Copyright Warning & Restrictions

The copyright law of the United States (Title 17, United States Code) governs the making of photocopies or other reproductions of copyrighted material.

Under certain conditions specified in the law, libraries and archives are authorized to furnish a photocopy or other reproduction. One of these specified conditions is that the photocopy or reproduction is not to be "used for any purpose other than private study, scholarship, or research." If a, user makes a request for, or later uses, a photocopy or reproduction for purposes in excess of "fair use" that user may be liable for copyright infringement,

This institution reserves the right to refuse to accept a copying order if, in its judgment, fulfillment of the order would involve violation of copyright law.

Please Note: The author retains the copyright while the New Jersey Institute of Technology reserves the right to distribute this thesis or dissertation

Printing note: If you do not wish to print this page, then select "Pages from: first page # to: last page #" on the print dialog screen

ANALYSIS OF SELECTED VOLATILE ORGANIC SUBSTANCES ASSOCIATED WITH RESIDENTIAL KEROSENE HEATER USE AND THE HEALTH IMPLICATIONS

by
Catherine Bobenhausen

Thesis submitted to the Faculty of the Graduate School
of the New Jersey Institute of Technology
in partial fulfillment of the requirements
for the degree of Master of Science
1984

APPROVAL SHEET

Title of Thesis: Analysis of Selected Volatile Organic Substances Associated with Residential Kerosene Heater Use and the Health Implications

Name of Candidate: Catherine Bobenhausen
Master of Science, 1984

Thesis and
Abstract Approved:

Joseph W. Bozzelli, Ph.D — Date
Professor of Chemistry
Department of Chemical
Engineering and Chemistry

Richard E. Trattner, Ph.D — Date
Professor of Chemistry
Department of Chemical
Engineering and Chemistry

VITA

Name: Catherine Coombs Bobenhausen

Permanent Address:

Degree and Date to be Conferred: Master of Science, 1984

Date of Birth:

Place of Birth:

Secondary Education: Horace Greeley High School (1973)

Collegiate Institutions Attended	Dates	Degree	Date of Degree
New Jersey Institute of Technology	'82 - '84	M. Sc.	1984
State University of New York (Purchase)	'73 - '78	B.Env.S.	1978

Major: Environmental Engineering (Toxicology Option)

Positions held: Environmental Analyst
Fred C. Hart Associates
530 Fifth Avenue
New York, New York 10036

ABSTRACT

Title of Thesis: ANALYSIS OF SELECTED VOLATILE ORGANIC SUBSTANCES ASSOCIATED WITH RESIDENTIAL KEROSENE HEATER USE AND THE HEALTH IMPLICATIONS

Catherine Bobenhausen, Master of Science, 1984
Thesis Directed by: Dr. Joseph W. Bozzelli, Professor

Volatile organic species (aliphatic hydrocarbons from hexane to dodecane, cyclohexane and aromatic species including benzene, toluene, ethyl benzene, m,p,and o-xylenes, nitrobenzene, styrene and naphthalene) associated with residential kerosene heater emissions were measured at two sites. One was a small room having a total volume of 23.66 cubic meters and an air change rate of 2.71 air changes per hour, and the other, a living/dining room area having a combined volume of 79.30 cubic meters and an estimated air change rate of .7 air changes per hour. The analytical procedure involved collection of a series of air samples in stainless steel cartridges containing porous polymer adsorbent (Tenax). The samples were recovered by thermal desorption, and analyzed by high resolution capillary column

gas chromatography employing a flame ionization detector. Mass spectral analysis was also conducted for qualitative identification of sample components. Moderately elevated levels of selected species (in the 1 - 100 ppb range) were detected; an average increase of each species by 4.14 was observed at the first site and by 7.35 at the second site. An estimation of health risk associated with exposure to benzene, a documented carcinogen, at the measured concentrations, was then provided, and the issue of risk analysis associated with trace concentrations of carcinogenic materials was explored in some detail.

ACKNOWLEDGEMENTS

I must take this opportunity to express appreciation to both professors - Dr. Joseph W. Bozzelli and Dr. Barbara B. Kebbekus - for their uncommon generosity with regard to time and attention; Dr. Kebbekus in familiarizing me with the instrumentation and in preparation for our first presentation (prior to her sabbatical in Britain); and Dr. Bozzelli, throughout the entire course of the project. I would also like to gratefully acknowledge the unfailing dedication given this project by my thesis partner, Mr. Kashi Banerjee. Thanks to Robert Barat, Mark Heimerdinger and David DeMos for their assistance in sample collection. Ms. Ilene Golvin is credited with the series of graphics presenting the results of our analyses. Finally, this thesis is dedicated to my husband, Bill, for all of his understanding.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1

INTRODUCTION

1.1 Background

Currently, indoor air quality is under close scrutiny. Air pollution analysts have gone indoors; bringing with them techniques which arose largely in response to the environmental legislation of the early 1970s.These methods were needed in order to monitor compliance with outdoor air standards and with regulations adopted to maintain a safe working environment. Sophisticated instrumentation, including gas chromatography, combined gas chromatography/mass spectrometry and high performance liquid chromatography, has enabled us to make increasingly precise measures of our environment. Advances in technology continue to press the limits of pollutant detection. Home, school and office environments are now in the spotlight, and with little wonder; one study (National Research Council, 1981) estimates that the average individual spends 16 hours daily in these settings. Complaints of undefined illness, unexplained

headaches and fatigue, and concern that weathertight buildings may serve to contain and concentrate air pollutants, have focused attention on these previously overlooked areas (Hollowell and Miksch,1981).

Similarly, the study of human health effects resulting from exposure to air pollutants at trace levels (in the part per billion (ppb) range) is also gaining serious professional consideration, as a direct result of our ability to monitor trace levels of contaminants (to parts per trillion in some cases!) in our air, soil and groundwater. Without clearcut answers to questions concerning the consequences of such inadvertent exposure, the public is resigned to a state of understandable anguish.

The field of research into the effects of low-level exposures relies on information concerning overt toxicity at considerably higher concentrations (typically in the 100 part per million (ppm) range and above). It also depends on an understanding of the dose:response relationship, on pharmacokinetic modeling and on careful epidemiological studies. Of course, in the particular case of the individual, there may be overwhelming circumstances, hypersensitivity to the agent or increased susceptibility to infection or disease, for example. It is clear that there will never be a straight, simple answer to the question "What concentration will be innocuous to even the most susceptible

group?" (because one can never be certain of zero risk), or, in designing cleanup or pollution control, "How clean is clean?". Instead, what will be attained is a more precise definition of the effects of an agent at trace levels and the relative risk of undesirable consequences at those concentrations.

1.2 Objective

The objective of this study is to apply two perspectives: quantitative analysis and toxicological assessment, to the analysis of air quality. The case involves measurement of volatile organic species generated from modern unvented kerosene heaters. An evaluation of the relative health risk presented by these contaminants (at the levels detected) is then provided. There is no published data currently available concerning analysis of specific organic pollutants associated with these heaters. Some of the species evaluated in this report include benzene, substituted aromatics such as toluene, ethylbenzene, xylenes, and selected alkanes including cyclohexane and the C-5 through C-12 aliphatic hydrocarbons.

This study follows in the wake of the controversial $41 million suit filed against Consumers Union by the country's

largest importer of portable kerosene heaters (Kero-Sun,Inc.). The suit challenges allegations concerning fire and health hazards associated with the heaters, which were made in the October 1982 cover story of Consumer Reports. In its study Consumers Union incorporated existing air quality data on kerosene heater emissions into a computer model (assuming typical room size, ventilation rate and heater operating efficiency) to estimate emissions of carbon monoxide, nitrogen dioxide, carbon dioxide and sulfur dioxide (Consumers Union, 1982). In each case, concentrations exceeded standards for nonworkplace indoor air quality adopted by the American Society of Heating, Refrigeration and Air Conditioning Engineers (ASHRAE).

Despite the negative publicity, sales of kerosene space heaters are continuing to climb; currently these flueless devices help heat about 10 million American homes (US CPSC, 1982). It is evident, however, that all products of incomplete combustion, and any outgassing from the fuel depot itself via the extinguished wick, are vented directly into the living space. The consequence of this potential exposure bears further analysis.

Several studies have focused on inorganic pollutants from kerosene heaters, such as particulates, carbon monoxide and dioxide, sulfur dioxide and nitric oxides, and comparisons may be made with similar published data obtained for gas

heaters and stoves (Leaderer, 1982; Traynor et al, 1983; Yamanaka et al, 1979). A summary of results of this published research is provided in the following section.

Chapter 2

PUBLISHED RESEARCH

2.1 Kerosene Heater Emissions

2.1.1 Composition of the Fuel

Water-clear premium-grade kerosene (commercially available as K-1) which contains a maximum of 0.04% sulfur (by weight) is the fuel type recommended for residential kerosene space heaters (Hobson, 1973). K-2, also widely available, contains higher concentrations of sulfur (up to 0.1% by weight) and is not recommended since its use may dramatically increase sulfur dioxide emissions and/or present a fire safety hazard as impurities accumulate on the wick (Hobson, 1973). Light kerosene (including K-1) is a straight-run distillate derived from naphtha. It contains the following classes of hydrocarbons in approximate proportions (expressed as volume percent): paraffins (alkanes) - 58.9 percent; cycloparaffins (cycloalkanes) - 20.5 percent; and aromatics - 20.6 percent (Elliott and Mekhior, 1982). The distillation temperature of light kerosene is 175-325 degrees Centigrade (Morrison and

Boyd, 1983). Premium kerosene may typically contain an antioxidant for storage stability, with few, if any, other additives (Elliott and Mekhior, 1982).

It should be noted that the petroleum from which kerosene is derived is composed of a complex mixture of hydrocarbons, and other compounds of carbon and hydrogen containing nitrogen, sulfur and oxygen, as well as nickel, vanadium and other trace metals. Fractionation and conversion processes (catalytic isomerization, catalytic reforming, cracking and catalytic hydrodesulfurization) yield numerous end products such as fuels and suitable feedstocks for the chemical industry. The American Petroleum Institute in 1925 engaged in an exhaustive program to define many of the constituents of crude oil (Rossini et al, 1953).

In its study, the API identified approximately 200 species of hydrocarbons. Each of the three classes of saturated hydrocarbons - the n-paraffins, isoparaffins and naphthenes (cycloalkanes) - were represented. All n-paraffins from methane through C-33 were detected. Naphthenes containing rings of five, six or seven carbon atoms were isolated. Alkyl substituted cyclopentanes and cyclohexanes were also identified, as were alkenes having predominantly trans-double bonds, in branched-chain or cyclic configurations. Aromatic compounds of almost every known type were detected, including benzene and each of its substituted alkyl

derivatives through the twenty isomeric decyl-isomers. Polycyclic aromatic compounds including indane, tetrahydronaphthalene, naphthalene, benz(a)anthracene, chrysene, benzopyrenes, perylene and benzo(ghi)perylene were identified.

The kerosene fraction of crude oil has variously been described as constituting the C-12 to C-18 fraction (Morrison and Boyd, 1983), the C-11 to C-13 fraction (Hunt, 1979), or, the C-9 to C-16 fraction with an average molecular weight of 170 (US DHEW, 1977). Its composition varies with the source of crude oil and method of refining. It has been reported that the kerosene fraction is the first to show a significant increase in the cyclic hydrocarbons that characterize the heavier fractions of crude oil (Hunt, 1979). In this same study, it was reported that aromatics typically constitute 10 - 40% of the kerosene fuel. Condensed bicyclic naphthenes and aromatics (tetralin and naphthalene) are common (Hunt, 1979). Naphthenic acids, phenols and thiophenes have also been identified in the kerosene fraction (Hunt, 1979).

The composition of the fuel obviously plays a role in defining emissions resulting from heater operation. However, a theoretical analysis is not complete without considering the combustion process itself, which may liberate, among other compounds, carbon monoxide, nitrogen dioxide, nitric oxide, products of pyrosynthesis (aldehydes), aromatic

species and particulates (National Research Council, 1981).

In order to estimate the total composition of kerosene heater emissions, it would be necessary to rigorously define all combustion parameters - temperature, combustion efficiency, availability of oxygen, composition of supply air, and all constituents of the fuel. This task is monumentous, and beyond the scope of currently available research on the subject. However, measurements of common combustion products - carbon dioxide, carbon monoxide, nitrogen oxides and sulfur dioxide - under a variety of experimental conditions have been reported and can be compared with established air quality standards (Leaderer, 1982; Traynor et al, 1983; Yamanaka et al, 1979). What follows is a brief description of modern kerosene heaters now commercially available and an overview of published research associated with measurement of kerosene heater emissions.

2.1.2 Results of Previous Research

Research has been conducted on blue-flame radiant heaters and white-flame convective portable kerosene heaters. Convective heaters typically are cylindrical, approximately .7 m high, 50 cm in diameter. Cool air enters through slots at the base of a metal shell around the burner; the heated air rises and exits through slots at the top of the unit. A convective current is thereby generated, distributing heat throughout the room.

The blue-flame radiant units are typically rectangular,and also roughly .7 m in height. Metal reflectors forming the two sides and back of the units radiate heat out from the burner. Both types of heaters lack thermostatic control; the heater's output is essentially constant. The wick may be adjusted, which results in reduced fuel consumption and altered pollutant emission rates. Improper wick height may result in a smoky flame, generating higher concentrations of aromatics and naphthenes. Manufacturers' ratings for radiant heaters range from 9,000 to 15,000 BTUs per hour; while standard manufacturers' ratings for convective units range from 15,000 to 22,000 BTUs per hour (Consumers Union, 1982).

Leaderer calculated kerosene heater emission rates (in mg/g of fuel) as a function of ventilation rate (from 5 to 500

liters/sec) and fuel consumption for a radiant heater (with a rated output of 9,600 Btu/hr, the rate was 2.59 ±0.035 g fuel/min) and for a convective heater (with a rated output of 8,700 Btu/hr, the rate was 2.25±0.027 g fuel/min) (Leaderer,1982). The experiment was conducted in small chamber having a volume of 34 cu m and a constant recirculation rate of 1,000 liters/sec (100 air changes/hour). The data were summarized in two graphs which elegantly associated NO2, SO2 and CO concentrations at various ventilation rates with percent depletion of O2 and percent production of CO2. The graphs also present air quality standards as references (although direct comparison requires information on concentration and duration of exposure).

The SO2 emission rates corresponded to combustion of a fuel with a sulfur content of approximately 0.035%, typical of K-1 kerosene. The ratio of % O2 consumption to % CO2 depletion was similar to calculated estimates. Concentrations of SO2 and NO2 exceeded relevant ambient air quality standards, while CO2 levels exceeded guidelines set by the American Society of Heating, Refrigeration and Air Conditioning Engineers (ASHRAE). It was determined that CO concentrations are especially of concern during radiant heater use in small rooms with moderate ventilation rates. Consumer Reports has cited the National Kerosene Heater Association reports that

kerosene heaters produce only 0.002 percent CO, the equivalent of 20 ppm, which is twice the U.S. EPA eight-hour outdoor standard (Consumers Union, 1982).

Traynor presented CO2, CO, NO2 and NO concentration profiles associated with use of a white-flame convective heater and a blue-flame radiant heater operated in a 27 cu m environmental chamber (Traynor et al, 1983). Both types of heater generated CO2 levels which are twice the eight-hour occupational standard of 5,000 ppm. The U.S. occupational standard for NO2 of 5.0 ppm was not exceeded in any of the tests, but the California short-term one hour outdoor standard of .25 ppm was exceeded by a factor of seven for the convective heater and by a factor of two for the radiant model. (Note: the basis of the California outdoor standard may be to control photochemical oxidant formation in the atmosphere, which would be irrelevant to this study). As with Leaderer's data, the values for CO concentrations generated by the convective heater model were low compared to those generated by the radiant heater. The authors attributed the lower CO emissions of the convective heater to its hotter flame and more complete combustion; the higher NOx emissions are also the result of a hotter flame.

Yamanaka also noted higher NOx concentrations associated with convective heater use (mean 1.3 ppm) compared with that resulting from radiant heater use (mean .29 ppm) (Yamanaka et

al, 1979).

2.1.3 Potential Health Effects at Published Levels

The U.S. EPA standards for carbon monoxide have been set to safeguard the most sensitive populations: patients with cardiac and peripheral vascular disease and healthy exercising individuals (this relates to the effect of carbon monoxide on oxygenation of skeletal muscles)(National Research Council,1981). The primary mechanism of CO toxicity is the preferential binding of CO to hemoglobin (producing carboxyhemoglobin) resulting in reduced oxygen transfer to the tissues. Whether there is a threshold carboxyhemoglobin concentration for an adverse health effect is unknown; current standards are believed to incorporate an adequate safety factor (National Research Council, 1981). Although the published levels associated with kerosene heater use did exceed these standards, it should also be noted that moderately severe exposures can result from other common activities. Carbon monoxide levels of 50 ppm resulting from routine gas stove use have been measured, and levels up to 100 ppm in ice-skating rinks have been detected (National Research Council, 1981).

NOx also binds to hemoglobin, producing methemoglobin. However, at NO2 levels typically associated with use of unvented heaters, acute toxicity is not expected (National

Research Council, 1981). Levels of approximately 0.05 ppm have been measured during use of gas stoves; at these levels, eye irritation may be experienced (Doull et al, 1980), and potentiation of respiratory infection may occur (Doull et al, 1980).

Chronic exposure to low (1 ppm) concentrations of sulfur dioxide may result in mild bronchial constriction and SO2 may be a respiratory irritant at low levels (Doull et al, 1980).

Clearly implied in the kerosene heater studies and in the National Academy of Science's study on indoor air quality (National Research Council, 1981) is the overriding importance of effective venting for the combustion products to the outdoor air and isolation of discharged air from makeup air. One simple means of reducing the buildup of pollutants in the indoor environment is installation of an air-to-air heat exchanger which recovers heat from the exhaust air stream and transfers it to the cold outdoor air stream entering the living space. An inexpensive unit sized to ventilate one or two rooms may be mounted into a window opening (Hollowell and Miksch, 1981). Perhaps with greater understanding of pollutant generation and retention within the indoor environment, these units will receive greater use.

Chapter 3

EXPERIMENTAL METHOD

3.1 Selection of Instrumentation

For this experiment, a high resolution capillary column gas chromatography, utilizing a support-coated open tubular column and flame ionization detector, was selected. The fused silica column is 50 meters in length, is coated with SP2100 methyl silicone stationary phase and has a rated efficiency of 4,100 theoretical plates/meter (or 205,000 plates in total). In addition, mass spectral analysis was applied for qualitative confirmation. The task of species separation prior to mass spectral analysis is accomplished by interfacing with a gas chromatograph containing the same type of capillary column. This method of separation is especially useful for isolation and identification of isomers (Chapter 4). In some cases, isomeric compounds may yield similar mass spectra but exhibit markedly different chromatographic mobility (Novotny, 1978).

The fused silica capillary column has been developed to

improve separation efficiency. Typically, the column has an inside diameter (i.d.) of .2mm with the stationary phase consisting of a film whose thickness ranges up to only a few tenths of a micron. The column's sample capacity is limited; approximately 500 ng per compound (species) represents the upper limit (Zweig and Sherma, 1972). In the analysis of trace organics present in the air, optimal results are obtained when the sample is preconcentrated to avoid exceeding the total volume of the capillary column.

Only a few of the detectors available for gas chromatography are applicable to the specialized field of the capillary column. The detector must be sensitive to the low range of concentrations that can be provided by the column, and the detector should have a cell volume compatible with the small internal diameter of the column and associated low flow rate (an extra carrier gas or "makeup gas" may be introduced at the column exit to compensate for a larger detector volume)(Novotny, 1978).

The flame-ionization detector (FID) is considered to be the most universal detector for the capillary column GC (Novotny, 1978). The FID ionizes the eluted species by burning them in a hydrogen-oxygen flame. The gas in the detector then generates an electrical current whose conductivity is directly proportional to the concentration of charged particles (ions). This is measured by a collector electrode

above the flame. When pure hydrogen gas is burned, few ions are formed and the conductivity is low; this provides the baseline on the chromatogram. The FID responds with greatest sensitivity to organic species; to a lower limit of 0.9 picogram/sec or a minimum detectable quantity of 20 picograms for alkanes (Zweig and Sherma, 1972). Its response is based on carbon weight percentage; for example, as the state of oxidation increases, the response of the detector decreases (Zweig and Sherma, 1972).

