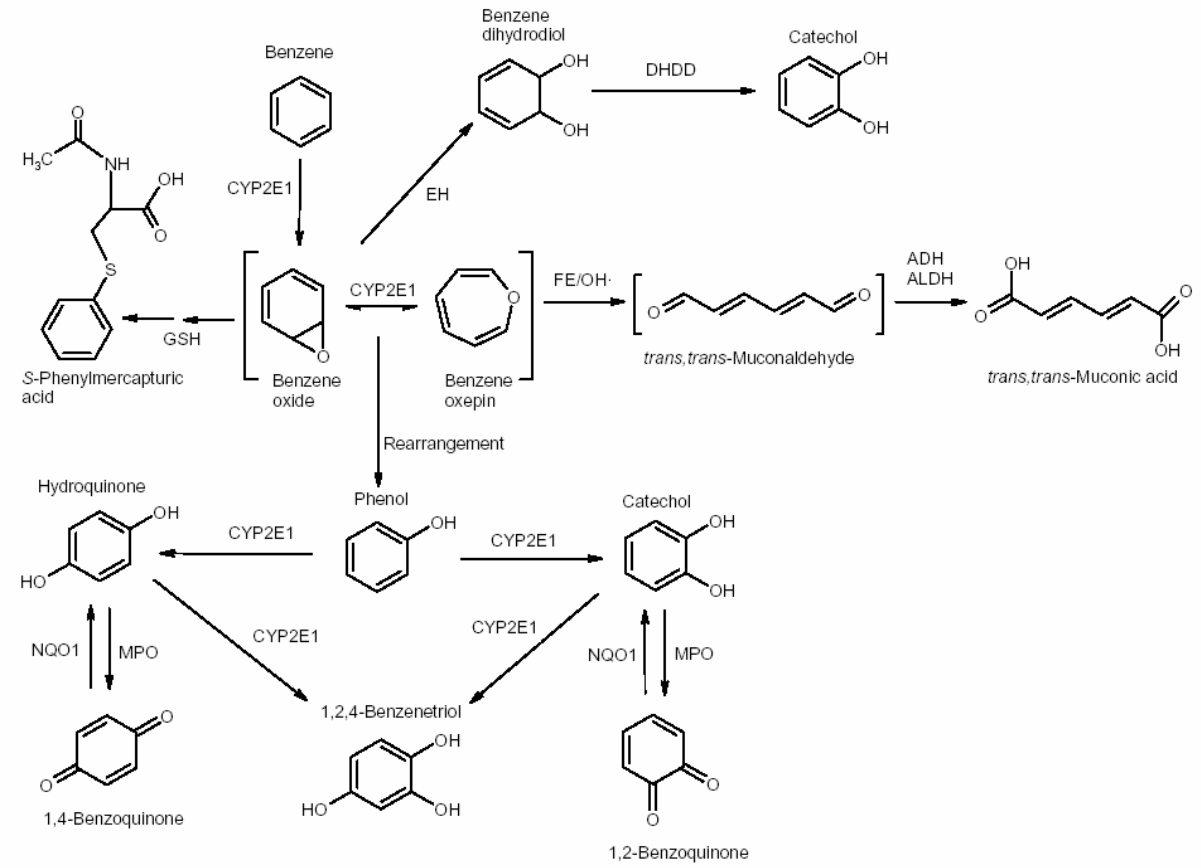
1.3.1 Benzene Metabolism

The metabolism of benzene in humans has been established primarily from studies using inhalation exposures. Benzene is excreted both unchanged through the lungs and as metabolites (as well as some unmetabolized benzene) in the urine. Metabolites are produced in the liver and carried to the bone marrow (though additional metabolism may occur in the marrow itself) where the greatest potential for benzene related toxicity exists. As illustrated in Figure 1, benzene metabolism is driven by cytochrome P-450 2E1 (CYP2E1) catalyzed oxidation to form benzene oxide (56-57). Several pathways are involved in the metabolism of benzene oxide, the predominant pathway being the nonenzymatic rearrangement to form phenol, the initial product of benzene metabolism of major importance regarding benzene toxicity (58-59). CYP2E1 also catalyzes the oxidation of phenol to catechol or hydroquinone, which are oxidized via myeloperoxidase (MPO) to the reactive metabolites 1,2- and 1,4-benzoquinone, respectively and the reverse reaction (reduction of 1,2- and 1,4-

benzoquinone to catechol and hydroquinone, respectively) is catalyzed by NAD(P)H quinone oxidoreductase (NQ01). Both catechol and hydroquinone may be converted to the reactive metabolite 1,2,4-benzenetriol, again, by CYP2E1 catalysis. 1,2,4-benzenetriol is potentially the most toxic metabolite as a result of having a third reactive hydroxyl group (60).

However, as a minor pathway, benzene oxide may also undergo epoxide hydrolase-catalyzed conversion to benzene dihydrodiol and subsequent dihydrodiol dehydrogenase-catalyzed conversion to catechol (60-62). Each of the phenolic metabolites of benzene (phenol, catechol, hydroquinone, and 1,2,4-benzenetriol) can undergo sulfonic or glucuronic conjugation, the conjugates of phenol and hydroquinone being the major urinary metabolites of benzene (60, 63-65). Other minor metabolic pathways for benzene oxide that produce potentially less toxic metabolites include the reaction with glutathione (GSH) to form S-phenylmercapturic acid, and the iron catalyzed ring-opening conversion to trans,trans-muconic acid, possibly through the reactive trans,transmuconaldehyde intermediate (60, 66-75).

Figure 1: Benzene metabolic pathways.



From the ATSDR Toxicological Profile on Benzene; originally adapted from Nebert et al. 2002 and Ross 2000 (11, 60, 67).

ADH = alcohol dehydrogenase; ALDH = aldehyde dehydrogenase; CYP2E1 = cytochrome P-450 2E1; DHDD = dihydrodiol dehydrogenase; EH = epoxide hydrolase; GSH = glutathione; MPO = myeloperoxidase; NQ01 = NAD(P)H:quinone oxidoreductase

1.3.2 Mechanism of Action

Several animal studies have found compelling evidence that the genotoxicity exhibited in mice after benzene exposure is directly attributed to the metabolites of benzene rather than benzene itself. Valentine et al. 1996a, 1996b used transgenic knockout mice for the hepatic CYP2E1 gene, which prevents these mice from metabolizing benzene in the liver. After both transgenic mice and wild-type mice

were exposed to 200 ppm of benzene for 6 hours a day for 5 days, the genotoxicity observed in the wild-type mice was notably absent in the transgenic mice (76-77). Similar results have been found in other studies where Cytochrome P-450 enzyme inhibitors were used on wild type mice to inhibit benzene metabolism, which effectively attenuated benzene induced genotoxicity (78-81).

Several investigations suggest that the covalent binding of benzene metabolites to cellular macromolecules is related to benzene's mechanism of toxicity, specifically the formation of adducts with nucleic acids, but also with various proteins (82-90). The reactive metabolites that exhibit these binding properties and have been proposed as agents of benzene hematotoxic and leukemogenic effects include benzene oxide, reactive products of the phenol pathway (catechol, hydroquinone, 1,2,4-benzenetriol, and 1,4-benzoquinone). Smith 1996a, 1996b noted that the phenolic metabolites can also be metabolized by bone marrow peroxidases, such as myeloperoxidase, to highly reactive semiquinone radicals and quinones that stimulate the production of reactive oxygen species (91-92). All of these reactive metabolites are capable of damaging nuclear proteins and enzymes such as tubulin, histone proteins, topoisomerase II, other DNA associated proteins, as well as DNA itself in the form of strand breakage, mitotic recombination, chromosome translocations, and aneuploidy. Damage to stem or early progenitor cells could potentially be expressed as hematopoietic and leukemogenic effects (82-97).

As benzene toxicity is thought to be driven by metabolism, it is important to note that the available data collected on metabolic pathways is primarily garnered from animal studies. This being the case, it is imperative to examine interspecies differences in the metabolism of benzene. Firstly, species differences exist in absorption and retention of benzene. It has been observed that following 6-hour exposures to concentrations of 7–10 ppm of benzene vapors, mice retain 20% of the inhaled benzene, whereas rats and monkeys retain only 3–4% (98-99). Secondly, the rate of metabolism differs among various species. Mice have a greater overall capacity to metabolize benzene, compared to rats. It has been shown that an inhalation exposure to 925 ppm results in an internal dose of 152 mg/kg in mice, only 15% of which was excreted as unmetabolized benzene compared to an internal dose of 116 mg/kg in rats, approximately 50% of which was excreted unchanged (98, 100). As it is generally thought that humans more closely resemble mouse metabolic profiles compared to rats, a more conservative metabolic rate is used to estimate human metabolite production. As well, the more conservative absorption rate is used in the development of the inhalation unit risk, with the assumption that humans absorb and retain 50% of inhaled exposures (48).

1.4 Environmental Benzene Exposure

The USEPA Toxic Release Inventory (TRI) records indicates that 333,089 pounds of benzene were released into the environment in the State of Florida in the year 2005 (101). Of these emissions, 115 pounds were recorded as releases into surface water, and there was no amount of direct release into the soil reported. With the exception

of potential point source contamination of water and soil from accidental spillage that results in extremely high levels of benzene in those media, environmental airborne benzene represents the greatest potential for exposure to the general public.

Benzene is released into the atmosphere from both natural and industrial sources. Natural sources include crude oil seeps, forest fires, and plant volatiles (102-103). Major anthropogenic sources of benzene include automobile exhaust, automobile refueling operations, and industrial emissions. It has been estimated that environmental benzene emissions are highest in coke oven blast furnaces. However, other sources that significantly contribute to emissions of benzene include automobiles, petrochemical industries, waste water treatment plants, and petroleum industries. Personal exposures include fueling passenger automobiles and cigarette smoke. Cigarette smoke is the most important personal exposure in moderate to heavy long-term smokers as it represents a persistent chronic exposure and can contribute to indoor air pollution to the extent that indoor levels may become significantly higher than ambient levels. Smokers are known to have measurably higher levels of benzene in exhaled breath than non-smokers (104). The amount of benzene measured in mainstream smoke ranges from 5.9 to 73 µg/cigarette. Larger amounts of benzene have been found in side-stream smoke, ranging from 345 to 653 µg/cigarette (105). Vaporized benzene in the atmosphere may persist for a matter of hours to approximately a week, depending on the concentration of hydroxyl molecules present, which are the primary reactants involved in reducing airborne benzene concentrations (106-107).

1.5 Research Objectives

It is evident that the majority environmental emissions of benzene are airborne, and consequently, the greatest opportunity for exposure to the general public is through the inhalation. It is also generally accepted that the health risk of greatest concern from low level benzene exposures is cancer, specifically AML. As a result, the primary objectives of this risk characterization deal directly with the cancer risks that may potentially exist from ambient airborne concentrations of benzene.

Specifically, the objectives of the current research are as follows:

1. To characterize the ambient airborne benzene exposures in the State of Florida by analyzing data from air sample measurements collected at air toxics monitoring sites in the most populous counties from the years 2003 to 2006.
2. To characterize the cancer risk that may exist using the USEPA Risk Assessment for Carcinogens methodology from the measured benzene concentrations in this study.
3. To extrapolate the cumulative lifetime benzene exposure from the measured benzene exposures in this study.
4. To perform a comparative analysis between epidemiological studies evaluating cancer risk from cumulative lifetime benzene exposures to the cumulative lifetime exposures as indicated by the measured benzene exposures in this study.
5. To draw conclusions as to the health risk presented by the ambient airborne benzene exposures measured in this study.

The hypotheses to be tested in this research are the following:

1. A regulatory risk analysis based on measured benzene concentrations will result in risk values in excess of the 1 x 10^{-6} acceptable risk level promulgated by the FLDEP;

2. Analysis of current epidemiological research will indicate that a threshold for benzene induced leukemogenesis is evident, and;

3. Cumulative exposures extrapolated from measured airborne benzene concentrations will be less than the evident threshold for benzene induced leukemogenesis.

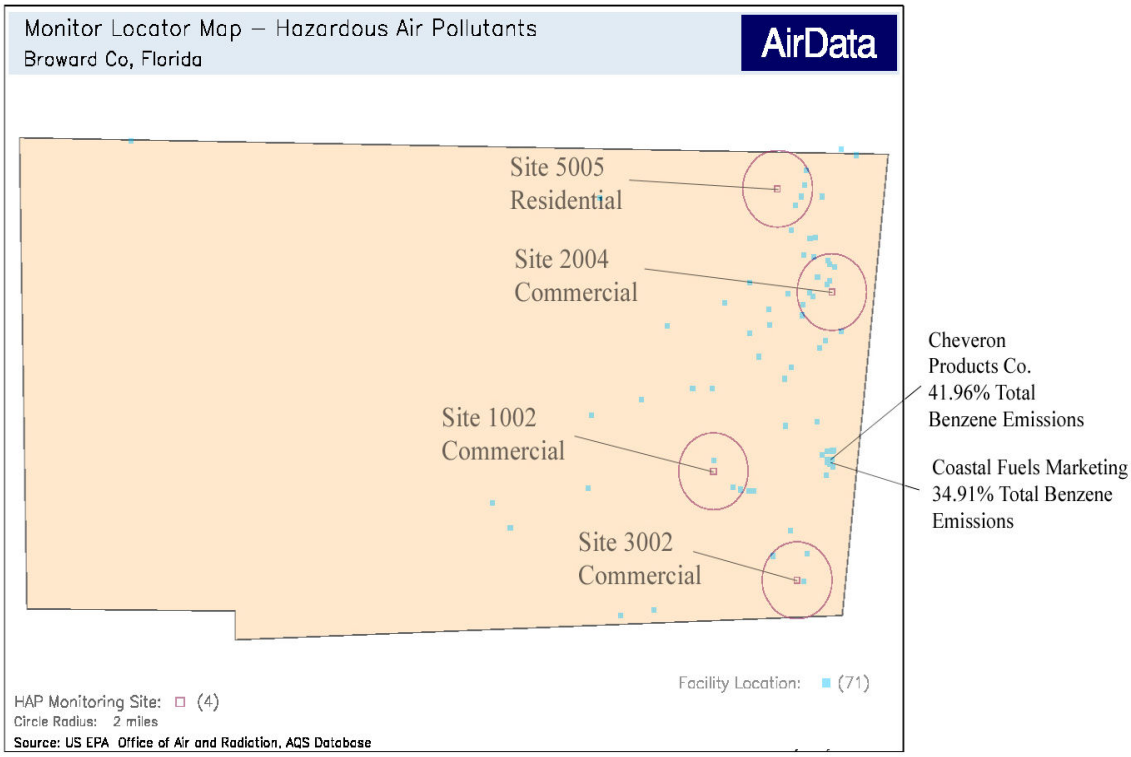
Chapter 2.0: Research Methods

2.1 Monitor Site Descriptions

In the State of Florida, six counties have active air toxics monitoring programs. Within each county, there are varying numbers of monitors, in various locations in terms of their proximity to benzene emission sources. Figures 2-7 represent the locations of each monitor within each county, and their proximity to known benzene emission sources, with the largest contributors of benzene emissions labeled. To provide a sense of scale, and the potential influence of these emission sources on the monitors, a two mile radius encircles the monitor sites. In Broward County (Figure 2) the four active monitors fall primarily in Commercial and Residential areas, with all monitors being located within two miles of known benzene emission sources. Duval County (Figure 3) possesses more air toxic monitoring stations than any other county in the State of Florida, and in addition to the Residential and Commercial monitor categories, Duval County employs 23 monitors located near major highways and roadways which may be heavily influenced by fugitive mobile benzene emissions. Hillsborough County (Figure 4) has 3 active monitors in Commercial, Residential, and Rural areas. Two monitors in Dade County (Figure 5) are located in Rural and Commercial areas, respectively. Orange County (Figure 6) has a single active monitoring station located in a Commercial area, with close proximity to major roadways. Pinellas County (Figure 7) has 3 active monitor locations in Residential areas, though it should be noted at least two of the monitors are within a two mile

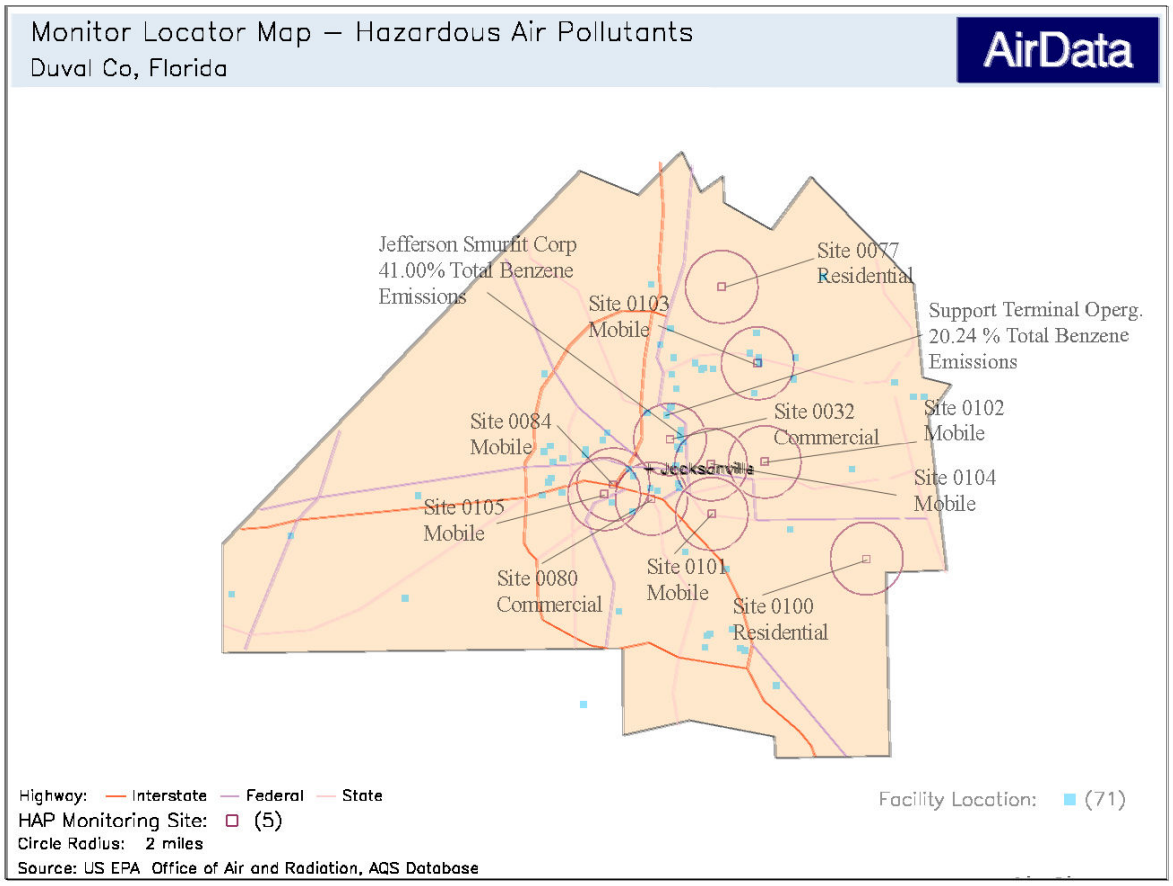
proximity of known benzene emission sites, Site #2 located within two miles of the largest benzene emission site for that county.

