Voluntary Children's Chemical Evaluation Program (VCCEP)
Tier 1 Pilot Submission for

BENZENE
(CAS No. 71-43-2)

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American Chemistry Council
Benzene, Toluene, and Xylenes VCCEP Consortium

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Benzene VCCEP Submission
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Glossary of Terms

μg	Microgram
AA	Aplastic Anemia
ACGIH	American Conference of Governmental Industrial Hygienists
ACH	Air Changes per Hour
ADD	Average Daily Dose
AEGL	Acute Exposure Guideline Level
ALC	Absolute Lymphocyte Count
AML	Acute Myelogenous Leukemia
ANLL	Acute Non-lymphocytic Leukemia
ATSDR	Agency for Toxic Substances and Disease Registry
BMCL	Benchmark Concentration Level (frequently used in reference to the lower confidence limit level from benchmark model)
CAA/CAAA	Clean Air Act/Clean Air Act Amendments of 1990
CARB	California Air Resources Board
CAS	Chemical Abstract Service
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFM	Cubic feet per minute
CNS	Central Nervous System
CPSC	Consumer Product Safety Commission
CSF	Cancer Slope Factor (EPA IRIS)
CYP 2E1	Cytochrome P450 system isoenzyme 2E1
EU	European Union
EHC	Environmental Health Criteria
EPA	Environmental Protection Agency
ETS	Environmental Tobacco Smoke
FAB	French-American-British (FAB) Classification of Acute Myeloid Leukemias
FDA	Food and Drug Administration
FHSA	Federal Hazardous Substances Act
g	Gram
GC/MS	Gas Chromatograph/Mass Spectrometry
GD	Gestation Day
HAP	Hazardous Air Pollutant (as defined by the Clean Air Act)
HEC	Human Equivalent Concentration
HI	Hazard Index
High-end exposure	An exposure that was calculated using exposure concentrations representative of a 90th or 95th percentile of the range of values in a given dataset, depending on availability in the published literature.
HQ	Hazard Quotient
IARC	International Agency for Research on Cancer
I-O	Indoor-Outdoor (ratio)
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
IUR	Inventory Update Rule (TSCA)
kg	Kilogram
kHz	Kilohertz (thousands of cycles per second)
LD	Lactation Day

LOAEL	Lowest observable adverse effect level
MACT	Maximum Achievable Control Technology
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MDS	Myelodysplastic Syndrome or Myelodysplasia
mg	Milligram
mL	Milliliter
MOPP	Murstargen, Oncovin, Prednisone, Procarbazine
MSDS	Material Safety Data Sheet
MSHA	Mine Safety and Health Administration
MTD	Maximum Tolerated Dose
NATA	National Air Toxics Assessment
NCEA	National Center for Environmental Assessment
NCOD	National Drinking Water Contaminant Occurrence Database
NESCAUM	Northeast States for Coordinated Air Use Management
NHANES	National Health and Nutrition Examination Survey
NOAEL	No Observed Adverse Effect Level
NTI	National Toxics Inventory
NTP	National Toxicology Program
OECD	Organization of Economic Cooperation and Development
OEHHA	Office of Environmental and Human Health Assessment (Cal.)
OPPTS	Office of Pollution Prevention and Toxic Substances (EPA)
OSHA	Occupational Safety and Health Administration
NCI	National Cancer Institute
NESHAPs	National Emission Standards for Hazardous Air Pollutants
NHANES	Health and Nutrition Examination Survey
NHEXAS	National Human Exposure Assessment Survey
NCOD	National Drinking Water Contaminant Occurrence Database
NIOSH	National Institute of Occupational Safety and Health
PAMS	Photochemical Assessment Monitoring Stations
PBPK	Physiologically-Based Pharmacokinetic (models, modeling)
PEL	Permissible Exposure Limit (OSHA)
POD	Point of Departure
ppb	Part Per Billion
ppm	Part Per Million
PPPA	Poison Prevention Packaging Act
RCRA	Resource Conservation and Recovery Act
REL	Recommended Exposure Limit
RfC	Inhalation Reference Concentration
RfD	Oral Reference Dose
RFG	Reformulated Gasoline
RR	Relative Risk
SARA	Superfund Amendments and Reauthorization Act
SD	Standard Deviation
SDWA	Safe Drinking Water Act
SDWIS	Safe Drinking Water Information System
SEM	Standard Error of the Mean
SIAM	SIDS Initial Assessment Meeting
SIAP	SIDS Information Assessment Profile
SIAR	Screening Information Assessment Report
SIDS	Screening Information Data Set

STEL	Short-Term Exposure Limit
TEAM	Total Exposure Assessment Method
TERA	Toxicology Excellence for Risk Assessment
TLV®	Threshold Limit Value
TRI	Toxic Release Inventory
TSCA	Toxic Substances Control Act
TWA	Time-Weighted Average
Typical Exposure	An exposure that was calculated using the average or median exposure concentrations in a given dataset (depending on availability) and average or median values for exposure parameters.
UCMR	Unregulated Contaminant Monitoring Rule
UF	Uncertainty Factor
USGS	United States Geological Survey
VOC	Volatile Organic Compound
VCCEP	Voluntary Children's Chemical Evaluation Program
WAGM	Weighted Average Geometric Mean
WBC	White Blood Cell
WHO	World Health Organization

1.0 EXECUTIVE SUMMARY

This submission by the American Chemistry Council Benzene, Toluene & Xylene Voluntary Children's Chemical Evaluation Program (VCCEP) Consortium (the "Consortium") covers the Tier 1 review of benzene (CAS No. 71-43-2) under the VCCEP Pilot Program. Benzene was included in the VCCEP Pilot Program because it was found in several biomonitoring and environmental monitoring databases that the U.S. Environmental Protection Agency (EPA) used to identify chemicals that may have the potential for children's exposure.

Production, Use, and Regulatory Status

Approximately 2-3 billion gallons of isolated or pure benzene is produced yearly in the United States. This pure benzene is consumed as a chemical feedstock for the production of cumene, cyclohexane, ethylbenzene, nitrobenzenes, and other chemical intermediates. Benzene has not been used as an industrial solvent for decades, and it is not used in consumer products. Benzene is a minor constituent in some petroleum fuels, gasoline in particular. Unleaded automobile gasoline generally has a benzene content of about 1%, whereas heavier fuels such as jet fuel, kerosene, and diesel fuel have much less benzene content, generally less than 0.02%.

Benzene exposure sources have been regulated for many years, and new regulations for mobile sources, which comprise a large portion of ambient sources, were announced in March 2006. Benzene emissions reductions have been achieved through a combination of regulatory programs under the Clean Air Act (fuels, evaporative emissions, tailpipe emissions, stationary sources, others). OSHA also began regulating benzene occupational exposures in the 1970s.

Health Hazard Assessment

Human Hazard Assessment

The potential for hematopoietic toxicity of benzene has long been recognized. As a result, there is a robust human literature base describing the adverse health effects associated with exposure to benzene, particularly those resulting from historic occupational exposures. Currently, all existing regulatory and occupational standards in the US for benzene are based on human data. Therefore, the VCCEP Hazard Assessment begins with sections describing key studies on benzene's toxicity in humans, especially those that form the basis for US EPA regulatory benchmarks (CSF, RfD and RfC). Additionally, occupational epidemiology studies are also briefly discussed to provide context on the dose-response relationship for benzene toxicity in humans.

Benzene, an aromatic organic compound, has been shown to be toxic to both humans and experimental animals via all routes of administration. High dose acute exposures will frequently result in toxic effects similar to many types of organic solvents, primarily involving systemic toxicity including CNS and respiratory depression. The most important consequence of benzene exposure is damage to the blood and bone marrow. The hematotoxicity of benzene has been demonstrated by multiple independent epidemiological studies, as well as a variety of long-term animal bioassays. Chronic benzene intoxication is often first manifested by some form of cytopenia (a significant depression in one or more types of the peripheral blood cells). In more severe exposures, pancytopenias are observed, representing a significant suppression in all mature blood cells found in the periphery. At sufficiently high enough concentrations,

benzene induced pancytopenias can progress to severe hematopoietic damage that can cause bone marrow failure leading to aplastic anemia, a serious and often fatal disease. Suppression of a type of white blood cell, the lymphocytes or lymphocytopenia, has been reported by many independent investigators to be the most sensitive end-point for benzene induced hematotoxicity. Chronic exposure to high concentrations of benzene has been positively associated with the development of acute myelogenous leukemia (AML). Leukemias are a diverse group of malignancies, with different cells of origins, clinical courses, prognosis and treatments. Despite extensive investigations, the only hematopoietic malignancy positively associated with benzene exposure is AML.

While there have been questions on the most applicable dose metric (numerical characterization of the dose-response relationship) for benzene exposure, most studies rely on cumulative exposure expressed as ppm-years. Intensity and frequency of exposure may also be important variables in determining toxicity and risk, but they are only addressed indirectly in cumulative exposure estimates. Accordingly, most studies have reported that cumulative exposure correlates best with risk of AML.

Lymphocytopenia is considered by the US EPA to be the most sensitive toxic endpoint for humans exposed to benzene and forms the basis for its non-cancer regulatory benchmark. Rothman et al. (1996) was selected by the Agency as the critical study. The methodologies and values are discussed as well as additional literature reporting cytopenias and hematopoietic toxicity in benzene exposed workers. The cancer potency factor for benzene is based on a variety of exposure estimates from a cohort of occupationally exposed workers involved with the manufacture of rubber hydrochloride (Pliofilm) at one of three plants in Ohio. As a result, the cancer potency or cancer slope factor (CSF) for benzene is presented as a range, based on the risk associated with the varying exposures. Additional literature on AML and benzene are briefly discussed to provide a better analysis of the dose response relationship between benzene exposure and AML. An overview of the most pertinent epidemiology literature dealing with refinery and petroleum workers, mechanics, and others was included to help understand the dose response relationship. These additional data show that low levels of benzene exposure have not been associated with an increased risk of AML.

Considerable research has been conducted to understand the mechanism of action for benzene induced carcinogenicity, including an extensive evaluation of a genotoxic mechanism for benzene and/or its reactive metabolites. There is still uncertainty regarding the human genotoxic potential of benzene and its metabolites with inconsistent results reported. Therefore, it is not possible to state with scientific certainty what role genotoxicity, including clastogenicity, plays in benzene induced transformation. Further, epigenetic processes such as altered gene regulation, cytotoxicity and cell proliferation are thought to be important, perhaps critical, for benzene induced leukemogenesis.

In summary, benzene is toxic to the blood and bone marrow and can induce AML in a small number of highly exposed individuals. A critical issue that has yet to be fully resolved is the shape of the dose response curve at low doses. The available epidemiology data on both cancer and non-cancer toxicity of benzene support the existence of a functional threshold (an exposure level below which adverse health effects would not be expected). As a result, use of a linear extrapolation to predict risk at low exposure levels is overly conservative and biologically inappropriate.

Based on a recent review of available scientific evidence, it is not possible to reach definitive conclusions regarding human developmental and/or reproductive toxicity associated with

benzene exposure. Relevant studies are limited by small size, inadequate exposure information, confounding chemical exposure and other factors, as well as potential recall and selection bias. For these reasons, the existing data on male and female reproductive toxicity or developmental effects do not establish a causal relationship with benzene exposure. Studies evaluating the role that paternal exposures may play in the development of childhood leukemia do not support a casual link with the development of childhood acute lymphoblastic leukemia (ALL). There is one study indicating that a potential association between maternal exposures to benzene and childhood AML might exist. However, this finding has not been independently confirmed and this single study is of insufficient quality to be used exclusively to support a causal relationship. Therefore, in the absence of additional, more reliable data, it is not possible to conclude that parental benzene exposure has not been showen to adversely affect the developing fetus (including the development of childhood leukemia) or adversely affect reproductive function in either exposed parent. The available studies on human reproductive and developmental toxicity of benzene are discussed in this assessment.

Animal Hazard Assessment

While the human data summarized above are the key data supporting this and other risk assessments and risk management decisions, benzene has also been studied extensively in laboratory animals. Similar to humans, hematotoxicity is frequently the most sensitive effect observed in animal studies; however, there is no animal toxicity model for benzene induced AML.

Acute animal toxicity studies of benzene have been conducted by the oral, inhalation, and dermal route. The results from these studies indicate that benzene is of a low order of acute toxicity for the inhalation, oral and dermal routes or exposure. Skin and eye irritation studies indicate that benzene is irritating to the skin and can cause damage to the eye.

In repeat dose studies, benzene effects depend on a variety of factors, including the animal species and strain, exposure duration, and whether exposure is intermittent or continuous. Serious toxicological effects are primarily confined to hematological parameters, from depression of stem cells up to pancytopenia and histopathological alterations in the marrow. Principal effects of subchronic treatment in rats and mice are hematotoxicity, reduction in body weight and weight gain, and dose-related increases in mortality. Hematologic effects include leukopenia, lymphocytopenia, lymphoid depletion in spleen, decreased incidence of primitive progenitor cells and granulocyte-macrophage colony forming units (CFU-GM).

Benzene does not induce *in vitro* gene mutation in bacteria using the standard Ames test conditions. Weakly positive effects were obtained in the presence of metabolic activation for *Salmonella typhimurium* TA 1535 exposed to benzene vapor and in another study with TA100 exposed in microsuspension wells. Mammalian cell gene mutation tests give mixed results. Chromosome aberrations and sister chromatid exchanges (SCE) have been reported in cultured human lymphocytes and other mammalian cells exposed *in vitro* to benzene and/or its metabolites. Further, oral doses of benzene induced dose-related increases in chromosome aberrations in mice sperm and inhalation exposure lead to micronuclei induction in both rats and mice and chromosome aberrations in rat bone marrow. However, *in vivo* exposuse to benzene in other studies of laboratory animals did not induce chromosome aberrations, increased incidence of micronuclei (MN), or SCE. Benzene and/or its metabolites have also been reported to bind to DNA and protein forming adducts in the bone marrow and liver of treated animals.

A fertility study in female rats exposed to benzene at vapor concentrations up to 300 ppm (960 mg/m^3) for 10 weeks prior to mating, and daily during gestation days (GD) 0-20 and lactation days (LD) 5-20 did not demonstrate any effect on female fertility or maternal performance. No effects on male reproductive capabilities were observed in a study of the performance of male mice exposed up to 300 ppm (960 mg/m^3) benzene for 10 weeks (one spematogenic cycle) then mated with untreated females. However, some effects on testicular weight, testicular atrophy and abnormal sperm have been reported in a 90-day subchronic study in mice at similar doses; whereas male rats were unaffected.

Benzene at high exposure concentrations typically causes maternal toxicity and stress, which can affect developmental processes, reflected in fetal growth retardation and/or skeletal variations. No benzene-induced malformations have been reported. Results of developmental studies suggest a general toxicity leading to growth retardation and delays in maturation that occur at levels considerably higher than those associated with hematopoietic toxicity.

Benzene has demonstrated transplacental effects on hematopoiesis and genotoxicity. Exposure of pregnant mice to benzene on GD 6-15 produced hematopoietic changes that were present 10 weeks after birth in bone marrow, spleen and liver. Clastogenicity of benzene in fetuses is correlated with the gestational day of benzene administration. Exposure on GD13, 14–15 appears to result in cytogenetic damage, whereas treatment after this period had no effect. These times of sensitivity correspond to the stages of hematopoiesis development in rodents: initiation beginning on GD10 in the fetal liver, with maximum activity by GD12, followed by initiation of hematopoiesis in bone marrow. Exposure on GD17-19 did not show adverse cytogenetic effects in fetal livers.

Benzene immune system effects appear to be operative at doses that also produce hematotoxicity. Studies address effects on lymphocyte proliferation, T and B cell lymphocyte response, antibody response and resistance to pathogens by oral and inhalation routes of exposure. Previous reviews by the EU and OECD concluded that benzene immunotoxic effects are likely a reflection of bone marrow toxicity.

Neurotoxicity in adults resulting from benzene exposure has been demonstrated to diminish and/or disappear with termination of exposure. Effects in animals including changes in activity levels, grip strength, and clinical behaviors occur at doses generally above those that induce hematologic effects.

Long term exposure to benzene has been evaluated in rats and mice in 2-year oral bioassays. Survival was reduced in both sexes. Systemic effects included reduced body weight gain, leukopenia in both sexes and lymphoid depletion in thymus and spleen of male rats. There are no reliable animal models for benzene-induced leukemogenesis; however, 2-year bioassays of benzene induced solid tumors in the zymbal gland, nasal and oral cavities, mammary gland (female), and skin (male) of rats, and the zymbal gland, lung, Hardarian gland (male), preputial gland, mammary gland (female) and ovaries of mice.

Metabolism and toxicokinetics of benzene have been studied in both animals and humans. Benzene is absorbed by all routes of exposure (inhalation, dermal and oral) with inhalation as the most important route. Benzene is rapidly distributed in the body and higher concentrations are found in fat and in lipid rich tissues compared to blood. After absorption, most benzene is metabolized and the metabolites are excreted after conjugation, mainly in the urine. Oxidative metabolism of benzene is a prerequisite to repeat dose toxicity and follows similar pathways in humans and animals. The liver is the major site of benzene metabolism, but metabolism in the

bone marrow may be associated with the hematotoxic and leukemogenic effects of benzene. The toxicity of benzene appears to result from formation of reactive metabolites, principally phenol, hydroquinone and catechol. Myelotoxicity and genotoxicity occur from combination of phenol with hydroquinone, muconaldehyde or catechol. There are apparent species differences in rate of benzene metabolism and the proportion of toxification (oxidative) versus detoxification (conjugation) metabolic pathways.

In summary, hematologic changes and production of solid tumors are the most significant results from benzene toxicity studies in animals. A few cytogenetic studies have reported results at lower doses than those seen for hematotoxicity but results vary with investigators. Benzene is a demonstrated animal clastogen and carcinogen.

Exposure Assessment

A child centered approach was used to define scenarios in which children may have exposures to benzene. Both typical and high-end estimates of exposure were made for five different age groups of children, as well as prospective parents. The environmental background/ambient sources of exposure included indoor air, outdoor air, diet, and water. In addition to these ubiquitous sources, certain subpopulations of children may be exposed to benzene in microenvironments depending on specific activities such as use of equipment or vehicles with internal combustion engines, or living in a home where tobacco smoking occurs.

Because of high volatility, the inhalation pathway dominates benzene exposure. Outdoor air concentrations for urban and rural settings were obtained from EPA's 1996 National Air Toxics Assessment (NATA) and the most recent AirData databases. Just prior to the submission of this assessment EPA released the 1999 NATA data. These data were reviewed and found to be similar to the 1996 NATA results, so the exposure values were not changed. Typical outdoor air concentrations were 0.72 µg/m3 and 1.57 µg/m3 for rural and urban settings, respectively. High-end outdoor air concentrations were 1.0 µg/m3 and 4.4 µg/m3 for rural and urban settings, respectively. Indoor air concentrations were obtained from 11 published studies of residential benzene air concentrations. Virtually all benzene in indoor air comes from fuels and combustion sources including infiltration of outdoor air, tobacco smoke, wood stoves, cooking, and infiltration from attached garages. The typical indoor air concentration of 2.5 µg/m3 was determined from the average of the median air benzene air concentrations from 11 residential studies. The high-end indoor air concentration of 11.5 µg/m3 was determined from studies of homes with attached garages. Alaskan children and prospective parents are a separate subpopulation because indoor air concentrations in Alaskan homes with attached garages are higher than those in the continental US, likely due to higher benzene levels in Alaskan gasoline and tighter home construction. However, recent research indicates that benzene levels in Alaskan gasoline, while still higher than the rest of the country, have dropped significantly which has likely lowered the indoor exposures in Alaska.

Oral exposures to benzene via ingestion of food, water and human milk were also quantified. Benzene concentrations in food and drinking water were obtained from various dietary surveys and government databases. The concentrations were used as input into the Lifeline® dietary exposure model, which calculated doses for ingestion of food, water, dermal uptake from contact with water and inhalation of benzene from showering. Infants were analyzed as a separate subpopulation for oral exposures through potential ingestion of human milk. Human milk concentrations were modeled using a published lactation model for typical and high-end urban exposures to the mother and typical and high-end occupational exposures to the mother. Since many employers remove nursing mothers from benzene exposed jobs, this exposure

estimate is very conservative both because of the conservative nature of the model and because it did not consider workplace administrative management controls. Benzene exposures from human milk were similar to that from other food sources except that from high-end occupationally exposed mothers, which were higher.

Exposures to benzene from gasoline were assessed for in-vehicle, refueling and small engine use scenarios. Published literature provided data for analysis of the in-vehicle and refueling scenarios.

Benzene exposure from tobacco smoke was assessed for ETS and mainstream smoking. Emission rates of benzene from cigarettes were used in an EPA indoor air model to calculate indoor air concentrations due to ETS. The model estimated that ETS adds slightly less than 1 µg/m3 to the background indoor air levels. Benzene exposures from mainstream smoking were calculated using the published emission rates from cigarettes and the common inhalation dose algorithm. Mainstream smoking resulted in doses similar to that of typical occupational exposures in the benzene manufacturing and production industries.

The exposure assessment indicated that the inhalation pathway is the primary route of exposure with systemic (absorbed) doses at least one order of magnitude higher than those received via oral ingestion or dermal pathways, except for infant ingestion of human milk from an occupationally exposed mother. Of the ambient background sources, inhalation of indoor air contributed approximately 95% of the overall dose to children and prospective parents. Food and water accounted for the remaining 5%. For nursing infants of occupational exposed mothers up to 22% of the overall infant's dose is estimated to be from benzene concentrations in human milk, though this estimate is likely to be very conservative given the model used and the typical practice of removing nursing mothers from benzene exposed jobs.

Risk Assessment

The risk assessment evaluates of the potential for age-related differences in the sensitivity towards benzene induced toxicity. In the absence of good relevant animal models for AML and with no child-specific epidemiology data on benzene, an alternate analysis is provided to address whether children are more sensitive to benzene induced hematopoetic toxicity or AML than adults. This alternative analysis was based on the literature describing children's therapeutic treatment with chemotherapeutic agents that can cause AML and hematopoetic toxicity. Chemotherapeutic agents (alkylating agents and topoisomerase II inhibitors) are known to cause AML secondary to the treatment regimen in a clear dose-response manner. The clinical data on leukemia risk associated with the treatment of primary pediatric cancers do not indicate that children are at increased risk of developing chemically induced AML. Likewise, published data on the myelosuppressive/hematotoxic effects of various chemotherapy agents in children and adults do not support the existence of an age related difference in sensitivity. Therefore, additional uncertainty/safety factors were not used to adjust the benzene reference values used in this risk assessment.

The EPA default (linear) approach of calculating HQs and excess cancer risk contains significant conservatism, as EPA acknowledges. The use of a single value for the HQ and/or CSF would inappropriately convey a level of confidence or certainty about the risk estimates, when in fact, the HQ and excess risk predicted using a single point estimate contain a large degree of uncertainty, and usually reflect, as with EPA's benzene Integrated Risk Information System (IRIS) values, the upper end of the conservative range of uncertainty. To fully evaluate the range of potential risks, a range of RfDs and cancer slope factors were used to provide

greater insights into the uncertain nature of the cancer and noncancer risk estimates and provides far more insight into the plausible effects analyzed in this benzene risk assessment.

The presence of a functional threshold for benzene-induced hematotoxic and leukemogenic effects is well supported by the peer-reviewed literature. Therefore, a margin of safety (MOS) risk assessment is also presented. The MOS analysis provides a rational and intuitive approach for evaluating the "safety" associated with children's exposures to benzene in the environment. The MOS is the point of departure (POD) divided by the average daily dose. The exposures for most scenarios evaluated in this VCCEP assessment are lower than both the cancer and noncancer PODs by several orders of magnitude, indicating a large MOS. The lowest MOS for benzene is associated with cigarette smoking.

2.0 BASIS FOR INCLUSION OF BENZENE IN VCCEP PILOT PROGRAM

The Pilot Program selection criteria are discussed in the VCCEP Federal Register Notice (Dec. 26, 2000) at III.Q. Based on these criteria, benzene was selected for the VCCEP Pilot Program, because it was (1) evaluated under the Organization for Economic Cooperation and Development (OECD) SIDS Program, (2) found in human blood in the National Health and Nutrition Examination Survey (NHANES) III biomonitoring study, (3) reported in the National Human Exposure Assessment Survey (NHEXAS) study, (4) reported in human exhaled air in the Total Exposure (TEAM) study, (5) detected in drinking water in the National Drinking Water Contaminant Occurrence Database (NCOD) databa se, and (6) detected in indoor air. Table 2.1 provides a summary of the EPA review of the available biomonitoring and environmental monitoring database for benzene.

Table 2.1: Criteria for EPA's Selection of VCCEP Candidate Chemicals

CAS No.	CHEMICAL NAME	SIDS	Chemicals Found in Human Tissues				Chemicals Found in Human Environment	
			NHANES	NHEXAS	TEAMS	HUMAN MILK	NCOD	INDOOR AIR
71-43-2	Benzene	Y	Y	Y	Y		Y	Y

Reference: EPA VCCEP Website (http://www.epa.gov/chemrtk/vccep/vccepmth.htm).

2.1 National Health and Nutrition Examination Survey III (NHANES III):

NHANES III was conducted in 1988 through 1994 on 33,994 people and focused primarily on basic health and nutritional parameters such as blood pressure, immunization status, and nutritional blood measures. NHANES III included a special study that looked at the blood levels of 32 volatile organic compounds (VOCs) in a sample of about 800 volunteers from the overall NHANES study. Eleven compounds were found with high frequency, and the data on these 11 compounds were sufficient to establish reference levels (e.g., median, 95th percentile) for the nonoccupationally exposed U.S. population.

Results on benzene from NHANES III were published in Ashley et al. (1994) and are presented in Table 2.2 (from the EPA VCCEP website). These blood concentrations are consistent with low-level benzene exposure and are discussed further in Section 7.

Table 2.2: Blood Concentrations for Benzene from NHANES III Study reported on EPA's VCCEP website

CAS No.	CHEMICAL NAME	MEDIUM	DETECTION FREQUENCY	CONCENTRATION
71-43-2	Benzene	blood	$\geq$ 75% of 883	med = 0.06 ppb

2.2 National Human Exposure Assessment Survey

The National Human Exposure Assessment Survey (NHEXAS) was a multimedia exposure survey of 24 volatile organic compounds (VOCs), including benzene, conducted in EPA Region 5, Arizona, and Baltimore, Maryland. Hundreds of randomly selected subjects from these areas were evaluated for exposure to benzene from air, food, drinking water, and other beverages. The soil and dust around the participating homes were also assessed for these VOCs. Measurements were also made of chemicals in biological samples (including blood and urine) provided by some participants. Finally, participants completed questionnaires to help identify possible sources of exposure to chemicals. Section 7 addresses the results of this and other exposure assessments.

2.3 Total Exposure Assessment Methodology Data

The Total Exposure Assessment Methodology (TEAM) study was designed to develop methods to measure individual total exposure (exposure through air, food, and water) and to apply these methods within a probability-based sampling framework to estimate the exposures of urban populations in several U.S. cities. The TEAM study reports the results of eight monitoring studies performed in five communities during different seasons of the year. The exposure information on benzene collected through the TEAM study effort is limited. However, extensive information on benzene exposure is available and is presented in Section 7.2.1.2. Information on benzene exposure from TEAM and many other sources is available in Section 7.

2.4 National Drinking Water Contaminant Occurrence Database:

The National Drinking Water Contaminant Occurrence Database (NCOD) provides data on the occurrence and concentration of unregulated contaminants in drinking water. NCOD was developed to satisfy the statutory requirements set by Congress in the 1996 SDWA amendments. The purpose of the database is to support EPA's decisions related to identifying contaminants for regulation and subsequent regulatory development. The NCOD contains occurrence data from both Public Water Systems and other sources (like the U.S. Geological Survey National Water Information System) on physical, chemical, microbial, and radiological contaminants for both detections and non-detects.

NCOD contains occurrence monitoring from sampling locations throughout a Public Water System; therefore, a detection value does not necessarily mean the contaminant would be found at the tap. There are some summary statistics, but no actual analysis of the data is provided. Also, NCOD contains data for only unregulated contaminants that public water systems are required to monitor, even though EPA has not set health-based drinking water maximum contaminant levels for this subset of contaminants. This subset is covered by the Unregulated Contaminant Monitoring Rule, or UCMR. At present, the NCOD does not contain occurrence data for all water systems and all states. The only Public Water System data contained in NCOD are data that have been reported by states to the Safe Drinking Water Information System (SDWIS). Historical data go back to 1983.

Information on benzene in drinking water is addressed in Section 7.2.1.2 of the exposure assessment.

2.5 Air Monitoring Data

Several of the air monitoring references cited by EPA for the VCCEP program provide data on indoor and/or outdoor air concentrations of benzene. The air data samples reported in these studies were generally collected between the mid-1980s and 1991. The most recent study was conducted by Shields et al. (1996) in March and April 1991 at telecommunication centers, data centers, and administrative offices. Daisey et al. (1994) collected indoor and outdoor air samples at 12 office buildings in the San Franciso Bay area between June and September 1990, including several buildings with indoor air quality complaints. Brown et al. (1994) compiled the results of several previous indoor air studies on established and new buildings and reported benzene air concentrations for dwellings, offices, and a hospital. Samfield (1992) and Shah and Singh (1988) also compiled the results of numerous indoor and outdoor air monitoring studies. Indoor and outdoor air monitoring data are discussed further in Section 7, Exposure Assessment.

3.0 PREVIOUS ASSESSMENTS

This section reviews several major assessments that have been conducted for benzene.

3.1 Integrated Risk Information System (IRIS)

The United States Environmental Protection Agency (EPA) has evaluated the toxicity of benzene and has derived a Reference Concentration (RfC) and Reference Dose (RfD) to protect against non-cancer health effects following inhalation and oral exposures, respectively (last revised by EPA in 2003), and Cancer Slope Factors (CSFs) for both inhalation and oral ingestion exposures (last revised by EPA in 1998 for the inhalation CSF and in 2000 for the oral CSF). Both the RfC and RfD were set to protect against the development of cytopenias based on decreases in absolute lymphocyte count (ALC) observed in occupationally exposed workers in China (Rothman et al., 1996) (U.S. EPA, 2003a). EPA classifies benzene as a known human carcinogen. The CSFs for both inhalation and oral exposures were set to protect against an increased risk of developing leukemia, based on observed risks of leukemia found in the "Pliofilm" cohort (U.S. EPA, 2003a). The RfC, RfD, and CSF are discussed in greater detail in the Risk Assessment (Section 8.0).

3.2 AEGL Committee

The National Advisory Committee for Acute Exposure Guideline Levels (NAC/AEGL) first met in June 1996, with the purpose of developing and recommending to EPA airborne guideline levels for short-term exposures to hazardous substances. It was intended that these levels could also be used by other federal, state, and local agencies, and by the private sector, for emergency planning, prevention, and response activities (U.S. EPA http://www.epa.gov/oppt/aegl/history.htm). There are three AEGL levels:

AEGL-1 is the airborne concentration above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or asymptomatic nonsensory effects; however, the effects are not disabling and are transient and reversible on cessation of exposure.

AEGL-2 is the airborne concentration above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

The AEGL development process consists of four basic stages: (1) draft AEGLs, (2) proposed AEGLs, (3) interim AEGLs, and (4) final AEGLs. Benzene has gone through the first two stages of the AEGL process. In December 2002 (for AEGL-1) and in June 2003 (for AEGL-2 and AEGL-3), the AEGL committee approved the proposed AEGLs for benzene that are listed in Table 3.1.

Table 3.1: Proposed Benzene AEGL Values (ppm)					
	10 min	30 min	60 min	4 hr	8 hr
AEGL 1	130	73	52	18	9.0
AEGL 2	2,000*	1,100	800	400	200
AEGL 3	** see below	5,600*	4,000*	2,000*	990

Lower Explosive Limit (LEL) = 14,000 ppm
* = ≥10% LEL; safety considerations against the hazard(s) of explosion(s) must be taken into account.
** = ≥50% LEL; AEGL 3–10 min = 9,700 ppm; extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

3.3 IARC

The International Agency for Research on Cancer (IARC) classifies benzene as a known human and animal carcinogen (Category 1). A summary of the IARC benzene review can be found at http://www-cie.iarc.fr/htdocs/monographs/vol29/benzene.html.

3.4 EU Risk Assessment/OECD SIDS Program

In 2003, the European Union (EU) completed its final draft risk assessment of benzene (ECB 2003). The EU risk assessment of benzene considers some of the same toxicology and exposure data reviewed in this VCCEP assessment, although the focus of this risk assessment was not on children. The EU risk assessment relied on a margin-of-safety analysis to evaluate the potential health risks for general and occupational populations exposed to benzene. The EU chose their points of departure for endpoints representing acute, chronic, fertility impairment, developmental effects, and cancer. After applying endpoint-specific "safety factors" (which they termed "minimal margins of safety"), the EU derived a "critical exposure level" for each endpoint. These critical exposure levels were considered thresholds for the specific endpoint, including cancer.

This final draft EU risk assessment was reviewed and approved by the Organization for Economic Cooperation and Development (OECD) Screening Information Data Sets (SIDS) program in October 2005 (SIAM- 21) along with the SIDS Initial Assessment Profile (SIAP) and SIDS dossier (a set of chemical information and robust study summaries – see Appendix D). The OECD concluded in the SIAP that benzene is a potential candidate for further exposure and risk assessment work noting possible health concerns and the possibility for exposure. The OECD did not recommend any further animal testing and specifically noted that that further testing on reproductive effects is not warranted given the already established hazards of the chemical.

3.5 Other Reviews/Assessments

Previous reviews of benzene have been conducted by the National Toxicology Program (NTP), International Programme on Chemical Safety (IPCS), the Agency for Toxic Substances and Disease Registry (ATSDR), California Office of Environmental Human Health Assessment (OEHHA) and others. The NTP's 11th Report on Carcinogens (RoC), January 2005, includes an

assessment of benzene (originally included in the first RoC) , concluding that benzene is “known to be a human carcinogen.” The IPCS evaluated benzene in the early 1990s and, in 1993, published an Environmental Health Criteria Review on benzene (EHC 150) evaluating toxicological and environmental effects of benzene. The ATSDR released a draft Toxicology Profile on benzene in October 2005, updating the previous profile published in September 1997; it provides a review of production, hazard, exposure, and pharmacokinetic data.

4.0 Regulatory Overview

This section provides an overview of the extensive federal environmental, health and safety, and related regulations controlling benzene exposures.

Benzene is broadly regulated by many federal agencies, including the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), the Consumer Product Safety Commission (CPSC), the Occupational Safety and Health Administration (OSHA), and the Department of Housing and Urban Development (HUD). Given the number, and in some cases, the complexity of these regulations, this overview necessarily is not an exhaustive survey of all regulations relating to benzene.

4.1 EPA Regulation

EPA regulates benzene under numerous statutes, including the Clean Air Act, 42 U.S.C. §§ 7401 *et seq.*; the Clean Water Act, 33 U.S.C. §§ 1251 *et seq*.; the Safe Drinking Water Act, 42 U.S.C. §§ 300f *et seq.* (SDWA); the Resource Conservation and Recovery Act, 42 U.S.C. §§ 321 *et seq.* (RCRA); the Comprehensive Environmental Response, Compensation, and Liability Act, 42 U.S.C. §§ 9601 *et seq.* (CERCLA, or Superfund); the Superfund Amendments and Reauthorization Act, 42 U.S.C. §§ 9601 *et seq.* (SARA); the Emergency Planning & Community Right-To-Know Act (EPCRA), 42 U.S.C. §§ 11011 *et seq.*; the Pollution Prevention Act, 42 U.S.C. §§ 13101 *et seq.* (PPA); and the Toxic Substances Control Act, 15 U.S.C. §§ 2601 *et seq.* (TSCA).

4.1.1 Clean Air Act

The Clean Air Act regulates benzene emissions from stationary sources (e.g., factories, refineries, and power plants) and mobile sources (e.g., trucks, cars, motorcycles) and as volatile organic compounds in products. Under the Clean Air Act, benzene is variously referred to as a Hazardous Air Pollutant (HAP), a volatile organic compound (VOC), or a Mobile Source Air Toxic (MSAT).

4.1.1.1 Hazardous Air Pollutant Regulation

Section 112 of the Clean Air Act establishes a two-step process for protecting the public and the environment from the effects of toxic air pollutant emissions from stationary sources. First, EPA promulgates extensive National Emission Standards for Hazardous Air Pollutants (NESHAPs), better known as Maximum Achievable Control Technology (MACT) standards, as required by section 112(d) of the Act. These technology-based MACT standards are imposed on specific manufacturing sectors on a category-by-category basis. (See generally 40 C.F.R. Parts 61, 63.) Second, within the eight years following the promulgation of each technology-based MACT standard, EPA has to regulate any remaining (or "residual") risk with an "ample margin of safety" [CAA § 112(f), 42 U.S.C. § 7412(f)]. In this second phase, EPA applies a risk-based approach to assess whether the MACT technology-based emission limits sufficiently reduce health and environmental risks.

Thus, benzene emissions from stationary sources are subject to both stringent, manufacturing-sector-specific MACT-based standards and any further regulation that EPA determines is necessary to ensure an ample margin of safety. Virtually all of the MACT standards have been

published, and EPA is in the process of considering where residual risk rules for facilities will be needed.

4.1.1.2 Volatile Organic Compound Regulations

Numerous regulations affect VOCs in regions where ozone formation is a concern. While these regulations are not necessarily specific to benzene, they do affect many industrial operations that emit benzene. (See, e.g., 40 C.F.R. Part 60, VOC standards for new stationary sources involving certain activities.) In general, the overriding effect of these regulations is a reduction of benzene emissions.

4.1.1.3 Mobile-Source Air Toxics, Reformulated Gasoline, and Limits on Gasoline Volatility

"Nationwide, mobile sources represent the largest contributor to air toxics" (EPA, Mobile Source Emissions – Past, Present, and Future). The Clean Air Act requires EPA to promulgate regulations to control hazardous air pollutants from motor vehicles and motor vehicle fuels. The regulations must reflect the greatest degree of emission reduction achievable, considering "the availability and costs of the technology, and noise, energy, and safety factors, and lead time" [CAA § 202(l)(2), 42 U.S.C. § 7521(l)(2)]. As a result, numerous regulations reduce emissions of mobile-source air toxics such as benzene, including EPA's reformulated gasoline ("RFG") program, limitations on gasoline volatility, and other provisions that affect MSATs.

On passage of the 1990 CAA amendments, EPA established the RFG program. This program requires the reformulation of gasoline to reduce emissions of smog-forming and toxic pollutants (see generally 40 C.F.R. Part 80).

Other regulations limit gasoline volatility, thereby reducing evaporative emissions (see, e.g., 40 C.F.R. § 80.27). Volatility is a measure of how easily gasoline evaporates. When gasoline evaporates, toxics such as benzene that are present in the gasoline are released to the air. EPA regulates the Reid vapor pressure of gasoline, a common measure of gasoline volatility, from May through September each year for certain "designated volatility nonattainment areas" and "designated volatility attainment areas" as defined in 40 C.F.R. § 80.2(cc) and 40 C.F.R. § 80.2(dd), respectively. Moreover, certain classes of motor vehicles are required to have evaporative emission controls, thereby further reducing the amount of gasoline volatiles that get into the air [see, e.g., 40 C.F.R. §§ 86.1811-01(d), 86.1811-04(e), 86.1812-01(d), 86-1813-01(d), 86.1814-01(d), 86.1814-02(d), 86.1815-01(d), 86.1815-02(d), 86.1816-05(d), 86.1816-08(d)].

In 2001, EPA promulgated a mobile-source air toxics final rule that identified 21 MSATs, including benzene, and set new gasoline toxic emission performance standards [see 66 Fed. Reg. 17230 (March 29, 2001)]. This rule establishes a framework for EPA's national mobile-source air toxics program and requires that refineries maintain the toxics performance of the gasoline they produced during the baseline period 1998–2000. The rule also contains a plan for continuing research and analysis on all MSATs.

In February 2006, the EPA Administrator signed another proposed mobile source air toxics rule designed to reduce emissions of benzene and other MSATs. As EPA again recognizes, "mobile sources are responsible for the majority of benzene emissions." 71 Fed. Reg. 15803. The proposed rule "would significantly lower emissions of benzene and the other air toxics in three ways: (1) by lowering benzene content in gasoline; (2) by reducing exhaust emissions from

passenger vehicles operated at cold temperatures (under 75 degrees F); and (3) by reducing emissions that evaporate from, and permeate through, portable gasoline containers (gas cans)." EPA Fact Sheet: Control of Hazardous Air Pollutants from Mobile Sources, Office of Transportation and Air Quality, EPA420-F-06-021 (Feb. 2006). Beginning in 2011, refiners would be required to lower average benzene content to 0.62 percent, down from today's average of 0.97 percent. *See id.*

EPA projects "annual nationwide benzene reductions of 35,000 tons in 2015, increasing to 65,000 tons by 2030." 71 Fed. Reg. 15803. As a result, "[p]assenger vehicles in 2030 would emit 45% less benzene;" "[g]as cans … would emit almost 80% less benzene;" and "[g]asoline would have 37% less benzene overall." 71 Fed. Reg. 15803.

Table 4.1: Timeline of Mobile-Source Regulatory Actions that Resulted in Reductions of VOCs in Emissions

Year	Description
1970	The Clean Air Act Amendments of 1970 set the first standards for emissions from motor vehicles. The standards are phased in over the next 5 years.
1971	New cars must meet evaporative emissions standards for the first time.
1975	New cars are required to use catalytic converters.
1981	New cars meet the amended Clean Air Act standards for the first time.
1983	Second-generation catalytic converters required for new cars.
1983	First inspection and maintenance programs established in areas with air pollution problems.
1989	EPA sets first fuel volatility limits aimed at reducing evaporative emissions.
1990	Clean Air Act Amendments of 1990 require further reductions in hydrocarbons, lower tailpipe standards, more stringent emission testing procedures, expanded I/M programs, new vehicle technologies, and clean fuels programs. California adopts a low emission vehicle ("LEV") program.
1991	EPA establishes lower tailpipe standards for hydrocarbons.
1992	Winter oxygenated fuel program begins in cities with high carbon monoxide levels. California has a similar "Phase I gasoline" program (oxygenated fuel required to limit carbon monoxide emissions also has a lower hydrocarbon content).
1994	Progressive introduction begins of national Tier 1 emission limits for light duty vehicles. On-board diagnostic systems become a requirement for light duty vehicles and trucks.
1995	Phase I RFG is required to be sold in areas of ozone non-attainment (Phase I RFG has lower volatility, and contains oxygenated compounds and lower benzene). California transitional gasoline introduced as a transition from Phase I to Phase II RFG.
1996	California Phase II RFG is introduced. (Phase II RFG has reduced vapor pressure and lower hydrocarbon and benzene content.) National Tier 1 emission limits introduced progressively from 1996 for light duty trucks. Phase-in begins of revised procedures and limits for evaporative emissions for light and heavy-duty vehicles. Dispensing rates for gasoline and methanol pumps are regulated.

Table 4.1 (cont.)

Year	Description
1998	Federal Tier 1 tailpipe emissions standards go into effect. California's Low Emission Vehicles ("LEV") fleet averaging program begins. National hydrocarbon emission limits introduced for vehicles using clean alternative fuels (provisions under LEV program). Voluntary Agreement for Cleaner Cars: Northeastern states agree to put cleaner cars on the road before they could be mandated under the CAAA. The first National Low Emissions Vehicles (NLEVs) under this agreement were released in New England in 1999 and were available nationwide in 2001.
1998	Phase-in begins of on-board refueling controls on passenger vehicles (1998–2000).
2000	NLEV program starts. California hydrocarbon emission limits introduced for vehicles using clean alternative fuels – provisions under LEV program.
2001	Phase-in begins of on-board refueling controls on light light-duty trucks (2001–2003).
2001	Japanese electric-gasoline hybrid automobiles become available.
2003	Federal Tier 2 tailpipe emissions standard phase-in begins.
2003	Phase-in of California's LEV II program begins.
2003	California requires a maximum level of sulfur in RFG of 600 ppm.
2004	Phase-in begins of on-board refueling controls on heavy light-duty trucks (2004–2006).
2004	For refiners and importers, EPA requires a maximum level of sulfur in gasoline of 300 ppm, and an average of 120 ppm.
2005	For refiners, EPA requires an average level of sulfur in gasoline of 30 ppm. For importers, the average requirement is 90 ppm, and the maximum is 300 ppm.
2006	For refiners, EPA requires a maximum level of sulfur in gasoline of 80 ppm. For importers, the average is set at 150 ppm.
2005	California requires a maximum level of sulfur in RFG of 30 ppm.
2007	Importers must meet the 30-ppm average and 80-ppm maximum sulfur content in gasoline.
2006	Phase-in of California's LEV II program complete.
2007	Planned finalization of additional EPA rule on mobile-source air toxics.
2010	Federal Tier 2 tailpipe emissions standard phase-in complete.

This list also includes regulatory actions that reduce sulfur in gasoline. Lower sulfur content increases catalytic converter efficiency, thus decreasing hydrocarbon emissions. Therefore, the new sulfur regulations have also been included in the table.

4.1.2 Clean Water Act

The Clean Water Act, originally enacted as the Federal Water Pollution Control Act Amendments of 1972, establishes the basic structure for regulating discharges of pollutants into the navigable waters of the United States. It prohibits any person from discharging any pollutant from a point source into navigable waters except as in compliance with the Act's permit requirements, effluent limitations, and other relevant provisions. The Act also grants EPA the authority to set wastewater standards for industry and water quality standards for all contaminants in surface waters.

Benzene has been designated a hazardous substance under the Clean Water Act (See 40 C.F.R. § 116.4). Because of this designation, discharges are regulated, and certain releases must be reported. Direct discharges of wastewater from sources using end-of-pipe biological treatment cannot exceed a benzene concentration above 136 μg/L on any particular day, and a monthly average of 37 μg/L (see 40 C.F.R. § 414.91). For indirect-discharge sources and direct-discharge sources that do not use end-of-pipe biological treatment, the maximum benzene concentrations are 134 μg/L daily and 57 μg/L monthly (see 40 C.F.R. §§ 414.101, 414.111). Other EPA regulations permit ocean dumping of wastewater containing benzene, but only when benzene is present in concentrations below its solubility in seawater [see 40 C.F.R. § 227.7(a)]. Releases in excess of 10 pounds of benzene from any facility must be reported (see 40 C.F.R. § 117.3).

In addition, EPA has established water quality standards, which vary by body of water, for states that do not comply with federal guidance for establishing their own standards under the Clean Water Act (see 40 C.F.R. §§ 131.31–.40).

4.1.3 Safe Drinking Water Act

The Safe Drinking Water Act creates a comprehensive scheme for regulating drinking water and its sources. Under the authority of the Act, EPA sets standards for approximately 90 contaminants in drinking water and its sources—rivers, lakes, reservoirs, springs, and groundwater wells. For each of these contaminants, EPA sets an enforceable limit, called a maximum contaminant level (MCL), and a non-enforceable public health goal, called a maximum contaminant level goal (MCLG), which allows for a margin of safety.

EPA has set the MCLG for benzene in public drinking water sources at 0.0 mg/L, and the MCL at 0.005 mg/L (see 40 C.F.R. §§ 141.50, 141.61). The permissible level for benzene in bottled water products is 0.005 mg/L [21 C.F.R. § 165.110(b)(4)(iii)(B)].

In addition to MCLGs, MCLs, and other similar drinking-water standards, EPA also promulgates health advisories, or guidance values, based on non-cancer health effects for different durations of exposure (e.g., one-day, ten-day, and lifetime exposures). These health advisories provide technical guidance to EPA, state and local government, and other public health officials regarding "health effects, analytical methodologies, and treatment technologies associated with drinking water contamination." EPA has promulgated several health advisory values for benzene [see Office of Water, EPA, 2004 Edition of the Drinking Water Standards and Health Advisories, EPA 822-R-04-005 (Winter 2004)].

4.1.4 Resource Conservation and Recovery Act

The Resource Conservation and Recovery Act regulates the transportation, storage, treatment, and disposal of hazardous wastes. RCRA includes benzene on its list of hazardous constituents (40 C.F.R. Pt. 261 App. VIII). Moreover, benzene and certain substances containing benzene are identified on two of RCRA's three hazardous waste lists—hazardous wastes from nonspecific sources (40 C.F.R. § 261.31) and commercial chemical products (40 C.F.R. § 261.33). Benzene also is on the groundwater monitoring list for owners and operators of hazardous waste facilities (see 40 C.F.R. Pt. 264 App. IX). Thus, benzene is subject to a variety of RCRA controls relating to its transportation, storage, treatment, and disposal.

4.1.5 Comprehensive Environmental Response, Compensation, and Liability Act

The Comprehensive Environmental Response, Compensation, and Liability Act, as amended by the Superfund Amendments and Reauthorization Act, provides EPA broad authority to respond directly to releases and threatened releases of hazardous substances, pollutants, and contaminants that may endanger public health or the environment.

Benzene also has been designated as a hazardous substance under CERCLA (see 40 C.F.R. § 302.4). As a result, benzene is subject to monitoring and numerous other requirements relating to releases and threatened releases. For example, releases of benzene in excess of 10 pounds from any facility must be reported (see 40 C.F.R. Part 302). In addition, certain amounts of other products containing benzene are reportable. Moreover, benzene present at listed Superfund sites is subject to varying levels of cleanup.

4.1.6 The Emergency Planning and Community Right-To-Know Act And The Pollution Prevention Act

The Emergency Planning and Community Right-To-Know Act, also known as Title III of SARA, was enacted by Congress to help inform local communities of chemical hazards in their areas. Section 313 of EPCRA requires EPA and state governments to annually collect data on releases and transfers of certain toxic chemicals from industrial facilities. These data are available to the public in the Toxics Release Inventory ("TRI"). In 1990, Congress amended these reporting requirements by passing the Pollution Prevention Act ("PPA"). Section 6607 of the PPA requires facilities to provide information on pollution prevention and recycling for each toxic chemical subject to reporting under TRI (see 42 U.S.C. § 13106).

Benzene is one of the more than 650 chemicals and chemical categories subject to reporting under TRI (see 40 C.F.R. § 372.65; EPA, 2004 Reporting Year List of TRI Chemicals). Thus, users of benzene in many industries, such as petroleum refineries, manufacturers, miners, petroleum bulk terminals, and chemical wholesalers, are subject to these reporting requirements.

4.1.7 Toxic Substances Control Act

The Toxic Substances Control Act authorizes EPA to obtain information on all new and existing chemical substances that could cause an unreasonable risk to public health or the environment and to regulate their manufacture, use, distribution, and disposal. Under TSCA, EPA classifies chemical substances as either "existing" chemicals or "new" chemicals. Existing chemicals are those listed on the Toxic Substances Control Act Chemical Substance Inventory, or TSCA Inventory, which EPA must compile, keep current, and publish [see TSCA § 8(b), 15 U.S.C. § 2607(b)]. TSCA provides authority to EPA to regulate and seek various kinds of safety and health data on existing chemicals, which include mandatory reporting under Section 8, 15 U.S.C. § 2607, and testing under Section 4, 15 U.S.C. § 2603.

4.2 CPSC Regulation

The Consumer Product Safety Commission regulates benzene under the Federal Hazardous Substances Act, 15 U.S.C. §§ 1261 *et seq.* (FHSA), and the Poison Prevention Packaging Act, 15 U.S.C.§§ 1471 *et seq.* (PPPA). More than 20 years ago, CPSC concluded that further regulation was not required, because "benzene use as an intentional ingredient in consumer

products had ceased" [46 Fed. Reg. 27910 (May 22, 1981)]. For further information about the absence of benzene in consumer products, see Section 7.2.4 below.

The FHSA requires precautionary labeling on the immediate containers of hazardous household products to help consumers safely store and use these products and to provide consumers information about immediate first aid steps in the event of an accident. Implementing regulations require special labeling of certain products containing benzene. Given that substances containing 5% or more by weight of benzene are "hazardous," products containing benzene require special labels, including "danger," "vapor harmful," "poison," and "harmful or fatal if swallowed" [16 C.F.R. § 1500.14(a), (b)].

The PPPA requires that certain products be packaged in child-resistant packaging to protect children under five from possible poisoning and death in the event that they open containers of hazardous products and eat or drink the contents. CPSC regulations impose special packaging requirements for numerous substances, including solvents for paint or other similar surface-coating materials that contain 10% or more by weight of benzene, or combinations of benzene and certain other solvents, and that have a viscosity of less than 100 Saybolt universal seconds at 100 °F (see 16 C.F.R. § 1700.14(a)(15)].

4.3 FDA Regulation

FDA regulates a myriad of products ranging from food ingredients and drugs to medical and surgical devices; therefore, only a sample of FDA's regulations relating to benzene are discussed below.

In general, FDA limits the amount, if any, of benzene that can be contained in food and drugs. Benzene is not an approved food additive that can be added directly to food for human consumption (see 21 C.F.R. Part 172). Benzene is not an approved substance for use in the food-contact surface of packaging for processing, transporting, or holding certain foods or for use in other food-contact surfaces (see, e.g., 21 C.F.R. §§ 176.180, 177.1010). Benzene also is not approved for use in food packaging cellophane (see 21 C.F.R. § 177.1200).

FDA limits the permissible amount of benzene in bottled water products to 0.005 mg/L [see 21 C.F.R. § 165.110(b)(4)(iii)(B)].

Furthermore, FDA also provides guidance on the amounts of residual solvents that are considered safe in pharmaceuticals. According to FDA, benzene "should not be employed in the manufacture of drug substances, excipients, and drug products because of [its] unacceptable toxicity or [its] deleterious environmental effect.". If, however, its use is unavoidable, then the level of benzene should be limited to 2 ppm (FDA, Guidance for Industry, Q3C—Tables and List).

4.4 OSHA Regulation

The Occupational Safety and Health Administration is the primary federal agency responsible for establishing and enforcing workplace standards, including exposure limits for many substances. The National Institute for Occupational Safety and Health (NIOSH) and the American Conference of Governmental Industrial Hygienists (ACGIH) also develop and recommend exposure limits for worker protection, although these limits are not enforceable.

OSHA sets both permissible exposure limits (PELs) and short-term exposure limits (STELs). A PEL is the maximum concentration to which workers may be exposed in any 8-hour work shift of a 40-hour work week, and a STEL is the maximum 15-minute concentration to which workers may be exposed during any 15-minute period of the workday.

For benzene, OSHA has set the PEL at 1 ppm as an 8-hour time-weighted average (TWA) concentration, and the STEL at 5 ppm as a 15-minute TWA STEL [see 29 C.F.R. § 1910.1028(c)]. These exposure limits apply to all industries, including construction and maritime, with the exception of certain subsegments (e.g., distribution and sale of fuels, sealed containers and pipelines, coke production, oil and gas drilling and production, natural gas processing, and the percentage exclusion for liquid mixtures) (see 29 C.F.R. §§ 1910.1028(c), 1915.1028, 1926.1128). For these subsegments of industry, OSHA has set an 8-hour TWA of 10 ppm, an acceptable ceiling of 25 ppm, and an acceptable maximum peak above this ceiling of 50 ppm for a maximum duration of 10 minutes (see 29 C.F.R. § 1910.1000, Table Z-1, note 1(d); Table Z-2).

The NIOSH-recommended exposure limit (REL) for benzene is 0.1 ppm as a TWA for up to an 8-hour work shift and a 40-hour work week, and the recommended STEL is 1 ppm (see NIOSH Pocket Guide to Chemical Hazards).

ACGIH has assigned benzene a threshold limit value (TLV®) of 0.5 ppm as a TWA for a normal 8-hour workday and a 40-hour work week, and a STEL of 2.5 ppm for periods not to exceed 15 minutes (see ACGIH, 2005 TLVs® and BEIs®).

4.5 HUD Regulation

The Department of Housing and Urban Development attempts to minimize exposure to benzene through regulations relating to the location of HUD-assisted projects. These regulations help calculate the acceptable separation distance between HUD-assisted projects and hazardous operations that store, handle, or process hazardous substances and provide guidance for identifying and assessing these hazardous operations. Benzene is one of the hazardous substances addressed by these regulations (see 24 C.F.R. Part 51, Subpart C, App. I).

4.6 State Regulation

In addition to the federal regulatory programs described briefly above, benzene is subject to a wide variety of state regulations. A description of such programs is well beyond the scope of this regulatory overview, but in many instances, these regulatory programs are more stringent than federal requirements. Many federal statutes, such as the Clean Air Act and the Occupational Safety and Health Act, permit or, in some instances, require states to apply additional regulatory measures. For example, California has extensive air toxics and VOC regulations that go well beyond federal requirements. These include specific air toxics programs, stringent mobile-source (both fuels and vehicle) controls, and other regulatory controls. In recent years, many of these California programs have been adopted or extended by other states, particularly those in the Northeast. More recently, several localities have enacted local air toxics programs that provide further controls on releases of benzene to the environment.

5.0 CHEMICAL OVERVIEW

This section provides general information for benzene, including physical and chemical properties, environmental fate, production, uses, and environmental sources and releases. Detailed discussions on benzene physical, chemical and environmental fate properties are available in the ATSDR (1997, 2005) profile and descriptions of the various sources of benzene can be found in EPA (U.S. EPA 1998). Detailed sector notebooks are also available for several industries (e.g., the organic chemical industry or petroleum refining industry) from the EPA Office of Compliance (U.S. EPA, 1995a,b). For the facilities that reported year 2003 Toxic Release Inventory (TRI) data, on-site air emissions accounted for 93% of total facility emissions. In addition to direct emissions to the air, over 99.9% of all benzene releases partition to the air (ATSDR, 1997, 2005). While the primary focus of this section is on sources of air emissions and air levels given benzene's release pattern and fate characteristics, releases to water and soil are also discussed briefly.

5.1 Chemical Identity

The information pertaining to the chemical identity of benzene is presented in Table 5.1 below.

Table 5.1: Chemical Identity of Benzene

Property	Value	Reference
Chemical name	Benzene	HSDB, 2002
Chemical formula	C_6H_6	HSDB, 2002
Chemical structure		Merck, 1989
CAS number	71-43-2	HSDB, 2002

HSDB = Hazardous Substance Data Bank

5.2 Physical and Chemical Properties

The key physical and chemical properties of benzene are presented in Table 5.2 below.

Table 5.2: Physical and Chemical Properties of Benzene

Property	Value	Reference
Molecular weight	78.11	Merck, 1989
Vapor pressure (25°C)	95 mm Hg	CRC, 1994
Density (25°C)	0.8729 g/cm^3	CRC, 1994
Water Solubility (25°C)	1791 mg/L	Howard, 1990
Henry's law constant (25°C)	5.5 x 10^{-3} atm-m^3/mol	Mackay, 1975. (in ATSDR, 1997)
Log K_{ow} (octanol-water partitioning)	2.13	HSDB, 2002
Log K_{oc} (organic carbon-water partitioning)	1.8-1.9	HSDB, 2002
Physical state at room temperature	Clear, colorless liquid	Merck, 1989
Melting point	5.5 °C	Merck, 1989
Boiling point	80.1 °C	Merck, 1989
Odor	Aromatic	NFPA, 1994 (in ATSDR, 1997)
Odor threshold (water)	2.0 mg/L	HSDB, 2002
Odor threshold (air)	4.9 mg/m^3 (1.5 ppm)	HSDB, 2002
Flashpoint	-11 °C (closed cup)	Merck, 1989
Flammability limits in air	Lower: 1.2%; Upper: 7.8 %	NFPA, 1994 (in ATSDR, 1997)

NFPA = National Fire Protection Association
CRC = CRC Press

5.3 Environmental Fate and Transport

Several environmental fate and transport characteristics of benzene are qualitatively summarized in Table 5.3. As demonstrated by this table, benzene is generally found in the air, and its presence in water is limited by benzene's water solubility and high vapor pressure. The small amount of benzene that is found in groundwater is relatively mobile, but biodegrades when a sufficient amount of dissolved oxygen is available. Benzene is not thought to bioconcentrate appreciably in marine organisms or plants. Atmospheric benzene degrades rapidly due to reaction with atmospheric hydroxyl radicals and has a residence time between a few hours and several days, depending on season. Due to the fate and transport characteristics of benzene, most human exposure occurs by the inhalation pathway.

Table 5.3: Environmental Fate and Transport Characteristics of Benzene

Characteristic	Description*	Reason
Volatility	High	High vapor pressure of 95 mm Hg @ 25°C.
Water Solubility	Low-moderate	Slight solubility of 1,791 mg/l @ 25°C.
Propensity of benzene to partition to the atmosphere from surface water	Moderate-high	High Henry's Law constant of 5.5×10^{-3} atm-m^3/mol.
Groundwater mobility	High	Low Log K_{oc} of 1.8 to 1.9.
Fraction of human exposure that occurs via the inhalation pathway	High (99%)	High fraction of benzene that partitions to the air (ATSDR 1997).
Biodegradation potential of benzene in groundwater	Moderate	Benzene biodegradation in groundwater function of presence of acclimated microorganisms and available electron acceptors or level of methanogenesis activity.
Residence time of benzene in the atmosphere	Low-Moderate (half life of less than two weeks)	Rapid chemical degradation reactions with hydroxyl radicals (ATSDR 1997).
Propensity of benzene to bioaccumulate in marine organisms	Low	Low log K_{ow} of 2.13 (ATSDR 1997).
Bioconcentration potential of benzene in plants	Low	Low amount of root uptake since most benzene is found in the vapor phase; limited amount of air-to-leaf transfer can occur in some plants (ATSDR 1997).
Fraction of benzene released to the environment that partitions into the air	High (99.9%)	High volatility and Henry's Law Constant; Low water solubility.

* The descriptions are based on the rankings reflective of those generally accepted in the scientific literature.

5.4 Pure Benzene Production

Pure benzene is isolated primarily for use as an intermediate feedstock in the production of other chemicals such as ethylbenzene. Benzene is produced by the petroleum industry and to a lesser degree, by the steel industry as a byproduct of coke production (Table 5.4). The major chemical processes used in benzene production include catalytic reforming [naphthene

(cycloparaffins) dehydrogenation], catalytic dealkylation (removal of an aryl alkyl group in the presence of a catalyst), steam cracking (breakdown of large hydrocarbons into smaller hydrocarbons by high temperature steam), distillation (chemical separation from crude or light oils based on boiling points), and destructive distillation (separation at high temperature in the absence of oxygen).

Table 5.4: Processes Used to Manufacture Benzene

Industry	Process	Inputs	Percentage of U.S. benzene production (ATSDR, 2005)
Petroleum	Catalytic reforming	Straight-run gasoline (C_5-C_{11}) or cycloparaffins (e.g., cyclohexane)	45%
Petroleum	Catalytic dealkylation	Toluene or toluene/xylene mixture	30%
Petroleum	Steam cracking / distillation	Pyrolysis gasoline (unsaturated aliphatic hydrocarbons produced by steam cracking of gas oil or heavy naphtha)	23%
Steel	Destructive distillation	Coal	< 2%

Historical benzene production levels are available from trade publications. Chemical and Engineering News (2001) and National Petrochemical Refiners Association (NPRA, 2004) reports benzene production for the petroleum industry (Table 5.5). Between 1990 and 2003, benzene production increased at an annual rate of 3.6%, while at the same time, annual air emissions, as reported to the TRI, decreased nearly 75% (U.S. EPA, 2003b).

Table 5.5: Production Levels of Benzene During the 1990s and Associated TRI Air Emissions

Year	Production Level (million gallons/year)	Total TRI Air Emissions (lbs)
1990	1,699	25,846,604
1991	1,569	19,302,759
1992	1,636	13,236,757
1993	1,677	11,362,731
1994	2,074	9,853,234
1995	2,168	9,401,776
1996	2,116	8,184,997
1997	2,342	8,791,685
1998	2,237	7,270,122
1999	2,401	7,270,481
2000	2,412	6,399,187
2001	1,921	5,893,897
2002	2,148	6,043,671
2003	2,094	6,261,791

In addition to industry production rates, the Chemical Market Reporter (CMR, 2002) provides information on benzene production capacity by petroleum producer and city (Table 5.6). In

general, the production rate is about 70 to 75% of capacity. Most of the benzene production capacity is found in Texas (20 facilities), Louisiana (5 facilities), Illinois (2 facilities), Pennsylvania (2 facilities), and Ohio (2 facilities).