3.2 Sample Collection

The organic vapors were collected on 60/80 mesh size Tenax, a polymeric sorbent which does not collect significant amounts of oxygen, nitrogen or water (Kebbekus and Bozzelli, 1982). The Tenax was first exhaustively extracted with acetone, cyclohexane and methanol, in sequence, for a period of fifteen hours per solvent, and then vacuum dried at 100 C. Approximately 0.4 g of the sorbent was weighed and packed into each stainless steel trap (having dimensions 0.64 cm o.d. (0.4 cm i.d.)by 15 cm) fitted with Swagelok compression connectors; the sorbent was held in place with plugs of silanized glass wool.

Sets of twelve traps were preconditioned by heating at 295

C for ten hours with a flow of prepurified grade nitrogen at approximately 10 ml/min through each trap. The conditioned traps were then cooled with continuous nitrogen flow to prevent contaminants from being drawn into the traps as they cooled. One trap per set was selected at random for chromatographic analysis to ensure completeness of conditioning.

Sampling cartridges were transported to the sites in individual glass culture tubes with Teflon-lined screw caps. At the site, duplicate cartridges were mounted with Swagelok fittings into a small metal container supported on a support rod two meters above the ground (approximately breathing level). At one of the sites (NJIT), the sampling apparatus was placed .9 meters from the radiant kerosene heater (and 2 meters in height), at the other (Elizabeth) the radiant heater was 5.5 meters from the sampling equipment (and 2 meters in height).

Sampling was initiated by removing the caps from the cartridges and activating a 6 volt pump which provided a flow rate of approximately 50 ml/min through the cartridge. The flows were controlled by a needle valve and measured with a calibrated rotameter. Upon completion of the sampling, exact sampling time and flow rate were recorded, the cartridges capped, placed in the glass culture tubes and returned to the laboratory for analysis.

3.3 Sample Desorption

The samples were thermally desorbed by distillation under partial vacuum into a 10 ml stainless steel sampling cylinder. One end of the sampling cartridge was connected to the sampling cylinder which was evacuated to 0.1 mm Hg and immersed in methanol chilled to -60 C with a refrigerator probe in a 1 liter dewar flask. The trap was placed in a small oven, fabricated from a solid cylinder of aluminum and heated with two 400-watt cartridge heaters. The other end of the trap was connected to a nitrogen gas inlet with the valve closed. Desorption began when the bellows valve on the sampling cylinder was opened, allowing the trapped material to distill into the cold cylinder for a period of thirty minutes. The gas inlet valve was then opened and the system flushed with sufficient nitrogen gas to result in a final cylinder pressure of 45 PSIG (59.69 PSIA). The sample was then defined by volume (10 ml), pressure (59.69 PSIA) and temperature (-60 C). The valve was closed and the cylinder transfered to a heating mantle where it was warmed to 90 C prior to injection of the sample into the Varian 3700 gas chromatograph. Sufficient pressure was therefore available within the cylinder to permit injection of at least three aliquots of the sample (Kebbekus and Bozzelli, 1982).

3.4 Analysis by Gas Chromatography

The hot cylinder was then attached to the GC inlet which is heated to 120 C with a portable heat gun. The vacuum valve on the inlet was opened for evacuation to -30 mm Hg. The vacuum valve was closed, and the sample cylinder slowly opened to transfer 5 PSIG (19.69 PSIA) of sample (2 ml in volume) into the GC inlet. The sample was cryogenically focused with liquid nitrogen (-30 C) at the beginning of the column. This permits the helium carrier gas to pass through the column (at a flow of 1.0 ml/min) while the sample enters and accumulates in a sharp plug. This technique results in sharp, well-resolved peaks. The GC temperature was programmed to maximize efficiency of separation (35 C for 6 minutes; raised 4 C per minute to 180 C where it is held for ten minutes). Nitrogen makeup gas is added at the end of the column to prevent peak broadening in the detector. The flow rates of hydrogen and air to the flame ionization detector were maintained at 30 ml/min and 250 - 300 ml/min, measured with a soap bubble meter at the detector outlet, respectively.

3.4.1 Preparation of Standard Gas Mixture

A standard gas mixture containing the targeted organic species was prepared, by injecting a 2 ul liquid solution containing known mole fractions of each species into an evacuated stainless steel gas cylinder. The cylinder was pressurized to 1000 PSIA with zero grade helium. The benzene concentration in the mixture was determined to be 11.82 ppm by comparison with an NBS traceable benzene-in-helium standard; the known mole fractions of other compounds permitted calculation of remaining concentrations.

The standard mixture was chromatographed daily at identical pressure to that of the samples (5 PSIG) for peak identification and to adjust for any minor variation in the instrument. Also, on a regular basis, following analysis of a sample, the cylinder containing the remainder of the sample was "spiked" with a small quantity of the standard mixture and rechromatographed. Enlarged peak areas confirmed identities of species originally labelled.

3.5 Calculation of Concentrations

The current generated at the flame ionization detector (in picoamps) is amplified by an electrometer which produces an output signal. This signal is relayed to a chart recorder, and to a Spectra-Physics Model 4000 multichannel integrator

which calculates area under the peak and relays data consisting of retention times, peak areas and percentages of total peak area to an Apple II computer for printout.

In order to convert peak area to concentration by volume of air (ppbv), several variables must be factored in: 1) original sample volume (obtained by multiplying flow rate in liters/min by sample time in minutes); 2) peak area of benzene contained in standard mixture (measured and entered daily); 3) peak area of the identified compound; 4) and relative response factor for the specific compound (compared with benzene, to correct for incomplete recovery).

In addition, several constants must be accounted for: 1) peak area and known concentration of benzene in the NBS traceable benzene-in-helium standard; (the peak area determined from a series of runs yielded a mean of 273,265 and the concentration was 9.12 ppmv); 2) pressure (19.69 PSIA), volume (.002 l) and temperature (120 C) of the GC sampling loop which receives the sample at the inlet of the capillary column; and 3) pressure (59.69 PSIA), volume (.01 l) and temperature (-60 C) of the sampling cylinder.

Adjustment must be made to account for "splitting" the sample (which is necessary because of the limited capacity of the capillary column). This is accomplished by dividing the number of moles originally contained in the .01 liter

sampling cylinder by the number of moles injected into the column, obtained via the Ideal Gas Law:

$$PV = nRT$$

where: P = pressure in atmospheres
V = volume in liters
n = total number of moles of gas
R = constant, 0.082 l-atm/ K-mole
T = temperature in degrees Kelvin

1. # Moles in Sampling Cylinder

$$n = \frac{(19.69/14.69 \text{ atm.})(.002 \text{ l})}{(.082 \text{ l-atm./ K-mole})(393 \text{ K})}$$

$$= 8.32 \text{ E } -5 \text{ moles}$$

2. # Moles in Sampling Loop

$$n = \frac{(59.69/14.69 \text{ atm.})(.01 \text{ l})}{(.082 \text{ l-atm./K-mole})(213 \text{ K})}$$

$$= 2.33 \text{ E } -3 \text{ moles}$$

Therefore, the correction factor is:

$$= 2.33 \text{ E } -3 \text{ moles}/8.32 \text{ E } -5 \text{ moles}$$

$$= 27.9/\text{liter}$$

Since the factor applies per liter, and only .002 liters of sample are injected into the GC, the factor must be multiplied by this volume. This will obtain a value of .054.

From a series of chromatograms of the NBS benzene-in-helium standard, it was determined that the benzene standard concentration of 9.12 ppmv yielded an area of 273,265. In addition, benzene in our specially prepared hydrocarbon standard averaged an area of 354,162.

Therefore, the benzene concentration in our mixed standard can be calculated as:

(9.12 ppmv/273,265)(354,162) = 11.82 ppmv

Incorporating the above constant(.054), and correcting so that our result will be in parts per billion rather than parts per million, we obtain an equation that will be utilized in converting area of identified species to parts per billion by volume:

ppbv(species) = [.054 x 1,000 ppb/ppm x 11.82 ppmv benzene x species area x relative response factor of species]/[volume of air sampled (liters) x benzene area]

This equation was incorporated into a Visicalc spread sheet, and all relevant data (site, sample identification number, sample volume, species areas and the daily benzene area) were entered to obtain concentrations in parts per billion by volume (which can be defined as the # of moles of species per billion moles of air).

The conversion from concentration by volume (ppbv) to concentration by weight (ug/cu m) was obtained from the following relationship:

micrograms/cubic meter

$$= \frac{[(x \text{ moles species})(g \text{ species/mole})(1 \text{ E } 6 \text{ ug/g})]}{[(1 \text{ E } 9 \text{ moles air})(24.45 \text{ 1/moles of air})(1 \text{ E } -3 \text{ cu m/1})]}$$

3.6 Confirmation by Gas Chromatography/Mass Spectrometry

In order to confirm identification of sample species and analysis of co-eluting species, samples were also routinely analyzed by mass spectrometry. Separation was first accomplished with a 50 meter support coated SP2100 fused silica capillary column identical to the column in the gas chromatograph, and mass spectral analysis was conducted via operation of a Varian MAT 44 quadrapole mass spectrometer.

Chapter 4

RESULTS

4.1 Introduction

Our selection of specific aliphatic and aromatic hydrocarbons for this study (Table 4-1) was based on the composition of the kerosene fuel (generally, hydrocarbons of the aliphatic series, C9 through C16) and likely combustion products (eg., straight chain hydrocarbons may form closed ring structures such as toluene and benzene). In retrospect, numerous substituted benzene species may also have served as potential candidates for analysis. A periodic review of the gas chromatograms throughout the analysis indicated that there was no persistent pattern of unknown peaks at characteristic retention times (which might signify that an unanticipated series of pollutants was consistently being generated). Mass spectral analysis confirmed the presence of the selected aliphatic species and revealed additional substituted aromatic compounds.

None of the species chosen, with the exception of benzene

TABLE 4-1

PROPERTIES OF TARGET COMPOUNDS

COMPOUND	FORMULA	MOLECULAR WT	BOILING PT °C	VAPOR PRESSURE * (mm Hg/20°C)
PENTANE	C_5H_{12}	72.15	36.3	450
HEXANE	C_6H_{14}	86.17	69.0	125
BENZENE	C_6H_6	78.11	80.1	78
CYCLOHEXANE	C_6H_{12}	84.17	81.4	77
HEPTANE	C_7H_{16}	100.20	98.4	35
TOLUENE	$C_6H_5CH_3$	92.13	110.8	22
OCTANE	C_8H_{18}	114.23	125.7	12
ETHYLBENZENE	$C_6H_5C_2H_5$	106.17	136.2	57(@60°C)
M, P- XYLENE	$C_6H_4(CH_3)_2$	106.17	139.3,138.5	6.4
O- XYLENE	$C_6H_4(CH_3)_2$	106.17	144.0	4.9
STYRENE	$C_6H_5C_2H_3$	104.15	145.0	40(@105°C)
NONANE	C_9H_{20}	128.26	150.5	2.5
DECANE	$C_{10}H_{22}$	142.29	174.0	.72
UNDECANE	$C_{11}H_{24}$	156.31	194.5	40(@105°C)
DODECANE	$C_{12}H_{26}$	170.34	214.5	68(@135°C)
NITROBENZENE	$C_6H_5NO_2$	123.11	210.9	1(@44.4°C)
NAPHTHALENE	$C_{10}H_8$	128.17	217.9	1(@52.6°C)

Reference:
* Ohe (1976)

(and possibly dodecane) are known to be harmful to human health at levels detected in our study (in the low ppb range)(Sax, 1979). Benzene is a recognized leukemogen (Goldstein,1977; WHO, 1982; US EPA, 1978) the "safe" ambient exposure to this ubiquitous solvent is currently in dispute (Goldstein,1983). It has been demonstrated under experimental conditions (using laboratory animals) that dodecane is a carcinogen (Sax, 1979). The current conservative theory of cancer holds that there is no "safe" level for exposure to a carcinogen; one molecule of a carcinogen represents a finite risk of cancer and that risk is linearly related to concentration (Doull et al, 1980).

At higher concentrations (hundreds of ppm), several of these hydrocarbons are asphyxiants because of oxygen exclusion. Except for the higher molecular weight hydrocarbons, which tend to adsorb on solids and settle, hydrocarbon emissions tend to remain airborne. In the indoor environment, air change appears to be the sole removal mechanism for these pollutants (Sittig, 1975; Bozzelli, and Greenberg 1984).

Table 4-2 provides an overview of demonstrated acute health effects and (where available) odor threshold values for the measured species. Little information concerning the impact of chronic low level (in the ppb range) exposure to these agents is available. Although the general consensus is that

TABLE 4-2

ACUTE HEALTH EFFECTS OF ORGANIC COMPOUNDS

COMPOUND	CLINICAL EFFECT (CONCENTRATION IN PPM)*
PENTANE	Central Nervous System Effects (at 130,000 ppm) Narcotic at High Concentrations Toxicity: Low via Inhalation
HEXANE	Fatigue, Loss of Appetite, Distal Paresthesia (500 - 1000 ppm/3 - 6 months) Documented cause of Motor Neuropathy in Exposed Workers (chronic exposure) Onset of Polyneuropathy (at 500 - 2,500 ppm) Toxicity: Low via Inhalation
HEPTANE	Central Nervous System Effects (1,000 ppm/6 minutes) Vertigo, Incoordination (5,000 ppm/4 minutes) Toxicity: Moderate via Inhalation **ODOR THRESHOLD: 930 mg/m^3 (227 ppm)
OCTANE	Acts as Simple Asphyxiant (acts by excluding oxygen from lungs) (330,000 ppm) Fatal Within Minutes (at 750,000 ppm) Narcotic at High Concentrations ODOR THRESHOLD: 710 mg/m^3 (152 ppm)
NONANE	Irritant to Respiratory Tract Narcotic at High Concentrations
DECANE	Acts as Simple Ashyxiant Narcotic at High Concentrations
UNDECANE	Transient Central Nervous System Depression
DODECANE	Irritant and Narcotic at High Concentrations An Experimental Carcinogen
TOLUENE	Central Nervous System Effects (at 200 ppm) Psychotropic Effects (at 100 ppm) Impairment of Coordination and Reaction Time (200 ppm/8 hours) Chronic Poisoning - Occasional Evidence of Anemia, Leukopenia, Bone Marrow Hypoplasia Few Symptoms up to 200 ppm Common Air Contaminant Toxicity: Moderate via Inhalation ODOR THRESHOLD: 1.03/140 mg/m^3 (.3 - 37 ppm)

References:
* Sax (1979)
** Sittig (1975)

TABLE 4-2 CONT'D

COMPOUND	CLINICAL EFFECT (CONCENTRATION IN PPM)
BENZENE	Acute Poisoning by Narcotic Action on Central Nervous System (at 3,000 ppm) Recognized Leukemogen due to Chronic Exposure Daily Exposure to Concentration of 100 ppm or less will cause Damage if continued over Protracted Period of Time Vague Symptoms: Fatigue, Dizziness, Nausea Great Variation in Signs and Symptoms of Chronic Benzene Poisoning Common Air Contaminant ODOR THRESHOLD: 10.5 - 210 mg/m^3 (3.3 - 65.7 ppm)
CYCLOHEXANE	Moderately Irritating via Inhalation Narcotic, may be Fatal due to Respiratory Paralysis
XYLENES (M,P-)	Irritating Effects (at 200 ppm) Some Temporary Corneal Effects as well as Conjunctival Irritation by Instillation Common Air Contaminant Toxicity: Moderate via Inhalation
XYLENE (O)	Toxicity: Moderate via Inhalation Common Air Contaminant ODOR THRESHOLD: 8.5 mg/m^3 (2 ppm)
STYRENE	Irritant, Violent Itching of Eyes, Lachrymation, Severe Eye Injuries Toxic Effects usually Transient and Result in Irritation and Possible Narcosis Central Nervous System Effects (at 376 ppm) Irritant Effects (at 600 ppm) ODOR THRESHOLD: .0775 - .455 mg/m^3 (.02 - .1 ppm)
ETHYLBENZENE	Moderate Irritant to Skin, Eyes, Mucous Membrane Eye Irritant (at 1,000 ppm) Dizziness, Extreme Nose and Throat Irritation, Chest Constriction (at 2,000 ppm)
NAPHTHALENE	Common Use - Mothballs Acute Oral Toxicity: 100 mg/kg (child) No Data on Inhalation
NITROBENZENE	No Data on Inhalation Common Air Contaminant
KEROSENE	Inhalation of High Concentration of Vapor can cause Headache and Stupor Suspect Carcinogen

these species pose no direct threat to health at normal concentrations, there is also no conclusive evidence proving their lack of toxicity under conditions of prolonged exposure.

4.2 Presentation of Data

Table 4-3 presents the results of monitoring data gathered at two sites. The NJIT site is a small office having a total volume of 23.66 cubic meters and the measured air change rate is 2.71 air changes per hour. Three phases were investigated: 1) air quality prior to installation of the heater (background) (average sample time: 2.0 hours); 2) air quality during heater operation (average sample time: 1.3 hours); and 3) air quality immediately after the heater was extinguished (average sampling time: 0.4 hours).

The Elizabeth site is a residential living room/dining room connected by an archway. The total heated area is approximately 79.30 cubic meters and the air circulation rate is estimated at .7 air changes per hour. Two conditions were assessed: 1) air quality during the summer months (background) (average sampling time: 10.1 hours); and 2) air quality during heater operation (average sampling time: 9.7 hours).

TABLE 4-3

MEAN CONCENTRATION OF SELECTED ORGANIC SPECIES
NJIT

	....HEATER OFF (CONTROL)...			.....HEATER ON.....			.....HEATER OFF (AFTER).....		
COMPOUND	MEAN (ppbv)	MEDIAN (ppbv)	MEAN (ug/cu m)	MEAN (ppbv)	MEDIAN (ppbv)	MEAN (ug/cu m)	MEAN (ppbv)	MEDIAN (ppbv)	MEAN (ug/cu m)
TOLUENE	11.94	9.55	1.84	43.19	24.44	6.66	55.26	7.79	8.52
BENZENE	5.28	4.33	0.69	112.07	62.75	14.62	29.60	3.83	3.86
CYCLOHEXANE	8.04	5.19	1.13	33.87	6.02	4.77	17.06	1.83	2.40
ETHYL BENZENE	0.53	0.00	0.09	4.72	1.45	0.84	1.56	0.31	0.28
M,P-XYLENE	2.31	2.45	0.41	3.98	3.98	0.96	4.47	0.84	0.79
O-XYLENE	0.82	0.42	0.15	1.85	1.75	0.33	1.95	0.61	0.35
NITROBENZENE	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
STYRENE	0.83	0.81	0.14	2.62	0.76	0.46	1.31	0.12	0.23
NAPHTHALENE	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
PENTANE	3.29	0.00	0.40	3.29	0.00	0.40	29.15	0.14	3.52
HEXANE	1.88	0.00	0.27	26.98	14.35	3.88	5.53	1.19	0.80
HEPTANE	0.84	0.00	0.14	4.36	0.60	0.73	6.09	1.12	1.02
OCTANE	0.58	0.39	0.11	0.22	0.00	0.04	0.04	0.00	0.01
NONANE	1.91	0.00	0.41	0.20	0.00	0.04	0.46	0.00	0.10
DECANE	0.07	0.00	0.02	0.30	0.00	0.07	0.07	0.00	0.02
UNDECANE	0.00	0.00	0.00	4.90	0.00	1.28	0.03	0.00	0.01
DODECANE	0.00	0.00	0.00	0.17	0.00	0.05	0.01	0.00	0.00

TABLE 4-3 contd

MEAN CONCENTRATION OF SELECTED ORGANIC SPECIES
ELIZABETH

	....HEATER OFF (CONTROL)...			.....HEATER ON.....		
COMPOUND	MEAN (ppbv)	MEDIAN (ppbv)	MEAN (ug/cu m)	MEAN (ppbv)	MEDIAN (ppbv)	MEAN (ug/cu m)
TOLUENE	10.73	4.30	1.65	34.26	28.86	5.28
BENZENE	3.70	3.17	0.48	10.71	11.76	1.40
CYCLOHEXANE	4.32	2.65	0.61	22.00	16.81	3.11
ETHYL BENZENE	1.98	0.95	0.35	3.40	2.59	0.60
M,P-XYLENE	2.07	0.75	0.37	8.29	6.33	1.47
O-XYLENE	0.82	0.36	0.15	2.58	2.01	0.46
NITROBENZENE	0.00	0.00	0.00	0.23	0.00	0.05
STYRENE	0.94	0.18	0.16	2.01	1.67	0.35
NAPHTHALENE	0.13	0.00	0.03	0.50	0.00	0.11
PENTANE	5.24	1.39	0.63	2.61	1.71	0.31
HEXANE	2.47	0.91	0.36	6.07	3.12	0.87
HEPTANE	1.25	0.35	0.21	2.86	2.34	0.48
OCTANE	0.33	0.11	0.06	0.93	0.89	0.18
NONANE	0.18	0.00	0.04	3.24	1.95	0.70
DECANE	0.34	0.00	0.08	5.92	2.06	1.41
UNDECANE	0.07	0.00	0.02	4.26	2.17	1.11
DODECANE	0.37	0.00	0.11	1.21	0.35	0.34