Figure 2: Benzene monitor locations and relevant benzene emission sources for Broward County.



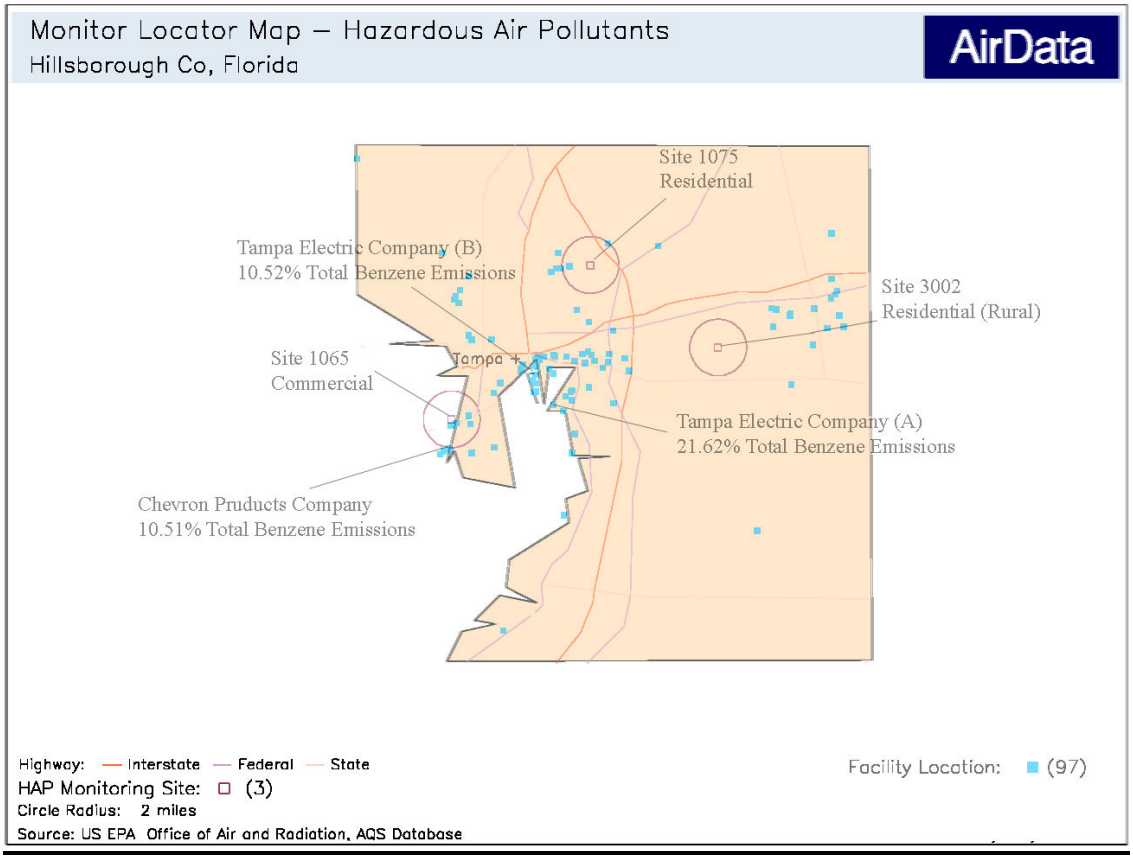
Benzene monitor locations within Broward County, Florida. Each site is encircled by a 2 mile radius. Blue marks indicate known benzene emission sites; the highest emission sources for this county are labeled (108).

Figure 3: Benzene monitor locations and relevant benzene emission sources for Duval County.



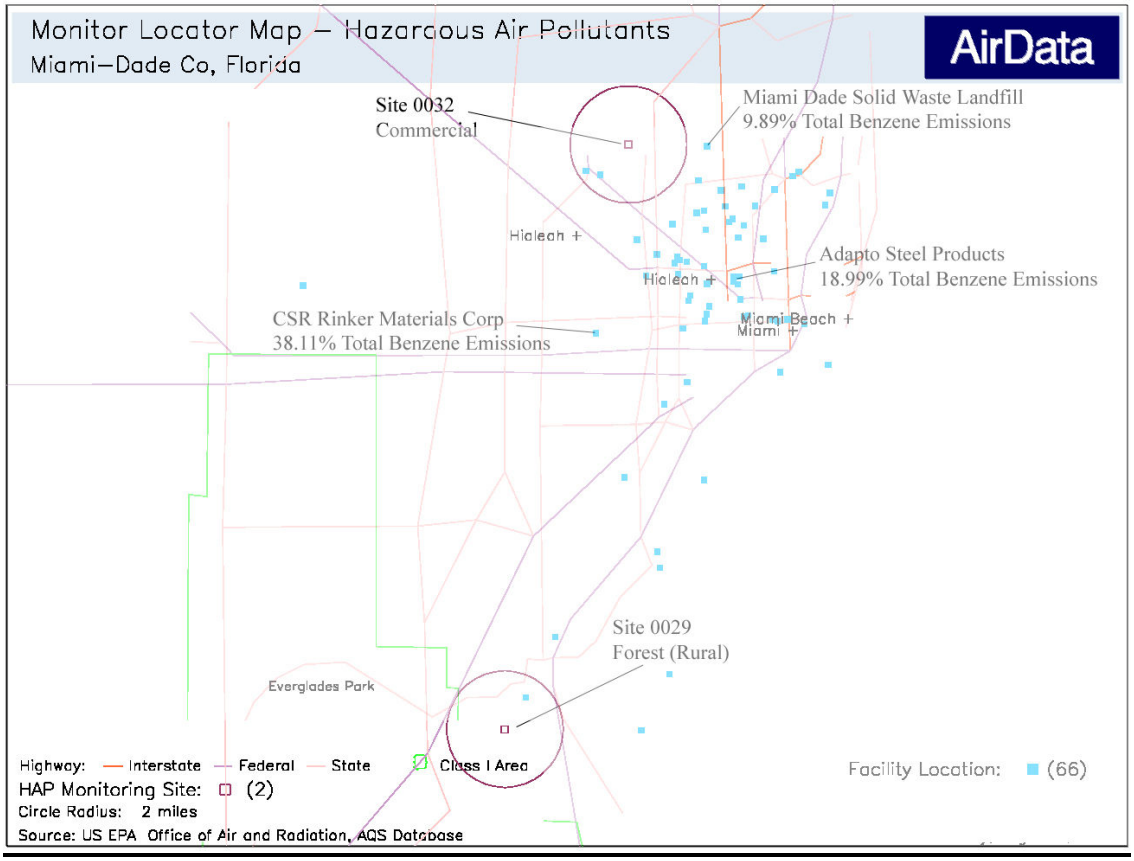
Benzene monitor locations within Duval County, Florida. Each site is encircled by a 2 mile radius. Blue marks indicate known benzene emission sites; the highest emission sources for this county are labeled (108).

Figure 4: Benzene monitor locations and relevant benzene emission sources for Hillsborough County.



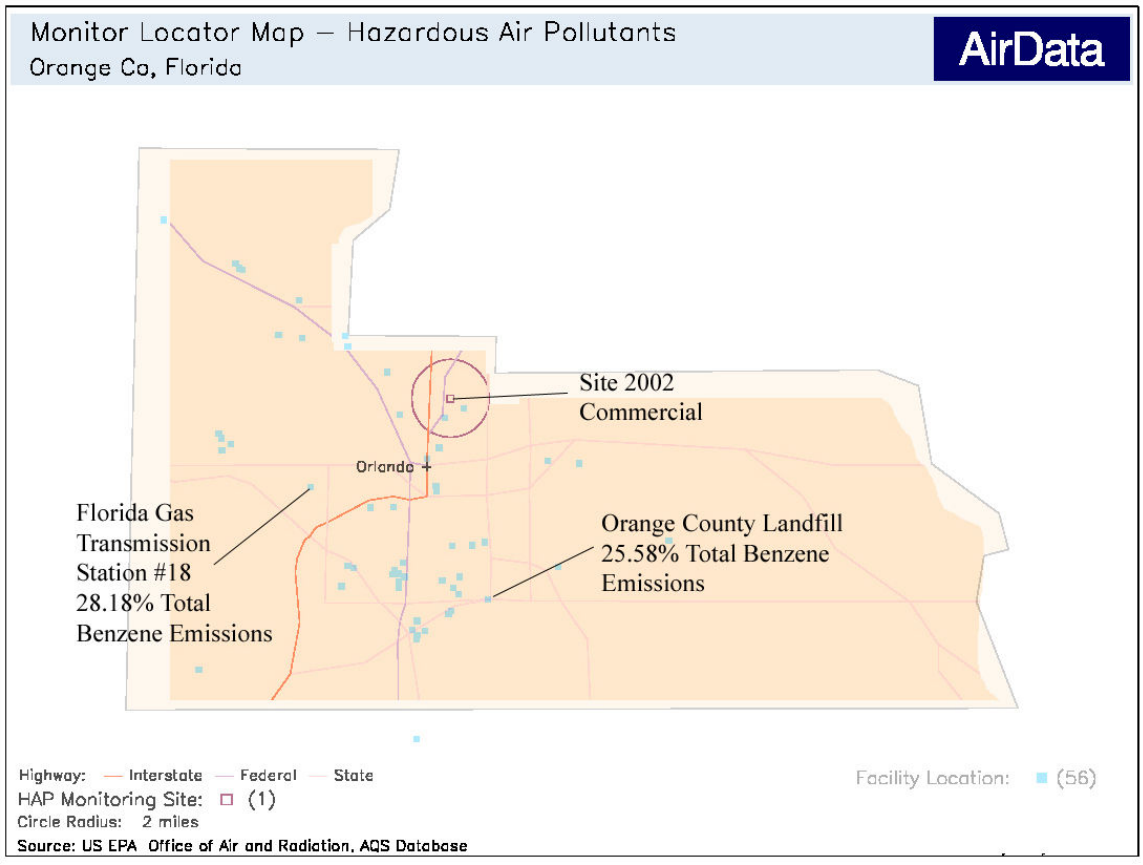
Benzene monitor locations within Hillsborough County, Florida. Each site is encircled by a 2 mile radius. Blue marks indicate known benzene emission sites; the highest emission sources for this county are labeled (108).

Figure 5: Benzene monitor locations and relevant benzene emission sources for Dade County.



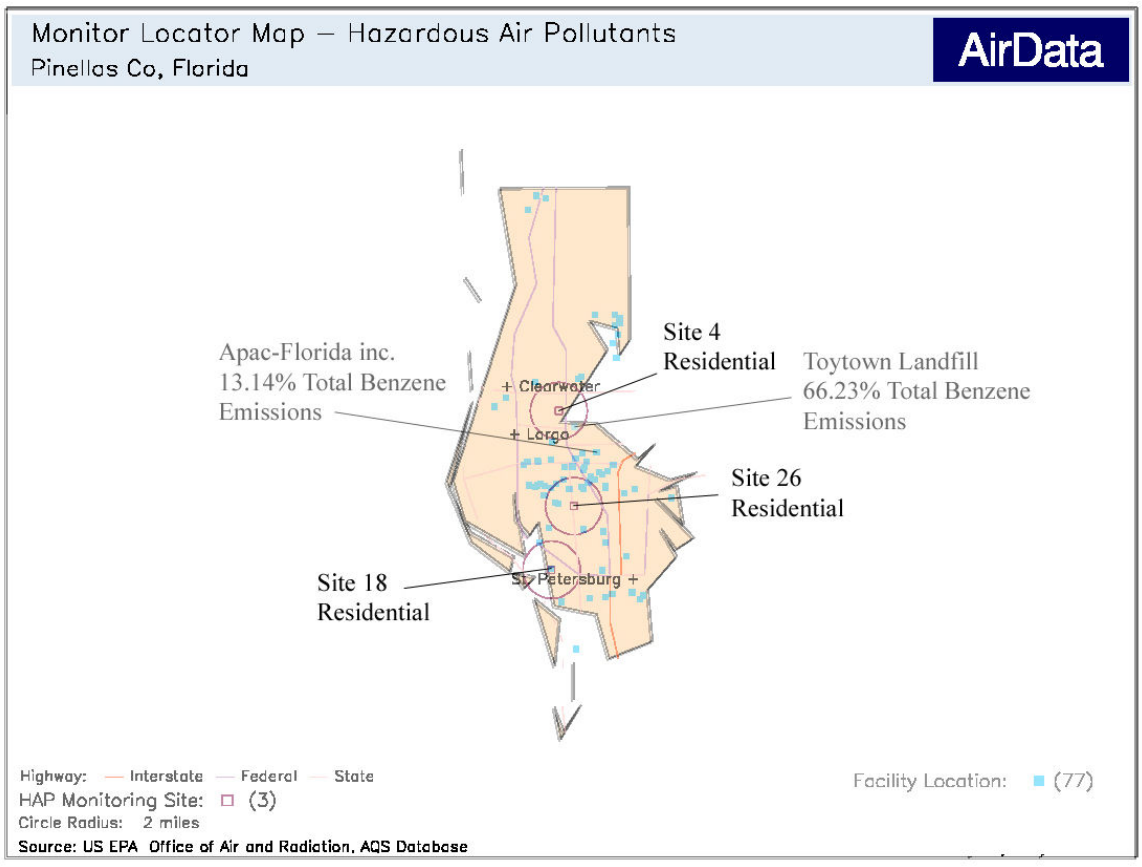
Benzene monitor locations within Dade County, Florida. Each site is encircled by a 2 mile radius. Blue marks indicate known benzene emission sites; the highest emission sources for this county are labeled (108).

Figure 6: Benzene monitor locations and relevant benzene emission sources for Orange County.



Benzene monitor locations within Orange County, Florida. Each site is encircled by a 2 mile radius. Blue marks indicate known benzene emission sites; the highest emission sources for this county are labeled (108).

Figure 7: Benzene monitor locations and relevant benzene emission sources for Pinellas County.



Benzene monitor locations within Pinellas County, Florida. Each site is encircled by a 2 mile radius. Blue marks indicate known benzene emission sites; the highest emission sources for this county are labeled (108).

2.2 Data Collection

Six Florida Counties (Duval, Pinellas, Miami-Dade, Hillsborough, Orange, and Broward) currently monitor and report air toxics levels to the United States Environmental Protection Agency (USEPA). From the USEPA air toxics database, all reported monitor levels were queried for Parameter 45201 Benzene in the State of Florida for years 2003 – 2006 (108). The final dataset contained all reported airborne benzene measurements from 23 individual monitoring sites during this time interval.

The sample collection method for Broward, Hillsborough, Miami-Dade, Orange, and Pinellas counties uses the EPA method code 176 (109). This method uses 6 liter, sub-ambient canisters for collection over either 12 or 24 hour periods. Chemical species are quantified by Entech Proconcentrator Gas Chromatography/Mass Spectroscopy. Duval County utilizes EPA method code 101 (109). This method utilizes sub-ambient pressure canisters to collect samples over either 3, 4, 8, 12, or 24 hours (all time periods were used for sampling beginning at various times throughout day or night time hours). Chemical Species are quantified by Multi-Detector Gas Chromatography. Both methods have the same calculated method detection limit (MDL).

2.3 Assigning Values to Measurements Below the Method Detection Limit

In assessing low level environmental exposures, quantifying concentrations can be limited by the physical capabilities of the equipment being used to measure the airborne concentrations of a substance. When a measured value is below the method

detection limit used in an exposure assessment, it is not considered a reliable value. For these measurements, values are assigned based on assumptions made as to the type of exposure being analyzed. For instance, as benzene is ubiquitous throughout the atmosphere, it would not be a reasonable assumption that values under the MDL would indicate a level of zero. Alternative methods have been proposed by Hornung and Reed 1990 (128). The most conservative method of assigning values is to apply the actual MDL to values that fall below the limit. This method will result in the highest estimated mean exposure levels, and may significantly overestimate the actual exposure in data for which there are many values below the MDL. Another proposed methodology that is less conservative than using the actual MDL is to divide the MDL by the square root of 2 (128). Hornung and Reed 1990 compared this method with known censored datasets and found the comparison to maximum likelihood estimates to be a highly accurate method of assigning values non-skewed data (128). Hornung and Reed 1990 also found this methodology to be more appropriate than the USEPA method of assigning values below the MDL as the MDL divided by 2 (128). Dividing the MDL by 2 results in the least conservative estimation of mean values, and might be criticized by some as resulting in an underestimation of mean exposure. As a principle goal of the current research is to analyze the exposure data with USEPA risk assessment methodology, it of great interest to calculate means that are consistent with USEPA methods. However, in order to explore the effects of this data treatment on estimated mean exposures, the alternative methods were also employed, and the results were compared using the students t-test to assess if statistically significant differences in estimated mean exposures have been produced as a result.