Table 5.6: U.S. Benzene Production Capacity (2002)

Producer	City	State	2002 Capacity (million gallons)
BP Chemicals	Alliance	LA	410
	Lima	OH	
	Texas City	TX	
Chalmette Refining	Chalmette	LA	55
Chevron Phillips Chemical	Pascagoula	MS	440
	Port Arthur	TX	
	Richmond	CA	
	Sweeny	TX	
	Guayama	PR	
Citgo	Corpus Christi	TX	170
	Lake Charles	LA	
	Lemont	IL	
Coastal	Corpus Christi	TX	100
	Westville	NJ	
ConocoPhillips	Wood River	IL	60
Dow Chemical	Freeport	TX	300
	Plaquemine	LA	
Equistar Chemicals	Alvin	TX	285
	Channelview	TX	
	Corpus Christi	TX	
ExxonMobil	Baton Rouge	LA	470
	Baytown	TX	
	Beaumont	TX	
Frontier Oil	El Dorado	KS	15
Hovensa	St. Croix	VI	70
Huntsman	Port Arthur	TX	50
Flint Hills Resources	Corpus Christi	TX	250
Lyondell	Houston	TX	50
Marathon Ashland	Catlettsburg	KY	65
Motiva	Delaware City	DE	15
Nova Chemicals	Bayport	TX	15
Shell Chemicals	Deer Park	TX	180
Sunoco	Marcus Hook	PA	85
	Philadelphia	PA	
	Toledo	OH	
TOTAL Petrochemical, USA	Port Arthur	TX	125
Valero Energy	Houston	TX	25
	Three Rivers	TX	
Total Capacity (2002)			3,235
Total Demand (2001)			2,670

5.5 Pure Benzene Consumption

Most benzene that is isolated as a pure chemical is used as a feedstock for the production of other chemicals. Table 5.7 presents the chemicals and products that are derived from benzene (ATSDR, 1997, 2005; CMR, 2006; U.S. EPA, 1998a). Although benzene was historically used as an industrial solvent, solvent use ceased many years ago (U.S. EPA, 1998a). Pure benzene however, may be sold to specialized laboratories for use in controlled environments.

Table 5.7: Major Uses of Benzene Isolated from Petroleum Products

Chemical Produced from Benzene	Percent of Consumption (2005)[a]	Typical Uses for Derived Chemical
Ethylbenzene	53%	Intermediate for styrene, which is used to manufacture plastics
Cumene	18%	Intermediate for phenol (used in manufacture of epoxy resins and caprolactam for nylon) and acetone (used in manufacture of solvents and plastics)
Cyclohexane	13%	Intermediate used to manufacture nylon and nylon intermediates
Nitrobenzenes	7%	Intermediate for aniline, which is used to manufacture isocyanates for plastics, dyes and polyurethane foam
Linear Alkylbenzenes	3%	Intermediate used to manufacture surfactants
Other (e.g., resorcinol, hydroquinone, chlorobenzene, or maleic anhydride)	6%	Resorcinol is used in the manufacture of resins, dyes and pharmaceuticals. Hydroquinone is used as a rubber antioxidant and in developing black-and-white photographic film. Chlorobenzene is used as pesticide solvent and as an intermediate in manufacture of nitrochlorobenzene (used in dyes and agricultural products). Maleic anhydride is used in manufacturing polyester resins, alkyd coating resins, permanent press resins (textiles), fumaric and tartaric acids, lubricant additives, plasticizers, agricultural chemicals and is a prepreservative for oils and fats.

[a]Chemical Week, January 4/11, 2006.

5.6 Production and Consumption of Refined Petroleum Products

Benzene is a minor constituent of crude oil. The petroleum product that is most likely to contain benzene is gasoline. Unleaded automobile gasoline generally has a benzene content of about 1% (U.S. EPA, 1998a), whereas jet fuel (military and commercial airline) generally has a benzene content less than 0.02% (ATSDR, 1998). Distillate fuel oil (e.g., diesel fuel) has a benzene content of 0.006% by weight (U.S. EPA, 2002a; WHO, 1996). In addition to benzene that is found in crude oil, benzene in automobile gasoline is also formed during the process of catalytic reforming, which is used to increase the octane rating of the naphtha fraction of

gasoline. Aromatic hydrocarbons, such as benzene, contribute to the anti-knock properties (prevention of engine pinging or rattling due to secondary detonations) of unleaded automobile gasoline. Table 5.8 summarizes petroleum based fuel production and consumption volumes (DOE, 2000).

Table 5.8: U.S. Petroleum-Based Fuel Production and Consumption

	U.S. Production or Consumption Rate, 1999 (million gallons per day)[a]			
Economic Activity	Motor Gasoline	Jet Fuel	Kerosene	Distillate fuel oil
Consumption (demand)	354	70	3.1	143
Production (supply)	341	66	2.8	150
Net import to U.S. to meet demand	13	5	0.3	7.3

[a]Consumption and production volumes based on assumption of 42 gallons per barrel.

5.7 Releases of Benzene to Ambient Air

Benzene is released to air during a number of processes including benzene production, benzene use, combustion of fuel (mobile and non-mobile sources), biomass combustion, and miscellaneous processes such as manufacturing of paper or disposal of municipal solid waste. Each of the various sources of benzene emissions to air is described in detail by the EPA (U.S. EPA, 1998a). Table 5.9 lists various emission sources of benzene and the section number where more information can be found in this EPA reference. The emissions from most of these identified sources are regulated and limited by the federal government.

Table 5.9: Summary of Sources of Benzene to Ambient Air

Type of Activity	Process or Source	Section of EPA (1998)
Releases from benzene production	Catalytic reforming (straight run gasoline)	Section 4.1: Catalytic reforming/separation process
	Catalytic dealkylation (toluene)	Section 4.2: Toluene dealkylation and toluene disproportionation process
	Steam cracking (pyrolysis gasoline)	Section 4.3: Ethylene production
	Destructive distillation (coke oven)	Section 4.4: Coke oven and coke by-product recovery plants
Releases from benzene use	Ethylbenzene and styrene production	Section 5.1: Ethylbenzene and styrene production
	Cumene production	Section 5.3: Cumene production Section 5.4: Phenol production
	Cyclohexane production	Section 5.2: Cyclohexane production
	Nitrobenzene production	Section 5.5: Nitrobenzene production Section 5.6: Aniline production
Releases from benzene use (*continued*)	Alkylbenzene production	Section 5.8: Linear alkylbenzene production
	Chlorobenzene production	Section 5.7: Chlorobenzene production
	Production of other chemicals (e.g., resorcinol or hydroquinone)	Section 5.9: Other organic chemical production
	Use as an industrial solvent (currently being phased out)	Section 5.10: Benzene use as a solvent

Table 5.9 (cont.)

Type of Activity	Process or Source	Section of EPA (1998)
Releases from mobile sources	On-road sources (e.g., gasoline and diesel cars and trucks)	Section 8.1: On-road mobile sources
	Off-road mobile sources (e.g., chain saws or construction machinery)	Section 8.2: Off-road mobile sources
	Marine vessels	Section 8.3: Marine vessels
	Locomotives	Section 8.4: Locomotives
	Aircraft and rocket engines	Section 8.5: Aircraft Section 8.6: Rocket engines
Releases from combustion sources	Waste incineration	Section 7.1: Medical waste incineration Section 7.2: Sewage sludge incinerators Section 7.3: Hazardous waste incineration Section 7.8: Portland cement production
	Commercial, industrial and utility boilers for heat and electricity generation	Section 7.4: External combustion of solid, liquid and gaseous fuels in stationary sources for heat and power generation
	Stationary engines (electricity generation) or heating equipment (kerosene heaters)	Section 7.5: Stationary internal combustion
	Secondary lead smelting (reclamation of lead from scrap automobile batteries)	Section 7.6: Secondary lead smelting
	Manufacture of cast iron and steel	Section 7.7: Iron and steel foundries
	Hot-mix asphalt production	Section 7.9: Hot-mix asphalt production
	Open burning of biomass and scrap	Section 7.10: Open burning of biomass, scrap tires, and agricultural plastic film
Other activities	Equipment leaks from oil and gas wells	Section 6.1: Oil and gas wellheads
	Dehydration of natural gas using glycol dehydration units	Section 6.2: Glycol dehydration units
	Refining of crude oil (e.g., production of gasoline, jet fuel or fuel oil)	Section 6.3: Petroleum refinery processes
	Distribution and sale of gasoline	Section 6.4: Gasoline marketing
	Treatment of industrial wastewater	Section 6.5: Publicly owned treatment works
Other activities (*continued*)	Disposal of municipal solid waste in landfills	Section 6.6: Municipal Solid Waste Landfills
	Manufacture of paper and paperboard	Section 6.7: Pulp, paper, and paperboard industry
	Manufacture of synthetic graphite for industrial uses (e.g., aerospace nose cones)	Section 6.8: Synthetic graphite manufacturing
	Manufacture of carbon black for use as a reinforcing agent in rubber compounds	Section 6.9: Carbon black manufacture
	Manufacture of rayon-based carbon fiber for aerospace industry	Section 6.10: Rayon-based carbon fiber manufacture
	Manufacture of aluminum parts from cast molds	Section 6.11: Aluminum casting
	Manufacture of asphalt roofing materials (e.g., felt rolls and shingles)	Section 6.12: Asphalt roofing manufacturing
	Application and use of consumer products or building supplies	Section 6.13: Consumer products/building supplies

The EPA Office of Air Quality Planning and Standards (OAQPS) collects emissions inventory data for hazardous air pollutants (HAP) pursuant to the 1990 amendments to the Clean Air Act. The most recent emissions inventory available in final form is the September 21, 2001 revision to the 1996 National Toxics Inventory (NTI). The NTI emissions estimates are based on the following sources of data:

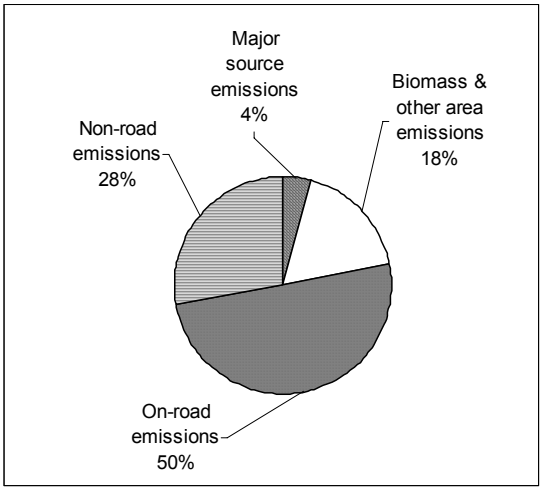
- State and local air pollution control agency HAP inventories;
- OAQPS Maximum Achievable Control Technology (MACT) databases;
- Toxic Release Inventory (TRI) data;
- Mobile source estimates from the EPA's Office of Mobile Sources; and
- Area source emission estimates using emissions factors and activity data.

Emission quantities for four general source categories are provided for the chemicals in the NTI database, including:

- Major sources (stationary facilities with potential to emit 10 tons of any one toxic air pollutant or 25 tons of more than one pollutant);
- Area and other sources (such as biomass burning including wildfires and agricultural burning, as well as small facilities with emissions less than that of major sources);
- On-road mobile sources (vehicles that travel on roads and highways such as cars, trucks and buses); and
- Non-road mobile sources (mobile sources that are not found on roads such as lawn mowers, snowmobiles, and heavy construction vehicles).

Figure 5.1 shows the relative contribution of the various sources to the total benzene emissions on a nationwide basis based on the NTI 1996 database. It should be noted that the contribution from biomass and other area sources is greater in rural areas (i.e., 31%), as there is less of a contribution from motor vehicles and more likely to be biomass burning. In addition, the relative contribution from biomass varies from year to year as a function of the size and number of wildfires in the U.S.

Figure 5.1: Relative Contribution of Various Benzene Emission Sources to Total Benzene Emissions from 1996 NTI database



5.8 Decrease in National Emissions

National air emissions for most pollutants peaked around 1970 (U.S. EPA, 2000a). Until 1989, benzene was not separately regulated, but rather was controlled as part of general VOC regulation; therefore, benzene emissions reductions since 1970 can only be generally judged by examining VOC reductions. Between 1970 and 1998, a 42% overall reduction in VOC emissions was observed, despite increases in vehicle miles traveled and the gross domestic product. The decrease in national VOC emissions since 1970 is illustrated in Table 5.10.

Table 5.10: Decrease in National VOC Emissions

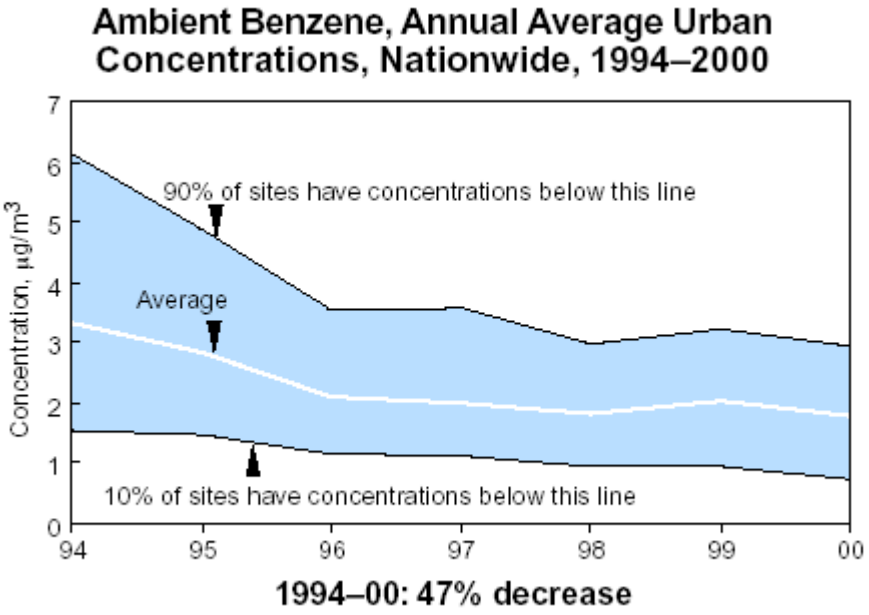
1970–1998	42%
1990–1998	26%
1997–1998	5%

From: *National Air Pollutant Emission Trends (1900-1998)* (EPA, 2000a)

The decreases in VOCs, including benzene, are mainly attributable to the Clean Air Act of 1970 (CAA), Clean Air Act Amendments of 1990 (CAAA), and voluntary emissions reductions. See Chapter 4 for a description of regulatory requirements that have contributed to the more recent 47% reduction in benzene emissions shown over the period 1994-2000 as shown in Table 5.5.

The EPA compiles an air toxics inventory as part of the National Emissions Inventory to estimate and track national emissions trends for the 188 toxic air pollutants regulated under the CAAA. Benzene is the most widely monitored air toxic with measurements taken from 95 urban monitoring sites around the country. Measurements taken at these sites show, on average, a 47% decrease in benzene levels from 1994 to 2000 (http://www.epa.gov/airtrends/toxic.html; accessed 7/1/03.). Figure 5.2 below graphically depicts the recent decline in ambient benzene concentrations.

Figure 5.2



From htttp://www.epa.gov/airtrends/toxic.html (accessed 7/1/03)

Significant decreases have also been seen at the state level. In both the state of California and in the Houston-Galveston, Texas area, the decrease in benzene from 1989 to 2001 was 79% (U.S. EPA, 1996; URS, 2002). Additionally, a study in Camden, New Jersey measured a 58% decrease in ambient benzene air concentrations from 1990 to 1997 (Weisel, 2002).

This drop in ambient benzene concentrations is largely a result of the decrease in mobile source emissions due to fleet turnover, Tier 1 car emission standards, and use of reformulated gasoline in many cities. Additionally, voluntary emissions reductions and the implementation of the maximum achievable control technology (MACT) and other federal, state and local regulations for the petroleum and chemical processing industries have brought about a decrease in benzene emissions from stationary sources.

Besides the reduction of VOCs and benzene specifically, there has also been a reduction of sulfur in gasoline. Lower sulfur content increases catalytic converter efficiency, thus decreasing hydrocarbon emissions, including benzene.

As indicated in Section 4, a number of regulatory actions aimed at reducing benzene emissions have been initiated or are scheduled to occur in the next 10 years. These regulations and the turnover of older cars will result in a continued reduction of benzene emissions. This downward trend has two implications. First, motor vehicles are major contributors to outdoor urban air levels, vehicle related exposures, and to indoor air levels (for homes with attached garages). Thus, in considering the ambient outside and indoor air exposure pathways exposure studies from the 1980s and 1990s are likely to be overestimates of the current exposures. Second, future benzene exposure from these sources are likely to be lower than current levels.

5.9 Releases of Benzene to Soil and Water

Benzene can be released to surface water by discharges of industrial or municipal wastewater that contains benzene or accidental spills during transfer of petroleum or chemical products (ATSDR, 1997, 2005). Sources of benzene to groundwater include leaks of gasoline underground storage tanks, accidental spills, and leachate from landfills (ATSDR, 1997, 2005). Benzene is also disposed in on-site industrial underground injection wells as part of the EPA Underground Injection Control (UIC) Program, which is regulated under the Safe Drinking Water Act. Under this program, liquids are pumped into deep, confined, and isolated formations that are located beneath potable water supplies. EPA's Underground Injection Control Program regulates the location, construction, operation, and enclosure of injection wells to insure that underground drinking water supplies are protected. Benzene can be released to soils as a result of land disposal of benzene-containing wastes or from gasoline as a result of a leaking underground storage tank (ATSDR, 2005).

The 2003 TRI estimates for benzene releases are summarized below in Table 5.11. Facilities that are subject to TRI reporting are those with ten or more full-time employees (or the equivalent in man-hours), those that exceed any one threshold for manufacturing (including importing), processing, or otherwise using a toxic chemical listed in 40 CFR Section 372.65, and that fall under the covered SIC codes below:

- Manufacturing (SIC codes 20 through 39);
- Metal mining (SIC code 10, except for SIC codes 1011, 1081, and 1094);
- Coal mining (SIC code 12, except for 1241 and extraction activities);
- Electrical utilities that combust coal and/or oil for the purpose of generating electricity for distribution into commerce (SIC codes 4911, 4931, and 4939);
- Resource Conservation and Recovery Act (RCRA) Subtitle C hazardous waste treatment and disposal facilities (SIC code 4953);
- Chemicals and allied products wholesale distributors (SIC code 5169);
- Petroleum bulk plants and terminals (SIC code 5171);
- Solvent recovery services (SIC code 7389 limited to facilities primarily engaged in solvent recovery services on a contract basis); and
- Federal facilities that meet the thresholds also must report by Executive Order.

Emissions from facilities that are not required to submit reports (i.e., those with few employees or chemical usage/production rates below regulatory threshold) are not expected to have a major impact on the overall evaluation because they would represent minor benzene sources. See Section 4 for regulatory requirements that have contributed to the 42% reductions in benzene emissions since 1970.

Table 5.11: Benzene Releases for All Industries Reporting TRI data for 2003

Type of Release	Release Amount (million pounds/year)	Percent of Total Release
Total air emissions	6.26	93%
Surface water discharges	0.019	0.3%
Underground injections	0.36	5.3%
Releases to land	0.033	0.5%
Transfer to disposal	0.075	1.1%
Total	6.75	100%

5.10 Contribution of Chain-of-Commerce Sources and Releases to Personal Exposure

"The central principal of measuring human exposure is [to] measure where the people are" (Wallace, 2001). This was the guiding principle of the EPA Total Exposure Assessment Methodology (TEAM) Studies, which took place between the 1980's and 1990's.

The TEAM studies consistently showed that indoor benzene exposures were greater than outdoor exposures (Wallace, 2001). They also concluded that "no effect on personal exposure of living close to major fixed sources of benzene (oil refineries, storage tanks, chemical plants, etc.) could be detected" in six cities where personal exposures to benzene were investigated (Wallace, 1996). Rather, most benzene exposure was found to be caused by personal activities, such as riding in a vehicle or smoking cigarettes (Wallace, 1996, 2001). For smokers, Wallace concluded that 89% of personal benzene exposure was attributable to mainstream cigarette smoke. Non-smoker's exposure to benzene was found to be primarily attributable to automobile exhaust or gasoline vapor emissions (e.g., vapor emissions during refueling or indoor exposures occurring as a result of vapor intrusion from an attached garage; Wallace, 1996, 2001).

The TEAM studies have concluded that the "following are not important sources of exposure to benzene on a nationwide basis" (Wallace, 1989a):

- Chemical plants;
- Petroleum refining operations;
- Oil storage tanks; and
- Drinking water.

The findings of Wallace regarding the contribution of community industrial sources on personal exposures to benzene have also been observed by more recent studies conducted by Mickey Leland National Urban Air Toxics Research Center (NUATRC) and other independent researchers. In contrast to the findings of Wallace however, the recent literature indicates that in-vehicle exposures and environmental tobacco smoke are not the primary sources of personal benzene exposure. Rather the personal exposures are driven by in-home indoor air concentrations and mainstream smoking. This is further discussed in Section 7.

6.0 Health Hazard Assessment

The Voluntary Children's Chemical Exposure Program (VCCEP) has established a set of toxicity endpoints and animal study guidelines to consider in evaluating chemical health hazards. For benzene, however, the existing database on human toxicity is an important component of the hazard database. Currently, all existing regulatory and occupational exposure standards in the U.S. for benzene are based on human data. Therefore, this VCCEP Hazard Assessment for benzene was prepared in two sections: first (Section 6.1) presenting the available studies on benzene's toxicity in humans, specifically those that form the basis for U.S. EPA's regulatory benchmarks (CSF, RfD and RfC), and; then (Section 6.2) analyzing the available animal studies on the VCCEP toxicity endpoints.

6.1 Benzene Toxicology—Human Hazard Assessment

6.1.1 Introduction

The hematopoietic toxicity of benzene has been recognized for many years. As a result, there is a robust literature base describing the adverse health effects associated with exposures to benzene, particularly those resulting from chronic high-dose occupational exposures. This section summarizes the available studies on benzene's toxicity in humans, specifically those studies that form the basis of EPA regulatory benchmarks (CSF, RfD, RfC). Additional human epidemiology studies are also discussed briefly to provide context on the shape of the dose-response relationships for benzene toxicity in humans.

6.1.2 Types of Adverse Health Effects Associated with Benzene Exposure

6.1.2.1 Acute Toxicity

Acute benzene exposure, primarily associated with inhalation of concentrated benzene vapor, will frequently result in a range of effects common to many other organic solvents. This includes systemic toxicity such as narcosis, non-specific CNS toxicity, and at sufficiently high concentrations, respiratory depression. Exposure to concentrations of benzene approaching 20,000 ppm is rapidly fatal to humans (Gerarde, 1959). Benzene exposures in the range of 3,000–10,000 ppm can result in a loss of consciousness within minutes and can also be fatal if the duration of exposure is sustained (Gerarde, 1959). However, responses to benzene exposure can vary dramatically, and some individuals exposed to these levels experience only lightheadedness or euphoria (Hayden and Comstock, 1976). Benzene levels in the 3000–10,000 ppm range have also been associated with cardiac arrhythmias, various renal problems, pulmonary edema, and hemorrhagic pneumonitis (Hayden and Comstock, 1976). As the concentration or duration of exposure decreases (e.g., 50–150 ppm for several hours), acute benzene intoxication will often result in non-specific, reversible CNS complaints, including drowsiness, headaches, dizziness, and nausea (Gerarde, 1959; Duarte-Davidson et al., 2001). In contrast, exposure to benzene at levels of 25 ppm or less for up to 8 hours has not been reported to result in any observable acute toxicity (Gerarde, 1959).

6.1.2.2 Chronic Toxicity

Toxicity associated with chronic long-term exposure to benzene is primarily limited to the hematopoietic and/or immune system. Manifestations can range from non-symptomatic, reversible suppression of a specific blood cell (cytopenia) to permanent, often fatal, damage to the bone marrow and resulting aplastic anemia (Irons, 1997; Rothman et al., 1996; Kipen et al., 1988; Santesson, 1897; Selling, 1916). Scientific and medical evidence also supports a casual link between benzene and the development of acute myelogenous leukemia (AML) (Rinsky et al., 1987; Irons, 1997). The adverse health effects associated with chronic exposure to benzene are discussed briefly below.

6.1.2.2a Peripheral Cytopenias

The first manifestation of chronic benzene toxicity is often some form of cytopenia (a significant depression in one or more types of the peripheral blood cells). Existing data suggest that this effect follows a predictable dose response in both experimental animals and humans. Early work in rodents indicated that inhalation of 25 ppm benzene or higher for several weeks resulted in suppression of white blood cells (WBC) (Cronkite et al., 1985; Cronkite et al., 1982; Snyder et al., 1978a, 1979; Green et al., 1981a). Suppression of WBC or leukopenia has also been observed in benzene-exposed humans, and in fact, alterations in WBC count were used historically as a clinical biomarker for occupational physicians to screen workers for early evidence of hematopoietic toxicity (Michiels, 1997; Ward et al., 1996; Kipen et al., 1988; Rothman et al., 1996). It has also been reported in both experimental animal and human studies that lymphocytes were highly sensitive to benzene toxicity (Irons et al., 1980; Pyatt et al., 2000). Suppression of absolute lymphocyte count (ALC) by benzene is considered by EPA to be the most sensitive non-cancer toxic endpoint in humans, and as such, forms the basis for its regulatory non-cancer values (RfC and RfD) (Ward et al., 1996; U.S. EPA, 2000). A depression in circulating red blood cells is also a common finding in highly exposed workers (Aksoy, 1989; Aksoy et al., 1971; Snyder et al., 1978a; Snyder et al., 1982). However, frank anemia usually occurs following higher doses or longer exposures to benzene than those required to induce lymphocytopenia (Aksoy, 1989). Though less common, thrombocytopenia (decrease in platelet production) has also been reported. In more severe exposure cases, pancytopenias are observed, representing a significant suppression in all mature blood cells found in the periphery (Aksoy, 1989; Aksoy et al., 1971).

6.1.2.2b Aplastic Anemia

At high enough concentrations, benzene can induce hematopoietic damage so severe that complete bone marrow failure occurs, resulting in aplastic anemia (AA) (Vigliani et al., 1976; Erf et al., 1939; Goldwater, 1941). This important adverse health effect will often present with pancytopenia (a clinically significant suppression in the production of all mature blood cells), which is clearly evident in the peripheral blood. Benzene-induced AA was frequently fatal, with death resulting from severe hemorrhage, infection, or an additional secondary factor related to a loss of mature blood cell function (Michiels, 1997). While a threshold for the development of AA from benzene exposure likely exists, the exact value is not known. What is known is that cases of AA were exposed to very high levels of benzene that caused frank cytotoxicity, often for extended periods (Vigliani and Forni, 1976; Erf and Rhoads, 1939; Goldwater, 1941). By way of an example, Turkish shoe workers who developed AA were often exposed to levels believed to have been as high as 600 ppm for the entire 8- to 10-hour work shift (Aksoy et al., 1978).

6.1.2.2c Acute Myelogenous Leukemia (AML)

The most important adverse health effect associated with chronic exposure to high concentrations of benzene is the development of acute myelogenous leukemia (AML) (Hamilton, 1922; Aksoy et al., 1972; Infante et al., 1977; Rinsky et al., 1981; Rinsky et al., 1987; White et al., 1982; Bond et al., 1986; Ryan et al., 1997; Yin et al., 1987). Benzene has been used extensively in many industrial settings, often historically at very high concentrations. These workplace exposures have, in turn, been shown to damage the bone marrow, often with adverse results for the worker. Beginning as early as 1897, case reports appeared in the scientific and medical literature linking or attempting to link chronic occupational benzene exposure with leukemia, specifically AML (Le Noire, 1897). These studies were conducted in different industries by multiple independent investigators (Le Noire, 1897; Delore et al., 1928; Lignac, 1932; Selling, 1916; Vigliani et al., 1964; Aksoy, 1977; Aksoy et al., 1972; Aksoy et al., 1974). Taken in isolation, many of these early studies possess significant methodological flaws or omissions, including a lack of reliable exposure estimates, questionable selection of control populations, confusing or archaic disease classification, etc. However, collectively, they provide strong evidence in support of an association between benzene exposure and the development of AML. A slightly broader term sometimes found in the older literature is ANLL (acute non-lymphocytic leukemia). This grouping includes acute myeloid leukemias that defy classification according to the established FAB subtypes.

By the late 1970s, quantitative epidemiological studies corroborated early case reports and provided clear evidence that high-dose occupational benzene exposure was causally linked to the development of AML in a small percentage of highly exposed workers (Ott et al., 1978; Infante et al., 1977; Rinsky et al., 1981, 1987). Since that time, numerous other studies have further strengthened the association between benzene and AML, including large-scale epidemiological studies from China, Australia, Canada, and the U.S. (Yin et al., 1987, 1996; Decouflé et al., 1983; Bond et al. 1986, 1987; Ott et al., 1989; Paci et al., 1989; Wong, 1987b). Despite the extensive data supporting the association, the actual mode of induction for benzene-induced AML has not been fully established.

6.1.2.2d Myelodysplastic Syndrome (MDS)

Myelodysplastic syndrome or myelodysplasia is a clonal, non-neoplastic hematopoietic disorder that can be classified into five subtypes based on morphology, prognosis, and propensity to progress to overt leukemia (Albitar et al., 2002; Mijovic et al., 1998). MDS (all types) is usually characterized by multi-lineage, often severe cytopenias, ineffective hematopoiesis, and a chaotic, hypercellular bone marrow (Barrett et al., 2000; Vallespi et al., 1998). Many of the blood dyscratias reported in the past to be caused by benzene exposure could be classified according to modern diagnostic criteria as MDS (Vallespi et al., 1998). This would include all cases of ‘preleukemia’, cases of aplastic anemia with ‘paradoxical hypercellular’ bone marrow, some erythroleukemia cases and even multi-lineage cytopenias (Aksoy and Erdem, 1978; Aksoy et al., 1974; Block et al., 1953; Mallory et al., 1939; Barrett et al., 2000; Anderson et al., 1981). MDS can also be primary or secondary to chemical exposure (Aul et al., 1998). In secondary MDS, cytogenetic abnormalities occur in an overwhelming majority of cases (~90%–95%), and the progression to AML is swift and usually unalterable (often within 1 year) (De Renzo et al., 1999). Cytogenetic abnormalities seen in secondary MDS are often indistinguishable from those reported in secondary AML (Westbrook et al., 2000; Sawyers, 1998; Pedersen-Bjergaard et al., 1998; Larson, 2000). Additionally, the well-described propensity of secondary MDS to progress to AML suggests that they may represent different stages of the same disease (Andersen et al., 1998; Pedersen-Bjergaard et al., 1987).

6.1.2.2e Other Hematopoietic Malignancies

To date, there is no reliable evidence to causally link benzene exposure with any other hematopoietic malignancy other than acute myelogenous leukemia. Other hematopoietic malignancies that are not positively associated with even high-dose, chronic exposure to benzene include Hodgkin's and non-Hodgkin's lymphoma, multiple myeloma, chronic and acute lymphocytic leukemia, and chronic myelogenous leukemia.

6.1.3 Animal Models for Benzene Induced AML/Hematotoxicity

While the AML potential of benzene in high-dose, chronically exposed humans has been demonstrated in multiple independent epidemiology investigations (Yin et al., 1987; Yin et al., 1989, 1996; Decouflé et al., 1983; Bond et al., 1986, 1987; Ott et al., 1989; Paci et al., 1989; Wong, 1987b), data obtained from experimental animal studies have revealed benzene-induced tumors at multiple sites with questionable relevance to humans (some tumor sites do not exist in humans; e.g., Zybal gland) (Cronkite et al., 1984, 1985, 1989; Snyder et al., 1982, 1980, 1984, 1988; Farris et al., 1993; Goldstein et al. 1982; NTP 1986). This information suggests that the available animal models are insufficient to evaluate human carcinogenic potential of benzene. Hematopoietic malignancies are seen in benzene-exposed rodents; however, myelogenous leukemia is extremely rare in rodents, and the primary hematopoietic malignancies reported in experimental animal studies are lymphoid in origin (Snyder et al., 1980; Cronkite et al., 1989; Snyder et al., 1984). Thymic leukemia/lymphoma has no precise analogy in human disease, and the propensity of various animal strains to develop lymphoid malignancies following chemical exposure is not reproduced in humans. Differences in the hierarchical regulation of stem cell differentiation and regulation between species (human and mouse) are known to exist, and the role that ecotropic retroviruses play in murine leukemogenesis is well established. Therefore, it appears that rodents do not represent a relevant experimental model for benzene-induced AML or other human lukemias.

Non-cancer effects of benzene exposure, such as peripheral cytopenias, appear to be more applicable across species. Early reports of benzene-induced hematopoietic toxicity in occupationally exposed workers were followed by experimental studies conducted on laboratory animals. For example, Weiskotten et al. (1916) administered benzene parentally to rabbits and observed a dose-related leukopenia and marrow aplasia (Weiskotten et al., 1916, 1917). Consistent with human data, many more recent studies of experimental animals have also reported that cytopenias (usually lymphocytopenia) are sensitive endpoints for benzene toxicity (Gerarde, 1959; Snyder et al., 1978a, 1980; Cronkite, 1986).

6.1.4 Role of Metabolism and Site of Injury

Extensive experimental evidence supports the hypothesis that benzene must be metabolized (bioactivated) to exert its hematotoxic effects. Early studies reported that various phenolic metabolites were more toxic in culture than benzene itself (Harrison et al., 1947). Further evidence came from experiments demonstrating that co-administration with toluene effectively competes for benzene metabolism and consequently reduces benzene toxicity (Andrews et al., 1977; Plappert et al., 1994). Likewise, partial hepatectomy lessens benzene metabolism, with a corresponding decrease in toxicity, while pretreatment of animals with metabolic inducers of benzene metabolism (e.g., ethanol) increases toxicity (Sammett et al., 1979; Gill et al., 1979; Gad-El-Karim et al., 1985). The primary step in benzene metabolism is oxidation to benzene oxide. This occurs via the 2E1 isozyme of the cytochrome P-450 system (CYP2E1).

Genetically engineered 'knock-out' mice that lack CYP2E1 are far more resistant to benzene-induced myelotoxicity, which provides solid evidence of the role that CYP2E1 plays in benzene toxicity (Valentine et al., 1996). While there is general agreement on the fact that benzene must first be metabolized to be myelotoxic, the metabolite or combination responsible for benzene toxicity lacks such consensus. Likely candidates include benzene oxide; quinones such as catechol, hydroquinone, and p-benzoquinone; as well as ring-opened metabolites such as trans-trans muconaldehyde (Andrews et al., 1979; Gill et al., 1979; Snyder et al., 1978a, 1996; Ross, 2000).

Although the primary site of benzene's oxidation by CYP2E1 occurs mainly in the liver, extra-hepatic metabolism also occurs in the bone marrow (Andrews et al., 1979) and in the lungs (Sheets and Carlson, 2004; Powley and Carlson, 1999, 2000, 2001). Human bone marrow lacks detectable levels of CYP2E1, but is a rich source of myeloperoxidase (MPO) (Ross et al., 1996). MPO can further oxidize various polyphenolic metabolites of benzene and is accorded an important role in myelotoxicity (Schlosser et al., 1989; Smith et al., 1989; Genter et al., 1994; Ross et al., 1996). For reasons that are not entirely clear, the bone marrow acts as a trap for benzene and its lipophilic metabolites (Irons et al., 1978; Sawahata et al., 1985; Rickert et al., 1979). This can potentially create locally high concentrations, and some studies report that the benzene levels found in the bone marrow are 150 times the concentrations measured in the peripheral blood (Irons et al., 1978; Srbova et al., 1950). This is particularly germane to any discussion of benzene toxicity, because the bone marrow is likely the most important target organ. In the lungs, the cytochrome P450 isoenzymes, CYP 2E1 and 2F2, have been reported to be responsible for metabolizing benzene (Sheets and Carlson, 2004; Powley and Carlson, 2001).

The primary route of excretion for inhaled benzene is via exhalation of the parent compound. However, Phase II metabolism does occur and generates an assortment of sulfate or glucuronide conjugated urinary metabolites (Ross, 2000). Mercapturic acid derivatives, as well as trans-trans-muconic acid, have also been identified as major urinary excretion byproducts (Snyder and Hedli, 1996). This subject has received considerable attention, not only in an attempt to better understand benzene metabolism, but also because urinary metabolites of benzene represent a potentially rich area of investigation for non-invasive biomarkers of exposure (Ruppert et al., 1997; Yu et al., 1996).

The complex metabolic pathways for benzene (bioactivation, detoxification, excretion) provide considerable variability in an individual's response to benzene exposure. The fact that genetic polymorphisms exist in metabolic enzymes is not novel; however, the role they potentially play in benzene toxicity, including leukemogenesis, is just now emerging. Polymorphisms believed to be important in this regard include CYP2E1, glutathione transferases, and others (Nebert, 2000; Naoe et al., 2000; Nedelcheva et al., 1999; Marsh et al., 1999). Probably the most significant polymorphism identified to date is NQO1 (aka DT diaphorase). NQO1 is a quinone reductase that helps maintain quinones in a reduced state, which in turn, facilitates their excretion (Ross et al., 1990). A homozygous mutation in NQO1 inactivates the enzyme and has been linked to increased benzene toxicity, as well as an increased risk for developing secondary leukemia from alkylating chemotherapy (Traver et al., 1997; Rothman et al., 1997; Kelsey et al., 1997; Larson et al., 1999).

6.1.5 Dose Metrics for Toxicity

The scientific community continues to study the most appropriate dose metric for benzene toxicity, particularly with regard to carcinogenic risk. This uncertainty is based on the possibility

that transient, high peak exposures may have a different (increased) toxicity profile compared to lower, more continuous exposures. There is some biological rationale for this hypothesis, because bone marrow damage can be correlated with the timing of treatment of myelotoxic chemotherapeutic agents. Further, high-dose, acute exposure to ionizing radiation is considerably more damaging to the bone marrow than the same cumulative dose spread out over a longer time (NRC, 1990). The underlying biology is complex but likely results from cell-cycle kinetics and proliferative regeneration of different populations of hematopoietic progenitor cells following toxic insult. Specifically with regard to benzene, the timing of exposures and related effects on toxicity has been addressed experimentally, as well as in numerous epidemiological investigations (Coffin et al., 1977; Luke et al., 1988a,b; Snyder et al., 1988; Rinsky et al., 1981, 1987).

A few examples of experimental animal studies that have reported timing related effects are presented. Coffin et al. (1977) determined that if the absolute dose of benzene was kept constant, high-dose intermittent exposures of benzene were less toxic (leukopenia) to treated mice than the same dose administered via continuous exposure. In contrast, Luke et al. (1988a,b) evaluated dosing regimens in mice and concluded that cytotoxicity, as evidenced by a decrease in erythrocyte precursors, was more pronounced in intermittent exposures. Synder et al. (1988) reported that chronic exposures, even if administered intermittently, were more tumorigenic than acute, high-dose exposures.

In humans, the majority of studies report that cumulative exposures, reported in ppm-years, are the best predictor of AML risk (Rinsky et al., 1981; Wong et al., 1993; Tsai et al., 1983; Wen et al., 1983). These include studies of the 'pliofilm' cohort, upon which EPA bases the cancer potency factor for benzene (Infante et al., 1977; Rinsky et al., 1987). Additionally, more recent epidemiological investigations from Australia indicate that peak exposures did not correlate with increased risk of acute non-lymphocytic leukemia (ANLL), as well as cumulative exposures (Glass et al., 2003). Wong et al. (1983, 1987a,b) reported on the mortality of male chemical workers who had been exposed to benzene during 1946–1975. Cumulative exposure to benzene, not peak exposure, was the best predicator of risk in these workers (Wong, 1983, 1987a,b). One study reported that intermittent, high-dose peak exposures were found to be a better predictor of AML risk than were cumulative exposures (Collins et al., 2003). Collins et al. (2003) evaluated the risk of AML in chemical workers and found an association between risk and the number of days on which peaks of 100 ppm or higher occurred. In this study, even when peak exposures occurred on more than 40 days, there was no significant elevation in AML risk reported (Collins et al., 2003; Ireland et al., 1997). Recently, Rappaport et al. (2005) used PBPK modeling to chacterize the effect of exposure variability to internal dose of benzene (and other VOCs). The conclusion reached by these authors was that cumulative exposure was the best predictor of internal dose of both the parent compound and the active metabolites of benzene (Rappaport et al., 2005).

6.1.6 Non-Cancer

6.1.6.1 Critical Study for EPA's Benzene RfC and RfD (Rothman et al., 1996)

The EPA oral reference dose (RfD) for benzene is 4.0×10^{-3} mg/kg/day and is based on a dose-related decrease in the absolute lymphocyte count (ALC) observed in benzene-exposed workers (Rothman et al., 1996). The EPA inhalation reference concentration (RfC) for benzene is 3×10^{-2} mg/m^3 and is based on data from the same study. Rothman and co-workers conducted a cross-sectional study of 44 workers exposed to benzene in the workplace

(inhalation), as well as 44 age- and gender-matched controls. All exposed workers and controls were from Shanghai, China. The exposed workers were selected from three types of industries with excessive benzene exposures: 1) a rubber padding manufacturing facility, 2) an adhesive tape manufacturing facility, and 3) a factory that used benzene-based paints. Exclusion criteria for potential subjects in this study included known prior exposure to ionizing radiation or chemotherapy, a prior history of cancer, or current pregnancy. The mean exposure duration for the exposed group was 6.3 years (range = 0.7–16 years). The median 8-hour time-weighted average (TWA) benzene exposure for all exposed workers was 31 ppm (99 mg/m^3). The exposed population was subdivided into low (<31 ppm) and high (>31 ppm) exposure groups. The median 8-hour TWA benzene exposures for the low and high exposure groups were 13.6 ppm and 91.9 ppm, respectively. A variety of routine hematology parameters were analyzed: total white blood count (WBC), ALC, hematocrit, red blood cell count, platelet count, and mean corpuscular volume (MCV). All six parameters were significantly different in the high exposure group (>31 ppm; median = 91.9 ppm). MCV was significantly increased; the other five parameters were significantly decreased. Several members of the low exposure group experienced exposures greater than 31 ppm on at least one day of monitoring; therefore, a subset of workers was created that did not have exposure greater than 31 ppm on any monitoring day (N = 11). These workers, selected from the low exposure group, had a median 8-hour TWA benzene exposure of 7.6 ppm (range 1–20 ppm). The only hematology parameter reported to be significantly decreased compared to controls in this subset was the ALC. As a result, lymphocytopenia (as measured by the ALC) was determined to be the most sensitive endpoint.

Benzene exposure was monitored by personal passive dosimetry badges worn by each worker for a full work shift on 5 days within a 1- to 2-week period prior to collection of blood samples. Benzene exposure was also evaluated qualitatively through urine analysis of benzene metabolites collected at the end of the benzene exposure period for the exposed subjects. Historical benzene exposure of the subjects was also estimated via employment records.

Benchmark dose (BMD) modeling of the ALC exposure-response data from Rothman et al. (1996) was done using EPA Benchmark Dose modeling software (version 1.2). The data were supralinear; therefore, in order to fit the data with a continuous linear model, the exposure levels were first transformed according to the equation d' = ln (d +1). The parameters were estimated using the method of maximum likelihood. A default benchmark response of one standard deviation change from the control mean was selected, as suggested in draft EPA guidance (Benchmark Dose Technical Guidance Document, 2000). This default benchmark response for continuous endpoints corresponds to an excess risk of approximately 10% for the proportion of individuals below the 2nd percentile (or above the 98th percentile) of the control distribution for normally distributed effects. A 95% lower confidence limit (BMCL) on the resulting benchmark concentration (BMC) was calculated using the likelihood profile method. Transforming the results back to the original exposure scale yields a BMC of 13.7 ppm (8-hour TWA) and a BMCL of 7.2 ppm (8-hour TWA). The BMCL was chosen as a departure point for the RfC derivation. An adjusted BMCL is calculated by converting ppm to mg/m^3 and adjusting the 8-hour TWA occupational exposure to an equivalent continuous environmental exposure. The adjusted BMCL ($BMCL_{adj}$) was calculated to equal 8.2 mg/m^3. The RfC was then derived by dividing $BMCL_{adj}$ by the overall uncertainty factor (UF) of 300 to yield the RfC of 3×10^{-2} mg/m^3. The overall UF comprises a UF of 3 for the effect-level extrapolation, 10 for intraspecies differences (human variability), 3 for subchronic-to-chronic extrapolation, and 3 for database deficiencies.

In order to calculate the oral RfD, an equivalent oral dose is estimated by taking the $BMCL_{adj}$ multiplied by the default inhalation rate. This is multiplied by 0.5 to correct for the higher oral

absorption compared to inhalation, and divided by the standard default human body weight of 70 kg (equivalent oral dose = 1.2 mg/kg/day). The RfD was then derived by dividing the equivalent oral dose by the overall uncertainty factor of 300 (4×10^{-4} mg/kg/day). The UFs are the same as described for the RfC above.

EPA considers the BMC to be an adverse-effect level; therefore, the effect-level extrapolation analogous to the LOAEL-to-NOAEL UF was used. A factor of 3 (vs. 10) was selected, because the BMD corresponded to an adverse effect that was not very serious. Second, a factor of 10 was used for intraspecies differences in response (human variability) as a means of protecting potentially sensitive human populations. Third, a subchronic-to-chronic extrapolation factor was applied, because the mean exposure duration for the subjects in the principal study was 6.3 years (7 years is the exposure duration used by EPA for deriving chronic RfDs). However, a value of 3 (vs. 10) was selected, because it was very close to the 7-year cutoff. Finally, a UF of 3 was chosen to account for database deficiencies, because no two-generation reproductive and developmental toxicity studies for benzene are available.

Importantly, decreased ALC is a very sensitive effect that can be measured in the blood, but there is no evidence that it is related to any functional impairment at levels of decrement near the benchmark response (U.S. EPA, 2003a). Further, WBC and ALC levels of the workers in the Rothman study were still within the normal range for hematology parameters [WBC = 5.6 +/- $1.9\times10^3/mm^3$; ALC = 1.6 +/- $0.3\times10^3/mm^3$] (Bakerman, 2002). The normal range for WBC in adults is $4.5–11.0\times10^3/mm^3$, and for lymphocytes, the range is $1–4.8\times10^3/mm^3$ (Bakerman, 2002). Additionally, the levels of benzene reported in this study were not trivial, with the lowest exposure group still exposed to a median benzene concentration of 7.6 ppm and the highest group exposed to benzene concentrations in excess of 90 ppm (Rothman et al., 1996). Even with prolonged, fairly significant exposures, there was no clinically relevant toxicity reported in these workers, and marginally significant effects, especially in the lower exposure groups (median benzene concentrations of 7.6 and 13.9 ppm). Finally, evidence in humans and experimental animals indicates that cytopenias occur within weeks or months of exposure, and upon removal from the environment or reduction in benzene concentration, small alterations are likely to return to normal values (Green et al., 1981b; Snyder et al., 1981). Therefore, there is no reason to suspect that the biological response from 6.3 years worth of exposure would be quantitatively or qualitatively different from that expected to occur following 7 years of exposure. This calls into question the biological rationale for EPA's subchronic-to-chronic uncertainty factor of 3.

6.1.6.2 Additional Literature for Non-Cancer Hematology Effects

A sufficient body of human data exists in the scientific literature to demonstrate the hematopoietic toxicity of chronic exposure to benzene. The majority of these studies suggest that this effect follows a predictable dose response, including the presence of a threshold, in both experimental animals and humans. Doses of benzene required to suppress various cell lineages vary to some degree from one study to another. Greenburg et al. (1939) reported clear evidence of benzene hematotoxicity in the printing industry, with air concentrations of benzene frequently in excess of 400 ppm and estimated to be as high as ~1000 ppm. Goldwater (1941) also evaluated various industries with excessive benzene concentrations (10–1060 ppm) and frequently observed cases of anemia and thrombocytopenia. Lymphocytopenia was also commonly observed, but neutropenia was rare (Goldwater, 1941). Aksoy et al. (1971) reported clear evidence of hematotoxicity (decreases in WBC) in Turkish shoe workers who were exposed to air concentrations of benzene as high as 210 ppm. Kipen et al. (1988) evaluated blood samples collected during medical surveillance from the 'pliofilm' cohort. Conclusions

reached by these investigators were that air concentrations of benzene in excess of 75 ppm were required before significant hematological alterations were evident. These authors found no evidence of hemotoxicity in workers exposed to 25 ppm or less. Consistently, Townsend et al. (1978) did not report hemotoxicity in workers exposed to air concentrations of benzene as high as 25 ppm. Tsai et al. (1983) also did not observe hematology changes (including WBC) in refinery workers exposed to air concentrations of benzene estimated to be as high as 25 ppm. Yardley-Jones et al. (1988) reported no difference in various hematology measures in workers exposed to air concentrations of benzene as high as 10 ppm. Yin et al. (1987), in a large, multiple-city survey of benzene-exposed workers in China, found no evidence of leukopenia at air concentrations less than ~12 ppm (40 mg/m^3), but did see hematopoietic toxicity at higher levels. Collins et al. (1991) reported no hematology differences in workers exposed to air concentrations of benzene ranging from 0.01 to 1.4 ppm. Recently, Tsai et al. (2004) studied refinery workers and reported no hematology alterations associated with air concentrations of benzene below 1 ppm.

In contrast, Ward et al. (1996) report significant hematopoietic changes at air concentrations of benzene at a maximum of 34 ppm and suggest that benzene concentrations as low as 5 ppm might have negative effects. Additionally, these authors claim that there is no evidence of a threshold for benzene's hematopoietic toxicity. Qu et al. (2002), conducted a study of Chinese workers with benzene concentrations of 0.08–54.5 ppm. These authors claim that significant hematopoietic toxicity was observed in these workers at exposure levels less than 5 ppm. However, this study only reports trend analysis and cannot be relied upon to establish toxicity at any given dose. In contrast to much of the rest of the published literature, these investigators did not find that lymphocytes were uniquely sensitive, and they present data that lymphocyte counts did not change with 90 ppm-years cumulative exposure. Moszczynski et al., (1982) evaluated workers exposed to benzene concentrations of 0–116 ppm, with an average value of 31 ppm. There was an observable decrease in WBC that was primarily accounted for by a decrease in T lymphocyte numbers. These authors conclude that, on the basis of this study, lymphocytes were likely the most sensitive cell lineage to benzene toxicity.

In a more recent study, Lan et al. (2004) reported significant depressions in WBC, granulocytes, lymphocytes, CD4 T cells, B cells, monocytes, and platelets at benzene concentrations less than 1 ppm. They also reported that clonogenic response of peripheral blood progenitor cells, as measured in *in vitro* colony-forming assays, was decreased in these workers. This led to the conclusion that immature peripheral blood progenitor cells were more sensitive to the effects of benzene than mature cells found in the peripheral circulation. The value or relevance in measuring changes in clonogenic output (functionality) in peripherally derived progenitor cells is not known. It has been shown that hematopoietic progenitor cells cultured in the absence of stromal cell contact are more susceptible to chemical toxicity than the same cells in contact with the microenvironment. For this reason, subtle alterations in peripheral blood progenitor cells likely do not accurately reflect what is happening in the bone marrow. Further, the *in vitro* colony forming assays are exquisitely sensitive to many experimental variables, particularly to the quality of the exogenously added growth factors required for colony growth. Quitt et al. (2004) also evaluated colony formation of peripheral blood progenitor cells in workers exposed to low levels of benzene and actually reported a slight increase in colony growth in unstimulated cultures compared to non-exposed control. This experimental discrepancy could easily be the result of slight differences in culture conditions between the two laboratories. The peripheral blood cell depressions reported in this study are also of questionable relevance. Although the reductions may carry statistical significance, the numbers reported in exposed individuals are fully within the normal range and do not carry clinical significance. There is no established relationship between subtle, non-clinically relevant alterations in peripheral blood counts and an

increased risk of disease. It should also be pointed out that this study is inconsistent with other recent studies that found no alterations in peripheral blood cell counts in individuals exposed to 1 ppm benzene (Tsai, 2004). As described above, most of the existing literature (including studies by many of these same authors) does not indicate hematotoxicity occurring at benzene concentrations below 5-10 ppm.

Therefore, existing human data support that prolonged occupational exposure to high concentrations of benzene (greater than 10–25 ppm) can result in peripheral cytopenias and observable hematopoietic toxicity. However, there is much less consistency in the literature regarding the potential adverse effects associated with low-dose exposure (less than 5 ppm).

6.1.7 Cancer

6.1.7.1 Critical Study for EPA's Benzene Cancer Slope Factor (Rinsky et al. 1987)

The most important study of benzene and AML is the National Institute for Occupational Safety and Health (NIOSH)–sponsored retrospective cohort mortality study of workers involved with the manufacture of rubber hydrochloride (Pliofilm) at one of three plants in Ohio (Infante et al., 1977; Rinsky et al., 1981, 1987). The original study evaluated 748 white male workers exposed for at least 1 day in a rubber manufacturing facility. Exposure to benzene occurred in these workers during 1940–1949. No effort was made to evaluate individual exposures to benzene that could be used to help characterize a dose response relationship (Infante et al., 1977). In an extension of this study, Rinsky et al. (1981) reported that all seven of the leukemias were of the acute myelogenous type. This cohort was updated in 1987 and expanded to include 1165 non-salaried white male workers employed for at least 1 day through December 1965 (Rinsky et al., 1987). Two additional AML cases were reported in this expanded cohort. Rinsky and co-authors attempted to reconstruct cumulative exposures to benzene in terms of ppm-years for all members of the expanded cohort and establish a dose-response relationship. The SMR for AML was non-significant in the 0–39.99 ppm-years and the 40–199.9 ppm-year cumulative exposure categories. At 200 ppm-year, the SMR for AML was 11.86, which was statistically elevated. The last follow-up through 1996 reported five additional cases of AML with an SMR of 3.37, statistically elevated at the highest exposure category (Rinsky et al., 2002). All workers with AML held jobs that first exposed them to benzene before 1950, and most of them before 1945 (Paxton et al., 1994, 1992). Few direct industrial hygiene data were available during this time frame, so several attempts have been made to provide refined quantitative estimates for the likely exposures that occurred during this time frame (Crump et al., 1984; Rinsky et al., 1987; Paustenbach et al., 1992; Schnatter et al., 1996b).

The Rinksy (1981, 1987) study analysis of the 'Pliofilm' cohort was selected by EPA as the critical study for dose-response analysis and for the quantitative estimation of cancer risk to humans (Rinsky et al. 1981, 1987). This study was selected because it has ample power, reasonably good estimates of exposure (except prior to 1946), a wide range of exposure from low to high levels, and a relative lack of potential confounding chemicals. Further, the job activities of the various workers were fairly well documented. Based on data obtained from this cohort, the carcinogenic risk of inhaled benzene was calculated by EPA. Cancer risk is expressed as the air unit risk and ranges from 2.2×10^{-6} to 7.8×10^{-6} as the estimated increased risk for an individual who is exposed for a lifetime to 1 $\mu g/m^3$ benzene in air. The range was set by the choice of exposure estimates used (Crump and Allen 1984; Paustenbach et al. 1992). The lowest unit risk is based on the exposure estimates of Paustenbach (1992), because the exposure estimates for the Rinsky cohort are the highest. That estimate is 7.1×10^{-3} at 1 ppm (2.2×10^{-6} at 1 $\mu g/m^3$). The highest unit risk is based on Crump and Allen exposure estimates,

which were lower than the Paustenbach estimates. The upper bound of this unit risk range is 2.5×10^{-2} at 1 ppm (7.8×10^{-6} at 1 $\mu g/m^3$). EPA recommends using the range of risk estimates, each with equal scientific plausibility. Crump also calculated an estimated range of unit risk based on a combination of models selected, disease endpoints, and exposure estimates. This range was large; 8.6×10^{-5} to 2.5×10^{-2} at 1 ppm (3200 $\mu g/m^3$) (Crump and Allen, 1984).

EPA states that risk estimates would likely fall in the lower range if a sub-linear exposure response model were found to be more plausible. EPA further concluded that the shape of the dose-response curve cannot be considered without a better understanding of the biological mechanism of benzene-induced leukemia (U.S. EPA, 2000). This remains uncertain and as a result, EPA's default public-health-protective approach is to use the linear extrapolation model (U.S. EPA, 2000).

EPA's quantitative oral unit risk estimate is an extrapolation from the known inhalation dose response to the potential oral route of exposure. The inhalation unit risk range is converted to an oral slope factor, which is expressed in units of risk per $\mu g/kg/day$. The inhalation-to-oral conversion assumes a standard air intake of 20 m^3/day, a standard body weight of 70 kg for an adult human, and 50% inhalation absorption. The drinking water unit risk was then calculated from the oral slope factor, assuming a drinking water intake of 2 L/day. For benzene, the range of EPA's oral slope factors was determined to be 1.5×10^{-2} to 5.5×10^{-2} per (mg/kg)/day. The drinking water unit risk has a corresponding range of 4.4×10^{-7} to 1.6×10^{-6} per ($\mu g/L$).

6.1.7.2 Additional Literature for Cancer Effects

The scientific and medical literature has the leukemogenic potential of chronic exposure to high concentrations of benzene. The following is a brief compilation of some of the more important studies on benzene carcinogenicity in humans.

Aksoy at al. (1974) reported the effects of benzene exposure among 28,500 Turkish shoe workers. Peak exposures were estimated to be as high as ~600 ppm. There was a significant elevation of leukemia or 'pre-leukemia' (likely MDS) observed when compared to the general Turkish population. This cohort was followed up in 1980, and eight additional cases of leukemia were reported (Aksoy, 1977; Aksoy and Erdem, 1978). While the Turkish shoe worker studies are consistent with the wider literature on AML and benzene, the study lacks detailed exposure information and a well-defined comparison population.

Ott et al. (1978) observed a non-significant increase in leukemia among 594 chemical workers exposed to benzene. Air concentrations in this study were estimated to be from less than 2 to over 25 ppm. Bond et al. (1986) updated this study and added an additional 363 exposed workers. The overall risk of leukemia was non-significant, but the risk for myelogenous leukemia was significantly elevated (SMR = 2.5). Unfortunately, the authors do not state whether the observed myelogenous leukemia cases were acute or chronic. Estimated cumulative exposures for workers in this study were reported to be 18–4211 ppm-months.

Wong (1983 and 1987a,b) reported on the mortality of 4602 male chemical workers. Dose-dependent increases were seen in the risk of leukemia (all types) and the biologically arcane category of lymphatic and hematopoietic cancers combined. Cumulative exposure to benzene at 60 ppm-years or greater exhibited a borderline significant risk of lymphatic and hematopoietic cancers. However, none of these cancers were myelogenous. These authors stated that, based on these data, the cumulative, not peak, exposures were the best predictor of cancer risk.

The National Cancer Institute (NCI) and the Chinese Academy of Preventative Medicine conducted an epidemiology study of over 74,000 benzene-exposed Chinese workers employed from 1972 to 1987 (Yin et al., 1987, 1989, 1996; Travis et al., 1994; Hayes et al., 1997). Workers came from a total of 672 Chinese factories and were employed in the painting, printing, footwear, rubber, or chemical industries. A statistically elevated risk of all hematological malignancies was observed with air concentrations of benzene less than 10 ppm, although a meaningful dose response was not evident (Hayes et al., 1997). The risk of ANLL and a combination of MDS and ANLL were not statistically elevated at less than 10 ppm benzene. At higher exposure levels (10–25 ppm), the risk of ANLL and MDS increased to a statistically significant level. Other leukemias (CML) were not significantly elevated at any exposure level. These authors also reported an increased risk of developing NHL at greater than 25 ppm benzene. At cumulative exposures estimated to be less than 40 ppm-years, there was no elevated risk of ANLL or MDS/ANLL (Hayes et al., 1997). Cumulative exposures were 40–99 ppm-years before a positive association was reported with ANLL or MDS/ANLL risk. The NCI/CAPM study was severely limited by the inclusion of concurrent exposures and the lack of reliable exposure information. Further, significant confounders in NHL etiology were not adequately accounted for. As a result, EPA does not view this data set as suitable for quantitative risk assessment (U.S. EPA, 2000).

Recently, Glass et al. (2003) published findings from the 11th Australian Health Watch and reported a significant increase in ANLL associated with benzene exposure. In this study, the authors report a significant elevation of ANLL at cumulative benzene exposures of greater than 8 ppm-years (estimated value is not reported). These authors state that they find no evidence of a threshold for ANLL. The reported cumulative exposures associated with a statistically elevated risk were much lower than those similar industries from other countries. As a result, these findings are inconsistent with the wider scientific and medical literature on ANLL risks associated with benzene exposure, including an update of this overall cohort published by Gun et al. (2004). Other methodological problems decrease the potential usefulness of this study for risk assessment purposes. Some investigators believe that the expected cases of ANLL in the baseline or control group in this study were under-represented. This would change the calculated risks, as well as the interpretation of this data, particularly at low exposures (Schnatter, 2004; Goldstein, 2004). There are also problems with case selection and controlling for various types of bias (Schnatter, 2004; Goldstein, 2004). As it stands, this study may suggest a relationship between benzene exposure and ANLL; however, a stronger interpretation regarding exposures is not possible.

6.1.8 Ongoing Studies

Two large epidemiology studies are concurrently being conducted in and around Shanghai, China. Shanghai was chosen for these studies, because it has a large population base (over 17 million), as well as numerous industries and factories where benzene exposures are still a significant occupational health hazard. Both of these independent studies are designed to further characterize the relationship between benzene exposure (in various industries) and hematopoietic and lymphoid malignancies.

The first study is a follow-up and extension of the NCI/CAPM study that began in the 1980s (Yin et al., 1987, 1989, 1996; Travis et al., 1994; Hayes et al., 1997). The likely goal of this investigation is to extend the follow-up period for study cohorts and to provide quantitative data to better characterize the benzene exposures. Early reports from this investigation have been discussed briefly (Lan et al., 2004).

A second, original epidemiological investigation is being conducted by the Benzene Health Research Consortium, a collaborative research program between the U.S. and China and includes the following organizations: Applied Health Sciences, University of Colorado, ExxonMobil Biomedical Sciences, Fudan University, Shanghai Municipal Institute of Public Health Supervision, Shanghai Center for Disease Prevention and Control, and as many as 29 separate hospitals in Shanghai (Wong et al., 2005). The Shanghai Health Study is a large-scale epidemiological investigation that includes a hospital-based, case-control study of NHL, MDS, benzene poisoning, and AML. Additional components of this investigation will provide data to better understand the progression and molecular epidemiology of benzene-related diseases, as well as exposure analysis.

The ongoing epidemiology studies are using modern diagnostic and molecular techniques to further study the molecular pathogenesis of benzene-associated diseases and the exposure-response relationship for benzene-related cancer and non-cancer effects.

6.1.9 Linear versus Non-Linear Extrapolation

Multiple epidemiological studies from the 1930s through the 1980s strongly support the hypothesis that a threshold exists for benzene's hematopoietic toxicity, including the risk for developing AML. The EPA cancer slope factor is based on the Rinsky et al. (1987) study. There have been at least three exposure analyses of this cohort (Rinsky, Crump, and Paustenbach), and although they differ with regard to methodologies and conclusions, none has reported an excess leukemia risk below 40 ppm-years, with an average value of ~200 ppm-years (Paustenbach et al., 1992; Rushton and Romaniuk, 1997; Paxton et al., 1994; Wong, 1995; Aksoy, 1980). Other authors believe that the threshold could be much higher and that, based on exposure estimates from Crump and Allen and Paustenbach, the AML threshold would correspond to 370 or 530 ppm-years, respectively (Crump and Allen, 1984; Paustenbach et al., 1992; Wong, 1995). In contrast, an analysis published by Glass et al. (2003) reports an increased ANLL risk at lower levels of cumulative benzene exposures than previously reported, but still published cumulative exposures to benzene that carried no elevated risk of ANLL (Glass et al., 2003). Therefore, the majority of the existing epidemiology evidence on the relationship between benzene and AML supports the existence of a threshold for this effect.