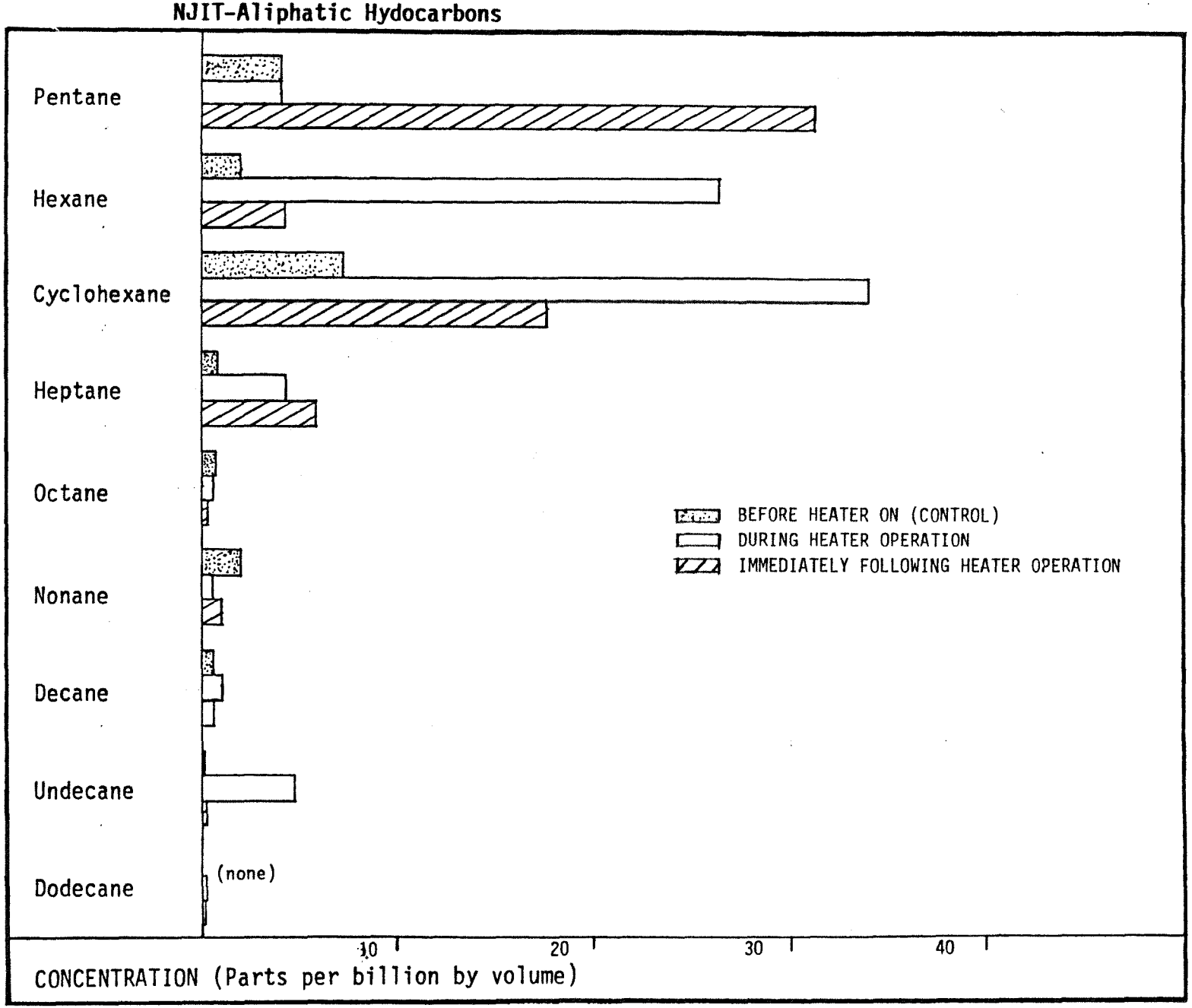
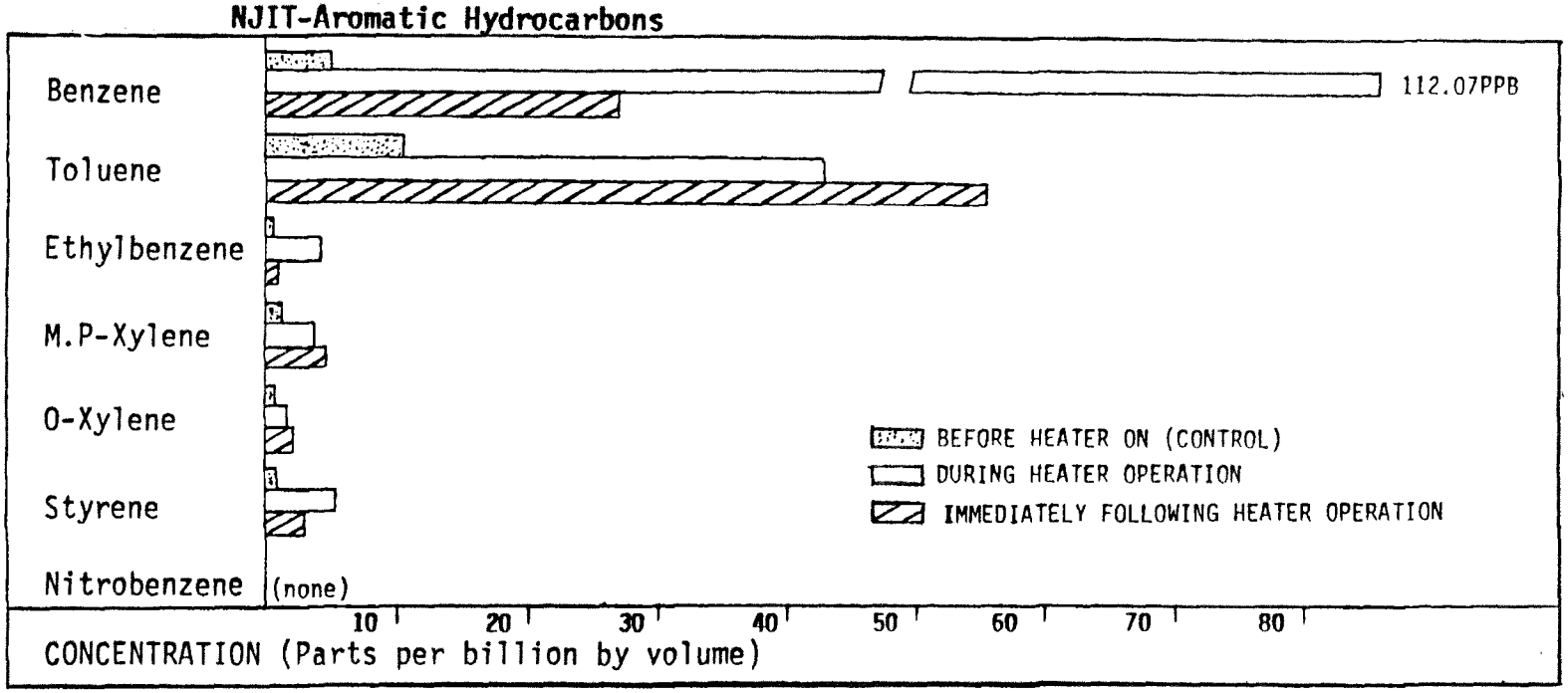

NJIT-Aliphatic Hydocarbons
Pentane
Hexane
Cyclohexane
Heptane
Octane
Nonane
Decane
Undecane
Dodecane
(none)
BEFORE HEATER ON (CONTROL)
DURING HEATER OPERATION
IMMEDIATELY FOLLOWING HEATER OPERATION
10
20
30
40
CONCENTRATION (Parts per billion by volume)

Figure 4-1


NJIT-Aromatic Hydrocarbons
Benzene
Toluene
Ethylbenzene
M.P-Xylene
O-Xylene
Styrene
Nitrobenzene
(none)
112.07PPB
BEFORE HEATER ON (CONTROL)
DURING HEATER OPERATION
IMMEDIATELY FOLLOWING HEATER OPERATION
10
20
30
40
50
60
70
80
CONCENTRATION (Parts per billion by volume)

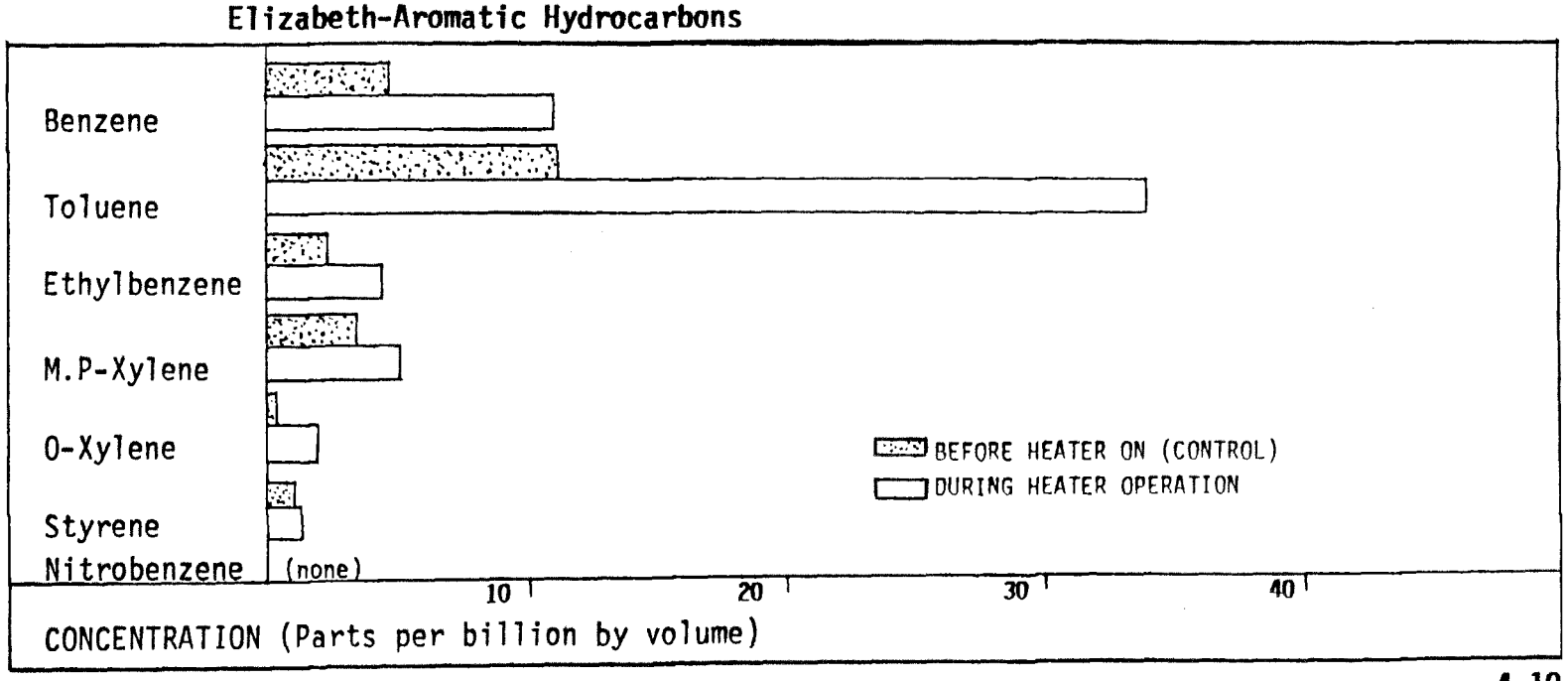

Elizabeth-Aromatic Hydrocarbons
Benzene
Toluene
Ethylbenzene
M.P-Xylene
O-Xylene
Styrene
Nitrobenzene
(none)
BEFORE HEATER ON (CONTROL)
DURING HEATER OPERATION
10
20
30
40
CONCENTRATION (Parts per billion by volume)

Figure 4-2

Elizabeth-Aliphatic Hydrocarbons

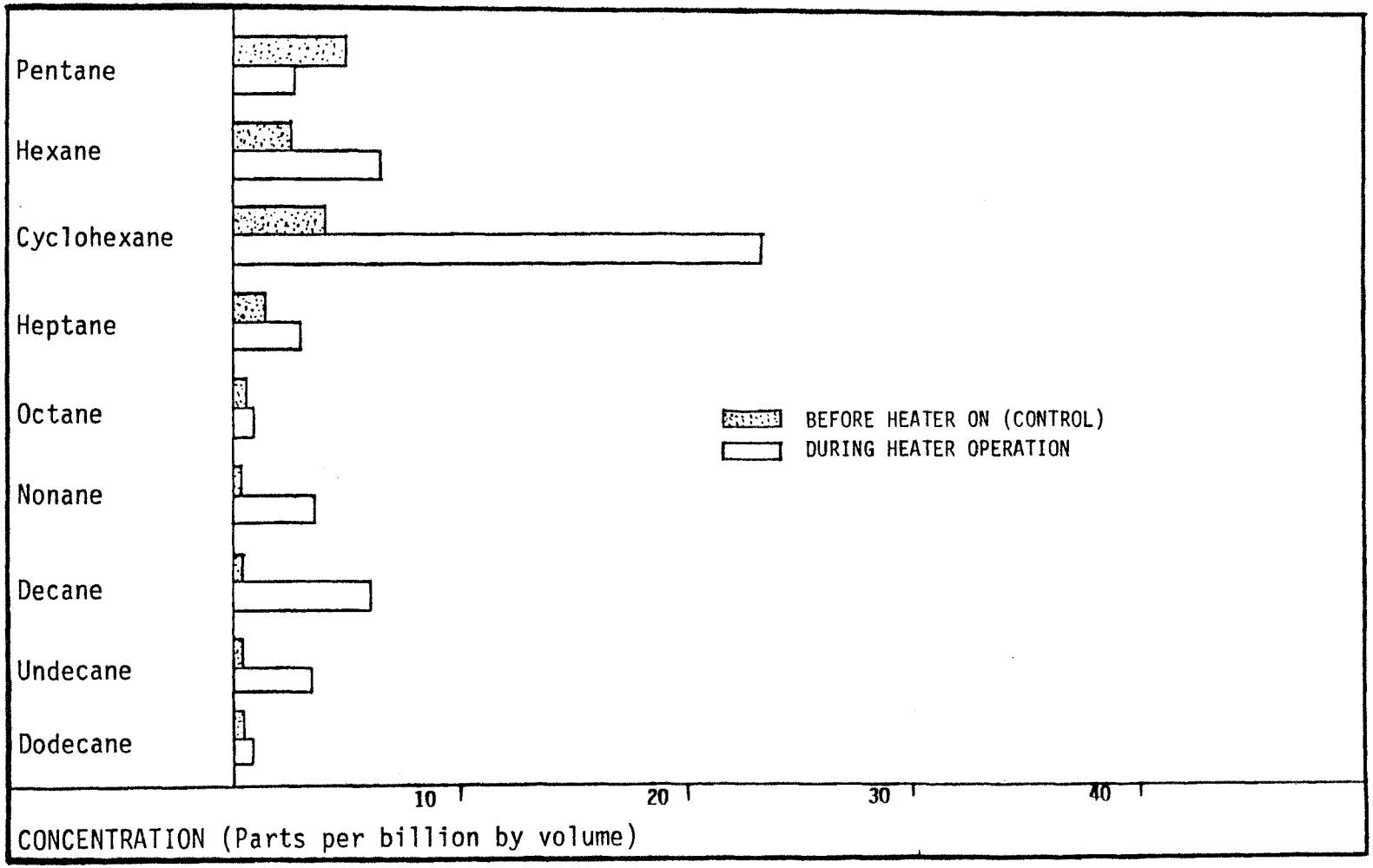
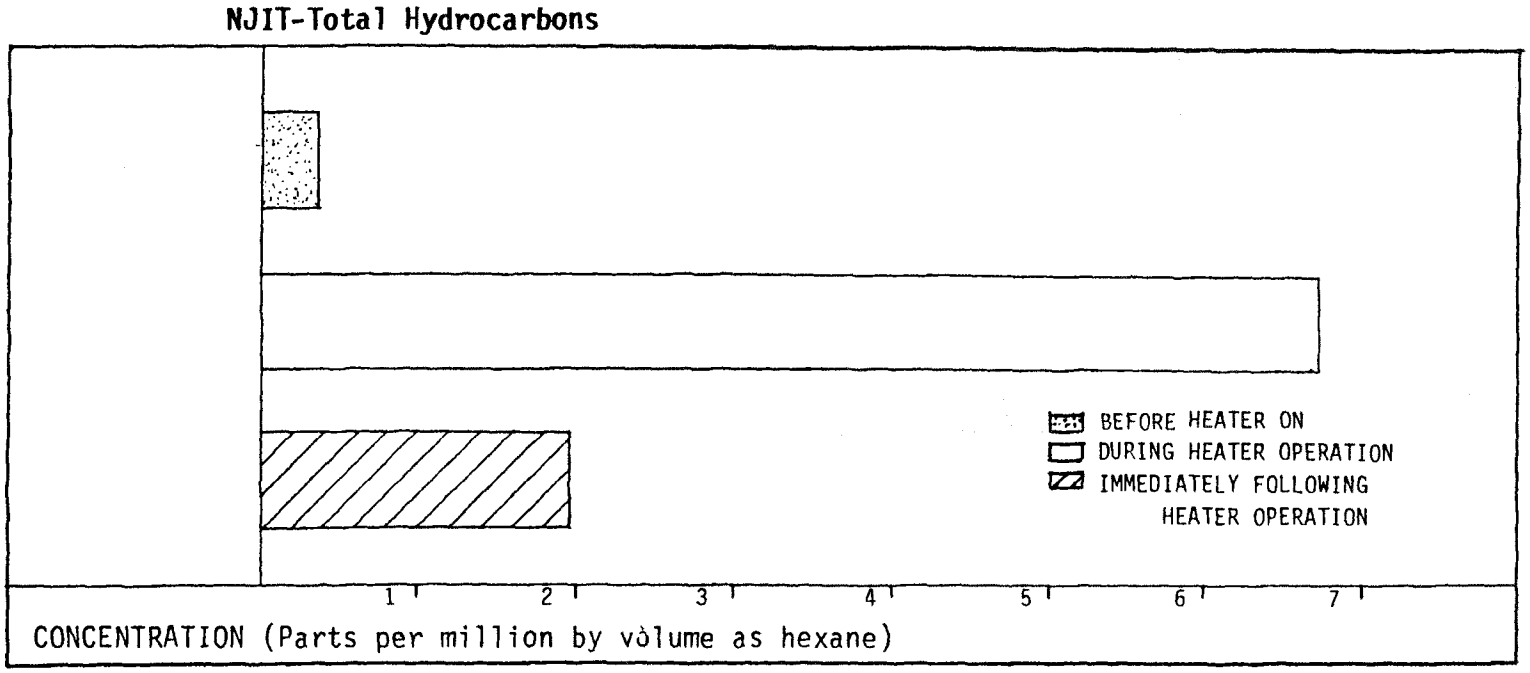


Figure 4-3


NJIT-Total Hydrocarbons
BEFORE HEATER ON
DURING HEATER OPERATION
IMMEDIATELY FOLLOWING HEATER OPERATION
1
2
3
4
5
6
7
CONCENTRATION (Parts per million by volume as hexane)