Assigning values to measurements that are below the MDL may significantly affect the calculated means if a large portion of the data set consists of values that fall below the MDL. The standard procedure for assigning values below the MDL, as indicated by the USEPA Guidelines for Carcinogen Risk Assessment, is to divide the MDL by 2 (110). This was the primary method used for calculating risk probabilities in the current study. In order to assess the impact of values falling below the MDL on the calculation of risk probabilities, two additional methods of assigning values to measurements under the MDL are considered. The Upper Confidence Limit of the Arithmetic Mean (UCL-AM) is also calculated by assigning values equal to the MDL, and assigning values equal to the MDL divided by the square root of 2, when recorded values are below the MDL. The students t-test has been used to determine whether or not the different methodologies used in assigning values to measurements under the MDL have a statistically significant impact on the calculation of UCL-AMs.

2.4 USEPA Risk Analysis

A risk analysis of the data was performed using the USEPA Risk Assessment for Superfund methodology (110). Risk estimates were produced for the probability of developing cancer (AML) as a result of the measured benzene concentrations. The exposure concentrations used in the calculation of risk and the risk probabilities were derived using the USEPA software ProUCL version 4. The ProUCL program calculates the 95% UCL-AM for normal, lognormal, gamma, and nonparametrically

(non-normal) distributed concentrations of chemicals in air and recommends the most appropriate UCL-AM for use depending on the distribution of the data. This analysis was performed for the data retrieved for each individual site.

Risk probabilities were then calculated from all previously described UCL-AMs for all sites. These risk probabilities were calculated by multiplying the UCL-AM by the Inhalation Unit Risk (IUR) as prescribed in the USEPA Guidelines for carcinogen risk assessment (110). The IUR used for benzene, 7.8×10^{-6}, is consistent with both the USEPA Integrated Risk Information System (IRIS) and the Florida Department of Environmental Protection risk assessment methodology (49, 111).

2.5 Comparative Analysis

In order to conduct a comparative analysis between the benzene exposures found in the current research and those found in epidemiological studies that have assessed the relationship between cumulative lifetime benzene exposures (expressed as ppm-years) and cancer, monitored levels in the current data set have been extrapolated to reflect cumulative lifetime exposures in ppm-years. This was performed using USEPA methodology presented in the Region/ORD Workshop on Inhalation Risk Assessment: A Superfund Focus (112). Using the UCL-AMs for calculating the risk probability associated with each monitoring site, the cumulative exposure was extrapolated into ppm-years with the following conversion factors: $20\ m^3/10\ m^3 \times 7$ days/5 days x 70 years/40 years = 4.9. This method of conversion accounts for both the decreased inhalation rate associated with non-occupational airborne exposures as

well as the increased exposure duration of 7 days a week for 70 years compared to occupational exposures of 5 days a week over a 40 year working lifetime. The ORD Workshop on Inhalation Risk Assessment indicates that the conversion factor affecting the difference in inhalation rates adequately compensates for the difference in daily exposure times (e.g. 24 hours of environmental exposure versus 8 hours of occupational exposure) and that an additional conversion factor for this difference is unnecessary (112).

A literature review using the PubMed/Medline database has been conducted to gather all published, peer reviewed scientific literature regarding airborne benzene exposure and cancer outcomes that contain comparisons of discreet ranges of lifetime exposure. In comparing the cumulative lifetime benzene exposures derived from the current research with cumulative benzene exposures from occupational cohorts, a weight of evidence approach using the criteria for causal analysis has been made to determine if there is potentially a threshold below which leukemogenesis does not occur. More specifically, this comparative analysis determined if there is research to indicate there is a potential association between levels of exposure measured in this dissertation with leukemogenesis by assessing the levels of cumulative lifetime exposures found in occupational cohorts that are associated with leukemogenesis.

Chapter 3.0: Results

3.1 Descriptive Statistics

Tables 1 – 6 contain the summary statistics of the airborne benzene measurements collected at each sampling site, by county. The number of samples, minimum measured concentrations, maximum measured concentrations, mean concentrations, median concentrations, and the standard deviation are reported for all sites for samples collected between January 2003 and December 2006. As three different methods were used to assign values to measurements below the MDL, summary statistics were produced for each method for those sites that had measurements below the MDL, and this is reflected in the following tables. For sites with no measurements below the MDL, results from using any value assigning methodology could not be reported.

Table 1: Summary Statistics for airborne benzene samples collected between January 2003 and December 2006 for all Broward County sampling sites. All concentrations are µg/m^3.

	Site 1002	Site 2004	Site 3002	Site 5005
Number of Samples	218	181	186	224
Number Below MDL	13	21	6	29
MDL[a]				
Minimum	0.29	0.2	0.2	0.22
Maximum	3.03	2.72	20.19	2.27
Mean	0.831	0.881	1.711	0.729
Median	0.73	0.8	0.93	0.64
SD[d]	0.399	0.463	3.256	0.359
MDL/2[b]				
Minimum	0.19	0.1	0.1	0.12
Maximum	3.03	2.72	20.19	2.27
Mean	0.817	0.856	1.705	0.7
Median	0.73	0.8	0.93	0.64
SD[d]	0.415	0.491	3.259	0.386
MDL/√2[c]				
Minimum	0.27	0.14	0.14	0.17
Maximum	3.03	2.72	20.19	2.27
Mean	0.823	0.866	1.707	0.712
Median	0.73	0.8	0.93	0.64
SD[d]	0.408	0.478	3.258	0.373

[a] Values below the MDL were assigned the value of the MDL.
[b] Values below the MDL were assigned the value of the MDL/2.
[c] Values below the MDL were assigned the value of the MDL/√2
[d] Standard Deviation

Table 2: Summary Statistics for airborne benzene samples collected between January 2003 and December 2006 for all Dade County sampling sites. All concentrations are µg/m^3.

	Site 29	Site 32
Number of Samples	**119**	**80**
Number Below MDL	**3**	**1**
MDL		
Minimum	**0.16**	**0.35**
Maximum	**2.84**	**3.1**
Mean	**0.803**	**1.221**
Median	**0.67**	**1.15**
SD	**0.523**	**0.569**
MDL/2		
Minimum	**0.16**	**0.19**
Maximum	**2.84**	**3.1**
Mean	**0.796**	**1.219**
Median	**0.67**	**1.15**
SD	**0.528**	**0.573**
MDL/√2		
Minimum	**0.16**	**0.28**
Maximum	**2.84**	**3.1**
Mean	**0.799**	**1.22**
Median	**0.67**	**1.15**
SD	**0.525**	**0.571**

[a] Values below the MDL were assigned the value of the MDL.
[b] Values below the MDL were assigned the value of the MDL/2.
[c] Values below the MDL were assigned the value of the MDL/√2
[d] Standard Deviation

Table 3: Summary Statistics for airborne benzene samples collected between January 2003 and December 2006 for all Duval County sampling sites. All concentrations are µg/m^3.

	Site 32	Site 77	Site 80	Site 84	Site 100
Number of Samples	96	54	48	89	48
Number Below MDL	0	0	0	0	0
Minimum	1.41	1.09	1.41	1.05	0.05
Maximum	24.79	24.09	34.50	28.62	14.95
Mean	6.09	4.28	6.18	7.68	3.62
Median	4.52	3.37	4.70	6.87	3.42
SD[a]	4.34	3.47	5.33	4.79	2.59

	Site 101	Site 102	Site 103	Site 104	Site 105
Number of Samples	240	504	210	430	25
Number Below MDL	0	0	0	0	0
Minimum	0.54	0.38	0.32	0.45	4.06
Maximum	116.10	134.40	46.67	23.96	13.13
Mean	8.23	9.01	5.53	3.93	7.76
Median	5.20	5.51	4.28	2.72	7.25
SD[a]	10.48	12.59	4.82	3.52	2.55

[a] Standard Deviation

Table 4: Summary Statistics for airborne benzene samples collected between January 2003 and December 2006 for all Hillsborough County sampling sites. All concentrations are µg/m^3.

	Site 1065	Site 1075	Site 3002
Number of Samples	**218**	**57**	**177**
Number Below MDL	**0**	**0**	**0**
Minimum	**0.19**	**0.38**	**0.16**
Maximum	**2.3**	**2.59**	**1.53**
Mean	**0.654**	**0.886**	**0.551**
Median	**0.58**	**0.77**	**0.48**
SD[a]	**0.298**	**0.452**	**0.263**

[a]Standard Deviation

Table 5: Summary Statistics for airborne benzene samples collected between January 2003 and December 2006 for all Orange County sampling sites. All concentrations are µg/m^3.

	Site 2002
Number of Samples	**122**
Number Below MDL	**3**
MDL[a]	
Minimum	**0.35**
Maximum	**1.69**
Mean	**0.734**
Median	**0.67**
SD[d]	**0.291**
MDL/2[b]	
Minimum	**0.32**
Maximum	**1.69**
Mean	**0.726**
Median	**0.67**
SD[d]	**0.298**
MDL/√2[c]	
Minimum	**0.35**
Maximum	**1.69**
Mean	**0.728**
Median	**0.67**
SD[d]	**0.296**

[a] Values below the MDL were assigned the value of the MDL.
[b] Values below the MDL were assigned the value of the MDL/2.
[c] Values below the MDL were assigned the value of the MDL/√2
[d] Standard Deviation

Table 6: Summary Statistics for airborne benzene samples collected between January 2003 and December 2006 for all Pinellas County sampling sites. All concentrations are µg/m^3.

	Site 4	Site 18	Site 26
Number of Samples	**59**	**240**	**147**
Number Below MDL	**0**	**0**	**0**
Minimum	**0.35**	**0.16**	**0.26**
Maximum	**1.92**	**2.78**	**4.66**
Mean	**0.853**	**0.826**	**1.039**
Median	**0.73**	**0.73**	**0.93**
SD[a]	**0.378**	**0.444**	**0.629**

[a] Standard Deviation

3.2 Comparative Statistics for the Different Methods of Assigning Values to Measurements Below the MDL

As previously stated, the method used by the USEPA to assign values to measurements under the MDL is to divide the MDL by 2. Other, more conservative methods, are often used to assign these values including assigning the value of MDL or assigning the value of the MDL divided by the square root of 2. In order to determine if the differences in value assignment methodologies have a statistically significant impact on the derivation of the mean (and consequently the UCL-AM of the mean), a two-tailed, paired t-test was conducted to compare the data that resulted from using the USEPA methodology (MDL/2) with the data that resulted from using both the actual MDL and the MDL/√2. A statistically significant difference was considered to be evident at a p-value less than 0.05. These results are summarized for each site that contained values below the MDL, by county, in Tables 7 – 12.

Table 7: The results of paired t-tests for each site in Broward County. A p-value <0.05 indicates a statistically significant difference in mean concentration values due to assigning values to measurements under the MDL with an alternative methodology than that used by the USEPA (MDL/2).

	MDL/√2 (p-value)	MDL (p-value)
Site 1002	<0.001*	<0.001*
Site 2004	<0.001*	<0.001*
Site 3002	0.019*	0.018*
Site 5005	<0.001*	<0.001*

*** Indicates a statistically significant difference in the derivation of means by using the alternative methodology of assigning values below the MDL compared to the method used by the USEPA (MDL/2).**

Table 8: The results of paired t-tests for each site in Dade County. A p-value <0.05 indicates a statistically significant difference in mean concentration values due to assigning values to measurements under the MDL with an alternative methodology than that used by the USEPA (MDL/2).

	MDL/√2 (p-value)	MDL (p-value)
Site 29	0.098	0.101
Site 32	0.320	0.320

Table 9: The results of paired t-tests for each site in Orange County. A p-value <0.05 indicates a statistically significant difference in mean concentration values due to assigning values to measurements under the MDL with an alternative methodology than that used by the USEPA (MDL/2).

	MDL/√2 (p-value)	MDL (p-value)
Site 2002	0.0833	0.0833

The paired t-tests indicate that only the data collected in Broward County (sites 1002, 2004, 3002, 5005) are affected at a statistically significant level by using alternative methods of assigning values to measurements under the MDL in the exposure assessment. Consequently, only these sites will be presented with results calculated from alternative methods of assigning values below the MDL in subsequent analyses.

3.3 The Calculation of the 95% UCL-AMs using ProUCL

The 95% UCL-AMs for measured airborne benzene concentrations were calculated using ProUCL software. These values, which are used in the subsequent risk analysis, are summarized by site for each county in Tables 13 – 18. In Figures 2-7, the 95% UCL-AMs are charted for a side by side comparison of the relative exposure levels measured within each county. Figure 8 provides a side by side comparison of all the 95% UCL-AMs for all monitoring sites in the State of Florida. As three different methods were used to assign values to measurements below the Method Detection Limit (MDL), 95% UCL-AMs were produced for each method for relevant sites, and this is reflected in the following tables and figures.

Table 10: The 95% UCL-AMs for all measured airborne benzene concentrations in Broward County between 2003 and 2006 by Site. All concentrations are µg/m^3.

	Site 1002	Site 2004	Site 3002	Site 5005
Concentration (MDL)[a]	**0.88**	**0.94**	**2.75**	**0.77**
Concentration (MDL/√2)[b]	**0.87**	**0.93**	**2.75**	**0.75**
Concentration (MDL/2)[c]	**0.86**	**0.92**	**2.75**	**0.74**

[a] Values below the MDL were assigned the value of the MDL.
[b] Values below the MDL were assigned the value of the MDL/√2.
[c] Values below the MDL were assigned the value of the MDL/2.

Figure 8: Summary of the 95% UCL-AMs for Broward County monitoring sites for data collected from the years 2003 to 2006. Concentrations are expressed in µg/m^3.

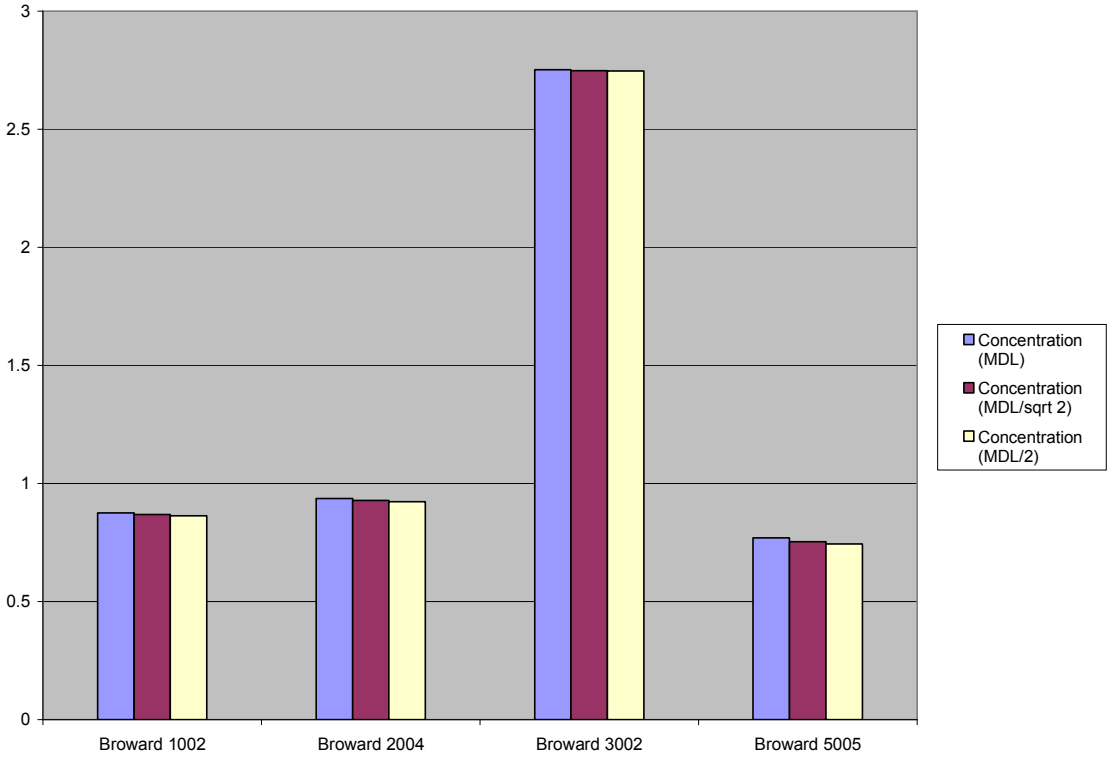


Table 11: The 95% UCL-AMs for all measured airborne benzene concentrations in Dade County between 2003 and 2006 by Site. All concentrations are µg/m^3.

	Site 29	Site 32
Concentration	**1.01**	**1.33**

Figure 9: Summary of the UCL-AMs for Dade County monitoring sites for data collected from the years 2003 to 2006. Concentrations are expressed in µg/m^3.