While the actual exposure/dose required for AML is not universally agreed upon, the existence of a threshold for AML is consistent with epidemiological data, as well as clinical data obtained from secondary leukemia arising from ionizing radiation and/or chemotherapy and the current understanding of bone marrow patho-physiology and biology. Emerging evidence in the biological mechanism of benzene-induced AML suggests that benzene and/or its metabolites may induce AML via toxic disruption of the regulatory mechanism of cell growth and differentiation (Irons et al., 1993; Irons et al., 1992; Snyder et al., 1994). Further, benzene metabolism has been determined to follow non-linear Michaelis-Menton kinetics (Travis et al., 1990). Given the non-linear nature of benzene metabolism, the use of a linear model for excess cancer risk calculations will likely overestimate the risk, particularly at low exposure levels (ACGIH, 2001). These observations provide a biological basis for the observed threshold evident in epidemiological data (Wong et al., 1995; World Health Organization, 1993; ACGIH, 2001).

The ACGIH utilized a non-linear analysis in deriving the TLV® for benzene and support a non-linear mechanism of benzene-induced leukemogenic transformation. The ACGIH concluded that a linear non-threshold model of benzene risk would likely overstate the risk at low levels of

exposure. This was also supported by Austin et al. (1988), who concluded that a "linear model is generally considered conservative in that it probably overestimates the leukemogenic effects at low doses" (Austin et al., 1988). Lamm and co-workers argued further that the benzene dose-response relationship for the induction of leukemia was strongly nonlinear (Lamm et al., 1989). Schnatter et al. (1996b) also concluded that a leukemogenic threshold was likely in the Pliofilm cohort and corresponded to an air concentration of at least 20 ppm. An analysis specific to AML revealed a threshold of higher than 20 ppm.

6.1.10 Petrochemical Industry and Refinery Epidemiology

Petroleum workers are exposed to benzene or benzene-containing products, such as gasoline. Therefore, studies of petroleum workers also provide data that can be useful in investigating the relationship between benzene and leukemia (or other hematopoietic endpoints of interest).

Wong and Raabe reviewed and summarized the results of 22 cohorts of petroleum workers from the U.S., the U.K., Canada, Australia, Italy, and Finland (Wong and Raabe, 1989). Data from these studies were reviewed individually and were combined into a pooled 'meta-analysis.' The combined multinational cohort consisted of 308,199 petroleum workers and covered an observation period of 1937 to 1996 (Wong and Fu, 2005). This large collection of workers is useful in evaluating the association between working in a refinery or petrochemical plant and the development of leukemia (many of these cohorts did not conduct a cell-type-specific analysis). One published study from this collection reported a significant elevation in leukemia risk associated with refinery workers, although one published study also reported a significantly decreased leukemia risk (McCraw et al., 1985; Wong and Raabe, 1989). The meta-analysis of the cohort revealed a standardized mortality ratio (SMR) for all types of leukemia (ICD-204-207) of 1.1 (95% CI: 0.97–1.23).

Wong et al. (1995) conducted a cell-type-specific leukemia analysis in a combined cohort of 208,741 petroleum workers employed in the U.S. and U.K. from 1937 through 1989 (Wong and Raabe, 1995). This combined cohort includes refinery employees; production, pipeline, and distribution workers; and all updates from the U.S. and U.K. studies first reported in the 1989 analysis (Wong and Raabe, 1989). The updated SMR for AML for the combined petroleum worker cohort was 0.96 (95% CI: 0.81–1.13) (Wong and Raabe, 1995). The authors conclude that levels of benzene exposure did not exceed a threshold required to produce a significant elevation of AML.

Rushton et al. (1981) published a cohort mortality study in 23,000 petroleum marketing and distribution workers (Rushton et al., 1981; Rushton, 1993a,b). The SMR for AML was 1.21 (95% CI: 0.78–1.79). Exposures for this cohort were estimated to be 0.003 ppm to 8.2 ppm, with cumulative exposures from less than 1 ppm-year to more than 200 ppm-year, although 81% of the workers had cumulative exposures less than 5 ppm-years (Lewis et al., 1997). In a related study, Rushton and colleagues also conducted a case-control study of petroleum marketing and distribution workers in the U.K. (Rushton and Romaniuk, 1997; Lewis et al., 1997). No statistically elevated risk of AML (nor any other type of leukemia or all leukemias combined) was reported in any exposure grouping. The highest exposure group was cumulative benzene exposures greater than 45 ppm-years.

Another large, independent cohort mortality study of petroleum workers with potential exposure to benzene (in gasoline) was conducted by Wong et al. (1993). No increase in overall leukemia risk (SMR = 0.89) or AML risk (SMR = 1.50; 95% CI 0.80–2.57) was demonstrated. Further, no

dose response was demonstrated in this study for either cumulative exposure or frequency of peak exposures.

Canadian petroleum workers were studied in a retrospective mortality study by Schnatter et al. (1993). Consistent with other refinery and petroleum worker studies, there was no significantly elevated increase in AML reported, nor evidence of a dose-response between leukemia risk and any measure of benzene exposure (Schnatter et al., 1996a,c). However, an elevated SMR of 3.87 (95% CI; 1.06–9.92) was reported for AML for tank truck drivers employed for more than 1 year (Schnatter et al., 1993). Cumulative exposures of benzene in this cohort were estimated to be as high as ~220 ppm-years (Schnatter et al., 1996a,c).

Wen et al. (1983) evaluated 16,880 employees who worked at the Port Arthur, Texas, refinery from 1937 through 1978. An SMR for all leukemia combined was reported to be 1.14 (no statistically significant increased risk).

One small study by McCraw et al. (1985) reported a statistically elevated SMR for AML in refinery workers. A second small case-control study by Sathiakumar et al. (1995) also reported an elevated OR for AML in oil and gas production workers, although no exposure data were included. However, in the Sathiakumar study, an elevated SMR was not seen in refinery workers. In addition to the studies described in this section, multiple independent refinery and petrochemical studies have been conducted and consistently report a non-elevated SMR for AML or leukemia (Theriault et al., 1979; Naumann et al., 1993; Raabe et al., 1998; Marsh et al., 1991; Wong et al., 1986; Dagg et al., 1992; Satin et al., 1996; Thomas et al., 1982; Austin et al., 1986; Divine et al., 1987; Austin et al., 1983). Taken collectively, the scientific literature is consistent in its demonstration that refinery workers do not have an elevated risk of developing AML, and suggests that a threshold exists for AML induction by benzene exposure.

6.1.11 Service Station Attendants and Vehicle Mechanic Epidemiology

Lynge et al. (1997) conducted a cancer incidence study in 19,000 service station workers exposed frequently to benzene-containing materials (gasoline) and found no increased risk of developing AML. This investigation was carried out in various Scandinavian countries and included service station attendants employed prior to 1972. There were no self-service stations in existence at this time; therefore, all gasoline was pumped by the attendants (increasing their potential for exposure). This cohort was exposed to average benzene levels estimated to be ~0.15–0.3 ppm. The benzene content in European gasoline at that time was between 2% and 10%, with an average value of at least 5%.

Schwartz (1987) conducted a small proportionality mortality ratio (PMR) analysis of deaths among gasoline service attendants and automobile mechanics. There was no elevation in mechanics and a slight increase in gasoline workers for all leukemias combined (ICD 204-207). The problems associated with PMR analysis are well documented. Lagorio et al. (1994) also conducted a small mortality study of filling station attendants and reported no increase in total leukemias. Lindquist et al. (1991) reported an elevated risk in all acute leukemias (including ALL) to professional drivers exposed to gasoline and diesel. However, other authors observed no relationship between leukemia risk and occupational exposure as a professional driver (Lindquist et al., 1991; Lagorio et al., 1994; Wong et al., 1999, 1993).

Another large, independent study of petroleum distribution workers with potential exposures to gasoline found no increase in total leukemia (SMR = 0.89) and no statistically significant increase in AML (SMR = 1.50; 95% CI 0.80–2.57 (Wong et al., 1993). In a nested case-control

follow-up of this same cohort, Wong et al. (1999) evaluated 18,000 petroleum distribution workers (including professional drivers and marine loading workers) exposed to gasoline containing 2%–3% benzene. These authors estimated that the cumulative lifetime exposure to benzene could be as high as 128 ppm-years and 8000 ppm-years total hydrocarbons (THC), including peaks. The average employment duration was 26 years. Risks of total leukemia, acute myeloid leukemia, multiple myeloma, and kidney cancer were examined. Total lymphatic and hematopoietic cancers were significantly decreased in this cohort, with an SMR of 0.69. There was no increased risk of developing AML observed in this cohort.

Many small case-control studies have been conducted, with inconsistent results. Some studies report small increases, and others report decreased or no excess risk (Siemiatycki et al., 1987; Jakobsson et al., 1993; Grandjean et al., 1991; Brandt et al., 1978).

Automobile mechanics constitute another occupational group that is exposed to benzene, primarily though exposure to gasoline (Hotz et al., 1997). There is considerable epidemiological literature available to evaluate the occupational risk of developing AML in automobile mechanics. A large-scale cancer survey was conducted by Williams et al. (1977) and found no increased risk of AML, ALL, CML, or ALL associated with automobile mechanics or gas station attendants. Loomis and colleagues conducted a case-control study and examined ANLL and leukemia rates in mechanics and service station attendants (Loomis et al., 1991). The number of eligible subjects was 615,843. The odds ratio (OR) for ANLL in 'motor mechanics' and 'service station attendants' was 0.8 (95% CI: 0.5–1.1). One study was found that reported an elevated SMR for all leukemias combined in car mechanics, fuel attendants, and painters exposed to 'high' levels of fuels and solvents (Hunting et al., 1995). The elevated SMR was based on only three leukemia cases (and only one was AML).

Collectively, the literature does not support the hypothesis that mechanics have an elevated risk of developing AML (Hotz and Lauwerys, 1997; Jarvisalo et al., 1984; Linos et al., 1980; Linet, 1988; Howe et al., 1983; Jacobs et al., 1993; Giles et al., 1984; Mele et al., 1994)

6.1.12 Other Human Data

6.1.12a Genotoxicity

Benzene is an established etiological factor in the development of AML in humans. Additionally, benzene is carcinogenic in multiple experimental animal species via all major routes of exposure. Consequently, considerable research has been undertaken to understand the mechanism of action for benzene induced carcinogenicity. This includes an extensive evaluation of possible genotoxic mechanisms for benzene and/or its reactive metabolites. Over 250 individual publications containing original data on the genotoxicity of benzene were found in the literature. Nonetheless, there is still uncertainty regarding the genotoxic potential of benzene and its metabolites with inconsistent as well as contradictory results reported. This variability could be the result of methodological differences, choice of metabolites, exposure conditions or a variety of other poorly defined factors. This inconsistent dataset complicates any attempt to generate a clear hypothesis regarding the role that genotoxicity plays in benzene induced animal or human carcinogenicity.

All standard genotoxicity tests in mammalian (including human) cells have been conducted for benzene and its reactive metabolites (see Section 6.2.2 for further discussion on animal genotoxicity). These include a variety of assays designed to measure DNA reactivity and adduct formation, micronuclei formation, clastogenicity (including chromosomal aberrations and

aneuploidy), sister chromatid exchange (SCE) formation, single or double stranded DNA breaks, unscheduled DNA synthesis, oxidative alterations to DNA and various gene mutations (International Agency for Research on Cancer (IARC), 1987; Whysner et al., 1995; Whysner et al., 2004). Benzene and its metabolites are generally negative in standard mutation assays using the bacteria, yeast and fruit flies and results are inconclusive in mammalian cell lines (ACGIH, 2001). Using human cells in the glycophorin A gene mutation assay, investigators observed examples of benzene induced mutations that are likely associated with mitotic recombination but not those typically associated with point mutations or deletions (Zhang et al., 1995; Rothman et al., 1995). The majority of scientific evidence does not support benzene acting as a mutagenic agent.

Consistent experimental proof for direct DNA reactivity is also lacking (Reddy et al., 1994; Pathak et al., 1995). Benzene induced micronuclei formation has been generally positive in rodents, but results from studies using human cells is less consistent (Zhang et al., 1993; Eastmond et al., 1994; Liu et al., 1996). SCE assays have also produced highly variable results, particularly in human cells (Clark et al., 1968; Watanabe et al., 1980; Funes-Cravioto et al., 1977). Assays designed to measure benzene induced DNA strand breaks (single or double) or induction of unscheduled DNA synthesis have also yielded inconsistent results in both humans and experimental animals.

There is reliable scientific evidence for benzene induced clastogenicity or chromosome damage. This 'genotoxic' event includes chromosome aberrations and/or aneuploidy. While there is continuing scientific debate regarding specific chromosomal lesions that may or may not be associated with benzene, there is solid evidence that excessive benzene exposure can result in both structural and numerical chromosomal changes.

As early as 1964, studies of occupational workers exposed to benzene revealed positive evidence of exposure-related chromosomal aberrations (Pollini et al., 1964; Forni et al., 1971; Olweus et al., 1996; Tough et al., 1970). Many of these studies possess important confounders such as smoking or co-exposures to other chemicals. Nonetheless, the overall pattern of chromosomal changes observed in these early studies was consistent. Some investigators also reported that decreases in exposure resulted in concomitant decreases in cytogenetic abnormalities, which further strengthens the association (Tompa et al., 1994). Most of these early studies reported gross structural changes, such as breaks and aneuploidy but stable and unstable rearrangements were also commonly observed (Picciani, 1979; Erdogan et al., 1973; Aksoy, 1989; Sarto et al., 1984; Yardley-Jones et al., 1990).

Data obtained from occupationally exposed workers have been corroborated and extended by studies of human lymphocytes or hematopoietic progenitor cells following in vitro exposure to hydroquinone or other metabolites. More recent laboratory based investigations benefit from sophisticated techniques that allow researchers to detect highly specific cytogenetic lesions (Stillman et al., 1999; Stillman et al., 1997; Niazi et al., 1997; Eastmond, Rupa, and Hasegawa, 1994; Smith et al., 2000; Zhang et al., 2002). Most of these in vitro analysis report involvement of chromosomes 5, 7 and 8, with less frequently reported changes in chromosome 21 (Zhang et al., 2005). In humans, chromosomes 5 , 7 or 8 appear to be the most commonly involved with the best evidence supporting interstitial deletions and/or aneuploidy (Zhang et al., 2002). These specific lesions have also been observed in workers (Zhang et al., 1998; Smith et al., 1998; Zhang et al., 2002).

It has been generally recognized within the hematology and medical communities that treatment of primary malignancies with drugs that act as alkylating agents can also result in the

development of MDS)and/or AML. It is also clear that AML arising secondary to treatment with alkylating chemotherapeutic agents is a clinical entity distinct from AML arising de novo, or primary, which has no readily identifiable cause (Coltman et al., 1990; Park et al., 1996). One hallmark of this type of secondary leukemia (s-AML) is the involvement of recognizable cytogenetic lesions, specifically the loss of part or all of chromosomes 7 and/or 5 (Rowley et al., 1989; 1997; Leone et al., 1999). It has been estimated that cytogenetic lesions involving chromosomes 7 and/or 5 occur 65–95% of the time in AML arising secondary to alkylating agents (Johansson et al., 1991). In contrast, deletions of chromosome 5 and/or 7 occur much less frequently in primary AML (Rowley et al., 1981; Leone et al., 1999). AML cases in workers occupationally exposed to benzene, where appropriate analysis has been conducted, often possess the same types of cytogenetic lesions which suggests a shared pathogenic mechanism (Zhang et al., 2002; Smith, et al., 1998; Zhang et al., 1996; Mitelman et al., 1981; Mitelman et al., 1978; Mitelman et al., 1984; Golomb et al., 1982; Fagioli et al., 1992; Cuneo et al., 1992; Narod et al., 1989; Van den Berghe et al., 1979). In a recent comprehensive review, authors concluded that monosomy 5 and monosomy 7 are the most common cytogenetic abnormalities observed in benzene induced AML (Zhang et al., 2002).

Recently, clinical studies have revealed that a different form of AML can arise secondary to treatment with drugs that primarily target topoisomerase II (e.g. epotoside), an enzyme required for DNA replication (Beaumont et al., 2003; Hoffmann et al., 1995; Anderson et al., 2002; Pedersen-Bjergaard et al., 2002). The most common cytogenetic abnormality in AML secondary to agents that target topoisomerase II is 11q23 (Pedersen-Bjergaard et al., 2002; De Renzo et al., 1999). There have also been examples of chemicals that inhibit topoisomerase II and do not form cleavable complexes. Bimolane acts in this manner and induces an AML with characteristics similar to classic topoisomerase poisons, but with a different predominant cytogenetic lesion (21q22) (Zhang et al., 2002). It has been shown that various benzene metabolites under appropriate enzymatic conditions can inhibit topoisomerase II and some investigators believe this may be an important pathway in benzene induced leukemia (Whysner et al., 2004). It is not clear what role inhibition of topoisomerase II may or may not play in the development of benzene induced AML (Chen et al., 1995). However, the patterns of cytogenetic abnormalities typically associated with inhibition of this enzyme have not been observed in occupationally exposed populations (Zhang et al., 2002).

The presence of specific cytogenetic abnormalities in both benzene and alkylating chemotherapy induced AML suggests that these lesions are non-random and could play a role in the pathogenesis of at least some cases of the disease. Monosomy 7 or an interstitial deletion at 7q- is the most commonly reported cytogenetic abnormality in therapy related AML. A number of gene loci have been mapped to chromosome 7, but their function in hematopoiesis and leukemogenesis remain largely unknown (Luna-Fineman et al., 1995). Additionally, 7- /7q- are often seen in sub-clones of the leukemia or as evolutionary events during disease progression (Pedersen-Bjergaard et al., 2002). In contrast, an interstitial deletion in chromosome 5 (5q31-) is the earliest cytogenetic abnormality that has been detected in therapy related AML (Le Beau et al., 1986b ; Le Beau et al., 1986a; Van den Berghe et al., 1985). There are a variety of important hematopoietic genes mapped to this region of the chromosome including hematopoietic cytokines/growth factors (GM-CSF, IL-3, IL-4, IL-5) and CD14, a myeloid specific surface molecule (Rowley and Le Beau, 1989). Additionally, the early growth response 1 (EGR-1) gene is located in this region of chromosome 5 and is required for monocyte-macrophage differentiation (Rowley and Le Beau, 1989). It is currently not clear how specific deletions on chromosome 5 or 7 could result in a dysregulated hematopoietic environment in the bone marrow or the development of a transformed leukemic clone

(Pedersen-Bjergaard et al., 1995; Pedersen-Bjergaard et al., 2002). It is also possible that alternative pathways leading to AML development secondary to benzene exposure exist.

Currently, the mechanism(s) by which exposure to benzene and its metabolites leads to carcinogenicity have not been defintively established. Therefore, it is not possible to state with scientific certainty what role genotoxicity, including clastogenicity, plays in benzene induced transformation. Further, epigenetic processes such as altered gene regulation, cytotoxicity and cell proliferation are thought to be important, perhaps critical for benzene induced leukemogenesis.

6.1.12b Human Reproductive Toxicity of Benzene

Very little published data is available to evaluate the potential reproductive toxicity of benzene. Additionally, the few studies that have addressed this question possess significant short-comings and uncertainties. Vara and Kinnunen (1946) were the first to publish reproductive effects associated with benzene exposure in women. The reported toxicity in exposed adult subjects included hypermenorrhea, hypomenorrhea, ovarian hypoplasia and sterility (Vara *et al.*, 1946). The nature and severity of the symptoms were subjective and no attempt was made to quantify exposure levels or rule out the effect of other potential confounding exposures. Subsequent studies also had findings of menstrual abnormalities but failed to account for potential effects from other chemicals or mixtures (Pushkina *et al.*, 1968; Michon, 1965; Mukhametova, 1972). Additionally, no information was presented on benzene exposure levels associated with reported effects. Interpretation of these early studies is further complicated by the lack of statistical analysis and appropriate comparison with control populations.

More recent studies partially overcome these deficiencies by providing some exposure data and by attempts to address confounding chemical exposures. Yin *et al.* (1987) reported a statistically significant increase in the incidence of hypermenorrhea in women exposed to benzene concentrations (8 hr mean TWA = 59 ppm). Huang *et al.* (1991) evaluated Chinese leather shoe workers and also reported elevated incidence rates of 'dysmenorrhea' in exposed workers. Additionally, an increase in spontaneous abortions associated with employment duration was observed in this study. Investigators did not quantify benzene exposures or adequately account for potentially confounding influences from other chemical exposures in this workplace on other non-chemical confounders (Huang, 1991). Historically, shoe workers have experienced extremely high benzene levels as well as significant co-exposures to a variety of other chemicals (Aksoy *et al.*, 1976; Aksoy *et al.*, 1974; Vigliani, 1976; Forni *et al.*, 1974). Another Chinese worker (petrochemical) study published in 2000 reported that women with more than 7 years on a job with benzene exposure experienced a significantly increased number of abnormal menstrual cycles compared to non-benzene exposed controls (OR = 1.71, 95% CI = 1.27-2.31) (Thurston *et al.*, 2000). This increase was not observed in women exposed for less than 7 years. Again, concomitant chemical exposures were not addressed and no quantification of benzene air concentrations was provided.

Only one study was located that investigated the effect of occupational benzene exposure on male reproductive function. Xiao *et al.* (1999) published an evaluation of benzene, toluene, and xylene exposure on semen quality in exposed workers (shoe-making, paint manufacturing and spray painting). Sperm vitality, motility and acrosin activity was reportedly decreased in exposed workers compared to non-exposed controls (Xiao *et al.*, 1999). It is not possible to separate the effects of benzene, toluene and xylene on these parameters as co-exposures to all three chemicals occurred continually (Xiao *et al.*, 2001). Additionally, there was no

quantification of benzene air concentrations provided and potential confounders were not adequately addressed.

Taken collectively, the data linking benzene exposure to male or female reproductive toxicity is insufficient to allow scientifically tenable conclusions to be reached. Available evidence suggests that the complex occupational exposures that occurred in these studies may have potentially contributed to the menstrual abnormalities in some women. However, co-exposures with other chemicals, genetics, various lifestyle factors and other potential confounders prevent a definitive link with benzene from being established. More importantly, inadequately characterized exposure histories make it impossible to establish concentrations of benzene; therefore, it is not clear how this information could be used for quantitative risk assessment purposes. Additionally, historic exposures, particularly in some Chinese industries (such as shoe-making), are considerably higher than those experienced in the US under current occupational practices.

6.1.12c Human Developmental Toxicity of Benzene

A few studies have attempted to address the potential association between benzene exposure and developmental toxicity. Some of these studies have suggested that benzene exposure may be associated with spontaneous abortions and developmental toxicity in the fetus, but this literature is highly inconsistent. Due to its lipophilic nature and relatively small molecular weight, benzene readily crosses the placenta and has been measured in cord blood at levels equal to or exceeding maternal levels (Dowty *et al.*, 1976). Therefore, it is assumed that maternal exposure would likely result in some benzene reaching the developing fetus.

Forni *et al.* (1971) published the first case report of a woman exposed to benzene during her entire pregnancy. Benzene exposures were high enough to have resulted in severe pancytopenia, but did not adversely affect the fetus (Forni, 1971). A 1972 Russian study reported evidence of fetal toxicity and premature interruptions of pregnancy in women exposed to gasoline and chlorinated hydrocarbons (Mukhametova, 1972). Due to this complex exposure, it was not possible to attribute this reported toxicity solely or even partially to benzene. Another study reported increased chromosomal aberrations in the lymphocytes of children whose mothers were exposed occupationally to benzene and/or organic solvents compared to non-exposed controls (Funes-Cravioto *et al.*, 1977). The relevance of peripheral cytogenetic findings is not clear nor is it clear if this affect was causally related to maternal benzene exposure. Benzene levels were not quantified, and it is not possible to rule out confounding chemical exposures.

A 1984 study of pregnant laboratory employees was conducted to evaluate the potential association between occupational exposures and pregnancy outcome (Axelsson *et al.*, 1984). There was no difference in miscarriages, perinatal death rates or prevalence of malformations between those with mixed solvent exposure (some recalled specifically using benzene) and those without. However, the lack of reliable exposure information, potential recall bias and complex chemical exposures, weaken the relevance of this study for risk assessment purposes (Axelsson *et al.*, 1984). Savitz, *et al.* (1989) analyzed data from three case groups of pregnancy outcome and reported a slight, but statistically significant increase in the risk of stillbirths associated with paternal exposure to benzene (OR = 1.5, 95% CI = 1.1-2.3). Benzene levels were not quantified, and it is not possible to rule out confounding chemical exposures (Savitz *et al.*, 1989). Strucker *et al.* (1994) evaluated the relationship between paternal benzene exposure and spontaneous abortions and found no evidence of an effect at benzene air concentrations greater than 5 ppm (Strucker *et al.*, 1994). Xu *et al.* (1998) conducted a retrospective

epidemiology study in Beijing, China to evaluate the potential relationship between petrochemical exposures and spontaneous abortions. The OR for spontaneous abortions and benzene exposure was statistically significant (OR = 2.5, 95% CI = 1.7 – 3.7). This data could have been influenced by recall and selection bias as well as potential confounding chemical exposures (Xu *et al.*, 1998). Chen *et al.* (2000) reported that birth weight among children born to benzene exposed workers in a petrochemical plant in Beijing was significantly reduced compared to unexposed controls. Again, benzene exposures were not quantified and confounding chemical exposure was likely (Chen *et al.*, 2000).

Only one study was found that specifically addressed the relationship between parental exposure to chemicals (including benzene) and malformations. Wennborg *et al.* (2005) completed a survey of Swedish laboratory workers exposed during their pregnancy. The OR ratio for neural crest malformations associated with benzene exposure was statistically significant (OR = 5.3, 95% CI = 1.4-21.1) (Wennborg *et al.*, 2005). Benzene exposures were not quantified and exposure to confounding chemicals likely occurred. Further, this study was based on an extremely small number of cases (major malformations was 2.3% in exposed and 1.9% in unexposed); therefore, misclassification of exposure or cases would have a significant impact.

Epidemiology studies investigating the potential for benzene as a developmental toxicant have many limitations. These include concomitant exposure to other chemicals, inadequate sample size, lack of adequate quantification of exposure levels as well as biases associated with case-control studies (recall, selection). Additionally, a variety of non-chemical confounders are also potentially present including genetics and various lifestyle factors, such as diet, stress and smoking history that are difficult to completely account for. Therefore, while there is limited evidence suggesting that benzene exposures may increase the risk of spontaneous abortions or malformations, the overall database on developmental toxicity in humans is currently insufficient to draw definitive conclusions.

6.1.12d Parental Exposure to Benzene and the Development of Childhood Leukemia

Childhood AML is the second most common leukemia in children (next to acute lymphoblastic leukemia or ALL) and represents about 20% of all cases of childhood leukemia (Colby-Graham *et al.*, 2003). Overall, the rate of childhood AML in the US is ~400 new cases per year and unlike ALL, the rates do not fluctuate significantly with age (Bhatia *et al.*, 1995; Lightfoot, 2005). Understanding potential environmental causes of childhood AML has been particularly challenging, mainly due to the rarity of the disease. There have been scattered reports suggesting that maternal and/or paternal exposure to benzene or other chemicals could lead to an increased risk of developing childhood AML. Recent studies have been specifically designed to evaluate the potential relationship between parental exposure to benzene (and other exposures) and the development of childhood leukemia in the offspring.

Shaw *et al.* (1984) conducted an early case-control study of childhood leukemia and paternal occupation. No association between paternal exposures to benzene and childhood leukemia (not specified) was observed. Maternal occupation was not considered. Exposures were not quantified and were based on occupations listed on the child's birth certificate (Shaw *et al.*, 1984). Shu *et al.* (1988) evaluated the relationship between parental occupational exposures and childhood leukemia in Shanghai, China using a case control study design (Shu *et al.*, 1988). A variety of potential etiological agents were investigated, including benzene. Paternal occupational exposure was not associated with either form of acute childhood leukemia (ALL or ANLL). However, maternal exposure to benzene was positively associated with ANLL (OR =

4.0, 95% CI = 1.8-9.3) but not ALL (Shu *et al.,* 1988). This is the only study to separate the two main forms of acute childhood leukemia in children and reported an increase in the leukemia type associated with benzene exposure in adults. There was no quantification of benzene air concentrations and exposures to confounding chemicals could have occurred. There was also no attempt to characterize children's direct chemical exposures that could have occurred in the home or from the general environment. Further, recall bias could have resulted in a misclassification of exposures or cases in this study. McKinney *et al.* (1991) also conducted a case-control study to evaluate maternal and paternal exposures to benzene and the relationship with childhood leukemia (subtype not identified). Few risk factors were identified for the mother, but paternal exposures to benzene during the pre-conception period were significantly associated with childhood leukemia (OR = 5.81, 95%CI = 1.67-26.44) (McKinney *et al.*, 1991). This study was potentially limited by a small numbers of cases, inadequately quantified benzene exposures, and potential exposures with confounding chemicals. As with most case-control studies, recall bias could have occurred.

Various other studies of childhood leukemia have failed to show an association with potential benzene exposures of parental occupations. Feingold *et al*, (1992) conducted a case-control study of childhood ALL and parental occupation. These investigators reported no association between maternal exposure to benzene and ALL (Feingold *et al.*, 1992). Kaatsch *et al.* (1998) conducted a case control study of childhood leukemia. Though the majority of the leukemias were ALL, there were 147 cases of childhood ANLL included in the analysis (but not analyzed separately). No association between parental exposure to benzene and childhood leukemia was found (Kaatsch *et al.*, 1998). Shu *et al.* (1999) examined childhood ALL with paternal or maternal exposure to benzene or 'petroleum products' (including during pregnancy) in a case-control study. There was no relationship reported (Shu *et al.*, 1999). Feychtling *et al.* (2001) conducted a case control study on paternal occupation and childhood cancers including leukemia (all combined). Paternal exposure to benzene (RR = 1.23, 95% CI = 0.39-3.85) was not positively associated with an increased leukemia risk (Feychting *et al.*, 2001). Infante-Rivard, *et al.* (2005) conducted a recent case-control study of childhood ALL and maternal exposure to various solvents. The OR for benzene was 0.82 (95% CI = 0.22-3.06) for exposure during the 2 years before birth, including pregnancy and 1.39 (0.31-6.25) for exposure during pregnancy (Infante-Rivard *et al.*, 2005). The significance of this study, like the others listed in this section, was limited by small numbers, inadequate exposure assessment and exposures with confounding chemicals. Potential recall bias could have resulted in a misclassification of cases or exposures and significant changes in the study findings.

In general, there is consistent support in the scientific and medical literature that parental exposure to benzene is not a causative factor in the development of childhood ALL. However, the type of leukemia most clearly associated with benzene exposure in adults is AML. It should be pointed out that the etiological risk factors for AML and ALL in both adults and children are different. Only one study was available that specifically addressed childhood AML. The other studies either combined all forms of childhood leukemia into a single group or evaluated ALL singly. Both approaches would limit the ability of these investigations to detect a positive association between benzene and childhood AML, while increasing the likelihood of finding an association despite differing etiologies for these types of childhood leukemia. In Shu *et al.,* (1988), such an association was reported, but has not been independently confirmed. Additionally, 23% of the leukemia cases occurred in children 10-14 years old. Clinical literature indicates that the latency period for t-AML is approximately 5-7 years. The latency period for benzene induced AML is less well characterized and could be longer, but the possibility exists that cases of leukemia occurring in older children were unrelated to *in utero* exposures. Therefore, data presented in Shu *et al,* (1988) should be interpreted cautiously.

6.1.12e Conclusions

Based on a recent review of all available scientific evidence, it is not possible to reach definitive conclusions regarding human developmental and/or reproductive toxicity of benzene. Relevant studies were severely limited by small populations of subjects, poorly defined or missing exposure information (including exposure to other confounding chemicals), as well as recall and selection bias. Most epidemiology studies evaluating the potential relationship between benzene and reproductive/developmental toxicity are case control studies. Case-control studies, while useful tools for generating hypotheses, rarely provide reliable quantitative exposure data. As a result, it is not possible to use data from most case-control studies in a quantitative risk assessment.

Reproductive epidemiology presents quite a challenge to investigators, in both study design and conduct. Many of the endpoints of interest (e.g., menstrual cycle abnormalities or spontaneous abortions) are relatively common occurrences in the human population. This fact compounds the difficulties faced by investigators attempting to establish environmental or occupational causes for reproductive endpoints. Additional confounders, such as diet, genetics, and lifestyle factors all likely play a role in the background incidence of these events. As such, without careful control of these confounder factors, appropriate interpretation of any data collected is greatly complicated.

These and other shortcomings in the available data have been reviewed by several organizations, including the ATSDR, the US EPA and the European Union (EU). To date, no federal regulatory agency or scientific body has established a regulatory toxicity value for benzene based on the reproductive or developmental toxicity in humans. The data are not robust enough for such a determination. The Organization for Economic Cooperation and Development (OECD) reviewed the EU risk assessment and concluded:

> "Evidence from human data for an effect of benzene exposure on female reproduction is not sufficient to demonstrate a causal association due to poorly designed studies and inadequately quantified exposure to benzene as well as to other chemicals. Epidemiological studies in males on effects on fertility are not available. Likewise epidemiological studies implicating benzene as a developmental toxicant have many limitations thus not providing sufficient information to assess the effects on the human fetus." (OECD, 2005)

As described herein, there are poorly documented studies that are suggestive of an association between un-quantified benzene exposures and maternal toxicity in the form of menstrual alterations. Additionally, there are both positive and negative studies on the potential adverse effect on the human fetus following parental exposure to benzene, including spontaneous abortion, low birth weight or specific malformations. While leukemia studies are consistent in their demonstration that parental exposure to benzene is not casually related to the development of ALL, there is limited evidence for a potential association with childhood AML (which has not been independently evaluated). Problems and short-comings inherent in the specific studies preclude the development of a causal relationship between these reported adverse effects and benzene exposure. In the absence of additional, more reliable data, it is not currently possible to conclude that parental benzene exposure will adversely affect the developing fetus (including the development of AML) or adversely effect reproductive function in either exposed parent.

6.2 Benzene Toxicology—Animal Hazard Assessment

This section of the hazard assessment addresses the available benzene animal toxicology data on the VCCEP endpoints.

6.2.1 Acute Toxicity

In rats, oral LD50 values range from 810 mg/kg (Cornish and Ryan, 1965) to 10,000 mg/kg (Smyth et al., 1962). Gerarde (1960) reported an LD50 of 5600 mg/kg. Clinical signs included sedation and narcosis, with pathological findings of hyperemic and hemorrhagic lungs, adrenals, brain and spine, hyperemia of stomach and intestines, and enlarged fatty liver. Values for acute inhalation exposure were low, with an LC50 of 13700 ppm (44.5 mg/L) with 4-hour exposure of female rats (Drew and Fouts, 1974) and 10,450 ppm (33.3 mg/L) for mice after 7 hours of exposure (Svirbely et al, 1943). Clinical signs included restlessness, twitching, tremor, changes in respiration, poor coordination, and narcosis with congestion of lung and liver as main pathological findings. Roudabush et al. (1965) reported a dermal LD50 >8260 mg/kg in rabbits and guinea pigs. Benzene was a slight to moderate irritant to rabbit ears after 10–20 exposures (Wolf et al., 1956) and an irritant according to OECD protocol 404 (Jacobs, 1992). Two drops (approx. 0.1 mL) in the eye of a rabbit caused moderation of the conjunctiva and transient lesions of the cornea (Wolf et al., 1956), and 0.1 mL caused grade 3 corneal lesions with 13%–37% necrosis of the cornea, according to Smyth et al. (1962). No skin sensitization studies have been reported.

6.2.2 Genetic Toxicity

Benzene has been tested in a wide variety of *in vitro* assays employing bacteria and mammalian cells in culture, and *in vivo* by inhalation, oral, and intraperitoneal (i.p.) routes of exposure. Extensive compilations of *in vitro* and *in vivo* data were prepared and updated by the Agency for Toxic Substances and Disease Registry (ATSDR, 1993, 1997) and are presented here as Tables 6.1 (*in vitro*) and 6.2 (*in vivo*), with additional studies addressed in the text.

In vitro studies provide convincing evidence that benzene's genotoxicity is derived primarily from its metabolites. Although benzene usually does not induce gene mutations in standard assays, some positive results have been obtained only when metabolic activation is employed. Benzene exposure primarily results in chromosome aberrations in numerous *in vitro* and *in vivo* assays and in workers exposed over long periods (U.S. EPA 1998b).

6.2.2.1 In Vitro

Benzene has generally yielded negative results in standard gene mutation assays in bacteria and *in vitro* mammalian cell assays (Ashby et al., 1985; Dean, 1985). Using the conventional *Salmonella typhimurium* plate incorporation assay and microsomal activation from Aroclor®-induced rat liver, benzene consistently gave negative results (Leibowitz et al., 1979; Shimizu et al., 1983). Venitt (1985) reported results from an IPECA–sponsored international collaborative study that involved five investigating laboratories using *Salmonella* plate-incorporation and preincubation protocols, a range of metabolic activation systems, seven bacterial strains (including TA97 and TA102), and a forward mutation system (*Sal*. TM677); benzene was not mutagenic in any assay. However, in a sensitive microsuspension assay, McCarroll et al. (1980) detected a significant increase in histidine revertants in *Sal*. TA100, in the presence of rat liver metabolic activation. When benzene was administered as a vapor to *Salmonella* plates

in dessicator jars, Glatt et al. (1989) were able to induce histidine reversion with metabolic activation. Jar set-up apparently allowed benzene vapor to be present long enough to be converted to biologically active metabolites by rat liver metabolism. Of 13 metabolites tested, only trans-1,2-dihydrodiol and the diol epoxides (with and without activation) were active. Seixas et al. (1982) and Kaden et al. (1979) induced azaguanine reversion in *Salmonella* with metabolic activation. Benzene (0.069M) inhibited cell survival in *E. coli* WP100 [uvrA-, recA-], a repair-deficient strain compared to *E. coli* WP100[uvrA+,rec+], its repair-proficient partner, and in *Bacillus subtilis* strain M45 [rec-] compared to H17[rec+] (McCarroll et al., 1981a,b). The authors suggested a requirement for recombinational mediated repair to benzene-induced DNA damage.

Mutational events have been reported in mammalian cells cultured from animals exposed *in vivo*. Ward et al. (1992) observed dose-related increases in mutations at the hprt locus in spleen lymphocytes of CD-1 mice exposed to benzene (0.04, 0.1, and 1.0ppm) by inhalation, 7days/week for 6 weeks, at the two lower concentrations but not at 1.0 ppm. However, effects were not paralleled by clear increases in numbers of labeled cells, and increases in mutant frequency may have been artificially inflated by variability in the labeling index, and co-exposure to a high dose of vinblastine. All these factors led the authors of the EU benzene risk assessment draft (ECB 2003) to consider this study equivocal. Mullin et al. (1995) detected increased mutant frequencies in the lacI transgene from lung and spleen cells, but not liver, of C57Bl/6 mice exposed to 300 ppm benzene, 6 hours/day, 5 days/week for 12 weeks. Mammalian forward mutation assays, as performed, cannot distinguish between true gene mutations and small deletions. Thus, interpretation of these results is consistent with action of a cytogenetic agent that causes chromosome breakage, loss, and/or rearrangement.

Benzene metabolites either tested directly or produced by metabolic activation, have induced various forms of DNA perturbation in mammalian cells. Exogenous metabolic activation was required to produce sister chromatid exchanges (SCE) in human lymphocyte cell cultures (Morimoto, 1983), and endogenous activation induced DNA synthesis in rat hepatocytes (Glauert et al., 1985), DNA adduct formation in rat liver mitochondria (Rushmore et al., 1984), and RNA synthesis in mitochondria of rat liver, and rabbit and cat bone marrow (Kalf et al., 1982). Studies in Chinese hamster V79 cells demonstrated that the benzene metabolites 1,2,3- and 1,2,4-trihydroxybenzene, quinone, hydroquinone, catechol, phenol, 1,2 dihydrodiol, and the diol epoxides produced genotoxicity ranging from SCE and micronuclei to gene mutation (Glatt et al., 1989). Trans, trans-muconaldehyde was also strongly mutagenic in V79 cells and weakly mutagenic in bacteria (Glatt and Witz, 1990); muconaldehyde and its metabolites—6-hydroxy-2,4-hexadienal and 6-oxo-*trans,trans* hexadienoic acid—were also active (Chang et al., 1994). The overall conclusion from a range of *in vitro* studies is that benzene does not induce toxicity and leukemogenesis as a gene mutagen. Chromosome alterations and hyperdiploidy were observed in human lymphocytes after exposure to hydroquinone *in vitro* (Eastmond et al., 1994), and Aubrecht and Schiestl (1995) reported that benzene itself induced intrachromasomal recombination in human lymphoblastoid cultures. Micronuclei were also seen in human cells exposed *in vitro* to various benzene metabolites and combinations of metabolites (Zhang et al., 1993; Eastmond, 1993). Synergistic increases in micronuclei were induced by catechol and hydroquinone, but not by catechol and phenol, or phenol and hydroquinone (Robertson et al., 1991). When mice were treated intraperitoneally with mixtures of these benzene metabolites, synergistic effects resulted only from mixtures of phenol and hydroquinone (Marrazzini et al., 1994); adding catechol was no more effective than hydroquinone alone in inducing micronuclei. Similar results were reported by Chen and Eastmond (1995), using an antikinetochore-specific antibody and fluorescent *in situ* hybridization (FISH). The relative frequency of chromosome

breakage and loss was comparable whether mice were treated with 440 mg/kg of benzene or a 60/160 mg/kg mixture of hydroquinone/phenol.

6.2.2.2 In Vivo

Consistently positive findings for chromosome aberrations in bone marrow and lymphocytes of benzene-treated animals support human case reports and epidemiology studies. Analyses of chromosomal aberrations, sister chromatid exchange, and micronuclei in bone marrow and lymphocytes of both mice and rats exposed orally or by inhalation, give positive results.

Inhalation: Bone marrow preparations from male rats exposed to 750 and 7500 ppm benzene for single and multiple exposure periods showed significantly increased frequencies of chromosomal aberrations (Anderson and Richardson, 1981). Male Wistar rats exposed to 100 and 1000 ppm benzene for 6 hours also had elevated frequencies of chromosomal aberrations in bone marrow cells (Styles and Richardson, 1984). Tice et al. (1980, 1982) reported that male and female DBA/2 mice acutely exposed to 3100 ppm showed significant increases in SCE in bone marrow cells, but chromosome aberrations were not significantly increased. Significant linear increases in SCE were also observed when DBA/2 and C56Bl/6 mice were exposed to benzene at concentrations of 28—5000 ppm; the response leveled at 3000 ppm for DBA/2 mice and at 2000 ppm for C57Bl/6 mice.

Evaluation of micronucleus frequencies in peripheral blood polychromatic erythrocytes (PCE) and normochromatic erythrocytes (NCE) permits assessment of both recently induced (PCE, 24-hour lifespan) and chronically accumulated bone marrow damage (NCE, 30-day lifespan) (ATSDR, 1993, 1997). Erexson et al. (1986) reported significant dose-dependent increases in lymphocyte SCE and in micronuclei of bone marrow PCEs in DBA/2 mice exposed to 10, 100, and 1000 ppm benzene for 6 hours. Increases in micronuclei were clear and dose-dependent for all doses, while doubling of SCE was seen only at 1000 ppm benzene. Dose-dependent increases in peripheral blood lymphocyte SCE at exposures of 3, 10, and 30 ppm, and in micronucleated-PCE of bone marrow at 1, 3, 10, and 30 ppm were reported in Sprague Dawley rats. Again, induction of increased micronuclei was significant, but SCE induction at 30 ppm was marginal (11.1 SCE/metaphase vs 8.6 SCE in controls). Effects of benzene exposure duration and dose regimen were examined by Luke et al. (1988a,b) by exposing male and female DBA/2 mice to 300 ppm benzene, 5 days/week or 3 days/week for 1–13 weeks. Micronucleated-PCEs were affected by benzene inhalation independent of exposure and regimen; micronucleated-NCE were affected only with 5-day/week exposure. Males were more sensitive than females. In a similar study, using male mice of DBA/2, C57Bl/6, and B6C3F1 strains, exposed to 300 ppm benzene, 6 hours/day, 5 days/week or 3 days/week for 13 weeks, micronuclei increases in PCE were strain specific (DBA/2 >C57Bl/6 = B6C3F1), while micronucleated-NCE were again regimen specific and strain specific in the reverse order from micronucleated-PCEs (C57Bl/6 = B6C3F1 >DBA/2). Farris et al. (1997) studied induction of micronucleated-PCE in bone marrow and blood, and micronucleated-NCE in blood of male mice at low inhalation concentrations of 1, 10, 100, and 200 ppm benzene for 1, 2, 4, and 8 weeks, but effects were seen only at 100—200 ppm. Hematological effects also were not observed until exposure reached 100 ppm and are discussed later in this document. Micronuclei/PCE frequency plateaued at week 2 (4.2% at 100 ppm, 8.6% at 200 ppm vs. 1.0% in control; micronuclei/NCE 1.34% at 100 ppm, 3.25% at 200 ppm vs. 0.18% in control). Using a benzene dose of 200 ppm for 5 days, Valentine et al. (1996) investigated reduction in benzene toxicity in transgenic knock-out mice lacking CYP2E1 compared to wild-type mice and B6C3F1 mice. CYP2E1 competent mice demonstrated decreased bone marrow cellularity and increased

micronucleated polychromatic erythrocytes, while transgenic mice did not exhibit changes in cellularity or micronucelated-PCE.

Oral exposure to benzene produces comparable significant increases in chromosome aberrations, and also demonstrates that male mice appear to be more sensitive than female. Oral administration of 440 and 879 mg/kg/day benzene for 3 days to male and female CD-1 mice resulted in significantly elevated frequencies of chromosomal aberrations and micronuclei in bone marrow. Male mice responded at 440 mg/kg, while 879 mg/kg was needed to elicit a response in females (Meyne and Legator, 1980). Siou et al. (1981) demonstrated that Chinese hamsters (both sexes) are less sensitive to benzene clastogenicity. Administration of 2198 or 8790 mg/kg/day for 2 days did not induce a significant increase in micronuclei in bone marrow cells, and chromosome aberrations were observed only in males after 2 days exposure at 8790 mg/kg. Swiss mice in the same study, given doses of 0, 56.2, 141, 352, and 2189 mg/kg/day for 2 days produced significant dose-dependent increases in chromosome aberrations and micronuclei, with males being the more sensitive. Fujie et al. (1992) examined dose-effect and time-effect relationships and sex and strain differences using Wistar, Sprague Dawley, and Long Evans rats. The incidence of aberrant cells increased progressively with time, reaching a maximum response of 65% aberrant cells at 12 hours after treatment with 750 µL/kg (660 mg/kg) in male Long Evans rats: lowest-observed-effect level (LOEL) = 15 µL/kg (132 mg/kg). Increased micronuclei in normochromatic peripheral blood erythrocytes were reported by Au et al. (1990) after oral treatment at 26.6–146.6 mg/kg body weight for 2, 8, or 14 days. Further increases in frequency were observed after cessation of treatment, with the strongest effect at 36 weeks from start of treatment. In a retrospective analysis of peripheral blood smears from the NTP oral cancer study in B6C3F1 mice, Choy et al. (1985) reported a significant dose-dependent elevation in micronucleated-NCE at doses of 50 mg/kg/day over 2 years. At each dose and sampling time, frequency was higher in males than in females. MacGregor et al. (1990) also reported induction of micronuclei in normochromatic erythrocytes of mice with oral long-term exposure. After 4 months exposure, a dose-dependent increase in micronuclei frequency was found over a dose range of 25—600 mg/kg, with effects in males more pronounced than in females: NOEL females = 25 mg/kg; LOEL males = 25 mg/kg. After 1–2 years of treatment, male rats still showed increased micronuclei frequencies, although the magnitude of response decreased with exposure time; females were not evaluated.

Table 6.1: In Vitro Genotoxicity of Benzene (Table 1 from ATSDR Toxicological Profile 1997)

Table 1. Genotoxicity of Benzene and metabolites *In Vitro*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium (Ames test)	Gene mutation	–	–	De Flora et al. 1984
S. typhimurium (histidine reversion)	Gene mutation	+	–	Glatt et al. 1989
S. typhimurium (azaquanine reversion)	Gene mutation	+	No data	Seixas et al. 1982
S. typhimurium (azaquanine reversion)	Gene mutation	+	No data	Kaden et al. 1979
Bacillus subtilis (histidine reversion)	Gene mutation	–	–	Tannoka 1977
Escherichia coli (DNA polymerase 1/cell-free DNA synthetic system)	DNA synthesis inhibition	No data	–	Lee et al. 1988
E. coli (host meditated DNA repair)	DNA synthesis	No data	No data	Hellmer and Bolcsfoldi 1992b
Plasmid DNA ϕX-174 RF I	DNA degradation	No data	+	Li et al. 1995
Eukaryotic organisms:				
Fungi:				
Aspergillus nidulans (methionine supressors)	Gene mutation	No data	–	Crebelli et al. 1986
Mammalian cells:				
Mouse (L5178Y cells/TK test)	Gene mutation	–	–	Oberly et al. 1984
Chinese hamster (ovary cell culture)	Chromosomal aberrations	–	–	Gulati et al. 1989
Human (lymphocyte cell culture)	Chromosomal aberrations	No data	+	Morimoto 1976
Human (lymphoblastoid culture)	Intrachromosomal recombination	No data	+	Aubrecht et al. 1995
Human (lymphocyte cell culture)	Chromosomal aberrations	No data	+	Eastmond et al. 1994
Human (lymphocyte cell culture)	Chromosomal aberrations	No data	–	Gerner-Smidt and Friedrich 1978
Human (leukemia cells)	DNA oxidative damage	No data	+	Kolachana et al. 1993
Chinese hamster (ovary cell culture)	Sister chromatid exchange	–	–	Gulati et al. 1989
Chinese hamster (ovary cell culture)	Sister chromatid exchange	–	–	Douglas et al. 1985
Human (lymphocyte cell culture)	Sister chromatid exchange	+	No data	Morimoto 1983
Human (lymphocyte cell culture)	Sister chromatid exchange	No data	–	Gerner-Smidt and Friedrich 1978
Chinese hamster (ovary cell culture)	Micronuclei increase	–	–	Douglas et al. 1985
Human (bone marrow)	DNA adducts	No data	+	Bodell et al. 1993
Human (leukemia cells)	DNA adducts	No data	+	Bodell et al. 1993
Human (bone marrow)	DNA adducts	No data	+	Levay and Bodell 1992
Human (leukemia cells)	DNA adducts	No data	+	Levay and Bodell 1992

Table 6.1 Continued: *In Vitro* Genotoxicity of Benzene (Table 1 from ATSDR Toxicological Profile 1997)

Table 1. Genotoxicity of Benzene and metabolites *In Vitro* (continued)

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Calf thymus DNA	DNA adducts	No data	+	Chenna et al. 1995
Rabbit (bone marrow mitoplasts)	DNA adducts	No data	+	Rushmore et al. 1984
Rat (liver mitoplasts)	DNA adducts	No data	+	Rushmore et al. 1984
Rat liver epithelial cells	DNA hyperphosphorylatioin	No data	+	Dees and Travis 1994
Rat (hepatocytes)	DNA breaks	No data	–	Bradley 1985
Chinese hamster (V79 cell culture)	DNA breaks	–	–	Swenburg et al. 1976
Chinese hamster (ovary cell culture)	DNA breaks	+	+	Douglas et al. 1985
Chinese hamster (ovary cell culture)	DNA breaks	+	+[a]	Lakhanisky and Hendricks 1985
Mouse (L5178Y cell culture)	DNA breaks	No data	–	Pellack-Walker and Blumer 1986
Rat (hepatocyte culture)	Unscheduled DNA synthesis	No data	–	Probst and Hill 1985
Rat (hepatocyte culture)	Unscheduled DNA synthesis	No data	–	Williams et al. 1985
Rat (hepatocyte culture)	Unscheduled DNA synthesis	No data	(+)	Glauert et al. 1985
Human (HeLa S3 cells)	Unscheduled DNA synthesis	–	–	Barrett 1985
Mouse (bone marrow cell culture)	DNA synthesis inhibition	No data	+	Lee et al. 1988
Mouse (bone marrow cell culture)	DNA synthesis inhibition	+	(+)	Lee et al. 1989
Calf (thymus DNA polymerase α/cell-free DNA synthetic system)	DNA synthesis inhibition	No data	+	Lee et al. 1988
Human (HeLa cells)	DNA synthesis inhibition	–	–	Painter and Howard 1982
Mouse (spleen lymphocytes)	RNA synthesis inhibition	No data	+	Post et al. 1985
Rat (liver mitoplasts)	RNA synthesis inhibition	No data	+	Kalf et al. 1982
Rabbit (bone marrow mitoplasts)	RNA synthesis inhibition	No data	+	Kalf et al. 1982
Cat (bone marrow mitoplasts)	RNA synthesis inhibition	No data	+	Kalf et al. 1982

[a]Benzene's effect on DNA breaks was reduced when metabolic activators were used.

– = negative results; + = positive results; (+) = weakly positive result; DNA = deoxyribonucleic acid; RNA = ribonucleic acid

From ATSDR, 1997

Table 6.2: *In Vivo* Genotoxicity of Benzene (Table 2 from ATSDR Toxicological Profile 1997)

Table 2. Genotoxicity of Benzene *In Vivo*

Species (test system)	End point	Results	Reference
Prokaryotic cells:			
Escherichia coli (host mediated DNA repair)	DNA synthesis	–	Hellmer and Bolcsfoldi 1992a
Invertebrate animal cells:			
Drosophila melanogaster	Sex-linked recessive lethal	–	Kale and Baum 1983
D. melanogaster (spermatocytes)	Recombination	–	Kale and Baum 1983
D. melanogaster (spermatogonia)	Recombination	+	Kale and Baum 1983
D. melanogaster (spermatocytes)	Heritable translocation	–	Kale and Baum 1983
Mammalian cells:			
Mouse (spleen lymphocytes)	Chromosomal aberrations	+	Rithidech et al. 1987
Mouse (spleen lymphocytes)	Chromosomal aberrations	+	Au et al. 1991a
Mouse (spleen lymphocytes)	Mutations	+	Ward et al. 1992
Mouse (peripheral erythrocytes)	Micronucleus increase	+	Hayashi et al. 1992
Mouse (bone marrow)	Chromosomal aberrations	(+)	Tice et al. 1982
Mouse (bone marrow)	Chromosomal aberrations	(+)	Tice et al. 1980
Mouse (bone marrow)	Chromosomal aberrations	+	Siou et al. 1981
Mouse (bone marrow)	Chromosomal aberrations	+[a]	Meyne and Legator 1980
Mouse (bone marrow)	Chromosomal aberrations	+	Shelby and Witt 1995
Mouse (bone marrow)	Micronucleus increase	+	Shelby et al. 1993
Mouse (bone marrow)	Micronucleus increase	+	Shelby and Witt 1995
Mouse (bone marrow)	DNA adducts	–	Reddy et al. 1994
Mouse (bone marrow)	DNA adducts	+	Pathak et al. 1995
Mouse (liver)	DNA adducts	–	Reddy et al. 1994
Mouse (mammary gland)	DNA adducts	–	Reddy et al. 1994
Rat (bone marrow)	DNA oxidative damage	+	Kolachana et al. 1993
Rat (bone marrow)	Chromosomal aberrations	+	Styles and Richardson 1984

Table 6.2 Continued: *In Vivo* Genotoxicity of Benzene (Table 2 from ATSDR Toxicological Profile 1997)

Table 2. Genotoxicity of Benzene *In Vivo* (continued)

Species (test system)	End point	Results	Reference
Rat (bone marrow)	Chromosomal aberrations	+[b]	Anderson and Richardson 1981
Rat (bone marrow)	Chromosomal aberrations	+	Philip and Jensen 1970
Rat (bone marrow)	Chromosomal aberrations	+	Fujie et al. 1990
Rat (bone marrow)	Chromosomal aberrations	+	Hoechst 1977
Rat (bone marrow)	Chromosomal aberrations	–	Hoechst 1977
Chinese hamster (bone marrow)	Chromosomal aberrations	+	Siou et al. 1981
Rabbit (bone marrow)	Chromosomal aberrations	+	Kissling and Speck 1972
Rabbit (bone marrow)	Chromosomal aberrations	+	Kissling and Speck 1973
Human (lymphocytes)	Micronucleus increase	+	Robertson et al. 1991a
Human (occupational exposure/lymphocytes)	Chromosomal aberrations	(+)	Yardley-Jones et al. 1990
Human (occupational exposure/lymphocytes)	Chromosomal aberrations	+	Sasiadek et al. 1989
Human (occupational exposure/lymphocytes)	Chromosomal aberrations	–	Jablonická et al. 1987
Human (occupational exposure/lymphocytes)	Chromosomal aberrations	+	Forni et al. 1971a
Human (occupational exposure/lymphocytes)	Chromosomal aberrations	+	Ding et al. 1983
Human (occupational exposure/lymphocytes)	Chromosomal aberrations	+	Tough and Court Brown 1965
Human (occupational exposure/lymphocytes)	Chromosomal aberrations	+	Picciano 1979
Human (occupational exposure/lymphocytes)	Sister chromatid exchange	+	Popp et al. 1992
Human (occupational exposure/lymphocytes)	Chromosomal aberrations	+	Tompa et al. 1994
Human (occupational exposure/lymphocytes)	Chromosomal aberrations	+	Sasiadek 1992
Human (occupational exposure/lymphocytes)	Chromosomal aberrations	+	Sasiadek and Jagielski 1990
Mouse (spleen lymphocytes)	Increased polyploidy	+	Rithidech et al. 1987
Mouse (peripheral blood PCEs)	Micronuclei increase	+[c,d]	Luke et al. 1988a
Mouse (peripheral blood NCEs)	Micronuclei increase	+[d,e]	Luke et al. 1988a
Mouse (peripheral blood NCEs)	Micronuclei increase	+	Rithidech et al. 1988
Mouse[f] (bone marrow PCEs)	Micronuclei increase	+[g]	Suzuki et al. 1989[h]

Table 6.2 Continued: *In Vivo* Genotoxicity of Benzene (Table 2 from ATSDR Toxicological Profile 1997)

Table 2. Genotoxicity of Benzene *In Vivo* (continued)

Species (test system)	End point	Results	Reference
Mouse (bone marrow PCEs)	Micronuclei increase	+[d]	Ciranni et al. 1988
Mouse (pregnant/bone marrow PCEs)	Micronuclei increase	(+)	Ciranni et al. 1988
Mouse (fetus/liver cells)	Micronuclei increase	+	Ciranni et al. 1988
Mouse (bone marrow PCEs)	Micronuclei increase	+	Erexson et al. 1986
Mouse (bone marrow PCEs)	Micronuclei increase	+	Toft et al. 1982
Mouse (bone marrow PCEs)	Micronuclei increase	+	Harper et al. 1984
Mouse (bone marrow PCEs)	Micronuclei increase	+	Siou et al. 1981
Mouse (bone marrow PCEs)	Micronuclei increase	+[a]	Meyne and Legator 1980
Mouse (bone marrow PCEs)	Micronuclei increase	+	Hite et al. 1980
Mouse (bone marrow PCEs)	Micronuclei increase	+	Barale et al. 1985
Mouse (bone marrow PCEs)	Micronuclei increase	+	Au et al. 1990
Mouse (peripheral blood NCEs)	Micronuclei increase	+	Barale et al. 1985
Mouse (peripheral blood NCEs)	Micronuclei increase	+	Choy et al. 1985
Mouse (bone marrow PCEs)	Micronuclei increase	+	Diaz et al. 1980
Chinese hamster (bone marrow)	Micronuclei increase	+	Siou et al. 1981
Rat (lymphocytes)	Micronuclei increase	+	Erexson et al. 1986
Mouse (bone marrow)	Sister chromatid exchange	+	Tice et al. 1982
Mouse (bone marrow)	Sister chromatid exchange	+	Tice et al. 1980
Mouse (lymphocytes)	Sister chromatid exchange	+	Erexson et al. 1986
Mouse (pregnant/bone marrow)	Sister chromatid exchange	+	Sharma et al. 1985
Mouse (fetus/liver cells)	Sister chromatid exchange	+	Sharma et al. 1985
Rat (lymphocytes)	Sister chromatid exchange	+	Erexson et al. 1986
Human (occupational exposure/lymphocytes)	Sister chromatid exchange	–	Yardley-Jones et al. 1988
Human (occupational exposure/lymphocytes)	Sister chromatid exchange	–	Seiji et al. 1990
Mouse (bone marrow)	DNA synthesis inhibition	+	Lee et al. 1988
Rabbit (bone marrow)	DNA synthesis inhibition	+	Kissling and Speck 1972
Mouse (bone marrow)	RNA synthesis inhibition	+	Kissling and Speck 1972

Table 6.2 Continued: *In Vivo* Genotoxicity of Benzene (Table 2 from ATSDR Toxicological Profile 1997)

Table 2. Genotoxicity of Benzene *In Vivo* (continued)

Species (test system)	End point	Results	Reference
Rat (liver mitochondria)	RNA synthesis inhibition	+	Kalf et al. 1982
Rat (liver cells)	DNA adducts	+	Lutz and Schlatter 1977
Mouse (spermatogonia)	Sperm head abnormality	+	Topham 1980

[a]This result was observed following both oral and intraperitoneal exposure.
[b]This result was observed following both inhalation and intraperitoneal exposure.
[c]Increase in micronuclei was exposure duration-independent.
[d]Males affected to a significantly greater degree than females.
[e]Increase in micronuclei was exposure duration-dependent.
[f]Two strains of mouse were tested; Ms/Ae and CD-1. The result applies to both strains.
[g]This result was observed following both oral and intraperitoneal exposure; however, oral exposure produced the greater effect.
[h]The authors of this study did not report statistical comparisons of their results.

+ = Positive result; – = negative result; (+) = weakly positive result; DNA = deoxyribonucleic acid; NCEs = normochromatic erythrocytes; PCEs = polychromatic erythrocytes; RNA = ribonucleic acid

From ATSDR, 1997

6.2.2.3 Transplacental Genotoxicity

Transplacental cytogenetic events demonstrate that benzene or its metabolites are biologically active across the placental barrier. Clastogenicity of benzene in fetuses is correlated with the gestational day (GD) on which benzene is administered. Exposure on GD 14–15 appears to result in cytogenetic damage, while treatment after this period gives negative results. These times of sensitivity correspond to the stages of hematopoiesis development in rodents, with initiation beginning on GD 10 in the fetal liver and maximum activity by GD 12, followed by initiation of hematopoiesis in bone marrow.

A comparison of effects of benzene on micronucleated-PCE in bone marrow in virgin females, pregnant females (administered on GD 13) and their offspring at a single oral dose of 80 mg/kg (Ciranni et al., 1988) demonstrated that virgin females had a higher frequency of micronuclei than pregnant females, and data from fetuses suggested that benzene sensitivity in offspring was comparable to adult females. Ciranni et al. (1991) also administered single oral doses of benzene to male rats at concentrations of 0, 0.25, 0.5, and 1.0 mL/kg (0, 220, 439, and 878 mg/kg) and demonstrated dose-related increases in chromosome breaks, fragments, and exchanges in sperm relative to controls. Effects in bone marrow cells at 878 mg/kg peaked at 24 and 30 hours (approximately 20% aberrant cells vs. 1% in controls). Ning et al. (1991) treated timed-pregnant mice with a single i.p. dose of benzene at concentrations of 0, 109, 291, 437, or 874 mg/kg on GD 14, sacrifice was 21 hours post-injection. Benzene caused a significant ($p<0.01$) increase in micronucleated-PCE in fetal liver cells at doses of 219–874mg/kg, and in fetal liver cells and maternal bone marrow cells at 437 and 874 mg/kg. Xing et al. (1992) reported that both micronucleated-PCE and SCE in fetal liver were elevated at the highest dose in fetuses of CD-1 mouse dams treated with 0, 439, 878, and 1318 mg/kg i.p. on GD 14–15. The frequency of micronuclei was higher in fetal liver than in maternal bone marrow cells; however, benzene was toxic to maternal bone marrow cells but not to fetal liver. Treatment of pregnant ICR mice orally at concentrations of 50 or 75 mg/kg on GD 17–19 did not induce significant micronucleus formation in dams or fetuses (Harper et al., 1989). Treatment of males and non-pregnant females at the same doses demonstrated higher response in male sperm than in females, similar to the results of the Ciranni et al. studies performed at higher doses with exposure to pregnant females on GD 13.