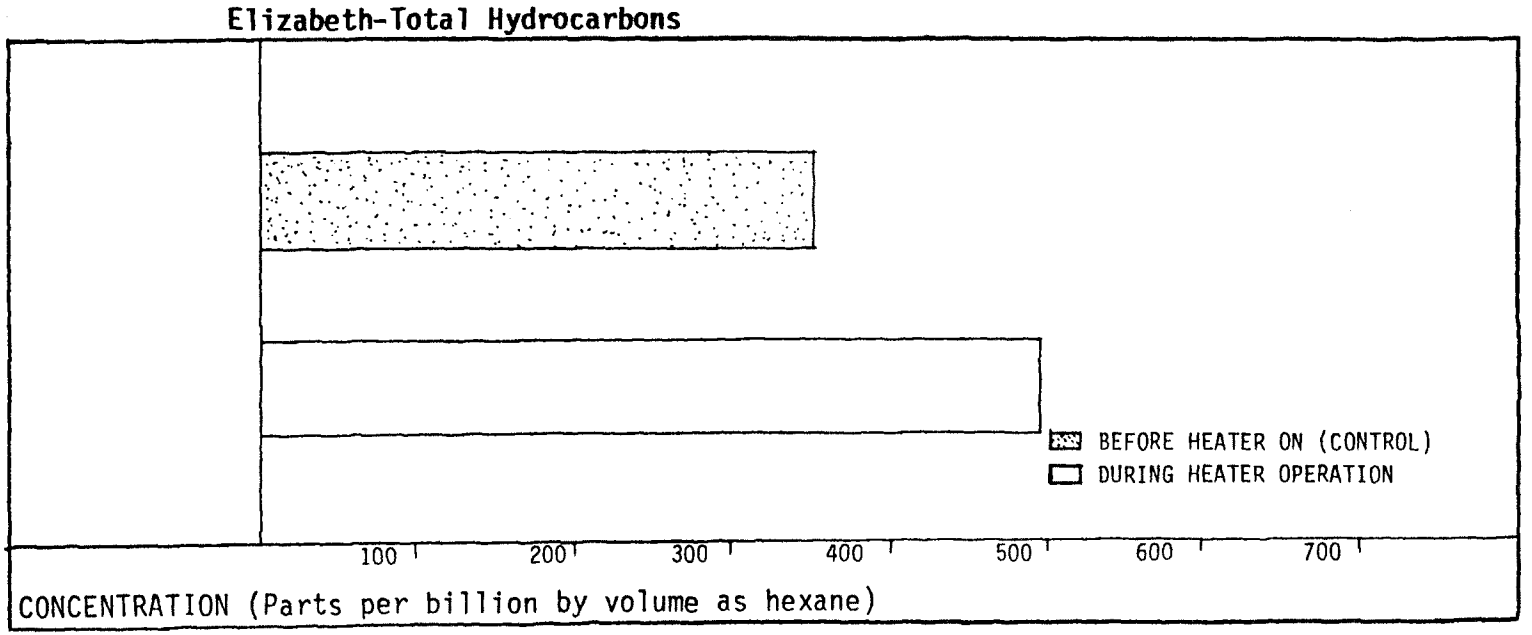
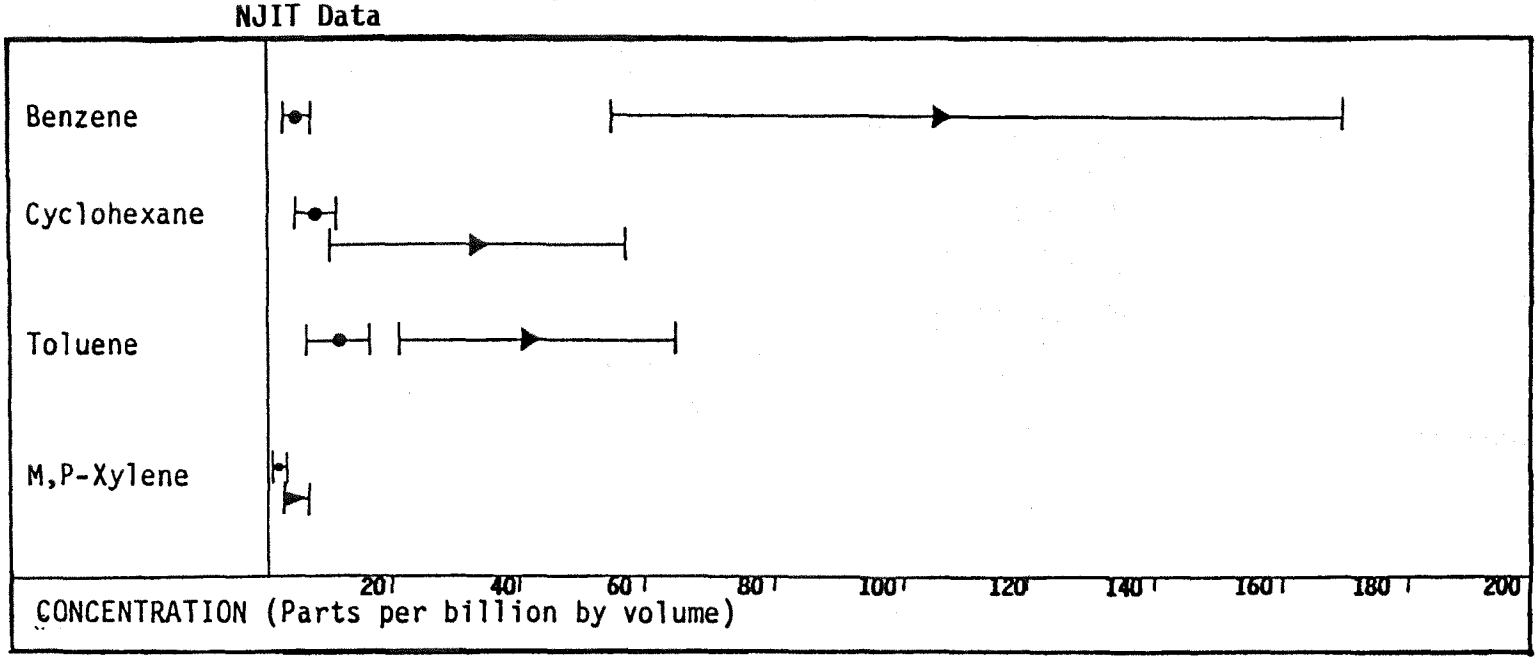
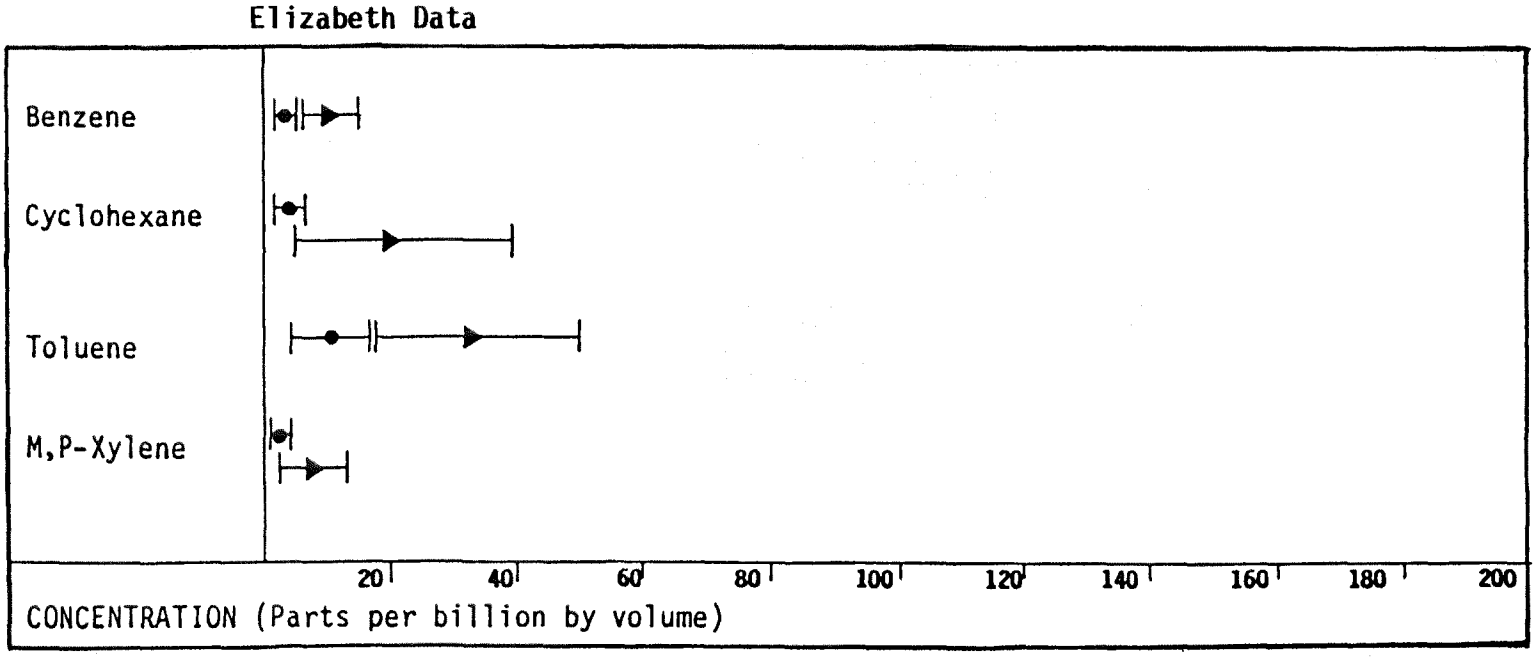

Elizabeth-Total Hydrocarbons
BEFORE HEATER ON (CONTROL)
DURING HEATER OPERATION
100
200
300
400
500
600
700
CONCENTRATION (Parts per billion by volume as hexane)

Figure 4-4

Confidence Intervals of Data





LEGEND: ▶ Mean value during heater operation
● Mean value backgrou

Figure 4-5

4.2.1 NJIT Data

4.2.1.1 Background vs Heater On

The most striking difference between air quality before the heater was introduced into the room and during heater operation was the significant increase in mean benzene levels (2022.5% change). In addition, hexane levels increased markedly (by 1335.1%); less dramatic but notable were increases in ethyl benzene (790.6%), heptane (419.0%), decane (328.6%) and cyclohexane (321.3%). No increase in octane and nonane levels was observed.

4.2.1.2 Heater On vs Heater Extinguished

Comparison of data acquired during heater operation with that collected immediately following heater use indicates a significant increase in mean hexane values (786.0%); more moderate increases in decane (133.3%) and nonane (130.0%). There was also a moderate drop in concentration among five aliphatic species: undecane (-99.4%), dodecane (-94.1%), octane (-81.8%), hexane (-79.5%) and cyclohexane (-49.6%). No increase in concentration of four aromatic species was also

indicated: benzene, ethyl benzene, styrene and m- and p-xylene.

4.2.1.3 Background vs Heater Extinguished

Finally, comparison between background levels and those encountered immediately after extinguishing the heater reveal significantly higher concentrations of hexane (786.0%), heptane (625.0%), benzene (460.6%), toluene (362.8%), ethyl benzene (194.3%) and pentane (194.1%). Two species experienced minor reductions in concentration: octane (-93.1%) and nonane (-75.9%). The overall pattern of variation is presented in Figures 4-1 and 4-3.

4.2.1.4 Total Hydrocarbons

The total weight (in micrograms per cubic meter) of identified species was calculated by summing the weights of the individual species. The following results were obtained: 38.32 ug/cu m (background); 283.62 ug/cu m (during heater operation); and 152.59 ug/cu m (immediately after heater use). Additionally, a second calculation procedure using the total concentrations of identified and unidentified organic species measured by flame ionization, correcting for sample

volumes yielded the following pattern of change similar to that observed when accounting only for identified species: background levels (308.26 ppbv expressed as hexane); levels during heater use (6838.34 ppbv as hexane); and levels following heater operation (1947.6 ppbv as hexane) (see Figure 4-4). When examined for relative change, the identified species concentration (by weight) increased by over seven fold from background while the heater was running and declined by approximately fifty percent after it was extinguished. Total volatiles, however, increased by over twenty-two fold during heater operation and dropped by over three fold following heater use.

4.2.2 Elizabeth Data

4.2.2.1 Background vs Heater On

The most significant differences from background observed during heater operation were levels of undecane (5985.7% increase), decane (1641.2 % increase) and nonane (1700.0% increase). Cyclohexane levels rose moderately (by 411.1%) while less marked increases in several aromatic species: m- and p-xylene (300.5%),naphthalene (284.6%), toluene (219.3%),

o-xylene (214.6%) and benzene (189.4%) were indicated. Octane and dodecane levels were similarly elevated (by 181.8% and 227.0% respectively). These species must be simply in the fuel itself and not products of incomplete combustion (Figures 4-2 and 4-3).

4.2.2.2 Total Hydrocarbons

Total background summer concentration by weight of identified species was 34.94 ug/cu m compared to 111.16 ug/cu m during heater operation. An analysis of total volatile organics detected by flame ionization indicated an average background concentration of 351.03 ppbv (expressed as pentane) compared to 490.23 ppbv (as pentane) while the heater was in use (Figure 4-4). The former analysis indicates slightly over a three-fold increase in levels of identified compounds while the latter represents an increase of approximately forty percent.

4.2.3 Mass Spectral Results

Mass spectral analysis of samples collected at both sites indicated the presence of aliphatic hydrocarbons ranging from C5 to C13. Substituted aromatic species including

trimethylbenzenes, propylbenzene, isopropylbenzene, and ethyltoluenes were also observed consistently. Additionally, C4-substituted benzenes including isobutylbenzene and propylmethylbenzene were identified.

4.2.4 Precision and Accuracy of Results

It has been previously reported that the minimum detectable limit for benzene is 0.005 ppbv using this capillary column gas chromatograph/flame ionization system (Bozzelli and Kebbekus, 1979). During refinement of the technique, known volumes of standard mixture were collected onto Tenax adsorbent (following the procedure outlined in Chapter 3). There was 89% (13% SD) recovery of benzene. Incomplete recovery was attributed to only partial desorption from the collection material. Cumulative error resulting from three key analytical steps, specifically, 1) variation in volume measurement including variation in flow resistance of adsorbent cartridges; 2) calibration of the chromatograph due to variations in instrumental stability and reproducibility of sample injection; and 3) inaccuracies in desorption and analysis, was estimated at 17% for benzene. Due to difficulties encountered in calibration and analysis, the overall standard deviation for nitrobenzene was calculated to be 58%. In our study, the only nitrobenzene value measured

was 1.81 ppbv at the Elizabeth site. Should further analysis for nitrobenzene be conducted, it is recommended that an alternate or modified method be adopted.

Confidence intervals ($x \pm 1.96$ SE) were calculated for each individual species and the results for several compounds are presented in Figure 4-5. A two-tailed Student's t test at $p<0.05$ was selected as the test for significance for the sample containing two sets of data (the Elizabeth site). There was some variation in results; the null hypothesis was rejected for nine of the sixteen species (excluding nitrobenzene), indicating that there was significant difference between the two data sets for the species indicated. Four of the remaining species (hexane, styrene, decane and dodecane) approximated significance at $p<0.10$ and for the remainder (pentane, ethylbenzene and naphthalene) significance was more difficult to establish.

Analysis of Variance (ANOVA) was selected for application to the NJIT data where three populations were to be compared. The technique compares the explained variance between the sample means with the unexplained variance within the samples. This statistical test was considerably less successful in establishing significance; only four of the data comparisons: hexane and benzene (at $F=0.05$) and cyclohexane and octane (at $F=0.25$) were indicated as deriving from statistically discrete populations. A less complex

comparison of the data (Figure 4-5) indicates no significant overlapping of values within the 95% confidence interval.

There are variations within the "heater on" values which can be attributed to differences in duration of sampling. Our total hydrocarbon analysis indicated that there is a sharp increase in organic pollutant levels once the heater is ignited; followed by a plateau during heater operation and then a slow decline once the heater is extinguished. The samples analyzed by gas chromatography are time-averaged; therefore, samples of only one hour would contain lower concentrations of pollutants than those of longer duration. Similarly, the samples collected immediately after the heater was extinguished may have minor variation due to differences in duration of sampling.

4.3 Comparative Air Quality

4.3.1 Outdoor Data

Only recently has analytical capability evolved to permit characterization of individual organic species at trace levels; published research on volatile organics is therefore limited. However, several references are available for a

broader perspective of the data.

Aromatic species consisting of toluene, benzene, m- and p-xylenes, ethylbenzene and o-xylene were measured at four sites: Sydney, Australia; Los Angeles, California; Phoenix, Arizona; and Oakland, California (Nelson and Quigley, 1982; Singh et al, 1979). Comparison with the kerosene heater data is provided in Table 4-4. Background indoor values for four of the species is extremely consistent between the NJIT and Elizabeth sites (i.e., toluene: 11.94 and 10.73 ppb, benzene: 5.28 and 3.70 ppb, m,p-xylenes: 2.31 and 2.07 ppb, and o-xylene: .82 and .82 ppb). Toluene measurements are within the same range of magnitude for both indoor and outdoor samples. All background benzene levels also are roughly equivalent, but significantly higher concentrations are indicated during and after heater use. The pattern is less evident for m,p-xylenes where our NJIT heater-related values are comparable with levels at three of the four outdoor sites; while the indoor air value obtained during heater operation at the Elizabeth site is almost twice the highest outdoor value. Similarly, the NJIT values for o-xylene are comparable to outdoor values whereas the Elizabeth data acquired during heater operation is moderately higher. Ethylbenzene values associated with heater operation at both sites are notably higher than those representative of outdoor air quality.

TABLE 4-4

COMPARISON OF KEROSENE HEATER EMISSIONS WITH AROMATIC SPECIES IN OUTDOOR AMBIENT AIR

(Concentrations in ppbv)

COMPOUND	OUTDOOR VALUES				INDOOR VALUES		HEATER (ON) VALUES	
	SYD[1]	LA [2]	PNX [3]	OKL[4]	ELIZ	NJIT	ELIZ	NJIT
TOLUENE	8.90	11.72	8.63	3.11	10.73	11.94	34.26	43.19
BENZENE	2.60	6.04	4.74	1.55	3.70	5.28	10.71	112.07
ETHYLBENZENE	1.30	2.25	2.00	.60	1.98	.53	3.40	4.72
M,P -XYLENES	3.90	4.61	4.20	1.51	2.07	2.31	8.29	5.42
O- XYLENE	1.50	1.93	1.78	.77	.82	.82	2.58	1.85

References:

[1] Nelson and Quigley (1982)

[2-4] Singh et al. (1979)

Analysis of thirty-seven sets of data measuring outdoor benzene concentrations yielded a frequency distribution strongly clustered within the range of 1 - 7 ppbv (US EPA, 1978; Nelson and Quigley, 1982; Singh et al, 1979; Singh et al, 1982; Bozzelli and Kebbekus,1979; Bozzelli and Kebbekus, 1982). The mean indoor background concentrations at the NJIT and Elizabeth sites are within this range, however the three heater-related means are notably elevated.

Analysis of benzene exposure at three self-service gasoline stations during pump operation yielded separate values of 43, 121 and 647 ppbv (Mara and Lee, 1978). The geometric mean of these data can be calculated as 149.9 ppbv; this value is within the same order of magnitude as that obtained during heater operation at the NJIT site.

4.3.2 Indoor Data

Within the indoor environment, organic pollutants may arise from a number of sources including:

- structural materials (particle board, plywood, panelling, insulation);
- furnishings (carpet, drapes, furniture);
- combustion (fireplace, furnace, unvented heater, stove);
- consumer products (aerosols, deodorizers, household solvents, cleaners, coatings;

- and activities such as smoking, hobbies and crafts.

A Danish study (Molhave, 1980) of organic gases and vapors in headspace over (presumably new) building materials was recently cited (Beall and Ulsamer, 1981) and concentrations of the species relevant to our study are presented in Table 4-5. These values are all approximately four orders of magnitude greater than those encountered in our study. An obvious distinction between the two study conditions is the effect of air change and ventilation. Our study did not measure emissions in the closed headspace of the heater but instead approximated a distance from the heater typical of that of a room occupant with the noted air exchange rates.