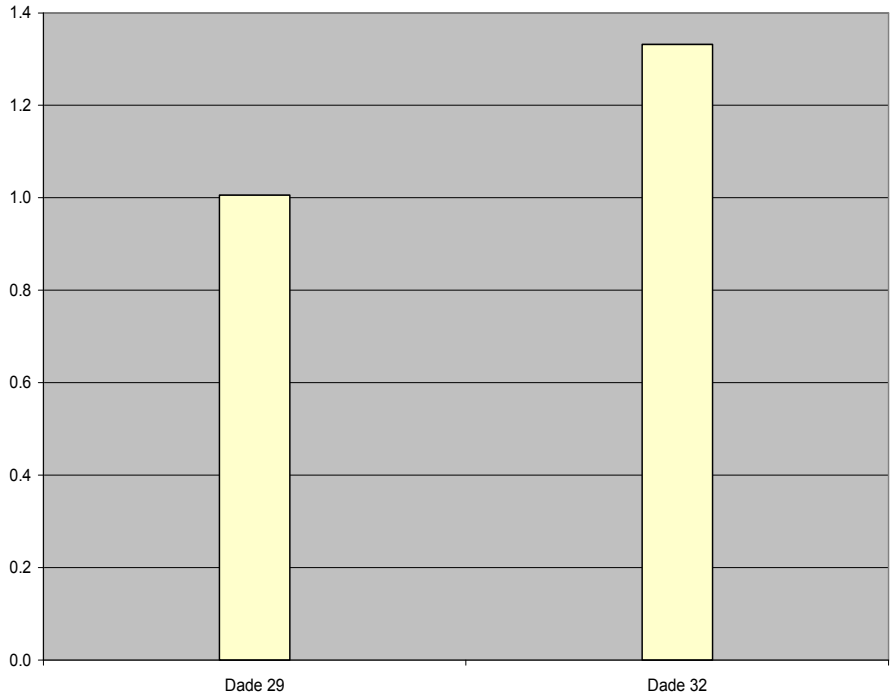


Table 12: The 95% UCL-AMs for all measured airborne benzene concentrations in Duval County between 2003 and 2006 by Site. All concentrations are µg/m^3.

	Site 32	Site 77	Site 80	Site 84	Site 100
Concentration	6.72	4.95	7.13	8.57	4.32

	Site 101	Site 102	Site 103	Site 104	Site 105
Concentration	11.18	11.45	5.94	4.67	8.63

Figure 10: Summary of the UCL-AMs for Duval County monitoring sites for data collected from the years 2003 to 2006. Concentrations are expressed in µg/m^3.

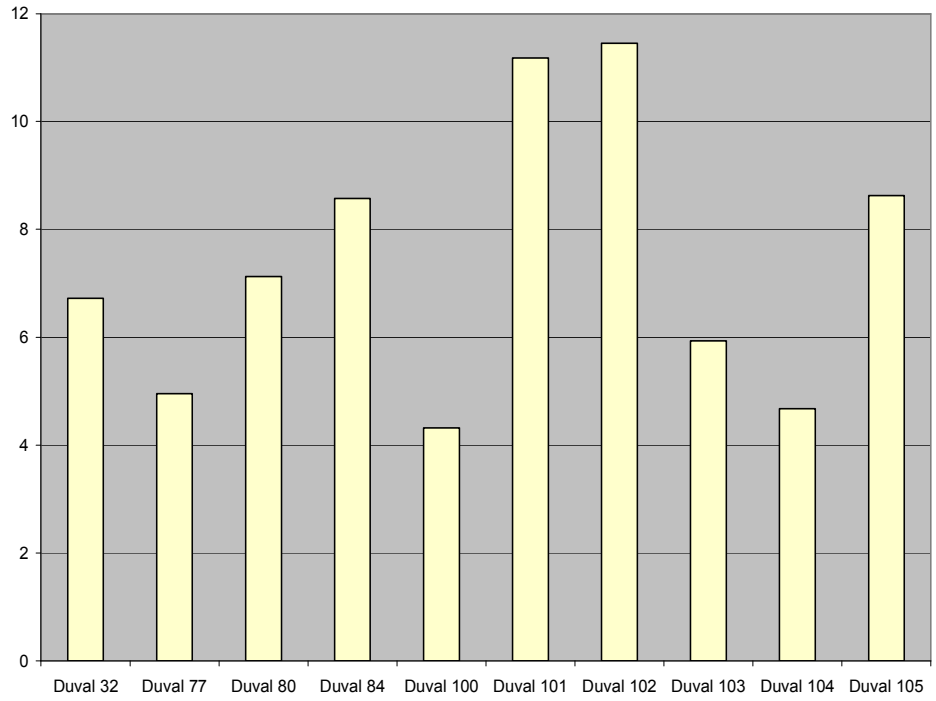


Table 13: The 95% UCL-AMs for all measured airborne benzene concentrations in Hillsborough County between 2003 and 2006 by Site. All concentrations are µg/m^3.

	Site 1065	Site 1075	Site 3002
Concentration	0.687	0.982	0.584

Figure 11: Summary of the UCL-AMs for Hillsborough County monitoring sites for data collected from the years 2003 to 2006. Concentrations are expressed in µg/m^3.

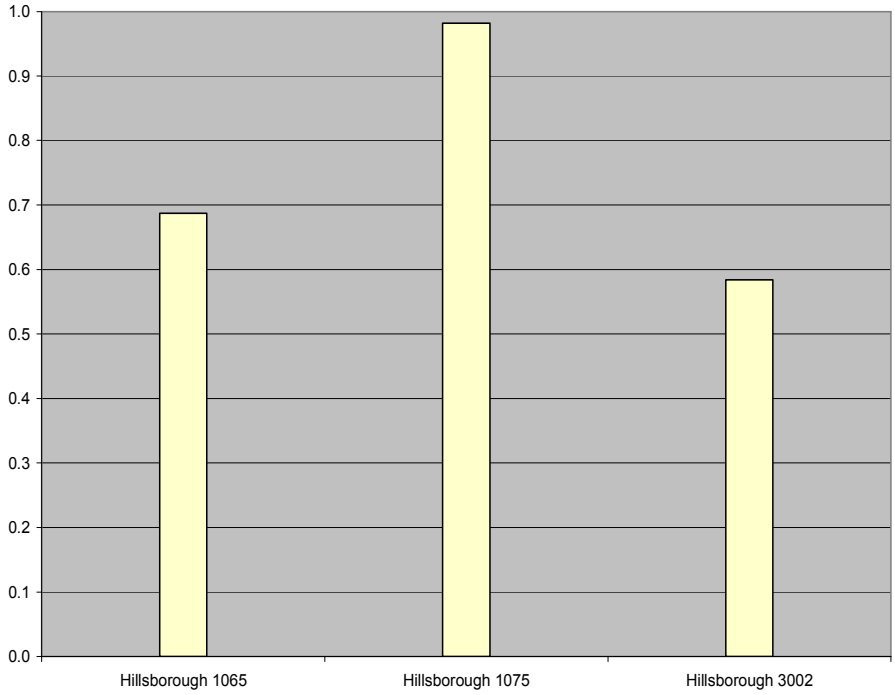


Table 14: The 95% UCL-AMs for all measured airborne benzene concentrations in Orange County between 2003 and 2006 by Site. All concentrations are µg/m^3.

	Site 2002
Concentration	0.771

Figure 12: Summary of the UCL-AMs for the Orange County monitoring site for data collected from the years 2003 to 2006. Concentrations are expressed in µg/m^3.

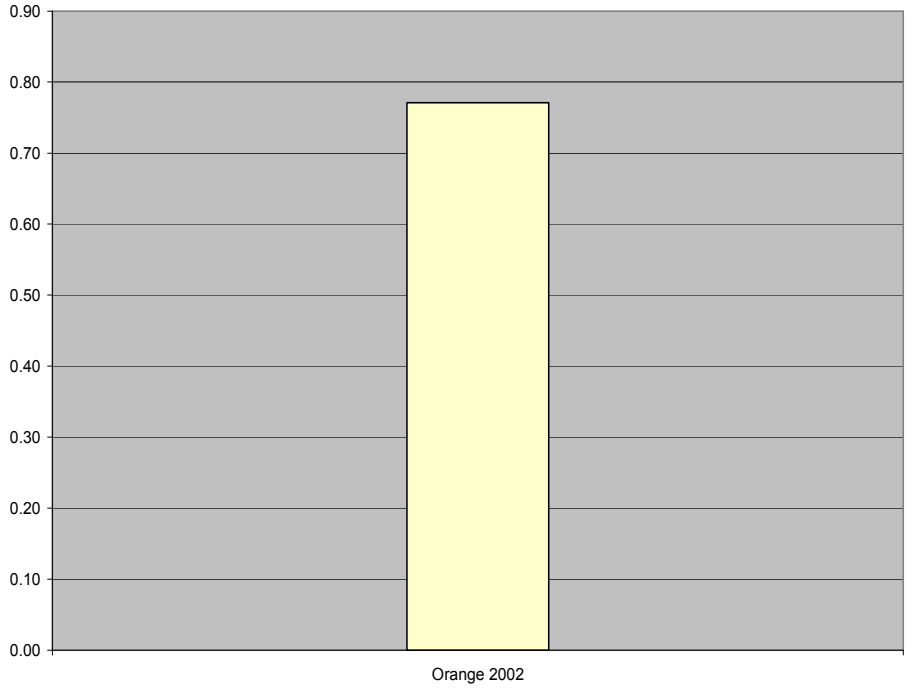


Table 15: The 95% UCL-AMs for all measured airborne benzene concentrations in Pinellas County between 2003 and 2006 by Site. All concentrations are µg/m^3.

	Site 4	Site 18	Site 26
Concentration	**0.938**	**0.885**	**1.265**

Figure 13: Summary of the UCL-AMs for Pinellas County monitoring sites for data collected from the years 2003 to 2006. Concentrations are expressed in µg/m^3.

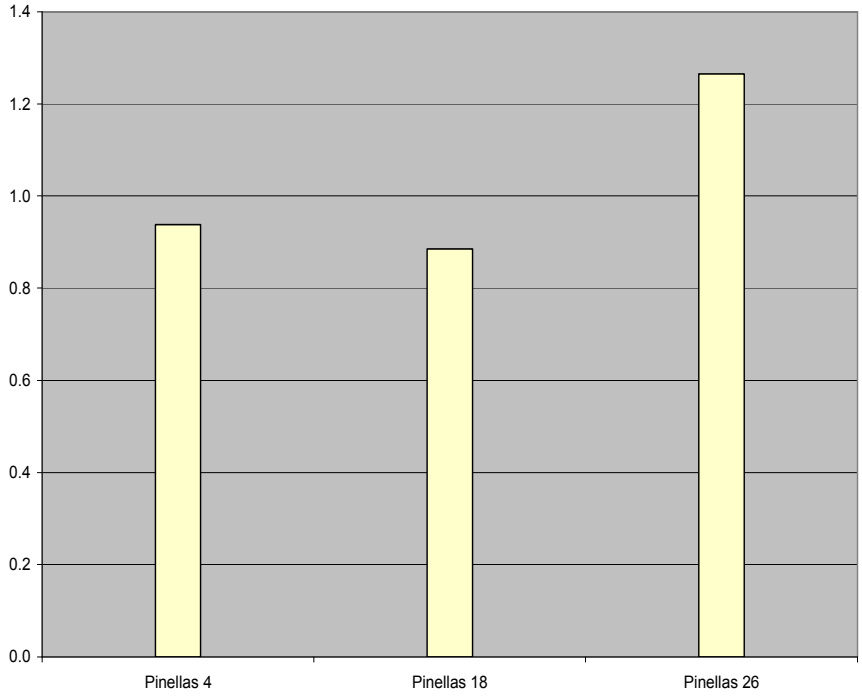
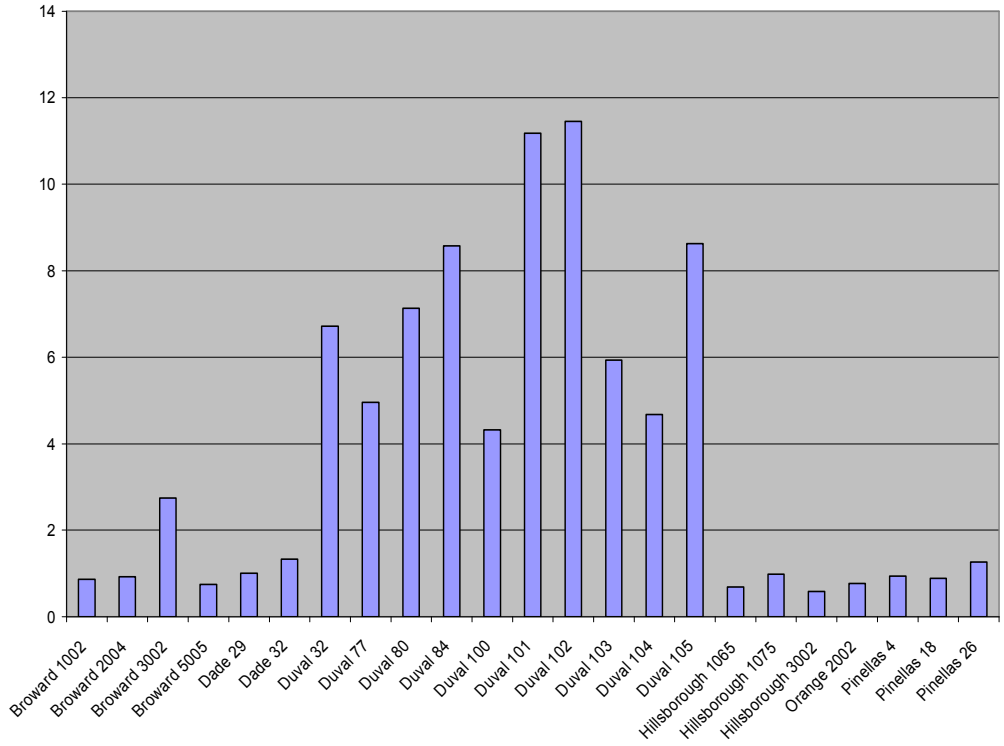


Figure 14: Summary of the UCL-AMs for all sites for data collected from the years 2003 to 2006. Concentrations are expressed in µg/m^3.



3.4 Risk Analysis

The risk analysis outcomes indicate that every monitoring site in the State of Florida measured benzene concentrations (based on the UCL-AMs) that are consistent with a lifetime (70 year) estimated cancer risk probability of greater than 1 x 10^{-6}. Risk values ranged from 4.56 x 10^{-6} to 8.93 x 10^{-5} using USEPA methodology for data treatment and analysis. Risk estimates are summarized for each site, by county, in tables 19 – 24. In Figures 9-14, risk estimates have been charted side by side, using the FLDEP regulatory limit of 1 x 10^{-6} as the baseline for reference. Figure 15 provides a side by side comparison for the risk estimates of all counties in the State of Florida, using the FLDEP regulatory limit of 1 x 10^{-6} as the baseline for reference. Risk estimates were also calculated for the monitoring data using both alternative

methods of assigning values to measurements below the MDL for relevant sites, and this is reflected in the following tables and figures.

Table 16: Lifetime cancer risk probability estimates for Broward County, by monitoring site, based on the measured concentrations of benzene from the years 2003 to 2006.

	Site 1002	Site 2004	Site 3002	Site 5005
Concentration (MDL)[a]	**6.83E-06**	**7.31E-06**	**2.15E-05**	**6.00E-06**
Concentration (MDL/√2)[b]	**6.77E-06**	**7.23E-06**	**2.14E-05**	**5.87E-06**
Concentration (MDL/2)[c]	**6.73E-06**	**7.19E-06**	**2.14E-05**	**5.80E-06**

[a] Values below the MDL were assigned the value of the MDL.
[b] Values below the MDL were assigned the value of the MDL/√2.
[c] Values below the MDL were assigned the value of the MDL/2.

Figure 15: Lifetime cancer risk probability estimates for Broward County, by monitoring site, based on the measured concentrations of benzene from the years 2003 to 2006. The baseline for this chart is 1 x 10^{-6}, the FLDEP's acceptable cancer risk.

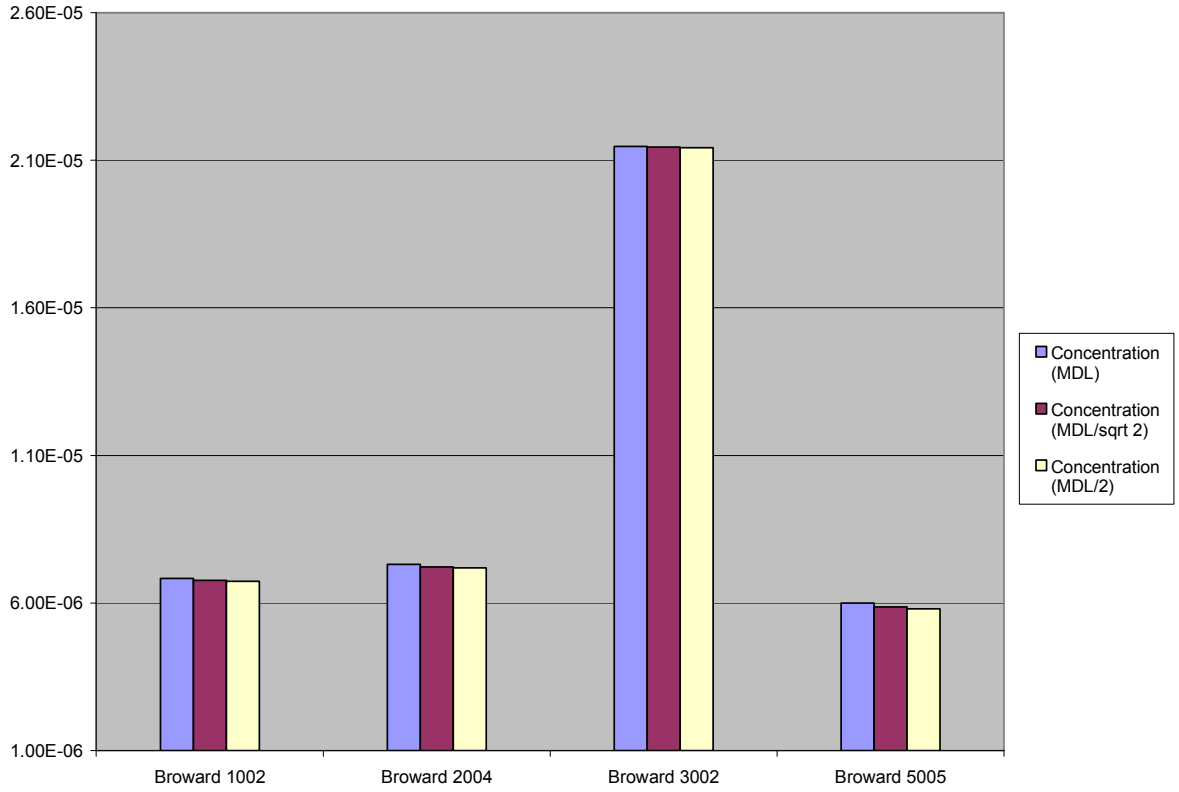


Table 17: Lifetime cancer risk probability estimates for Dade County, by monitoring site, based on the measured concentrations of benzene from the years 2003 to 2006.