6.2.2.4 DNA Damage

Measurements of single-strand breaks in DNA by single-gel electrophoresis (comet assay) were used by Plappert et al. (1994) to evaluate benzene-induced damage to DNA in peripheral blood of female BDF1 mice exposed to 0, 100, 300, and 900 ppm, 6 hours/day, 5 days/week for 4 weeks. DNA damage was seen in liver and bone marrow after 5 days at 100 ppm; increased damage in peripheral blood was not recorded until 4 weeks at 100 ppm. Maximal damage was seen after 5 days at 300 ppm, and little increase was observed with longer exposure. Damage returned to or approached control levels after a 24- to 48-hour post-treatment recovery period, following 5-day exposure. After 4 weeks exposure with a 24- to 48-hour recovery period, repair was not complete in blood of 300-ppm mice nor in liver of 100- and 300-ppm mice. Tuo et al. (1996) used the alkaline comet assay to evaluate the role of CYP 2E1 protein in benzene genotoxicity. Increased levels of DNA damage allowed DNA from lysed treated cells to move more freely when subjected to an electric field, producing a “comet tail” after fluorescence staining. Six hours after a single oral dose of 40, 200, or 450 mg/kg body weight, male mice exhibited increased dose-related comet-tail lengths in bone marrow cells at all dose levels, and in peripheral lymphocytes at 200- and 450-mg/kg doses. Pretreatment with propylene glycol,

which inhibits CYP 2E1, reduced the increase in tail length by 50% in both cell types. These results corroborate *in vivo* findings of Valentine et al. (1996) for absence of increased incidence of micronuclei in mice lacking CYP 2E1.

6.2.2.5 DNA Adducts

Arfellini et al. (1985) and Mazzullo et al. (1989) reported that benzene binding to nucleic acids and proteins in rodents was low in most organs, with greatest activity in liver and negligible effect in lung. Labeling of RNA and protein was an order of magnitude greater than labeling of DNA. Mazzullo et al (1989) observed a linearity of dose response for benzene (labeled with ^{3}H or ^{14}C) DNA-binding in the rat liver at very low doses (6.23×10^{-6} to 6.23×10^{-1} mmole/kg), with a saturation of benzene binding activity at 6.23 mmole/kg, approximately equivalent to 60 ppm. A single DNA adduct was detected by high-pressure liquid chromatography (HPLC) in benzene-treated liver DNA, but in the absence of analytical identification, this effect may be the result of protein contamination. Parodi et al. (1989), in a paper that included Mazzullo as coauthor, used these adduct data, in conjunction with animal and human data, to propose that benzene toxicity can best be described by a sigmoid curve, rather than linear, that appears sublinear below 10—30 ppm and flattens above 50—100 ppm. DNA adducts of phenol, hydroquinone, or benzoquinone have been reported *in vitro* (Reddy et al., 1990; Lévay et al., 1993; Bodell et al., 1993). However, Reddy et al. (1990), using the P^{1} enhanced ^{32}P-postlabeling assay, did not detect DNA adducts in rat bone marrow, Zymbal gland, liver, or spleen, which are target organs for benzene-induced toxicity, after daily oral gavage treatments of phenol or a 1:1 mixture of phenol and hydroquinone. Great care was exercised to separate DNA adducts from contaminating protein adducts. Reddy et al. (1994) also did not detect adducts in liver, bone marrow, or mammary glands of mice after daily i.p. injections of 500 mg/kg benzene in corn oil for 4 days. Subsequently, Pathak et al. (1995), using a range of benzene concentrations from 25 to 880 mg/kg and a variety of injection schedules for periods of up to 14 days, identified one major and two minor DNA adducts in bone marrow of mice receiving 440 mg/kg, i.p. twice daily for 3 days. Effects were not seen at single doses up to 880 mg/kg. Co-chromatography indicated that adducts were identical to those seen after *in vitro* treatment of bone marrow with hydroquinone.

Accelerator mass spectrometry (AMS), a nuclear physics technique for detecting cosmogenic isotopes, has been adapted by Turteltaub and colleagues (1993) to detect DNA adducts induced by low doses of ^{14}C-labelled carcinogens, at sensitive levels of 1—10 adducts per 10^{12} nucleotides. Creek et al. (1997) examined adduct formation in B6C3F1 male mice given ^{14}C-benzene at doses ranging from 700 pg/kg to 500 mg/kg body weight. Tissues, DNA, and proteins were analyzed by AMS between 0 and 48 hours post-dose. Liver DNA adducts peaked at 0.5 hour post-dose, while DNA adducts in bone marrow peaked at 12–24 hours. A larger percentage of available dose in bone marrow bound to DNA than to liver. Protein adducts were 9- to 43-fold greater than DNA adducts. Both DNA and protein adduct formation were linear over the dose range. The AMS technique was also used by Mani et al. (1999) to demonstrate differences in benzene-induced adduct formation between mouse strains and Fischer rats. At a dose of 5 µg/kg, the magnitude of ^{14}C-benzene-induced DNA and protein adducts in bone marrow was greater in B6C3F1 mice > DBA/2 mice > C57Bl/6 mice, and lowest in Fischer rats. AMS is extremely sensitive to adduction at low exposure levels, but it is expensive and of limited availability. Further, the occurrence of transient, very low levels of adducts may not be biologically significant.

Although cytogenetic changes induced by benzene in animals are similar to those reported in humans, there are no reliable animal models for benzene leukemogenesis. Benzene does

induce solid tumors in animals in the Zymbal gland of rats, as well as forestomach, preputial gland, oral and nasal tumors, and mammary tumors; humans do not get benzene-induced solid tumors. DNA adducts have not been identified in target organs for tumors, but Angelosanto et al. (1996) did detect chromosome damage, expressed as increased incidence of micronucleated cells in primary cultures of epithelial cells from rat Zymbal explants, following *in vivo* oral exposure to benzene for 3 days at doses of 12.5—250 mg/kg/day in female Sprague Dawley rats and 1—200 mg/kg/day in male Fischer 344 rats.

6.2.2.6 Summary of genotoxic data

The genotoxic potential of benzene and its metabolites has been studied extensively. More than 220 publications with original data have been evaluated and reviewed by regulatory organizations (ATSDR, 1993, 1997; IRIS, 1998; EPA-NCEA, 1998; ECB, 2003) for mutagenic significance and in relation to benzene-induced cancer. *In vitro* studies have demonstrated that benzene does not generally induce gene mutation in standard bacteria and *in vitro* mammalian cell systems, but that metabolites produced by exogenous or endogenous activation can produce positive results in some systems. Benzene exposure did result in structural and numerical chromosome abnormalities in mammalian cells in culture or in laboratory animals. Significant chromosome aberrations in humans usually occurred at exposure levels sufficient to produce toxicity to the hematopoietic system. Cytogenetic effects were expressed as chromosome breakage and aberrations, increased incidence of micronucleated polychromatic and/or normochromatic erythrocytes in bone marrow or peripheral blood, and as sister chromatid exchanges. DNA damage, measured by single-strand breaks, was also identified in blood of exposed mice. Whysner (2000) and Whysner et al. (1995) suggested that the mechanism for benzene-induced clastogenicity and leukemogenesis involves inhibition of topoisomerase II, an enzyme involved in DNA replication. Formation of a stable benzene-topoisomerase II-DNA complex could produce the SCE, nonhomologous recombination, gene deletion, and rearrangements seen in benzene genotoxicity. Other proposed mechanisms have included DNA-reactive benzene metabolites forming adducts or cross-links, oxidative DNA damage leading to strand breaks and missense mutations, and aneugenesis due to damage to components of mitotic apparatus.

6.2.3 Reproductive and Developmental Toxicity

6.2.3.1 Reproductive Toxicity

The potential for benzene to affect the reproductive system is available from animal studies found in the literature. These studies include a female rat fertility study (Kuna et al., 1992), a dominant lethal assay in rats (API, 1980), the evaluation of reproductive organs in repeat-dose systemic toxicity studies (Wolf, 1956; Ward et al., 1985; NTP, 1986), and two early Russian studies involving exposure of rats prior to impregnation and during pregnancy (Gofmekler, 1968; Vozovaya, 1975, 1976).

The ability of benzene to affect the process of producing viable gametes in sexually mature animals has been reported in several studies. In Kuna, et al. (1992), the effects of benzene (99.96% purity) exposure on fertility in female Sprague Dawley rats exposed at vapor concentrations of 0, 1, 30, and 300 ppm (0, 3.2, 96, and 958 mg/m^3), 6 hours/day, 5 days/week for 10 weeks premating and mating, then daily from gestation day (GD) 0–20 and lactation days 5–20 were assessed. No treatment-related effects were observed on maternal mortality, estrus cycle, body weight and body-weight changes, physical parameters, pregnancy rate, length of

gestation, and number of live and dead pups at birth and sex distribution. No effects were observed in pup survival. Reduced body weight and absolute organ weight trends were observed in 21-day-old pups from the 30- and 300-ppm groups, but the only statistically significant result was reduced liver weight in the female pups of 300-ppm dams. The authors did not assign a lowest-observed-adverse-effect level (LOAEL) or a no-observed-adverse-effect level (NOAEL); the observed effects were limited to relatively minor effects in the pups and were not related to reproduction, so the NOAEL for reproduction is 300 ppm. The pup results are discussed further in the developmental toxicity section (see Section 6.2.3.2). Two earlier Russian studies (Gofmekler 1968 and Vozovaya 1975, 1976) also investigated the effect of benzene exposure on reproductive performance, although these studies have previously been determined to be unreliable due to poor documentation (ECB 2003). Gofmekler (1968) exposed female rats to 3–210 ppm benzene, 24 hours/day, 10–15 days prior to mating, and for 3 weeks during gestation. A complete absence of litters was observed in the top dose females (210 ppm), but not at lower concentrations (3 to 20 ppm). Differences in individual organ weights of the dams were indicated for all exposure levels, but no impairment of weight or malformations were reported in the newborns. There is insufficient information to explain the absence of litters in the 210-ppm dose group. Vozovaya (1975, 1976) exposed female rats to benzene to 0, 116, or 559 ppm (0, 370, 1783 mg/m^3) for 4 months prior to mating and through gestation, although no information is available on the daily and weekly duration of exposure. Decreased pup body weight was reported in both exposure groups, but no malformations were observed at 116 ppm or 559 ppm. Given the questionable reliability of both the Gofmekler (1968) and Vozovaya (1975, 1976) studies, the primary study available to assess reproductive performance in animals is the Kuna 1992 study. While there were limited pup effects observed in the Kuna 1992 study, and reduced liver weight in female pups of top dose dams, the study suggests that benzene exposures up to 300 ppm did not affect female reproductive parameters.

The ability of benzene exposure to affect male reproductive processes can be inferred from an inhalation dominant lethal study in which male rats were exposed to benzene at concentrations of 1–300ppm for 10 weeks (through one cycle of spermatogenesis). Following this exposure, the male rats were then mated to untreated female rats, and the pregnant female rats were sacrificed on GD 16 for determination of dominant lethal effects. No effects on reproductive performance were reported, although 2/20 males exposed to 300 ppm had microscopically observed testicular lesions (API, 1980). The usefulness of dominant lethal studies in understanding male reproductive toxicity is limited, in that sperm parameters are not determined, and the pregnant female rats are not allowed to deliver, so the viability of the offspring is not known.

Evaluations of reproductive organs in subchronic inhalation studies include a publication by Wolf (1956) that reported moderately increased testicular weight in rats exposed to 6600 ppm (21,084 mg/m^3) benzene for 13 weeks but not in rats exposed to 88 ppm (287 mg/m^3) or 2200 ppm (7,172 mg/m^3) for 30 weeks, 4400 ppm (14,344 mg/m^3) for 5 weeks, or to 9400 ppm (30,644 mg/m^3) over 1–19 days. Male guinea pigs exposed to 88 ppm for approximately 9.6 months had slight increases in testicular weight, but exposure for 4 weeks had no effect. Rabbits showed slight degeneration of seminiferous tubules after exposure to 88 ppm for approximately 8.5 months. A 13-week inhalation study (Ward et al., 1985) employed Sprague Dawley rats and CD-1 mice exposed to benzene concentrations of 0, 10, 30, and 300 ppm (0, 32, 96, and 958 mg/m^3). Body weights of both species were unaffected, but mice exposed to 300 ppm exhibited statistically significant decreases in testes weight at days 28, 56, and 91; decreased testes/body-weight ratio at days 56 and 91; and testicular atrophy (7/10 mice), decrease in spermatozoa in epididymal ducts (6/10 mice), and minimal to moderate increase in abnormal sperm forms (9/10 mice) at terminal sacrifice after 91 exposures. Four in 10 female

mice in the 300-ppm group had bilateral ovarian cysts after 91 days of exposure. Rats showed no evidence of damage to reproductive organs. In the National Toxicology Program (1986), benzene was evaluated for toxicity over 90 days and 2 years in F344 rats and B6C3F1 mice at oral gavage doses of 0 and 25–600 mg/kg/day, 5 days/week for 90 days; and 0, 5, 100, and 200 mg/kg/day for male rats, or 0, 25, 50, and 100 mg/kg/day for female rats and all mice for 2 years. No effects were seen in reproductive organs in either species treated for 90 days or in rats treated for 2 years. Ovarian lesions ranging from atrophy to neoplasia were observed in mice treated for 2 years, although no dose response was established, with a higher incidence of lesions occurring in the lowest dose (25 mg/kg/day).

Spano et al. (1989) examined effects on mouse germ cells (C57Bl/Cne x C3H/Cne F1 male mice) using flow cytometry DNA content measurements on testicular monocellular suspensions, following a single oral dose by gavage of 0, 1, 2, 4, 6, and 7 mL/kg (approx. 0, 878, 1756, 3512, 5268, and 6146 mg/kg) benzene. Treatment did not affect body or testes weights, but did alter the ratio of testicular cell types at the higher doses, suggesting acute toxicity to differentiating spermatogonia, with substantial to complete recovery by 70 days post-exposure. Mice exposed to benzene in intraperitoneal (ip) doses of 0.1–1.0 mL/kg (88–878 mg/kg) daily for 5 days exhibited statistically significant dose-related increases in sperm-head abnormalities at 0.4 mL/kg and higher, with peak effect at 0.6 mL/kg (Topham, 1980). Benzene also caused dose-related increases in chromosome aberrations in sperm of mice following single oral doses of 0.25, 0.5, or 1.0 mL/kg benzene (Ciranni et al., 1991)

The ability of benzene to affect female reproductive fertility appears limited. The Kuna et al. study suggests 300 ppm to be a NOAEL when exposures are limited to 6 hours/day. Effects on male fertility have been assessed only indirectly. Male rats appear to be relatively resistant to adverse effects of benzene exposure on fertility, as measured by insemination of females and effects on reproductive organs. Male mice appear to be more sensitive than male rats in terms of effects on the testes, and CD-1 mice appear to be more sensitive than B6C3F1 mice, although differences in exposure routes complicate this comparison. There are no studies available where both parental animals have been exposed to benzene prior to mating.

6.2.3.2 Developmental Toxicity

Possible toxic effects of benzene during the embryonic and fetal periods are included under the heading of developmental toxicity. Transplacental genotoxicity is discussed in Section 6.2.2.3 of the genotoxicity section. Data are available on developmental effects of benzene during embryogenesis in rats, mice, and rabbits, by the inhalation and oral routes - see Table 6.3, from EPA IRIS (U.S. EPA 1998b). Studies describing exposures during both the embryonic and fetal period, with subsequent examination of the fetuses (as would be done under current testing guidelines), are not available.

Inhalation

Kuna and Kapp (1981) exposed pregnant Sprague Dawley rats to benzene concentrations of 0, 10, 50, and 500 ppm (0, 32, 160, and 1600 mg/m^3), 7 hours/day on GD6–15, with maternal sacrifice at GD20. Hematological evaluations performed on GD 5 and 20 included red blood cells (RBC), white blood cells (WBC), and differential counts. There were no maternal deaths, illness, or hematologic changes. During GD5–15, decreased maternal body weight gains were observed in the 50- and 500-ppm exposed groups, and increased body-weight gains were observed in the 10- and 500-ppm groups during GD15–20. No differences from controls were observed in the number of implantation sites per number of corpora lutea; incidences of

resorbed, dead, or live fetuses; or fetal sex distribution. Fetal crown-rump length was decreased in the 500ppm group, and the mean body weights of live fetuses were decreased in the 50 and 500ppm groups. Abnormalities were observed in four litters exposed to 500 ppm: one fetus with exencephaly, one fetus with angulated ribs, and two fetuses in two separate litters with ossification of forefeet out of sequence. Other skeletal variations included delayed ossification of skull, vertebral column, ribcage, pelvic girdle, and extremities, and fewer tail-bones than controls. Statistical analyses of skeletal variants and abnormalities were based on the fetus rather than the litter. The maternal and developmental LOAEL was 50ppm (160mg/m^3), and the NOAEL was 10ppm (32mg/m^3). Developmental effects were observed at concentrations that caused maternal toxicity.

As discussed in the Reproductive Toxicity section, a separate study by Kuna (1992) evaluated some developmental parameters of offspring of female Sprague Dawley rats exposed at vapor concentrations of 0, 1, 30, and 300ppm (0, 3.2, 96, and 960mg/m^3), 6 hours/day, 5 days/week for 10 weeks premating and mating, then daily on GDs 0–20 and lactation days 5–20. No treatment-related effects were observed on maternal mortality, estrus cycle, body weight and body-weight changes, physical parameters, pregnancy rate and length of gestation, and number of live and dead pups at birth and sex distribution. No effects were observed on pup survival. Reduced body weight and absolute organ weight trends were observed in 21-day-old pups from the 30 and 300ppm groups, but the only statistically significant result was reduced liver weight in the female pups of 300ppm dams. Therefore, the developmental toxicity NOAEL from this study appears to be 300 ppm for male pups and 30 ppm for female pups. While the Kuna (1992) study is somewhat limited in developmental parameters (e.g., no skeletal growth parameters were reported), an important aspect of the study is that it exposed the developing rats throughout gestation and through lactation (days 5–20), which is an important period of development for newborn rats. Kuna (1992) reported no effect on newborn pup weight, suggesting that there would not be additional growth decrements due to exposure during the fetal period up to 300 ppm.

In a study by Coate et al. (1984), inhalation doses of 0, 1, 10, 40, and 100 ppm were administered to Sprague Dawley rats during GDs 6–15,. No adverse effects were reported in maternal body-weight gain, resorption rate, or ability to deliver offspring. Fetuses in the 100-ppm group exhibited significant decreases ($p \leq 0.05$) in fetal body weight, and statistically non-significant decreases in fetal length. Delays in ossification of skull, vertebral centra, and extremities occurred at 100 ppm. The investigators concluded that benzene was weakly toxic to the fetus at 100 ppm, a concentration that was not toxic to the dam. The developmental LOAEL was 100ppm, and the NOAEL was 40 ppm. A prior study conducted for the American Petroleum Institute (API, 1982), reported statistically significant increases in resorptions at both doses of 10 and 40 ppm, with no other maternal or fetal effects. However, control rats appeared to have an abnormally low resorption incidence, making the apparent LOAEL of 10ppm questionable, especially considering subsequent results by Coate et al. (1984). Green et al. (1978) reported that benzene concentrations of 100, 300, and 2200 ppm on GDs 6–15, with sacrifice on GD 21, were maternally toxic to rat dams at 2200 ppm (body weight reduced from GD8-20). These concentrations did not induce malformations but did induce fetal toxicity, manifested as skeletal variants in all dose groups at concentrations that were not maternally toxic. In the 2200-ppm group, the number of females with unossified sternebrae was significantly increased over males, suggesting increased sensitivity to benzene-induced effects.

Investigators who exposed rats to benzene for 24 hours/day reported increased toxicity for similar endpoints. Hudak and Ungváry (1978) administered benzene to CFY rats in a single dose at 313 ppm (1000 mg/m^3), 24 hours/day on GDs 9–14, resulting in statistically significant

decreases in maternal weight gain, fetal body weight, and percentage of weight-retarded fetuses, as well as increased incidence of extra ribs and fused sternebrae. In a follow-up study (Tátrai et., 1980), concentrations of 0, 47, 140, 465, and 930 ppm (0, 150, 450 1500, and 3000 mg/m^3) benzene were administered, 24hours/day, on GDs 7–14. Decreased maternal body-weight gains (not corrected for gravid uterus) were concentration dependent at doses of 47–465 ppm, but decreases were less at 930 ppm. Fetal body weights were decreased at all doses, and fetal loss (30%–40% total implantation sites), and skeletal variations were increased at 140 ppm and above.

When rats were exposed to benzene (400 mg/m^3) combined with toluene (100 mg/m^3) or xylene (600 mg/m^3), 24 hours/day on GDs 7–15, sacrificed on GD 21, decreased maternal weight gain and retardation of fetal and skeletal growth were observed, but no increases in skeletal anomalies, malformations or abnormal survivors occurred. Developmental effects of combined solvents were not additive. However, each solvent, when administered along with acetylsalicytic acid (ASA), enhanced expression of ASA-induced malformations (Ungváry and Tátrai, 1985).

Table 6.3: Inhaltion Developmental Toxicity of Benzene (Table 3 from EPA IRIS 1998)

Table 3. Developmental toxicity of inhaled Benzene in test animals

Strain/species	No. of dams/group	Exposure	Effects		Effect levels maternal/developmental (mg/m^3)	Reference
			Maternal	Developmental		
Sprague-Dawley rat	14–15 exposed 11 controls	0, 32, 160, or 1597 mg/m^3, 7 hr/day on GD[b] 6–15; sacrifice on day 20	Decreased body weight and body weight gain at 160 and 1597 mg/m^3, day 5–15; dose-related[c]	Decreased mean live body weight at 160 and 1597 mg/m^3, day 20[d]; decreased crown–rump distance, 1597 mg/m^3 [d]; skeletal and visceral (brain) abnormalities at 160 and 1597 mg/m^3, increased incidence of malformations at 1597 mg/m^3	LOAEL: 160/160 NOAEL: 32/32	Kuna and Kapp, 1981
Sprague-Dawley rat	35–37 exposed 32–34 controls	0, 3.2, 32, 128, or 319 mg/m^3, 6 hr/day on GD 6–15; sacrifice on day 20	None in any group	Decreased body weight at 319 mg/m^3 ($p \leq 0.05$); variants in all but one group (including controls), not dose-related; no increase in incidence of malformations	LOAEL: NA/319 NOAEL: NA/128	Coate et al., 1984
Sprague-Dawley rat	14–18	0, 319, 958, or 7028 mg/m^3, 6 hr/day on GD 6–15; killed on day 21	Decreased body weight gain at 7028 mg/m^3 ($p < 0.01$)	Decreased body weight and length at 7028 mg/m^3 ($p < 0.05$); increased skeletal variants all exposure groups ($p < 0.05$ at 319 and 7028 mg/m^3; females more sensitive than males); no increase in incidence of malformations	LOAEL: 7,028/319 NOAEL: 958/NA	Green et al., 1978
Sprague-Dawley rat	No data	32 or 128 mg/m^3, 6 hr/day on GD 6–15	None observed	Increased resorptions at 32 and 128 mg/m^3; no increase in incidence of malformations	LOAEL: NA/32[e] NOAEL: 128/NA	Litton Bionetics, 1977
Rat	5–12	1.0–670 mg/m^3 24 hr/day, 10–15 days before mating and throughout pregnancy	No data	Tendency toward decreased litter sizes at 64 mg/m^3; complete absence of litters at 670 mg/m^3	LOAEL: ND NOAEL: ND	Gofmekler, 1968

Table 6.3 Continued: Inhaltion Developmental Toxicity of Benzene (Table 3 from EPA IRIS 1998)

Table 3. Developmental toxicity of inhaled Benzene in test animals (continued)

Strain/species	No. of dams/group	Exposure	Effects		Effect levels maternal/developmental (mg/m^3)	Reference
			Maternal	Developmental		
CFY rat	19 exposed 28 controls	0 or 1000 mg/m^3, 24 hr/day on days 9–14 of pregnancy	Decreased body weight gain ($p< 0.01$)	Decreased body weight ($p<0.01$) and growth retardation ($p< 0.05$); retarded skeletal development and increased incidence of extra ribs and fused sternebrae ($p<0.05$ for both); no increase in incidence of malformations	LOAEL: NA NOAEL: NA	Hudak and Ungvary, 1978
CFY rat	20–22 exposed 48 controls	0, 150, 450, 1500, or 3000 mg/m^3, 24 hr/day on GD 7–14; killed on day 21	Decreased body weight gain at ≥150 mg/m^3 ($p<0.001$), somewhat dose-related; liver/body wt. increased ($p<0.05$ or 0.01)	Decreased body weight at ≥150 mg/m^3 ($p<0.001$), increased resorptions and skeletal and weight retardation ($p<0.01$–0.05); effects not dose-related; no increase in incidence of malformations	LOAEL: 150/150 NOAEL: NA	Tatrai et al., 1980
CFY rat	17	400 mg/m^3, 24 hr/day on GD 7–15	Decreased body weight gain ($p<0.001$); increased relative liver wt. ($p<0.05$)	Retarded weight gain ($p< 0.01$); skeletal growth retardation ($p<0.001$)	LOAEL: NA NOAEL: NA	Ungvary, 1985

Table 6.3 Continued: Inhaltion Developmental Toxicity of Benzene (Table 3 from EPA IRIS 1998)

Table 3. Developmental toxicity of inhaled Benzene in test animals (continued)

Strain/species	No. of dams/group	Exposure	Effects		Effect levels maternal/developmental (mg/m^3)	Reference
			Maternal	Developmental		
Swiss-Webster mouse	5	16, 32, or 64 mg/m^3, 6 hr/day on GD 6–15	None observed	16-day-old fetus: no effect on hematological parameters 2-day-old neonates: reduced circulating erythroid precursor cells (all concentrations) ($p<0.05$ at 64 mg/m^3); increased hepatic hematopoietic blast cells, lymphocytes, and granulopoietic precursor cells and decreased hepatic erythropoietic precursor cells (all $p<0.05$ at 64 mg/m^3); 6-week-old adult: similar pattern of enhanced granulopoiesis (64 mg/m^3)	LOAEL: NA/64 NOAEL: 64/32	Keller and Snyder, 1988
Swiss-Webster mouse	8	(a) 32 mg/m^3 benzene GD 6–15 (b) 5% ethanol in drinking water ad lib (c) 32 mg/m^3 benzene + 5% ethanol (d) air + distilled water	No data	Bone marrow samples from 6-week-old offspring: protocols (a) and (b) caused changes in CFU-E counts, males only; protocol (c) caused changes in CFU-E counts, females only[f]	LOAEL: NA NOAEL: NA	Corti and Snyder, 1996
CF-1 mouse	35–37	0 or 1597 mg/m^3 ppm, 7 hr/day on GD 6–15; killed on day 18	None	Decreased body weight ($p<0.05$), "significantly" increased skeletal variants of fetuses; no increase in incidence of malformations but was toxic to fetuses	LOAEL: NA NOAEL: NA	Murray et al., 1979

Table 6.3 Continued: Inhaltion Developmental Toxicity of Benzene (Table 3 from EPA IRIS 1998)

Table 3. Developmental toxicity of inhaled Benzene in test animals (continued)

Strain/species	No. of dams/group	Exposure	Effects		Effect levels maternal/developmental (mg/m^3)	Reference
			Maternal	Developmental		
CFLP mouse	15 exposed 115 controls	0, 500 or 1000 mg/m^3, 24 hr/day on GD 6–15	Not mentioned	Weight and skeletal retardation, both concentrations ($p< 0.05$), somewhat dose-related	LOAEL: ND/500 NOAEL: NA/NA	Ungvary and Tatrai, 1985
New Zealand rabbit	20	0 or 1597 mg/m^3, 7 hr/day on GD 6–18; killed on day 29	None	Statistically significant decrease in minor skeletal variants, lumbar spurs and proportion with 13 ribs, in exposed fetuses	LOAEL: NA NOAEL: NA	Murray et al., 1979
New Zealand rabbit	11 or 15 exposed 60 controls	0, 500 or 1000 mg/m^3, 24 hr/day on GD 7–20	Decreased weight gain and increased relative liver wt. at 1000 mg/m^3 ($p< 0.05$)	Decreased body weight and increased abortions and skeletal variants at 313 ppm ($p< 0.05$ for all effects)	LOAEL: 1,000/1,000 NOAEL: 500/500	Ungvary and Tatrai, 1985

[a]Conversion factors, 1 ppm = 3.26 mg/m^3; 1 mg/m^3 = 0.31 ppm
[b]GD = gestation day
[c]Statistically different from control as determined by pairwise multiple comparison procedures
[d]Statistically different from control as determined by Cochran's approximation to *t (t')*
[e]ND = not determined; NA = not applicable
[f]Data from abstract; no other details available

From IRIS, 1998

Oral

In a 1979 meeting abstract, Nawrot and Staples reported that benzene administered at doses of 0.3, 0.5, and 1.0 mL/kg to CD-1 mice on GDs 6–15 produced maternal lethality, increased embryonic lethality at 0.5 and 1.0 mL, and significantly decreased fetal body weight at all three doses. No malformations were seen. Exposure of pregnant Sprague Dawley rats to benzene orally by gavage at doses of 0, 50, 250, 500, and 1000 mg/kg/day on GDs 6–15 resulted in decreased food consumption, decreased maternal body weight, and body-weight gain at 500 and 1000 mg/kg/day, and increased incidence of alopecia at 1000 mg/kg/day. Developmental toxicity was limited to decreased fetal body weight at 500 and 1000 mg/kg/day; no external malformations were observed, and skeletal and soft-tissue evaluations were not performed (Exxon Chemical Co., 1986). Using the Chernoff/Kafloff screening procedure, Seidenberg et al. (1986) demonstrated that benzene, administered orally at 1300 mg/kg/day to ICR/SIM mice on GDs 8–12, had no effect on maternal body weight but did produce significantly lower neonatal body weight on days 1 and 2 after birth.

Exposure of mice and rabbits to benzene induced developmental effects similar to those seen in rats. CF-1 mice exposed to 0 or 500 ppm (1597 mg/m^3), 7 hours/day, on GDs 6–15, with sacrifice on GD 18, produced fetuses with decreased body weight and significantly increased skeletal variants but no malformations in the absence of maternal toxicity. New Zealand White (NZW) rabbits exposed to the same concentrations on GDs 6–18, with sacrifice on GD29, produced fetuses with statistically significant decreases in minor skeletal variants (lumbar spurs and increased proportion of fetuses with 13 ribs) and no maternal toxicity (Murray et al., 1979). Ungváry and Tátrai (1985) exposed CFLP mice and NZW rabbits to 0, 156, and 313 ppm (0, 498, and 1000 mg/m^3) benzene, 24 hours/day on GDs 6–15 (mice) and GDs 7–20 (rabbits). Moderate concentration-dependent maternal toxicity was reported in mice, and fetuses showed weight and skeletal retardation at both concentrations ($p<0.05$), producing a developmental LOAEL of 156 ppm in the presence of maternal toxicity. In rabbits, does showed concentration-dependent decreased weight gain and increased relative liver weight at 313 ppm. Developmental effects included increased incidence of abortion, a concentration-dependent increase in the percentage of dead or resorbed fetuses, decreased fetal body weight, and skeletal variants at 313 ppm.

6.2.3.3 Summary of Reproductive and Developmental Toxicity

The reproductive toxicity effects of benzene appear to be limited. The study by Kuna (1992) showed no effect on reproduction in female rats. Effects on male fertility have been assessed only indirectly. Male rats appear to be relatively resistant to adverse effects of benzene exposure on fertility, as measured by insemination of females and effects on reproductive organs. Male mice appear to be more sensitive than male rats in terms of effects on the testes, and CD-1 mice appear to be more sensitive than B6C3F1 mice, although differences in exposure routes complicate this comparison. There are no studies available where both parental animals were exposed to benzene prior to mating.

The developmental toxicity database indicates that benzene at high exposure concentrations typically causes maternal toxicity or stress, and can affect mammalian development processes. However, the majority of the reported effects suggests a nonspecific, generalized toxicity to the embryo, rather than toxicity to a specific developmental process, because there is no specific pattern of malformations associated with exposure. The major effects reported include decreased fetal body weight, decreased crown rump length, delayed skeletal development, and

increased resorptions. The effects were frequently associated with maternal toxicity or stress, such as maternal weight-gain effects and diet effects. These parameters suggest a general toxicity leading to growth retardation and delayed maturation, but they do not appear to be particularly sensitive and at levels considerably higher than those related to cancer risk.

6.2.4 Transplacental Effects

6.2.4.1 Carcinogenesis

Maltoni et al. (1989) exposed pregnant Sprague Dawley rats to 200 ppm benzene from GD 12 through lactation (dams and pups) and for an additional 85 weeks (pups for 104 weeks total). Increased incidence of Zymbal gland tumors was observed in female offspring, two-fold greater than the incidence among dams (exposed for 85 weeks total). Increases in exposure time by 20% resulted in a two-fold increase in tumor response, making it unclear whether the increased rate reflects increased overall exposure or differential susceptibility of the fetus and weanling.

6.2.4.2 Hematopoietic Toxicity

In mice, hematopoiesis is initiated in fetal liver on GD 10, peaks at GD 12—13, and continues through GD 14–15, as initiation in bone marrow increases. Snyder and coworkers evaluated *in utero* and neonatal effects of benzene on the developing hematopoietic system. Initially, pregnant Swiss Webster mice were exposed to vapor concentrations of 0, 5, 10, and 20 ppm (0, 16, 32, and 64 mg/m^3), 6 hours/day on GD 6–15 (Keller and Snyder, 1986). Animals were sacraficed on GD 16 (two fetuses/sex/litter were examined), postnatal day 2 (two neonates/sex/litter) and 6 weeks postnatal (one adult/sex/litter) for measurement of hematopoietic progenitor cells—CFU-E (erythropoietic precursor cells), BFU-E (blast cells), and GC-CFU-C (granulopoietic precursor cells) from livers of fetuses and neonates, and bone marrow and spleen from adults. Additionally, 10-week-old offspring from the 10-ppm group and concurrent controls were exposed to 10 ppm benzene for 2 weeks, sacrificed, and bone marrow and spleen were examined. No maternal or non-hematopoietic developmental toxicity occurred at any dose level. Benzene treatment *in utero* induced hematopoietic alterations in offspring that persisted for at least 10 weeks after birth. Responses were typically biphasic: BFU-E cells were increased in 16-day-old fetuses (both sexes) at 5 and 10 ppm. CFU-E cells were increased at 5 and 10 ppm and decreased at 20 ppm in fetuses, increased and decreased at 10 ppm (analyses from different animals) and increased at 20 ppm in male neonates, and decreased in bone marrow and increased in spleen at 10 ppm in adult males. Liver GM-CFU-C cells were decreased at 10 ppm (males only) and increased at 20 ppm in neonates. Among mice exposed to 10 ppm *in utero* and to 10 ppm benzene as adults for 2 weeks, decreased bone marrow CFU-E (males only) and splenic GM-CFU-C cells were observed. For mice exposed to air *in utero* and 10 ppm benzene for 2 weeks as adults, no change in bone marrow or splenic CFU-E, but significant decreases in splenic GM-CFU-C (females only), were observed. The LOAEL of 5 ppm (16 mg/m^3), based on the statistically significant changes in BFU-E and CFU-E in 16-day-old fetuses, presents a high degree of uncertainty as to whether effects are truly adverse (IRIS, 1998). The pattern of hematopoietic response was variable at different ages; only five pregnant mice per dose group were exposed to benzene, and only two fetuses, two neonates, and one adult F1 mouse/sex/litter were examined. The other offspring were probably evaluated for RBC, WBC, blood cell differentials, hemoglobin levels (Hgb), and number of liver cells in the hematopoietic differentiating pool (DDP) later reported by Keller and Snyder in 1988 (ATSDR, 1998). The 6-week-old progeny were evaluated based on peripheral

WBC and RBC counts, Hgb and smears from femur bone marrow or spleen for number of cells in DDP. No changes in hematopoietic parameters were seen in livers of 16-day-old fetuses, in contrast to effects on CFU reported in 1986. The authors concluded that benzene-induced hematotoxicity in offspring of mice exposed during pregnancy was evidenced by reduction in number of early nucleated red cells in peripheral blood of 2-day-old neonates at all exposure levels, and by increases in the number of dividing cells granulocytes in the livers of 2-day-old neonates and spleens of 6-week-old adults (20 ppm). The only clearly dose-related response was a decrease in early nucleated red cells in peripheral blood of 2-day-old neonates (statistically significant at 20 ppm), present only in very young animals and not in 8-week-old adults. In reviewing these Keller and Snyder studies (1986, 1988), Irons (2001) concluded that these studies did not meet the minimal criteria necessary for use in risk assessment, citing the variability of data, also addressed by IRIS (1998), the absence of a dose relationship, and the facts that the biological significance of the endpoints has not been established and none of the findings correlate with significant adverse health effects. Using exposure at 10 ppm to age-matched male, virgin female, and pregnant Swiss Webster mice, 6 hours/day for 10 consecutive days (GD 6–15 for pregnant mice) and treatment of one-half of all mice with 5% ethanol in drinking water, Corti and Snyder (1996) evaluated the influence of gender, development, pregnancy, and ethanol consumption on hematotoxicity of inhaled benzene. On Day 11, bone marrow cells from adults and liver cells from fetuses were examined for CFU-E and bone marrow cells isolated from 6-week-old offspring of exposed mice that were allowed to deliver. Depression of CFU-E cells was seen only in livers of male fetuses from dams exposed to benzene, benzene+ethanol but not ethanol alone; in adult animals, CFU-E cells were depressed in bone marrow of all treated males. The Keller and Snyder studies, and Corti and Snyder, are cited prominently in the 2001 Office of Environmental Health Hazard Assessment (OEHHA) draft on Prioritization of Toxic Air Contaminants under Children's Environmental Health Protection Act.

6.2.4.3 Genotoxicity

Significant increased incidence of micronuclei in fetal livers was observed when 80 mg/kg benzene was administered orally to pregnant mice on GD 13 (Ciranni et al., 1988), and on GD 14 or 15 at an i.p. dose of 1318 mg/kg (Xing et al., 1992), or at i.p. doses of 219–874 mg/kg (Ning et al., 1991). However, oral exposure to 50 and 75 mg/kg benzene administered to pregnant ICR mice on GD 17–19 did not induce increased micronuclei in fetal liver or adult bone marrow erythrocytes (Harper et al., 1989); this result correlates with developing hematopoiesis. When comparing genotoxic effects of benzene in males, females, and fetuses, Cirrani et al. (1988) found slightly larger increases in micronucleated-PCE in virgin females than in pregnant dams and fetuses exposed on GD 13, but a much larger effect in males. Harper et al. (1989) reported large effects in males, smaller effects in virgin females, and no effects in pregnant dams and fetuses exposed on GD 15–19.

Speculation has been advanced concerning the mechanisms of developmental and reproductive toxicity of benzene. Pushkina et al. (1968), from a study of factory workers with ovarian hypofunction related to benzene exposure, suggested that alteration in ascorbic acid and RNA and DNA content are possible mechanisms. Ascorbic acid content decreased in whole fetuses and in maternal organs as concentrations of benzene increased, first in maternal liver and later in placenta and fetal livers. Benzene also increased DNA content and decreased RNA content in placenta, fetal liver, and fetal brain, and decreased DNA content in maternal liver. Ungváry and Donath (1984) suggested that damage to peripheral noradrenergic fibers in pregnant rats might result in disturbed control of ovarian and uterine blood flow and steroid production, contributing to the embryotoxic action of organic solvents. Tátrai et al. (1980)

proposed that transplacental effect of benzene and some of its metabolites (e.g., phenol), and conversion of benzene to benzene-oxide at the site of activity could be responsible for embryotoxicity. Benzene can also damage maternal circulation and cause bone marrow depression.

Iba et al. (2001) treated lactating adult mice with a single i.p. dose of 800 mg/kg [14C] benzene, and their 2-day-old neonates were either treated similarly or nursed by treated dams. Comparison of their ability to metabolize benzene to urinary products or reactive intermediates was assessed by covalently bound benzene derivatives in whole blood or liver DNA. Metabolite fractions were identified in urine of i.p.-treated neonates by high-performance liquid chromatography. Results showed that excretable, as well as reactive, metabolites of benzene were formed substantially by the neonatal mouse, and that the extent of bioactivation is comparable in the adult and the suckling neonate.

6.2.4.4 Developmental Neurotoxicity

No studies were available, with the exception of a trial by Ungváry and Donath (1984), who reported that the abundant noradrenergic fibers normally found in the ovary and uterus of pregnant rats decreased with benzene exposure at 1500 mg/m^3, 8 hours/day on GD 8–10. The authors suggested a differential toxic effect on postganglionic neurons with a potential for embryotoxicity.

6.2.4.5 Summary

Overall, a substantive body of data is available in several species to demonstrate that benzene at doses above 47 ppm can induce developmental toxicity, sometimes at maternally toxic levels, but does not cause malformations. Transplacentally, benzene also affects hematopoiesis and clastogenicity in fetuses and may contribute to carcinogenesis in neonatal animals. According to the EU Benzene Risk Assessment draft (ECB 2003), the absence of teratogenic effects, fetotoxicity primarily at maternally toxic high doses and negative results in the available fertility study (Kuna et al., 1992), no further testing is needed.

Although benzene has been demonstrated to induce neurotoxic effects in adult animals and humans after short-term exposure to relatively high concentrations, there are no studies in the published literature that evaluate neurotoxic potential during fetal or neonatal development.

6.2.5 Repeated-Exposure Toxicity in Experimental Animals

The categories of subchronic toxicity, chronic toxicity, and carcinogenicity are used to classify and describe the types of effects that are observed in test animals or humans over a continuum. The test distinctions are relative to time elapsed and are arbitrary; the time periods for the categories actually overlap. Cancer studies usually include the standard parameters for determining general toxicity as well as tumorigenesis. For the following discussion, the descriptor subchronic toxicity is used for animal studies of 28 days or longer but less than 1 year in duration, and the term chronic for studies of one year or longer in duration.

6.2.5.1 Subchronic Toxicity

Repeat-dose toxicity studies were conducted primarily by the oral and inhalation routes, but several studies have been performed by the intraperitoneal (i.p.) and intravenous (i.v.) routes. Also, benzene has been used as a vehicle and control substance in evaluating the toxicity of

petroleum fractions dissolved in benzene to facilitate dermal administration. At present, there is no acceptable animal model for the human leukemogenic effects. Recently, French and Saulnier (2000) reported that leukemia can be produced in the TgAC mouse after dermal administration of benzene. However, it is not known whether experiments with this mouse will ultimately yield a satisfactory model.

In animal studies, responses to benzene administration are variable and may depend on a variety of factors, including species, strain, exposure duration, and whether exposure is intermittent or continuous. Serious toxicological effects are primarily confined to hematological parameters and involve all aspects of the hematopoietic system, from depression of stem cells up to pancytopenia and histopathological alterations in the marrow. Effects have been observed after acute, sub-acute, subchronic, and chronic exposure via different routes of administration. However, AML, which is of primary concern in humans, is not produced reliably in standard laboratory test species, and occasional reports of cancer in experimental animals (usually the mouse) are of questionable value in cancer risk assessments. The subchronic toxicity of benzene has been studied primarily in the mouse and rat. Depending on the level of dosing, the effects are hematotoxicity, reduction in body-weight gain, and death. Effects on body weight and mortality may be secondary to hematotoxicity. Thus, hematotoxicity is the parameter for quantifying toxic effects of benzene and for estimating risk from exposure. The hematotoxicity in the rodent appears to compare well with benzene-induced hematologic changes in cases of human exposure.

Results of benzene-induced mortality and hematotoxicity in key rodent studies conducted by inhalation and oral routes of exposure are summarized below. Information was obtained mainly from several major reviews of benzene toxicity (ATSDR, 1997; U.S. EPA, 1998a, 2003a).

Inhalation (see Table 6.4)

Mortality: In the rat, exposure of males and females to 200 ppm, 4–7 hours/day, 4–5 days/week, caused significant mortality (Maltoni et al., 1983, 1985). In the mouse, deaths occurred in males and females at 300–302ppm, 6 hours/day, 5 days/week, for 16–26 week (Cronkite et al., 1985; Cronkite et al., 1989; Farris et al., 1993; Green et al., 1981a,b).

Hematological Effects: Mouse and rat studies were identified that evaluated effects on peripheral blood and/or hematopoiesis (IRIS, 1998). Only one of the rat studies was performed over a dose range, and the results are considered here as being representative of effects in the rat. Male and female rats (10 M, 10 F/group) were exposed to benzene at concentrations of 0, 1.0, 100, and 300 ppm, 6 hours/day, 5 days/week for up to 90 days, with serial sacrifice after 7, 14, 28, 56, and 91 days of exposure. Results showed significant decreases in WBC counts in males (day 14), and females (days 14–19) and slightly decreased femoral cellularity at 300 ppm.

Of the mouse studies, only one was performed over a dose range in both males and females. Results are consistent with other single-sex and single-dose studies and are considered to be representative of effects in the mouse in standard-protocol toxicity studies. In this assay, groups of 30 male and 30 female mice were exposed at 0, 1.0, 3.0, 30, and 300 ppm, 6 hours/day, 5 days/week for up to 91 days, with serial sacrifices after 7, 14, 28, 56, and 91 days of exposure (Ward et al., 1985). Hematological effects were not observed at 1, 10, or 30 ppm. However, at 300 ppm, mice showed reduced hematocrit, total hemoglobin concentration, RBC count, WBC count, platelet count, myeloid/erythroid ratios, and percent of lymphocytes. Red blood cells had increased mean corpuscular volume, mean cell hemoglobin,

glycerol lysis time, and incidence and severity of red cell morphological changes. Values for red blood cells, mean corpuscular hemoglobin and glycerol lysis were significant in males and females; other effects were significant only in males. Other mouse studies contribute to understanding the hematopoietic effects of benzene. Mice were exposed to benzene for 10 weeks (Green et al., 1981a,b), and samples of peripheral blood, bone marrow, and spleen were examined. Mice exposed to 300 ppm had decreased numbers of lymphocytes and RBC in peripheral blood, decreased granulocyte/macrophage progenitor cells in bone marrow, decreased spleen weight and number of lymphocytes, decreased multipotential stem cells and committed granulocyte/macrophage progenitor cells in the spleen, and increased atypical cell morphology in peripheral blood, bone marrow, and spleen. A second study by Green et al. was performed at 10 ppm for 10 weeks, and spleen weight, nucleated cells/spleen, and nucleated RBC/spleen were significantly increased.

A study by Farris et al. (1997) demonstrated the progression of effects from inhaled benzene on hematological parameters after exposing male mice to 0, 1, 5, 10, 100, and 200 ppm benzene, 6 hours/day, 5 days/week for 1, 2, 4, or 8 weeks. A subset of mice from the 4-week exposure were allowed a recovery period of up to 25 days. There were no significant effects until exposure level reached 100 ppm. At 100 ppm and above, there was a reduction in bone marrow cells. Highly proliferative potential primitive progenitor cells were decreased at all time points at 200 ppm and at 2, 4, and 8 weeks at 100 ppm. The number returned to control level during recovery in all but the 200-ppm group. Replication of these cells increased to compensate for toxicity during exposure. The number of granulocyte-macrophage colony-forming units was reduced at 2, 4, and 8 weeks at 100 and 200 ppm. Granulocytic marrow cells were decreased by 100 ppm at week 4 and by 200 ppm at all time points. Blood leukocytes were lowered at week 2 onward at 100 and 200 ppm. Platelets were reduced at 2 weeks at 100 ppm and at all time points at 200 ppm.

Snyder et al. (1988) examined the influence of two modifications in dosing regimens on hematotoxicity in two strains of mice. In one procedure, intermittent exposures (1 week benzene at 300 ppm) were followed by 2 weeks of non-exposure for life; in the second procedure, exposure was to 1200 ppm, 6 hours/day, 5 days/week for 10 weeks. The intermittent exposures produced earlier mortality than was seen in the 10-week study. Both exposures caused severe lymphocytopenia and moderate anemia. Tumor incidences were increased in both procedures, but neither strain had leukemia or lymphoma. With intermittent exposures, there is a rise in the population of cells that are actively dividing, and a larger target cell population. This increased population might increase the risk of myelodysplastic syndrome and myelocytic leukemia in human populations (Irons and Stillman, 1996)

Table 6.4: Summary of Subchronic Inhalation Toxicity

Effect	NOAEL/LOAEL	Study	Comments
Mortality	Rat LOAEL (M,F) = 200 ppm	Maltoni et al., 1983,1985	In general, mortality in subchronic studies is secondary to the hematotoxicity.
	Mouse LOAEL (M) = 100 ppm	Rosenthal and Snyder, 1987	Due to depressed cell immunity after tumor cell inoculation, not directly induced mortality.
	Mouse LOAEL (M, F) = 300 ppm	Cronkite et al., 1989	
Hematological alterations	Rat LOAEL (M) = 88 ppm	Wolf et al., 1956	
	Rat LOAEL (F) = 300 ppm Rat NOAEL (M, F) = 30 ppm Mouse NOAEL (F) = 30 ppm	Ward et al., 1985	
	Mouse LOAEL (M) = 10 ppm	Baarson et al., 1984	
	Mouse LOAEL (F) = 100 ppm	Seidel et al., 1989	
	Mouse NOAEL (M) = 3.1 ppm	Li et al., 1992	

Oral

Subchronic oral studies have been conducted in both mice and rats over a dose range (NTP, 1986; Huff et al., 1989). In the NTP study, rats and mice were treated with 0, 18, 36, 71, 143, 286, and 429mg/kg/day (actual volume in corn oil; nominal concentrations were, 0, 25, 50, 100, 200, 400, and 600mg/kg) 5 days/week for 17 weeks. Five additional animals/sex/group were administered 0, 143, and 429mg/kg/day for 60 days. Hematological analyses were performed at 60 days and after 17 weeks; necropsies were performed on all rats, and spleens were evaluated histopathologically. No compound-related deaths were observed in rats or mice.

Body-Weight Effects: In the rat, body-weight depression was observed at 143mg/kg and higher (14%–22% decrease). In the mouse, body-weight depression was observed at 71 mg/kg/day and higher (4%–10% decrease).

Hematological Effects: In the rat, dose-related leukopenia was observed in both sexes. Lymphoid depletion in spleen was seen in males and females at 143 and 429 mg/kg for 60 days, and at 429mg/kg for 120 days. Increased extramedullary hematopoiesis was seen in males and females at 429mg/kg for 120 days. In mice, dose related leukopenia and lymphocytopenia were seen in males at and above 36mg/kg, and in females at 286 and 429mg/kg.

6.2.5.2 Chronic Toxicity

Repeat-dose chronic toxicity studies have been conducted by the oral route in both rats and mice.

Rat: Two chronic rat studies have been conducted by gavage (Maltoni et al., 1985; NTP, 1986; Huff et al., 1989). The Maltoni study did not provide detailed toxicological information, and statistical evaluations were not included. The more thorough NTP study was conducted according to good laboratory practices (GLP). In this latter study, rats of both sexes were treated by gavage with benzene at 0, 36, 71, and 143 mg/kg/day (actual analyzed concentrations); females received 0, 18, 36, and 71 mg/kg/day (actual analyzed concentrations) for up to 24 months. Dose-related changes in weight gain were pronounced in the males and lower than controls by week 22, thereafter reaching a reduction of 23% by week 103 in the 143-mg/kg group. At 71mg/kg, weight-gain reduction was similar in both males and females by study termination. No notable clinical signs were observed. There was a dose-related decline in survival for both males and females. Dose-related leukocytopenia was seen in females at 18 mg/kg and higher from 3 to 12 months but was similar after 15 months. In males, leukocytopenia was significant at 36 mg/kg and above. Dose-related lymphoid depletion was seen in the thymus of male rats at all treatment levels. In the spleen, lymphoid depletion was significantly increased at all treatment levels in males.

LOAEL (females) = 18 mg/kg/day (leukopenia/lymphocytopenia) – lowest dose tested
(males) = 36 mg/kg/day (leukopenia/lymphocytopenia) – lowest dose tested

NOEL (females) <18 mg/kg/day (leukopenia/lymphocytopenia)
(males) <36 mg/kg/day (leukopenia/lymphocytopenia)

Mouse: The NTP (NTP, 1986; Huff et al., 1989) conducted a mouse chronic study, exposing 60 males and 60 females to oral gavage doses of 0, 18, 36, and 71 mg/kg/day for up to 2 years. Body weights of both males and females at 71 mg/kg were reduced. No notable clinical signs were observed. There was a dose-related decline in survival for both sexes. Significantly decreased leukocyte counts were found in males at 3 months and beyond at 36 or 71 mg/kg; at 18 mg/kg, decreased leukocyte counts were seen at 6 and 21 months. In females, leukopenia was seen only at 12 and 18 months but at all treatment levels. Decreased lymphocyte counts were seen in males at 3 months and beyond at 36 and 71 mg/kg/day, but at 18 mg/kg, counts were decreased only after 12 months. In females, lymphocytopenia was seen at 12 and 18 months at doses of 18 mg/kg and higher, and was seen in 3 months at 71 mg/kg/day. Hematopoietic hyperplasia of marrow was seen at all treatment levels in both sexes. A dose-responsive increase in hematopoiesis was observed in males. In females, an increased incidence of epithelial hyperplasia of the ovary occurred at all treatment levels.

LOAEL (males and females) = 18 mg/kg/day (leukopenia/lymphocytopenia) – lowest dose
NOAEL (males and females) <18 mg/kg/day (leukopenia/lymphocytopenia)-

6.2.5.3 Carcinogenesis

The malignancy clearly associated with benzene exposure in humans is acute myelocytic leukemia. In experimental animals, however, benzene induces solid tumors in several organs but does not generally cause leukemia. Chronic bioassays conducted by Maltoni et al. (1989) and by the NTP (NTP, 1986, Huff et al., 1989) have shown that oral administration of benzene in rats produces solid tumors in several organs, including Zymbal gland, nasal and oral cavity,

mammary gland (female), and skin (male). In the mouse, Zymbal gland, lung, Hardarian gland (male), preputial gland (female), mammary gland (female), and ovary tumors are produced. Thus, the target organs for carcinogenesis differ between rodents and humans.

In several inhalation studies, one or a few examples of bone marrow malignancies in mice were found (Snyder et al., 1980; Goldstein et al., 1982). The findings were not statistically significant but were unusual, in that spontaneous occurrences of these tumors had not been reported previously. Cronkite et al. (1989) produced thymic lymphoma in 6 of 90 C57Bl/6 mice exposed to 300 ppm benzene. In this study, exposure was for 16 weeks, with clinical observations until death. However, the C57Bl/6 strain does have a background level of spontaneous leukemia. Cronkite et al. (1989) later showed that CBA/Ca mice exposed to 300 ppm benzene for 16 weeks developed an increased incidence of myelogenous neoplasms. However, in an attempt to study this event further, Farris et al. (1993) were unable to reproduce the effect seen by Cronkite et al. (1989) in the CBA/Ca mouse, but did find malignant lymphoma and preputial gland carcinoma, Zymbal gland carcinoma, and squamous cell carcinoma in the forestomach.

Except for the study conducted by Goldstein et al. (1982), other studies (prior to the work of French and Saulnier [2000]) have failed to produce AML in rodents via benzene exposure. Thus, while the hematopoietic abnormalities associated with benzene exposure are reproducible in test animals, leukemogenic effects are generally not observed, and therefore, the animal studies are of limited utility in elucidating the mechanism(s) of leukemogenic effect. Furthermore, the solid tumors seen in the animal studies have not been reported in humans exposed to benzene, and therefore, the carcinogenic effects seen in animals have questionable relevance for humans.

The chronic toxicity/carcinogenicity studies conducted by the NTP via the oral route are the most thorough studies performed to date; the carcinogenic effects are described below. The experimental procedures for both mouse and rat have been described under chronic toxicity.

Rat: In male rats, benzene caused increased incidences of Zymbal gland carcinomas, squamous cell papillomas and carcinomas of the oral cavity, and squamous cell papillomas and squamous cell carcinomas of the skin. These effects were dose-related, and increased incidences were statistically significant at the lowest dose (36 mg/kg/day). In female rats, benzene caused increased incidences of Zymbal gland carcinomas, and squamous cell papillomas and squamous cell carcinomas of the oral cavity. These effects were dose related; for the Zymbal gland, statistical significance was seen at the lowest dose (18 mg/kg/day), and for the oral cavity, significance was reached at 36 mg/kg/day.

Mouse: In the male mouse, benzene caused increased incidences of Zymbal gland squamous cell carcinomas, malignant lymphomas, alveolar/bronchiolar adenomas and carcinomas (combined), Hardarian gland adenomas and carcinomas (combined), and squamous cell carcinomas of the preputial gland. These effects were dose related. For the Hardarian gland adenomas and carcinomas combined, significance was reached at 18 mg/kg/day, and for other tumors, significance was reached at 36 mg/kg/day. In the female mouse, benzene caused increased incidences of malignant lymphomas, ovarian granulosa cell tumors and carcinomas, carcinomas and carcinosarcomas of the mammary gland, alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinomas, and Zymbal gland squamous cell carcinomas. All effects of benzene were dose-related. Significance was reached at 36 mg/kg/day for lymphoma, ovarian granulosa cell tumors and carcinomas, carcinomas of the mammary gland, and alveolar/bronchiolar carcinomas. For Zymbal gland carcinomas and alveolar/bronchial adenomas, significance was reached at 71 mg/kg.

LOAELs for carcinogenic effects in the oral rat and mouse studies (NTP, 1986; Huff et al, 1989):

Rat: LOAEL (male) = 36 mg/kg/day
LOAEL (female) = 18 mg/kg/day
Mouse: LOAEL (male) = 18 mg/kg/day
LOAEL (female) = 36 mg/kg/day

Overall, subchronic toxicity, chronic toxicity, and carcinogenicity of benzene have been adequately addressed by researchers over the past 40+ years, such that there is little to be gained by performing additional standardized toxicity testing.

6.2.6 Adult Neurotoxicity

Inhalation and oral (mostly acute) studies demonstrate the potential of benzene to affect the nervous system at fairly high doses in animals, effects that are reduced or eliminated with cessation of exposure.

6.2.6.1 Oral

Sprague-Dawley rats given a single oral dose of 1870 mg/kg exhibited tremors and tonic-clonic convulsions, and died within minutes. A dose of 352 mg/kg to mice produced slight nervous system depression (Cornish and Ryan, 1965). To evaluate effects of potential groundwater contaminants, Hsieh et al (1988a) administered benzene to CD-1 male mice at concentrations of 0, 40, 200, and 1000 mg/L benzene in drinking water (estimated daily doses of 0, 8, 40, and 180 mg/kg/day) for 4 weeks. Animals were euthanized after 4 weeks, and brains were sectioned—hypothalamus, medulla oblongata, cerebellum, corpus striatum, cerebral cortex, and mid-brain—and analyzed for catecholamines; norepinephrine, dopamine, and their metabolites; and indoleamine seratonin and 5-hydroxyindoleacetic acid, by high-performance liquid chromatography. No effects on behavior, body weight, and food or water consumption were observed. Dose-related increases in levels of monoamine neurotransmitters occurred at 8 and 40 mg/kg/day, but no further increases were seen at 180 mg/kg. Increases in levels of parent compounds were associated with increases in corresponding metabolites, reflecting increased turnover of the amines. A NOAEL could not be determined; the LOAEL was 8 mg/kg/day. Although a potential biomarker for exposure, the biological significance of these findings is uncertain (ATSDR, 1997). Oral administration of 8, 40, or 180 mg/kg/day benzene in drinking water to male CD-1 mice for 4 weeks markedly stimulated hypothalamic-pituitary-adrenocorticoid activity (Hsieh et al., 1991). At all doses, serum corticosterone levels collected at days 2, 7, and 14 of treatment were increased at day 7, decreased to control levels at day 14, and were re-elevated at termination.

6.2.6.2 Inhalation

In an early study (Carpenter et al., 1944), rabbits exposed to approx. 45,000 ppm (143,760 mg/m^3) benzene exhibited light narcosis after 3.7 minutes of exposure; tremors, chewing, excitement, and running movements after 5 minutes; loss of pupillary reflex to strong light, blink reflex, pupillary contraction, and involuntary blinking over 6.5–15.6 minutes; and death after 36.2 minutes. Anderson et al. (1983) evaluated effects of high concentrations of benzene in dopamine and noradrenaline turnover in parts of the hypothalamus in Sprague Dawley rats exposed to 1500 ppm (4792 mg/m^3), 6 hours/day for 3 days. The benzene control group (four rats, no inhibitor) were sacrificed immediately after exposure; the + inhibitor group

(six rats) were injected with tyrosine hydroxylase inhibitor immediately following exposure, and were sacrificed 2 hours later. Depletion of catecholamines was determined by calculating the percent depletion in the + inhibitor group compared to levels of catecholamine in the benzene (no–inhibitor) controls using quantitative microfluorimetry. Benzene (no-inhibitor) controls produced increases in catecholamines in some hypothalamic regions, and the benzene + inhibitor group enhanced disappearance in other regions. Benzene produced a pattern of discrete changes in noradrenalin and dopamine turnover in certain areas of the hypothalamus.

Ungváry and Donath (1984) demonstrated that the noradrenergic innervation of reproductive organs could be affected by benzene exposure. CFY rats were exposed to 1500 mg/m^3, 8 hours/day on GD 8–10. The abundance of fluorescent noradrenergic fibers normally found in ovaries and uteri of pregnant rats decreased while background fluorescence increased, interpreted to indicate an increased release of nonadrenalin. The authors concluded that benzene has a selective and differential toxic effect on post-ganglionic neurons, with potential for embryotoxicity.

Dempster et al. (1984) correlated behavior with hematological effects of inhaled benzene using mice exposed to concentrations of 100—3000 ppm, 6 hours/day for the number of days necessary to achieve (concentration × time) product of 3000 ppm-days. Lymphocyte counts decreased to 68% of control after five exposures to 100 ppm, to 50% after two exposures to 300 ppm, or to one exposure of 1000 or 3000 ppm benzene. The maximum decrease occurred in 10 days of 300-ppm exposure; lymphocyte counts remained depressed throughout each sub-study. Increased milk-licking from a sipper tube was statistically significantly increased following 1–2 days at 100 ppm, and after 4–5 days at 300 ppm, with the maximal effect at 7–8 days at 300 ppm, following a course similar to that of hematological changes. No effects on grip strength were seen, except when 1000 ppm was administered for 1 day, causing reduced hind-limb grip strength. All behavioral effects disappeared following termination of exposure. Other behavioral effects were measured in male CD-1 and C57Bl/6 mice exposed to 300 or 900 ppm (958 or 2875 mg/m^3) benzene, 6 hours/day for 5 days, with a 2-week recovery period, followed by a repeat of the exposure regime (Evans et al., 1981). Behaviors monitored were: stereotypic behavior, sleeping, resting, grooming, eating, locomotion, and fighting. For both strains, a greater increase in activity was observed among 300-ppm mice, compared to the 900-ppm mice, probably due to narcosis-like effects at the higher dose. Exposure of Wistar male rats for 4 hours to 929 ppm (2968 mg/m^3) benzene in glass chambers decreased evoked electrical activity in the brain by 30%. A comparable 30% depression was produced in female H-strain mice exposed to 856 ppm (2735 mg/m^3) benzene for 2 hours (Frantik et al., 1994).