In a Norwegian study (Ramdahl, 1981) characterizing emissions from wood-fired stoves, benzene values of 68 - 1290 mg/kg of dry wood were detected. For comparison with our benzene emission rates, we assume that the heating value of dry wood is approximately 6,000 Btu/lb, then:

(68 mg benzene/kg of dry wood)(1b of wood/6,000 Btu)
(.4536 kg/1b)(Btu/1.055 KJ)(ug/.001 mg) = 4.9 ug/KJ

Using the same equation, the upper value for Norwegian wood stoves (1290 mg/kg) yields an equivalent of 92.4 ug/KJ. The NJIT kerosene heater data yielded a value of approximately 3.7 ug/KJ, roughly equivalent (24% difference) to the lower value (68 mg/kg) and approximately twenty-five times smaller than the upper value (1290 mg/kg). Again, it should be noted

TABLE 4-5

COMPARISON OF KEROSENE HEATER EMISSIONS WITH ORGANICS IN HEADSPACE OVER BUILDING MATERIALS *

	CONCENTRATION BY WEIGHT (ug/m^3)		CONCENTRATION BY VOLUME (ppbv)	
COMPOUND	Mean Heater (On) Value	Headspace of Bldg Materials	Mean Heater (On) Value	Headspace of Bldg Materials
HEXANE	2.38	8700.	16.50	2468.
HEPTANE	.61	7300.	3.61	1781.
OCTANE	.11	290.	.58	62.
NONANE	.37	920.	1.72	175.
DECANE	.74	1450.	3.11	249.
UNDECANE	1.2	580.	4.58	91.
TOLUENE	5.97	36000.	38.73	9553.
M, P - XYLENE	1.22	37600.	6.14	8659.
O-XYLENE	.40	5800.	2.22	1336.
STYRENE	.41	610.	2.32	143.
ETHYLBENZENE	.72	4100.	4.06	944.

Reference:
* Molhave (1980).

that the Norwegian study measured flue gases, which are much more likely to be more concentrated than volatiles measured in a vented room because the chimney prevents loss and dilution in ambient air. The two measurements are, however, comparable.

Preliminary results of a sampling program initiated by the Centers for Disease Control and the National Institute of Occupational Safety and Health to characterize indoor air pollution in "complaint" office buildings may also be compared with our findings (Hollowell and Miksch, 1981). These buildings are primarily new, with hermetically sealed windows, receiving attention in response to complaints from office workers. Simultaneous indoor and outdoor measurements were made. Total hydrocarbon concentrations of 1627 ± 26 ug/cu m (2.5 ppm expressed as methane) were detected indoors, whereas the mean outdoor concentration was 210 ±60 ug/cu m (.32 ppm as methane).

Qualitative analysis by gc/ms revealed the presence of three classes of compounds. In greatest predominance were the aliphatics - straight chain plus derivatives of cyclohexane; alkylated aromatic hydrocarbons (predominantly toluene, as well as xylenes, trimethyl- and other substituted benzenes, methyl- and dimethylnaphthalenes) followed by chlorinated hydrocarbons (probably from ambient air only). The concentrations were estimated to be in the 1 to 100 ppbv

range. Unfortunately,no additional data was available on the sampling program. A rough comparison with our total hydrocarbon results can be made (Table 4-6).

Detailed analysis of the differences and similarities between the two studies is not feasible without additional documentation of such parameters as air circulation rate and pollutant sources. The authors do, however, provide a listing of "typical" sources of organics in office spaces including the wet process photocopier which they estimate generates 25 g/hr-office of aliphatic hydrocarbons in an office having a total volume of 100,000 cu ft. This is equivalent to 8.8 ug/cu m per hour of operation (13.4 ppb or .01 ppm expressed as methane); a very small percentage of the total hydrocarbons measured, and roughly two orders of magnitude lower than the values obtained in the kerosene heater studies.

TABLE 4-6

COMPARISON OF KEROSENE HEATER EMISSIONS WITH TOTAL HYDROCARBONS MEASURED IN OFFICE BUILDINGS

CONDITION	MEAN CONCENTRATION BY WEIGHT (ug/m^3)	MEAN CONCENTRATION BY VOLUME (ppm_v) (AS METHANE)
OUTDOOR[1] (office vicinity)	210	.32
INDOOR OFFICE[1]	1627	2.50
KEROSENE HEATER ON[2]	1050	1.60

References:

[1]Hollowell and Miksch (1981)
[2]Banerjee (1984)

Chapter 5

DISCUSSION

5.1 Benzene Toxicity

For the purposes of this toxicological review, benzene has been selected for detailed investigation. Of all the volatile organics identified in this study, benzene is the only species for which exposure to the levels detected is relatively close to the OSHA permissible exposure limit (Table 5-1). Additionally, considerable concern has been registered within the medical community that tangible risk may be present at ppb levels (US EPA, 1979; Laskin and Goldstein, 1977; Snyder and Kocsis, 1975). Since 1897, the published literature has documented innumerable cases of benzene exposure linked to hematological disorders (damage relating to blood and/or the blood-forming organs, principally the bone marrow) (Laskin and Goldstein, 1977; Santesson, 1897). Despite these accounts, it has yet not been clearly established whether there is a "safe" level of ambient benzene or whether, in fact, <u>any</u> detectable level of

TABLE 5-1

OCCUPATIONAL STANDARDS

COMPOUND	OSHA PERMISSIBLE EXPOSURE LIMIT
PENTANE	1000 ppm TWA
HEXANE	500 ppm TWA
HEPTANE	500 ppm TWA
OCTANE	500 ppm TWA
NONANE	200 ppm TWA (under review)
DECANE	400 ppm TWA
UNDECANE	NS
DODECANE	NS
CYCLOHEXANE	300 ppm TWA
BENZENE	10 ppm TWA
TOLUENE	200 ppm TWA
STYRENE	100 ppm TWA
ETHYLBENZENE	100 ppm TWA
M,P - XYLENE	100 ppm TWA (recommended standard)
O - XYLENE	100 ppm TWA (recommended standard)

NS = no standard yet promulgated
TWA = time weighted average

Reference: U.S. Department of Health and Human Services (1983)

benzene may present the risk of adverse health effect. Notably, alkyl substitution of the benzene ring significantly alters the metabolic pathway and also largely removes potential for bone marrow toxicity (Doull et al, 1980).

5.2 Leukemia

Benzene is a proven human carcinogen - it has been shown to cause a severe form of adult leukemia - acute myelogenous leukemia and its variants (acute myelomonocytic leukemia, acute promyelocytic leukemia and erythroleukemia) - among individuals who have been occupationally exposed (Goldstein and Snyder, 1982). Leukemia is characterized by malignant, unrestrained proliferation of abnormal white blood cells in the circulating blood and/or within the bone marrow. The filling and replacement of bone marrow by these abnormal cells results in anemia (diminished red blood cell count), thrombocytopenia (reduced platelet count) and a deficiency of functional leukocytes (Golden, 1982).

Intensive therapy leads to remission in 70 percent of patients with acute myelogenous leukemia but there is often a relapse in less than a year. Survival statistics have been grim; fewer than 5 percent survive five years after diagnosis (Golden,1982). However, continuing advances in chemotherapy

result in an improved prognosis.

The dose of benzene inhaled by individuals who subsequently develop acute myelogenous leukemia has not been established (Goldstein, 1982a). Monitoring of ambient benzene levels has been inadequate in published accounts; either the concentrations have not been measured at all; or only at peak concentrations; or only once or twice yearly. Accordingly, researchers have resorted to adoption of retrospective approximations or best estimates (Aksoy, 1974; Infante et al, 1977; Albert et al, 1979).

In the few cases of industrial exposure where benzene levels are reported, concentrations have generally been above 100 ppm. However, in one study documenting excessive leukemia deaths, the factories involved initially were believed to be in compliance with the existing benzene standard (Infante et al, 1977; Lave, 1982). Largely because of this case study, the Occupational Safety and Health Administration in 1977 attempted to establish a more stringent standard (1 ppm TWA). (The next section will explore the regulatory history in greater detail). Also lacking in the literature are details concerning periods of occupational benzene exposure and a clear definition of the population at risk. Despite their shortcomings, the studies have served to establish a qualitative association between benzene and leukemia.

The incidence of acute myelogenous leukemia in the general population is very low (in the U.S., approximately 8 deaths per 100,000 persons/yearly are attributed to all forms of leukemia) (Lave, 1982). The incidence due to benzene represents a small absolute increase in cases per year (Albert et al, 1979). Hence, development of a statistically significant research model may conceivably be difficult. But even more importantly, the search for the mechanism by which benzene acts has, until recently, been impeded by the absence of a suitable animal model (Snyder et al, 1982).

Fifty years of benzene research have failed to demonstrate acute myelogenous leukemia in laboratory animals (Synder et al, 1980). Finally, in 1980, an inducible lymphoma was observed in a strain of black mice exposed to 300 ppm benzene for six hours daily, five days weekly, lifetime (Green et al, 1981). In 1981, four cases of myeloproliferative disease were observed (Goldstein et al, 1982). One was identified as chronic myelogenous leukemia, another as acute myeloblastic leukemia and a third as granulocytic hyperplasia, among forty mice exposed to 300 ppm benzene for six hours daily, 5 days weekly, lifetime. One case of chronic myelogenous leukemia was detected among forty rats similarly exposed to 100 ppm benzene. These findings are not statistically significant. However, the authors believe that the CD-1 mice selected for the study may be the appropriate strain for developing an

experimental model for benzene leukemogenesis.

If it is proven that benzene exerts its carcinogenic effect directly, that is, without any intervening phase of hematological damage, then it can be described as a classic carcinogen. The theory of carcinogenicity assumes that each chemical molecule has an equal probability (compared with other molecules of the same substance) of altering a cell, and that any alteration that makes a single cell carcinogenic has an equal probability of producing a tumor. The resulting dose:response curve is linear, with response directly proportional to dose at low levels of exposure but in which any dose has a positive probability of producing cancer (no threshold) (Goldstein, 1983b).

A curious but evidently common observation from bioassays is that the time between exposure and tumor induction is inversely related to the rate of exposure, where the total dose remains constant, i.e., low dose; long induction period (Lave, 1982). What this implies is that, if the dose rate is sufficiently low (--- and concentration is also accordingly low), the latency period will exceed lifespan. If this is the case, an argument can be made that a practical threshold does exist at low benzene levels. As it is, induction of leukemia after exposure to benzene typically follows a long latency period of 15 to 27 years (Lave, 1982).

5.3 Pancytopenia

Benzene has also been shown to exert hematotoxic effects (WHO, 1982). Pancytopenia, or diminished counts of all formed elements of the blood (eg., white blood cells, red blood cells and platelets), has frequently been observed; some evidence indicates that the survival of circulating cells may be shortened also (Laskin and Goldstein, 1977). In severe cases, pancytopenia may be accompanied by hemorrhagic effects, with the potential of fatal bleeding, or by critical infection, due to impaired immumological function resulting from the decrease in granulocytes (Laskin and Goldstein, 1977).

Numerous cases of pancytopenic individuals with known benzene exposure have been followed through a preleukemic phase into the onset of acute myelogenous leukemia (Laskin and Goldstein, 1977). Whether pancytopenia is a prerequisite for benzene-induced acute myelogenous leukemia is unknown (Goldstein, 1983). In its attempt to compensate for the severe reduction in leukocytes, the body's repair systems may trigger excessive production of these cells, leading to the onset of leukemia. Or, the cancer may be the result of compromised immune surveillance, resulting in survival of

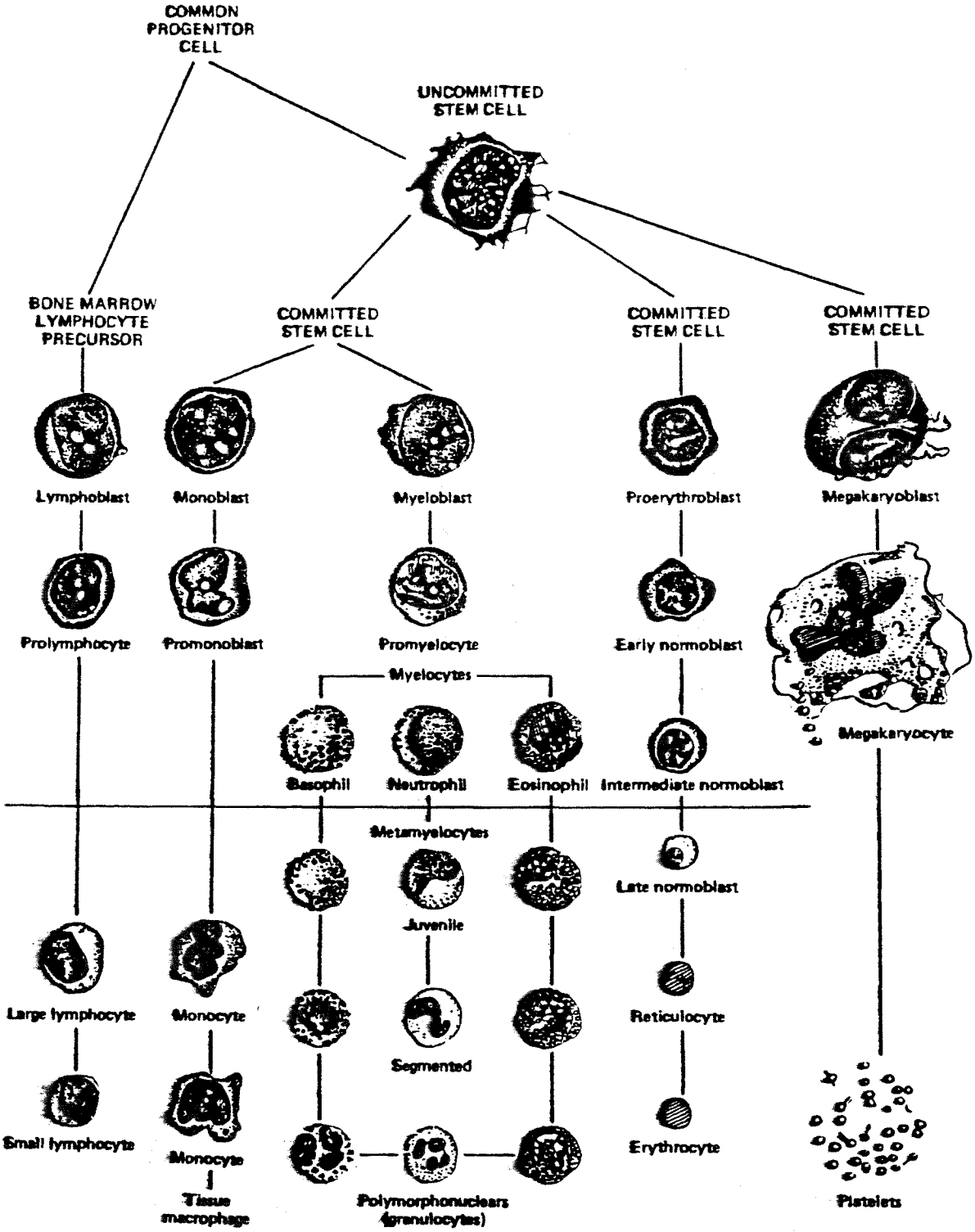
abnormal leukocytes which then proliferate.

Benzene's mode of action on the bone marrow, where the end result is panyctopenia, has not yet been elucidated. According to the current theory of hematopoeisis, the bone marrow contains pluripotent uncommitted stem cells from which unipotent committed stem cells may arise on demand (triggered by circulating hormones, eg., erythropoeitin, which stimulates formation of red blood cell precursors).(See Figure 5-1 which illustrates the pathway for the production of the various blood elements). Benzene conceivably exerts its toxic effect on this pluripotential cell. Some evidence also exists for a precursor to this pluripotential cell, called the common progenitor cell, which is believed to differentiate into both lymphocytic and myelocytic precursors. Benzene may, in fact, exert its effect here; clinical evidence indicates that pancytopenic individuals with a history of benzene exposure also exhibit lymphocytopenia (US EPA, 1978). Recent progress in isolating and characterizing bone marrow precursor cells promises to be of great use in at last discovering the effects of benzene on its target cell.

5.4 Aplastic anemia

FIGURE 5-1

DEVELOPMENT OF FORMED ELEMENTS OF BLOOD
FROM BONE MARROW CELLS



REFERENCE: GANONG (1981)

Aplastic anemia (a disease in which blood-forming precursor cells within the bone marrow are either absent or significantly reduced) has historically been distinguished from pancytopenia (Laskin and Goldstein, 1977). This disease is diagnosed by aspiration of bone marrow, and analysis of a minute amount of hematopoietic tissue. Sampling error is thus associated with the test, possibly skewing results. Some researchers have, for the purposes of analysis, included cases of aplastic anemia within the overall subject of benzene-induced pancytopenia (and others may use the terms interchangeably). Hyperplastic bone marrow has been observed in pancytopenic individuals following benzene exposure, as has aplastic anemia; in either case, depressed blood counts are evident.

Severe aplastic anemia is associated with a mortality rate of over 50% (Laskin and Goldstein, 1977). In its extreme, the disease may result in complete destruction of the myeloid and erythroid (respectively, white and red blood cell-producing) components of the bone marrow. In laboratory animals, aplastic anemia is the inevitable consequence of benzene-induced pancytopenia. In both humans and laboratory animals, bone marrow damage appears proportional to the dose of benzene, with aplastic anemia apparently resulting from higher concentrations or unusual host susceptibility (Laskin and Goldstein, 1977). More commonly, occupational benzene

exposure may result in a mild case of pancytopenia or individual cytopenia (leukopenia, anemia or thrombocytopenia).

It should be noted that there is a fairly large "safety factor" associated with circulating blood counts. Symptoms of anemia typically occur when hemoglobin levels fall to about 10 g% (normal: 14 - 18 g%); increased susceptibility to infection may occur when granulocyte counts drop to 1,000 - 1,200 per cubic millimeter (normal: 3,000 - 6,000 per cubic millimeter) and abnormal bleeding is a risk when platelet counts are reduced to 30,000 per cubic millimeter (normal: 150,000 - 350,000 per cubic millimeter) (Laskin and Goldstein, 1977). Little research is available concerning chronic effects of mildly depressed blood counts; in many cases, the depression is reversible.

Aplastic anemia has classically been associated with an increased risk of acute myelogenous leukemia when caused by other agents, for example, administration of the drug, chloromycetin (Goldstein and Snyder, 1982). Should this disease (or pancytopenia) be an absolute prerequisite for benzene-induced leukemia, it is believed that the current OSHA maximum exposure limit of 10 ppm provides adequate protection (Goldstein, 1982(a)).

5.5 Chromosomal Damage

Benzene is also known to cause chromosomal breakage and rearrangement, in the bone marrow and in circulating lymphocytes of laboratory animals and humans (US EPA, 1978; Laskin and Goldstein, 1977). Significantly, it has been demonstrated that chromosomal abherrations persist in individuals who have recovered from benzene-induced pancytopenia (Forni et al, 1971). Following chromosomal damage, the cell may pursue one of two paths; either the damage is sufficient to interrupt cell division and the cell eventually dies (so the effect is cytotoxic) or the alteration is replicated (so the effect is mutagenic) and the mutation will be carried through each cell division. The resulting structural change may alter function of the daughter cells and increase the probability that an abnormal proliferative state will arise. It is believed that all carcinogens are also mutagens, and this also accounts for a delay in the onset of a disease following exposure to a carcinogen (Lave, 1982).

A dose-response relationship between benzene exposure and the extent of chromosomal damage has not been documented. One controversial study recorded excessive chromosomal damage among workers employed in a chemical factory where benzene levels were less than 10 ppm (Wolman, 1979). Another study

indicated significant chromosomal abnormalities in workers at one factory where ambient concentrations ranged from 25 to 150 ppm (US EPA, 1978). Similar benzene levels were present in a second factory; in this case both the control and the exposed groups exhibited elevated levels of chromosomal abherrations. It has been demonstrated that chromosomal damage persists in individuals who have recovered from benzene-induced pancytopenia (US EPA, 1978). It has not yet been conclusively established whether low levels of benzene are capable of producing chromosomal damage.

5.6 Benzene Metabolites

How does benzene damage chromosomes within bone marrow cells and circulating lymphocytes? How does benzene cause hematotoxicity and acute myelogenous leukemia? Perhaps a more reactive form of benzene, arene oxide or epoxide, as a strong electrophile, is the responsible agent. Substantial research involving laboratory animals has elucidated various metabolic pathways of benzene following exposure (US EPA, 1978). The benzene epoxide is formed by oxidation of benzene via the cytochrome P450 monooxygenase system. It is capable of covalently binding with many biological elements, including nucleic acids (DNA and RNA), proteins, nucleotides and amino acids. However, as a highly reactive species, it

has an extremely short half life, and thus is most likely to act at its site of formation (principally the liver).