	Site 29	Site 32
Concentration	7.85E-06	1.04E-05

Figure 16: Lifetime cancer risk probability estimates for Dade County, by monitoring site, based on the measured concentrations of benzene from the years 2003 to 2006. The baseline for this chart is 1 x 10^{-6}, the FLDEP's acceptable cancer risk.

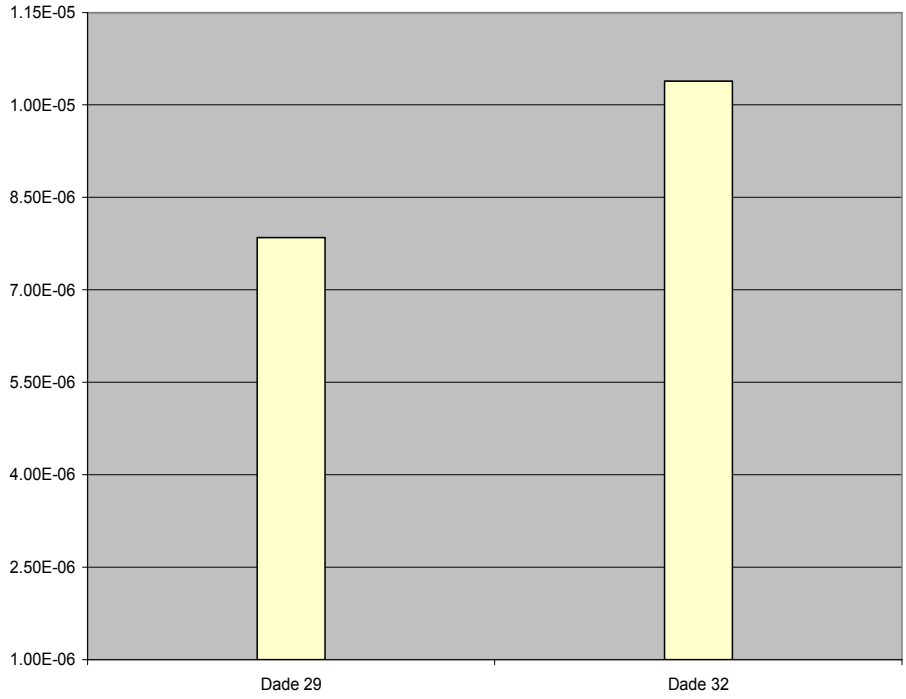


Table 18: Lifetime cancer risk probability estimates for Duval County, by monitoring site, based on the measured concentrations of benzene from the years 2003 to 2006.

	Site 32	Site 77	Site 80	Site 84	Site 100
Concentration	5.24E-05	3.86E-05	5.56E-05	6.69E-05	3.37E-05

	Site 101	Site 102	Site 103	Site 104	Site 105
Concentration	8.72E-05	8.93E-05	4.63E-05	3.65E-05	6.73E-05

Figure 17: Lifetime cancer risk probability estimates for Duval County, by monitoring site, based on the measured concentrations of benzene from the years 2003 to 2006. The baseline for this chart is 1 x 10^{-6}, the FLDEP's acceptable cancer risk.

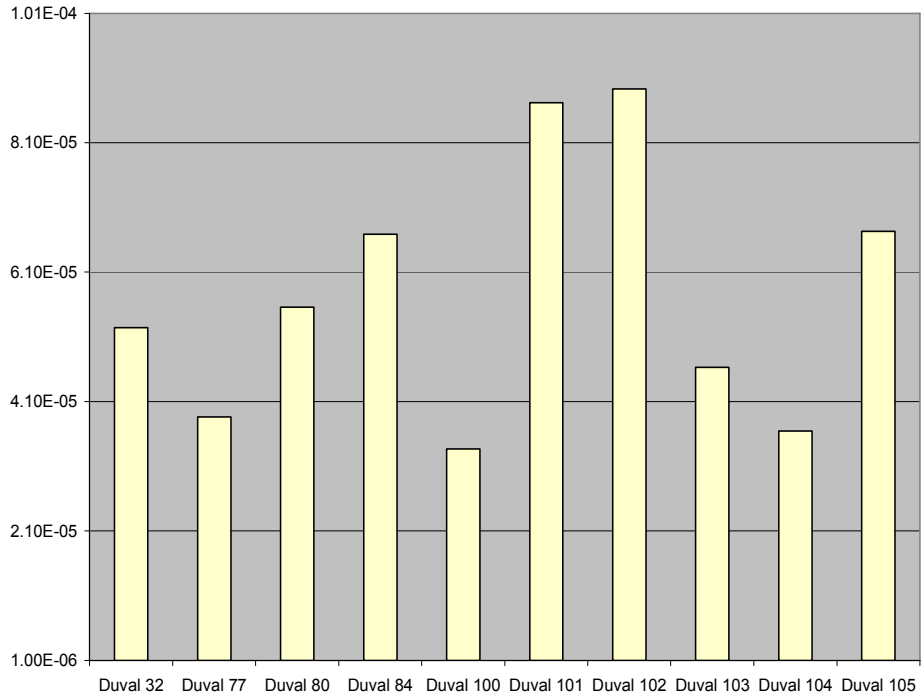


Table 19: Lifetime cancer risk probability estimates for Hillsborough County, by monitoring site, based on the measured concentrations of benzene from the years 2003 to 2006.

	Site 1065	Site 1075	Site 3002
Concentration	5.36E-06	7.66E-06	4.56E-06

Figure 18: Lifetime cancer risk probability estimates for Hillsborough County, by monitoring site, based on the measured concentrations of benzene from the years 2003 to 2006. The baseline for this chart is 1 x 10^{-6}, the FLDEP's acceptable cancer risk.

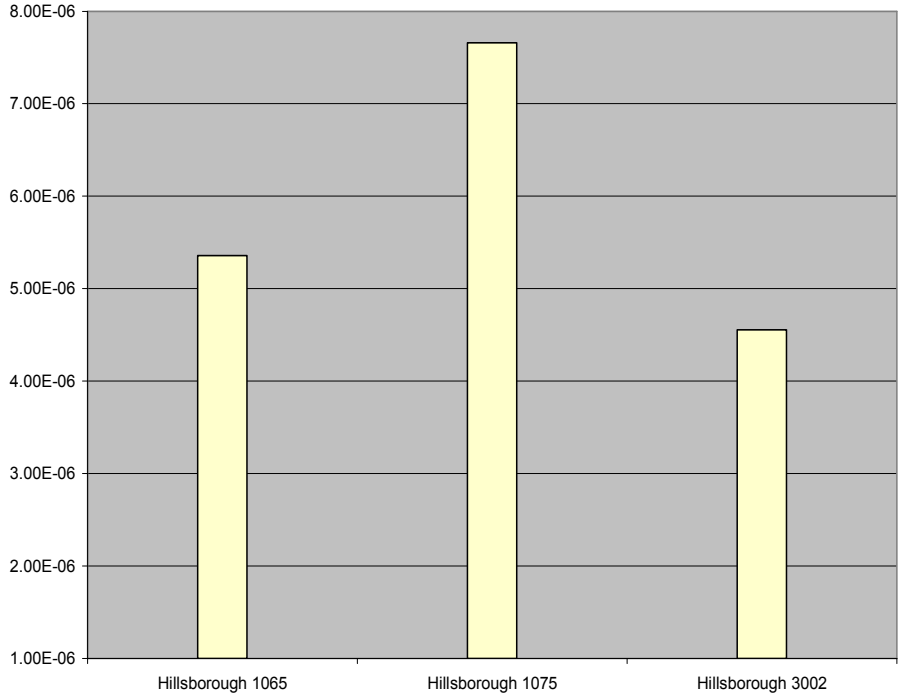


Table 20: Lifetime cancer risk probability estimates for Orange County, by monitoring site, based on the measured concentrations of benzene from the years 2003 to 2006.

	Site 2002
Concentration	6.01E-06

Figure 19: Lifetime cancer risk probability estimates for Orange County, by monitoring site, based on the measured concentrations of benzene from the years 2003 to 2006. The baseline for this chart is 1 x 10^{-6}, the FLDEP's acceptable cancer risk.

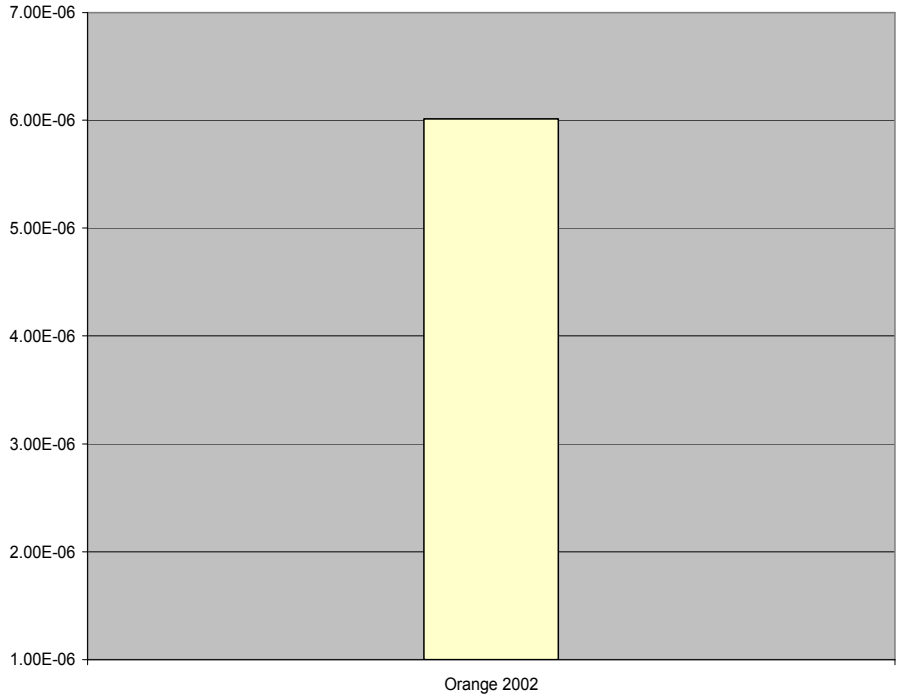


Table 21: Lifetime cancer risk probability estimates for Pinellas County, by monitoring site, based on the measured concentrations of benzene from the years 2003 to 2006.

	Site 4	Site 18	Site 26
Concentration	7.32E-06	6.90E-06	9.87E-06

Figure 20: Lifetime cancer risk probability estimates for Pinellas County, by monitoring site, based on the measured concentrations of benzene from the years 2003 to 2006. The baseline for this chart is 1 x 10^{-6}, the FLDEP's acceptable cancer risk.

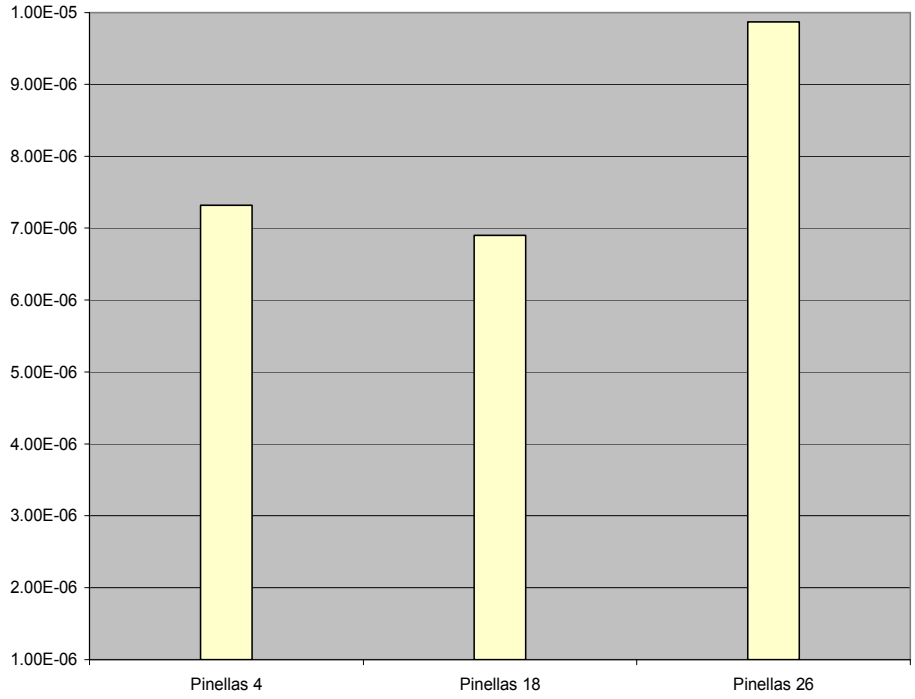
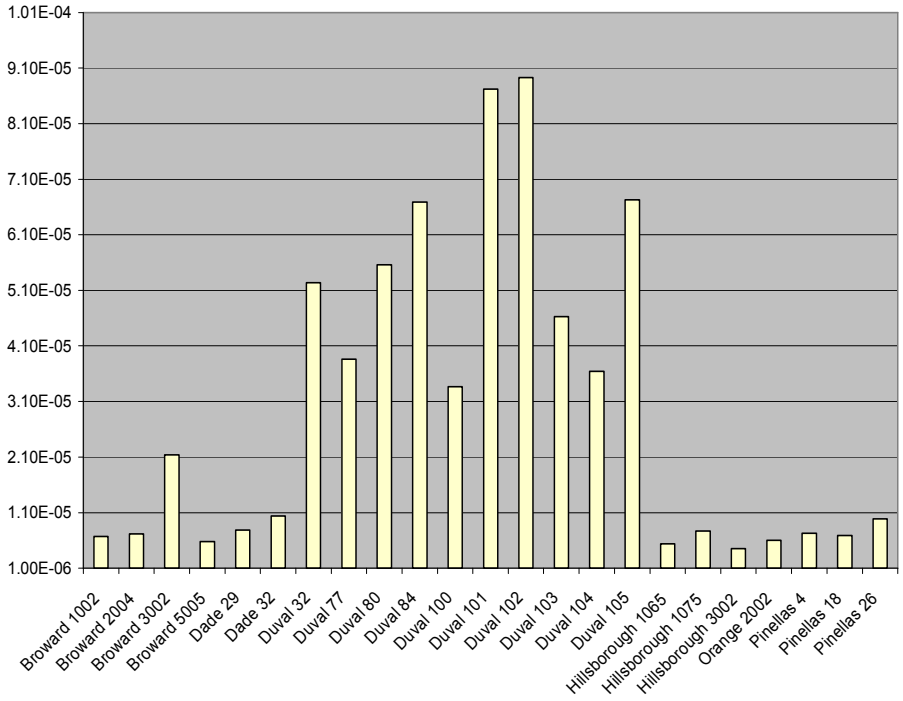


Figure 21: Lifetime cancer risk probability estimates for all counties, by monitoring site, based on the measured concentrations of benzene from the years 2003 to 2006. The baseline for this chart is 1 x 10^{-6}, the FLDEP's acceptable cancer risk.



3.5 Cumulative Lifetime Exposures in ppm-years

In order to compare the collected exposure data to epidemiological studies involving occupational cumulative lifetime benzene exposures, the UCL-AM concentrations must be converted from $\mu g/m^3$ to ppm, and then extrapolated into 70 year cumulative environmental lifetime exposures based on the ORD Workshop on Inhalation Risk Assessment methodology previously described. Cumulative lifetime exposures to benzene ranged from 0.04 ppm-years to 0.70 ppm-years. The extrapolated cumulative lifetime exposures for all sites, by county, are summarized in Tables 25 – 30. Figures 15 – 21 charts the side by side comparison of lifetime cumulative exposures for the monitoring sites within each county. Figure 22 charts the side by

side comparison of lifetime cumulative exposures for all monitoring sites in the State of Florida. Lifetime cumulative exposures were extrapolated for the monitoring data using both alternative methods of assigning values to measurements below the MDL for relevant sites, and this is reflected in the following tables.

Table 22: Extrapolated 70 year lifetime cumulative exposures for Broward County by monitoring site. All values are ppm-years.

	Site 1002	Site 2004	Site 3002	Site 5005
Cumulative exposure (MDL)[a]	**0.05**	**0.06**	**0.17**	**0.05**
Cumulative exposure (MDL/√2)[b]	**0.05**	**0.06**	**0.17**	**0.05**
Cumulative exposure (MDL/2)[c]	**0.05**	**0.06**	**0.17**	**0.05**

[a] Values below the MDL were assigned the value of the MDL.
[b] Values below the MDL were assigned the value of the MDL/√2.
[c] Values below the MDL were assigned the value of the MDL/2.