Behavioral parameters, acetylcholine esterase (AChE) activity in blood and brain, organ weight, and bone marrow cellularity were evaluated in male Kunming mice (five per group) exposed to reported benzene concentrations of 0, 078, 3.13, or 12.52 ppm (0, 2.5, 10, or 40 mg/m^3) for 2 hours/day, 6 days/week for 30 days, under static conditions, in a 300-m^3 chamber (Li et al., 1992). Benzene levels were monitored by gas chromatography every 30 min for 3 days but, apparently, not thereafter. Forelimb grip strength and rapid response in running a Y-maze increased at 0.78 ppm (2.5 mg/m^3) but declined significantly at higher concentrations. No statistically significant differences were observed in AChE activity in blood or brain, or in locomotor activity at any dose level. Relative liver weight increased, and relative spleen weights decreased ($p \leq 0.05$) at 12.52 ppm. Bone marrow cellularity was affected only at 12.52 ppm (40 mg/m^3), with reduction of 91% in myeloblasts, 64% in premyeloblasts, 77% in metamyelocytes, 100% reduction in reticulum, and 100% in erythroblasts. The behavioral effects follow the profile of hyperactivity at low doses demonstrated by Dempster et al. (1984) and Evans et al. (1981) but at much lower doses and shorter duration of exposure. However,

the measurements of doses are suspect, because the very large decreases in several blood parameters are in contrast to most other studies, which found minimal or no response in bone marrow cellularity at similar low exposure concentrations with 6 hours or more daily exposure. Because benzene concentrations were not reported to have been measured after the first 3 days, the toxicity to bone marrow parameters suggests that actual benzene concentrations were much higher than reported by the authors (IRIS, 1998).

Benzene-induced neurotoxic effects have been identified in humans and laboratory animals, and demonstrated to diminish and/or disappear on termination of exposure. Effects usually appeared at the same or higher doses than doses that induced hematopoietic toxicity (LOAEL mice = 10 ppm; rats = 30 ppm) (ECB, 2003), and hematotoxic effects are routinely used to establish LOAELs and NOAELs.

6.2.7 Immunotoxicity

Studies in which mice were exposed to benzene in drinking water have been performed by several investigators to measure immunotoxic and hematotoxic effects. Hsieh et al. (1988b) treated male CD-1 mice with 0, 31, 166, or 790 mg/L (0, 8, 40, or 180 mg/kg/day) benzene for 28 days. Statistically significant dose-related decreases in relative spleen weight, and non-statistically significant deceases in thymus weight were observed at all doses, while body weight, liver weight, clinical signs, and necropsy results were comparable to controls. Dose-related hematological effects (erythrocytopenia, leukocytopenia, lymphocytopenia, increased motor conduction velocity) were observed at all exposure levels. Biphasic responses were reported in immunological tests (mitogen-stimulated splenic lymphocyte proliferation, mixed splenic lymphocyte culture response, and cytotoxic splenic T-lymphocyte response to allogenic yeast artificial chromosome [YAC-1] cells), with significantly increased responses at 8 mg/kg and significantly decreased responses at 40 and 180 mg/kg. Primary antibody response to sheep red blood cells was significantly decreased at 40 and 180 mg/kg and similar to or higher than controls at 8 mg/kg. A LOAEL of 8 mg/kg/day was designated by the authors. Hsieh et al. (1991) later reported that, when supernatants from splenic T-lymphocyte cultures, stimulated with ConA, were assayed for interleukin 2 (IL-2) content, splenic IL-2 production was suppressed in the 40- and 180-mg/kg/day groups. The impact of benzene on cell-mediated immunity and cytotoxic T-lymphocyte response in these studies support earlier work by Rosenthal and Snyder (1987), in which reduced tumor lytic abilities of splenic cells were demonstrated in C57Bl/6J mice exposed to 100 ppm (320 mg/m^3) benzene, 6 hours/day, 5 days/week for 10 days prior to tumor inoculation. Splenic T-cells from mice exposed to 10 ppm and 100 ppm for 20 days showed delayed mixed lymphocyte reaction to alloantigens, possibly due to benzene-induced impairment of functional abilities of alloreactive T-cells rather than benzene-induced suppressor cells. Exposure to 100 ppm benzene for 20 days had not altered relative proportions of splenic leukocytes, the percentage of splenic T-cell subsets, or the ratio of splenic helper/suppressor cells.

Studies on humoral immune response in addition to Hsieh et al. (1988b) include work by Aoyama (1986) in which male BALB/c mice, exposed to 50 or 200 ppm benzene vapor for 14 days showed reduced numbers of IgG- and IgM-plaque-forming cells/spleen in response to sheep red blood cells (SRBC) in the plaque-forming assay. In contrast, male Sprague Dawley rats showed no effect on humoral immune response measured in an ELISA [enzyme-linked immunosorbent assay] of serum anti-SRBC IgM after 2–4 weeks exposure to 30, 200, or 400 ppm benzene, 6 hours/day, 5 days/week (Robinson et al., 1997). A reduction in the number of B- and T-lymphocytes was observed at 400 ppm benzene for 2 weeks (B-cell only) and 4 weeks.

The toxicity of benzene to natural killer cells (NK cells) involved in non-specific host resistance, and on interleukin-2, an important growth factor for T, B, and NK cells and in regulation of granulocyte and eosinophil production, was examined by Fan (1992). Male C57Bl/6 mice were exposed to benzene in drinking water at concentrations of 0, 152, or 853 mg/L (0, 27, or 154 mg/kg/day) for 7–28 days, with sacrifices at 7, 14, 21, or 28 days of exposure. A separate group was exposed to 152 mg/L (27 mg/kg/day) for 28 days, and sacraficed at 7, 14, or 21 days after the last dose. No overt signs of toxicity were seen, but significant decreases in number of spleen cells were observed after 21 days of exposure at 27 mg/kg, and after 14 days at 154 mg/kg. After 21 days, a significant increase in spleen NK cell activity was observed at both doses, but this activity was not present after 28 days in either group. Spleen cell numbers and interleukin-2 production were depressed in mice given 27 mg/kg for 28 days, and 7 and 14 (interleukin-2 only) days after exposure. The LOAEL was determined to be 27 mg/kg/day (152 mg/L), the lowest dose tested. White et al. (1984) exposed female B6C3F1 mice to benzene in drinking water (containing emulphor to increase the solubility of benzene) at higher concentrations of 0, 50, 1000, or 2000 mg/L (0, 12, 195, or 350 mg/kg/day) for 30 days. Body weight was significantly decreased ($p<0.05$) at 350 mg/kg, and a dose-related decrease in absolute and relative spleen weight was observed. Spleen cellularity was decreased at all levels in one test, but only at 195 and 350 mg/kg in a separate test. Other significant effects were dose-related (<0.05) leukopenia and lymphocytopenia, and a dose-related decrease in eosinophils. Significant decreases in erythrocytes and Hgb were seen at 360 mg/kg, but no effects were observed in clinical chemistry parameters. Immunologically, decreases in IgM antibody-forming cells/spleen in response to SRBC, lymphocyte proliferation in response to T-cell mitogen, Concanavalin A, and B-cell mitogen LPS, and a decrease in the number of T-lymphocytes and femoral CFU-GM were observed. An increase in bone marrow cell DNA synthesis was also reported. The investigators identified a hematological NOAEL of 12 mg/kg/day and a LOAEL of 195 mg/kg/day, and an immunological LOAEL of 12 mg/kg/day, based on a decreased stimulation index for lymphocyte proliferation of spleen cells in response to Con A. This decreased response to mitogen stimulation was the only statistically significant immunological effect observed at 12 mg/kg.

When male C57Bl/6J mice were exposed to benzene by whole-body inhalation at concentrations of 0, 10.2, 31, 100, or 301 ppm (0, 32.6, 99, 319, or 962 mg/m^3) 6 hours/day for 6 days, significant dose-related depression of lymphocytes were observed at all doses, 65% at 10.2 ppm, and to 32% at 100 and 300 ppm (Rozen et al., 1984). Erythrocyte counts were significantly increased at 10.2 ppm and then depressed at 100 and 300 ppm. The frequency of femoral B-lymphocyte colony-forming cells was reduced to 30% of control at 10.2 ppm; however, the actual number of B-lymphocytes was not reduced at 10.2 ppm but was reduced to less than 10% control at 100 and 300 ppm. Similarly, splenic PHA-induced blastogenesis was depressed at 31 ppm without concomitant depression of the number of T-lymphocytes until doses of 100 and 300 ppm were reached. Investigators considered the LOAEL to be 10.2 ppm (32.6 mg/m^3), the lowest dose tested. Exposure to concentrations of 300 ppm (960 mg/m^3) for 6, 30, or 115 days resulted in decreased numbers and proliferative capacity of T- and B-lymphocytes in male C57Bl/6J mice (Rozen and Snyder, 1985). Depression in B-lymphocyte CFU proliferation increased progressively to the point of no observable mitogen-induced response after 115 doses; T-cell response was markedly depressed without evidence of progressive decline with time.

To determine whether benzene-induced effects on immune parameters translated into decreased resistance to a pathogen, Rosenthal and Snyder (1985) exposed male C57Bl/6J mice to 0, 10, 30, 100, or 300 ppm benzene for 5 days and infected the mice with the facultative

intracellular pathogen, *Listeria monocytogenes*. Benzene exposure was stopped for half of each group, and the other half was exposed for an additional 7 days after infection, for a total of 12 days. Bacterial proliferation was measured at 4 and 7 days after infection for all mice. No effect on bacteria counts in the spleen was observed one day after infection. Pre-exposure to benzene at 300 ppm only resulted in a 7-fold increase in bacteria counts at day 4 after infection. With continued benzene exposure after infection, dose-dependent increases in spleen bacteria were observed at 30 ppm and above at day 4. However, by day 7, spleen bacterial counts had returned to normal for all treatment groups. The authors suggest that benzene exposure caused a delay in cell-mediated immune response, because there was a temporary increase in spleen bacterial cell counts. Both T- and B-lymphocytes were depressed at benzene exposures ≥30 ppm, and counts did not return to control levels even after cessation of exposure. The immune system LOAEL was determined to be 30 ppm, and a NOAEL of 10ppm was identified in this study. Reduced tumor resistance mediated via T-cells was observed in 90% of male C57Bl/6J mice exposed to 100 ppm benzene for 100 days (20 weeks), 6 hours/day, 5 days/week, and challenged with 10.00 polyoma virus-induced tumor cells/mouse. Lethal tumor incidence in control mice, and those exposed to 10 or 30 ppm, was 30% of the group or less (NOAEL = 30 ppm). Stoner et al. (1981) reported that exposure of female BNL mice to 200 ppm (640 mg/m^3) benzene for 10 to 20 days, or to 400 ppm for 5, 12, or 22 days, suppressed T-cell-dependent primary antibody response to tetanus toxin on day 21 after immunization. Exposure to 200 ppm for 5 days showed no effect. The NOEL was determined to be 50 ppm (160 mg/m^3) after 5, 10, or 20 days of exposure.

Effects on the immune system appear to be operative at doses that also produce hematotoxicity. The studies described above provide a profile of benzene-induced suppression and alteration of the immune system by the oral and inhalation routes, addressing effects on mitogen-stimulated lymphocyte proliferation, T- and B-lymphocyte responses, primary antibody response to sheep RBC and spleen cell proliferation (Heish et al., 1988b; White et al., 1984; Rozen et al., 1984), natural killer cell and interleukin-2 (Fan, 1992), and resistance to pathogens (Rosenthal and Snyder, 1985, 1987). Immunotoxic LOAELs ranged from 8 to 27 mg/kg/day for benzene in drinking water, and 10.2 to 30 ppm by inhalation in mice. In the only rat study, Robinson et al. (1997) reported a NOEL of 200 ppm for humoral response. Only Rosenthal and Snyder (1985) established a NOAEL of 10 ppm (32 mg/m^3). Using the inhalation NOAEL of 10 ppm, an estimated European Air Quality Standard (AQS) average daily dose (ADD) in mice was calculated to be approximately 12.8 mg/kg/day, an estimated NOAEL similar to the animal LOAEL for hematopoietic effects. Immune effects in animals seem to be initiated at higher exposures than other hematologic effects. Benzene immunotoxic effects are probably reflections of bone marrow toxicity (BU 2000). The equivalent human inhalation ADD was estimated to be 35 ppm (112 mg/m^3) (CONCAWE, 1996).

6.2.8 Metabolism

It is now generally believed that benzene-linked toxicity/carcinogenicity is caused by metabolites of benzene interacting with target organs (Ross, 2000; Valentine et al., 1996). Benzene is metabolized in liver, and metabolites are released from the liver into the general circulation, and from there, to the target organs and to the kidneys for excretion. A large amount of research has focused on the metabolism of benzene in liver, via a variety of *in vivo* and *in vitro* techniques, and metabolic pathways leading to the final products of excretion have been developed using measurements of dose vs. absorption by different routes of administration. The proposed catabolic pathway models have been developed for evaluating the pharmacokinetics of benzene in experimental animals and man. Little work has been carried out on metabolism of benzene in organs other than liver or of the further metabolism of liver-

derived metabolites in target organs. Benzene is known to be metabolized in the lung (Snyder and Hedli, 1996 Sheets and Carlson, 2004; Powley and Carlson, 1999, 2000, 2001) and rabbit bone marrow (Andrews et al., 1977). It is probable that benzene itself is not metabolized in human marrow, which lacks the P450 enzyme CYP2E1 (Genter and Recio, 1994). A current map of the pathways for benzene metabolism is shown in Fig. 1 (from Ross, 2000). This map is simplified to focus on metabolites that are thought to be important for toxicity and does not include the conjugation pathways and their products that are excreted or, perhaps, are further metabolized in target organs. Metabolites that have been proposed as being responsible for benzene toxicity include: 1) benzene oxide (epoxide), 2) mucondialdehyde, 3) quinones (e.g., benzoquinone, p-benzoquinone 4,4'-diphenoquinone), and 4) polyphenols (e.g., benzene dihydrodiol, catechol, trihydroxybenzene).

Benzene oxide is a highly reactive intermediate and would be expected to form adducts with proteins in the vicinity of its synthesis and with DNA, and it is difficult to explain why toxicity would be higher in bone marrow than in liver. Also, stable DNA adducts in rodents are not detected consistently by the ^{32}P postlabeling technique after acute benzene exposure or after long-term administration (Reddy et al., 1990, 1994), although protein adducts are observed (McDonald et al., 1994) even in untreated animals.

Small amounts of mucondialdehyde are probably produced *in vivo* from benzene (Kline et al., 1993), and it is a reactive intermediate, but there is no evidence that it is involved in benzene-induced toxicity or carcinogenicity.

Polyphenols are produced in large amounts via benzene metabolism and are released into the blood either as the phenols themselves (phenol, benzene dihydrodiol, catechol trihydroxybenzene, and catechol) or in conjugated form (e.g., as sulfate or glucuronide) where they can subsequently reach target organs (Ross, 2000). Reactive phenolic benzene metabolites such as hydroquinone and trihydroxybenzene produce DNA damage in human myeloid cells *in vitro* similar to that seen in mouse bone marrow by benzene (Kolachana et al., 1993). Phenol itself is probably not solely responsible for the toxic effects of benzene, because the administration of phenol alone does not reproduce the myelotoxicity caused by benzene (Tunek et al., 1981). However, concomitant administration of both phenol and hydroquinone does reproduce the toxicity (Eastmond et al., 1987; EPA-NCEA, 1998). It is plausible that the target-organ and target-cell toxic effects induced by benzene *in vivo* result from polyphenols, based on known effects of the polyphenols and the known enzymology (Ross et al., 2000). p-Benzoquinone might be a key reactive intermediate in the formation of acute myeloid leukemia, because only the myeloid cell line has the enzymatic capacity (e.g., myeloperoxidase) to convert hydroquinone to p-benzoquinone (Ross et al., 1996). Also, p-benzoquinone is a known clastogen (Smith et al., 1989). Hydroquinone can enhance the number of myeloid progenitor cells, which could then increase the conversion of hydroquinone to p-benzoquinone, thereby raising the cellular concentration (Irons and Stillman, 1996). Because the formation of stable DNA adducts has not been detected *in vivo* for the highly reactive p-benzoquinone, a potential mechanism for leukemogenic effects might be through protein binding, such as to histone protein, which in turn, might produce chromosomal damage. This type of mechanism might be considered a secondary toxic effect for which a threshold could exist.

The main conclusions regarding metabolism from the EPA IRIS benzene assessment are:

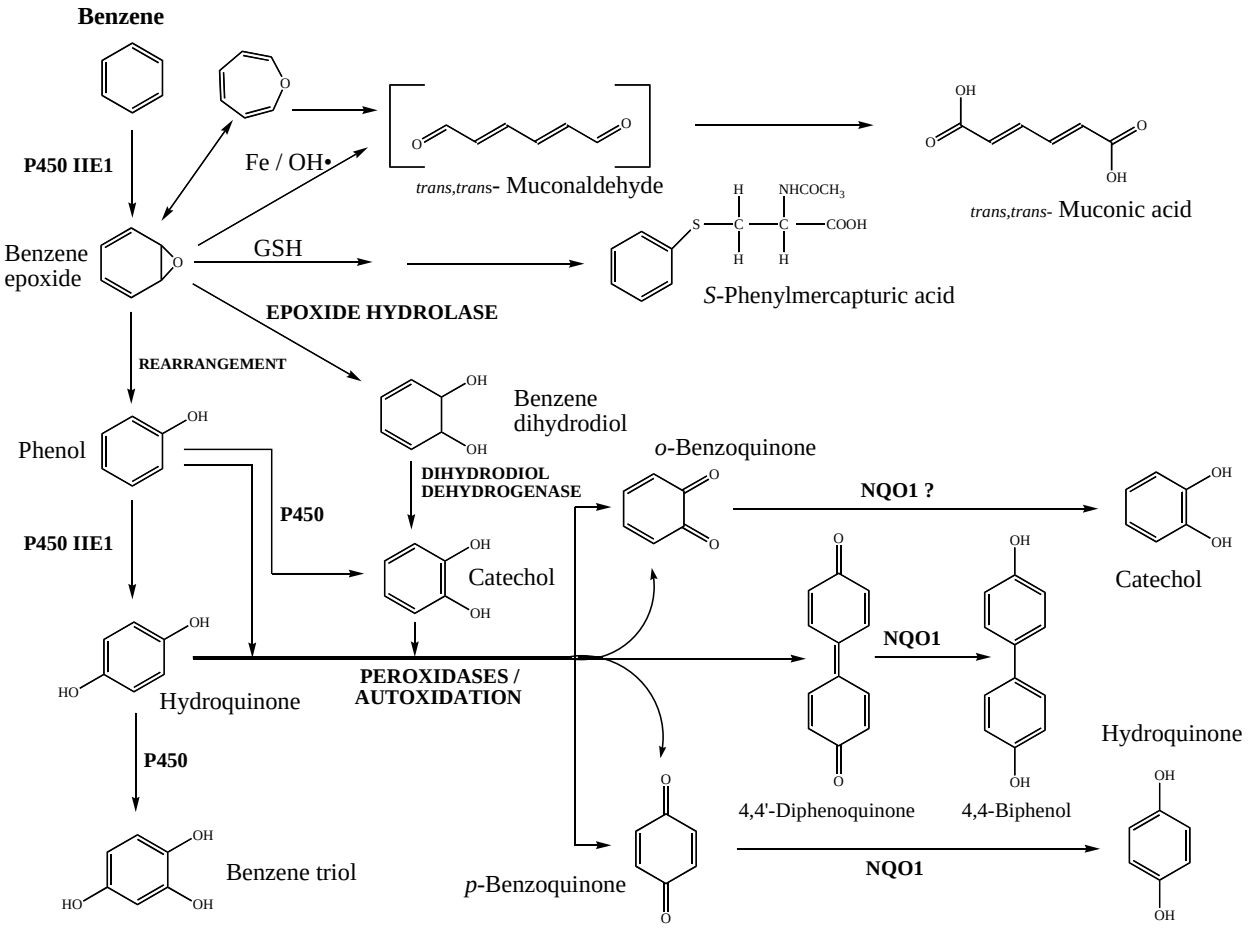
1. It is generally agreed that chronic toxicity of benzene in animals and humans results from the formation of reactive metabolites.

2. Evidence indicates that myelotoxicity and genotoxicity occur from a combination of phenol with hydroquinone, muconaldehyde, or catechol.

3. The pathways of oxidative benzene metabolism are understood, and the first metabolic step is catalyzed by CYP2E1 (see Figure 6.1 – adapted from Ross, 2000).

4. The major metabolites in animals and humans are phenol, hydroquinone, and catechol.

Figure 6.1: Major Metabolic Pathways for Benzene



Source: Ross 2000.

7.0 Exposure Assessments

This section summarizes the methodology, results and conclusions of the Tier I exposure assessment for benzene under VCCEP. As part of this pilot program, EPA has requested exposure information to be submitted to determine the extent of children's exposure to benzene. The types of exposure information needed for the Tier 1 assessment include the identification and characterization of the population groups exposed, and sources of the exposure, as well as frequencies, levels, and routes of exposure.

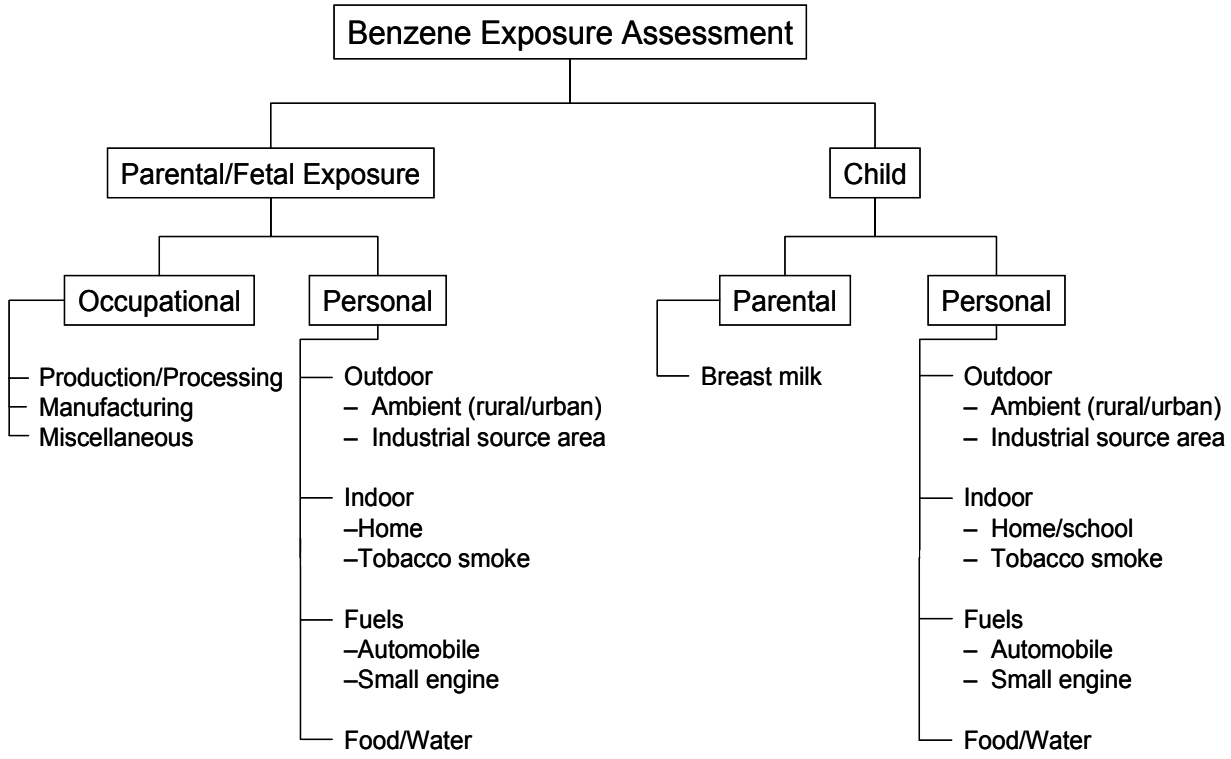
The methodology employed in this assessment provides for both a thorough determination of childhood exposures to benzene and uses the available data to focus on those sources of exposure that are likely to have the most significant contribution to individuals' total benzene exposures. In accordance with the numerous studies of personal benzene exposure, a child activity-based approach was used (Ott and Roberts, 1998; Wallace, 1996; Wallace et al., 1989a; Kinney et al., 2002; Philips et al., 2004; Adgate et al.; 2004a,b).

7.1 Methodology/Scope of the Assessment

As suggested by EPA, exposure assessments for both children and prospective parents were conducted. Sources of exposure to benzene in the ambient environment can come from both chain-of-commerce and non-chain of commerce sources. In accordance with the notice of the program published in the Federal Register (2000), this assessment focused primarily on the evaluation of benzene exposures from chain of commerce sources (i.e., manufacturing, processing, and use of benzene). When relevant, exposures to benzene from non-chain of commerce sources were also quantified. For example, tobacco smoke was evaluated because it is a well documented source of personal benzene exposure (Wallace, 1988; Brunnemann, et al., 1990a, Daisey et al., 1994; and Darrall, et al., 1998). Additionally, the exposure assessments did not include exposures from intentional misuse scenarios.

A child-centered approach has been used to define scenarios in which children may have exposure to benzene. Children may be exposed directly via personal proximity to benzene sources, or indirectly, during gestation or through human milk through their mothers. Women of childbearing age may be exposed via personal contact with benzene sources, and they may be exposed occupationally. Figure 7.1 graphically depicts the potential sources of benzene exposure for children and prospective parents. In defining these scenarios, chain-of-commerce information and data on naturally occurring levels have been used to determine the activities and settings that result in exposures. The prospective father has also been included in this exposure analysis due to potential reproductive effects that may result from the father's exposure to benzene.

Figure 7.1



Benzene exposures to children and the prospective parents have been quantified by evaluating the ambient or background benzene levels in a child's/parent's air (indoor and outdoor), diet, and water as well as specific sources and microenvironments to which subpopulations of children may be exposed. Available data indicate that all children are exposed to background levels of benzene in the ambient air, water, and food supply as a result of releases from natural sources, mobile sources, and the chain of commerce sources described in Section 5. In addition to these ubiquitous sources, certain subpopulations of children may be exposed to benzene in microenvironments depending on specific activities, such as use of equipment or vehicles with internal combustion engines or living in a home where tobacco smoking occurs (either used by parents or teenage children).

For most people, exposure to benzene is a daily occurrence. Inhalation is the primary and dominant pathway of exposure, comprising the major component of individuals' total benzene exposure (WHO, 1993). Also, benzene has been shown to occur at low levels in a large number of foods as the result of naturally occurring levels or possibly as a result of cooking processes. Although dermal exposures to benzene are generally insignificant due to its high volatility, this exposure route was also evaluated.

Benzene exposures vary by age. This age variation occurs because individuals interact with different sources in different ways at different ages. Thus, a small child may be passively exposed to benzene while riding in a car, whereas only an older child (teenager) or an adult will have an exposure when actively refueling the car. Age variation also occurs because exposure-related characteristics such as body weight, breathing rate, and diet vary with age. As such, exposure scenarios have been developed for different age groups. Five age groups have been chosen based on relevant activities upon which children spend substantial amounts of time

throughout childhood, see Table 7.1. Also, the recent Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens was used to define relevant age groupings (EPA, 2005). In accordance with this guidance age groupings with a "break point" of less than two years of age and less than 16 years if age were included.

Table 7.1: Age Groupings Used in the Benzene Exposure Assessment

Age Group	Category	Subcategory
<1 year	Children	Infant
1 to <2 years		Infant
2 to <6 years		Toddler
6 to <16 years		Child
16 to <19 years		Teenager
19 to <36 years	Prospective parents	Prospective parents

Exposures from each source of benzene are characterized using scenarios. The exposure scenarios define the population, source, and the exposure factors that determine the child's benzene intake. A summary of ambient and the source-specific exposure scenarios for specific age groups is provided in Table 7.2.

Table 7.2: Summary of Ambient and Source Specific Benzene Exposure Scenarios

Exposure Scenarios	Age Group					
	< 1 year old	1 to < 2 year old	2 to < 6 year old	6 to < 16 year old	16 to < 19 year old	19 to < 36 year old
Ambient Exposures						
Outdoor Air						
Urban	✓	✓	✓	✓	✓	✓
Rural	✓	✓	✓	✓	✓	✓
Industrial Source Area	✓	✓	✓	✓	✓	✓
Indoor Air						
In-home	✓	✓	✓	✓	✓	✓
In-School				✓	✓	
In-Vehicle	✓	✓	✓	✓	✓	✓
Food	✓	✓	✓	✓	✓	✓
Water	✓	✓	✓	✓	✓	✓
Source-Specific Exposures						
Tobacco Smoke						
ETS	✓	✓	✓	✓	✓	✓
Mainstream					✓	✓
Refueling					✓	✓
Small Engine Use					✓	✓
Occupational						
Production/Processing						✓
Non-Production						✓

✓ Included in evaluation.

A child's exposure to benzene depends upon a number of variables, or exposure factors. These exposure factors can be activity or physiologically related and vary with age. The benzene childhood exposure assessment includes male and female children of all ages, and prospective parents. The relevant exposure parameters associated with each exposure scenario and age group are presented in Appendix A-1.

For the various types of exposure, efforts were made to characterize both typical exposures and high-end exposures. In general, typical exposures were calculated using the average of the reported values of exposure concentrations and exposure parameters (i.e., exposure frequency, body weight, inhalation rate, etc.) that reflect the average values in the exposed populations. High-end exposures for sources of benzene were calculated using exposure concentrations representative of a 90 - 95th percentile of the range of values in a dataset (where data were sufficient to allow the determination of a range).

7.2 Sources of Benzene Exposure

Childrens' exposures to benzene were quantified based on information provided in the scientific peer-reviewed literature or through exposure modeling using various EPA exposure models. The sources of benzene have been defined in terms of two general source categories: ambient sources of exposures and exposures resulting from specific sources.

7.2.1 Ambient Environmental Exposures

Ambient childhood exposures to benzene could occur from four general sources: 1) ambient air, 2) food, 3) drinking water, and 4) human milk. Potential exposures to each source are described further below.

7.2.1.1 Ambient Air

During the 1980s and early 1990s the EPA funded and provided oversight for human exposure research with the objective of directly measuring exposure to VOCs using personal air samplers. The conclusion of this extensive research project, known as the EPA Total Exposure Assessment Methodology (TEAM) Studies, was that the most important sources of exposure are small and originate close to the person (Wallace, 2001). The presence of major point sources, such as refineries and chemical facilities, was not correlated with increased personal exposure to organic chemicals. For many chemicals, including benzene, distant sources of air releases play a smaller part in the determination of total exposure than localized sources such as use of petroleum products, time spent in vehicles, and use of tobacco products.

The Clean Air Act Amendments of 1990 provided for creation of the National Urban Air Toxics Research Center (NUATRC). The goal of this organization is to promote, develop and support research related to human health risks from air toxics. As part of the NUATRC mission, several studies were conducted where VOC exposures to children were evaluated. The Health Effects Institute (HEI) and the Mickey Leland National Urban Air Toxics Research Center (NUATRC) jointly funded a project called the Relationship between Indoor, Outdoor and Personal Air (RIOPA); a large urban air toxics project that was comprised of three studies. The RIOPA project tested the hypothesis that personal exposure to air toxics is influenced by outdoor sources of these air toxics. It involved 3 cities with different air pollution source profiles: Los Angeles, California is dominated by mobile sources; Houston, Texas is dominated by industrial point sources; and Elizabeth, New Jersey includes a mixture of mobile and point sources. In each city, 100 homes were monitored for 48 hours in each of 2 seasons. The homes were monitored indoors and outdoors for particulate matter smaller than 2.5 microns ($PM_{2.5}$), VOCs, and aldehydes. In addition, personal exposure to $PM_{2.5}$, VOCs, and aldehydes, and in-vehicle exposure to aldehydes were measured for residents of these homes. In general it was found that indoor air benzene concentrations were higher than outdoor air, but lower than the personal benzene concentrations.

A community based study conducted by Buckley et al., (2005) in Baltimore also evaluated the impact of industry on community air quality and individual resident exposure to15 VOCs. The study was designed to examine the potential industry effect by comparing indoor, outdoor, and personal air concentrations in South Baltimore to those in Hampden, an urban Baltimore community with a less intense industrial presence. Buckley et al. concluded that except for ethylbenzene and m,p-xylene, the VOC concentrations at all three levels of monitoring (outdoor, indoor, and personal) were comparable in the two communities, suggesting no industrial impact or an impact smaller than that detectable with the sample size of the study. For the two

chemicals where there appeared to be a possible impact, the indoor and outdoor differences did not translate into significant differences in personal exposure levels between the two communities.

Inhalation of benzene in outdoor and indoor air was evaluated for each childhood age grouping and the prospective parents. For ambient outdoor air, both urban and rural settings were considered. For indoor air, both in-home and in-school exposures were considered.

7.2.1.2 Ambient Outdoor Air

General urban and rural ambient air concentrations of benzene were obtained from EPA's National Air Toxics Assessment (NATA) database (EPA, 1996). This national-scale assessment was conducted in 1996 for 33 air pollutants, including benzene. NATA compiled the 1996 national emissions inventory of air toxics emissions from outdoor sources, and estimated ambient concentrations using the ASPEN air dispersion model.

The NATA database was designed to help EPA, state, local and tribal governments and the public better understand air toxics in the U.S. It is comprised of data from the following primary sources of data for the NATA database:

- State and local toxic air pollutant inventories;
- Existing databases related to EPA's air toxics regulatory program;
- EPA's TRI database;
- Estimates developed by EPA's Office of Transportation and Air Quality using mobile source methodology; and
- Emission Estimates generated from emissions factors and activity data.

As compared to random measured concentrations in various literature studies, the NATA database is a comprehensive ambient air database that is representative of the US, and the various US counties. It provides a nationwide average as well as provides urban and rural averages. Although there are uncertainties inherent in the database, benzene has the highest confidence of all of the air pollutants. An EPA comparison of the estimated NATA benzene concentrations to actual data from monitoring sites indicated a relatively good agreement between the two. In general, for all pollutants, the NATA data erred on the low side when compared to exact monitoring locations, but at greater distances (e.g. 10 – 20 km), the modeled concentrations appeared to be in better agreement. For benzene, 89% of the modeled concentrations were within a factor of 2 of the actual concentrations at monitoring sites.

Queries for "all urban counties" and "all rural counties" were run and the results are presented in Table 7.3 below.

Table 7.3: Outdoor Ambient Air Benzene Concentrations from NATA 1996

NATA Query	Setting Utilized	Median ($\mu g/m^3$)	Mean ($\mu g/m^3$)	95th Percentile ($\mu g/m^3$)
Nationwide	Nationwide	1.21	1.39	2.8
All Urban Counties	Urban	1.41	1.57	3.0
All Rural Counties	Rural	0.66	0.72	1.2
Texas	Harris County	2.1	2.3	3.3
New York	New York County	4.8	5.4	9.3

In determining a representative ambient outside air concentration for the child and prospective parents, the NATA database mean values of 1.57 $\mu g/m^3$ for an urban setting and 0.72 $\mu g/m^3$ for a rural setting have been selected. The mean concentrations were selected as they are reasonable estimates of concentrations likely to be contacted over time (EPA, 1989). It should be noted that the NATA results represent modeled ambient air concentrations from emissions data collected in 1996[1] and thus may not reflect the potentially significant emission reductions that have taken effect in the last ten years, including those from: 1) mobile source regulations which are being phased in over time; 2) many of the air toxics regulations that EPA has issued for major industrial sources; 3) state or industry initiatives; and 4) any facility closures (EPA, 1996). Because of this, the NATA concentrations listed on Table 7.3, may overestimate the current national averages. For example, Kinney et al. (2002) conducted an air monitoring study in New York City during 1999 to characterize levels and factors affecting exposure to benzene. This study reported benzene concentrations 2.8 times lower than the NATA 1996 modeled mean concentrations for New York County.

Although Wallace and more recently, Buckley et al., have concluded that industrial sources of benzene are not important with regards to personal benzene exposures on a nationwide basis (Wallace, 2001; Buckley et al. 2005), potential benzene exposures were evaluated for those living in close proximity to the highest industrial benzene emitters in urban and rural locations. For such residents, the NATA data and that from individual air monitoring stations can be used to understand the potential differences in benzene exposure a child might receive from outdoor air if residing in close proximity to an industrial source. For this exposure assessment, the top five TRI reporting facilities for benzene air releases were evaluated. The currently available TRI release data are for reporting year 2003. The TRI was queried to identify the top five urban and rural benzene air emitters, which are listed on Table 7.4.

[1] Since the time of this analysis, the EPA released an updated NATA using the 1999 emissions inventory. The updated NATA for benzene indicated that the predicted 1999 ambient air concentrations of benzene nationwide and for the 'all urban' and 'all rural' counties were similar to the 1996 modeled estimates.

Table 7.4: Top Five 2003 TRI Sources of Benzene in Rural and Urban Settings

Urban	Total Air Releases (pounds)	Rural	Total Air Releases (pounds)
1. U.S. Sugar Corp. Bryant Mill, Palm Beach County, FL	296,864	1. Georgia-Pacific Big Island Mill, Bedford County, VA	154,000
2. Holcim (US) Inc. Dundee Plant, Monroe County, MI	272,854	2. Holcim (US) Inc. Clarksville Plant, Pike County, MO	150,000
3. ExxonMobil Baytown Chemical Plant, Harris County, TX	121,052	3. U.S. Sugar Corp. Clewiston Mill, Hendry County, FL	101,272
4. Equistar Chemicals LP, Harris County, TX	112,000	4. Wheeling-Pittsburgh Steel Corp. Follansbee Plant, Brooke County, WV	90,000
5. Chalmette Refining LLC, St. Bernard Parish, LA	110,430	5. Valero Three Rivers Refinery, Live Oak County, TX	59,403

As shown on Table 7.4, two of the top five urban emitters (i.e., ExxonMobil and Equistar Chemicals) are located in the same county, Harris County. Together these two facilities emit approximately 80% of the benzene to the ambient air that the largest emitter nationwide, – U.S. Sugar Corp does. Ten of the top 100 facilities that report benzene air releases on the TRI are in Harris County, TX. As such, Harris County is an example of an industrial area with significant point source releases of benzene to the ambient air.

The NATA database was queried to obtain predicted concentrations for the counties in which the Top 5 TRI reporting facilities are located. Additionally, EPA's AIRS Database was queried to obtain measured ambient air benzene concentrations. The data in the AIRS database come from fixed monitoring stations around the country, where samples are collected approximately weekly (every 6 to 10 days). For the most part, these monitoring stations are located in urban or suburban environments, with very few in rural settings. A summary of the NATA and AIRS data is presented on Table 7.5.

Table 7.5: County-Wide 24-hour Ambient Air Benzene Concentrations

URBAN		1996 NATA		2003 AirData*		
Facility	County	Mean ($\mu g/m^3$)	95th Percentile ($\mu g/m^3$)	N*	Mean ($\mu g/m^3$)	95th Percentile ($\mu g/m^3$)
1. U.S. Sugar Corp. – Bryant Mill	Palm Beach County, FL	1.1	1.6	--	--	--
2. Holcim (U.S.) Inc. Dundee Plant	Monroe County, MI	1.0	1.3	--	--	--
3. ExxonMobil Baytown Chemical Plant*	Harris County, TX	2.3	3.3	49 26	1.8 8.4	3.3 16.7
4. Equistar Chemicals, LP*	Harris County, TX	2.3	3.3	45 6,956	2.8 3.1	6.1 8.8
5. Chalmette Refining LLC	St. Bernard Parish, LA	1.8	3.8	--	--	--

RURAL		1996 NATA		2003 AirData		
Facility	County	Mean ($\mu g/m^3$)	95th Percentile ($\mu g/m^3$)	N	Mean ($\mu g/m^3$)	95th Percentile ($\mu g/m^3$)
1. Georgia-Pacific Big Island Mill	Bedford County, VA	0.82	10.3	--	--	--
2. Holcim (US) Inc. Clarksville Plant	Pike County, MO	0.58	0.69	--	--	--
3. U.S. Sugar Corp. Clewiston Mill	Hendry County, FL	0.61	0.68	--	--	--
4. Wheeling-Pittsburgh Steel Corp. Follansbee Plant	Brooke County, WV	1.2	2.5	--	--	--
5. Valero Three Rivers Refinery	Live Oak County, TX	0.61	0.65	--	--	--

* There are available data from two adejacent monitoring stations for both Baytown, TX and Channelview, TX.

Table 7.5 shows that for Harris County, the predicted concentrations from NATA are in general agreement with the measured concentrations obtained from the AIRS database. Data from these monitors indicate 24-hour mean ambient benzene concentrations ranging from 1.7-4.4 $\mu g/m^3$. Thus, although these averages exceed the predicted national urban benzene mean of 1.57 $\mu g/m^3$ (See Table 7.1), they are the same order of magnitude, with the ratio of the Harris County concentrations to the national urban mean ranging from 1.1 to 2.8.

Comparing the nationwide urban benzene concentrations from NATA to that of measured ambient air concentrations in urban areas where significant industrial releases of benzene to the atmosphere occur (i.e., Harris County, TX), shows that outdoor air exposures in industrial release areas may be 1 to 3 fold higher than the national mean for urban settings. Thus, although they may not necessarily directly correlate to personal exposures, ambient air benzene exposures to children in these areas may be higher than national exposures.

The data used to represent typical urban and rural concentrations are presented on Table 7.6a. These values were obtained from the 1996 NATA data. The data used to represent the urban and rural high-end exposure concentrations are presented on Table 7.6b. The 2003 urban value is from 2000 AirData. Because there were no rural data near the top five rural sources in 2003 AirData, the rural value is from 2000 AirData.

Table 7.6a: Representative Typical Ambient Air Benzene Concentrations in Rural and Urban Areas

Setting	Typical Exposure Concentration (µg/m^3)	Description
Rural	0.72	1996 NATA mean of "all rural" data
Urban	1.57	1996 NATA mean of "all urban" data

Table 7.6b: Representative High-End Ambient Air Benzene Concentrations in Areas of Industrial Releases

Setting	High-End Exposure Concentration (µg/m^3)	Description
Rural	1.0	2000 AirData; Rural mean concentration
Urban	4.4	2003 AirData; mean concentration at the monitoring station closest to highest urban TRI emitter (Harris County, TX)

The typical and high-end exposure concentrations listed above were used to calculate benzene intakes from exposure to outdoor ambient air. Exposure was quantified for residents living in urban and rural settings according to the following equation:

$$ADD = \frac{C \times ED \times EF \times ET \times IR \times ABSi \times CF}{BW \times AT}$$

where:

ADD = average daily dose (mg/kg-day)
C = concentration of benzene in ambient air (µg/m^3)
ED = exposure duration (years)
EF = exposure frequency (days/year)
ET = exposure time (hours/day)
CF = conversion factor (0.001 mg/µg)
ABSi = benzene inhalation absorption factor; 0.5 (unitless)
IR = inhalation rate (m^3/hour)
BW = body weight (kg)
AT = averaging time (days)

Age-specific benzene intakes are presented below in Tables 7.7 and 7.8. In this exposure assessment, ambient exposures were calculated so as to appropriately represent the exposure frequencies and exposure times for school days and non-school days. For children, ambient outdoor exposures for school and non-school days were summed to ADDs representing a full year of exposure. For the infant and adult, it was assumed that all days are non-school days. Table 7.9 presents the total ADDs from outside ambient air exposures.

Table 7.7: ADDs for School Day Exposure to Benzene in Ambient Air

		Rural – Typical				Rural- High-end			
Exposure Parameter	**Units**	**1 to <2 year old**	**2 to <6 year old**	**6 to <16 year old**	**16 to <19 year old**	**1 to <2 year old**	**2 to <6 year old**	**6 to <16 year old**	**16 to <19 year old**
C	$\mu g/m^3$	0.72	0.72	0.72	0.72	1.0	1.0	1.0	1.0
ET	h/d	1.6	2.3	1.6	1.9	1.6	2.3	1.6	1.9
EF	d/y	180	180	180	180	180	180	180	180
ED	years	1	4	10	3	1	4	10	3
IR	M^3/h	0.28	0.33	0.52	0.60	0.28	0.33	0.52	0.60
CF	Mg/µg	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
AT	days	1095	1095	3650	1095	1095	1095	3650	1095
BW	kg	11.4	16.1	41	67	11.4	16.1	41	67
ABSi	unitless	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Dose	***mg/kg-d***	***2.3E-06***	***1.1E-05***	***3.6E-06***	***3.0E-06***	***3.2E-06***	***1.5E-05***	***5.0E-06***	***4.2E-06***
		Urban – Typical				**Urban – High-end**			
C	$\mu g/m^3$	1.57	1.57	1.57	1.57	4.4	4.4	4.4	4.4
ET	h/d	1.6	2.3	1.6	1.9	1.6	2.3	1.6	1.9
EF	d/y	180	180	180	180	180	180	180	180
ED	years	1	4	10	3	1	4	10	3
IR	M^3/h	0.28	0.33	0.52	0.60	0.28	0.33	0.52	0.60
CF	Mg/µg	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
AT	days	1095	1095	3650	1095	1095	1095	3650	1095
BW	kg	11.4	16.1	41	67	11.4	16.1	41	67
ABSi	unitless	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Dose	***mg/kg-d***	***5.1E-06***	***2.4E-05***	***7.8E-06***	***6.6E-06***	***1.4E-05***	***6.8E-05***	***2.2E-05***	***1.9E-05***

Table 7.8: ADDs for Non-School or Non-Work Day Exposure to Benzene in Ambient Air

Exposure Parameter	Units	Rural- Typical							Rural- High-end						
		<1 year old	1 to <2 year old	2 to <6 year old	6 to <16 year old	16 to <19 year old	19 to <36 year old female	19 to <36 year old male	<1 year old	1 to <2 year old	2 to <6 year old	6 to <16 year old	16 to <19 year old	19 to <36 year old female	19 to <36 year old male
C	µg/m^3	0.72	0.72	0.72	0.72	0.72	0.72	0.72	1.0	1.0	1.0	1.0	1.0	1.0	1.0
ET	h/d	1.4	1.6	3.1	2.2	2.3	1.5	1.5	1.4	1.6	3.1	2.2	2.3	1.5	1.5
EF	d/y	365	185	185	185	185	365	365	365	185	185	185	185	365	365
ED	years	1	1	4	10	3	17	17	1	1	4	10	3	17	17
IR	m^3/h	0.19	0.28	0.33	0.52	0.60	0.47	0.63	0.19	0.28	0.33	0.52	0.60	0.47	0.63
CF	mg/µg	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
AT	days	365	1095	1095	3650	1095	6205	6205	365	1095	1095	3650	1095	6205	6205
BW	kg	7.2	11.4	16.1	41	67	62.4	76.3	7.2	11.4	16.1	41	67	62.4	76.3
ABSi	unitless	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Dose	***mg/kg-d***	***1.3E-05***	***7.2E-06***	***1.2E-05***	***5.1E-06***	***3.8E-06***	***4.1E-06***	***4.5E-06***	***1.8E-05***	***1.0E-05***	***1.6E-05***	***7.1E-06***	***5.2E-06***	***5.6E-06***	***6.2E-06***
		Urban – Typical							Urban – High-end						
C	µg/m^3	1.6	1.6	1.6	1.6	1.6	1.6	1.6	4.4	4.4	4.4	4.4	4.4	4.4	4.4
ET	h/d	1.4	1.6	3.1	2.2	2.3	1.5	1.5	1.4	1.6	3.1	2.2	2.3	1.5	1.5
EF	d/y	365	185	185	185	185	365	365	365	185	185	185	185	365	365
ED	years	1	1	4	10	3	17	17	1	1	4	10	3	17	17
IR	m^3/h	0.19	0.28	0.33	0.52	0.60	0.47	0.63	0.19	0.28	0.33	0.52	0.60	0.47	0.63
CF	mg/µg	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
AT	days	365	1095	1095	3650	1095	6205	6205	365	1095	1095	3650	1095	6205	6205
BW	kg	7.2	11.4	16.1	41	67	62.4	76.3	7.2	11.4	16.1	41	67	62.4	76.3
ABSi	unitless	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Dose	***mg/kg-d***	***2.9E-05***	***1.6E-05***	***2.5E-05***	***1.1E-05***	***8.2E-06***	***8.9E-06***	***9.7E-06***	***8.1E-05***	***4.4E-05***	***7.1E-05***	***3.1E-05***	***2.3E-05***	***2.5E-05***	***2.7E-05***

Table 7.9: Total ADDs for Exposure to Benzene in Ambient Air (mg/kg-day)

	<1 year old	1 to <2 year old	2 to <6 year old	6 to <16 year old	16 to <19 year old	19 to <36 year old female	19 to <36 year old male
Rural Typical	1.3E-05	1.4E-05	2.0E-05	8.7E-06	6.8E-06	4.1E-06	4.5E-06
Rural High-End	1.8E-05	2.0E-05	2.8E-05	1.2E-05	9.4E-06	5.6E-06	6.2E-06
Urban Typical	2.9E-05	3.1E-05	4.4E-05	1.9E-05	1.5E-05	8.9E-06	9.7E-06
Urban High-End	8.1E-05	8.6E-05	1.2E-04	5.3E-05	4.2E-05	2.5E-05	2.7E-05

7.2.1.3 Ambient Indoor Air

Indoor air concentrations of benzene were obtained from the summary of the residential indoor air data reported in the ATSDR Toxicological Profiles for benzene (ATSDR, 2005), various residential indoor air studies and indoor air quality studies of schools. All of these data sources demonstrate that the indoor air generally has higher concentrations of benzene than the outdoor ambient air. The reason for this is the other sources of benzene that contribute to the overall indoor load, in particular those related to tobacco smoke and attached garages.

The indoor environment in which children and prospective parents spend the most time is the home. Benzene in indoor air occurs as a result of a variety of sources including infiltration from the outdoor air, smoking tobacco products, infiltration from attached garages, wood stoves, and cooking. Given that benzene is not a chemical constituent found in solvent-based household products such as paints, varnishes, glues, or personal/beauty care items, it is believed that all indoor benzene results from combustion sources or gasoline (both outdoor ambient air contribution and indoor sources from attached garages).

A number of monitoring studies have been performed for benzene in indoor air. ATSDR estimated that indoor benzene concentrations in US homes range from 2.0 $\mu g/m^3$ to 47.5 $\mu g/m^3$, and has an average of 5.74 $\mu g/m^3$ (ATSDR, 2005). The data used to generate this range come from records entered into the Volatile Organic Compound National Ambient database (1975-1985), representing data from 30 cities in 16 different states. Because of reductions in benzene levels in the outdoor ambient air as a result of improved vehicle emission controls and reductions in benzene content in gasoline, the ATSDR average and high-end indoor concentrations may overestimate current in-home levels. Several studies from the mid 1990s to the present were identified (Adgate et al., 2004a.b; Bozzelli et al., 1995; Buckley et al., 2005; Clayton et al., 1999; Gordon et al., 1999; HEI, 2005; Hodgson et al., 2000; Kinney et al., 2002; Phillips et al., 2004; and Van Winkle and Scheff, 2001). Table 7.10 summarizes the data from these studies. Additionally, a recent study by Batterman et al. (2006) provided data for benzene concentrations in garages. However, this study did not provide the associated indoor air concentrations for the homes studied and therefore was not useful for the indoor air analyses.

Table 7.10: Summary of Current Published Indoor Air Studies of Benzene

Study	Location and Date	Indoor Concentration ($\mu g/m^3$)	Notes
Adgate et al., 2004a	Minneapolis, MN, St. Paul, MN, Rice County MN, and Goodhue County MN 1997	3.9 (mean) 2.8 (25^{th} percentile) 3.1 (50^{th} percentile) 7.5 (95^{th} percentile)	Evaluated 101 private residences for indoor air, outdoor air and personal air concentrations of VOCs. Examined both urban and non-urban households and included smoking and non-smoking households and those with and without attached garages
Adgate et al., 2004b	Minneapolis, MN 2000	2.2 (median) 0.7(avg of winter and spring 10^{th} percentiles) 6.7 (avg of winter and spring 90^{th} percentiles)	Evaluated 113 different households measuring indoor home air, outdoor air, in-school air and personal air concentrations of VOCs in an urban area. Both single family homes (43%) and apartments (55%) were surveyed, and included both smoking and non-smoking households.
Bozzelli, et al., 1995	Elizabeth, NJ Prior to 1994	12 – 17	Evaluated indoor air impacts during use of kerosene heaters. Data on this table is without the heaters in use.
Buckley, et al., 2005	South Baltimore, and Hampden MD Jan 2000 – July 2001	1.9 (mean) 1.0 (25^{th} percentile) 1.9 (50^{th} percentile) 3.0 (90^{th} percentile)	Evaluated 36 non-smoking homes in South Baltimore and 21 non-smoking homes in Hampden, MD for outdoor, indoor and personal air VOC exposures. Children were included in the personal monitoring program. Questionnaires were provided to each household to document indoor activities and home characteristics.
Clayton et al., 1999	EPA Region 5 (Illinois, Indiana, Ohio, Michigan, Minnesota, and Wisconsin 1995 - 1997	7.21 (mean) 4.35 (median) 12.95 (90^{th} percentile)	This is a report of the National Human Exposure Assessment Survey (NHEXAS) Phase I field study and included 402 indoor air measurements for 4 different VOCs. Both urban and non-urban households were included in the study including those with attached garages

Table 7.10 (cont.)

Study	Location and Date	Indoor Concentration (µg/m^3)	Notes
Gordon et al., 1999	Arizona 1995 - 1998	1.3 (median) 4.0 (75th percentile) 9.5 (90th percentile) 90 (maximum)	This is a report of the National Human Exposure Assessment Survey (NHEXAS) Phase I conducted in Arizona. 185 households were included in the study including those with attached garages.
Hodgson et al., 2000	East and Southeast US November 19, 1997 and May 1, 1998	1.6 – 4.8	Measured values in 11 newly constructed homes prior to occupancy. Both manufactured and site-built homes included
Kinney et al., 2002	New York City, NY 1999	5.97; 1.75(winter and summer means, ranges not reported)	Study of 8 homes to characterize personal exposures to urban air toxics in inner city neighborhoods.
Phillips et al., 2004	Oklahoma City, OK; Tulsa, OK; Ponca City, OK; Stillwater, OK 2000 - 2001	0.62 (median, day) 1.2 (median, night) 14 (max day) 110 (max night)	Study of 37 U.S. homes in urban and rural Oklahoma to characterize indoor, outdoor and personal air concentrations of various VOCs. Presence of refinery was a primary factor investigated.
Van Winkle and Scheff, 2001	Chicago, IL 1994 - 1995	1.3 – 34 2.9 (median)	Study of 10 homes where simultaneous indoor and outdoor samples were collected.
Weisel, 2005	Los Angeles, CA; Houston, TX and Elizabeth, NJ Summer 1999 through Spring 2000	3.5 (mean) 0.48 (5th percentile) 2.19 (50th percentile) 10 (95th percentile)	Studies were conducted in three urban centers and measured benzene among 16 VOCs to evaluate the relationship between outdoor, indoor and personal air. For all three cities combined, 554 indoor air samples for benzene were collected.

The average of the medians, 2.5 µg/m^3 was used as the exposure point concentration for the typical indoor air concentration.

As indicated in Table 7.10, indoor air concentrations will vary greatly from home to home depending on the presence of various sources. High-end indoor air concentrations of benzene were estimated by evaluating source specific contributions to the indoor air. Unlike toluene and

other solvents which can be found in household products and off-gassing from indoor furnishings, the primary sources of benzene are gasoline and combustion sources.

Studies have shown that homes with attached garages have a higher range of indoor concentrations of benzene than homes without attached garages (Adgate et al., 2004; Thomas et al., 1993, Brown and Crump, 1998; Schlapia and Morris, 1998; Isbell et al., 1999; Phillips et al., 2004; Tsai and Weisel, 2000 and Mann et al., 2001). Attached garages elevate indoor levels when benzene from garage sources such as evaporative emissions from automobiles, small engine equipment (i.e., lawnmowers, trimmers, and leaf blowers) storage containers and infiltrate the home.

An attached garage can be thought of as a discrete emission source to a home. However, the amount of benzene that actually enters the home will vary with the rate of infiltration from the garage to the home and the air levels of benzene in the garage. One investigation attributed more than 75% of benzene exposures in homes with attached garages to air entering from attached garages (Fulger et al., 2002), with the resultant levels in the home also being influenced by outdoor air levels and the whole house air exchange rates. Whole house air exchange rates vary with the season and are lower in cold weather (Murray and Burmaster, 1995). From the various attached garage studies, the following factors have been found to influence indoor benzene concentrations in homes with attached garages:

- Heating systems (forced air);
- Season in which the measurement is taken;
- Frequency and duration of parking the car in the garage;
- Emission characteristics of the car;
- Ventilation of the garage and home;
- Availability of vapor migration pathways from the garage to the living space;
- Other indoor sources and outdoor levels of benzene; and
- Amount and type of car maintenance undertaken in the garage.

A summary of indoor air studies of homes with attached garages used in this assessment is presented in Table 7.11. Several of the studies cited above were not used in the high-end indoor air scenario evaluation. Tsai and Weisel (2000) was not deemed representative for purposes of understanding typical benzene exposures because an experimental gasoline, M85, which is 85% methanol and 15% conventional gasoline, was used in the study. Phillips et al (2004) was not used in this analysis as the authors indicated that the presence of an automobile or other gasoline source(s) were not documented at the time of the study (personal communication with Phillips and J. Panko, 2004). And several studies (Isbell et al., 1999 and Schlapia and Morris, 1998, Morris 2004) conducted in Alaska are discussed separately in Section 7.2.1.5. The remaining four studies were selected for use in deriving the estimate of the mean concentrations in homes with attached garages.

Table 7.11: Summary of Benzene Measurements from Attached-Garage Studies

Study	Location	Benzene Concentration ($\mu g/m^3$)	Comments
Thomas et al., 1993	Home 1	21	New Jersey, December 1987. Benzene content in gasoline not assessed. Information about automobiles parked in garages not given. Measurements obtained in the living rooms and bedrooms.
	Home 2	5.7	
	Home 3	34	
	Home 4	15.5	
	Study Mean	19.1	
Brown and Crump, 1998	Study Mean (11 homes)	11.1	UK, March 1994 - November 1995. Benzene content in gasoline not assessed. Information about automobiles parked in garages not given. Measurements obtained in the living rooms and bedrooms.
Mann et al., 2001	Home 1	7.8	Southampton, UK, June 1998 - November 1999. Benzene content in gasoline between 1 and 5%. Car model years ranged from 1986 - 1992; all carbureted engines. Measurements obtained in the living rooms, bedrooms and rooms above or adjacent to the garage.
	Home 2	8.7	
	Home 3	28.3	
	Home 4	9.7	
	Study Mean	13.6	
Adgate et al., 2004b	94 homes	11.5 (mean) 3.3 (10^{th} percentile) 27.5 (90^{th} percentile) (See Note)	Evaluated 426 private residences in 1997 for indoor air, concentrations of benzene. Of those homes 94 had attached garages with at least one vehicle parked in it during the study period. Additionally 44 homes had sources of gasoline other than or in addition to a vehicle (i.e., gas cans, small engine equipment, etc.)

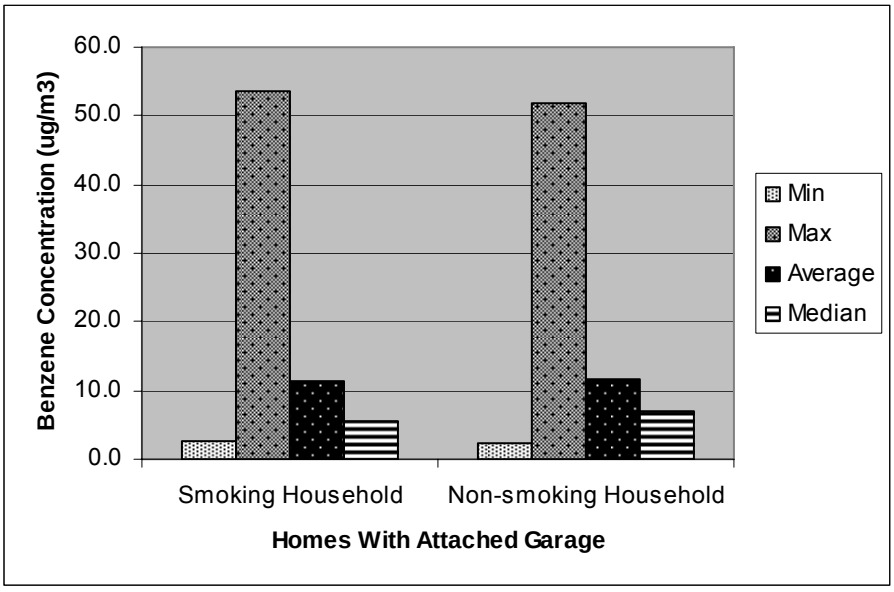
Note: These data were presented in the published manuscript, but were derived from the raw study data.

Of the studies listed on Table 7.11, Adgate et al. (2004) was determined to be the best available study for assessing high-end indoor air benzene concentrations. Brown and Crump, 1998 and Mann et al., 2001 were determined to be not representative because the studies were conducted in the U.K where the benzene content in the gasoline was reported as up to 3 times higher than gasoline used in the US during the same time period. Additionally, Thomas et al., (1993) was conducted in 1987 and has limitations because of the small sample size (N-4) and older vehicle fleet years.

The raw data from the Adgate et al. (2004b) study were obtained from the Minnesota Department of Health and analyzed for homes with attached garages. The study also included homes where the presence of a smoker was documented. The indoor air concentrations of benzene for these households ranged from 3.1 to 53.6 $\mu g/m^3$ with an average concentration of 11.5 $\mu g/m^3$. The data were also analyzed to determine if the presence of a smoker in the home

influenced the indoor air benzene concentratons. Figure 7.2 shows a comparison of various descriptive statistics of the attached garage homes.

Figure 7.2 Comparison of Indoor Air Benzene Concentrations in Smoking and Non-Smoking Households with Attached Garages



As shown on Figure 7.2, the presence of a smoker in a home with an attached garage has little to no impact on the indoor air concentrations of benzene in the home. This indicates that the attached garage is a more significant source of benzene in the indoor air, than benzene from environmental tobacco smoke (ETS). The contribution to children's benzene exposure is further discussed in Section 7.2.2.2. Accordingly, the high-end indoor air concentration used in this assessment was 11.5 µg/m^3.

7.2.1.4 Indoor Air Trends Analysis

Given the continued improvements in vehicle emission controls and the widespread use of reformulated gasoline, it is likely that indoor air concentrations of benzene will continue to decrease. In an effort to understand this likely trend, a factor was developed to normalize the "historical" measured indoor air data to current day conditions. This factor was derived using EPA's MOBILE 6.2 model. MOBILE is an EPA emissions factor model for estimating pollution from on-road motor vehicles. The model accounts for the emission impacts of factors such as changes in vehicle emission standards, changes in vehicle populations and activity (i.e., fleet differences), and variation in local meteorological conditions, fuel properties and air quality programs.

In deriving the normalization factor (NF), MOBILE 6.2 was used to estimate the change in benzene emission rates given the historical and current conditions of fleet and fuel properties. Fleet and fuel properties in Minnesota served as the basis for the normalization factor because the Adgate et al. (2004b) study (conducted in Minnesota in 1997) was the most recent and robust dataset that was available. The fleet and fuel properties in Minnesota in 1997 and that in 2003 were modeled to estimate the change in evaporative emission rates (i.e., hot-soak, diurnal, and resting). The change in emission rates was then used to estimate the emission

factor change attributable to benzene content decreases in gasoline and those attributable to fleet emission control improvements. A detailed description of the methods used to derive the NF is presented in Appendix A.

The NF ranged from 1.07 to 1.24, depending on whether it was assumed that there were only cars in the garage, a mix of cars and small engine sources or small engines only. When the NF is applied to the measured air concentrations from Adgate et al. (2004b), the normalized concentrations ranged from 7% reduction in benzene concentrations for homes with small engines only in the garage to 18% reduction in homes with small engines and cars in the garage.

Based on this analysis, it is believed that the indoor air concentrations used in this assessment are conservative (i.e. exposure enhancing) estimates of children's exposure. Future residential indoor air studies will likely show that benzene air concentrations are lower than those used in this analysis.

7.2.1.5 Alaskan Indoor Air Studies

Several attached garage studies that measured benzene levels in indoor air have been conducted in Alaska (Isbell et al., 1999, Schalapia and Morris, 1998, and Morris 2004). The benzene measurements from these studies are provided in Table 7.12.