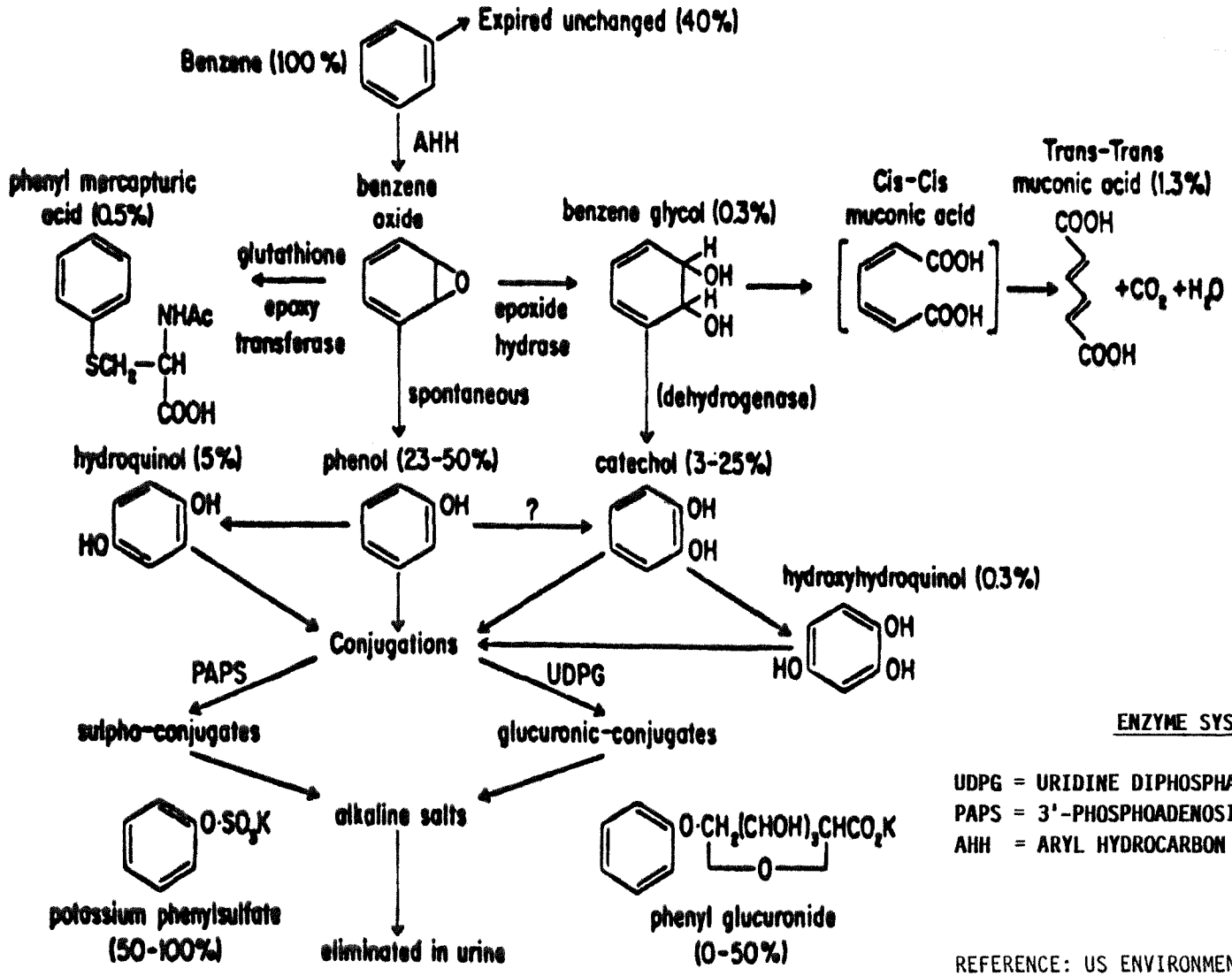
The benzene epoxide may bind to hepatic macromolecules. Alternatively, it can spontaneously rearrange to form the more stable phenol which may then undergo conjugation reactions: with sulfate, catalyzed by sulfate transferase, to yield sulpho-conjugates (eg., potassium phenylsulfate); or with glucuronic acid, catalyzed by glucuronyl transferase, to form glucuronic conjugates (eg., phenyl glucuronide) (US EPA, 1978). Epoxide can also be transformed into the corresponding dihydrodiol (benzene glycol) by epoxide hydrase. (Activity attributed to this enzyme has been identified in the endoplasmic reticulum of a number of tissues and organs, but, significantly, not in blood components) (Doull et al, 1980).

Benzene glycol may then be dehydrogenated, yielding catechol; or, conceivably, the benzene ring may be broken, to form trans-trans muconic acid. The epoxide may also react with glutathione, catalyzed by glutathione-transferase, forming a glutathione derivative which may ultimately yield phenyl mercapturic acid.

Figure 5-2 traces a simplified metabolic pathway for benzene in experimental animals. Many questions remain unanswered; eg., what decides the metabolic fate of a given exposure to benzene? Preliminary evidence suggests that

FIGURE 5-2

SIMPLIFIED PATHWAY OF BENZENE METABOLISM
IN EXPERIMENTAL ANIMALS



ENZYME SYSTEMS

UDPG = URIDINE DIPHOSPHATE GLUCURONYL TRANSFERASE
PAPS = 3'-PHOSPHOADENOSINE-5'-PHOSPHOSULFATE
AHH = ARYL HYDROCARBON HYDROXYLASE

REFERENCE: US ENVIRONMENTAL PROTECTION AGENCY (1978)

alternate pathways may be pursued once the more traveled routes are saturated. Which metabolite(s) may be the actual hematotoxin(s)? Currently, research is being undertaken to determine whether muconaldehyde, a six carbon diunsaturated dialdehyde, may play a role in hematotoxicity (Goldstein, 1982b). Muconaldehyde has been formed in vitro from benzene following interaction with hydroxyl radicals. (In vivo, microsomes provide a source of hydroxyl radicals). And yet, if it can be proven that muconaldehyde is a biological metabolite of benzene, the question previously asked for epoxide applies - "How is it transfered from its site of formation (the liver) to its site of action (the bone marrow)?" This discussion begins to illustrate the complexity inherent in tracing the effects of exposure to varying concentrations of a foreign compound over the lifetime of an individual.

Chapter 6

RISK ASSESSMENT

6.1 Benzene Exposure Limits

Currently, fifteen countries have adopted regulations or recommended guidelines to limit occupational exposure to benzene (Table 6-1). The U.S. Occupational Safety and Health Administration (OSHA) standard (10 ppm TWA; with a ceiling of 25 ppm and a peak limit of 50 ppm for no more than 10 min. per 8 hour period) was established in 1971 to safeguard against noncarcinogenic (i.e., hematotoxic) effects (WHO, 1982). A review of the available health-related information on benzene led a panel at the National Academy of Sciences to designate benzene a suspected leukemogen in 1976 (National Academy of Science, 1976). Later that year, the National Institute of Occupational Safety and Health (NIOSH) submitted a revised criteria document concerning occupational exposure to benzene, describing benzene as a leukemogen. It further recommended that, since no safe level for benzene exposure could be determined, an emergency standard should be

TABLE 6-1

INTERNATIONAL EXPOSURE LIMITS FOR BENZENE

Table 1. National occupational exposure limits for benzene[a]

Country	Year	Concentration mg/m³	Concentration ppm	Interpretation[b]	Status
Australia	1978	30	10	TWA[c]	Guidelinge
Belgium	1978	30	10	TWA[c]	Regulation
Czechoslovakia	1976	50	—	TWA	Regulation
		80	—	Ceiling (10 min)	
Finland	1975	32	10	TWA[c]	Regulation
Hungary	1974	20	—	TWA[d]	Regulation
Italy	1978	30	10	TWA[c]	Guideline
Japan	1978	80	25	Ceiling	Guideline
The Netherlands	1978	30	10	TWA[c]	Guideline
Poland	1976	30	—	Ceiling[c]	Regulation
Romania	1975	50	—	Maximum[c]	Regulation
Sweden	1978	15	5	TWA[c]	Guideline
		30	10	Maximum (15 min)	
Switzerland	1978	6.5	2	TWA[c]	Regulation
USA[a]					
OSHA	1980	—	10	TWA	Regulation
		—	25	Ceiling	
		—	50	Peak[e]	
ACGIH	1981	30	10	TWA	Guideline
		75	25	STEL	
NIOSH	1980	3.2	1	Ceiling (60 min)	Guideline
USSR	1980	5	—	Ceiling[c]	Regulation
Yugoslavia	1971	50	15	Ceiling[c]	Regulation

a From American Conference of Governmental Industrial Hygienists (ACGIH) (1981); International Labour Office (1980); National Institute for Occupational Safety and Health (NIOSH) (1980); US Occupational Safety and Health Administration (OSHA) (1980)

b TWA, time-weighted average; STEL, short-term exposure limit

c Skin irritant notation added

d May be exceeded 5 times per shift as long as average does not exceed value

e Peak limit above ceiling - 10 minutes

REFERENCE: WORLD HEALTH ORGANIZATION (1982)

promulgated by OSHA, revising the occupational exposure limit downward to 1 ppm (Lave, 1982).

On May 3, 1977, OSHA issued such a standard, to take effect May 21, 1977. Institution of an emergency temporary standard is highly unusual and is permitted only on the basis that OSHA ascertains "that employees are exposed to grave danger from exposure to substances or agents determined to be toxic or physically harmful or from a new hazard, and...that such emergency standard is necessary to protect employees from such danger" (Lave,1982). On May 20th, the Fifth Circuit Court of Appeals issued a temporary restraining order, ruling on legal challenges by the American Petroleum Institute and others. The emergency standard never became effective.

During July and August of 1977, OSHA received testimony concerning the adoption of a proposed permanent standard which incorporated the 1 ppm exposure limit. OSHA regarded 1 ppm as the lowest standard achievable, estimating the cost to industry at approximately $500 million. Case reports and epidemiological observations provided the foundation for OSHA's action, notably an investigation conducted by Peter Infante of NIOSH (Infante et al, 1977; Rinsky et al 1981).

Infante studied mortality patterns among workers occupationally exposed to benzene in the production of natural rubber cast film at two manufacturing plants in Ohio.

No solvents other than benzene were used at these two sites. Records of workers employed between 1940 and 1949 were examined (a cohort size of 748 employees) and their status followed up in 1975. A significant ($p<0.002$) excess of leukemia was observed, in comparison to the general population and to a cohort of workers not exposed to benzene. Nine deaths from leukemia were reported; this represents a five-fold excessive risk of all leukemias and a ten-fold excess of deaths from myeloid and monocytic leukemias combined.

To what benzene concentrations were the workers exposed? This critical factor was and is subject to considerable dispute. Infante reported, in response to a recommendation from management at one of the plants in 1942 that "a closed system of ventilation where the workman comes in contact with no fumes is ideal. Any other type of ventilation is not entirely safe", extensive ventilation equipment was installed. In 1946, the Industrial Commission of Ohio surveyed the plant and reported that "tests were made with benzol detectors and the results indicate that concentrations have been reduced to a safe level and in most instances range from zero to 10 or 15 parts per million". Based on this and other evidence, Infante estimated that benzene exposure at both locations was generally within the recommended limits of the time (from a maximum allowable concentration of 100 ppm

in 1941 to an 8 hour time weighted average of 35 ppm in 1948).

On October 5, 1978, the Fifth Circuit Court of Appeals ruled on challenges to OSHA's proposed 1 ppm permanent standard (American Petroleum Institute v. OSHA, 581 F. 2d 493 (5th Cir. 1978)). Based on additional evidence, the court concluded that ambient benzene concentrations associated with the Infante study were underestimated and were more likely in the range of 100 ppm for most of the period studied, with occasional excursions as high as several hundred parts per million (Lave, 1982).

The American Petroleum Institute contended that a no-effect threshold for benzene occurs above the existing 10 ppm standard. The Fifth Circuit Court rejected this argument but ruled in favor of the API on the basis that OSHA had not performed an adequate cost-benefit analysis to justify the standard. The court observed that "...OSHA must have some factual basis for an estimate of expected benefits before it can determine that a one-half billion dollar standard is reasonably necessary. For example, when studies of the effects of human exposure to benzene at higher concentration levels in the past are sufficient to enable a dose:response curve to be charted that can reasonably be projected to the lower exposure levels, or when studies of the effects of animal exposure to benzene are sufficient to make projections

of the risks involved with exposure at low levels, then OSHA will be able to make rough but educated estimates of the extent of benefits expected..." (Carter, 1979).

The Secretary of Labor, representing OSHA, filed a brief with the Supreme Court asserting that the difficulties involved in estimating exposures and in attributing the cancer to a single cause precluded concluding with any precision how many cancers could be avoided by reducing exposure from 10 ppm to 1 ppm (Carter, 1979). This issue is not yet resolved; however, quantitative analysis of risk associated with low-level benzene exposure (near levels typically encountered in urban air) has been attempted by the U.S. Environmental Protection Agency's Carcinogen Assessment Group (US EPA, 1979). The methodology adopted by this panel will be outlined in the following section.

6.1.1 Quantitative Risk Assessment

The U.S. EPA's Carcinogen Assessment Group selected three epidemiological case studies where worker exposure (natural rubber cast film plant; shoeworkers exposed to benzene as solvent for adhesives; petrochemical plant) resulted in excess leukemia deaths (Infante et al, 1977; Rinsky et al, 1981; Ott et al, 1977; Aksoy et al, 1977, 1976, 1974). It estimated the total occupational exposure to benzene for those workers. From this data, it calculated the "change in

leukemia rate per 1 ppm benzene for each of the cases, resulting in the values: .014854; .020252; and .046380. The geometric mean of these values (.024074) was used in an expression to calculate the total probability of deaths due to 1 ppm of benzene in air breathed over a lifetime. This is given as:

$$N(D) = (.02407 \times D \times 1{,}000)/70.96 = .339262D$$

where N(D) is the expected # of leukemia deaths per year; D is the exposure index expressed in units of 1.0 E 6 ppb-person-years; and 70.96 is average life expectancy in the United States (US EPA, 1979).

Based on exposure estimates for a variety of sources (chemical manufacturing, coke ovens, petroleum refineries, highways, gasoline service stations) and for vicinity of residence, exposure indices (millions of ppb-person-years) were set and the above equation used to estimate number of benzene-caused leukemia deaths per year. The CAG estimate for lifetime exposure to urban air (at low average levels of 1 ppb) generated a benzene exposure index of 264.7 E 6 ppb-person-years and a N(D) of 89.80, or about 90 expected deaths per year resulting from this exposure. This value has a 95% confidence interval from 34 to 235 which corresponds to .23% to 1.62% of the total leukemia deaths in the U.S.

This model can be adopted to evaluate the risk associated

with operation of kerosene heaters in an estimated ten million American homes. Our assumptions are the following:

1) average heater use is five years (over the course of a lifetime);

2) Exposure of fourteen hours per day (6 pm - 8 am), seven days per week for twenty weeks (the heating season);

3) number of people using the heaters is 20 million (10 million homes with two residents);

4) benzene concentration with heater on:
   high (112.07 ppb - NJIT site);
   low (10.71 ppb - Elizabeth site);
   geometric mean (34.64 ppb);

5) indoor control benzene concentration:
   high (5.28 ppb - NJIT site);
   low (3.70 ppb - Elizabeth site);
   geometric mean (4.42 ppb).

TABLE 6-2

DETERMINATION OF BENZENE RISK ASSOCIATED WITH KEROSENE HEATER EMISSIONS USING EPA MODEL

CONDITION	MEAN BENZENE CONCENTRATION (ppb_v)	DURATION OF EXPOSURE (HRS/YR)	POPULATION EXPOSED (x 10^6)	EXPOSURE (10^6 x ppb-person yrs)	EXPECTED # OF BENZENE-CAUSED LEUKEMIA DEATHS/YR
HEATER ON (NJIT)	112.07	1960 hrs/9125 hrs	20	481.44	163.30
HEATER ON (ELIZ)	10.71	1960 hrs/9125 hrs	20	46.01	15.60
HEATER ON (WEIGHTED AVERAGE)	34.64	1960 hrs/9125 hrs	20	148.81	50.49
HEATER OFF (NJIT)	5.28	1960 hrs/9125 hrs	20	22.68	7.69
HEATER OFF (ELIZ)	3.70	1960 hrs/9125 hrs	20	15.89	5.39
HEATER OFF (WEIGHTED AVERAGE)	4.42	1960 hrs/9125 hrs	20	18.99	6.44

References:

U.S. Environmental Protection Agency (1979)
Mara and Lee (1978)

Table 6-3

SUMMARY OF ESTIMATED POPULATION EXPOSURES TO ATMOSPHERIC BENZENE FROM SPECIFIC BENZENE EMISSION SOURCES[a]

Source	Number of People Exposed to Benzene Concentrations (ppb)[b]					Comparison Among Sources (10^6 ppb-person-years)
	8-hour Worst Case: 2.5-25.0 Annual average: 0.1-1.0	25.1-100.0 1.1-4.0	100.1-250.0 4.1-10.0	>250.0 > 10.0	Total[c]	
Chemical manufacturing	6,000,000	1,000,000	200,000	80,000	7,300,000	8.5
Coke ovens	300,000				300,000	0.2
Petroleum refineries	5,000,000	3,000			5,000,000	2.5
Solvent operations	d				--	--
Storage & distribution of gasoline	e				--	--
Automobile emissions - urban[f]	69,000,000	45,000,000			110,000,000	150.0
Gasoline service stations - urban[f]	30,000,000	2,000,000			32,000,000	19.0
People using self-service gasoline				g	37,000,000	1.6

[a] Assumes that people living in the vicinity of benzene sources spend 24-hours of each day in that location.

[b] To convert to $\mu g/m^3$, multiply each exposure level by 3.2; to estimate one-hour worst case concentrations multiply 8-hour worst case by 10.

[c] Population estimates are not additive vertically, because double-counting exists. Totals are rounded to two significant figures.

[d] Exact determination is impossible.

[e] Estimated at << 0.1 ppb annual average. The population exposed was not determined but is assumed to be very small.

[f] 8-hour worst case is estimated by multiplying each exposure level by 4.1.

[g] Estimated at 245 ppb for 1.5 hr/yr/person.

Reference: Mara and Lee (1978)

TABLE 6-4

RELATIVE RISK TO U.S. POPULATION ASSOCIATED WITH BENZENE-RELATED EXPOSURES

SOURCE OF EXPOSURE	EXPOSURE IN 10^6 ppb-PERSON-YRS	EXPECTED # OF BENZENE-CAUSED LEUKEMIA DEATHS/YEAR
CHEMICAL MANUFACTURING	8.5	2.88
COKE OVENS	.2	.07
PETROLEUM REFINERIES	2.5	.85
AUTOMOBILE EMISSIONS	150.0	50.89
GASOLINE SERVICE STATIONS	19.0	6.44
SELF SERVICE GASOLINE	1.6	.54
KEROSENE HEATERS	148.81	50.49

References:

U.S. Environmental Protection Agency (1979)
Mara and Lee (1978)

TABLE 6-5

RELATIVE PERSONAL RISK ASSOCIATED WITH BENZENE-RELATED EXPOSURES

SOURCE OF EXPOSURE	RISK OF LEUKEMIA DEATH/YEAR (1×10^{-7})
CHEMICAL MANUFACTURING	3.0
COKE OVENS	2.3
PETROLEUM REFINERIES	1.7
AUTOMOBILE EMISSIONS	46.0
GASOLINE SERVICE STATIONS	2.0
SELF SERVICE GASOLINE	.2
KEROSENE HEATER USE	25.0
INDOOR AIR (WITHOUT HEATER)	3.0

References:

U.S. Environmental Protection Agency (1979)
Mara and Lee (1978)

The results are presented in Table 6-2. If total number of leukemia deaths in the U.S. per year is approximately 14,600, the benzene weighted average during heater operation yields a value of 50.48 leukemia deaths per year which is equivalent to .35% of all leukemias. The benzene weighted average for the control yielded a value of 6.44 leukemia deaths, or .04% of total leukemias. Exposure to benzene from other common activities has been estimated (Table 6-3). In simple terms, the national risk associated with kerosene heater use is roughly half that associated with overall exposure to urban air (Table 6-4).

At first glance, the risk associated with benzene exposure at self-service gasoline stations appears minor; with a N(D) of .54, the risk is two orders of magnitude lower than that associated with kerosene heater use. Yearly exposure to automobile emissions in an urban area yielded a N(D) value of 50.89; very comparable to exposure associated with kerosene heater emissions. However, this data is predicated upon evaluation of the exposed population as a whole (this model was developed to assist to formulating public policy). The personal risk can also be calculated so that comparison may become more concrete in terms of personal choice (Table 6-5).