Figure 22: Extrapolated 70 year lifetime cumulative exposures for Broward County by monitoring site in ppm-years.

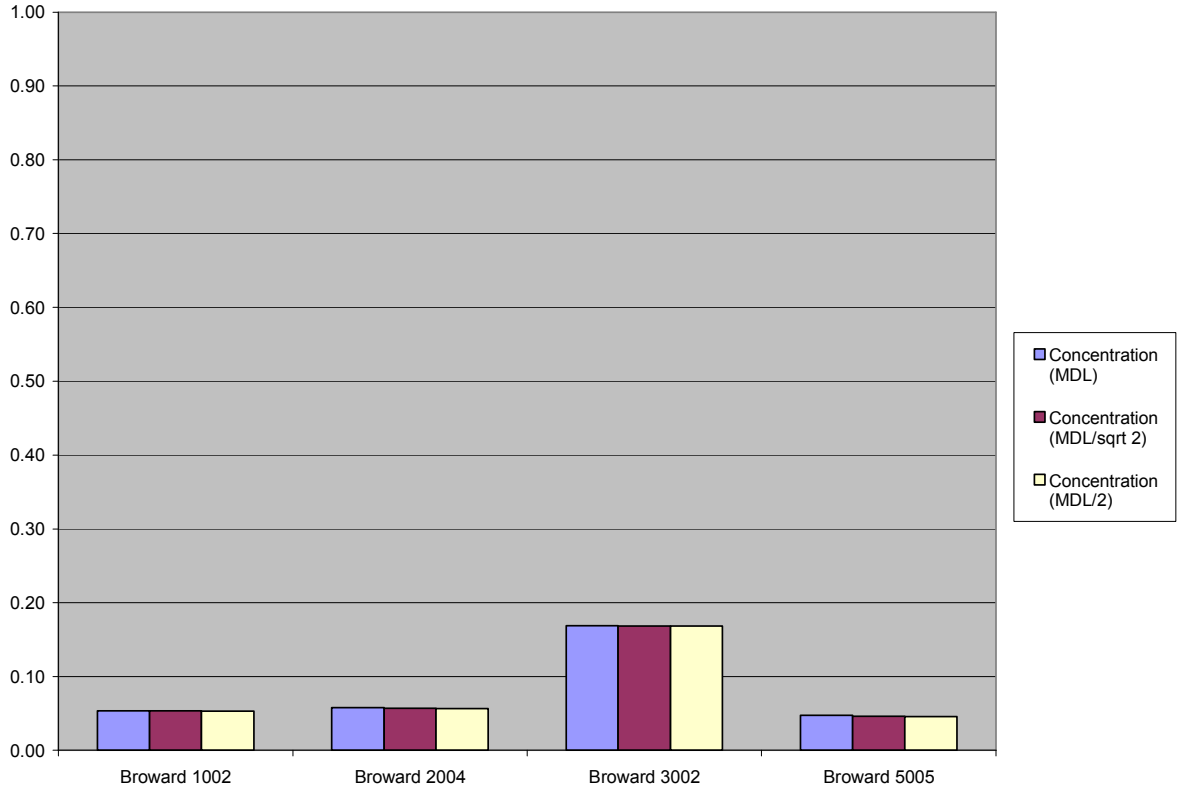


Table 23: Extrapolated 70 year lifetime cumulative exposures for Dade County by monitoring site. All values are ppm-years.

	Site 29	Site 32
Cumulative exposure	0.06	0.08

Figure 23: Extrapolated 70 year lifetime cumulative exposures for Dade County by monitoring site in ppm-years.

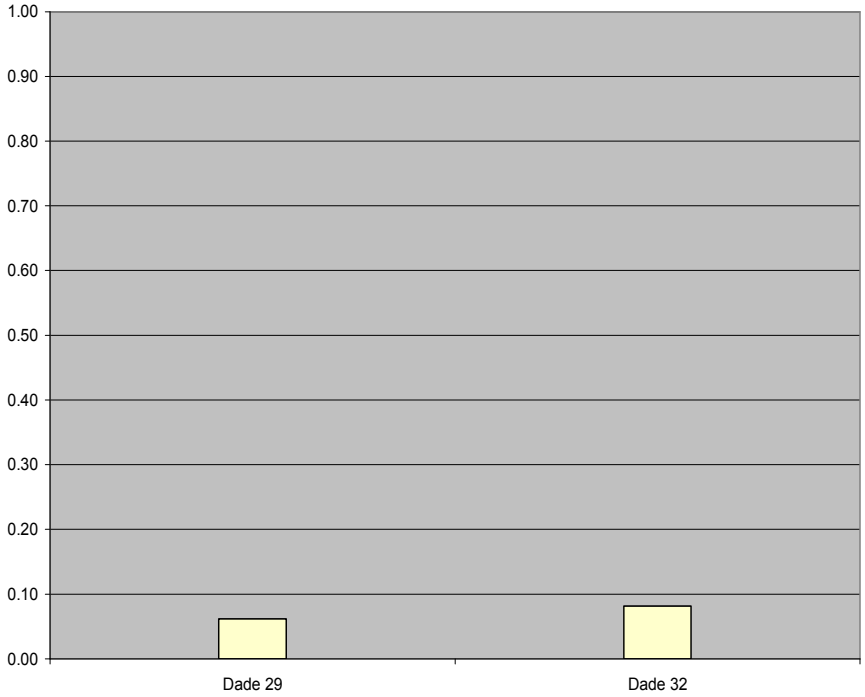


Table 24: Extrapolated 70 year lifetime cumulative exposures for Duval County by monitoring site. All values are ppm-years.

	Site 32	Site 77	Site 80	Site 84	Site 100
Cumulative exposure	0.41	0.30	0.44	0.53	0.26

	Site 101	Site 102	Site 103	Site 104	Site 105
Cumulative exposure	0.69	0.70	0.36	0.29	0.53

Figure 24: Extrapolated 70 year lifetime cumulative exposures for Duval County by monitoring site in ppm-years.

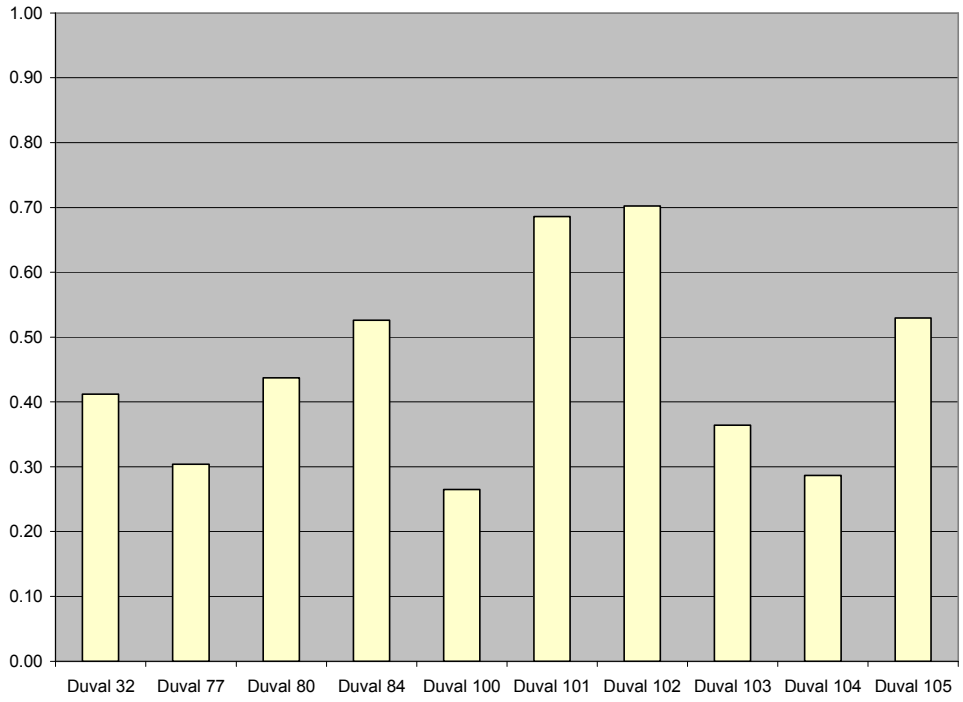


Table 25: Extrapolated 70 year lifetime cumulative exposures for Hillsborough County by monitoring site. All values are ppm-years.

	Site 1065	Site 1075	Site 3002
Cumulative exposure	0.04	0.06	0.04

Figure 25: Extrapolated 70 year lifetime cumulative exposures for Hillsborough County by monitoring site in ppm-years.

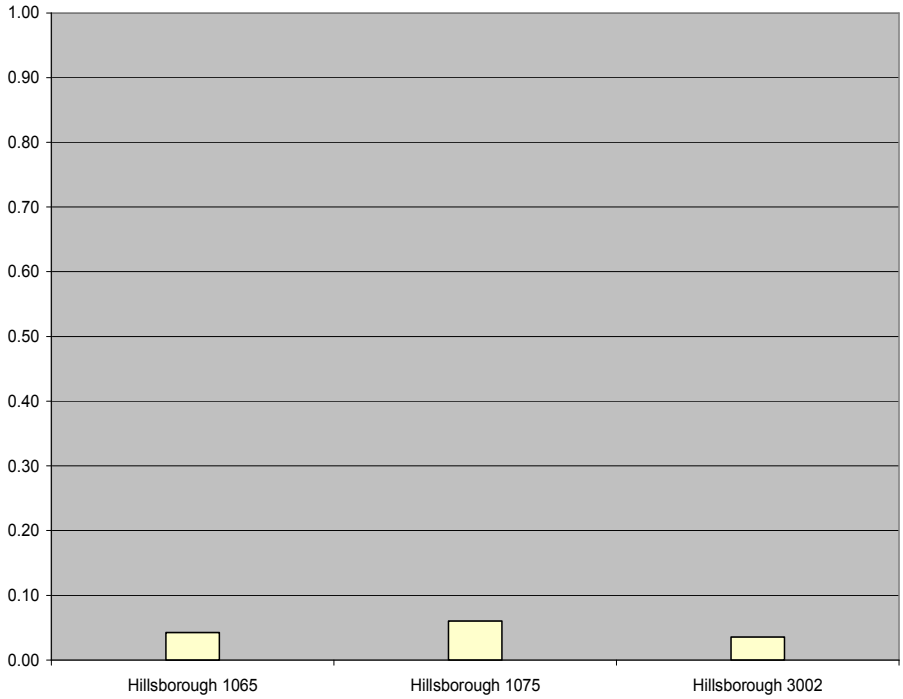


Table 26: Extrapolated 70 year lifetime cumulative exposures for Orange County by monitoring site. All values are ppm-years.

	Site 2002
Cumulative exposure	0.05

Figure 26: Extrapolated 70 year lifetime cumulative exposures for Orange County by monitoring site in ppm-years.

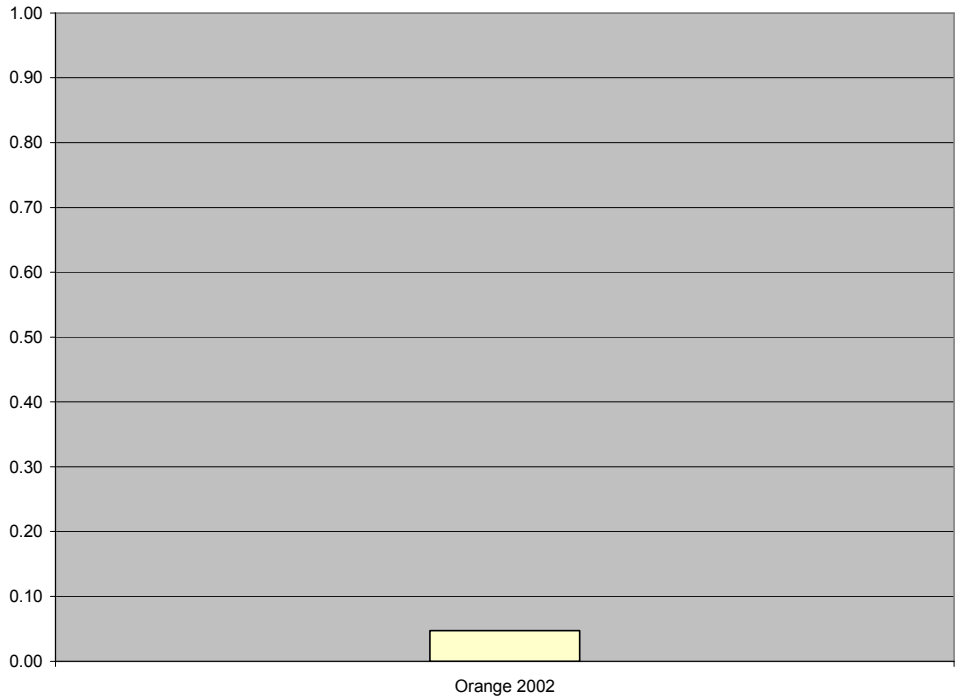


Table 27: Extrapolated 70 year lifetime cumulative exposures for Pinellas County by monitoring site. All values are ppm-years.

	Site 4	Site 18	Site 26
Cumulative exposure	0.06	0.05	0.08

Figure 27: Extrapolated 70 year lifetime cumulative exposures for Pinellas County by monitoring site in ppm-years.

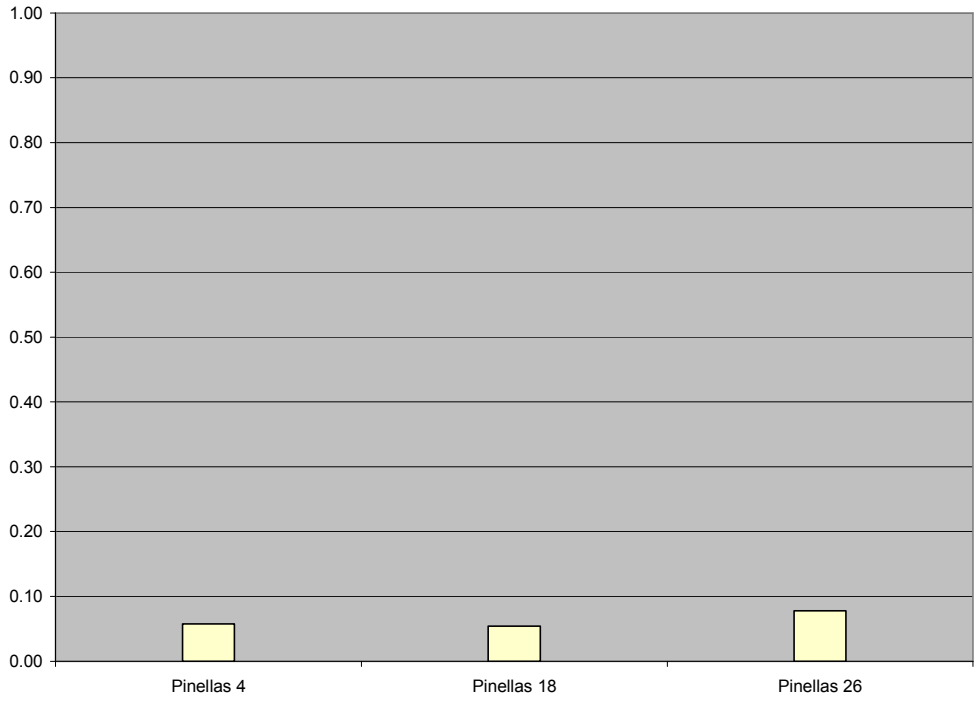
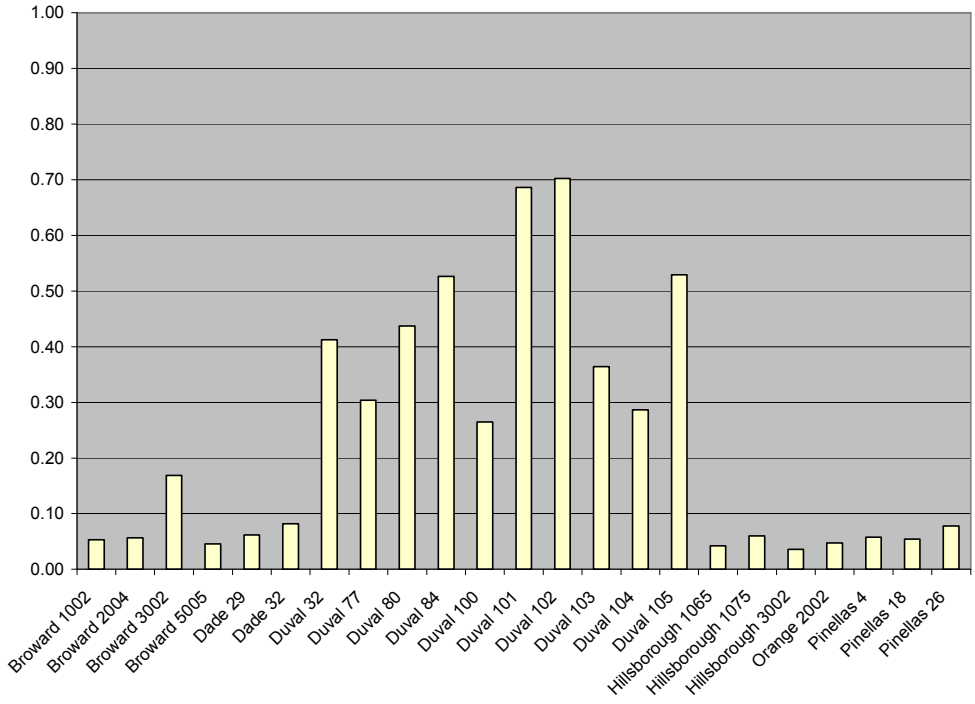


Figure 28: Extrapolated 70 year lifetime cumulative exposures for all counties by monitoring site in ppm-years.