The indoor air concentrations of benzene measured in the Alaskan studies have been higher than those measured in the other attached garage studies (See Table 7.11). Also of note, Isbell et al. (1999) found that the reported concentrations were strongly correlated to the number of small engines stored in the garage and whether the home had a forced ventilation system or ventilated naturally via the building shell, windows and doors (Isbell, et al., 2005).

Several factors are believed to be related to these higher observed values. The benzene content of conventional gasoline produced in the lower 48 states is roughly 1% - well below the regulatory (Complex Model) limit of 5%. Due to equipment and demand limitations on refining operations, gasoline produced in Alaska generally contains higher levels than in the lower 48 states, ranging from 2.2 – 4.5% in the three indoor air studies conducted. It should be noted that although the benzene content in Alaskan gasoline is higher than that in the lower 48 states, levels have recently been declining and have dropped approximately a percentage point from 2002 (3.2 – 3.6%) to 2005 (2.3 – 2.8%) (AAM 2002-2005). Another probable reason that the Alaskan indoor air levels are higher is that the homes and garages are believed to have better insulation and lower air exchange rates. Based on these data, children in Alaska may be exposed to higher indoor air levels of benzene than the remainder of the U.S.

Table 7.12: Summary of Benzene Measurements from Attached Garage Studies in Alaska

Study	Location	Number of Small Engines in Garage	Benzene Concentration ($\mu g/m^3$)	Comments
Isbell et al., 1999	Home 1	0	3.8	Fairbanks, AK, July 1998. Benzene content in gasoline 3 - 4%. Information about automobiles parked in garages not given. Reported benzene concentrations were strongly correlated to the number of small engines (snowmobiles, snow blowers, chainsaws, etc.) stored in the garage. Location(s) sampled within the home were not discussed.
	Home 2	4	230.4	
	Home 3	0	1.3	
	Home 4	2	109.4	
	Home 5	0	16.3	
	Home 6	0	17	
	Home 7	0	35.8	
	Home 8	1	28.2	
		Study Mean:	**55.3**	
Schalapia and Morris, (1998)	91 homes with attached garages		Min = 0.64 Max = 1,161 Arithmetic mean = 71.5 Geometric mean = 21	Anchorage, AK, 1994 – 1996. Benzene content in gasoline from 2 major distributors in Anchorage ranged from 2.2 – 4.5%. Homes included single and multi-family structures, and approximately 15% of the homes were considered smoking households. No significant difference was found between homes with at least one smoker and those without. Benzene higher in homes with cars parked in garages, with forced air heating systems, a living area above the garage, and a fuel container opened within 3 days of indoor air testing.
Morris, (2004)	46 single family homes with attached garages		Mean = 24.2 Median = 16.4 Max = 113	Anchorage, AK, 2003 – 2004. Benzene content in gasoline described as 3.9% in presentation, though source is unclear. AAM survey indicates benzene levels in Alaskan gasoline ranged from 3.3 - 3.8 in 2003 and 2.1 – 3.5% in 2004. Homes included single family homes with attached garages that were selected as representative based on age of home and square footage. Air exchange rates were measured for each home and the garage. No significant association was shown between the benzene level in the garage and the number of vehicles parked in the garage, the age of vehicles in the garage, and the number of trips originating from the garage.

7.2.1.6 Daily Doses for Ambient Indoor Air

Age-specific average daily doses were calculated for in-home exposures using 2.5 $\mu g/m^3$ as the typical in-home exposure concentration (average of the median values presented on Table 7.10), and 11.5 $\mu g/m^3$ as the high-end exposure concentration from the attached garage study of Adgate et al. (2004b). Exposures were also quantified for residents in Alaska using the mean concentration of 24.2 $\mu g/m^3$ from Morris (2004). Exposure was quantified according to the following equation:

$$ADD = \frac{C \times ED \times EF \times ET \times IR \times ABSi \times CF}{BW \times AT}$$

where:

ADD = average daily dose (mg/kg-day)
C = concentration benzene in home air (μg/m^3)
ED = exposure duration (years)
EF = exposure frequency (days/year)
ET = exposure time (hours/day)
ABSi = benzene inhalation absorption factor; 0.5 (unitless)
CF = conversion factor (0.001 mg/μg)
IR = inhalation rate (m^3/hour)
BW = body weight (kg)
AT = averaging time (days)

The age-specific ADDs from in-home benzene exposures are presented in Tables 7.13-16.

Table 7.13: ADDS from School Day In-Home Benzene Exposures

		Typical			
Exposure Parameter	**Units**	**1 to <2 year old**	**2 to <6 year old**	**6 to <16 year old**	**16 to <19 year old**
C	μg/m^3	2.50	2.50	2.50	2.50
ET	h/d	19.5	17.4	15	14.2
EF	d/y	180	180	180	180
ED	years	1	4	10	3
IR	m^3/h	0.28	0.33	0.52	0.6
CF	mg/μg	0.001	0.001	0.001	0.001
AT	days	1095	1095	3650	1095
BW	kg	11.4	16.1	41.1	66.8
ABSi	unitless	0.5	0.5	0.5	0.5
Dose	***mg/kg-d***	***3.0E-04***	***2.2E-04***	***1.2E-04***	***7.9E-05***
		High-end			
C	μg/m^3	11.5	11.5	11.5	11.5
ET	h/d	19.5	17.4	15	14.2
EF	d/y	180	180	180	180
ED	years	1	4	10	3
IR	m^3/h	0.28	0.33	0.52	0.6
CF	mg/μg	0.001	0.001	0.001	0.001
AT	days	1095	1095	3650	1095
BW	kg	11.4	16.1	41.1	66.8
ABSi	unitless	0.5	0.5	0.5	0.5
Dose	***mg/kg-d***	***1.4E-03***	***1.0E-03***	***5.4E-04***	***3.6E-04***

Table 7.14: ADDS from Non-School or Non-Work Day In-Home Benzene Exposures

Exposure Parameter	Units	<1 year old	1 to <2 year old	2 to <6 year old	6 to <16 year old	16 to <19 year old	19 to <36 year old female	19 to <36 year old male
				Typical				
C	µg/m^3	2.50	2.50	2.50	2.50	2.50	2.50	2.50
ET	h/d	21.4	21.3	19.6	20.5	20.3	21.2	21.2
EF	d/y	365	185	185	185	185	365	365
ED	years	1	1	4	10	3	17	17
IR	m^3/h	0.19	0.28	0.33	0.52	0.6	0.47	0.63
CF	mg/µg	0.001	0.001	0.001	0.001	0.001	0.001	0.001
AT	days	365	1095	1095	3650	1095	6205	6205
BW	kg	7.2	11.4	16.1	41.1	66.8	62.4	76.3
ABSi	unitless	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Dose	***mg/kg-d***	***7.1E-04***	***3.3E-04***	***2.5E-04***	***1.6E-04***	***1.2E-04***	***2.0E-04***	***2.2E-04***
				High-end				
C	µg/m^3	11.5	11.5	11.5	11.5	11.5	11.5	11.5
ET	h/d	21.4	21.3	19.6	20.5	20.3	21.2	21.2
EF	d/y	365	185	185	185	185	365	365
ED	years	1	1	4	10	3	17	17
IR	m^3/h	0.19	0.28	0.33	0.52	0.6	0.47	0.63
CF	Mg/µg	0.001	0.001	0.001	0.001	0.001	0.001	0.001
AT	days	365	1095	1095	3650	1095	6205	6205
BW	kg	7.2	11.4	16.1	41.1	66.8	62.4	76.3
ABSi	unitless	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Dose	***mg/kg-d***	***3.2E-03***	***1.5E-03***	***1.2E-03***	***7.6E-04***	***5.3E-04***	***9.2E-04***	***1.0E-03***

Table 7.15: ADDs for Alaska In-Home Benzene Exposures

Exposure Parameter	Units	< 1 year old	1 to < 2 year old	2 to < 6 year old	6 to < 16 year old	16 to < 19 year old	19 to < 36 year old female	19 to < 36 year old male
		Average Daily Dose for Alaska In-home Non-School or Non-Work Day *						
C	µg/m^3	24.2	24.2	24.2	24.2	24.2	24.2	24.2
ET	h/d	21.4	21.3	19.6	20.5	20.3	21.2	21.2
EF	d/y	365	185	185	185	185	365	365
ED	years	1	1	4	10	3	17	17
IR	m^3/h	0.19	0.28	0.33	0.52	0.6	0.47	0.63
CF	mg/µg	0.001	0.001	0.001	0.001	0.001	0.001	0.001
AT	days	365	365	1460	3650	1095	6205	6205
BW	kg	7.2	11.4	16.1	41.1	66.8	62.4	76.3
ABSi	unitless	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Dose	***mg/kg-d***	***6.8E-03***	***3.2E-03***	***2.5E-03***	***1.6E-03***	***1.1E-03***	***1.9E-03***	***2.1E-03***

* Assumes an attached garage and the presence of a gasoline source such as a vehicle or small engine

Table 7.16: Total ADDS from In-Home Benzene Exposures (mg/kg-day)*

Indoor Scenario	<1 year old	1 to <2 year old	2 to <6 year old	6 to <16 year old	16 to <19 year old	19 to <36 year old female	19 to <36 year old male
Typical	7.1E-04	6.3E-04	4.7E-04	2.8E-04	1.9E-04	2.0E-04	2.2E-04
High-end	3.2E-03	2.9E-03	2.2E-03	1.3E-03	8.9E-04	9.2E-04	1.0E-03

* Excludes Alaskan dose estimates

7.2.1.7 In-School Air

There are no systematic program in the United States requiring the collection of indoor air samples for VOC analyses in schools. In cases where data is collected, the data are usually collected by a private consultant in response to an indoor air quality complaint. Results from these studies are not usually published; rather, they are typically presented as a private report to the school administration. Thus, database searches of the scientific published literature did not identify a large number of studies of schools and indoor concentrations of benzene that would be representative of schools nationwide.

EPA conducted 10 indoor air studies (n=39) of schools from 1995-1998 (EH&E, 2000). The purpose of these studies was to determine whether intervention actions could improve indoor air quality and other endpoints. The detection frequency of benzene in the schools was 79%, and the mean and high-end (95th percentile) concentrations were 3.1 µg/m^3 and 7.6 µg/m^3, respectively.

This study did not include information regarding the setting of the schools (i.e., urban, suburban, or rural). The representativeness of the data is questionable for schools nationwide because the schools that were studied were those for which complaints about the air quality had been made, and the air samples were collected prior to implementation of any interventions in any given building. Additionally, no data regarding the outdoor benzene concentrations were presented.

Two other studies of indoor air at public schools indicate that the in-school levels of benzene, are likely more comparable to concentrations found in the outside ambient air than concentrations typically found in homes. This was most evident in a nine-school study conducted in the Saugus Union School District in Santa Clarita, California (Speilman, 2000). In-school concentrations ranged from 0.83 to 2.3 µg/m^3 and had an average of 1.7 µg/m^3, and outdoor concentrations ranged from 0.86 to 2.8 µg/m^3 and had an average of 1.8 µg/m^3. The study was initiated under the EPA's Tools for Schools Program, which was developed to evaluate and ensure healthy indoor air quality for students and staff at U.S. schools. Indoor levels of total VOCs were measured concurrently with outdoor levels in each of the schools, and the researchers found that the indoor school concentrations were similar to the outdoor ambient concentrations. An additional study for a portable school building in the Saugus District (Spielman, 1999) found similar results: in-school concentrations ranged from 0.78 to 0.95 µg/m^3 and had an average of 0.9 µg/m^3, and outdoor concentrations ranged from 0.58 to 0.92 µg/m^3, and had an average of 0.79 µg/m^3.

In addition to the Spielman studies, an investigation by Brown et al. (1994) provides summary indoor air concentration data from numerous U.S. and overseas sources. Although benzene

wasn't specifically reported, the total VOC concentrations measured in this study indicated that the concentrations in-school were on average 6 times lower than those measured in homes.

Because none of the published studies are necessarily representative of in-school air quality nationwide, exposures have been estimated using both the findings of the Speilman and the EPA studies. The typical exposure is represented by the urban outdoor ambient concentration and the high-end exposure is represented by the high-end concentration from EPA's 10-school study (EH&E, 2000). These values are presented on Table 7.17.

Table 7.17: Typical and High-End In-School Benzene Exposures

Exposure	Benzene Concentration ($\mu g/m^3$)
Typical	1.6
High-End	7.6

Both typical and high-end benzene intakes from in-school exposures were calculated using the following equation:

$$ADD = \frac{C \times ED \times EF \times ET \times IR \times ABSi \times CF}{BW \times AT}$$

where:

ADD = average daily dose (mg/kg-day)
C = concentration of benzene in school air ($\mu g/m^3$)
ED = exposure duration (years)
EF = exposure frequency (days/year)
ET = exposure time (hours/day)
CF = conversion factor (0.001 mg/µg)
ABSi = benzene inhalation absorption factor; 0.5 (unitless)
IR = inhalation rate (m^3/hour)
BW = body weight (kg)
AT = averaging time (days)

The in-school total benzene ADDs were calculated and are presented on Table 7.18

Table 7.18: Summary of Age-Specific Doses from In-School Benzene Exposure

Exposure Parameter	Units	1 to <2 year old	2 to <6 year old	6 to <16 year old	16 to <19 year old
Typical					
Concentration	$\mu g/m^3$	1.6	1.6	1.6	1.6
Exposure Time	hours/day	1.8	3.0	6.1	6.5
Exposure Frequency	days/year	180	180	180	180
Exposure Duration	years	1	4	10	3
Inhalation Rate	m^3/h	0.28	0.33	0.52	0.60
Conversion Factor	mg/µg	0.001	0.001	0.001	0.001
Averaging Time	days	1095	1095	3650	1095
Body Weight	kg	11.4	16.1	41	67
Absorption Factor	unitless	0.5	0.5	0.5	0.5
Dose	***mg/kg-d***	***1.7E-05***	***2.4E-05***	***3.0E-05***	***2.3E-05***
High-end					
Concentration	$\mu g/m^3$	7.6	7.6	7.6	7.6
Exposure Time	hours/day	1.8	3.0	6.1	6.5
Exposure Frequency	days/year	180	180	180	180
Exposure Duration	years	1	4	10	3
Inhalation Rate	m^3/h	0.28	0.33	0.52	0.60
Conversion Factor	mg/µg	0.001	0.001	0.001	0.001
Averaging Time	days	1095	1095	3650	1095
Body Weight	kg	11.4	16.1	41	67
Absorption Factor	unitless	0.5	0.5	0.5	0.5
Dose	***mg/kg-d***	***8.3E-05***	***1.2E-04***	***1.4E-04***	***1.1E-04***

7.2.1.8 Food and Tap Water

Benzene occurs in both food and water; therefore, exposure to benzene can occur as a result of diet and tap water consumption. Benzene in tap water also causes exposure by inhalation and dermal routes during showering. Benzene exposures from these sources and routes are evaluated using LifeLine™ Version 2.0, a publicly available software program for the simulation of aggregate exposures to chemicals. This software allows the determination of the total concurrent intake from the oral exposures, ingestion of food and tap water, from dermal exposure to benzene in shower water, and inhalation exposures to benzene that is released from shower water. Infant exposure to benzene in human milk was determined separately as described in Section 7.2.1.3.

In the past, the published literature indicated that only trace amounts of benzene exist in food. A study of 50 foods found levels of 0 to 2 ppb benzene for foods without added benzoates (McNeal et al., 1993). A range of <1 to 38 ppb benzene was found in foods containing added benzoate (e.g., taco sauce or imitation strawberries). The U.S. Food and Drug Administration's (FDA's) Total Diet Study (TDS) program has been monitoring benzene levels in foods as consumed since 1995, and findings from this survey indicate that levels may be higher than

previously thought (Wallace et al., 1989). Data from this survey indicate that residues up to 190 ppb have been found in some prepared foods such as pan-fried ground beef.

The sources of the benzene residues are unclear, but are not likely to be a function of the commercial use of the chemical. Benzene is not used in food processing and is not approved as a direct or indirect food additive. McNeal et al. (1993) speculated that the added benzoates might be reduced by ascorbates present in certain foods to form benzene. A second source of exposure could be the concentration of benzene in fatty foods by absorption from air. This may explain the levels reported in oils and fatty materials such as cheese and salad dressings. Finally, benzene was consistently found in a variety of cooked meats. Because of its volatility, solubility and the ability of mammals to metabolize benzene, bioaccumulation in animals is not believed to occur. This suggests that cooking processes may cause the formation of benzene in meat.

The residue data from market basket surveys were entered into the LifeLine™ program and intakes were calculated for the various age ranges. A detailed description of the food consumption modeling is provided in Appendix A-3.

Exposure concentrations for the determination of benzene exposure from drinking water were obtained from EPA's National Drinking Water Contaminant Occurrence Database (NCOD) for water from public water supplies and the U.S. Geological Survey (USGS) National Water Quality Assessment (NAWQA) program for a representation of private well users. The typical and high-end concentrations were characterized by mean and 95th percentile values as shown on Table 7.19 and 7.20 below.

Table 7.19: Public Water Supply Summary Statistics (May 1987 through December 2000)[a]

Statistic	Public Water Supply Concentration (N= 40,880) (µg/L)
Maximum	355
Mean	0.27
Median	0.25
95th Percentile (by rank)	0.5

[a]The mean, median, and 95th percentile values were calculated using half the detection limit for non-detects.

Table 7.20: Summary Statistics for Benzene Analyses from Ambient Groundwater and Surface Water (July 1986 through September 2000)[a]

Statistic	Groundwater (N = 3,759) (µg/L)	Surface Water (N = 586) (µg/L)	All (N = 4,345) (µg/L)
Maximum Detect	100	24	100
Mean	0.32	0.48	0.34
Median	0.05	0.03	0.05
95th Percentile (by rank)	0.10	0.20	0.10

[a]The mean, median, and 95th percentile values were calculated using half the detection limit for non-detects.

Details of the determination of exposure concentrations for drinking water and the input into the Lifeline model are contained in Appendix A-4. The results of the food and drinking water exposure analysis are presented on Tables 7.21 through 7.25 below. Both typical and high-end intakes are presented. The typical intake is estimated based on the median intake of a simulated population of 1,000 individuals. The high-end is based on the 95th percentile of the 1,000 simulated individuals.

As shown in Table 7.23, the highest benzene exposures (in terms of mass per body weight) via ingestion of food and tap water are for the children ages one to less than two years. The lowest benzene exposures are for children ages 16 to less than 19 years. Inhalation and dermal exposures are at least 5 times less than that of oral ingestion. Hence inhalation and dermal absorption of benzene from exposure to tap water are minor in comparison to ingestion.

.

Table 7.21: Oral Exposures to Benzene from Tap Water

Oral Exposures from Tap Water		
	Annual Average Daily Dose (mg/kg-day)	
Age Range	**Median**	**95th**
Birth-<1	1.26E-05	4.36E-05
1-<2	6.08E-06	3.05E-05
2 to <6	4.56E-06	1.14E-04
6 to <16	1.95E-06	1.13E-05
16 to <19	1.20E-06	8.55E-06
19 to <36	1.42E-06	8.87E-06

Table 7.22: Oral Exposures to Benzene from Diet

Oral Exposures from Diet		
	Annual Average Daily Dose (mg/kg-day)	
Age Range	**Median**	**95th**
Birth-<1	1.04E-05	7.47E-04
1-<2	2.78E-05	5.82E-04
2 to <6	2.83E-05	3.70E-04
6 to <16	1.12E-05	1.86E-04
16 to <19	6.12E-06	1.30E-04
19 to <36	6.82E-06	1.22E-04

Table 7.23: Total Oral Exposures to Benzene from Tap Water and Diet

Oral Exposures from Tap Water and Diet		
	Annual Average Daily Dose (mg/kg-day)	
Age Range	**Median**	**95th**
Birth-<1	3.37E-05	7.72E-04
1-<2	3.98E-05	5.93E-04
2 to <6	3.82E-05	4.01E-04
6 to <16	1.54E-05	1.92E-04
16 to <19	9.12E-06	1.34E-04
19 to <36	1.01E-05	1.25E-04

Table 7.24: Inhalation Exposure to Benzene in Tap Water During Showering

Inhalation Exposures from Showering		
	Annual Average Daily Dose (mg/kg-day)	
Age Range	**Median**	**95th**
Birth-<1	0.00E+00	1.54E-04
1-<2	2.25E-05	4.76E-04
2 to <6	7.20E-06	1.17E-04
6 to <16	1.43E-06	2.71E-05
16 to <19	1.04E-06	1.93E-05
19 to <36	5.65E-07	1.08E-05

Table 7.25: Dermal Exposure to Benzene in Tap Water During Showering

Dermal Exposures from Showering		
	Annual Average Daily Dose (mg/kg-day)	
Age Range	**Median**	**95th**
Birth-<1	0.00E+00	1.91E-06
1-<2	8.60E-07	2.48E-06
2 to <6	8.90E-07	2.28E-06
6 to <16	6.00E-07	1.75E-06
16 to <19	5.00E-07	1.41E-06
19 to <36	4.20E-07	1.27E-06

Although the estimated benzene intake from food presented in this exposure assessment is higher than typically assumed (ATSDR, 2005), they are consistent with other estimates made recently. For instance, the U.K. Ministry of Agriculture, Fisheries and Food (MAFF; now known as the Department for Environment, Food and Rural Affairs) determined in a Total Diet Study that the average U.K. intake of benzene is less than 2.5 µg/day (MAFF, 1995). The survey consisted of twenty food groups collected at 10 U.K. locations and included retail food product in amounts representative of UK consumption patterns. The method detection limit of 1 ppb was the same as the FDA's TDS detection limit. The median dietary intakes (excluding tap water) derived from the Lifeline dose estimates are presented on Table 7.26.

Table 7.26: Oral Intake Based on Lifeline Dietary Doses

	Body Weight (kg)	Annual Average Intake (μg/day)
Age Range		Median
<1	7.2	0.41
1 to ≤ 2	11.4	1.45
2 to <6	16.1	1.03
6 to <16	41.1	0.94
16 to <19	66.8	0.97
19 to <36 female	62.4	0.85
19 to <36 male	76.3	1.04
	Average	0.96

The average median intake among the age groups evaluated in this assessment of approximately 1 μg/day is consistent with U.K. estimate of average intake of less than 2.5 μg/day.

7.2.1.9 Human Milk

Benzene has been detected in human milk, and thus was considered as a potential exposure pathway for nursing infants (ATSDR, 2005). Only one study was identified in which benzene concentrations in human milk were quantified (Fabietti, et al., 2004). In this study, Fabietti et al (2004) reported concentrations of benzene from 23 samples of human milk which ranged from 0.01 μg/kg to 0.18 μg/kg, with a mean concentration of 0.06 μg/kg. The samples came from women in Italy, and the highest concentrations were almost always associated with women that lived in urban, suburban or high traffic areas.

The literature search also identified one study that provided information on performing a limited quantification of human milk benzene concentrations following occupational exposures. Fisher et al. (1997) developed a physiologically based pharmacokinetic (PBPK) model for lactating women to estimate the amount of volatile organic chemicals that a nursing infant ingests for a given nursing schedule and maternal occupational exposure. The results of this modeling assumed that the mother was exposed at the outdated ACGIH TLV® for benzene of 10 ppm.

Because of the limited data describing measured levels of benzene in human milk, the PBPK model was used to estimate human milk concentrations for this assessment. Because it is believed that the majority of occupational exposures are well below the TLV® (See Section 7.2.3), and non-occupationally exposed mothers have much lower ambient air exposures, the estimation of benzene concentrations in human milk and lactational transfer of benzene were recalculated. In doing so, the maternal exposure levels estimated in this assessment were used in conjunction with the conservative schedule described by Fisher et al. (1997). Accordingly, during the workday, the mother was assumed to be exposed for 8 hours at the respective workplace TWA concentrations of 0.11 ppm (0.35 mg/m^3) for typical and 0.39 ppm (1.22 mg/m^3) for high-end and background concentrations of benzene for the remainder of the day. Eight

nursing events were assumed to occur each day, lasting 12 minutes each, with 115 mL of milk ingested per nursing event, yielding a daily milk consumption of 0.92 L. Three individual nursing events were assumed to occur during working hours and the remainder five nursing events were assumed to occur after working hours. The nursing events that occurred during working hours all occurred after the benzene blood concentrations had reached steady-state with the workplace exposures and occurred at 2.1, 4.1 and 7.1 hours into the workday. The remaining five nursing events occurred at 2, 5, 10, 13 and 15 hours post-work-shift. If the working day were assumed to begin at 8:00 a.m., this would amount to nursing events occurring at 2:00 a.m., 5:00 a.m., 7:00 a.m., 10:00 a.m., 12:00 p.m., 3:00 p.m., 6:00 p.m., and 9:00 p.m.

All parameters for the PBPK model of benzene were obtained from Fisher et al. (1997), except the metabolic rate constants for benzene which were obtained from Tardif et al. (1995). The Fisher et al. (1997) model was reproduced successfully before using it to simulate the lactational transfer of benzene according to the defined exposure scenarios. The human milk concentrations for both the non-occupationally exposed mother (urban, typical and high-end) and the occupationally exposed mother were calculated.

The parameters of the model and the simulations of lactational transfer are included in Appendix B. The results of the model are summarized in Table 7.27 below.

Table 7.27: Modeled Benzene Concentrations in Human Milk using the Fisher et al. (1997) Lactation Model

Scenario	Modeled Human Milk Benzene Concentration (µg/L)	Mass Ingested (mg/day)
Urban, typical	0.02	0.000016
Urban, high-end	0.1	0.00012
Occupational, typical	1.5	0.0014
Occupational, high-end	5.3	0.0049

The results of the modeling for the nursing mother in an urban environment are consistent with those measured by Fabietti et al. (2004) where the measured values ranged from 0.01 to 0.18 µg/kg. Although information regarding the mothers' occupational exposures to benzene were collected by Fabietti et al., it was not reported. However, given that the occupational exposures are at least one order of magnitude higher than the 'urban' exposure scenario, it is reasonable to predict human milk concentrations from occupationally exposed mothers that are an order of magnitude higher.

Intakes of benzene in terms of mass per body weight for an infant were calculated and are presented on Table 7.28 below.

Table 7.28: Average Daily Doses of Benzene to Nursing Infant of Occupationally Exposed and Urban Mothers

Scenario	Average Daily Dose (mg/kg-day)
Urban, typical	2.3E-06
Urban, high-end	1.6E-05
Occupational, typical	1.9E-04
Occupational, high-end	6.8E-04

The intake of benzene via ingestion of human milk by a nursing infant of an occupationally exposed mother ranges from 0.9 to 6 times that received via ingestion of food and tap water. For infants of non-occupationally exposed mothers, the benzene exposure from human milk is 0.02 to 0.07 times that received via ingestion of food and tap water. Thus, human milk ingestion may be a significant dietary source of benzene for infants of occupationally exposed mothers. The human milk modeling results for occupationally exposed mothers are likely to be conservative for benzene since many employers apply administrative and management controls that remove nursing mothers from benzene exposed jobs.

7.2.1.10 Summary of Ambient Background Benzene Exposures

Of the ambient background sources described in Section 7.2.1, inhalation of indoor air is the predominant pathway of exposure for children and prospective parents (See Figure 7.3). For nursing infants of occupationally exposed mothers, the predominant pathway of exposure from ambient sources is still inhalation, but ingestion of human milk accounts for a larger portion of background exposure (i.e., 22% vs. 5% for occupationally exposed and urban typical mothers, respectively) (See Figure 7.4). Section 7.5 provides further discussion of estimated benzene intake from exposure to various sources.

Figure 7.3. Predominant Pathways of Benzene Exposure for Children and Prospective Parents from Ambient Sources

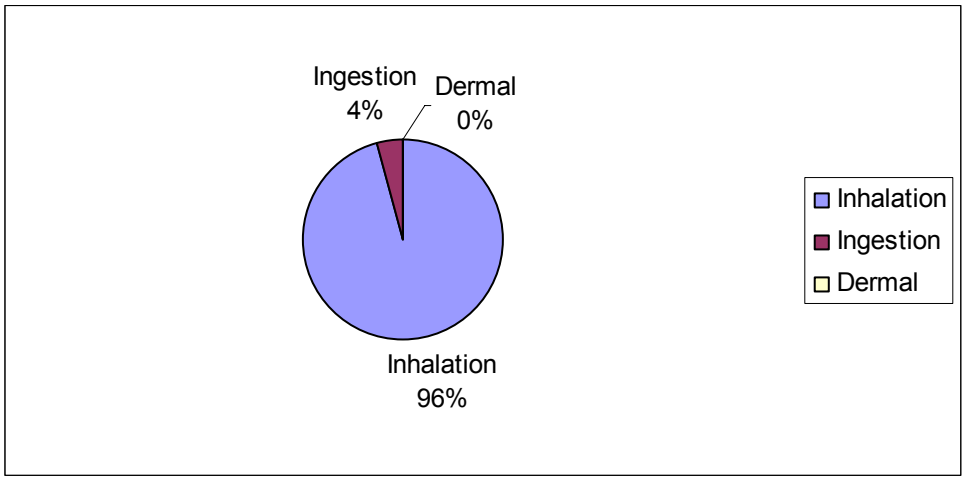
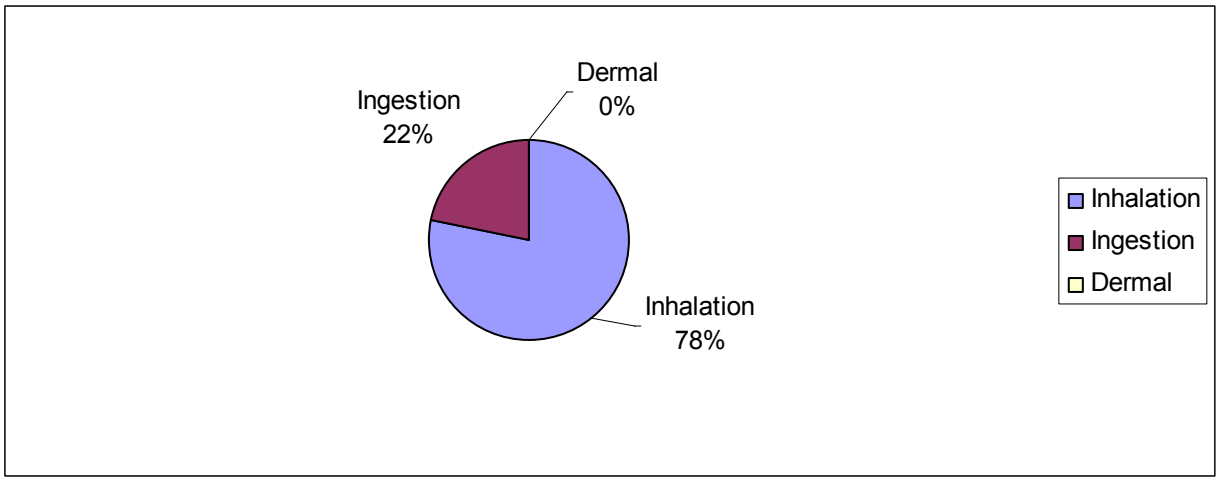


Figure 7.4 Predominant Pathways of Benzene Exposure for Nursing Infants (with occupationally exposed mothers) from Ambient Sources



7.2.2 Source-Specific Exposures

In addition to the ambient sources of benzene exposure, certain subpopulations of children and prospective parents may be exposed to benzene in specific microenvironments related to gasoline exposures during in-vehicle transportation, refueling and use of small engine equipment, or from tobacco smoke, either through ETS or mainstream smoke. Exposures to each of these specific sources have been quantified and are discussed below.

7.2.2.1 Gasoline Sources of Exposure

Benzene is among various aromatic constituents in gasoline. As noted in Section 5, benzene emissions from motor vehicles are on the decline as a result of the 1990 Clean Air Act Amendments, which called for lower tailpipe emissions, more stringent emissions testing, expanded inspection and maintenance programs, new vehicle technologies, and clean fuels programs. Unlike other aromatics in gasoline, benzene has its own reduction requirements. As of 2002, the average benzene concentration in gasoline (in both conventional gasoline and oxygenated gasoline) in the U.S. was approximately 1.1% by volume (U.S. EPA 2002a). The current RFG regulations limit the content of benzene in gasoline to an average of 0.95% by volume, where RFG is used. However, fuel benzene levels are higher in some non-RFG ozone attainment areas (e.g. Alaska).

While benzene in gasoline contributes to the overall concentration of benzene in the ambient air, exposures to gasoline may also occur while riding in a vehicle, during refueling of a vehicle and use of small engine equipment such as lawn mowers, chain saws, leaf blowers, edge trimmers, snow blowers, ATVs, and snowmobiles. As such, benzene exposures from these localized benzene sources have been evaluated.

In-Vehicle Exposures

In-vehicle exposure to benzene is due to the penetration of benzene in roadway air (e.g., tailpipe emissions) and from engine running loss into the vehicle cabin while driving (Graboski et al., 1998 Chan et al., 1991b). It should be noted however, that at least one investigator suggested that there is only a weak relationship between benzene content in gasoline and benzene concentration from tailpipe emissions (Wallace, 1996). In-vehicle benzene exposure occurs exclusively via inhalation. In-vehicle VOC exposure levels can be affected by various conditions including mode of transportation, driving route, time of day (rush vs. non-rush), type of fuel distributions system, season of the year, meteorological conditions and vehicle ventilation conditions (Chan et al., 1991a,b; Dor et al., 1995; Lawryk and Weisel, 1996; Batterman et al., 2002; Fedoruk and Kerger, 2003). In many cases, the findings of the various studies can be conflicting, and in-vehicle VOC concentrations can vary considerably with sampling day and time (Lawryk et al.,1995; Batterman et al., 2002).

Of all modes of transportation involving potential non-occupational exposure to gasoline constituents (e.g., automobile, bus, subway, walking, biking), in-vehicle exposures while driving in an automobile are the highest (Chan et al., 1991a). Although many children commute in school buses, studies show that because of variables including vehicle height, location of engine, ventilation conditions and fuel type, exposure in a car is greater (Chan et al., 1991a; Jo and Choi, 1996; Jo and Park, 1998; 1999a,b; Jo and Yu, 2001) or the same (Batterman et al., 2002) as that of a bus. The transportation route and traffic density (e.g., urban or rural, following closely or far behind a lead car, rush or non-rush) have been determined to be the most important in-vehicle exposure variables (Batterman, et al., 2002). It is expected that in-vehicle exposures in suburban areas, rural areas and in general, areas with lower automobile densities, will have lower in-vehicle concentrations.

Numerous studies have been conducted in the U.S., which have evaluated in-vehicle benzene exposures (SCAQMD et al., 1989; Chan et al., 1991a,b; Weisel et al., 1992; Lawryk et al., 1995; CARB, 1998b; Chang et al., 2000, Fedoruk and Kerger, 2003; Batterman et al., 2002). Due to the emission reduction and fuel-changing initiatives discussed above, only the most recent U.S. data were included in this analysis. Although the CARB, 1998 study is relatively recent, it was excluded because the study design required evaluation of highly unusual and unrealistic conditions (i.e., travel behind a high emitting vehicle for 2 hours). It is unlikely that a driver would closely tail a high-emitter during the entirety of his or her driving time. It is more likely that the driver would move from behind such a vehicle, and would be behind a variety of vehicles while driving during any given time period. The studies used to derive representative exposure concentrations are summarized in Table 7.29 below. Each of the automobile studies evaluated specifically excluded smokers and/or the influence of smoking on VOC in-vehicle concentrations.

Table 7.29: Summary of Key In-Vehicle Studies

Study	Type of Vehicle Used	Comments
Chang et al., 2000	Minivan, occasionally a bus.	Baltimore, MD, Summer 1998 - Winter 1999. This study was designed to simulate activities performed by older adults. Samples were obtained in 1-hour increments. The data used in this study were not published with the paper, but obtained separately. RFG was in regular use in Baltimore at the time of the study.
Batterman et al., 2002	Car	Detroit, MI, Fall 1999. This study was conducted during 2- 3 hour urban rush hour commutes. Information on the car used was not provided. Use of RFG was not required in Detroit.
Fedoruk and Kerger, 2003	Car	Los Angeles, CA, 1997. This study was conducted during urban commutes. 90 minute TWAs were obtained. A 1993 Toyota, in good condition, was used. The time of day that measurements were obtained was not reported. RFG was in regular use in Los Angeles at the time of the study.

In-vehicle exposure scenario concentrations were derived from means presented in the three studies above and summarized on Table 7.30.

Table 7.30: Average of Mean In-Vehicle Concentrations

Study	Description	Mean In-Vehicle Concentration (µg/m^3)
Chang et al. (2000)	Urban, Baltimore in Summer 1998 and Winter 1999	10.2
Batterman et al. (2002)	Urban commute, Detroit, fall 1999	4.5
Fedoruk and Kerger (2003)	Urban communte, Los Angeles , 1997	2.4
	Average of study means	***5.7***

Due to various driving conditions under which a person may be exposed to in-vehicle concentrations of benzene, mean concentrations best portray long-term exposure concentrations. An average concentration was derived using the means of each of the three key studies above. This average is used as the typical representative in-vehicle exposure concentration and is considered to be an average of a high-end scenario, as it is representative of urban exposures where traffic densities are highest.

Age-specific in-vehicle benzene exposures were quantified according to the following equation:

$$ADD = \frac{C \times ED \times EF \times ET \times IR \times ABSi \times CF}{BW \times AT}$$

where:

ADD = average daily dose (mg/kg-day)
C = concentration of benzene in vehicle air (µg/m^3)
ED = exposure duration (years)
EF = exposure frequency (days/year)
ET = exposure time (hours/day)
CF = conversion factor (0.001 mg/µg)
ABSi = benzene inhalation absorption factor; 0.5 (unitless)
IR = inhalation rate (m^3/hour)
BW = body weight (kg)
AT = averaging time (days)

Table 7.31: Summary of ADDs From In-Vehicle Benzene Exposure

Exposure Parameter	Units	Typical						
		<1 year old	1 to <2 year old	2 to <6 year old	6 to <16 year old	16 to <19 year old	19 to <36 year old female	19 to <36 year old male
C	µg/m^3	5.7	5.7	5.7	5.7	5.7	5.7	5.7
ET	H/d	1.2	1.1	1.3	1.3	1.4	1.3	1.3
EF	D/y	365	365	365	365	365	365	365
ED	years	1	1	4	10	3	17	17
IR	M^3/h	0.19	0.28	0.33	0.52	0.6	0.47	0.63
CF	Mg/µg	0.001	0.001	0.001	0.001	0.001	0.001	0.001
AT	days	365	1095	1095	3650	1095	6205	6205
BW	kg	7.2	11.4	16.1	41.1	66.8	62.4	76.3
ABSi	unitless	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Dose	***Mg/kg-d***	***9.0E-05***	***7.7E-05***	***7.6E-05***	***4.7E-05***	***3.6E-05***	***2.8E-05***	***3.1E-05***

As shown in Table 7.31, the benzene exposures received while riding in a vehicle range from 2.8 x 10^{-5} for an adult to 9 x 10^{-5} for an infant. These exposures are similar to that received from ambient urban outdoor air exposures, and 7 to 30-fold lower than that from in-home exposures.

Refueling Exposures

A variety of researchers have reported that, historically, self-serve automobile refueling is one of the most common short-term peak gasoline exposures to benzene in the the general population (Pope and Rall, 1995; Wixtrom & Brown, 1992). Exposure occurs primarily via inhalation of vapors during automobile refueling. There are many potential sources of exposure to gasoline vapors at service stations, including breathing and working losses from underground storage tanks, displacement air losses from filler pipes during refueling, fuel spillage during refueling, and evaporative and exhaust emissions from motor vehicles in the station. The uncontrolled displacement of fuel vapors from the gas tank while refueling, however, is the primary source of exposure to benzene during refueling (Backer et al., 1997; Egeghy, et al., 2000; Guldberg, 1992).

Gasoline blends contain slightly different benzene concentrations depending on the season. To ensure good drivability and to comply with regulations restricting evaporative hydrocarbon emissions, concentrations of volatile compounds are higher in winter blends than in summer blends. Studies have reported higher exposures in winter than in summer, also identifying body orientation as an important contributor (e.g., the tendency to huddle closer to car in cold weather) (Tironi et al., 1986; Cheng et al., 1990).

The amount of exposure to gasoline vapors by any one individual can vary greatly depending on a number of environmental conditions at the time of sampling and personal filling procedure of the individual. The published literature indicated both inter- and intra-study variability of exposure concentrations. In one study, factors such as fuel octane grade, season and duration of refueling, were determined to be associated with benzene exposures during refueling, rather than inter-individual differences such as body size, behavior or vehicle type (Egeghy et al., 2000). In Finland, Vainiotalo (1999) found that the individual exposure measurements in customer's breathing zones yielded widely distributed concentrations, with the lower concentrations being the most frequent. The mean values observed by Vainiotalo were found to

be similar to those in other U.S. studies, despite the various gasoline benzene contents. Egeghy, et al. (2000) also found that exposure levels decreased with increasing refueling time. This counter-intuitive result was believed to have occurred due to inclusion of non-refueling activities (e.g., cleaning the windshield, paying for gas) in the recorded 'refueling' time period. API (1993) and Vainiotalo, (1999) used more tightly defined refueling periods that excluded such ancillary activities.

Four studies were selected as having the best representative data for this exposure assessment and are summarized in Table 7.32. These key studies focus on the exposure of a self-service customer while refueling; occupational exposure concentrations were excluded. Data collected before 1990 were not considered to be representative of current gasoline formulations. The gasoline content of benzene in each of the key studies is similar. The presence or absence of VRS controls at the pump was also documented in the studies.

Table 7.32: Summary of Key Refueling Studies

Study	Date/location data collected	Controls at the Pump	Type of Gasoline[a]
Smith, 1999	Toronto, Canada Completion by March 21, 1999	Varied	Regular, mid-grade, premium
Vainiotalo, 1999	August 1996, Helsinki, Finland	No Stage II VRS, had splash collars	Unleaded 95-, 98-, and 99-RON RFG
API, 1993	October - November 1990 Cincinnati, OH, Phoenix, AZ and Los Angeles, CA	Only LA had Stage II VRSs and extensively used pump safety latches	Three grades of gasoline were evaluated: regular unleaded, mid-grade unleaded, super (premium) unleaded. Regular leaded gasoline was also measured for 4 samples at one Phoenix station and 2 samples at the other Phoenix station.
Backer, et al., 1997	January - March, 1995 Fairbanks, AK	No stage II VRS	Regular gas and E10 gas

Based on decreases in benzene content in gasoline and improvements in vehicle emission controls since the time of these studies, it is likely that the air concentrations reported in these studies overestimate current day exposures. Therefore a refueling normalization factor (NF) was derived to account for these changes.

The refueling NF was derived similar to that for the indoor air. EPA's MOBILE6.2 model was used to estimate the change in benzene emission rates given the historical and current conditions of fleet and fuel properties. In doing so, the year-specific fuel and fleet properties for each of the studies listed on Table 7.32 (excluding the Finland study) and that for 2003 were used to model refueling emission rates. The change in the emission rate was then used to estimate the emission factor change attributable to benzene content decreases and emission factor changes attributable to fleet improvements. A detailed discussion of the refueling NF derivation is presented in Appendix B.

Refueling NFs ranged from 1.3 for the study conducted in Cincinnati to 5.4 for the study conducted in Los Angeles. The refueling NFs were used to calculate normalized refueling exposure concentrations as follows:

$$C_N = \frac{C_H}{NF}$$

where;

C_N = Refueling air concentration of benzene normalized to 2003 (mg/m^3)
C_H = Historical air concentration of benzene from the studies (mg/m^3)
NF = Normalization factor (unitless)

The air concentrations for the various studies normalized to 2003 fuel and fleet properties are summarized in Table 7.33.

Table 7.33: Normalized Benzene Air Concentrations During Refueling (mg/m^3)

			Study Concentration for the Year of Data Collection (Historical Fleet and Benzene Content)		Study Estimate Normalized to Year 2003 Fleet and Benzene Content[a]	
Study	City	Year of Data Collection	Mean	Maximum	Mean	Maximum
Smith, 1999	Toronto	1999	1.1	4.1	0.27	1.01
API, 1993	Cincinnati	1990	0.49	2.5	0.38	1.95
	Phoenix		1.725	8.4	0.42	2.03
	Los Angeles		0.965	3.9	0.18	0.72
Backer, et. al., 1997	Fairbanks (RG)	1995	1.21	2.36	0.87	1.70
	Fairbanks (E10)		0.83	2.70	0.60	1.9
Average			1.0	4.0	0.45	1.6

[a]Estimated using Mobile 6.2 refueling emissions for study year fleet and benzene content versus year 2003 fleet and benzene content.

The Northeast States for Coordinated Air Use Management (NESCAUM) reviewed nine pre-1989 refueling studies and determined mean and high-end exposure concentrations for benzene and other VOCs (NESCAUM, 1989). Data were reviewed and weighted, yielding mean and high-end benzene exposure estimates of 2.9 and 13.4 mg/m^3. A comparison of the NESCAUM mean to the exposure concentrations shown on Table 7.33 demonstrates that the refueling exposure concentrations of benzene have decreased over the years. Thus, refueling exposure concentrations are expected to continue to decline as RFG continues to be phased in.

Benzene intakes were estimated for male and female adults and a teenager 16 to <19 considering both typical and high-end refueling exposures. It was assumed for the purposes of this assessment that children younger than 16 would not pump gasoline on a regular basis. The exposure estimates are limited to refueling only (i.e., the time spent pumping gasoline into the

vehicle); the total amount of time spent at the service station is not evaluated. It is also assumed that the refueler remains at the pump the entire time that he or she is refueling without the nozzle refueling latch.

Exposure was quantified according to the following equation:

$$ADD = \frac{C \times ED \times EF \times IR \times ABSi}{BW \times AT}$$

where:

ADD = average daily dose (mg/kg-day)
C = concentration of benzene in refueling air (mg/m^3)
ED = exposure duration (years)
EF = exposure frequency (days/year)
ABSi = benzene inhalation absorption factor; 0.5 (unitless)
IR = inhalation rate (m^3/day)
BW = body weight (kg)
AT = averaging time (days)

Age-specific refueling ADDs are presented in Table 7.34 below.

Table 7.34: Summary of ADDs from Refueling Benzene Exposure

		Typical			High-End		
Exposure Parameter	**Units**	**16 to <19 year old**	**19 to <36 year old female**	**19 to <36 year old male**	**16 to <19 year old**	**19 to <36 year old female**	**19 to <36 year old male**
C	mg/m^3	0.45	0.45	0.45	1.6	1.6	1.6
ET	h/d	0.0267	0.0267	0.0267	0.0617	0.0617	0.0617
EF	d/y	70	70	70	104	104	104
ED	years	3	17	17	3	17	17
IR	m^3/h	0.5	0.47	0.63	0.5	0.47	0.63
CF	mg/µg	1	1	1	1	1	1
AT	days	1095	6205	6205	1095	6205	6205
BW	kg	66.8	62.4	76.3	66.8	62.4	76.3
ABSi	unitless	0.5	0.5	0.5	0.5	0.5	0.5
Dose	***mg/kg-d***	***1.0E-05***	***8.7E-06***	***9.5E-06***	***1.3E-04***	***1.1E-04***	***1.2E-04***

The typical and high-end refueling exposures differ by about 10-fold. These benzene exposures are about 10-fold higher than that received while riding in a vehicle, however they occur much less frequently.

In-vehicle-while-refueling concentrations are more comparable to ambient concentrations at gasoline service stations and with in-vehicle concentrations while commuting. (Vayghani and Weisel, 1999; Smith, 1999; Vainiotalo, 1999; API, 1993). Thus, a child who remains in the car while it is being refueled was not evaluated, as it was determined that the benzene exposure concentrations were much lower (i.e., about 2 orders of magnitude) than measured refueling exposures.

Small Engine Equipment Exposures

Use of small off-road engines in the U.S., such as lawn mowers, ATVs, snowmobiles, chainsaws, leaf blowers and trimmers, is common. It is estimated that on average there are more than 1.4 million snowmobile users, nearly 3 million ATV users, and more than 25 million lawn equipment users (EPA, 1999a, b, 2000a). The EPA has been evaluating air emissions from small, off-road engines and has drafted proposed emission control regulations. Additionally, the State of California Air Resources Board has conducted preliminary evaporative emission estimates for small off-road engines using their OFFROAD model, although currently, only emissions for total hydrocarbons can be assessed, not specific compounds.

Because children and prospective parents could be exposed to benzene during the use of small engine equipment, these potential sources of exposure were considered. However, the data from studies which evaluated benzene exposure from small engine equipment use is very limited and none were found to be satisfactory for quantitative exposure assessment. These studies are presented below, but children's exposures to benzene from use of small engine equipment have not been quantified.

Wallace et al., 1989: This study measured VOC exposures of people performing common activities. One personal sample of benzene was collected of a person while mowing the lawn, yielding a concentration of 0.032 mg/m^3.

Nilsson et al., 1987: For this study, investigators measured benzene emissions from two-stroke engine chainsaws. Emissions data were collected for various scenarios, including snow and no-snow situations. Under snow conditions, benzene concentrations ranged from 0.3 to 1.8 mg/m^3, and had an average of 0.7 mg/m^3. Under no-snow conditions, benzene concentrations ranged from 0.1 to 2.4 mg/m^3, and had and an average of 0.6 mg/m^3.

Bailey, 2001: In this study, benzene exposure while snowmobiling was estimated from measurements of carbon monoxide tailpipe emissions and an empirical model for the prediction of snowmobile drivers' CO exposures (Snook and Davis, 1997). The basis for the Snook and Davis model is that CO is an inert gas, such that photochemical and physical removal processes in a plume of snowmobile exhaust should not be significant determinants of exposure. Thus, transport processes such as diffusion and turbulence govern its dilution. Bailey theorized that given CO's stability, the empirical relationships between emission rates and exposure should be applicable to any inert gas emitted from a tailpipe, such as benzene. Using a regression analysis of benzene emission rates from snowmobiles, Bailey demonstrated that benzene emission rates are correlated with CO emission rates and therefore calculated benzene exposures using the Snook and Davis model. Exposure estimates were presented for numerous scenarios, including riding behind a single snowmobile, as well as 5^{th} in a line of five snowmobiles at various speeds. Such "trains" are common in snowmobile parks. For the train scenarios, it was assumed that exposures from several snowmobiles are additive, which discounts the role played by multiple snowmobiles in creating additional turbulence, which may cause more rapid dispersion of exhaust. Modeled benzene exposures were estimated to range from 0.12 mg/m^3 for a rider behind a single snowmobile to 3.5 mg/m^3 for a rider fifth in line; with a mean estimated exposure of 1.7 mg/m^3, depending on speed of the vehicle.

Because of the difficulty in estimating benzene exposure from emissions data collected for total hydrocarbon or total VOC analysis, only those studies providing exposure measurements of benzene are suitable for use in characterizing children's potential exposures to benzene from

use of small non-road engine equipment. However, the following limitations render the few studies that provide exposure concentrations unsuitable for this exposure assessment:

- Because the studies conducted by Wallace et al., and Nilsson et al., were conducted in the late 1980's prior to the introduction of oxygenated and reformulated gasoline, the benzene concentrations are likely to be higher than exposures which would result from use of the equipment with RFG.

- In the Wallace et al., study there is only one data point available for evaluating lawn mower exposures, thus deviations around this value are unknown.

- The Nilsson et al. study focused on occupationally exposed logging operators who would have a significantly different usage pattern than an average homeowner and thus, the exposures measured may overestimate that for the general population using landscaping equipment.

- Use of 4-stroke small engine equipment is more common today than during the years that the studies were conducted, thus exposure estimates from use of 2-stroke engines would not be representative of contemporary exposures.

- The exposure estimates made by Bailey for snowmobile use were obtained from internal EPA memos, and thus have not been published in the scientific literature although the information was used in the notice of proposed rulemaking (NPR) for Control of Emissions from Nonroad Large Spark Ignition Engines (66 Fed.Reg. 51098). External peer-review by the International Snowmobile Manufacturers Association (ISMA) indicates that the EPA exposure estimates are significantly overstated and that the Snook and Davis model is invalid for predicting both CO and benzene exposures from snowmobile use (ISMA, 2001). In comments submitted to EPA's Air docket regarding the NPR, ISMA submitted an analysis conducted by Sierra Research, which demonstrated:

    - The wake radius calculated based on Snook & Davis' CO emissions monitoring was unrealistically low in comparison to EPA's inventory estimates which lead to overestimates of CO exposure;

    - Benzene exposures were calculated for the last person in the snowmobile train by summing the individual exposures of a single sled following a lead sled at variable distances. This method ignores the turbulence and mixing that would occur as multiple sleds passed through the wake of the lead sled and results in overestimates of benzene exposure.

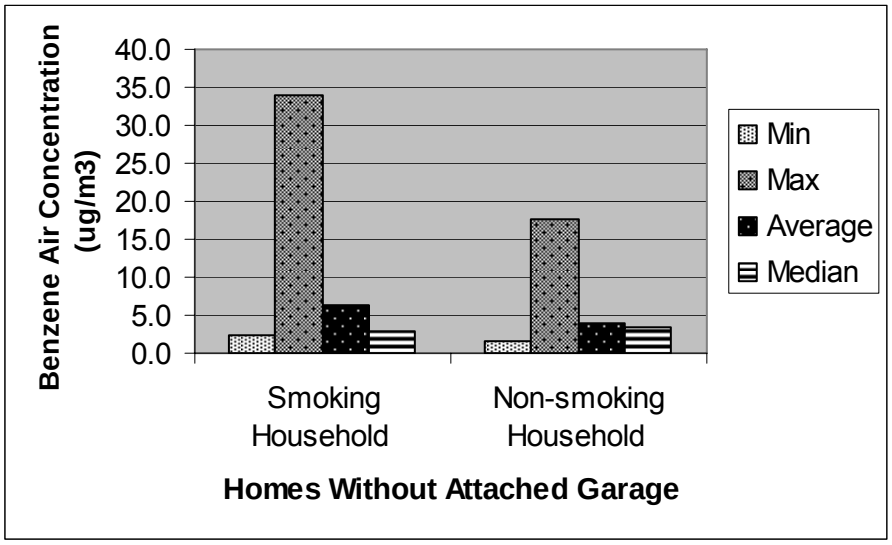
EPA and the state of California are in the process of updating emissions regulations for small off-road engines, which are being phased in during the years 2001 – 2007. EPA's and California's Phase II emissions controls for small handheld and non-handheld engines are expected to reduce hydrocarbon and NOx emissions by 59% and 74%, respectively (EPA 1999c, CARB, 2000). Thus, regulatory actions on the small off-road engine equipment, coupled with use of oxygenated and reformulated gasoline will continue to result in lower operator exposures.

Because there is considerable uncertainty associated with the exposure estimates currently available, reasonable estimates of typical and high-end benzene exposures from use of small engine equipment by children and prospective parents cannot be made at this time.

7.2.2.2 Tobacco Smoke

Benzene concentrations in the homes of smokers and nonsmokers were measured by Wallace et al. in the 1980s. At that time, the median level of benzene in 300 homes with one or more smokers was 3.5 µg/m^3 more than the median level of benzene in a group of 200 homes without smokers. A similar increase was reported by Heavner et al. (1995). Raw data from Adgate et al. (2004b) were also analyzed to evaluate the impact of ETS on indoor air levels. Figure 7.5 compares the indoor air benzene levels measured by Adgate et al. (2004b) in smoking and non-smoking households. Because there was little or no difference in benzene air concentrations in homes with attached garages regardless of the presence of a smoker, only homes without attached garages were considered in this analysis.

Figure 7.5: Comparison of Indoor Air Concentrations of Benzene in Smoking and Non-Smoking Households



As shown in Figure 7.5, the smoking households from Agate et al., 2004b had slightly higher average indoor air benzene concentrations than non-smoking households. The smoking households had an average benzene concentration of 6.3 µg/m3 and non-smoking households had an average benzene concentration of 3.8 ug/m3. The difference of 2.5 µg/m3 is lower than that measured by Wallace et al. in the 1980s. This could be due to lower rates of smoking or reduced ambient benzene concentrations.

Benzene is present in both the mainstream tobacco smoke inhaled by the smoker directly from the cigarette and sidestream smoke released to the environment from the smoldering end of a cigarette. Wallace (1996) found for non-smokers that environmental tobacco smoke (ETS), which is comprised of both sidestream smoke and exhaled mainstream smoke (Daisey et al., 1994, NAP, 1986) was responsible for 10% of exposure to benzene in the late 1980s. For smokers, Wallace indicated that 89% of benzene exposure is due to inhaled mainstream smoke, and 2% due ETS.

Children may be exposed to benzene from tobacco smoke directly as smokers (mainstream smoke) or indirectly as non-smokers (ETS). Numerous studies have been conducted to identify and quantify the individual chemical constituents from tobacco smoke. Researchers have identified over 4,800 individual constituents, including benzene, in both mainstream smoke and ETS. Due to physical and chemical differences in burning conditions, benzene has a higher rate of release per cigarette into sidestream smoke than into mainstream smoke (Wallace and O'Neill, 1987, Daisey et al., 1994, Fowles et al., 2000, NAP, 1986, Brunnemann et al., 1990a,b, Darrall et al., 1998).

In order to calculate exposure to benzene, from tobacco smoke exposure, the benzene cigarette emission rate was determined. Numerous studies have been conducted to evaluate the chemical emission rates. The following five studies provide the best information:

Daisey et al., 1994. This study tested six commercially available cigarettes that represented 62.5% of the market share in California in 1990 and consisted of filtered, non-filtered, and mentholated cigarettes. A room-sized environmental chamber was used to measure ETS emission factors from diluted sidestream smoke, which was emitted into the chamber. This study concluded that the average emission factor for benzene is 406 µg/cig.

Lance Wallace (Wallace and O'Neill., 1987; Wallace et al. 1989a,b; Wallace, 1996). Several studies on exposure to benzene and other VOCs from active and passive smoking were conducted. Wallace determined that the sidestream smoke concentration of benzene (µg/cig) is 5 to 10 times higher than that in mainstream smoke (Wallace and O'Neill, 1987). In another study, the breath concentration of benzene in smokers and nonsmokers was measured and reported to be approximately 14 $\mu g/m^3$ and 2 $\mu g/m^3$, respectively (Wallace, 1989a,b). Additionally, benzene concentrations in the homes of smokers and nonsmokers were measured (Wallace, 1989a,b). The median level of benzene in 300 homes with 1 or more smokers was 3.5 $\mu g/m^3$ more than the median level of benzene in a group of 200 homes without smokers. In the most recent study, Wallace calculated the benzene daily exposure to smokers and nonsmokers. He determined that smokers are exposed to 2.0 mg benzene/day of which 1.8 mg benzene/day comes from mainstream smoke and 0.04 mg benzene/day comes from ETS (Wallace, 1996). He determined that nonsmokers are exposed to 0.2 mg benzene/day of which 0.02 mg benzene/day comes from ETS (Wallace, 1996).

Fowles and Bates, 2000. This study compared the emission rates of benzene in sidestream smoke and mainstream smoke. It was determined that the exposure of a nonsmoker must take into account the room dimensions, room ventilation rate, and the amount of time spent with a smoker. In mainstream smoke, the emission rate of benzene was 46.3 µg/cig. In sidestream smoke, the emission rate of benzene was 272 µg/cig. These rates are comparable, although somewhat less than that reported by Daisey et al.

National Academy Press (NAP), 1986. Fresh, undiluted mainstream smoke was measured to determine the concentrations of benzene. Benzene was measured between 12 and 48 µg in mainstream smoke and was 5 to 10 times greater in sidestream smoke. Using this information, it was determined that a nonsmoker living with a smoker has an ETS exposure equivalent to smoking from 0.36 to 2.79 cig/day. This study also measured the concentration of benzene in public places to be between 20 and 317 $\mu g/m^3$.

Brunnemann et al., 1990a,b. The emission rate of benzene in several commercially available cigarettes was measured. In mainstream smoke, benzene ranged from 5.9 µg/cig to 73 µg/cig.

In sidestream smoke, benzene ranged from 345 µg/cig to 653 µg/cig. These rates are comparable to the average rates reported by Daisey et al., (1994). Also measured was the concentration of benzene in a smoke-polluted tavern. In these settings, the benzene concentration ranged from 26 µg/m^3 to 36 µg/m^3.

On a daily basis, children spend most of their time inside at home and therefore their greatest potential for benzene exposure from ETS would be if they lived with a smoker. Also, although significant decreases in teenage smoking have been demonstrated in recent years, many teenagers are cigarette smokers. Thus, exposures to benzene via tobacco smoke were quantified for children from mainstream smoke and ETS.

Benzene Exposures Resulting from ETS

In order to evaluate the exposure to benzene from tobacco smoke, the general school year weekday microenvironment activity patterns for children as presented in Section 5 (Table 5.4) were considered. It was assumed that the average smoking household had one adult smoking off-and-on at home except while that person was sleeping. As presented in Appendix A-1, an adult is at home approximately 13 hours per day, of which 7 are assumed to be spent asleep. The adult is assumed to smoke regularly during the remaining 6 hours spent awake at home.

The total time spent with smokers was obtained for children from the Exposure Factors Handbook (EFH), and is presented in Table 7.35 (U.S. EPA, 1997b). As indicated on Table 7.35, an appreciable difference in children's exposure times to ETS is not evident for weekdays versus weekends. Therefore, the analysis was simplified by using the weekday activity pattern to represent the entire year. The complete hourly activity patterns for the ETS exposure calculations are presented in Table 7.36 and were selected to maintain consistency with the information presented in Appendix A-1.

Table 7.35: Time Spent With Smokers Present

Age Group	Mean Number of Hours per Day Spent With Smoker[a]
1–4 years old	6.1
5–11 years old	5.3
12–17 years old	4.1
All ages	6.3
Weekday	6.2
Weekend	6.6

[a] U.S. EPA, 1997b. Table 15-141.

Table 7.36: Typical School Year Weekday Activity Pattern Used in ETS Assessment

Time	Adult Actively Smoking in Home	<1 year old	1 to <2 year old	2 to <6 year old	6 to <16 year old	16 to <19 year old	19 to <36 year old
12:00 – 5:59 AM		In Home	In Home	In Home	In Home	In Home	In Home
6:00 AM	✓	**In Home**	**In Home**	**In Home**	**In Home**	**In Home**	**In Home**
7:00 AM		In Home	In Home	In Home	In Home	In Home	Out
8:00 AM		In Home	In Home	In Home	In Home	In Home	Out
9:00 AM		In Home	In Home	In Home	Out	Out	Out
10:00 AM		In Home	Out	Out	Out	Out	Out
11:00 AM		In Home	Out	Out	Out	Out	Out
12:00 PM		In Home	In Home	In Home	Out	Out	Out
1:00 PM		In Home	Out	Out	Out	Out	Out
2:00 PM		Out	Out	Out	Out	Out	Out
3:00 PM		Out	Out	Out	Out	Out	Out
4:00 PM		In Home	In Home	In Home	In Home	In Home	Out
5:00 PM	✓	**In Home**	**In Home**	**In Home**	**In Home**	**In Home**	**In Home**
6:00 PM	✓	**In Home**	**In Home**	**In Home**	Out	Out	**In Home**
7:00 PM		Out	Out	Out	Out	Out	Out
8:00 PM	✓	**In Home**	**In Home**	**In Home**	**In Home**	Out	**In Home**
9:00 PM	✓	**In Home**	**In Home**	**In Home**	**In Home**	**In Home**	**In Home**
10:00 PM	✓	**In Home**	**In Home**	**In Home**	**In Home**	**In Home**	**In Home**
11:00 PM		In Home	In Home	In Home	In Home	In Home	In Home
Hours with Smoker (see Table 7.39)	--	6	6	6	5	4	6
Hours in Home (see Appendix A-1)	--	21	18	18	15	14	13

Note: Bold type indicates that exposed individual is present in the home while a parent or other adult is smoking.

In a survey of smokers, the majority indicated that the number of cigarettes smoked at home during a day is 10 (U.S. EPA, 1997b - EFH Table 15-148). The total mass of benzene released in cigarette smoke was calculated based on the emission factor presented in Daisey et al., (1994). The total mass was divided by the 6 hours that the adult is awake and at home to account for smoking "off and on" during this time. Table 7.37 lists the emission factor and resulting emission rate.