If exposure to urban automobile emissions is rated 1.00, the relative risk in one year associated with other activities is:

ACTIVITY	RELATIVE RISK
Kerosene Heater Use	.543
Indoor Control (No Kerosene Heater)	.065
Urban Gas Service Station	.043
Chemical Manufacturing	.065
Self Service Gasoline	.004

Duration of exposure weighs heavily in this rating. The exposure level associated with self-service gasoline station use was estimated at 245 ppb for only 1.5 hours/year/person, which accounts for the low relative risk factor. It should also be recognized that this relative risk applies only to benzene and does not account for other carcinogenic constituents (eg. benzo(a) pyrene). Although these estimates are highly uncertain, the model does represent state-of-the-art.

6.1.2 Nonthreshold Linear Dose:Response

The U.S. EPA, in evaluating the dose:response relationship of benzene exposure with leukemia induction, adopted a non-threshold linear model. This model is assumed to be conservative at low doses (i.e., if anything, it will overestimate the adverse effect). It implies there is no safe level of exposure, that there is, for example, measurable risk associated with even an infinitesimal concentration of a carcinogen (eg. exposure to ambient

benzene levels results in 90 excess leukemia deaths per year). This linear dose:response curve is known to describe the relationship between human exposure to certain forms of ionizing radiation and incidence of mortality; and with the association between frequency of smoking and lung cancer. This curve also describes the pattern of response which is elicited from experimental induction of genetic mutations.

This linear model may be seen as describing the probability of cancer based on the random point mutation theory of carcinogenesis (one molecule:one hit). The more molecules of carcinogen (or, presumably, its active metabolite) the greater the probability of cancer induction (Albert and Burns, 1977). This model is not without its proponents as a conservative means of evaluating known carcinogens and for use in relative scaling of carcinogens. However, it should by no means be adopted uncritically. Some concerns remain unanswered. For example:

1. Does the metabolic fate of the compound change with the magnitude of the dose?

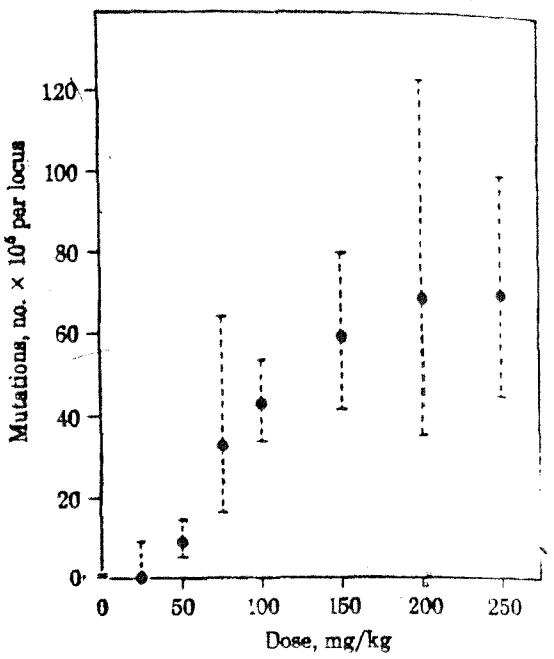
Adverse effects experimentally observed at high concentrations may be the result of saturating detoxification mechanisms. Repair has been implicated at very low doses of N-ethyl N-nitrosourea, which is the most effective known mutagen in mouse spermatogonia (Russell et al, 1982a). The

choice of this mutagen permitted accumulation of extensive dose:response data (administered dose ranged from 0 to 250 mg/kg) (Figure 6-1). The curve appears to be sigmoidal; however, the authors tested statistical departure from linearity separately for the portion of the curve above and below the point of inflection. In the lower portion of the curve (corresponding to an administered dose of 0-100 mg/kg) the response was lower than expected by a linear model; the drop was statistically significant, falling below a maximum likelihood fit to a straight line. In the upper portion of the curve, there was no statistically significant departure from a straight line (fitted by method of maximum likelihood). Independent evidence suggests that doses of 10 and 100 mg/kg reach the spermatogonia cells in amounts directly proportional to the injected dose (Russell et al, 1982b). The authors concluded, therefore, that the decrease was not due to the fact that the proportion of injected chemical reaching the target organ was declining with decreasing dose. They suggested that a repair mechanism may be operable when not overwhelmed by high dosages. This has important implications in understanding the realistic effect of low dose and in risk estimation at those levels.

2. Does the "dose" accurately reflect the actual concentration of active toxic chemical reaching the target tissue?

FIGURE 6-1

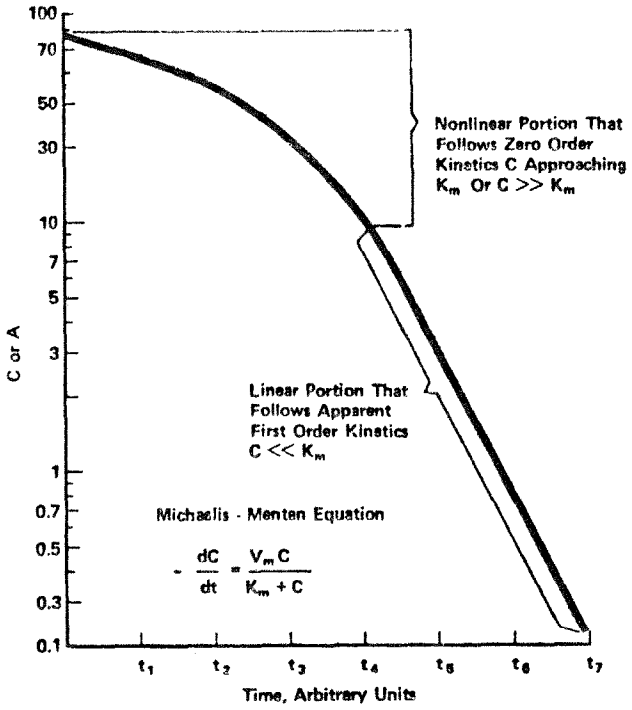
FREQUENCIES OF INDUCED MUTATIONS



REFERENCE: RUSSELL et al (1982)

FIGURE 6-2

MICHAELIS-MENTEN
PHARMACOKINETICS EQUATION



REFERENCE: GEHRING et al (1977)

It has been shown that for some inhalants, a simple linear association between inhaled concentration and arterial blood concentration (and concentration at the target tissue) does not exist. Styrene, for example, has a particular steady-state blood:gas concentration ratio specific for each inhaled concentration which is not directly proportional to the ambient concentration (Andersen, 1981b). When the ambient styrene concentration was 200 ppm, the steady-state blood:gas concentration ratio was 2.3, whereas with an ambient concentration of 1200 ppm, the ratio was greater than 12.

The toxicity of many inhalants (including benzene) has been related to the formation of toxic metabolite(s). Accordingly, dose:response relationships for these species are often indexed to the rate of metabolism of the parent chemical. Classically, pharmacokinetic modelling has focused on the velocity of the enzymatic reaction as the rate-limiting step in the biotransformation of parent chemical into active metabolite. The theory of metabolite formation is based on a one-step system in which one enzyme or enzyme system containing a finite # of active sites, and one substrate (i.e., inhalant) are involved. Enzymes are biological catalysts which are highly specific both in the reactions they accelerate and in their choice of reactants ("substrates"). Formation of an enzyme-substrate complex in which the substrate is bound to a specific region ("active

site") of the enzyme is a necessary intermediate in catalysis. The enzyme catalyzes a chemical alteration in the substrate, whereupon the enzyme-substrate complex breaks down to release the new entity and regenerate free enzyme (Stryer, 1981).

The graphical representation of the velocity of enzymatic reaction as a function of substrate concentration yields a hyperbole (Figure 6-2). At very low substrate concentrations, the metabolizing rate is proportional to the concentration of substrate (i.e., the parent compound) and independent of the number of available enzymatic sites (i.e., the reaction is first order). At this level, a constant fraction of the available substrate is metabolized. At higher substrate concentrations, the rate of reaction becomes independent of either reactant, and the rate of metabolite formation becomes relatively constant (zero order reaction). At these higher concentrations, it is believed that the limiting factor becomes the finite number of active enzymatic sites; these sites become saturated with substrate and the reaction velocity asymptotically approaches a value refered to as Vmax (maximum velocity). The Michaelis constant (Km) is defined as the concentration (in moles/liter) of parent compound at the enzymatic sites when the reaction rate is half its maximal value. Typically, Km ranges between 1 E -8 to 1 E -2 moles/liter and the maximum velocity lies within the range of

1 E 5 to 1 E 9 molecules of product/molecule of enzyme/second (Koshland, 1980).

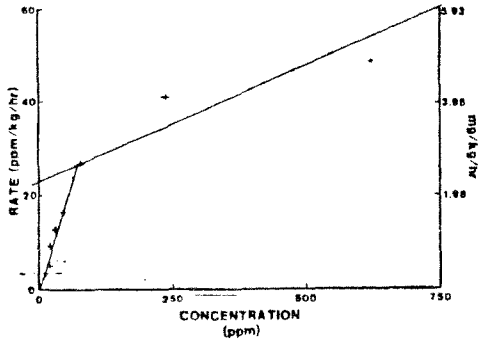
Use of this model typically assumes that substrate concentration in the vicinity of the metabolizing enzyme is proportional to the inhaled concentration. Other physiological factors such as alveolar ventilation (uptake of the inhalant from the lungs) or hepatic perfusion (delivery to the liver by the bloodstream) are unaccounted for and hence are presumed to play less significant roles in the biotransformation process.

Gas uptake experimentation with benzene has been conducted to evaluate the validity of the Michaelis-Menten curve in describing benzene metabolism (Andersen, 1981). In this test, experimental animals (rats) were placed in a closed atmosphere chamber (31-liter battery jar) and the rate of loss of benzene from the chamber was determined by timed automatic sampling with a gas chromatograph at a variety of exposure concentrations. The rate was determined 90 to 120 minutes after benzene was injected into the chamber to ensure that the richly and moderately well-perfused tissues were equilibrated with inhalant, and uptake was due to metabolism and continued uptake by poorly perfused tissues.

Benzene had a complex rate curve (Figure 6-3). At low atmospheric concentrations, the rate was accurately first

FIGURE 6-3

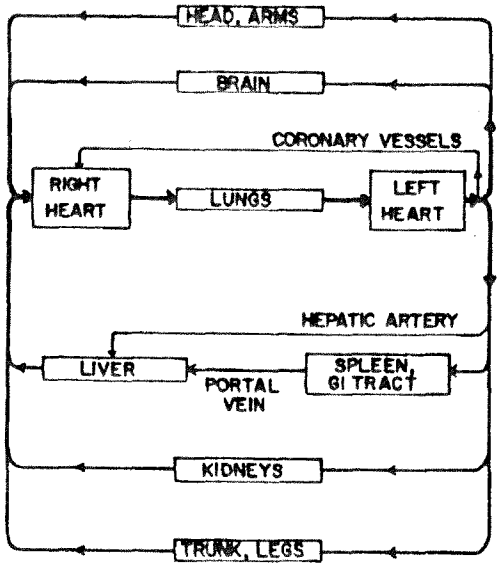
RATE OF UPTAKE
OF INHALED BENZENE



REFERENCE: ANDERSEN (1981)

FIGURE 6-4

DYNAMICS OF
SYSTEMIC CIRCULATION



REFERENCE: GANONG (1981)

order to a breakpoint; at higher concentrations the curve abruptly converted to a slower first order (presumably the result of tissue storage). So, for the range of doses obtained in our kerosene heater study, the kinetics of absorption appears to be linear. As long as the first order process predominates, a tenfold increase in dose will increase the tissue concentration tenfold. However, as metabolic and excretory processes become saturated at higher doses, it can be predicted that there will be a loading of parent chemical at the tissue. For this stage, a slower first order process will apply.

3. Is the nonthreshold model truly conservative at low doses?

Currently, there is accumulating evidence that cancer is a multistage process, for example, one concept is two-stage initiation-promotion. It has been demonstrated on laboratory mice that after a single dermal application of a carcinogen at a dose well below levels that will produce overt tumors, and followed by repetitive applications of a virtually noncarcinogenic promoter, a large yield of tumors will result (Albert and Burns, 1977).

In one study benzo(a)pyrene was administered at graded initiating doses (ranging from approximately 5 micrograms to 130 micrograms) using a standardized regimen of phorbol ester

(5 micrograms three times weekly)(Albert and Burns, 1977). As the subthreshold dose of benzo(a)pyrene increased, the tumor yield increased proportionately, and the data yielded a linear, nonthreshold dose:response curve. In addition, when the total dose of initiator was subdivided into split doses, the yield of tumors did not vary for the total dose administered.

The authors concluded that each fraction must result in equal and additive effects, so that the linear response could be experimentally justified for a dose range of about 100 micrograms to 0.1 micrograms of benzo(a)pyrene. The authors further observed that, since continuous exposure of mouse skin to benzo(a)pyrene at 6 micrograms per week for 70 weeks is known to yield about 0.1 tumor per mouse, the number of latent "initiated" tumor sites with a total dose of 420 micrograms benzo(a)pyrene would be about 15 per mouse. Therefore the ratio of "initiated sites" to tumors would be roughly 150:1.

Their conclusion relates to the effect of trace concentrations of environmental carcinogens. Conventional linear back extrapolation may indicate relatively low levels of risk associated with ambient levels of a carcinogen; the actual effect may rather be a large incidence of irreversible and latent damage (initiation). The realistic cancer risk may be much higher than indicated, and will be closely predicated

on exposure to otherwise noncarcinogenic substances which can promote these changes into neoplastic disease.

4. What is the significance of effect at low dose if the predicted risk falls below statistical rates (i.e., it falls within expected levels occuring normally in population)? In this case, the risk falls within "background noise" and it appears difficult to verify or differentiate.

6.1.3 Experimental Risk Model

Physiologically, what happens when an individual is exposed to very low (and fairly constant) concentrations of benzene in the air? At room temperature (approximately 25 C) and atmospheric pressure, 1 cubic centimeter (cc) contains 2.5 E 19 molecules. If benzene is homogeneously distributed in the air at a concentration of 10 ppb, then with every breath, an individual would inspire 1.25 E 14 molecules of benzene (of a total 1.25 E 22 molecules in a breath of air), i.e.:

500 ml per breath * 10 molecules benzene/1 E 9 molecules air * 2.5 E 19 molecules air/1 cc * 1,000 cc/liter

Of each 500 milliliters inspired, 150 milliliters will remain in the "respiratory dead space" (the conducting zone) of the lungs. A person normally breathes 12 to 15 times per minute so the alveolar ventilation (amount of air available for exchange with the blood) is 4.2 liters/minute. Thus the number of benzene molecules in this volume of air can be

calculated as 1.03 E 15.

What proportion of benzene is immediately expired? Estimates vary. Six volunteers exposed to 52 to 62 ppm benzene for four hours demonstrated a constant retention after three hours of 30.2 percent (3.77 E 10 molecules at 10 ppb per breath without accounting for effect of lower ambient concentration) (Doull et al, 1980).

Inspired air mixes with the gas in the alveoli, and, by simple diffusion, enters the blood in the pulmonary capillaries. The alveoli are small pockets (.025 mm in diameter) surrounded by a fine network of capillaries supported by connective tissue. The capillaries are separated from the gases by an exceedingly thin layer of endothelial cells (1 micron thick) which is lubricated with a surfactant to reduce surface tension. A normal individual has approximately 300 million of these alveoli with a total area of 70 square meters in contact with the pulmonary capillaries. Approximately 250 milliliters of oxygen enters the bloodstream each minute while 200 milliliters of carbon dioxide are removed from it (Ganong, 1981).

The air reaching the alveoli has been saturated with water vapor (the partial pressure of the water at body temperature is 47 mm Hg). The partial pressure of gases reaching the lungs at 37 C is therefore:

Species	Partial Pressure (mm Hg)
Oxygen	149
Nitrogen (plus other inert gases)	564
Carbon dioxide	0.3
Benzene	7.13 E -6

(Derivation: (760 mm Hg - 47 mm Hg water vapor)(relative concentration of gas in air))

Gases diffuse from areas of high pressure to areas of low pressure; and the concentration gradient and the nature of the membrane separating the two areas define the rate of diffusion. The mixture of gases in the alveoli are virtually in contact with the blood in the pulmonary capillaries; each of the gases will dissolve in the blood according to its partial pressure and its solubility in the blood. The solubility of a gas in a liquid is expressed by the partition coefficient, which is the ratio of the concentration of a gas in the liquid to that in the gas phase at equilibrium. For benzene, the blood:gas partition coefficient has been measured as 7.8 (Sato and Nakajima, 1979).

For a highly volatile chemical of low water solubility such as benzene, equilibration of the chemical between the blood and the atmosphere is quickly achieved. The cardiac output in one minute (approximately 6 liters) is equal to the entire volume of the vascular system. If the chemical under consideration passes slowly out of the bloodstream, it is

diluted into the total blood volume as a consequence of turbulent mixing and unequal flow through various vascular beds. Benzene, however, a highly lipid soluble species (having an oil:water partition coefficient of 177) (Sato and Nakajima, 1979) leaves the blood almost instantaneously in passage through the tissues.

The liver is a highly perfused organ, receiving 25% of the cardiac output directly via the hepatic artery (Figure 6-4). It is also the primary site of metabolism, where benzene is biotransformed into both more polar, more easily excretable metabolites, and presumably, into a leukemogenic species. In the liver, a chemical diffuses or is actively transported from the sinusoidal spaces across cell membranes to enzymes located in the microsomal fraction. At low concentrations, benzene uptake is perfusion limited (dependent on rate of delivery to the liver via the bloodstream). However, it is unclear whether the fate of benzene changes with the magnitude of the dose; i.e., under what conditions the critical metabolic changes (leading to onset of leukemia) occur.

During exposure, large proportions of benzene may be processed by the liver, while relatively small amounts become stored in secondary, nonmetabolizing depots such as the poorly perfused fat (which has a much larger storage capacity). When the exposure ends, benzene levels in the

blood and richly perfused organs would drop as exhalation cleared the inhaled species. The chemical sequestered in the fat is more slowly released, becoming available for metabolism and excretion in the days and weeks following exposure.

Benzene, with its high oil:water partition coefficient, would have a long persistence in the body, passing easily across membranes and accumulating in the fat. However, much of it is metabolized in the liver to phenolic compounds, which are easily excreted as sulfonates or glucuronides (Doull et al., 1980).

One report states that the average concentration of benzene in the blood is 2.1 mg/liter for each 100 ppm benzene in the inhaled air, at equilibrium (Gerarde, 1963). If one disregards metabolism, the rate of transfer of an inhalant moving into the bloodstream can be expressed as a direct function of the blood:gas partition coefficient,

C(blood) = N * C(air)
where N is blood:gas partition coefficient.

This equation (Andersen, 1983) indicates that, disregarding metabolism and assuming an ambient concentration of 100 ppm, uptake of benzene from the air would result in a benzene concentration in the blood of 2.49 mg/liter, which is very close (84.3%) to the above, experimentally-attained value.

The effect of ongoing metabolism of the inhalant is that the loading of the chemical into the blood cannot keep pace with the amount removed by metabolism. Correcting for metabolism yields the following equation for steady-state equilibrium:

$$N(eff) = N/[1 + (Cl_t)N]$$

where N(eff) is steady-state blood:gas concentration ratio for a metabolized inhalant; and Cl_t is the fraction of cardiac output cleared of parent compound by metabolism (if complete, assume value of .25)). At higher concentrations, Cl_t will approach zero as the metabolic pathways approach saturation (N(eff) will approach N).

For the above experimental value (2.1 mg/liter benzene in blood per 100 ppm in air), if we assume that all the benzene is metabolized, N(eff) would be equal to 2.64. Substituting this value for N would yield a blood benzene concentration of .84 mg/liter; clearly, the assumption that benzene is 100% metabolized is inappropriate. If we estimate that the fraction of cardiac output cleared of parent compound by metabolism (Cl_t) is .025, however, we obtain an N(eff) of 6.53 and a resulting blood benzene concentration of 2.08 or approximately 2.1 mg/liter. This indicates that roughly 10% of the parent compound is being cleared by metabolism, at equilibrium. If we contend that a metabolite is the agent

which triggers acute myelogenous leukemia, this is the fraction of primary concern.

It is clear that our understanding of the metabolic fate of benzene lacks sufficient detail with which to continue this discussion to its logical conclusion. With greater knowledge of the physiological processes involved, one may be able to determine more clearly the conditions (eg., range of concentrations, duration of exposure, etc.) associated with measurable health risk and proceed towards safeguarding against such exposures. At the current time, however, the Carcinogen Assessment Group model offers an estimate of risk, whose validity, although imprecise, appears to be a "best approximation" based on limited information.