3.6 Comparative Risk Analysis with Occupational Cohorts

A review of published literature examining the relationship between discreet ranges of occupational benzene exposure and leukemia is summarized in Table 31. For all studies, the highest exposure category that did not result in a statistically significant association between benzene and leukemia was considered the No Observable Adverse Effect Level (NOAEL) for that study. For all studies, the lowest exposure category that resulted in a statistically significant association with leukemia was considered the Lowest Observable Adverse Effect Level (LOAEL). No studies were discovered that established a relationship between benzene and leukemia outcomes for cumulative exposures below 1 ppm-years.

Table 28: The No Observable Adverse Effect Levels (NOAEL) and the Lowest Observable Adverse Effect Levels (LOAEL) for all studies used in the comparative risk analysis.

Study	Measure of Association	NOAEL	LOAEL	Evidence for association between leukemogenesis and cumulative exposures under 1 ppm-years
Swaen et al. 2005	SMR	401.5 ppm-years	N/A[a]	NO
Seniori et al. 2003	SMR	100-199 ppm-years	>200 ppm-years	NO
Guenel et al. 2002	OR	≥5.5 - <16.8 ppm-years	≥16.8 ppm-years	NO
Rushton et al. 1997	OR	>45 ppm-years	N/A[a]	NO
Wong et al. 1995	SMR	40-200 ppm-years	200-400 ppm-years	NO
Collins et al. 2003	SMR	>6 ppm-years	N/A[a]	NO
Paxton 1996	SMR	>5-50 ppm-years	>50-500	NO
Glass et al. 2006	OR	Not Reported	>8 ppm-years	NO
Glass et al. 2003	OR	>1-2 ppm-years	>2-4 ppm-years	NO
Hayes et al. 1997	RR	<40 ppm-years	40-99 ppm-years	NO
Rinsky et al. 1987	SMR	40-200 ppm-years	200-400 ppm-years	NO
Schnatter et al. 1996	OR	20-219.8 ppm-years	N/A[a]	NO

Wong and Gerhard 1995	**SMR**	**40-200 ppm-years**	**200-400 ppm-years**	**NO**

SMR = Standardized Mortality Ratio, OR = Odds Ration, RR = Risk Ratio

[a]N/A indicates no association between cumulative lifetime benzene exposure and leukemia was found in this study.

Chapter 4.0: Discussion

4.1 USEPA Risk Assessment for Benzene

Using the USEPA Risk Assessment for Carcinogens methodology, the 70 year lifetime risk of developing cancer from the exposure levels measured in this study exceed the Florida DEP's acceptable risk of 1×10^{-6} for all sites. In order to determine what these results mean in terms of actual cancer outcomes that may result from this exposure, it is necessary to examine the nature of regulatory risk assessment and its limitations. Further, a comparison between historical and contemporary epidemiological studies must be conducted to determine if the risks suggested by the risk analysis using the USEPA Risk Assessment for Carcinogens methodology are consistent with empirical evidence.

The basis for the model used to perform risk analysis for inhalational exposure to benzene used by both the USEPA and FLDEP is published by the USEPA Integrated Risk Information System (IRIS) (48). The risk model currently employed produces risk probabilities specifically for the leukemia "tumor type", based primarily on data gathered from the Pliofilm Rubber Factory cohort in a study of workers occupationally exposed to benzene, originally described by Infante et al. 1977 (10). The data from this cohort is considered the be the highest quality amongst all current studies examining the relationship between benzene exposure and leukemia as it has a sufficient sample size to provide adequate statistical power, the least amount of

uncontrolled ancillary exposures that may result in confounding, and the most accurate exposure assessment compared to other occupational cohorts. This is not to say, however, that the exposure assessment conducted in this cohort is absolutely precise, in that the direct measurements of exposure do not describe the entirety of all working lifetime exposures. Several exposure matrices have been proposed, based on job classification, time spent on the job, and employment duration, combined with direct exposure measurements to estimate the cumulative exposures of the Pliofilm workers. USEPA IRIS identifies the exposure matrices proposed by Crump and Allen 1984 and Paustenbach et al. 1993 to be the most compelling estimates of cumulative exposure, and present both resulting models in their risk analysis methodology (48, 113-114). As the model resulting from the Paustenbach et al. 1993 is the more conservative exposure matrix (which results in a risk model that produces higher risk values than the model based on the Crump and Allen 1984 exposure matrix), it is the model commonly employed by regulatory agencies, including the FLDEP (113-114). The resulting IUR of 7.8×10^{-6} has been used to calculate risk probabilities in the current research (48).

The second mitigating factor in the estimation of risk is the use of the linearized multistage model to extrapolate risk values for exposures below that of which exposure data actually exists. In the USEPA Guidelines for Carcinogen Risk Assessment, the following qualification is indicated for risk probabilities produced using the linearized multistage model:

"It should be emphasized that the linearized multistage procedure leads to a plausible upper limit to the risk that is consistent with some proposed mechanisms of carcinogenesis. Such an estimate, however, does not necessarily give a realistic prediction of the risk. *The true value of the risk is unknown, and may be as low as zero*." (110)

In the current dissertation, the above qualification is pointedly relevant to the interpretation of the outcomes associated with the risk analysis of ambient airborne benzene levels measured throughout the State of Florida. As we compare the risk values produced in this research with actual exposure/outcome data present in the scientific literature, it will become apparent that the true value of risk associated with these measured exposure levels, is in fact, *almost certainly zero*.

4.2 Comparative Analysis

Rinsky et al. 1981, 1987 produced one of the first epidemiological studies describing discrete categories of cumulative exposures to benzene and associated cancer outcomes that had both a sufficient sample size to produce statistically significant results and a limited amount of confounding chemical exposures (45, 115). As indicated in Table 31, the NOAEL found in that research fell in the category of 40-200 ppm-years of exposure. As a result of the risk model proposed by Rinsky et al. 1981, 1987 the data from this cohort has been scrutinized by several other researchers including Crump and Allen 1984, Crump 1994, Paustenbach et al. 1993, and Wong 1995 with the intent of evaluating both the exposure matrix used by Rinsky et al. 1981, 1987 as well as the methodology used to develop a risk model (45, 113, 115-117). While all authors who evaluated the Rinsky et al. 1981, 1987 exposure estimates deemed them to underestimate the actual exposures experienced by the

cohort, when evaluating the association between the same discreet categories used by Rinsky et al. 1981, 1987, they produced similar results, in that no statistically significant association was found between cumulative exposures ranging between 40-200 ppm-years (or below) and leukemogenesis (45, 113, 115-117).

Several authors who have evaluated this cohort have been quite specific in noting the evidence to support the supposition that benzene is a threshold carcinogen (though the actual threshold is still debated). Paxton 1996 used the exposure estimates of Rinsky et al. 1987, Crump 1994, and Paustenbach et al. 1993 to compare the association of benzene cumulative exposures to leukemias using different exposure categories for comparison than previous studies (45, 113, 116, 118). With any exposure matrix used in previous studies, she found no association between benzene and leukemia at cumulative exposures below 50 ppm-years, indicating: "The newly gathered information continues to be consistent with a threshold model for leukemogenesis by benzene" (118).

Wong 1995 used the data from this cohort to analyze the association between leukemia (specifically AML), multiple myeloma, and cumulative exposure to benzene (117). The results indicated no association exists for any cumulative exposure and multiple myeloma, while the association between cumulative benzene exposures and AML were confined to exposures exceeding 200 ppm-years (117). Wong 1995 indicates that the concept of specificity has largely been ignored in the causal analysis for this exposure/disease relationship, noting:

"Three decades ago, Hill set forth criteria for assessment of causation. The same criteria were used in evaluating cancer risks related to tobacco in the Surgeon General's report on smoking, and by the International Agency for Research on Cancer in evaluation of carcinogenicity. Specificity is one of the major criteria for causation analysis. The analysis specific to AML presented in this report shows the importance of taking specificity into consideration. Previous analyses based on all leukaemia cell types combined have incorrectly set the estimated threshold too low but underestimated risk above the threshold. The estimated threshold specific to AML was found to be at least 200 ppm-years based on one set of exposure estimates; and much higher, had other exposure estimates (most likely more accurate) been used" (117).

Another large benzene cohort exists, consisting of Chinese industrial workers, which is currently under study (47). While this cohort is larger than the pliofilm cohort, significant criticisms have prevented the research from being considered in the creation of regulatory levels, as is indicated by the USEPA IRIS:

"Although the ongoing Chinese cohort studies (Dosemeci et al., 1994; Hayes et al., 1996, 1997; Yin et al., 1987, 1989, 1994, 1996) provide a large data set and perhaps may provide information in the future to better characterize risk of cancer at low dose exposure, their use in the derivation of risk estimates remains problematic at present…Limitations of this study include possible concurrent exposures to many different chemicals found in the factories where the benzene exposure occurred. There is a lack of reliable exposure information in the early days of the observation period, when only 3% of the exposure estimates were based on actual measurements…The limitations of these studies, except for Rinsky et al. (1981, 1987), preclude their use in quantitative risk estimation" (48).

Despite these issues, research based on this cohort does provide some valuable evidence towards the discovery of a threshold level of cumulative lifetime benzene exposure, below which there is no association with leukemogenesis. Hayes et al. 1997 provides a comprehensive analysis of the Chinese worker cohort, which produced no statistically significant associations between <40 ppm-years of cumulative benzene exposure and leukemia, non-Hodgkin's lymphoma, acute

lymphocytic leukemia, acute lymphocytic leukemia and myelodysplastic syndromes, or other leukemias (47).

Hayes et al. 1997 did find a statistically significant association when they compared all hemotologic neoplasms to their lowest cumulative exposure group (<40 ppm-years). In light of the circumstances surrounding that finding, it is difficult to regard it as meaningful, in terms of assigning a causal association between low levels of cumulative benzene exposure and hemotologic neoplasms. As was noted by USEPA IRIS, and is confirmed by Hayes et al. 1997, the workers in this cohort were exposed to a variety of industrial manufacturing solvents, which could not be controlled for in analysis (47-48). As well, to reiterate the proposition made by Wong 1995, specificity is often overlooked in the assessment of causal associations between exposures and diseases; and in this case, we have an association which is neither specific in terms of exposure, nor in terms of disease (119). As well, when the dose response for increasing levels of exposure is examined for this disease category, a dose response is notably absent. The Risk Ratios for each in increasing exposure category were reported as: 2.2 (<40 ppm-years), 2.9 (40 – 99 ppm-years), and 2.7 (≥100 ppm-years), displaying no clear increase of risk with relatively large increases of cumulative exposure (47). The lack of dose response found in this study is also evident in the outcomes for leukemia. The Risk Ratios reported for leukemia were non-significant at (<40 ppm-years), 3.1 at (40 – 99 ppm-years), and 2.7 at (≥100 ppm-years) (47). It is not clear from these results that there is an increased risk of leukemia from 100 ppm-years of exposure compared to 40 ppm-years of exposure.

With a study cohort of 74,828 exposed workers, it is unlikely that sample size was limiting factor of the analysis; more likely, this lack of a robust dose-response is due to the fact that the cohort is made up of workers from a diverse field of industries which makes an accurate exposure assessment difficult (especially when the same methodology is used to assign exposures to workers in different environments), as well as making it nearly impossible to control for confounding chemical exposures. It is principally these reasons that the USEPA rejects the Hayes et al. 1997 data as being acceptable for developing quantitative risk analysis. In light of these shortcomings, it is fair to say that the pliofilm cohort provides clearer evidence of a threshold for leukemogenesis due to cumulative benzene exposure (somewhere between 50 – 200 ppm-years), whereas the Hayes et al. 1997 data suggests a threshold somewhere below 40 ppm-years (47-48). It is certain that the Hayes et al. 1997 data do not provide *any* evidence that there may be any risk of leukemogenesis at exposures below 1 ppm-years, and as well, do not provide strong evidence to contradict the threshold of $\geq$50 ppm-years found in the pliofilm cohort (45-48, 113, 115-117).

Wong and Gerhard 1995 conducted another cell type specific meta-analysis of leukemias associated with cumulative benzene exposures in a cohort of petroleum workers from the United Kingdom and the United States (119). The results of this analysis were directly comparable to the findings in numerous analyses in the American pliofilm cohort. No statistically significant associations were found between any leukemia type and cumulative benzene exposures below 200 ppm-years (119). One of the major strengths of this study is the large sample size, including the

evaluation of 208,741 exposed workers (119). It should be noted that the authors indicate exposures may have been underestimated for some groups (especially those in the highest exposure groups) because in addition to their less well controlled working conditions, it is believed many workers were exposed more than 8 hours a day for a 5 day work week, which was the exposure standard used in the exposure assessment (119). This potential underestimation of exposure leads Wong and Gerhard 1995 to believe that risk at 200 ppm-years of cumulative exposure may actually be overestimated, and that the threshold for leukemogenesis may actually be much higher (119).

Rushton and Romaniuk 1997 performed a smaller case control study (91 exposed cases), also using petroleum workers from the United Kingdom (120). Workers in this study had significantly lower exposures than found in previously discussed studies, the highest exposure group evaluated being $\geq$45 ppm-years of exposure (120). The authors of this study were not able to find any association between cumulative benzene exposure and leukemia, supporting the previous findings that a threshold exists for cumulative benzene exposures exists for leukemogenesis, and that the threshold is in great excess of environmental levels (120).

Guenel et al. 2002 performed a small case control study (72 exposed cases) in Gas and Electric Utility Workers (121). These workers were typically classified has having much lower cumulative exposures than other occupational groups previously examined, with the highest exposure group being $\geq$16.8 ppm-years (121). The initial

findings of this study indicate a statistically significant association between all leukemias and cumulative benzene exposures of ≥16.8 ppm-years, however, further evaluation of this study diminishes the importance of this finding (121). The exposure assessment performed by Guenel et al. 2002 suffers from the common affliction found in the majority of epidemiological studies examining the relationship between benzene and leukemia: the potential underestimation of exposure levels (121). As is often criticized by other researchers examining this issue, low level exposures are not found to be specifically associated with any specific cell type, and this was apparent in Guenel et al. 2002 who failed to demonstrate any statistically significant association between cumulative benzene exposures and any specific leukemia, including AML, acute lymphoid leukemia, all chronic leukemias, chronic myeloid leukemia, and chronic lymphoid leukemia (121). Finally, when the odds ratio for all leukemias and cumulative exposure group of greater than 16.8 years is adjusted for confounding exposures (asbestos, chlorinated solvents, and coal tars), the estimated association loses statistical significance, and thereby also loses any utility as evidence for determining that low level cumulative benzene exposure is a causative agent for leukemia (121).

Glass et al. 2003, 2006 also attempts to find an association between low cumulative benzene exposure levels and various hemotopoietic cancers in a small case control study (79 total cases, 33 cases of leukemia) examining Australian petroleum workers (122-123). The authors report a statistically significant association between leukemias and cumulative benzene exposure at >2-4 ppm-years [OR = 6.1 (1.4–

26.0)], a non-significant association at >4-8 ppm-years [OR = 2.4 (0.4–13.6)], a significant association at >8-16 ppm-years [OR = 5.9 (1.3–27.0)], and a greatly elevated significant association at >16 ppm-years [OR = 98.2 (8.8–1090)] (122-123). The first notable weakness of these results is the inconsistency of dose response throughout the exposure categories (122-123). As almost all of the cases selected for this analysis fall into a narrow range of low level exposures, if a true association existed at these exposure levels, one would expect a clear dose-response to be apparent when the cumulative exposure essentially doubles by every increasing exposure category (122-123). As the results are presented, it is clear this is not the case. In fact, due the extreme variance in the data, it is difficult to determine if a dose-response is occurring between any levels of exposure, even the between the two highest categories (122-123). While superficially, it may seem that a quantifiable increase is occurring between the >8-16 ppm-years exposure level (OR = 5.9) and the highest exposure level of >16 ppm-years (OR = 98.2), an examination of the extensive confidence intervals associated with those OR point estimates indicates two important characteristics of these data (122-123). Firstly, the point estimates for these are relatively meaningless (especially for the highest exposure group), as there is equal probability that the point estimate indicated by the regression model could actually be any value within the 95% confidence interval (122-123). Therefore, the actual strength of association presented in these results is unknown. Secondly, the width of the confidence intervals show a significant amount of overlap between the outcomes of the last two exposure groups, indicating that while the point estimates would seemingly suggest a tremendous dose response from 5.9 to 98.2, it is actually

impossible to ascertain whether or not such a large dose-response is occurring in this study, or if any dose-response relationship exists at all at these levels of exposure (122-123).

Perhaps the greatest criticism that could be made of this research is the exposure assessment methodology. The authors disclose that they used essentially the same methodology of assigning exposure to workers exposed after 1975 as workers exposed before 1975 as a result of "uncertainty about exposures before 1975" (123). By doing this, the authors have undoubtedly underestimated exposures in this study by not accounting for changes in workplace practices and regulations that would have led to significantly different exposure levels in the workplace. In some cases, they have attributed more current exposure levels to workers whose principle exposures occurred before 1975, which for some workers, represented of 30 or more years of their exposure duration (122-123)!