Table 7.37: Emission Factor and the Calculated Emission Rate

Chemical	Emission factor (µg/cig)	Usage (cig)	Time (hours)	Emission rate (mg/hour)
Benzene	406	10	6	0.68

Air concentrations were modeled using the Multi-Chamber Concentration and Exposure Model (MCCEM). This model accounts for the emission of benzene over discrete time periods and exposure of the individual based on their activity patterns (see Appendix A-1). Default values

for the air exchange rate (which assumes no open doors or windows) and the volume of the residence were used (U.S. EPA, 1997b). The following equation was used to calculate the average daily dose of benzene from ETS exposure:

$$ADD = \frac{C \times ED \times EF \times ET \times IR \times ABSi \times CF}{BW \times AT}$$

where:

ADD = average daily dose (mg/kg-day)
C = exposure concentration of benzene (mg/m^3)
ET = exposure time (hours/day); 24 hours/day
EF = exposure frequency (days/year); 365 days/year
ED = exposure duration (years)
ABSi = benzene inhalation absorption factor; 0.5 (unitless)
BW = body weight (kg)
AT = averaging time (days)

Age-specific benzene concentrations and intake resulting from ETS exposure in the home were calculated and are presented on Table 7.38 and 7.39.

Table 7.38: Summary of Average Daily Concentrations (ADCs) during ETS Benzene Exposure (mg/m^3)

	<1 year old	1 to <2 year old	2 to <6 year old	6 to <16 year old	16 to <19 year old	19 to <36 year old female	19 to <36 year old male
Benzene	9.1E-04	8.8E-04	8.8E-04	7.7E-04	6.9E-04	7.7E-04	7.7E-04

Table 7.39: Summary of ADDs from ETS Benzene Exposure (mg/kg-day)

Exposure Parameter	Units	<1 year old	1 to <2 year old	2 to <6 year old	6 to <16 year old	16 to <19 year old	19 to <36 year old female	19 to <36 year old male
C	mg/m^3	9.1E-04	8.8E-04	8.8E-04	7.7E-04	6.9E-04	7.7E-04	7.7E-04
ET	h/d	24	24	24	24	24	24	24
EF	d/y	365	365	365	365	365	365	365
ED	Years	1	1	4	10	3	17	17
IR	m^3/h	0.19	0.28	0.33	0.52	0.6	0.47	0.63
AT	D	365	1095	1095	3650	1095	6205	6205
BW	Kg	7.2	11.4	16.1	41.1	66.8	62.4	76.3
ABSi	Unitless	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Dose	***mg/kg-d***	***2.9E-04***	***2.6E-04***	***2.2E-04***	***1.2E-04***	***7.4E-05***	***7.0E-05***	***7.6E-05***

An addition of less than 1 μg/m^3 benzene is estimated from the model results. This is less than the 3.5 μg/m^3 additional benzene calculated by Wallace and less than the 2.5 μg/m3 calculated from the raw data of Adgate et al. (2004a), in smoking households. The reasons for this result may be an artifact of modeling results versus monitoring results and the fact that the modeled exposure concentrations account for an age-specific activity pattern that accounts for a child's time outside of the home.

A further comparison of the estimated benzene intake by smokers, however, compares reasonably to those reported by Wallace (1989a ,b), when expressed as an intake rate (i.e. mg/day). For instance, in our analysis for the adult, the daily intake would be 4 μg/day. If the Wallace assumptions, including smoking of 32 cigarettes/day and no inhalation absorption factor for benzene, are taken into account, the benzene intake rate would be approximately 46 μg/day, which is consistent with Wallace's estimate of 50 μg/day.

Benzene Exposure Resulting from Mainstream Smoke

Exposure to benzene from mainstream smoke was evaluated for adults (19-35 years) and teenagers (16<19 years). Breathing patterns for the inhalation of mainstream smoke (MS) and ETS differ considerably; active smokers inhale intensely and intermittently and usually hold their breath for some time at the end of inspiration. This increases the amount of smoke components that are deposited and absorbed (EPA, 1992). Thus, an absorption factor was not used.

$$ADD = \frac{C \times SF \times CF}{BW}$$

where:

ADD	=	average daily dose (mg/kg-day)
C	=	concentration of benzene in mainstream smoke (μg/cigarette)
SF	=	smoking frequency (cigarettes/day)
CF	=	conversion factor (0.001 mg/μg)
BW	=	body weight (kg)

The exposure was calculated using the average benzene emission factor from Brunneman et al. (1990) of 40 μg/cigarette. A teenager smokes an average of about 7 cigarettes per day, whereas, adults smoke an average of 14 to 17 cigarettes per day (EFH Table 15-146). This smoking frequency results in a daily intake of benzene from mainstream smoke of 0.28 mg/day for the teenage smoker and 0.6 mg/day for the adult smoker. The annual average daily doses were calculated and are presented in Table 7.40.

Table 7.40: Summary of ADDs from Exposure to Benzene in Mainstream Smoke (mg/kg-day)

Exposure Parameter	Units	16 to <19 year old	19 to <36 year old female	19 to <36 year old male
C	µg/cig	40	40	40
SF	Cig/day	7	14	17
CF	Mg/µg	0.001	0.001	0.001
BW	kg	66.8	62.4	76.3
Dose	*mg/kg-d*	*4.2E-03*	*9.0E-03*	*8.9E-03*

The intake rate of benzene for the adult smoker of 0.56 mg/day is lower than the rate reported by Wallace (1989a) of 1.8 mg/day, but if the smoking frequency were adjusted to the 32 cigarettes/day that Wallace assumed, the intake rate calculated here would be comparable at 1.3 mg/day. Thus, the uncertainty surrounding the benzene intake from mainstream cigarette smoke is primarily associated with the smoking frequency.

7.2.3 Occupational Exposure

Occupational exposure to benzene occurs primarily in two types of occupations: (1) production/processing of benzene and (2) use of benzene as feedstock for the manufacturing of other chemicals. Through a literature search, benzene exposures in miscellaneous occupations were identified such as military aircraft workers and firefighters. Exposure data relevant to these general occupational settings were obtained from industry trade organizations, and the recent peer-reviewed literature. As discussed in Section 7.2.4, benzene is not a component of solvent-based products. Therefore occupational exposures to solvent-based products such as paints, lacquers and varnishes were not included.

Members of the BTX VCCEP Consortium provided benzene exposure information for both the benzene production/processing and chemical manufacturing segments of the industry. The data provided include that for the broad categories of manufacturing and distribution. The Consortium's benzene exposure data are summarized in Table 7.41. The exposure data presented on this table are representative of employees who are not required to wear respirators as part of their normal job tasks.

Table 7.41: ACC BTX VCCEP Consortium Members' Occupational Benzene Exposure Survey

		Benzene Exposure Concentrations for Normal Full-Shift Operations	
Operation	Number of Samples	Mean (ppm)	95th Percentile (ppm)
Manufacturing	6,443	0.11	0.39
Distribution	42	0.07	0.06

In the mid-1990s, the American Petroleum Institute (API) representing the oil and gas industry conducted an occupational benzene exposure survey of the petroleum workers. It included data that were representative of worker's exposures in the manufacturing (refining) and distribution (i.e. pipeline, marketing, and marine) aspects of the oil and gas industry during the years 1990 through 1995. The data consisted of approximately 50,000 full-shift and short-term personal air monitoring sample results. This study did not collect information about the use of respiratory protection associated with these industrial hygiene samples, so the actual exposure associated with these data can not be fully determined; the use of respiratory protection would substantially reduce exposures. A summary of the results of the API study by broad industry area is presented in Table 7.42.

Table 7.42: API Benzene Industrial Hygiene Air Sampling Study

Operation	Number of Samples	Mean (ppm)
Refinery	10,956	0.147
Pipeline	1,207	0.124
Marine	179	0.282
Marketing	1,352	0.192

The data presented are representative of full-shift typical exposures, not including turnarounds, or upset conditions.

A supplemental literature search for data regarding benzene exposed workers in the U.S. published since 1997 was conducted and yielded information related to exposure to benzene during chemical production, exposure to jet fuel during military aircraft maintenance, exposure to ambient air at an incinerator facility, exposure to smoke at western wildfires, and exposure to smoke during structural firefighting activities, especially during overhaul (i.e. the post-suppression inspection for hidden fires). The literature search also identified recent exposure databases. These include the Navy Occupational Exposure Database (NOED), which contains 80,000 air samples collected by Navy industrial hygienists to assess workers' chemical exposures, and a similar database maintained by the U.S. Army. However, data from these sources are not publicly available and therefore could not be considered in this exposure assessment.

The recently published (i.e., 1997-2001) literature is summarized on Table 7.43. The firefighters' exposure to benzene is an example of a non-chain of commerce exposure. It is expected that firefighters use their self-contained breathing apparatus (SCBA) when smoke production is highest (i.e., initial attack or knockdown) (Reinhart and Ottmar, 2000), which is also when the highest benzene levels have been measured (Austin et al., 2001a). Thus the high benzene levels reported for the municipal fire fighter may not be representative of a fire fighter's actual benzene exposure.

Table 7.43: Recently Published Data on Occupational Exposure to Benzene

Occupation	Average 8-hour TWA Concentration (ppm)	Reference
Chemical Manufacturing	0.22	Collins et al., 1997
Aircraft Maintenance Personnel – Military	0.006 - 0.05	Lemasters et al., 1997, 1999
Wildland Firefighter – General Crew	0.003 – 0.004	Reinhart and Ottmar, 2000
Wildland Firefighter – Engine Operator	0.13	Reinhart and Ottmar, 2000
Municipal Firefighter	0.4 - 3.4	Austin, et al 2001a,b; Bolstad-Johnson,et al, 2000
Incinerator	0.005	Thrall et al., 2001

Because the data suggest that except for the municipal fire fighter, benzene exposures in these occupations are either similar to or much lower than that of a worker employed in the benzene production industry, occupational exposures to benzene have been quantified using the data from the Consortium. The occupational exposure for a prospective parent employed in the benzene manufacturing industry is assumed to be 0.11 ppm as typical 8-hour TWA exposure and 0.39 ppm as a high-end 8-hour TWA exposure; the mean and 95th percentile in Table 7.41.

Dermal Exposures

Occupational chemical exposure studies typically do not report dermal exposure due to the difficulty of properly estimating the contribution of the dermal route, and very few *in vivo* human studies of dermal exposure to solvents have been published (Kezic et al., 2001). EPA's "Dermal Exposure Assessment: Principles and Applications" provides guidance related to assessing dermal exposure. This document, as well as most other published guidance on dermal exposure focuses on two pathways: direct contact with water and direct contact with soil. Unless a site has been contaminated, however, most workers' dermal exposure to benzene will occur during use or production of chemical products.

The basic theory of calculating the intake resulting from dermal contact with a substance is that the outermost layer of the epidermis (the surface layer of dead skin cells) provides the major barrier to absorption of a chemical into the blood stream. The percent absorbed (ABS) is the fraction of a dose applied to the skin that is absorbed across the outer layer of the epidermis in a specified time. The dermal intake could then be calculated by multiplying the absorption factor by concentration of the chemical in its carrier vehicle, the area of skin in contact with the chemical and the thickness of the vehicle on the skin. Absorption factors for chemicals with high vapor pressures, such as benzene, are generally low due to their high volatility. Absorption factors for benzene are summarized on Table 7.44.

Table 7.44: Dermal Benzene Absorption Factors

% Dose Absorbed	Exposure	Species	Reference
0.07%	Neat Benzene	Human	Maibach 1980
0.08%	Benzene in solvent (0.36%)	Rhesus Monkey	Maibach and Anjo 1981
0.2%	Benzene in toluene (0.5%)	Human	Franz 1984
6.2%	Benzene in water (0.5%)	Human	Franz 1984

These studies indicate that a very low proportion of the applied volatile chemical is actually absorbed by the skin.

In an occupational setting such as the petroleum processing or chemical manufacturing industries, benzene or benzene containing products are handled in nearly 100% closed systems. Thus, dermal exposure to the product is not common except under "upset" conditions, where personal protective clothing including gloves and suits would be worn. Because of the low probability for dermal contact with benzene in an occupational setting and the low dermal absorption of benzene from a solvent-type mixture, dermal exposures for the prospective parents have not been quantified.

Occupational Exposure Calculation

In evaluating the prospective parent's occupational benzene exposure, the average of 0.11 ppm (0.35 mg/m^3) and 95th percentile value of 0.39 ppm (1.22 mg/m^3) from the ACC BTX Consortium benzene survey have been used as typical and high-end exposure concentrations. It should be noted that these values are below the current OSHA PEL of 1 ppm and action level of 0.5 ppm. Exposures were quantified according to the following equation:

$$ADD = \frac{C \times ED \times EF \times ET \times IR \times ABSi}{BW \times AT}$$

where:

ADD = average daily dose (mg/kg-day)
C = concentration (mg/m^3)
ED = exposure duration (years)
EF = exposure frequency (days/year)
ET = exposure time (hours/day)
IR = inhalation rate (m^3/hour)
ABSi = inhalation absorption factor (50%)
BW = body weight (kg)
AT = averaging time (days)

The typical and high-end occupational intakes for prospective parents are presented in Table 7.45.

Table 7.45: Summary of ADDs from Occupational Benzene Exposure

Exposure Parameter	Units	Female Worker Typical	Female Worker High-end	Male Worker Typical	Male Worker High-End
C	mg/m^3	0.35	1.22	0.35	1.22
ET	h/d	8	8	8	8
EF	d/y	250	250	250	20
ED	Years	17	17	17	17
IR	m^3/h	0.47	0.47	0.63	0.63
AT	D	6205	6205	6205	6205
BW	Kg	62.4	62.4	76.3	76.3
ABSi	Unitless	0.5	0.5	0.5	0.5
Dose (ADD)	**mg/kg-d**	**7.24E-03**	**2.6E-02**	**7.94E-03**	**2.81E-02**

7.2.4 Consumer Products

As discussed in Section 4.3, the CPSC determined that by the late 1970's, benzene had been phased out of consumer products intended for use in the home (CPSC, 1978, 1980; NTP, 2002). In deciding to withdraw a proposed ban of benzene in consumer products, the CPSC also determined that trace amounts of benzene are not likely to result in significant exposure to benzene vapor (NTP, 2002). The only consumer product which contains benzene in percent quantities is gasoline and exposures to gasoline in various scenarios have been evaluated (i.e., in-vehicle, refueling, small, non-road engine). A consumer product study conducted by EPA (Sack and Steele, 1991) identified several products containing benzene. In this study, 1,159 consumer products from 65 product categories were analyzed for VOC content by GC/MS with a detection limit of 0.1% by weight. Of the 63 product categories tested, four product categories were identified that contained greater than 0.1% benzene and are listed on Table 7.46.

Table 7.46: Summary of Benzene Consumer Product Weight Contents Quantified by Sack and Steele (1991) Greater than 0.1% by Weight

Product Category	% by weight*
silicone lubricant	0.1 – 0.25
carburetor and choke cleaner	0.25 – 0.75
gasket adhesives/removers	0.25 – 0.75
spot remover	0.25 – 0.75

* Product categories were placed in weight ranges based on the average of the test results for individual products. Weight percents were calculated by excluding those products where benzene was not detected.

Because the Sack and Steele study is somewhat dated (i.e., 1991) benzene composition for each of the products was verified with current material safety data sheets (MSDS). Tables 7.47 and 7.48 show the product categories and representative products that Sack and Steele identified as containing greater than 0.1% benzene. When the benzene contents of these products were verified using the actual product MSDSs, it was found that all benzene contents were less than 0.1% and that benzene was not listed as an ingredient on any MSDS.

Table 7.47: Product Names and Manufacturers for Data Presented in Table 7.50

Product ID	Name	MSDS Date	Company
061	Engine Spot Remover	Dec-93	L&F Products
062	Pyratex Spot Remover	Jun-92	Street R R and Co Inc
063	Spotcheck Cleaner/Remover	May-99	Illinois Tool Work Inc Magnaflux Div
064	Incredible Spot and Stain Remover	Feb-95	Rite-Kem Inc
065	Lift (Spot/Stain & Odor Remover)	Jan-94	Chempace Corp
251	Carb and Choke Cleaner	Jul-97	Permatex Industrial Corp
252	3M Choke and Carb Cleaner	Jan-01	Minnesota Mining and Manufacturing
253	STP Carb Spray Cleaner	Dec-97	First Brands Corp
254	Pyroil Carb & Choke Cleaner	May-00	Valvoline Oil Co
255	Gunk Carb Medic	Feb-99	Radiator Specialty Company
401	Heavy Duty Silicone	Aug-99	CRC Industries, Inc
402	All Purpose Silicone	Aug-98	Sherwin Williams Diversified Brands
403	Silicone Lube	Mar-96	Krylon Div of Sherwin Williams
404	3M Silicone Lubricant	Jul-93	Minnesota Mining and Manufacturing
405	Silicone Lubricating Grease	Feb-93	GE Silicones
521	Permatex High Tack Sealant	Dec-00	Permatex, Inc
522	Permatex Right Stuff Gasket Maker	Mar-02	Permatex, Inc
523	Gasket Remover	Mar-99	Imperial, Inc
524	Permatex Ultra Blue	Mar-02	Permatex, Inc
525	Gasket Remover Aerosol	Mar-99	CRC Industries, Inc

Table 7.48: Benzene Content of Consumer Products Based on MSDS Sheets and Benzene Containing Product Categories Identified by Sack and Steele (1991)

Product Category	Product ID	Content (%)[a]	Product ID	Content (%)[a]	Product ID	Content (%)[a]	Product ID	Content (%)[a]	Product ID	Content (%)[a]
Spot Remover	061	<0.1	062	<0.1	063	<0.1	064	<0.1	065	<0.1
Carburetor and Choke Cleaner	251	<0.1	252	<0.1	253	<0.1	254	<0.1	255	<0.1
Silicone Lubricant	401	<0.1	402	<0.1	403	<0.1	404	<0.1	405	<0.1
Gasket Adhesives/ Remover	521	<0.1	522	<0.1	523	<0.1	524	<0.1	525	<0.1

[a]When benzene is not listed as a hazardous ingredient on a MSDS, the concentration of benzene is less than 0.1% by weight in accordance with the OSHA Hazard Communication Standard at 1910.1200(d)(5)(ii).

The OSHA Hazard Communication standard, 29CFR 1910.1200, requires that manufacturers list the chemical name of all carcinogenic ingredients which have been determined to be health hazards under the following conditions:

- The chemical is present in an amount equal to or greater than 0.1% by weight; or

- The chemical is present in an amount less than 0.1% by weight, but there is evidence that use of the product could result in an air concentration that would exceed the OSHA PEL (1 ppm for benzene) or ACGIH TLV® (0.5 ppm for benzene), or that the product could present a health risk to employees.

Based on the MSDS verification, benzene is not present in any consumer products in levels that exceed the weight content detection limit of 0.1% and that usage of the products in accordance with the label directions would not result in air concentrations exceeding the ACGIH TLV® or present an appreciable health risk to the user. Due to lower exposure duration and usage amount for amateurs versus professionals, the typical amateur use of consumer products such as carburetor cleaner with trace levels of benzene is expected to result in air concentrations well below the ACGIH TLV® of 0.5 ppm.

Therefore, except for gasoline, it is concluded based on the CPSC findings, MSDS survey and the OSHA Hazard Communication Standard that exposure to benzene in consumer products is negligible and therefore no further evaluation of children's exposure to benzene in consumer products has been conducted.

7.3 Summary of Children's Exposures

Childhood exposure to benzene has been quantified in terms of background exposures and specific source exposures. Table 7.49 is a summary of the exposures expressed as annual average daily doses calculated for each type of exposure.

Table 7.49: Summary of Age-Specific Benzene Doses (mg/kg-day)

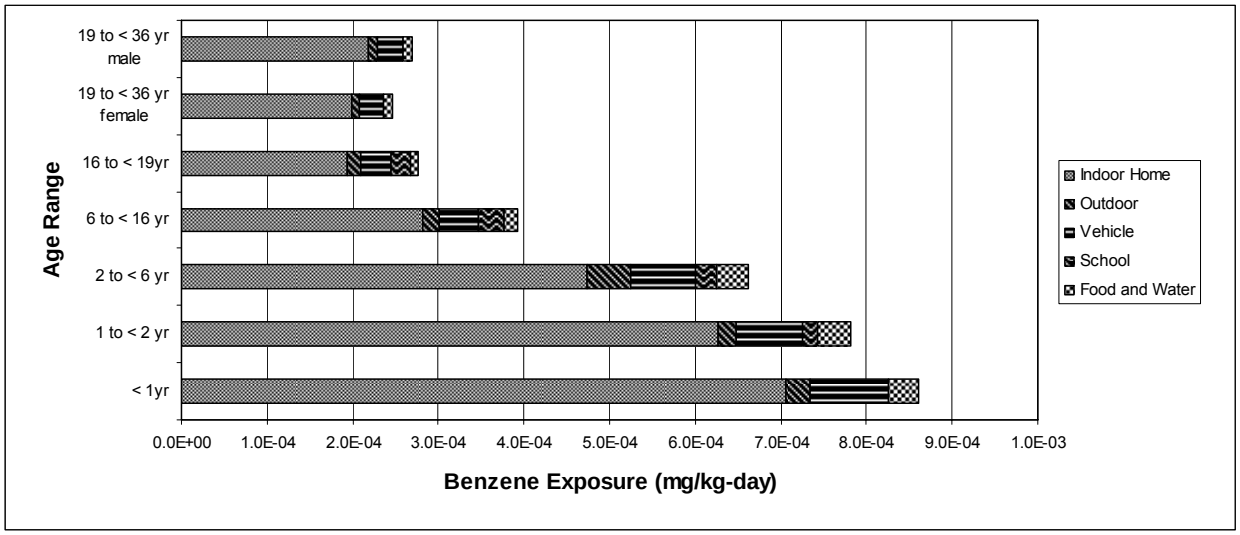
	Age Group						
Scenario	**< 1 year old**	**1 to < 2 year old**	**2 to < 6 year old**	**6 to < 16 year old**	**16 to < 19 year old**	**19 to < 36 year old female**	**19 to < 36 year old male**
BACKGROUND DOSES - OUTDOOR AIR							
Ambient Outdoor Air - School Day/Work Day							
Rural - Typical	--	2.3E-06	1.1E-05	3.6E-06	3.0E-06	--	--
Rural - High-end	--	3.2E-06	1.5E-05	5.0E-06	4.2E-06	--	--
Urban - Typical	--	5.1E-06	2.4E-05	7.8E-06	6.6E-06	--	--
Urban - High-end	--	1.4E-05	6.8E-05	2.2E-05	1.9E-05	--	--
Ambient Outdoor Air - Non-School/Non-Work Day							
Rural - Typical	1.3E-05	7.2E-06	1.2E-05	5.1E-06	3.8E-06	4.1E-06	4.5E-06
Rural - High-end	1.8E-05	1.0E-05	1.6E-05	7.1E-06	5.2E-06	5.6E-06	6.2E-06
Urban - Typical	2.9E-05	1.6E-05	2.5E-05	1.1E-05	8.2E-06	8.9E-06	9.7E-06
Urban - High-end	8.1E-05	4.4E-05	7.1E-05	3.1E-05	2.3E-05	2.5E-05	2.7E-05
Ambient Outdoor Air - Total							
Rural - Typical	1.3E-05	9.5E-06	2.3E-05	8.7E-06	6.8E-06	4.1E-06	4.5E-06
Rural - High-end	1.8E-05	1.3E-05	3.2E-05	1.2E-05	9.4E-06	5.6E-06	6.2E-06
Urban - Typical	2.9E-05	2.1E-05	5.0E-05	1.9E-05	1.5E-05	8.9E-06	9.7E-06
Urban - High-end	8.1E-05	5.8E-05	1.4E-04	5.3E-05	4.2E-05	2.5E-05	2.7E-05
BACKGROUND DOSES - INDOOR AIR							
In Home - School Day/Work Day							
Typical	--	3.0E-04	2.2E-04	1.2E-04	7.9E-05	--	--
High-end	--	1.4E-03	1.0E-03	5.4E-04	3.6E-04	--	--
In Home - Non-School /Non-Work Day							
Typical	7.1E-04	3.3E-04	2.5E-04	1.6E-04	1.2E-04	2.0E-04	2.2E-04
High-end	3.2E-03	1.5E-03	1.2E-03	7.6E-04	5.3E-04	9.2E-04	1.0E-03
In Home – Total							
Typical	7.1E-04	6.3E-04	4.7E-04	2.8E-04	1.9E-04	2.0E-04	2.2E-04
High-end	3.2E-03	2.9E-03	2.2E-03	1.3E-03	8.9E-04	9.2E-04	1.0E-03
Alaska	6.8E-03	3.2E-03	2.5E-03	1.6E-03	1.1E-03	1.9E-03	2.1E-03
In School							
Typical	--	1.7E-05	2.4E-05	3.0E-05	2.3E-05	--	--
High-end	--	8.3E-05	1.2E-04	1.4E-04	1.1E-04	--	--
In-Vehicle							
Typical	9.0E-05	7.7E-05	7.6E-05	4.7E-05	3.6E-05	2.8E-05	3.1E-05
BACKGROUND DOSES - FOOD & WATER							
Food & Tap Water Ingestion							
Urban - Typical	3.6E-05	4.0E-05	3.8E-05	1.5E-05	9.1E-06	1.0E-05	1.0E-05
Urban - High-end	7.9E-04	5.9E-04	4.0E-04	1.9E-04	1.3E-04	1.3E-04	1.3E-04
Occupational - Typical	2.3E-04	--	--	--	--	--	--
Occupational - High-end	1.5E-03	--	--	--	--	--	--

Table 7.49 (cont.)

Scenario	Age Group						
	< 1 year old	1 to < 2 year old	2 to < 6 year old	6 to < 16 year old	16 to < 19 year old	19 to < 36 year old female	19 to < 36 year old male
BACKGROUND DOSES - FOOD & WATER (continued)							
Showering – Dermal							
Typical	0.0E+00	8.6E-07	8.9E-07	6.0E-07	5.0E-07	4.2E-07	4.2E-07
Upper Bound	1.9E-06	2.5E-06	2.3E-06	1.8E-06	1.4E-06	1.3E-06	1.3E-06
Showering – Inhalation							
Typical	0.0E+00	2.2E-05	7.2E-06	1.4E-06	1.0E-06	5.7E-07	5.7E-07
Upper Bound	1.5E-04	4.8E-04	1.2E-04	2.7E-05	1.9E-05	1.1E-05	1.1E-05
BACKGROUND DOSES - SUM OF AMBIENT AIR, INDOOR AIR, FOOD & WATER							
Inhalation Pathway							
Rural - Typical	8.1E-04	7.5E-04	6.0E-04	3.7E-04	2.6E-04	2.3E-04	2.5E-04
Rural - Upper Bound	3.5E-03	3.5E-03	2.5E-03	1.5E-03	1.1E-03	9.6E-04	1.1E-03
Urban - Typical	8.3E-04	7.6E-04	6.3E-04	3.8E-04	2.7E-04	2.4E-04	2.6E-04
Urban - Upper Bound	3.6E-03	3.6E-03	2.6E-03	1.6E-03	1.1E-03	9.8E-04	1.1E-03
Ingestion Pathway							
Urban - Typical	3.6E-05	4.0E-05	3.8E-05	1.5E-05	9.1E-06	1.0E-05	1.0E-05
Urban - High-end	7.9E-04	5.9E-04	4.0E-04	1.9E-04	1.3E-04	1.3E-04	1.3E-04
Occupational - Typical	2.3E-04	--	--	--	--	--	--
Occupational - High-end	1.5E-03	--	--	--	--	--	--
Dermal Pathway							
Typical	0.0E+00	8.6E-07	8.9E-07	6.0E-07	5.0E-07	4.2E-07	4.2E-07
Upper Bound	1.9E-06	2.5E-06	2.3E-06	1.8E-06	1.4E-06	1.3E-06	1.3E-06
SOURCE SPECIFIC DOSES							
Tobacco Smoke							
ETS	2.9E-04	2.6E-04	2.2E-04	1.2E-04	7.4E-05	7.0E-05	7.6E-05
Mainstream	--	--	--	--	4.2E-03	9.0E-03	8.9E-03
Refueling							
Typical	--	--	--	--	1.0E-05	8.7E-06	9.5E-06
Upper Bound	--	--	--	--	1.3E-04	1.1E-04	1.2E-04
Occupational							
Typical	--	--	--	--	--	7.2E-03	7.9E-03
Upper Bound	--	--	--	--	--	2.6E-02	2.8E-02

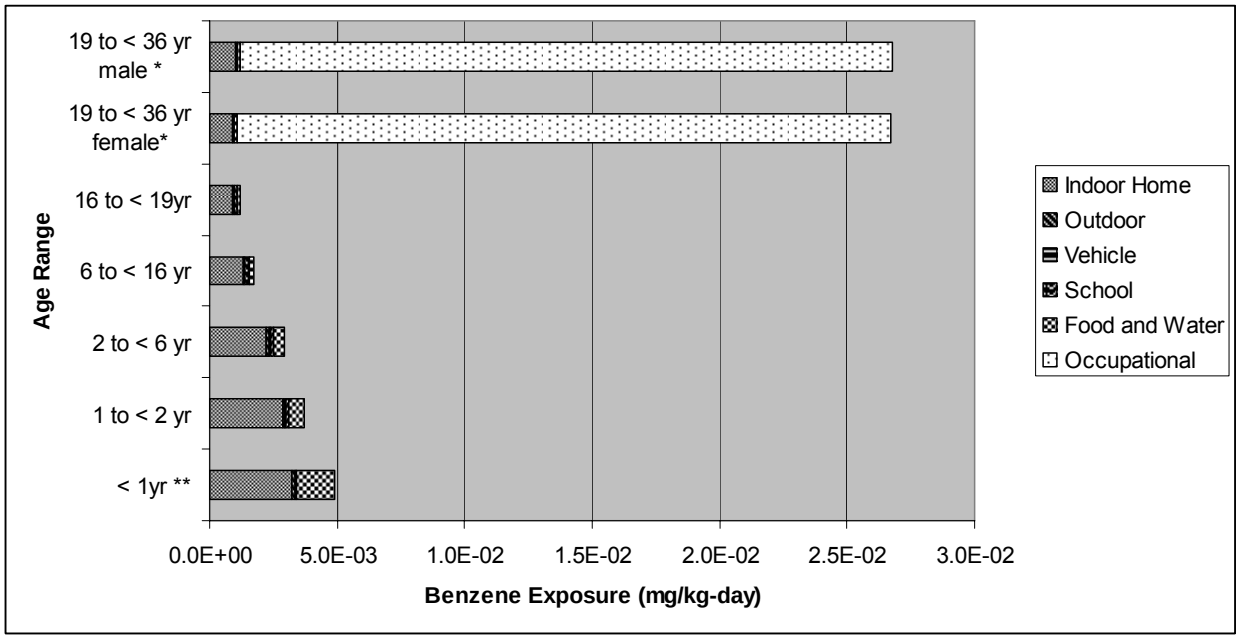
For children and non-smoking adults, inhalation of benzene from in-home indoor air is the predominant pathway of exposure, followed by inhalation of benzene from in-vehicle exposures, ingestion of benzene in dietary sources and tap water and lastly, the outdoor ambient air. This is graphically presented on Figure 7.6. For nursing infants of high-end occupationally exposed mothers, inhalation of benzene from in-home indoor air remains the predominant pathway of exposure but the secondary pathway of exposure is ingestion of human milk. This is graphically presented on Figure 7.7.

Figure 7.6: Contribution of Various Ambient Sources to Typical Total Background Benzene Exposures



*Representative of a nursing infant (<1year) with a non-occupationally exposed mother.

Figure 7.7 Contribution of Various Ambient Sources to High-end Total Background Benzene Exposures

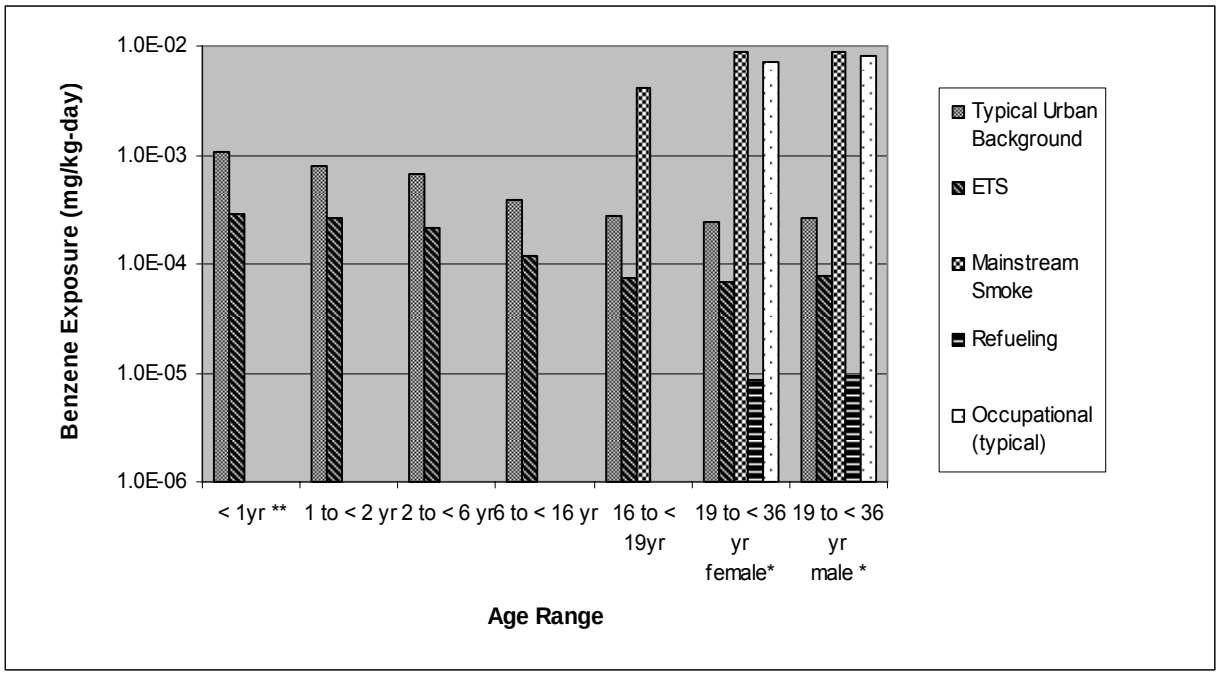


*Includes high-end occupational exposure
** Representative of a nursing infant (<1 yr) of a high-end occupationally exposed mother

The in-home indoor air concentrations are influenced the most by the presence or absence of an attached garage. While the evaporative emissions from vehicles contribute to the in-home benzene concentrations, recent studies indicate that the number of small engine sources or gasoline storage containers has a greater impact on the source strength of the garage, than the vehicles.

In addition to background sources of exposure, specific benzene sources were evaluated in terms of their contribution to overall exposure. A comparison of the various source specific exposures is graphically presented in Figure 7.8.

Figure 7.8: Comparison of Benzene Exposures from Typical Urban Background (Ambient) Sources to Specific Sources



* Includes typical occupational exposures

** Representative of a nursing infant (<1year) with a mother exposed to typical occupational levels.

As shown on Figure 7.8, of the specific benzene sources quantified, the highest source specific benzene exposures come from mainstream smoke and occupational exposures and the lowest come from refueling. Similar to that observed by Wallace (1996), cigarette smoke for those without occupational exposures contributes nearly 90% of a smokers total benzene dose. In fact, the potential benzene exposures resulting from mainstream cigarette smoke are similar to that of occupational exposures in the benzene manufacturing and production industries. ETS contributes far less to overall benzene exposures than mainstream smoke and is about a factor of 3-fold lower than that of typical background exposures.

8.0 Risk Assessment

Risk assessment integrates findings of a hazard assessment and exposure assessment for a given chemical and provides a numerical, quantitative characterization of risk. This risk assessment was specifically designed to evaluate the potential for exposure to benzene in the U.S. to result in adverse health effects in children and prospective parents. It incorporates an analysis of the noncancer and cancer risks from benzene, including an evaluation of existing data on the likelihood that children will have an altered susceptibility or response to benzene-induced toxicity.

As the Exposure Assessment indicates (see Section 7), benzene is in the air in many environments where children are present, and it is also present in food, drinking water, and human milk (for nursing infants) at levels well below historical, and even more current, occupational levels. The U.S. Environmental Protection Agency (EPA), in its Integrated Risk Information System (IRIS) database (U.S. EPA, 2003a) has established noncancer (last revised in 2003) and cancer risk levels (last revised in 2000) for benzene that were derived from human occupational epidemiology studies involving exposures that were many orders of magnitude higher than levels to which children are exposed in the U.S.

While the hazards identified from these studies are relevant for human risk assessment because they analyze human toxicological effects, the extrapolation of effect levels from these high-exposure studies to much lower environmental exposures presents challenges. In the IRIS database, EPA used linear default extrapolation methods, even though there is considerable data suggesting that benzene-induced cancer requires a sufficient threshold of exposure to pose a hazard.

To evaluate the potential impact of EPA's assumptions regarding low-dose extrapolation of risk, this risk assessment compares the risks based on the EPA IRIS values and the risk based on a margin of safety (MOS) approach, using the same key studies and critical effects on which the IRIS values were developed to choose the points of departure (PODs). The risk assessment considers a margin of safety analysis for both cancer and noncancer effects.

8.1 Risk Assessment Approach

This risk assessment was conducted using two different approaches;

1) An EPA default (linear) type of risk assessment using the Reference Dose (RfD) and Cancer Slope Factor (CSF) to characterize risks.[2]

2) A Margin of Safety (MOS) approach that utilizes a point of departure (POD) to characterize risks.

Both cancer and noncancer risks to children and prospective parents are characterized based on the quantitative estimates of exposure presented in Section 7. Exposures from all

[2] Within the EPA default approach, a range of hazard quotients (HQ) are calculated using a range of RfCs/ RfDs. A range of RfCs/RfDs are employed to better characterize the debate about what constitutes a scientifically justified Reference Value (RV).

background pathways of exposure, including inhalation, ingestion, and dermal contact, have been added together to determine a total average daily dose for each age bin. Additionally, exposures resulting from gasoline sources (i.e., refueling) have been aggregated with background exposures, and risks characterized. Estimates of potential risks for smokers and their children are made separately from benzene exposures derived from other background or source-specific sources. Comparing benzene exposures from smoking-derived sources with other sources provides important insights.

The exposure assessment provides estimates of typical and high end exposures for almost every exposure scenario. For this risk assessment, aggregate exposures are calculated for the typical and high end exposures by summing the respective typical and high end exposure estimates from the inhalation, ingestion, and dermal pathways. This approach will undoubtedly yield some overly conservative results. In particular, aggregating for the "high end" will undoubtedly compound conservative assumptions and may over-estimate actual exposures that are likely to occur in the U.S. (even for the high end). However, to the degree that exposures are dominated by one or a few exposure scenarios, this compounding issue becomes less critical.

The exposure assessment presented in this report suggests that indoor air (in the home) is the predominant pathway, and may contribute upward of 70%–80% of aggregate exposures for children in non-smoking households. For children in a smoking household, the background indoor air contributes approximately 50%–60% of total exposures, with exposures from environmental tobacco smoke (ETS) contributing approximately 20%–25% of total exposures. Therefore, the compounding of conservative estimates to develop an aggregate "high end" exposure may be less significant than would be the case if all the exposure scenarios contributed equally to the aggregate exposures.

Indoor air levels of benzene in Alaskan homes are addressed as a separate exposure scenario. Age-specific risks are quantified using the exposures from inhalation of indoor air in Alaskan homes. These risks are then compared to the risks calculated for typical and high end continental U.S. home indoor air inhalation pathway.

For carcinogenic effects, exposures are calculated by averaging the total cumulative dose over a lifetime. The estimate of the average lifespan is assumed to be 70 years, based on EPA guidance (U.S. EPA 1991b). The lifetime average daily dose is calculated as a time-weighted value over a 70-year lifespan using the average daily dose (ADD) and the applicable exposure duration for each age group.

$$\text{Lifetime Average Daily Dose} = \frac{(ADD_{<1yr} \times 1\text{ yr}) + (ADD_{1\text{ to }<2\text{ yr}} \times 1\text{ yr}) + (ADD_{2\text{ to }<6\text{ yr}} \times 4\text{ yr}) + (ADD_{6\text{ to }<16\text{ yr}} \times 10\text{ yr}) + (ADD_{16\text{ to }<19\text{ yr}} \times 3\text{ yr}) + (ADD_{19\text{ to }70\text{ yr}} \times 51\text{ yr})}{70\text{ years}}$$

8.1.1 Dose Metrics

The options for quantifying benzene exposures as the basis for dose calculations in a risk assessment include inhaled air concentration, calculating an absorbed dose, and an internal dose using an appropriate physiologically based pharmacokinetic (PBPK) model. Using an internal dose is preferable if the mechanism of action (MOA) of the compound (for both non-

cancer and cancer effects) has been definitively established. There have been numerous PBPK models developed for benzene. These have been useful in assessing:

- species differences in benzene metabolism (McMahon et al., 1994; Spear et al., 1991),
- testing theories about non-linear dose-response relationships between benzene exposures and hematopoetic/leukemogenic effects (Cox, 1996; Weisel et al., 1996; Kenyon et al., 1996; Cox and Ricci, 1992),
- interpreting biomonitoring data collected from humans (Thrall et al., 2001; Sherwood and Sinclair, 1999; Roy and Georgopoulos, 1998; Thomas et al., 1996),
- predicting concentrations of benzene in breast milk among exposed mothers (Fisher et al., 1997),
- assessing potential gender differences in benzene metabolism (Brown et al., 1998), and
- for assessing the potential for co-exposures to toluene, ethyl benzene, and xylenes to modulate the metabolism of benzene (Dennison et al., 2004; Krishnan et al., 2002; Haddad et al., 2001; Tardif et al., 1997).

For PBPK models to form the basis for conducting a scientifically appropriate PBPK-based risk assessment, the mechanism of action for the toxic endpoint of concern (e.g., hematopoetic toxicity) must be known so that the critical dose measure can be established. While metabolism seems to be a critical determinant for benzene's hematopoetic toxic action, many questions remain; 1) which specific metabolites or combinations of metabolites are critical, 2) whether phase 1 metabolism or the bioactivation step of benzene must occur in the bone marrow or the liver (or both) (Bird et al., 2005). Currently, the mechanism of action for benzene-induced AML is still under investigation. Further, not enough is known at this time to choose a defensible critical dose measure to form the basis of a PBPK-based risk assessment. Therefore, this VCCEP risk assessment for benzene was conducted using absorbed doses of benzene as the critical dose metric. This is consistent with USEPA's approach used in developing their cancer slope factors and Reference Dose and Reference Concentration. As mentioned in the exposure assessment (Section 7.2.1.8), a PBPK model for benzene was used to calculate the dose of benzene to an infant via breast milk from an exposed mother.

8.1.2 Mixed Exposures

Exposures to pure benzene rarely occur in environmental or occupational settings. More commonly, benzene exposure will involve co-exposures to other chemicals, including complex mixtures such as gasoline. BTEX (benzene, toluene, ethyl benzene, and xylenes) represent the components that are most often focused on when assessing exposures to gasoline. It has been shown in experimental animals and purified enzyme systems that co-exposures to toluene, ethyl benzene or xylenes can inhibit the metabolism of benzene. However, this is only considered relevant at high exposure concentrations (greater than 100 ppm) for each constituent, which results in competitive inhibition of the metabolizing enzymes. Therefore, this competitive inhibition is not likely to occur to any significant degree at environmentally relevant exposure concentrations (e.g., less than 1 ppm). The ATSDR treats mixtures of BTEX as additive when addressing neurological impairment (ATSDR, 2004). However, the ATSDR has stated that co-exposures with toluene, ethyl benzene or xylenes do not potentiate the hematopoetic or leukemogenic effects of benzene (ATSDR, 2004). Thus, while exposures to benzene alone are rare, it is not anticipated that other constituents in gasoline will potentiate or inhibit the hematopoetic or leukemogenic effects of benzene, especially at environmentally relevant exposure concentrations (ATSDR, 2004). Therefore, co-exposures are not quantitatively addressed in this risk assessment.

8.1.3 EPA Default Risk Assessment

Non-cancer:
EPA has developed equations to estimate potential risks of noncarcinogenic and carcinogenic health effects (U.S. EPA, 1989). For noncarcinogenic health effects, a Hazard Quotient (HQ) is calculated, which is the ratio of the estimated exposure to the reference dose (RfD).

$$HQ = \frac{\text{Exposure (mg/kg-day)}}{\text{RfD (mg/kg-day)}}$$

For noncancer health effects, exposures are averaged over the duration of the exposure period and are expressed as the average daily dose (Table 7.53). All exposures quantified in the exposure assessment were calculated as absorbed doses. EPA's RfD is used in all HQ calculations, because it is an absorbed-dose based Reference Value (RV)[3].

Exposures resulting in an HQ that is less than 1 are unlikely to result in noncancer adverse health effects. As HQ values increase, the potential for toxicity increases. EPA states that the range of possible values around RfDs is "perhaps an order of magnitude" (Dourson 1993); therefore, the significance of intakes exceeding the RfD by one-half order of magnitude or less (i.e., HQs less than 5) must be considered carefully. As recommended by EPA guidance, all noncancer HQs and cancer risk estimates are expressed with one significant figure (U.S. EPA, 1989).

Cancer:
For carcinogenic endpoints, risk estimates are calculated by multiplying the exposure by the carcinogenic slope factor (CSF), expressed in $(\text{mg/kg-day})^{-1}$.

$$\text{Risk} = \text{Exposure (mg/kg-day)} \times \text{CSF (mg/kg-day)}^{-1}$$

This yields a unitless estimate of risk, and should be interpreted as the probability of increased incidence of cancer in a lifetime. Therefore, a cancer risk estimate of 1×10^{-5} or 1×10^{-4} indicates a probability of 1 in 100,000 and 1 in 10,000, respectively, or 1 cancer in a population of 100,000 or 10,000 people, respectively, exposed to the levels used in the calculations.

8.1.3.1 Approach for Margin of Safety Assessment

EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005b) provides guidance for performing risk assessments on compounds that exhibit non-linear dose-response trends. According to the guidance, a Margin of Exposure (MOE) analysis should be conducted when the mode of action dictates a non-linear mechanism, yet not enough information and

[3] EPA derived their RfD from the RfC by calculating the absorbed dose associated with the RfC:

$$\text{Reference Dose (absorbed)} = \frac{\text{Reference Concentration} \times \text{Inhalation Rate (10 m}^3\text{/day)} \times \text{Absorption Factor (50\%)}}{\text{Body Weight (70 kg)}}$$

understanding of the biological processes exist to develop a validated biologically based dose-response model (Andersen et al., 2000; U.S. EPA, 2005b). The MOE approach provides some advantages, because "cancer slope factors derived from the linear option give estimates of population risks that provide inappropriate risk-communication information to the public. The MOE does not provide an analysis as easily abused for estimating specific population risks" (Andersen et al., 2000).

There is a distinction between a margin of exposure (MOE) and margin of safety (MOS) assessment and in the way the MOS is being used in this risk assessment. The MOE approach uses a point of departure (POD) that represents a NOAEL or a "functional" threshold. The MOS, on the other hand, uses a POD that already contains some safety factors. This was also recognized by the European Union when they performed a MOS analysis and developed PODs that already contained safety factors for benzene[4] (ECB, 2003).

The MOS approach compares a calculated exposure to a point of departure (POD).

$$\text{MOS} = \frac{\text{POD (mg/kg-day)}}{\text{Exposure (mg/kg-day)}}$$

The MOS represents the ratio between the POD and the exposure dose. For example, an MOS of 100 indicates that the exposure is 100 times lower than the POD. An MOS of 1 would indicate that the estimated exposure equals the POD, and if the value is less than 1, the estimated exposures exceed the POD. Using this approach, larger MOSs indicate lower potential for risk. MOSs will be calculated both for cancer and noncancer health effects in this assessment. For noncancer health effects, exposures are expressed as the average daily dose (Table 7.53). For cancer, exposures are expressed as the lifetime average daily dose, as described above.

8.2 Toxicology Reference Values

The toxicology reference values used in this risk assessment for both the EPA default risk assessment approach (RfD and CSF) and in the MOS risk assessment approach (POD) are discussed below. Both the RfD and the CSF for benzene were derived from human occupational epidemiology studies. Since this risk assessment is designed to evaluate the risks to children, it must first be determined if children are more sensitive than adults to the toxic effects of benzene and thus require some children's sensitivity adjustment factors to the current RfD, CSF, and any PODs established for this risk assessment. The following is an evaluation of the potential for children to be more sensitive to benzene's toxic effects. The findings from this evaluation help guide whether the toxicology reference values should be adjusted further to protect children.

[4] The EU termed their POD a Critical Exposure Level (CEL). The CEL was derived by choosing a No Observed Adverse Effect Concentration (NOAEC) and then applying a "safety factor" which they termed a minimal MOS. The CEL was then used as the POD to calculate the Margins of Safety.

8.2.1 Potential for Increased Sensitivity of Benzene-Induced Hematopoietic Toxicity and AML in Children

The EPA's Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (U.S. EPA 2005a) provides generic guidance that should be used in the absence of chemical specific information. There are no published data on the adverse effects of high-dose benzene exposure in children. Additionally, there is no reliable animal model for benzene-induced AML. Therefore, experimental studies using rodents cannot be used to address the issue of whether young animals are more sensitive than older animals to the leukemogenic effects of benzene.

In the absence of benzene-specific data, another known etiological agent for AML in children was used as a surrogate. Data that allowed for an evaluation of the effect of age on a child's risk of developing secondary leukemia was found in the cytotoxic chemotherapy literature. Several studies were located that reported treatment of different-aged children with the same disease with potentially leukemogenic drugs.

With cautious interpretation, studies describing therapy related or secondary AML (t-AML; treatment-induced AML) and hematopoietic toxicity (myelosuppression) in children following treatments with a variety of cancer therapeutic drugs may be a relevant surrogate to investigate age-related differences in susceptibility. This information is briefly described below and more fully in (Pyatt et al., 2005; Pyatt et al., 2006 in press).

8.2.1.1 Children's Sensitivity Toward Therapy (Chemical)-Induced AML (t-AML)

Acute myelogenous leukemia (AML) has been positively linked to treatment with certain classes of cytotoxic chemotherapy. Drugs known to cause AML following chemotherapy of primary malignancy are usually alkylating agents or topoisomerase II inhibitors. Both children and adults can develop AML, yet rarely develop ALL, following treatment with these anti-neoplastic drugs.

The first criterion that had to be evaluated to show that the chemotherapy-induced AML issue might be a reasonable surrogate for benzene-induced leukemia was to determine whether the secondary AML was a result of the chemotherapy treatments and not some other factor associated with the primary disease being treated or with some other component of the treatment (such as radiation). This could be proved by showing a clear dose-response between the relative risk (RR) of t-AML incidence and the dose of chemotherapy drugs. Many, if not all, of the studies evaluated present data that clearly support a position that chemotherapy-induced leukemia in children (from both classes of leukemogenic therapies) follows a predictable dose response, with increasing risk associated with increasing cumulative doses (Deley et al., 2003; Tucker et al., 1987). Tucker et al. (1987) calculated an "alkylator score" based on the dose of the drugs used (Tucker et al., 1987) and showed a clear dose-response (Figure 8.1). A dose response for AML risk has also been reported for cycles of MOPP therapy (which includes nitrogen mustard, vincristine, procarbazine, and prednisolone), cumulative alkylating agent dose, and total cumulative dose of etoposide (Neglia et al., 2001; Deley et al., 2003; Meadows et al., 1989; Kaldor et al., 1990; Donaldson, 1993; van der Velden et al., 1988; Hawkings et al., 1992). As an example, Kaldor et al (1990) reported a dose response and risk of t-ANLL with cycles of MOPP. With 6 cycles, the relative risk of t-ANLL was reported to be 4.7, but with more than 6 cycles, the relative risk rose to 14 (Kaldor et al., 1990). Pedersen-Bjergaard et al., (1987) also reported a dose-response relationship with increasing alkylating agents. Using dose metrics of low, medium, and high exposure, the risk of t-AML was 6.4, 11.3, and 37.5, respectively (Pedersen-Bjergaard et al., 1987).

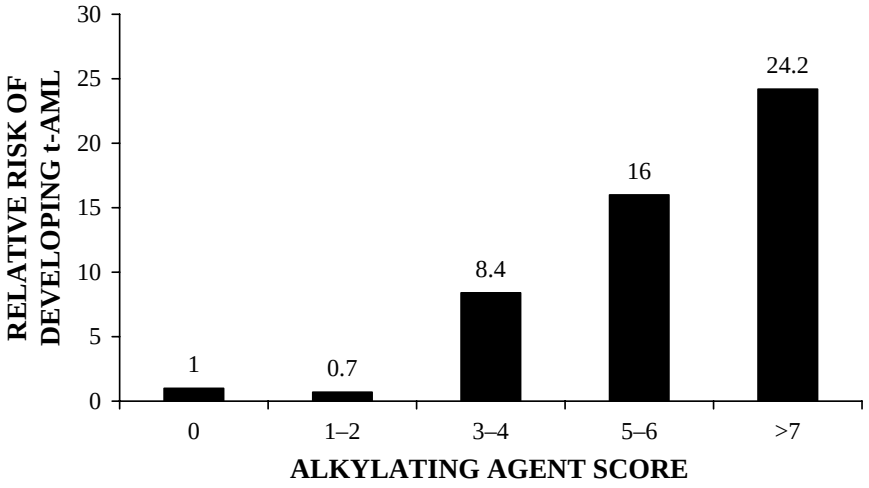


Figure 8.1: Relationship between RR of developing t-AML and the dose of the alkylating agent (represented by an "alkylating agent score"). Adapted from Tucker et al., (1987).

Next, the relationship between age and risk of developing t-AML following chemotherapy treatment was evaluated. A thorough review of the chemotherapy treatment literature indicated that there is no consistent evidence indicating younger children will be at increased risk; in fact, some studies indicate that younger children might actually have a decreased susceptibility (see Figure 8.2 and 8.3). Winick et al. (1993) reported the absolute risks of developing t-AML in children treated with etoposide for ALL. As can be seen in Figure 8.2, there was no age-related effect evident, with the exception that very young children (less than 3) had a slightly lower incidence rate of t-AML. Tucker et al. (1987) found that the absolute excess risk of t-AML following MOPP treatment rose progressively with the age of the patient (Figure 8.3). Similar results were found in numerous other studies. Pyatt et al. (2006 in press) provides a thorough review of this information. The consistent finding throughout is that children do not appear to be more sensitive to chemotherapy-induced AML, and in some cases are reported to be less sensitive.

Furthermore, there is clear evidence in the published clinical literature that the effects of age on the risk of developing a secondary malignancy are highly dependent on the type of disease in question. As previously discussed, the risk of developing t-AML following chemotherapy does not appear to be related to the age of the patient. In contrast, the risk of developing various solid tumors is highly dependent on the age of the patient, with younger patients having a higher risk. Neglia et al (2001) reported that younger age correlated well with increased risk for solid tumors (CNS, breast, and thyroid) but not t-AML. An age dependency for risk of developing secondary solid tumors, but not secondary leukemia, in pediatric patients was also reported in a study by Loning et al. (2000). Mauch and co-authors report that the risk for secondary breast cancer was highly age dependent and that young girls less than 15 had a much higher relative risk (RR) and absolute excess risk (AER) than older girls and women (Mauch et al., 1996). This age dependency on risk was not observed with ANLL in this study (Mauch et al., 1996). Kuttesch et al. (1996) demonstrated that age (3–40 years old) was not an independent risk factor for any secondary malignancies (including ANLL) following treatment of Ewing's Sarcoma.

These findings illustrate examples of studies with sufficient power that discern age-related differences, but did not find that the risk of AML was dependent on age. Currently available scientific and medical literature describing chemotherapy-induced AML in children appears to indicate that children are not more sensitive for developing AML following leukemogenic chemical exposure.

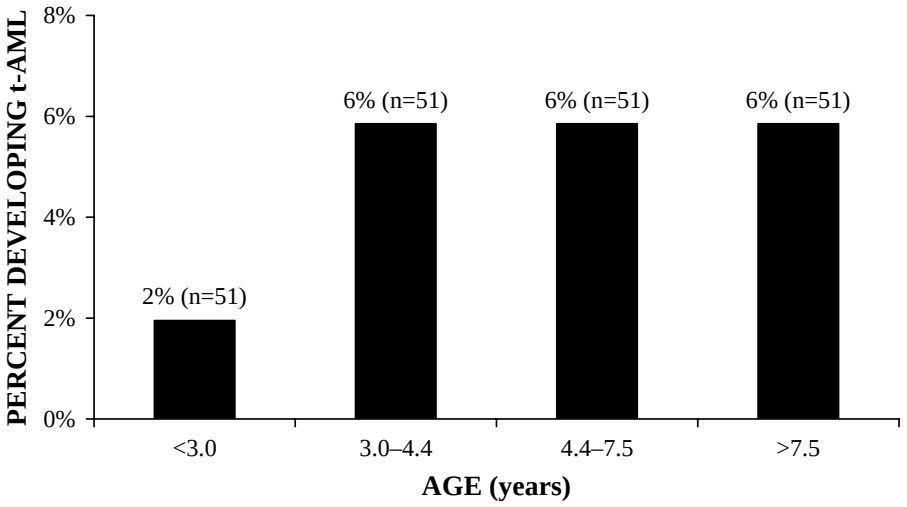


Figure 8.2: Percent of children who developed t-AML following treatment for ALL with etoposide (adapted from Winick et al., 1993).

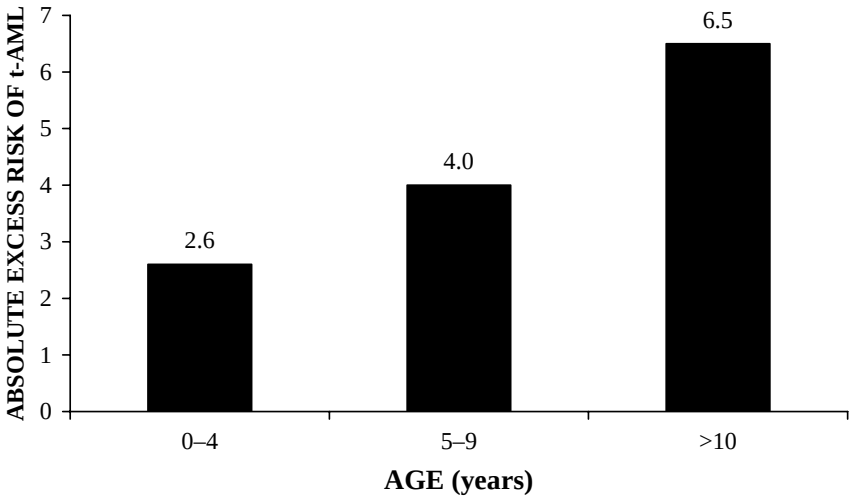


Figure 8.3: Age dependency of absolute excess risk of developing t-AML following treatment with alkylating agents. Adapted from Tucker et al. (1987)

8.2.1.2 Children's Sensitivity Toward Therapy (Chemical)-Induced Hematopoietic Toxicity

There are no available data to allow a direct comparison of benzene exposure required to result in hematopoietic toxicity between children and adults. However, limited data exist that do allow for an age-related comparison of bone marrow toxicity associated with exposure to various chemotherapeutic agents. Researchers from the National Cancer Institute (NCI) and associated institutions (Glaubiger et al., 1982; Marsoni et al., 1985) compared the maximum tolerated dose (MTD) for a variety of anti-neoplastic agents in children and adults (data obtained from various NCI sponsored clinical trials). Myelosuppression was the dose-limiting toxicity in both children and adults for 10 of the 17 drugs evaluated in this study. For 6 of the 10 drugs for which myelosuppression was the dose-limiting toxic effect in both populations, children had a higher MTD than adults. For the other four drugs, children had an equivalent MTD for three of the 17 drugs and a lower MTD in only one of the 17 drugs. The mean ratio of children/adult MTDs was 1.2. In addition, for every drug tested that had myelosuppression as the dose-limiting effect, the Phase II dose given to children was higher than that administered to adults on a mg/m^2 basis. Based on these results, investigators at NCI concluded that in the majority of cases, children are more resistant to the toxicity (myelosuppression) of anti-tumor drugs than adults (Glaubiger et al., 1982; Marsoni et al., 1985). This provided an independent line of evidence in support of the lack of an increased susceptibility in children to hematopoietic toxicity.

8.2.1.3 Children's Sensitivity Adjustment Factors

There is no consistent evidence in the published medical or scientific literature to support the hypothesis that children have an increased susceptibility to developing t-AML following chemical exposure. This was true for children treated with both classes of established leukemogenic drugs (alkylating agents and topoisomerase inhibitors). These two drug classes are known to act through separate mechanisms; therefore, the lack of increased sensitivity for development of t-AML may be applicable to all chemical leukemogens. The available clinical literature also suggests that children are no more, and may be less, sensitive to chemical-induced hematopoetic toxicity following exposures to a range of chemotherapeutic drugs. While uncertainties exist in this comparison, the available published data indicate that an age-related sensitivity difference to chemically induced leukemia and hematopoetic toxicity does not exist.

Based on these findings, there is no need to add additional children's sensitivity safety factors to any of the regulatory health guidance values (RfC or CSF) and the PODs for both noncancer and cancer.

8.2.2 Reference Values for EPA Default Risk Assessment

The following summarizes EPA's RfD/ RfC and CSFs for benzene.

8.2.2.1 Reference Concentration and Reference Dose

As discussed in Section 6.1, peripheral cytopenias are the most sensitive noncancer effect following exposures to high concentrations of benzene. Section 6.2.3 provides a thorough review of the literature on the reported reproductive (fertility) and developmental effects

information associated with benzene exposures. This review and reviews conducted by other groups (ACGIH, 2001; ECB, 2003, U.S. EPA 2003a) indicate that reproductive and developmental effects appear to occur at maternally toxic doses and at exposures above those associated with cytopenias. Therefore, this risk assessment is conducted using health benchmarks based on the most sensitive noncancer endpoint, cytopenias. The decrease in absolute lymphocyte count (ALC) reported in Rothman et al. (1996) forms the basis of EPA's RfC and RfD (U.S. EPA, 2003a). EPA derived an RfC of 3×10^{-2} mg/m^3 and an RfD of 4.0×10^{-3} mg/kg/day based on the same study and extrapolating based on total absorbed dose. There are several issues with how EPA derived their RfC and RfD that warrant discussion.

Issues with how EPA calculated the RfC and RfD

EPA used data from Rothman et al. (1996) to calculate both a reference concentration (RfC) for inhalation exposures and, by route-to-route extrapolation, a reference dose (RfD) for oral exposures (U.S. EPA 2003). The RfC and RfD were based on benchmark dose (BMD) modeling of the ALC data. Unlike the presence or absence of a tumor, ALC is a continuous endpoint; that is, there is a range of "normal" ALC values and thus no single clear definition for an adverse level. EPA selected as a default benchmark response (BMR) a one standard deviation change from the control mean. That is, an ALC would represent an adverse effect if it is more or less than one standard deviation from the mean of the control population. It should be noted that the range of ALCs reported by Rothman (even for the exposed workers) was all within the normal range of ALC values reported for adults. Therefore, while a dose-response was established, the ALCs for the workers from this cohort were all within the normal range of ALC values, despite having some extremely high exposures (in excess of 100 ppm TWA benzene concentration).

EPA's BMD modeling yielded a benchmark concentration (BMC) of 13.7 ppm (8-hr TWA), and a benchmark concentration lower limit (BMCL; 95% lower bound on the BMC) of 7.2 ppm (8-hr TWA). The BMCL was then converted from an occupational exposure (8-hr TWA, 5 days/wk) to a continuous exposure (24-hr/day, 7 day/wk), with a resulting value of 8.2 mg/m^3. The final step in the calculation of the RfC is the application of an uncertainty factor. The EPA applied an uncertainty factor (UF) of 300, which is a combination of four different values.