Chapter 7

CONCLUSION

This study documented moderately elevated levels of aromatic and aliphatic species during operation of residential kerosene heaters at two sites, these species specifically included benzene, toluene, ethylbenzene, m,p-xylenes, o-xylene, styrene, hexane, cyclohexane, heptane and undecane. Additionally, at the Elizabeth site, elevated levels of octane, nonane, decane and dodecane during heater operation were detected. Immediately after extinguishing the heater, organic pollutant levels were generally reduced, but did remain above background levels. This is consistent with the findings of a companion analysis of total hydrocarbons (the reader is refered to the thesis of Mr. Kashi Banerjee, M.S. En. E., 1984 (New Jersey Institute of Technology) for detailed presentation of this study) and with the calculations of total organics detected by gas chromatography/flame ionization.

The analysis also indicated that three species actually increased in concentration immediately after the heater was

extinguished: toluene, pentane and heptane. The slow clearance of pollutants after heater use, which is more completely documented in the study of total hydrocarbons, is consistent with previous research documenting decay (of CO, SO2, CO2, NO and NO2) from steady state conditions once the kerosene heater was extinguished (Leaderer, 1982). In that report, decay curves from steady state were not significantly different from those expected from the distillation rate. The authors therefore concluded that there was no measurable removal of contaminants on chamber surfaces; the pollutants remained airborne until cleared by ventilation.

Toxicological research focused on benzene, ambient concentrations of which had increased on average by a factor of twenty (from 5.28 ppbv to 112.07 ppbv) at one site (NJIT) and by a factor of three (from 3.70 ppbv to 10.71 ppbv) at the second site (Elizabeth), as a result of kerosene heater use. Benzene was the subject of indepth analysis because, of all the compounds studied, it is the species for which human health effects may occur at the trace levels encountered in this study.

One objective of this thesis was to propose a "rating" of the relative health risk associated with kerosene heater use. Conveniently, the U.S. EPA's model for evaluating risk associated with ambient benzene levels provided a mechanism for arriving at this type of rough approximation. The model

was applied, and simply, the benzene risk (defined as potential for developing leukemia) associated with residential kerosene heater use for an individual was ranked as roughly one-half the risk associated with exposure to benzene in urban auto emissions. For the population as a whole, if the user population is estimated at 20 million, the risk is roughly equivalent to that associated with exposure to urban auto emissions.

The remainder of the discussion sought to reconcile some of the shortcomings inherent in the Carcinogen Assessment Group's model, and to address some of the unresolved issues in low-dose risk estimation, specifically:

- does a single value obtained for cumulative lifetime exposure apply when there may be differences in size of dose (concentration) and duration of exposure (eg., intermittent vs. continual)?
- does the metabolic fate (and hence, toxicity) of benzene change with concentration?
- how might benzene (or its metabolite(s)) exert its adverse health effect(s)?
- how appropriate is it to assume direct correlation between ambient exposure and concentration of active chemical at the target tissue?
- is the linear no-threshold model truly conservative at low doses?
- if "excess leukemia deaths" attributed to benzene exposure actually fall within the range of normally occuring rates, how can we be conclusive about risk?

Other apparent reservations concerning the use of the Carcinogen Assessment Group's model may include:

- it is based on retrospective estimation of ambient benzene levels. Possibly the affected workers may have been exposed to accidently high levels of benzene during the course of their work.

- the effects of workplace exposure may not correspond to the effects of exposure related to kerosene heater use (i.e., duration of exposure is different; eight hour five day exposure compared to seasonal fourteen hour seven day exposure).

A physiological overview was presented in an effort to approach formulation of a more finely-tuned risk assessment. The rate of transfer of an inhalant moving into the bloodstream has been expressed as a direct function of its blood:gas partition coefficient, with an adjustment for metabolism. Based on experimental evidence, we were able to obtain a finding that roughly ten percent of the parent compound (benzene) is cleared from the blood by metabolism, at equilibrium. If the leukemogen is a benzene metabolite, it is this fraction of the inhaled concentration which is of critical concern and it is this metabolic activity which must be more clearly defined if we are to better delineate the risk associated with benzene exposure.

Our assessment fell short of developing an alternative model because of the lack of sufficient specific information on the behavior of benzene in the human system. One also must be aware that, in the larger forum of the scientific community, no answer to this puzzle has yet been discovered. In the words of one of the leading scientists in the field of

benzene risk analysis, after years of research and intensive evaluation, "benzene is still with us", and the key questions (most critically, what is the shape of the dose-response curve relating benzene exposure to acute myelogenous leukemia?) remain (Goldstein, 1983). Ironically, new research implicating benzene as a hepatocarcinogen (causing a cancer of the liver) in experimental animals may result in a major shift in the direction of benzene risk analysis and standard setting, as the methodology is applied to evidence of this newly-discovered but as yet inconclusive threat.

BIBLIOGRAPHY

Aksoy, M., Erdem, S., and Dincol, G. (1974). "Leukemia in Shoe Workers Exposed Chronically to Benzene". Blood, 52:285.

Albert, R. E., and Burns, F. J. (1977). "Carcinogenic Atmospheric Pollutants and the Nature of Low-Level Risks" in Origins of Human Cancer. Book A: Incidence of Cancer in Humans. H. H. Hiatt, J. D. Watson, and J. A. Winsten (eds.). Cold Spring Harbor Conferences on Cell Proliferation, 4:289.

Andersen, M. E. (1981a). "Physiologically Based Toxicokinetic Description of the Metabolism of Inhaled Gases and Vapors: Analysis of Steady State". Toxicology and Applied Pharmacology, 60:509.

Andersen, M. E. (1981b). "Saturable Metabolism and Its Relationship to Toxicity". CRC Critical Reviews in Toxicology, 9:105.

Banerjee, K. (1984). Thesis: Master of Science in Environmental Engineering. New Jersey Institute of Technology. Newark, New Jersey.

Beall, J. R., and Ulsamer, A. G. (1981). "Toxicity of Volatile Organic Compounds Present Indoors". Bulletin of New York Academy of Medicine, 57:978.

Bozzelli, J. W. (1982). "PPM, PPB, NG/M3, PPBC, PPBV: Trace Concentration Units". Air Currents: NJIT Air Monitoring Laboratory, New Jersey Institute of Technology, 2(2):3.

Bozzelli, J. W. and Greenberg, A. (1984). "Organic Pollutants from Kerosene and other Home Heating Sources". Proposal submitted to New Jersey Department of Environmental Protection Office of Research, Trenton, NJ.

Bozzelli, J. W., and Kebbekus, B. B. (1979). Analysis of Selected Volatile Organic Species in Ambient Air. New Jersey Department of Environmental Protection Program on Environmental Cancer and Toxic Substances.

Bozzelli, J. W., and Kebbekus, B. B. (1982). "A Study of Some Aromatic and Halocarbon Vapors in the Ambient Atmosphere of New Jersey". Journal of Environmental Science and Health, A17(5):693.

Carter, L. J. (1979). "Dispute over Cancer Risk Quantification". Science, 203:1324.

Consumers Union (1982). "Are Kerosene Heaters Safe?". Consumer Reports. October:499.

Crump, K. S., Hoel, D. G., Langley, C. H. and Peto, R. (1976). "Fundamental Carcinogenic Processes and their Implications for Low Dose Risk Assessment". Cancer Research,36:2973.

Doull, J., Klaassen, C. D. and Amdur, M. O. (1980). Casarett and Doull's Toxicology: The Basic Science of Poisons. 2nd Ed. New York: Macmillan Publishing Co., Inc.

Elliott, J. J. and Mekhior, M. T. (1982). "Petroleum (Composition)" in Encyclopedia of Chemical Technology 3rd ed. Vol. 17. New York: John Wiley and Sons.

Fiserova-Bergerova, V., Vlach, J., and Singhal, K. (1974). "Simulation and Prediction of Uptake, Distribution and Exhalation of Organic Solvents". British Journal of Industrial Medicine, 31:45.

Forni, A. M., Cappellini, A., Pacifico, E., and Vigliani, E. C. (1971). "Chromosome Changes and their Evolution in Subjects with Past Exposure to Benzene". Archives of Environmental Health, 23:385.

Ganong, W. F. (1981). Review of Medical Physiology. 10th ed. Los Altos: Lange Medical Publications.

Gehring, P. J., Watanabe, P. G., and Park, C. N. (1978). "Resolution of Dose-Response Toxicity Data for Chemicals Requiring Metabolic Activation: Example - Vinyl Chloride". Toxicology and Applied Pharmacology,44:581.

Gehring, P. J., Watanabe, P. G., and Young, J. D. (1977). "The Relevance of Dose-Dependent Pharmacokinetics in the Assessment of Carcinogenic Hazard of Chemicals" in Origins of Human Cancer. Book A: Incidence of Cancer in Humans. H. H. Hiatt, J. D. Watson, and J. A. Winsten (eds). Cold Spring Harbor Conferences on Cell Proliferation, 4:187.

Gerarde (1963). "The Aliphatic (Open Chain, Acyclic) Hydrocarbons" in Industrial Hygiene and Toxicology. F.A.Patty (ed.). Vol 2, 2nd Ed. New York: Interscience.

Golden, A. (1982). Pathology: Understanding Human Disease. Baltimore: Williams and Wilkins.

Goldstein, B. D. (1982a). "Editorial: Benzene Is Still With Us". American Journal of Industrial Medicine,4:585.

Goldstein, B. D. (1982b). "Muconaldehyde, A Potential Toxic Intermediate of Benzene Metabolism" in Biological Reactive Intermediates - II, Part A. Snyder, Parke, Kocsis, Jollow, Gibson and Witmer (eds). New York: Plenum Publishing Corp.

Goldstein, B. D. (1983). "Toxic Substances in the Atmospheric Environment: A Critical Review". Journal of the Air Pollution Control Association,33:454.

Goldstein, B. D., and Snyder, C. A. (1982). "Benzene Leukemogenesis" in Genotoxic Effects of Airborne Agents. R. R. Tice, D. L. Costa, and K. M. Schaich (eds.). New York: Plenum Publishing Corp.

Goldstein, B. D. Snyder, C. A., Laskin S., Bromberg, I., Albert, R. E. and Nelson, N. (1982). "Myelogenous Leukemia in Rodents Inhaling Benzene".Toxicology Letters,13:169.

Green, J. D., Snyder, C. A., LoBue, J., Goldstein, B. D., and Albert, R. E. (1981). "Acute and Chronic Dose/Response Effect of Benzene Inhalation on the Peripheral Blood, Bone Marrow, and Spleen Cells of CD-1 Male Mice". Toxicology and Applied Pharmacology. 59:204.

Hobson, G. D. (ed.) (1973). Modern Petroleum Technology. 4th ed. London: Applied Science Publishers, Ltd.

Hoel, D. G. (1977). "Some Problems in Low Dose Extrapolation" in Origins of Human Cancer. Book C: Human Risk Assessment. H. H. Hiatt, J. D. Watson, J. A. Winsten (eds.). Cold Spring Harbor Conferences on Cell Proliferation, 4:1391.

Hoel, D. G., Kaplan, N. L., and Anderson, M. W. (1983). "Implications of Nonlinear Kinetics on Risk Estimation in Carcinogenesis". Science,219:1032.

Hollowell, C. D., and Miksch, R. R. (1981). "Sources and Concentrations of Organic Compounds in Indoor Environments". Bulletin of New York Academy of Medicine,57:962.

Hunt, J. M. (1979). Petroleum Geochemistry and Geology. Woods Hole Oceanographic Institution. San Francisco: W. H. Freeman and Co.

Infante, P. F., Rinsky, R. A., Wagoner, J. K., and Young, R.

J. (1977). "Leukemia in Benzene Workers". Lancet,2:76.

Kebbekus, B. B. and Bozzelli, J. W. (1982). "Determination of Selected Toxic Organic Vapors in Air by Adsorbent Trapping and Capillary Gas Chromatography". Journal of Environmental Science and Health,5:713.

Koshland, D. E. (1980). "Enzyme" in Encyclopedia Brittanica. 15th ed. Pt III. Vol. 6. Chicago: Encyclopedia Britanica Inc.

Laskin, S. and Goldstein, B. D. (1977). "Benzene Toxicity: A Critical Evaluation". Journal of Toxicology and Environmental Health Supplement 2.

Lave, L. B. (1982). Quantitative Risk Assessment in Regulation. Washington, D.C.: The Brookings Institute.

Leaderer, B. P. (1982). "Pollutant Emissions from Kerosene Space Heaters". Science,218:1113.

Magrath, I., O'Connor, G. T., and Ramot, B. (1984). "Pathogenesis of Leukemias and Lymphomas: Environmental Influences" in Progress in Cancer Research and Therapy,27. New York: Raven Press.

Mantel, N. (1977). "Aspects of the Hartley-Sielken Approach for Setting "Safe Doses" of Carcinogens" in Origins of Human Cancer. Book C: Human Risk Assessment. H. H. Hiatt, J. D. Watson, and J. A. Winsten (eds.). Cold Spring Harbor Conferences on Cell Proliferation,4:1397.

Mantel, N., Schneiderman, M. (1975). "Estimating "Safe" Levels, a Hazardous Undertaking". Cancer Research,35:1379.

Mara, S. J., Lee, S. S. (1978). Assessment of Human Exposures to Atmospheric Benzene. U. S. Environmental Protection Agency Office of Air and Waste Management. Research Triangle Park, NC. EPA-450/3-78-031.

McClellan, R. O. (1983). "Role of Inhalation Studies with Animals in Defining Human Health Risks for Vehicle and Power Plant Emissions". Environmental Health Perspectives,47:283.

Miller, J. M., Harmon, R. L. (1978). Elementary Theory of Gas Chromatography with Bibliography and Experiments. Madison, NJ: Gow-Mac Instrument Co.

Molhave, L. (1980). Indoor Air Pollution due to Building Materials. Draft Report. Denmark: Institute of Hygiene,

University of Aarhus.

Morrison, R. T., and Boyd, R. N. (1983). Organic Chemistry. 4th ed. Boston: Allyn and Bacon, Inc.

Munro, I. C., and Krewski, D. R. (1981). "Risk Assessment and Regulatory Decision Making". Food and Cosmetics Toxicology,19:549.

National Academy of Science (1976). Health Effects of Benzene: A Review. Washington, D.C.

National Research Council (1981). Indoor Pollutants. National Academy of Science/National Research Council. Washington, D.C.: National Academy Press.

Nelson, P. F., and Quigley, S. M. (1982). "Non-Methane Hydrocarbons in the Atmosphere of Sydney, Australia". Environmental Science and Technology,16:650.

Nielsen, G. D., and Alarie, Y. (1982). "Sensory Irritation, Pulmonary Irritation and Respiratory Stimulation by Airborne Benzene and Alkylbenzenes: Prediction of Safe Industrial Exposure Levels and Correlation with their Thermodynamic Properties". Toxicology and Applied Pharmacology,65:459.

Novotny, M. (1978). "Contemporary Capillary Gas Chromatography" in Analytical Chemistry,50:16A.

Ohe, S. (1976). Computer Aided Book of Vapor Pressure. Tokyo: Data Book Publishing Co.

Ott, M. G., Townsen, J. C., Fishbeck, W. A., and Langner, R. A. (1978). "Mortality Among Individuals Occupationally Exposed to Benzene". Archives of Environmental Health,33:3.

Ramdahl, T. (1981). "Chemical Characterization of Emissions from Wood-Fired Stoves". Oslo, Norway:Sentralinstitutt for Industriell Forsking.

Rinsky, R. A., Young, R. J., and Smith, A. B. (1981). "Leukemia in Benzene Workers". American Journal of Industrial Medicine,2:217.

Rossini, F. D., Mair, B. J. and Streiff, A. J. (1953) Hydrocarbons from Petroleum. American Chemical Society Monograph Series No. 121. New York: Reinhold.

Russell, W. L., Hunsicker, P. R., Carpenter, D. A., Cornett, C. V., and Gunn, G. M. (1982). "Effect of Dose

Fractionation on the Ethylnitrosurea Induction of Specific-Locus Mutations in Mouse Spermatogonia". Proceedings of National Academy of Science,79:3592.

Russell, W. L., Hunsicker, P. R., Raymer, G. D., Steele, M. H., Stelzner, K. F., and Thompson, H. M. (1982). "Dose-Response Curve for Ethylnitrosurea-Induced Specific Locus Mutations in Mouse Spermatogonia". Proceedings of National Academy of Science,79:3589.

Santesson, C. G. (1897). "Ueber chronische Vergiftungen mit Steinkohleerbenzin; vier todesfalle". Arch. Hyg. Berl.,31:336.

Sato, A. and Nakajima, T. (1979). "Partition Coefficients of Some Aromatic Hydrocarbons and Ketones in Water, Blood and Oil". British Journal of Industrial Medicine,36:231.

Sax, N. I. (1979). Dangerous Properties of Industrial Materials. 5th ed. New York: Van Nostrand Reinhold.

Singh, H. B., Salas, L. J., Smith, A., and Shigeishi, H. (1979).Atmospheric Measurement of Selected Toxic Organic Chemicals. Interim Report. U.S. Environmental Protection Agency Environmental Sciences Research Laboratory. Research Triangle Park, NC.

Singh, H. B., Salas, L. J., and Stiles,R. E. (1982). "Distribution of Selected Gaseous Organic Mutagens and Suspect Carcinogens in Ambient Air". Environmental Science and Technology,16:872.

Sittig, M. (1975). Environmental Sources and Emissions Handbook. Park Ridge, NJ: Noyes Data Corp.

Snyder, C. A., Goldstein, B. D., Sellakumar, A., Bromberg, I., Laskin, S., and Albert, R. E. (1982). "Toxicity of Chronic Benzene Inhalation: CD-1 Mice Exposed to 300 PPM". Bulletin of Environmental Contaminant Toxicology,29:385.

Snyder, C. A., Green, J. D., LoBue, J., Goldstein, B. D., Valle, C. D., and Albert, R. E. (1981). "Protracted Benzene Exposure Causes a Proliferation of Myeloblasts and/or Promyelocyte in CD-1 Mice". Bulletin of Environmental Contaminant Toxicology,27:17.

Snyder, R., and Kocsis, J. J. (1975). "Current Concepts in Chronic Benzene Toxicity". Critical Reviews in Toxicology,265.

Spengler, J. D., and Sexton, K. (1983). "Indoor Air

Pollution: A Public Health Perspective". Science,22:90.

Stryer, L. (1981). Biochemistry. 2nd Ed. San Francisco: W. H. Freeman and Co.

Thilly, W. G., Longwell, J. and Andon, B. M. (1983). "General Approach to the Biological Analysis of Complex Mixtures". Environmental Health Perspectives,48:129.

Traynor, G. W., Allen, J. R., Apte, M. G., Girman, J. R., and Hollowell, C. D. (1983). "Pollutant Emissions from Portable Kerosene-Fired Space Heaters". Environmental Science and Technology,17(6):369.

U.S. Consumer Product Safety Commission (1982). "No. 97: Kerosene Heaters". Product Safety Fact Sheet.

U.S. Department of Health, Education and Welfare (1977). Criteria for a Recommended Standard: Occupational Exposure to Refined Petroleum Solvents. Public Health Service, Centers for Disease Control. NIOSH Report 77-192.

U.S. Department of Health and Human Services (1983). Registry of Toxic Effects of Chemical Substances. Public Health Service, Centers for Disease Control.

U.S. Environmental Protection Agency (1978). Assessment of Health Effects of Benzene Germane to Low-Level Exposure. Office of Research and Development Office of Health and Ecological Effects. EPA-600/1-78-061.

U.S. Environmental Protection Agency (1979). Carcinogen Assessment Group's Final Report on Population Risk from Ambient Benzene Exposure. NTIS PB 82-227372.

Weisburger, J. H. and Williams, G. M. (1981). "The Decision-Point Approach for Systematic Carcinogen Testing". Food and Cosmetics Toxicology,19:561.

Wolman, S. R. (1979). "Cytologic and Cytogenetic Effects of Benzene". Journal of Toxicology and Environmental Health. Supplement 2:63.

World Health Organization (1982). International Agency for Research on Cancer - Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Industrial Chemicals and Dyestuffs,29.

Yamanaka, S., Hirose, H., and Takada, S. (1979). "Nitrogen Oxide Emissions from Domestic Kerosene-Fired and Gas-Fired Appliances". Atmospheric Environment,13:407.

Zweig, G. and Sherma, J. (1972). CRC Handbook of Chromatography. 1st ed. Cleveland: CRC Press.