It is obvious that the exposure assessment of the cohort used in Glass et al. 2003, 2006 has not been scrutinized to the degree that the more highly regarded exposure assessment in the pliofilm cohort has. The research by Glass et al. 2003, 2006 essentially represents 33 cases of leukemia that produce widely variant measures of association, no definitive dose response, and an analysis based on an exposure assessment that almost certainly underestimated worker exposure to a significant degree (122-123). In addition, these results are a unique finding, which have failed to be replicated by other researchers. Without addressing these key factors, this research

cannot provide adequate evidence to invalidate the threshold exposure level of $\geq$50 ppm-years as found in the pliofilm cohort, and without question, the evidence provides no support to the supposition that there may be a risk of leukemogenesis when exposed to 1 ppm-years or less of airborne benzene.

There have been several other recent epidemiological studies evaluating the relationship between benzene exposed workers and leukemogenesis, including Collins et al. 2003, who specifically evaluated low level cumulative exposures in their analysis (124). Collins et al. 2003 examined a cohort of 4417 chemical plant workers with cumulative exposure categories of: unexposed, less than 1 ppm-years, 1-6 ppm-years, and >6 ppm-years (124). No association between cumulative benzene exposure and leukemia could be established for any exposure group, the authors noting, "The dose rate of benzene and a threshold for exposure response may be important factors for evaluating lymphohaematopoietic risk (124)."

Seniori-Constantini et al. 2003 evaluated benzene exposure and leukemia deaths amongst 1687 exposed shoe factory workers (125). To make their results comparable to the findings of other larger cohorts, specifically the Pliofilm cohort (Rinsky et al. 1987, Paustenbach et al. 1993, Crump 1994, Paxton 1996), similar exposure categories were evaluated; that of <40 ppm-years, 40-99 ppm-years, 100-199 ppm-years, and >200 ppm-years (45, 113, 116, 118, 125). Seniori-Constantini et al. 2003 failed to find an association between cumulative benzene exposure and leukemia at any exposure level except for those exposed to more than 200 ppm-years. These

results are in direct agreement with those found in the pliofilm cohort, clearly supporting historical evidence of a threshold for benzene exposure and leukemogenesis (125).

Swaen et al. 2005 evaluated 311 Caprolactam workers in the Netherlands with benzene exposure (126). The authors of this study chose to divide their exposure categories into the mean cumulative exposures for each tertile (126). The mean cumulative exposures for each tertile were 3.4 ppm-years, 68.8 ppm-years, and 401.5 ppm-years (126). The results of this analysis did not find an association between benzene exposure and excess leukemia (126). An obvious weakness of this study is the small sample size of the cohort, though using the tertile divisions created exposure categories that were nearly equivalent in size from the first to the third quartile (n = 94, 88, and 93 respectively) (126). While this study admittedly does not share the degree of statistical power found in previous studies, it certainly adds to the weight of evidence supporting a threshold level of benzene exposure below which there is no risk of leukemogenesis, and as well, this study contributes evidence to the supposition that this threshold exists at or above 50 ppm-years (126).

Similarly, Schnatter et al. 1996 performed a case control study with a small group of Canadian petroleum workers (14 cases) to evaluate the relationship of their benzene exposure and leukemia (127). The cumulative benzene exposures ranged from 0 to 219.8 ppm-years (127). The authors attempted to assess various exposure categories to create the largest exposure groups possible, despite their small sample size, with

the highest exposed category being those with 20 to 219.8 ppm-years of exposure (127). The authors of this study failed to find an association between any exposure category and leukemia (127). Obviously, the small sample size would hinder the ability to find a significant association between cumulative benzene exposure and leukemia if it existed, but it is important to note that the sample size did provide enough statistical power to find statistically significant associations between smoking history, and a family history of cancer with leukemia (127). So, while this study does have significant limitations, it is consistent with the compilation of studies that examine cumulative lifetime benzene exposures (127).

The lifetime cumulative benzene exposures calculated in the current risk characterization, extrapolated from the measured exposures from each monitoring site, ranged from 0.04 ppm-years to 0.70 ppm-years. Based on the weight of scientific evidence presented, which indicates that the threshold for leukemogenesis exists at or above 50 ppm-years of cumulative lifetime benzene exposure, it can be seen that the measured exposures in this study are approximately 50 to 1000 times lower than cumulative exposures that are capable of producing leukemogenesis. Without exception, no research to date has found evidence of an association between leukemogenesis and the lifetime cumulative benzene exposures measured in this study, of which all fall below 1 ppm-years.

Another finding in the scientific literature that is of direct interest to the current risk characterization is that of the relationship between peak exposure concentrations in

addition to cumulative lifetime exposure as a driver for leukemogenesis. Several authors have noted that in addition to a significant cumulative exposure ranging from 50 to greater than 200 ppm-years, an extended period of peak exposure must also be experienced in order for leukemogenesis to occur. Schnatter et al. 1996b found that leukemia cases were associated with extended exposures of 20 – 25 ppm using minimal exposure estimates, but potentially as high as 50 – 60 ppm using higher exposure estimates in addition to significant cumulative exposure (127). Collins et al. 2003 noted that there was no indication of risk from the low levels of cumulative exposure experienced by their cohort, but that increased risk could be attributed to those who were exposed to 100 ppm for 40 days or more (124). The maximum benzene level recorded in the State of Florida from 2003 to 2006, was 134.4 $\mu g/m^3$ (0.042 ppm) and can be found in Table 3 for monitoring site 102 in Duval County. When comparing these peak levels of exposure to those found in occupational settings that may be required to initiate, or otherwise drive leukemogenesis, it is clear that this potential mechanism for leukemogenesis does not come into play in terms of the ambient environmental exposures reported in this research.

4.3 Statistical Considerations for the Method Detection Limit

As is indicated in Table 7, the alternative methods of assigning values below the MDL did produce statistically different mean values for all monitoring sites in Broward County. This indicates that a considerable number of values within those data sets were reported as being under the method detection limit. The meaningfulness of this finding can be interpreted by examining the results of the risk

analysis and cumulative exposure analysis between these three data treatment methods.

In Table 19, the risk values produced for each monitoring site in Broward County are shown for all three methods of assigning values. The results for all sites, and all methods, are homogenous in the following: all methods produce risk values that are in excess of the 1 x 10^{-6} acceptable risk as indicated by the FLDEP. In fact, the differences in probabilities fall on the order of minutia, the largest difference occurring in the data from Site 5005 where the largest estimate of risk (assigning the MDL) equals 6.00 x 10^{-6} and the lowest estimate of risk (assigning the MDL/2) equals 5.80 x 10^{-6}. This represents a 0.2 millionth increase in risk using the more conservative method. In Table 25, the cumulative exposure values for all monitoring sites in Broward Country are shown. As values have been rounded to the nearest hundredth, no discernable difference is seen in the calculation of cumulative exposure, regardless as to which method has been used.

In Table 8 and Table 10, the t-test comparisons are shown for Dade County and Orange County, respectively. These results indicate that no statistically significant difference on the outcomes was produced regardless of what method of assigning values was used.

Tables 9, 10, and 12 show the t-test comparisons for Duval, Hillsborough, and Pinellas Counties, respectively. As no values below the method detection limit were reported for any monitoring sites in these counties, no statistical comparisons could

be made for methodological differences, and obviously, it can be said that values under the method detection limit had no influence in the risk analysis or cumulative exposure analysis for these any of these county's monitoring sites.

4.4 Study Limitations

A primary criticism of the current study may be the generalizability of the exposure assessment. Unfortunately, air toxics monitoring at this time is very limited, to the extent that few counties have active monitoring sites, and those that do, have very few monitors. While the ability to perform exposure and risk calculations based on actual sampling data has the advantage of using a validated methodology to enumerate airborne benezene concentrations, emissions modeling has the advantage of estimating exposures in locations that are not monitored. So with the data used in this dissertation, it is not possible assert that there are no locations within the State of Florida that are polluted with higher concentrations of benzene than are represented in this study. However, an examination of the monitor locations and the proximity of potential emission sources would indicate that the monitoring data used in this study represents an accurate cross section of typical ambient exposures in populated areas, with monitor locations ranging from more rural locations to more industrial locations, several within two miles of some of the largest benzene emission sources in their respective county. Indeed, when examining the monitor location maps (Figures 2-7) we find that the highest measured ambient levels are found in Duval County. Several of the Duval County monitors are located in dense Commercial/Industrial areas, and are consequently subjected to the benzene emissions from these point source

polluters. As well, most monitors are located near major roadways and highways, whose fugitive emissions from automobiles contribute significantly to the ambient levels of benzene.

Likewise, when we examine the lowest monitored levels, they are found in rural areas, such as Site 3002 in Hillsborough County (Figure 4) and in residential areas such as Site 5005 in Broward County, which are further removed from both fugitive and point source benzene emissions. While it is fair to say the exposure assessment performed in this study is not comprehensive, the results should provide a reasonable description of the exposure intensity for a large proportion of the general public.

It has been noted that Duval County uses a different sampling methodology than all other Florida Counties. At the same time, the results indicate Duval County measured the highest maximum levels, the highest mean levels, and maintained the largest variance in measurements of any county. Several Duval monitoring sites measured peak levels, mean levels, and standard deviations over an order of magnitude higher than sites in other counties (Table 3). A potential cause of these differences would be the shorter sample times (3 and 4 hour samples) sometimes used by Duval county. If samples are taken during peak emissions times for a 3 hour period, it would potentially overestimate the mean concentrations at that site. This is not clear evidence that the Duval County measurements are erroneous, and the higher mean levels may be explained by greater industrial and interstate highway density within that county; however the extreme variance found within the Duval County

may be indicative of poor sampling methodology that results in an over estimation of exposure. Even if this is the case, however, it does not affect the fundamental conclusions of this research.

All research is subject to limitations, the current research being no exception. However, the limiting factors in this research are not sufficient to warrant a rejection of the primary conclusions drawn from the study results.

Chapter 5.0: Conclusions

This investigation used historic airborne monitoring data from six counties in the State of Florida to characterize the cancer risk from airborne benzene concentrations used current Federal and State regulatory risk characterization methodologies, and a comparative risk analysis based on occupational epidemiologic evidence. Airborne benzene concentrations were collected from 23 air toxics monitoring stations in Broward, Duval, Orange, Miami-Dade, Hillsborough, and Pinellas counties during the years 2003-2006. Using the risk calculation methodology found in the EPA and the Florida Department of Environmental Protection (FLDEP) guidelines, the resulting cancer risk estimates ranged from 4.37×10^{-6} to 8.56×10^{-5}, which exceed the FLDEP's acceptable cancer risk level of 1×10^{-6} for all monitoring sites. The cumulative lifetime exposures were calculated in ppm-years, by site, and ranged from 0.036 - 0.702 ppm-years. A comparative analysis with available epidemiological literature revealed that the association between benzene exposure and cancer risk is related to cumulative exposure clearly in excess of 1 ppm-years, with a threshold of carcinogenesis potentially in excess of 50 ppm-years. The results of this investigation indicate that it is unreasonable to expect additional cancer cases in Florida residents due to measured ambient airborne benzene levels, despite the fact that all regulatory risk calculations exceed acceptable cancer risk levels in the State of Florida.

The implications of these results are highly relevant to contemporary practices of risk assessment and risk communication in terms of the economic consequences as well as the impact on public perception of risk from regulatory risk assessments. The FLDEP utilizes the same regulatory risk assessment methods found in this research to determine remediation levels for soil contaminated with benzene. The unit risk values used to analyze risk from soil intake or water intake resulting from contaminated soil is derived from the same cancer slope factor used for determining inhalation risk, a product of the linearized multi-stage model. Consequently, risk values for those two media have the same validity (or rather lack of validity) as those calculated for airborne exposures.

Gasoline fuel stations are common targets of soil remediation in Florida due to benzene contamination resulting in risk values above 1×10^{-6} for either soil or water intake. It has been reported that the typical gas station site costs $97,000 for soil treatment, with a range in costs from $22,000 to $260,000 (129). This money is spent under the assumption that by remediating the contaminated soil, a significant reduction to public health risk will be achieved. The results of the current research indicate that this is clearly not the case in any instance in which the soil or water benzene concentration results in a risk 1 to 2 magnitudes of order over the allowable limit using the regulatory risk analysis methodology. Under these circumstances, not only are economic resources essentially wasted, but over the course of 26 – 60 months (the typical remediation period) needless amounts of fuel is consumed, and needless amounts of combustant pollution is produced during this process (129).

Communicating health risk to the general populace is a significant responsibility held by researchers and regulators alike. Is it a responsible act to communicate to the public trust that, essentially, the air they breathe may be putting their health at risk? By using the USEPA and FLDEP specified methods and the linearized multistage model to "quantify" risk, we are essentially communicating to the public that not only does every molecule of benzene in the air pose some calculable amount of risk to their health, but further, that the amount of benzene present exceeds the amount of risk we, as researchers and regulators charged with serving the public trust, deem acceptable. Clearly, this is not a responsible means of presenting risk and the current research illustrates the inherent fallacy in using the current regulatory method to assess the health risk of low level carcinogen exposures in the State of Florida.

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APPENDIX A

Summary of Epidemiological Studies used for Comparative Analysis

Study	Measure of Association	NOAEL	LOAEL	Comments on Utility for Causal Inference
Rinsky et al. 1987	SMR	40-200 ppm-years	200-400 ppm-years	*High number of actual exposure measurements (considered the best exposure assessment among similar studies); Specific exposure\disease outcomes; Significant measures of association; Clear dose-response; Consistent results compared to similar studies. Suitable evidence for causal inference.

Paxton 1996	SMR	>5-50 ppm-years	>50-500	*Same cohort as Rinsky et al. 1987 with updated exposure matrices; more refined exposure categories to assess lower level exposures; Specific exposure\disease outcomes; Significant measures of association; Clear dose-response; Consistent results compared to similar studies; Most conservative measures of association using the best exposure assessment; This study is the basis for the estimated threshold of benzene induced leukemogenesis being in excess of 50 ppm-years. Suitable evidence for causal inference.
Wong and Gerhard 1995	SMR	40-200 ppm-years	200-400 ppm-years	*High number of actual exposure measurements; Specific exposure\disease outcomes (cell specific analysis); Significant measures of association; Clear

				dose-response; Consistent results compared to similar studies. Suitable evidence for causal inference.
Seniori et al. 2003	SMR	100-199 ppm-years	>200 ppm-years	*High number of actual exposure measurements; Specific exposure\disease outcomes; Significant measures of association; Clear dose-response; Consistent results compared to similar studies. Suitable evidence for causal inference.
Wong et al. 1995	SMR	40-200 ppm-years	200-400 ppm-years	*High number of actual exposure measurements; Specific exposure\disease outcomes (cell specific analysis); Significant measures of association; Clear dose-response; Consistent results compared to similar studies. Suitable evidence for causal inference.

Hayes et al. 1997	RR	<40 ppm-years	40-99 ppm-years	*Large sample size; Various incomparable working environments and exposures applied to all workers; Exposure assessment somewhat speculative; Lacks specificity. Less suitable for causal inference.
Collins et al. 2003	SMR	>6 ppm-years	N/A	*Large sample size; Examines low level exposures; Less actual measured exposures in exposure matrix; Failed to find an association between benzene exposure and leukemogenesis. Less suitable for causal inference.
Schnatter et al. 1996	OR	20-219.8 ppm-years	N/A	*Largely speculative exposure assessment; Smaller sample size; Relatively large statistical variance; Uncontrolled confounders; Less desirable case-control study design; No definitive dose response; Failed to find an association

				between benzene exposure and leukemogenesis. Unsuitable for causal inference.
Glass et al. 2006	OR	Not Reported	>8 ppm-years	*Largely speculative exposure assessment; Smaller sample size; Relatively large statistical variance; Uncontrolled confounders; Less desirable case-control study design; No definitive dose response. Unsuitable for causal inference.
Glass et al. 2003	OR	>1-2 ppm-years	>2-4 ppm-years	*Largely speculative exposure assessment; Smaller sample size; Relatively large statistical variance; Uncontrolled confounders; Less desirable case-control study design; No definitive dose response. Unsuitable for causal inference.

Guenel et al. 2002	OR	>5.5 - <16.8 ppm-years	>16.8 ppm-years	*Largely speculative exposure assessment; Smaller sample size; Relatively large statistical variance; Uncontrolled confounders; Less desirable case-control study design; No definitive dose response; Failed to find a statistically significant association between benzene exposure and AML. Unsuitable for causal inference.
Rushton et al. 1997	OR	>45 ppm-years	N/A	*Largely speculative exposure assessment; Smaller sample size; Relatively large statistical variance; Uncontrolled confounders; Less desirable case-control study design; No definitive dose response; Failed to find an association between benzene exposure and leukemogenesis. Unsuitable for

				causal inference.
Swaen et al. 2005	SMR	401.5 ppm-years	N/A	*Largely speculative exposure assessment; Smaller sample size; Relatively large statistical variance; Uncontrolled confounders; Less desirable case-control study design; No definitive dose response; Failed to find an association between benzene exposure and leukemogenesis. Unsuitable for causal inference.

ABOUT THE AUTHOR

Mr. Giffe Thomas Johnson is a graduate of Rollins College with a B.A. in Biology (1999) and a MPH in Epidemiology from the College of Public Health at the University of South Florida (2005). In 2005, Mr. Johnson was accepted into the Ph.D. program in Public Health at the University of South Florida by the Department of Environmental and Occupational Health. His degree has focused primarily on toxicology, risk assessment and environmental/occupational health. Mr. Johnson has participated in research designed to elucidate mechanisms of chemical-induced hepatotoxicity associated with industrial solvents, toxins and pharmacological agents, as well as aiding the Director of the Center for Environmental Occupational Risk Analysis and Management in daily operations. Additional positions held by Mr. Johnson included Primary Instructor and Graduate Teaching Assistant. He was involved with the teaching of graduate level risk assessment courses, in addition to undergraduate public health courses.