- **3**: for effect-level extrapolation, analogous to the UF used to extrapolate from a LOAEL to a NOAEL. EPA recognized that a decreased ALC "is not very serious in and of itself. Decreased ALC is a very sensitive sentinel effect that can be measured in the blood, but is not a frank effect, and there is no evidence that it is related to any functional impairment at levels of decrement near the benchmark response" (U.S. EPA, 2003a).

- **10**: for intraspecies differences in response (human variability), intended to protect potentially sensitive human subpopulations.

- **3**: for subchronic to chronic extrapolation.

- **3**: for database deficiencies, because no two-generation reproductive and developmental toxicity studies for benzene were available.

That is, the UF = 3×10×3×3 = 270 (which was rounded by EPA to 300), would yield an RfC of 3.0×10^{-2} mg/m^3 (8.2 / 270 = 2.7×10^{-2} mg/m^3).

While considerable professional judgment and policy decisions go into the selection of UFs, these values merit scientific analysis. The following discusses the issues surrounding EPA's choice of UFs used to derive the RfC/RfD for benzene and some suggestions for alternative UFs. The quantitative impact on the reference value of modifying the various UFs is summarized in Table 8.1.

- UF for effect level extrapolation: The effects reported in the cohort of workers studied by Rothman were still within the range of normal ALC, despite having some extremely high exposures to benzene (>100 ppm TWA for some workers). The selection of the POD to be one standard deviation from the control group is also a health protective (conservative) measure. EPA chose a value of 3 for the effect level extrapolation UF, recognizing that the effects were not severe. EPA recognized that a decreased ALC "is not very serious in and of itself. Decreased ALC is a very sensitive sentinel effect that can be measured in the blood, but is not a frank effect, and there is no evidence that it is related to any functional impairment at levels of decrement near the benchmark response" (U.S. EPA, 2003a). Had Rothman and coworkers performed their analysis using more exposure groups than just the < 31 ppm and > 31 ppm exposed groups, a NOAEL could likely have been identified and there would be no need for this adjustment factor. Despite this, it is most enlightening that all of the workers had ALCs within the normal range, despite some extremely high exposures. This, combined with the fact that the slight decrements in ALC is considered to be a very sensitive marker and is not, according to EPA, related to any "frank effects," questions the scientific justification for EPA's use of a factor of 3 for an effect level extrapolation.

- UF for intraspecies sensitivity: Clinical data would suggest that children are not more sensitive than adults to the myelosuppressive effects of a variety of drugs, and in some cases may actually be less sensitive than adults. Therefore by analogy, children would not be expected to be more sensitive to the myelosuppressive or hematopoietic toxicity of benzene. Thus, children do not appear to be one of the sensitive populations for benzene's toxic effects. Since the subject of this risk assessment is children, it would appear there is evidence to support that an UF of 3 (rather than 10) would be sufficiently protective.

- UF for subchronic to chronic adjustment: Evidence in humans and experimental animals indicates that cytopenias occur within weeks or months of exposure and upon removal from the environment or reduction in benzene concentration, alterations are likely to return to normal values (Green et al., 1981a; Snyder et al., 1981). Rothman et al. noted in their publication "Neither estimated cumulative life-time benzene exposure nor number of years worked in an exposed factory was significantly associated with any hematologic outcome" (Rothman et al., 1996). Therefore, there is no reason to suspect that the biological response from 6.3 years of exposure would be quantitatively or qualitatively different than that expected to occur following 7 years of exposure. This calls into question the biological rationale for EPA's subchronic to chronic uncertainty factor of 3. Accordingly, this UF should not be used.

- UF for database deficiency: EPA determined that the absence of a two-generation reproductive study warrants an additional UF of 3. Benzene is one of the most thoroughly studied chemicals regulated by EPA, with a vast number of studies having been conducted on the effects in exposed humans. The reproductive and developmental toxicology and epidemiology studies conducted for benzene were thoroughly reviewed in Section 6.2.3. From this review, it is clear that some rodent

species are more sensitive than others (mice are more sensitive than rats) to the reproductive/developmental effects of benzene. It is unclear how results from sensitive rodent species would be applicable for predicting risks of reproductive/developmental effects in humans, thus a two-generation reproductive study may be uninformative for benzene. Therefore, this UF may be unwarranted.

Table 8.1 provides a summary of the RfCs and RfDs (absorbed dose) calculated using combinations of these alternate UFs. The range of RfDs (EPA's IRIS value as the low estimate and Alternative 3 as the high estimate) will be used in calculating HQs in this risk assessment (Table 8.2). Using a range of values for the RfC/RfD provides valuable information for risk managers. One of the shortcomings of a default risk assessment approach using a single estimate of the RfC/RfD to calculate a HQ is that the uncertainty about the "safe" exposure level of a chemical is already built into the RfC/RfD and thus the risk calculation process. Therefore, risk managers are less informed of the uncertainty involved in the calculated risks unless a formal uncertainty analysis is conducted. For this risk assessment, a range of HQs was calculated using EPA's RfD as published in IRIS as well as an alternative RfD calculated using a modified set of uncertainty factors (Table 8.1 and 8.2). The resulting range of HQs provides a better characterization of the range of estimated risks and highlights the regulatory, rather than scientific, uncertainty that is involved in using the EPA default risk assessment approach.

The HQs associated with occupational exposures are calculated using the ACGIH TLV® of 0.5 ppm (adjusted to an absorbed dose; ACGIH 2001). The ACGIH reviewed all of the literature and data on the carcinogenic and non-carcinogenic effects associated with benzene (including reproductive and developmental effects) and set its TLV® at a level that would be health protective for cancer (the endpoint they deemed the most sensitive endpoint for benzene). Therefore, HQs less than 1.0 for occupational exposures should also indicate a lack of potential for reproductive and developmental effects. The ACGIH TLV® of 0.5 ppm was chosen over the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) of 1 ppm because the TLV® was derived more recently.

8.2.2.2 Cancer Slope Factor

The literature on the leukemogenic potential of benzene in occupationally exposed workers has been thoroughly reviewed in Section 6.1. The literature demonstrates that benzene has been shown to cause AML in a small subset of highly exposed workers. One of the most important studies of benzene and AML is the NIOSH sponsored retrospective cohort mortality study of workers involved with the manufacture of rubber hydrochloride (Pliofilm) at one of three plants in Ohio (Infante et al., 1977; Rinsky et al., 1981; Rinsky et al., 1987). EPA has derived a CSF based on this cohort.

The Rinksy et al. (1981, 1987) study analysis of the 'pliofilm' cohort was selected by the US EPA as the critical study for dose response analysis and for the quantitative estimation of cancer risk to humans (Rinsky et al., 1981, 1987). This study was selected because it has ample power, reasonably good estimates of exposure (except prior to 1946), a wide range of exposure from low to high levels and a relative lack of potential confounding chemicals. Further, the job activities of the various workers were fairly well documented. Based on data obtained from this cohort, the carcinogenic risk of inhaled benzene was calculated by Crump (1984). Crump presented 96 different unit risk calculations by considering different combinations of 1) disease endpoint, 2) additive or multiplicative models, 3) linear or non-linear exposure-response models, 4) exposure estimates for the Pliofilm cohort (Crump and Allen

[1984] and Paustenbach et al. (1992), and 5) cumulative or weighted exposure estimates (U.S. EPA, 2000). The unit risk estimates calculated by Crump (1996) span a factor of approximately 300 ranging from 8.6×10^{-5} to 2.5×10^{-2} at 1 ppm of benzene air concentration (U.S. EPA, 2000). EPA states that the risk estimates in the lower range correspond with the use of a sublinear exposure-response model and the risk estimates in the upper range correspond with the use of a linear exposure-response model.

EPA chose a narrow range of unit risk estimates of 7.1×10^{-3} to 2.5×10^{-2} at 1 ppm (only a factor of approximately 3 between these values) for their IRIS values (U.S. EPA, 2000). EPA states that this conservative range of cancer unit risk estimates was selected because "the shape of the exposure dose-response curve cannot be considered without a better understanding of the biological mechanism(s) of benzene induced leukemia" (U.S. EPA, 2000). Therefore, EPA made a policy decision to choose a narrow range of the most conservative unit risk estimates calculated by Crump (1996).

Using only the narrow range of CSFs chosen by EPA provides a narrower range of risk estimates, implying less uncertainty. However, using only the narrow range of CSFs chosen by EPA actually conveys a false sense of certainty about risk estimates for children exposed to benzene. Therefore, for the purposes of this risk assessment, cancer risk estimates are calculated using the range of CSFs chosen by EPA (U.S. EPA, 2000) and by using the lower bound on the values calculated by Crump (1996) as reported by EPA (U.S. EPA, 2000). Using a range of CSFs that span the broader range of risk estimates calculated by Crump from the Pliofilm cohort provides a better perspective on the range of risk estimates that could be derived using the Pliofilm cohort, but yet still using a dose-response model to calculate risks below the exposures encountered by the Pliofilm cohort.

Table 8.2 provides details on how the CSFs were calculated. The quantitative oral unit risk estimate is an extrapolation from the known inhalation dose-response to the potential oral route of exposure. The inhalation unit risk range is converted to an absorbed-dose slope factor, which is expressed in units of risk per mg/kg-day. The inhalation to absorbed-dose conversion assumes a standard air intake of 20 m^3/day, a standard body weight of 70 kg for an adult human and 50% inhalation absorption.

The CSFs used in the risk assessment are (Table 8.2):
Upper-bound linear model = 5.5×10^{-2} $(mg/kg/day)^{-1}$
Lower-bound linear model = 1.5×10^{-2} $(mg/kg/day)^{-1}$
Lower-bound nonlinear model = 1.9×10^{-4} $(mg/kg/day)^{-1}$

8.2.3 Points of Departure for Margin of Safety Assessment

The following is a summary of the PODs chosen for this MOS risk assessment. The PODs chosen for this risk assessment are values that have already been established by regulatory agencies and scientific organizations and established as "safe" exposure limits. Therefore, the PODs summarized below already contain some measures of safety built into them. Based on our current understanding of the science (see Section 6.1), the "functional" thresholds for both cancer and noncancer effects would undoubtedly be higher than the PODs used in this risk assessment.

8.2.3.1 Point of Departure for Non-Cancer Effects

The European Union (EU) recently conducted a risk assessment for occupational and environmental exposures to benzene (ECB, 2003). The EU performed its risk assessment by employing a Margin of Safety (MOS) analysis which is identical to the MOS approach described above. The MOS analysis conducted by EU scientists was based on deriving a "threshold" effect level for noncancer hematopoietic toxicity to compare with quantified exposures estimates. The Critical Exposure Level (CEL), as calculated by the EU is essentially a "threshold," a level of exposure below which no adverse effect would be predicted to occur. The CEL was derived by first choosing a No Observed Adverse Effect Concentration (NOAEC). The EU calculated their CEL by dividing the NOAEC by a "minimal MOS" (which serves essentially the same purpose as EPA's uncertainty factors). The EU derived a CEL for a variety of endpoints, including cancer.

For their repeated dose toxicity, the EU used the Rothman et al. (1996) study as the critical study and they derived a NOAEC of 1 ppm. This was considered an effective threshold for reductions in ALC and used a minimal MOS of 1. The EU therefore derived a CEL of 1 ppm or 3.2 mg/m^3. Converting this to an absorbed dose yields a POD of 0.5 mg/kg/day. This value will be used as the POD for the noncancer MOS calculations (Table 8.3).

8.2.3.2 Point of Departure for Cancer

As described in Section 6.1, a functional threshold for the induction of benzene-induced AML is supported by the available epidemiological data. While the actual exposure/dose required for AML has not been clearly determined, the existence of a "functional" threshold for AML is consistent with epidemiological data, as well as clinical data obtained from secondary leukemia arising from ionizing radiation and/or chemotherapy and the current understanding of bone marrow patho-physiology and biology. Emerging evidence in the biological mechanism of benzene-induced AML suggests that benzene and/or its metabolites may induce AML via toxic disruption of the regulatory mechanism of cell growth and differentiation (Irons and Stillman, 1993; Irons et al., 1992; Snyder and Kalf, 1994). Further, benzene metabolism has been determined to follow non-linear Michaelis-Menton kinetics (Travis et al., 1990). Given the non-linear nature of benzene metabolism, the use of a linear model for excess cancer risk calculations will likely overestimate the risk, particularly at low exposure levels (ACGIH, 2001). These observations provide a biological basis for the observed threshold evident in epidemiological data (Wong and Raabe, 1995; World Health Organization, 1993; ACGIH, 2001).

Multiple epidemiological studies from the 1930s through the 1980s strongly support the hypothesis that a threshold exists for benzene's hematopoietic toxicity, including the risk for developing AML. The EPA cancer slope factor is based on the Rinsky et al. (1987) study. There have been four exposure analyses of this cohort (Rinsky et al. 1987; Crump and Allen 1984; Paustenbach et al. 1992; Williams and Paustenbach, 2003), and although they differ with regard to methodologies and conclusions, none has reported an excess leukemia risk below 40 ppm-yrs, with an average value of ~200 ppm-years (Paustenbach et al., 1992; Rushton and Romaniuk, 1997; Paxton et al., 1994; Wong, 1995; Aksoy, 1980). Other authors believe that the threshold could be much higher and that, based on exposure estimates from Crump and Allen and Paustenbach, the AML threshold would correspond to 370 or 530 ppm-yrs, respectively (Crump and Allen, 1984; Paustenbach et al., 1992; Wong, 1995). An analysis published by

Glass et al. (2003) reports an increased ANLL[5] risk at lower levels of cumulative benzene exposures (> 8 ppm-years) than previously reported, but still appear to have a functional threshold in their cohort[6] (Glass et al., 2003). The vast majority of the existing epidemiology evidence on the relationship between benzene and AML supports the existence of a threshold for this effect.

In support of a "functional" threshold, the scientific literature is consistent in its demonstration that refinery workers do not have an elevated risk of developing AML (Theriault and Goulet, 1979; Naumann et al., 1993; Raabe et al., 1998; Marsh et al., 1991; Wong et al., 1986; Dagg et al., 1992; Satin et al., 1996; Thomas et al., 1982; Austin et al., 1986; Divine et al., 1987; Austin and Schnatter, 1983). The literature also suggests that auto or truck mechanics do not have an elevated risk of developing AML despite having exposures to benzene that are orders of magnitude greater than those experienced by the general population (Hotz and Lauwerys, 1997; Jarvisalo et al., 1984; Linos et al., 1980; Linet, 1988; Howe and Lindsay, 1983; Jacobs et al., 1993; Giles et al., 1984; Mele et al., 1994).

The EU calculated a Critical Exposure Level (CEL) for their cancer risk assessment of 0.1 ppm. The EU derived their CEL by choosing 1 ppm as their "starting point" and applied a minimal margin of safety (MOS) of 10 to yield a CEL of 0.1 ppm (1 ppm / 10 = 0.1 ppm) (ECB, 2003). A POD of 0.1 ppm was chosen for cancer effects for the general population scenarios in this MOS analysis. The POD was converted to an absorbed dose (Table 8.3) to yield:

General population POD: 0.05 mg/kg/day

8.3 Results

8.3.1 EPA Default Risk Assessment Approach

The results of the noncancer risk calculations are provided in Tables 8.4 (for children's exposures) and 8.5 (for adults' exposures). High and low HQs are provided for each exposure scenario and corresponding age group. The high risk estimate was based on EPA's RfD (adjusted to absorbed dose). The low risk estimate is calculated by dividing exposures by Alternative 3 RfD listed in Table 8.1. This higher RfD yields lower estimated risks and is provided to highlight the uncertainty about the RfD and estimated noncancer risks from benzene exposures.

Using the EPA IRIS RfD, HQs of 1 were calculated for children < 1 year old and 1 to <2 years of age exposed to high end background sources of benzene (all routes aggregated) and for adolescents and adults who smoke cigarettes. Using the Alternative 3 RfD, no exposure scenarios exceed an HQ of 1. HQs for an infant ingesting human milk from an occupationally exposed mother were the same as HQs for a nursing infant whose mother was not occupationally exposed.

[5] Glass et al. (2003) used the term ANLL (acute non-lymphocytic leukemia) because they included two leukemia cases that were not classified as AML, but were thought to be closely related.

[6] Some methodological problems decrease the potential usefulness of this study for risk assessment purposes. Some investigators believe that the expected cases of ANLL in the baseline or control group in this study were under-represented. This would change the calculated risks, as well as the interpretation of this data, particularly at low exposures (Schnatter, 2004; Goldstein, 2004). There are also problems with case selection and controlling for various types of bias (Schnatter, 2004; Goldstein, 2004).

Cancer risks were calculated using the range of CSFs provided by U.S. EPA (2003) and using the lower bound on the CSF calculated by Crump (1996) as reported by U.S. EPA (2003). Table 8.6 provides potential excess risk estimates for males and females based on lifetime average daily doses. Using the upper-bound linear model CSF, background aggregated exposures (from urban and rural, typical and high end) are predicted to be associated with excess cancer risks greater than 1×10^{-5}. Using the lower-bound linear model CSF, background aggregated exposures (from urban and rural, typical and high end) are predicted to be associated with excess cancer risks less than 1×10^{-6}. Only smoking tobacco (direct mainstream smoking) leads to predicted excess cancer risks greater than 1×10^{-4}.

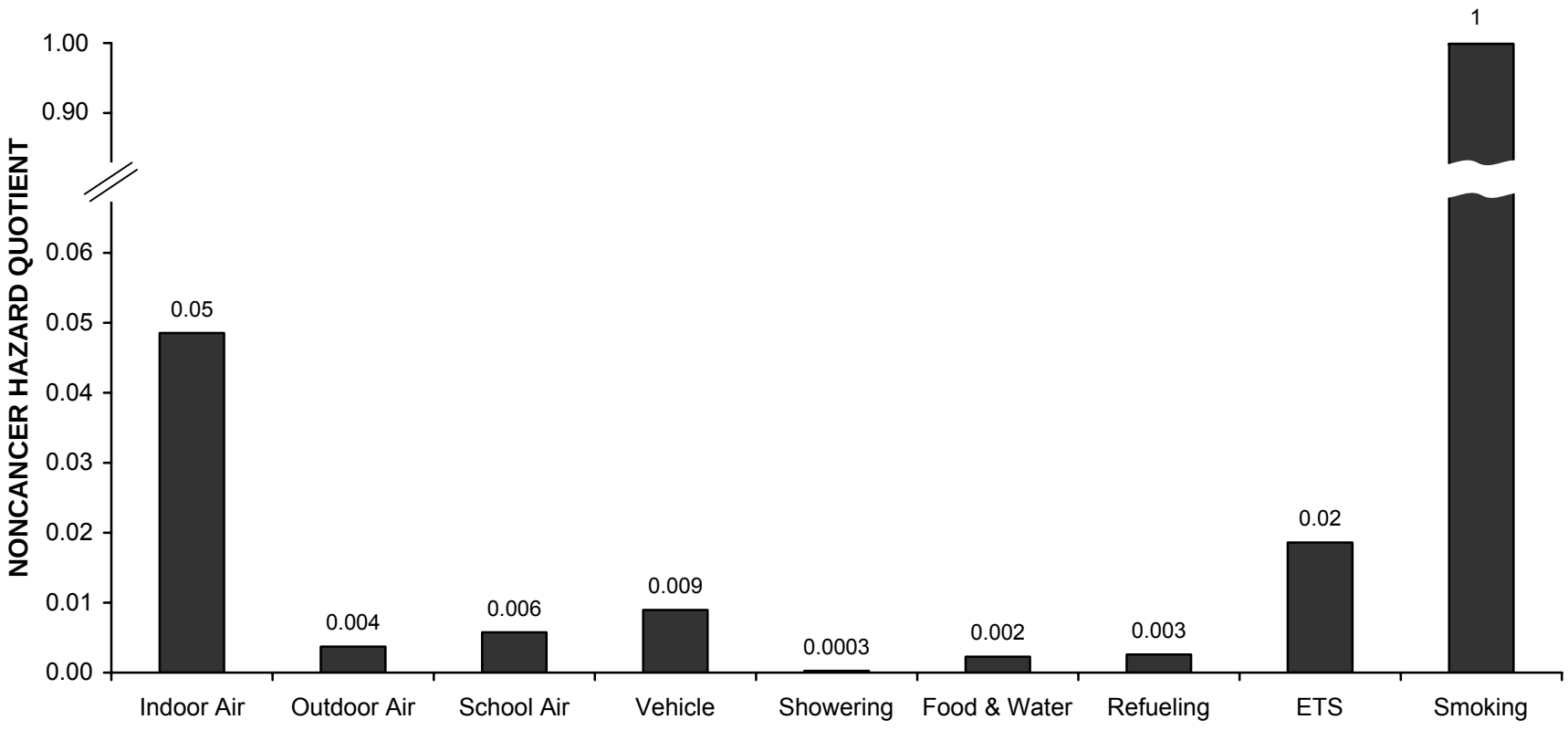
Table 8.7 provides both HQs and potential excess cancer risk estimates from indoor air (in-home), comparing the typical and high end estimates from the Continental U.S. and the exposure from Alaskan homes. As was discussed in Section 7.2.1.5, concentrations of benzene in Alaskan homes with attached garages are significantly higher than concentrations of benzene in homes in the continental U.S. The resulting HQs for children living in Alaskan homes with attached garages vary considerably. The HQ for the <1 year old ranges from 0.07 (low HQ estimate using Alternative 3 RfD) to 2 (using EPA's RfD from IRIS). Using EPA's RfD, the only age group that has an HQ higher than 1 is the <1 year old age group. Using the Alternative 3 RfD, all HQs are below 1 for both Alaska and the continental U.S. Estimated potential excess cancer risks do not exceed 1×10^{-4} for Alaskans using the upper-bound linear model CSF and are predicted to be 4×10^{-7} using the lower-bound nonlinear model CSF. Table 8.8 provides a comparison of HQs for adults exposed to indoor air from homes in the Continental U.S. (typical and high end) and Alaskan homes. HQs do not exceed 1 using EPA's RfD and are significantly less than 1 using Alternative 3 RfD.

Figures 8.4 and 8.5 provide insight on the exposure scenarios that contributed most to the overall exposures and HQs for the 'typical' exposures. Figure 8.4 shows the relative contribution of the individual exposure scenarios for a 16 to 19 year old adolescent. As can be seen, smoking is the predominant contributor to overall benzene exposures and HQs when the adolescent smokes. Because of the limited durations and frequency with refueling a car and riding in a car, these exposure sources provide little towards a child's aggregate exposures and HQ. Indoor air contributes the largest fraction of the remaining sources towards benzene exposures and HQs, with ETS providing the second most significant exposure source. Figure 8.5 provides estimates of the HQ for all age groups comparing aggregated background sources to the HQs from ETS, refueling a car and from active smoking in adolescents and adults. As can be seen, the HQ associated with active smoking is significantly greater than all other exposures combined. These figures illustrate the fact that smoking is the dominant source of benzene exposures and thus HQ and potential health risks from benzene exposures.

8.3.2 Margin of Safety Analysis

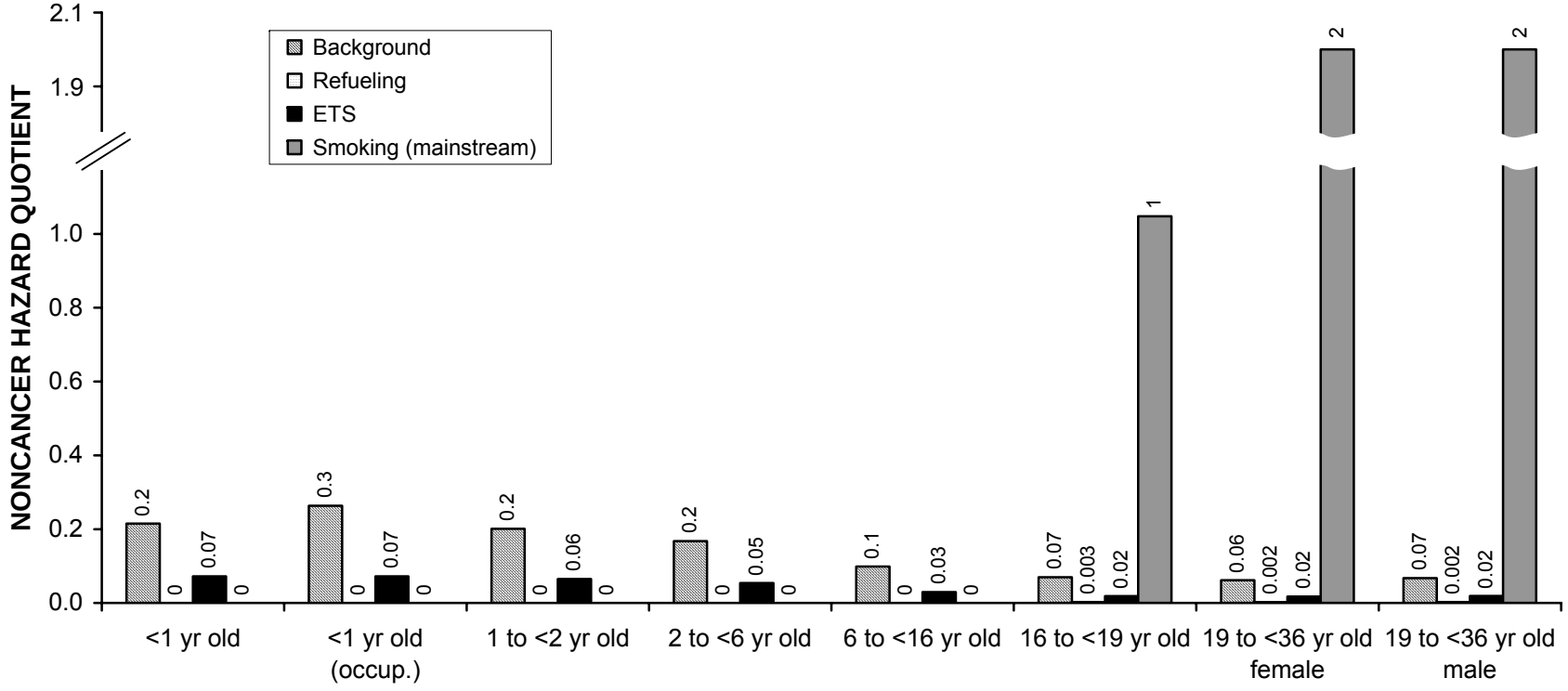
Table 8.9 provides estimates of the MOSs for noncancer effects for the different exposure scenarios/sources and for aggregated exposures for each age group. For aggregate exposures, the MOSs range from approximately 100 to 2,100. The MOSs for smoking are estimated to range from approximately 50 to 100. Table 8.10 provides estimates of the MOSs for noncancer effects in adults. Tables 8.11 and 8.12 provide MOS estimates for children and adults, respectively, associated with in-home inhalation exposures from living in homes in the continental U.S. and Alaskan homes with attached garages. Table 8.13 provides estimates of the MOSs for cancer. The MOS for lifetime average daily doses for males and females are

provided for each exposure source and for aggregate exposures. The cancer MOSs for aggregate exposures for all background sources of exposure range from approximately 30 to 160. The MOS for smoking is estimated at approximately 7.5. Table 8.14 compares the MOSs for cancer associated with lifetime average in-home inhalation exposures from living in Continental U.S. homes and Alaskan homes with attached garages. The predicted MOSs associated with in-home inhalation exposures for children living in Alaskan homes with attached garages ranges from 70 to 450 for noncancer effects (Table 8.11) and approximately 25 for cancer (Table 8.14).



Notes: Hazard quotients were calculated using the default IRIS reference dose.
Typical values were used for all pathways and outdoor air is urban.

Figure 8.4. Comparison of source-specific noncancer hazard quotients for 16 to <19 year olds.



Notes: Hazard quotients were calculated using the default IRIS reference dose.
Typical values were used for all pathways and outdoor air is urban.

Figure 8.5. Comparison of noncancer hazard quotients from various sources by age group.

Table 8.1. Derivation of noncancer references values for benzene

Calculation of absorbed-dose noncancer reference values for benzene based on Rothman et al. 1996. Table demonstrates the quantitative impact of selecting different uncertainty and modifying factors.

	Units	Uncertainty Factor Category			
		IRIS Value	Alternative 1	Alternative 2	Alternative 3
Bench Mark Concentration Lower Limit (BMCL)	ppm	7.2	7.2	7.2	7.2
Adjusted from workplace to general population					
From 5 to 7 days/week exposure frequency (5/7)		0.714	0.714	0.714	0.714
From 10 to 20 m^3/day inhalation rate (10/20)		0.5	0.5	0.5	0.5
BMCL - general population	ppm	2.57	2.57	2.57	2.57
Convert units from ppm to mg/m^3					
M.W./24.45 (78.11/24.45)		3.19	3.19	3.19	3.19
BMCL - general population	mg/m^3	8.20	8.20	8.20	8.20
Uncertainty and Modifying Factors					
Effect level extrapolation		3	3	3	3
Intraspecies variability		10	3	3	3
Subchronic to chronic		3	3	1	1
Database deficiency		3	3	3	1
Composite UF		300 [a]	81	27	9
RfC (Reference Concentration): BMCL-general pop./Composite UF	mg/m^3	**0.027**	**0.10**	**0.30**	**0.91**
Converted from concentration to absorbed dose					
Inhalation rate	m^3/day	20	20	20	20
Absorption factor	%	50%	50%	50%	50%
Body weight (kg)	kg	70	70	70	70
RfD (Reference dose, absorbed)	**mg/kg-day**	**0.004**	**0.01**	**0.04**	**0.1**

Note: Boxed values are those that are different than the IRIS default approach.

[a] Calculated value of 270 was round to 1 significant figure, yielding a value of 300.

Table 8.2. Toxicity values for benzene: EPA default approach

Calculation of absorbed-dose noncancer reference values and cancer slope factors for benzene. Table demonstrates the range of values obtained from various assumptions and modeling approaches.

		Noncancer Reference Values			Cancer Slope Factors		
	Unit	IRIS default	Alternative 3[a]	TLV-Based[b]	Lower-Bound Nonlinear Model	Lower-Bound Linear Model	Upper-Bound Linear Model
Initial value (air concentration)	ppm	--	--	0.5	--	--	--
Initial value (air unit risk)	ppm^{-1}	--	--	--	8.6E-05		
Conversion factor 1	mg/m^3 per ppm	--	--	3.19	3.19	--	--
Initial value (air concentration)	mg/m^3	0.03	0.9	1.6	--	--	--
Initial value (air unit risk)	$(\mu g/m^3)^{-1}$	--	--	--	2.7E-08	2.2E-06	7.8E-06
Conversion factor 2	µg/mg	--	--	--	1,000	1,000	1,000
Inhalation rate	m^3/day	20	20	10	20	20	20
Absorption factor	%	50%	50%	50%	50%	50%	50%
Body weight	kg	70	70	70	70	70	70
Reference Dose [RfD] (absorbed)	**mg/kg-day**	**0.004**	**0.1**	**0.1**	**--**	**--**	**--**
Cancer Slope Factor [CSF] (absorbed)	**$(mg/kg\text{-}day)^{-1}$**	**--**	**--**	**--**	**1.9E-04**	**1.5E-02**	**5.5E-02**

Note: Because both the reference dose and the cancer slope factor were calculated on an absorbed-dose basis, the same value is used for all pathways (inhalation, ingestion, and dermal).

[a] See Table 8-1 and text for details.

[b] Value for adult occupational exposures, based on the ACGIH threshold limit value (TLV).

$$\text{Reference Dose (absorbed)} = \frac{\text{Initial Value} \times \text{Inhalation Rate} \times \text{Absorption Factor}}{\text{Body Weight}}$$

$$\text{Cancer Slope Factor (absorbed)} = \frac{\text{Initial Value} \times \text{Conversion Factor 2} \times \text{Body Weight}}{\text{Inhalation Rate} \times \text{Absorption Factor}}$$

Converting units on air unit risks from ppm^{-1} to $(\mu g/m^3)^{-1}$

$$\frac{8.6\times10^{-5}}{\text{ppm}} \times \frac{1\ \text{ppm}}{3.19\ \text{mg/m}^3} \times \frac{1}{1{,}000\ \mu\text{g/mg}} = \frac{2.7\times10^{-8}}{\mu\text{g/m}^3}$$

Table 8.3. Points of departure for margin of safety approach

Calculation of absorbed-dose points of departure (POD) for benzene.

	Unit	Cancer General Population	Noncancer General Population
Initial value	ppm	0.1	1
Conversion factor 1	mg/m^3 per ppm	3.19	3.19
Inhalation rate	m^3/day	20	20
Absorption factor	%	50%	50%
Body weight	kg	70	70
Point of departure	**mg/kg-day**	**0.05**	**0.5**

Note: Because all points of departure are calculated on an absorbed-dose basis, the same value is used for all pathways (inhalation, ingestion, and dermal).

$$\text{Initial value (general population)} = \text{Initial Value}_{\text{workplace}} \times \frac{5 \text{ days}}{7 \text{ days}} \times \frac{10 \text{ m}^3\text{/day}}{20 \text{ m}^3\text{/day}}$$

$$\text{Point of departure} = \frac{\text{Initial Value}_{\text{gen. pop.}} \times \text{Conversion Factor 1} \times \text{Inhalation Rate} \times \text{Absorption Factor}}{\text{Body Weight}}$$

Table 8.4. Noncancer hazard quotients associated with benzene exposures—children

Results of noncancer risk calculations. High and low hazard quotients are provided for each exposure scenario and corresponding age group for children.

	Noncancer Hazard Quotient (unitless)[a]					
	<1 yr old		<1 yr old (occup.)[b]		1 to <2 yr old	
	Low	High	Low	High	Low	High
INHALATION PATHWAYS						
Outdoor air (ambient, total)						
Rural - Typical	0.0001	0.003	0.0001	0.003	0.00009	0.002
Rural - High End	0.0002	0.005	0.0002	0.005	0.0001	0.003
Urban - Typical	0.0003	0.007	0.0003	0.007	0.0002	0.005
Urban - High End	0.0008	0.02	0.0008	0.02	0.0006	0.01
Indoor air (in-home, total)						
Typical	0.007	0.2	0.007	0.2	0.006	0.2
High End	0.03	0.8	0.03	0.8	0.03	0.7
In school						
Typical	--	--	--	--	0.0002	0.004
High End	--	--	--	--	0.0008	0.02
In vehicle - typical	0.0009	0.02	0.0009	0.02	0.0008	0.02
Showering						
Typical	0	0	0	0	0.0002	0.006
High End	0.002	0.04	0.002	0.04	0.005	0.1
BACKGROUND (summed by pathway)						
Inhalation Pathway (indoor & outdoor air, showering, in-vehicle)						
Rural - Typical	0.008	0.2	0.008	0.2	0.008	0.2
Rural - High End	0.04	0.9	0.04	0.9	0.04	0.9
Urban - Typical	0.008	0.2	0.008	0.2	0.008	0.2
Urban - High End	0.04	0.9	0.04	0.9	0.04	0.9
Ingestion Pathway (food & water)						
Typical	0.0004	0.009	0.002	0.06	0.0004	0.01
High End	0.008	0.2	0.01	0.4	0.006	0.1
Dermal Pathway (showering)						
Typical	0	0	0	0	9.0E-06	0.0002
High End	0.00002	0.0005	0.00002	0.0005	0.00002	0.0006
BACKGROUND (all pathways)						
Rural - Typical	0.008	0.2	0.01	0.3	0.008	0.2
Rural - High End	0.04	1	0.05	1	0.04	1
Urban - Typical	0.009	0.2	0.01	0.3	0.008	0.2
Urban - High End	0.04	1	0.05	1	0.04	1
SOURCE-SPECIFIC DOSES						
Tobacco Smoke						
ETS (nonsmoker's dose)	0.003	0.07	0.003	0.07	0.003	0.06
Mainstream (smoker's dose)	--	--	--	--	--	--
Refueling						
Typical	--	--	--	--	--	--
High End	--	--	--	--	--	--
BACKGROUND PLUS REFUELING						
Rural - Typical	0.008	0.2	0.008	0.2	0.008	0.2
Rural - High End	0.04	1	0.04	1	0.04	1
Urban - Typical	0.009	0.2	0.009	0.2	0.008	0.2
Urban - High End	0.04	1	0.04	1	0.04	1

(footnotes at end of table)

Table 8.4. (cont.)

	Noncancer Hazard Quotient (unitless)[a]					
	2 to <6 yr old		6 to <16 yr old		16 to <19 yr old	
	Low	High	Low	High	Low	High
INHALATION PATHWAYS						
Outdoor air (ambient, total)						
Rural - Typical	0.0002	0.006	0.00009	0.002	0.00007	0.002
Rural - High End	0.0003	0.008	0.0001	0.003	0.00009	0.002
Urban - Typical	0.0005	0.01	0.0002	0.005	0.0001	0.004
Urban - High End	0.001	0.03	0.0005	0.01	0.0004	0.01
Indoor air (in-home, total)						
Typical	0.005	0.1	0.003	0.07	0.002	0.05
High End	0.02	0.5	0.01	0.3	0.009	0.2
In school						
Typical	0.0002	0.006	0.0003	0.008	0.0002	0.006
High End	0.001	0.03	0.001	0.04	0.001	0.03
In vehicle - typical	0.0008	0.02	0.0005	0.01	0.0004	0.009
Showering						
Typical	0.00007	0.002	0.00001	0.0004	0.00001	0.0003
High End	0.001	0.03	0.0003	0.007	0.0002	0.005
BACKGROUND (summed by pathway)						
Inhalation Pathway (indoor & outdoor air, showering, in-vehicle)						
Rural - Typical	0.006	0.2	0.004	0.09	0.003	0.07
Rural - High End	0.03	0.6	0.02	0.4	0.01	0.3
Urban - Typical	0.006	0.2	0.004	0.09	0.003	0.07
Urban - High End	0.03	0.7	0.02	0.4	0.01	0.3
Ingestion Pathway (food & water)						
Typical	0.0004	0.01	0.0002	0.004	0.00009	0.002
High End	0.004	0.1	0.002	0.05	0.001	0.03
Dermal Pathway (showering)						
Typical	9.0E-06	0.0002	6.0E-06	0.0002	5.0E-06	0.0001
High End	0.00002	0.0006	0.00002	0.0004	0.00001	0.0004
BACKGROUND (all pathways)						
Rural - Typical	0.006	0.2	0.004	0.1	0.003	0.07
Rural - High End	0.03	0.7	0.02	0.4	0.01	0.3
Urban - Typical	0.007	0.2	0.004	0.1	0.003	0.07
Urban - High End	0.03	0.8	0.02	0.4	0.01	0.3
SOURCE-SPECIFIC DOSES						
Tobacco Smoke						
ETS (nonsmoker's dose)	0.002	0.05	0.001	0.03	0.0007	0.02
Mainstream (smoker's dose)	--	--	--	--	0.04	1
Refueling						
Typical	--	--	--	--	0.0001	0.003
High End	--	--	--	--	0.001	0.03
BACKGROUND PLUS REFUELING						
Rural - Typical	0.006	0.2	0.004	0.1	0.003	0.07
Rural - High End	0.03	0.7	0.02	0.4	0.01	0.3
Urban - Typical	0.007	0.2	0.004	0.1	0.003	0.07
Urban - High End	0.03	0.8	0.02	0.4	0.01	0.3

(footnotes on following page)

Table 8.4. (cont.)

Notes:

-- – No value calculated because no benzene exposures are applicable to this category for this age group.
Hazard quotient [HQ] = Average Daily Dose / Reference Dose
Average daily doses are summarized in Table 7.53.
Reference doses used for calculations in this table are presented in Table 8.2.
ETS – environmental tobacco smoke

[a] Noncancer hazard quotients are calculated using the IRIS RfD (labeled High) and Alternative 3 RfD (labeled Low). See Tables 8.1,8.2, and text.

[b] Values represent hazard quotients associated with an infant ingesting human milk from a mother who is occupationally exposed to benzene, in addition to other applicable background exposures.

Table 8.5. Noncancer hazard quotients associated with benzene exposures—adults

Results of noncancer risk calculations. High and low hazard quotients are provided for each exposure scenario for adults.

	Noncancer Hazard Quotient (unitless)[a]			
	19 to <36 yr old female		19 to <36 yr old male	
	Low	High	Low	High
INHALATION PATHWAYS				
Outdoor air (ambient, total)				
Rural - Typical	0.00004	0.001	0.00004	0.001
Rural - High End	0.00006	0.001	0.00006	0.002
Urban - Typical	0.00009	0.002	0.0001	0.002
Urban - High End	0.0002	0.006	0.0003	0.007
Indoor air (in-home, total)				
Typical	0.002	0.05	0.002	0.05
High End	0.009	0.2	0.01	0.3
In school				
Typical	--	--	--	--
High End	--	--	--	--
In vehicle - typical	0.0003	0.007	0.0003	0.008
Showering				
Typical	6.0E-06	0.0001	6.0E-06	0.0001
High End	0.0001	0.003	0.0001	0.003
BACKGROUND (summed by pathway)				
Inhalation Pathway (indoor & outdoor air, showering, in-vehicle)				
Rural - Typical	0.002	0.06	0.003	0.06
Rural - High End	0.01	0.2	0.01	0.3
Urban - Typical	0.002	0.06	0.003	0.06
Urban - High End	0.01	0.2	0.01	0.3
Ingestion Pathway (food & water)				
Typical	0.0001	0.003	0.0001	0.003
High End	0.001	0.03	0.001	0.03
Dermal Pathway (showering)				
Typical	4.0E-06	0.0001	4.0E-06	0.0001
High End	0.00001	0.0003	0.00001	0.0003
BACKGROUND (all pathways)				
Rural - Typical	0.002	0.06	0.003	0.07
Rural - High End	0.01	0.3	0.01	0.3
Urban - Typical	0.002	0.06	0.003	0.07
Urban - High End	0.01	0.3	0.01	0.3
SOURCE-SPECIFIC DOSES				
Tobacco Smoke				
ETS (nonsmoker's dose)	0.0007	0.02	0.0008	0.02
Mainstream (smoker's dose)	0.09	2	0.09	2
Refueling				
Typical	0.00009	0.002	0.0001	0.002
High End	0.001	0.03	0.001	0.03
Occupational				
Typical	0.07 [b]		0.08 [b]	
High End	0.3 [b]		0.3 [b]	
BACKGROUND PLUS REFUELING				
Rural - Typical	0.003	0.06	0.003	0.07
Rural - High End	0.01	0.3	0.01	0.3
Urban - Typical	0.003	0.06	0.003	0.07
Urban - High End	0.01	0.3	0.01	0.3

(footnotes on following page)

Table 8.5. (cont.)

Notes:

-- – No value calculated because no benzene exposures are applicable to this category for this age group.

Hazard quotient [HQ] = Average Daily Dose / Reference Dose

Average daily doses are summarized in Table 7.53.

Reference doses used for calculations in this table are presented in Table 8.2.

ETS – environmental tobacco smoke

[a] Noncancer HQs are calculated using the IRIS RfD (labeled High) and Alternative 3 RfD (labeled Low). See Tables 8.1,8.2, and text.

[b] Value is calculated using the occupational threshold limit value (TLV) instead of a reference dose. See Table 8.2 and text for details.

Table 8.6. Cancer risk estimates associated with benzene exposures

Potential excess cancer risks calculated using a range of CSFs. Estimates provided for males and females based on lifetime average daily doses.

	Cancer Risk Estimate (unitless)					
	Using Lower-Bound Nonlinear Model CSF		Using Lower-Bound Linear Model CSF		Using Upper-Bound Linear Model CSF	
	Female	Male	Female	Male	Female	Male
INHALATION PATHWAYS						
Outdoor air (ambient, total)						
Rural - Typical	1E-09	1E-09	9E-08	1E-07	3E-07	3E-07
Rural - High End	2E-09	2E-09	1E-07	1E-07	5E-07	5E-07
Urban - Typical	3E-09	3E-09	2E-07	2E-07	7E-07	8E-07
Urban - High End	7E-09	7E-09	6E-07	6E-07	2E-06	2E-06
Indoor air (in-home, total)						
Typical	5E-08	5E-08	4E-06	4E-06	1E-05	1E-05
High End	2E-07	2E-07	2E-05	2E-05	6E-05	6E-05
In school						
Typical	1E-09	1E-09	1E-07	1E-07	4E-07	4E-07
High End	6E-09	6E-09	5E-07	5E-07	2E-06	2E-06
In vehicle - typical	7E-09	7E-09	5E-07	6E-07	2E-06	2E-06
Showering						
Typical	3E-10	3E-10	2E-08	2E-08	8E-08	8E-08
High End	5E-09	5E-09	4E-07	4E-07	2E-06	2E-06
BACKGROUND						
Inhalation Pathway (indoor & outdoor air, showering, in-vehicle)						
Rural - Typical	6E-08	6E-08	4E-06	5E-06	2E-05	2E-05
Rural - High End	2E-07	2E-07	2E-05	2E-05	7E-05	7E-05
Urban - Typical	6E-08	6E-08	4E-06	5E-06	2E-05	2E-05
Urban - High End	2E-07	2E-07	2E-05	2E-05	7E-05	7E-05
Ingestion Pathway (food & water)						
Typical	3E-09	3E-09	2E-07	2E-07	7E-07	7E-07
High End	3E-08	3E-08	3E-06	3E-06	9E-06	9E-06
Occupational - Typical[a]	3E-09	3E-09	2E-07	2E-07	9E-07	9E-07
Occupational - High End[a]	3E-08	3E-08	3E-06	3E-06	1E-05	1E-05
Dermal Pathway (showering)						
Typical	9E-11	9E-11	7E-09	7E-09	3E-08	3E-08
High End	3E-10	3E-10	2E-08	2E-08	8E-08	8E-08
BACKGROUND (all pathways)						
Rural - Typical	6E-08	6E-08	5E-06	5E-06	2E-05	2E-05
Rural - High End	3E-07	3E-07	2E-05	2E-05	8E-05	8E-05
Urban - Typical	6E-08	6E-08	5E-06	5E-06	2E-05	2E-05
Urban - High End	3E-07	3E-07	2E-05	2E-05	8E-05	8E-05
BACKGROUND (all pathways, including indirect occupational)[a]						
Rural - Typical	6E-08	6E-08	5E-06	5E-06	2E-05	2E-05
Rural - High End	3E-07	3E-07	2E-05	2E-05	8E-05	8E-05
Urban - Typical	6E-08	6E-08	5E-06	5E-06	2E-05	2E-05
Urban - High End	3E-07	3E-07	2E-05	2E-05	8E-05	8E-05
SOURCE-SPECIFIC DOSES						
Tobacco Smoke						
ETS (nonsmoker's dose)	2E-08	2E-08	1E-06	1E-06	5E-06	5E-06
Mainstream (smoker's dose)	1E-06	1E-06	1E-04	1E-04	4E-04	4E-04
Refueling						
Typical	1E-09	1E-09	1E-07	1E-07	4E-07	4E-07
High End	2E-08	2E-08	1E-06	1E-06	5E-06	5E-06
BACKGROUND PLUS REFUELING						
Rural - Typical	6E-08	6E-08	5E-06	5E-06	2E-05	2E-05
Rural - High End	3E-07	3E-07	2E-05	2E-05	8E-05	8E-05
Urban - Typical	6E-08	6E-08	5E-06	5E-06	2E-05	2E-05
Urban - High End	3E-07	3E-07	2E-05	2E-05	8E-05	9E-05

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Table 8.6. (cont.)

Notes:

Cancer risk estimate = Lifetime Average Daily Dose × Cancer Slope Factor

Lifetime average daily doses are calculated from values presented in Table 7.53, and are time-weighted based on the exposure duration over a 70-yr lifespan.

Cancer slope factors are presented in Table 8.2.

[a] Values represent cancer risk estimates associated with an infant ingesting human milk from a mother who is occupationally exposed to benzene, in addition to other applicable background exposures.

Table 8.7. Indoor air comparison (in-home): EPA default approach—children

Results of noncancer and cancer risk calculations for in-home indoor air exposures to benzene in the continental United States vs. Alaska.

	Noncancer Hazard Quotients (unitless)[a]										Cancer Risk (unitless)					
	<1 yr old		1 to <2 yr old		2 to <6 yr old		6 to <16 yr old		16 to <19 yr old		Using Lower-Bound Nonlinear CSF		Using Lower-Bound Linear CSF		Using Upper-Bound Linear CSF	
	Low	High	Low	High	Low	High	Low	High	Low	High	Female	Male	Female	Male	Female	Male
In-Home Indoor Air																
Typical[b]	0.007	0.2	0.006	0.2	0.005	0.1	0.003	0.07	0.002	0.05	5E-08	5E-08	4E-06	4E-06	1E-05	1E-05
High End[b]	0.03	0.8	0.03	0.7	0.02	0.5	0.01	0.3	0.009	0.2	2E-07	2E-07	2E-05	2E-05	6E-05	6E-05
Alaska	0.07	2	0.03	0.8	0.02	0.6	0.02	0.4	0.01	0.3	4E-07	4E-07	3E-05	3E-05	1E-04	1E-04

Notes:

Hazard quotient [HQ] = Average Daily Dose / Reference Dose

Cancer risk estimate = Lifetime Average Daily Dose × Cancer Slope Factor

Average daily doses are summarized in Table 7.53.

Reference doses and cancer slope factors are presented in Table 8.2.

Lifetime average daily doses are calculated from values presented in Table 7.53, and are time-weighted based on the exposure duration over a 70-yr lifespan.

[a] Noncancer HQs are calculated using the IRIS RfD (labeled High) and Alternative 3 RfD (labeled Low). See Tables 8.1, 8.2 and text for explanation.

[b] Typical and high end values for the continental United States.

Table 8.8. Indoor air comparison (in-home): EPA default approach—adults

Results of noncancer risk calculations for in-home indoor air exposures to benzene in the continental United States vs. Alaska for adults.

	Noncancer Hazard Quotients (unitless)[a]			
	19 to <36 yr old female		19 to <36 yr old male	
	Low	High	Low	High
In-Home Indoor Air				
Typical[b]	0.002	0.05	0.002	0.05
High End[b]	0.009	0.2	0.01	0.3
Alaska	0.02	0.5	0.02	0.5

Notes:

Hazard quotient [HQ] = Average Daily Dose / Reference Dose
Average daily doses are summarized in Table 7.53.
Reference doses are presented in Table 8.2.

[a] Noncancer HQs are calculated using the IRIS RfD (labeled High) and Alternative 3 RfD (labeled Low). See Tables 8.1, 8.2, and text for details.

[b] Typical and high-end values for the continental United States.

Table 8.9. Noncancer margins of safety associated with benzene exposures—children

Results of noncancer margin of safety for children under various exposure scenarios

	Noncancer Margin of Safety (unitless)					
	<1 yr old	<1 yr old (occup.)[a]	1 to <2 yr old	2 to <6 yr old	6 to <16 yr old	16 to <19 yr old
INHALATION PATHWAYS						
Outdoor air (ambient, total)						
Rural - Typical	38,000	38,000	53,000	22,000	58,000	74,000
Rural - High End	27,000	27,000	38,000	16,000	42,000	53,000
Urban - Typical	17,000	17,000	24,000	10,000	26,000	34,000
Urban - High End	6,200	6,200	8,600	3,600	9,400	12,000
Indoor air (in-home, total)						
Typical	710	710	800	1,100	1,800	2,600
High End	150	150	170	230	390	560
In school						
Typical	--	--	29,000	21,000	16,000	22,000
High End	--	--	6,000	4,300	3,500	4,600
In vehicle - typical	5,500	5,500	6,500	6,600	11,000	14,000
Showering						
Typical	n/a	n/a	22,000	69,000	350,000	480,000
High End	3,200	3,200	1,000	4,300	18,000	26,000
BACKGROUND (summed by pathway)						
Inhalation Pathway (indoor & outdoor air, showering, in-vehicle)						
Rural - Typical	620	620	660	830	1,400	1,900
Rural - High End	140	140	140	200	330	470
Urban - Typical	610	610	650	790	1,300	1,900
Urban - High End	140	140	140	190	320	450
Ingestion Pathway (food & water)						
Typical	14,000	2,200	13,000	13,000	32,000	55,000
High End	630	340	840	1,200	2,600	3,700
Dermal Pathway (showering)						
Typical	n/a	n/a	580,000	560,000	830,000	1,000,000
High End	260,000	260,000	200,000	220,000	290,000	350,000
BACKGROUND (all pathways)						
Rural - Typical	590	480	630	780	1,300	1,800
Rural - High End	120	100	120	170	290	420
Urban - Typical	580	470	620	750	1,300	1,800
Urban - High End	110	99	120	160	280	400
SOURCE-SPECIFIC DOSES						
Tobacco Smoke						
ETS (nonsmoker's dose)	1,700	1,700	1,900	2,300	4,300	6,700
Mainstream (smoker's dose)	--	--	--	--	--	120
Refueling						
Typical	--	--	--	--	--	48,000
High End	--	--	--	--	--	4,000
BACKGROUND PLUS REFUELING						
Rural - Typical	590	480	630	780	1,300	1,800
Rural - High End	120	100	120	170	290	380
Urban - Typical	580	470	620	750	1,300	1,700
Urban - High End	110	99	120	160	280	370

(footnotes on following page)

Table 8.9. (cont.)

Notes:

-- – No value calculated because no benzene exposures are applicable to this category for this age group.
n/a – not applicable; exposure was zero for this scenario.
Margin of Safety [MOS] = Point of Departure / Average Daily Dose
Average daily doses are summarized in Table 7.53.
Point of departure is presented in Table 8.3.
Values are rounded to two significant figures.

[a] Values represent hazard quotients associated with an infant ingesting human milk from a mother who is occupationally exposed to benzene, in addition to other applicable background exposures.

Table 8.10. Noncancer margins of safety associated with benzene exposures—adult

Results of noncancer margin of safety for adults under various exposure scenarios

	Noncancer Margin of Safety (unitless)	
	19 to <36 yr old female	19 to <36 yr old male
INHALATION PATHWAYS		
Outdoor air (ambient, total)		
Rural - Typical	120,000	110,000
Rural - High End	89,000	81,000
Urban - Typical	56,000	51,000
Urban - High End	20,000	18,000
Indoor air (in-home, total)		
Typical	2,500	2,300
High End	540	500
In school		
Typical	--	--
High End	--	--
In vehicle - typical	18,000	16,000
Showering		
Typical	880,000	880,000
High End	46,000	46,000
BACKGROUND (summed by pathway)		
Inhalation Pathway (indoor & outdoor air, showering, in-vehicle)		
Rural - Typical	2,200	2,000
Rural - High End	520	470
Urban - Typical	2,100	1,900
Urban - High End	510	470
Ingestion Pathway (food & water)		
Typical	49,000	49,000
High End	4,000	4,000
Dermal Pathway (showering)		
Typical	1,200,000	1,200,000
High End	390,000	390,000
BACKGROUND (all pathways)		
Rural - Typical	2,100	1,900
Rural - High End	460	420
Urban - Typical	2,000	1,900
Urban - High End	450	420
SOURCE-SPECIFIC DOSES		
Tobacco Smoke		
ETS (nonsmoker's dose)	7,200	6,600
Mainstream (smoker's dose)	56	56
Refueling		
Typical	58,000	53,000
High End	4,700	4,300
Occupational		
Typical	69	63
High End	20	18
BACKGROUND PLUS REFUELING		
Rural - Typical	2,000	1,800
Rural - High End	420	390
Urban - Typical	2,000	1,800
Urban - High End	410	380

(footnotes on following page)

Table 8.10. (cont.)

Notes:

-- – No value calculated because no benzene exposures are applicable to this category for this age group.

n/a – not applicable; exposure was zero for this scenario.

Margin of Safety [MOS] = Point of Departure / Average Daily Dose

Average daily doses are summarized in Table 7.53.

Point of departure is presented in Table 8.3.

Values are rounded to two significant figures.

[a] Values represent hazard quotients associated with an infant ingesting human milk from a mother who is occupationally exposed to benzene, in addition to other applicable background exposures.

Table 8.11. Indoor air comparison (in-home): noncancer margins of safety—children

Results of noncancer margin of safety analysis for children exposed to indoor air.

	Noncancer Margin of Safety (unitless)				
	<1 yr old	1 to <2 yr old	2 to <6 yr old	6 to <16 yr old	16 to <19 yr old
In-Home Indoor Air					
Typical[a]	710	800	1,100	1,800	2,600
High End[a]	150	170	230	390	560
Alaska	73	160	200	310	450

Notes:

Margin of Safety [MOS] = Point of Departure / Average Daily Dose
Average daily doses are summarized in Table 7.53.
Points of departure are presented in Table 8.3.
Values are rounded to two significant figures.

[a] Typical and high-end values for the continental United States.

Table 8.12. Indoor air comparison (in-home): noncancer margins of safety—adults

Results of noncancer margin of safety analysis for adults exposed to indoor air.

	Noncancer Margin of Safety (unitless)	
	19 to <36 yr old female	19 to <36 yr old male
In-Home Indoor Air		
Typical[a]	2,500	2,300
High End[a]	540	500
Alaska	260	240

Notes:

Margin of Safety [MOS] = Point of Departure / Average Daily Dose
Average daily doses are summarized in Table 7.53.
Points of departure are presented in Table 8.3.
Values are rounded to two significant figures.

[a] Typical and high-end values for the continental United States.

Table 8.13. Cancer margins of safety associated with benzene exposures

Results of cancer margin of safety analysis for the general population under various exposure scenarios.

	Cancer Margin of Safety (unitless)	
	Female	Male
INHALATION PATHWAYS		
Outdoor air (ambient, total)		
Rural - Typical	8,200	7,800
Rural - High End	5,900	5,600
Urban - Typical	3,700	3,600
Urban - High End	1,300	1,300
Indoor air (in-home, total)		
Typical	210	200
High End	45	43
In school		
Typical	7,200	7,200
High End	1,500	1,500
In vehicle - typical	1,400	1,300
Showering		
Typical	36,000	36,000
High End	1,800	1,800
BACKGROUND		
Inhalation Pathway (indoor & outdoor air, showering, in-vehicle)		
Rural - Typical	170	160
Rural - High End	41	39
Urban - Typical	170	160
Urban - High End	40	38
Ingestion Pathway (food & water)		
Typical	3,800	3,800
High End	300	300
Occupational - Typical[a]	3,100	3,100
Occupational - High End[a]	280	280
Dermal Pathway (showering)		
Typical	100,000	100,000
High End	35,000	35,000
BACKGROUND (all pathways)		
Rural - Typical	160	160
Rural - High End	36	35
Urban - Typical	160	150
Urban - High End	36	34
BACKGROUND (all pathways, including indirect occupational)[a]		
Rural - Typical	160	160
Rural - High End	36	34
Urban - Typical	160	150
Urban - High End	35	34
SOURCE-SPECIFIC DOSES		
Tobacco Smoke		
ETS (nonsmoker's dose)	550	520
Mainstream (smoker's dose)	7.4	7.5
Refueling		
Typical	7,400	6,800
High End	610	560
BACKGROUND PLUS REFUELING		
Rural - Typical	160	150
Rural - High End	34	33
Urban - Typical	160	150
Urban - High End	34	32

(footnotes on following page)

Table 8.13. (cont.)

Notes:
Cancer Margin of Safety [MOS] = Point of Departure / Lifetime Average Daily Dose
Lifetime average daily doses are calculated from values presented in Table 7.53, and are time-weighted based on the exposure duration over a 70-yr lifespan.
Point of departure is presented in Table 8.3.
Values are rounded to two significant figures.

[a] Values represent cancer risk estimates associated with an infant ingesting human milk from a mother who is occupationally exposed to benzene, in addition to other applicable background exposures.

Table 8.14. Indoor air comparison (in-home): cancer margins of safety

Results of cancer margin of safety analysis for exposures to indoor air.

	Cancer Margin of Safety (unitless)	
	Female	Male
In-Home Indoor Air		
Typical[a]	210	200
High End[a]	45	43
Alaska	25	24

Notes:
Margin of Safety [MOS] = Point of Departure / Lifetime Average Daily Dose
Points of departure are presented in Table 8.3.
Lifetime average daily doses are calculated from values presented in Table 7.53, and are time-weighted based on the exposure duration over a 70-yr lifespan.
Values are rounded to two significant figures.

[a] Typical and high-end values for the continental United States.

8.4 Risk Characterization Summary

The EPA default (linear) approach of calculating HQs and excess cancer risks contains, as EPA's acknowledges, has a significant degree of conservatism. The use of a single value for the HQ and/or CSF inappropriately conveys a level of confidence or certainty about the risk estimates, when in fact the HQ and excess risk predicted using a single point estimate contain a large degree of uncertainty, and usually reflect, as with EPA's benzene IRIS values, the upper end of the conservative range of uncertainty. Rounding to one significant figure does not alleviate this problem. Providing a range of risk estimates though, with some discussion and transparency about the uncertainty involved in the "high" and "low" guidance values (e.g.,

RfC/RfD and CSF) gives greater insight into the plausibility of risk estimates (HQ and/or excess cancer risks) for a given evaluation.

The use of a range of Reference Values for benzene in this assessment (the range of RfDs is approximately a factor of 30) provides greater insights into the uncertain nature of the noncancer risk estimates and provides the risk manager far more insight into the plausible effects predicted in this benzene risk assessment. Even though EPA provides a range of CSFs for benzene, the range of CSFs chosen by EPA do not adequately reflect the uncertainty about its estimates of cancer risks. Most importantly, EPA has neglected to capture the uncertainty about the dose-response model used to fit the 'Pliofilm' cancer mortality data and thus the "model-dependent" impact on risk estimates at low (environmental) exposures. EPA chose a range of CSFs that represented the most conservative estimates of risk from fitting the Pliofilm cohort. Other dose-response models (that assumed a sublinear dose-response) that were used to fit the Pliofilm mortality data derived risk estimates as much as 300 times lower than the EPA chosen CSFs. Therefore, much of the cancer risk predicted using EPA's default linear approach is largely a function of the low-dose extrapolation model used by EPA. As a result, the cancer risk estimates using EPA's default (linear) approach reflect more on EPA policy decisions than on a realistic biological understanding of cancer risks resulting from background exposures to benzene. The theoretical excess cancer risks predicted using the lower-bound nonlinear model derived CSF helps to provide greater insight on this issue.

The MOS analysis provides a rational and intuitive approach for evaluating the "safety" associated with children's exposures to benzene in the environment. By demonstrating that exposures are lower than the PODs by several orders of magnitude for most exposure scenarios, this MOS approach indicates that the exposures quantified have a large MOS.

Risk assessment is an important tool that should inform on choices, costs and priorities so public health officials can make informed decisions to protect public health. However, risk assessment is an inexact science. Many layers of conservatism are built into both the exposure assessment component and in the dose-response component where the "acceptable" exposure guideline is developed. Therefore, it is often helpful to conduct reality checks to put these estimates of health risks in perspective.

As summarized in Section 5.4, levels of benzene in the environment have declined substantially since the early 1970s and dramatically over the past 15 years. If benzene were to be causing increased incidences of leukemia (and specifically AML) among children, then we would expect to see some decline in the incidence of childhood leukemia in the U.S. that paralleled this decline in environmental benzene. However, the opposite is true; there has been an increase in the incidence of childhood leukemia in the U.S. Most of this increase is attributed to a rise in the incidence of ALL among children. The incidence of AML, which is the most applicable to benzene exposures, among children has remained largely unchanged over the past 30 years (Ries et al., 1999).

The available exposure information on Alaskan homes indicates that they have the potential for significantly higher indoor benzene levels than in homes in the Continental U.S. (section 7.2.1.5). The EPA default (linear) approach would predict that there should be an excess incidence of AML in Alaska compared to the rest of the U.S. This possibility was investigated by analyzing the Alaska cancer registry (Alaska, 2000a; 2000b). The reports for 1997 (Alaska, 2000a) and 1998 (Alaska 2000b) contain incidence and mortality data on specific leukemia subtypes. The Alaska reports provide age-adjusted rates of incidence and mortality (per 100,000 individuals) and confidence intervals for each and the incidence and mortality rate for

the continental U.S. for each leukemia subtype. In the 1997 report, the cancer incidence for leukemias were broken into subtypes of origin of cell-line (myeloid, lymphocytic, monocytic, other) but did not differentiate between acute or chronic. The incidence of myeloid leukemias in 1997 in Alaska was 3.9 per 100,000 (95% CI: 2.2 - 6.6) and the US rate for the years 1993-1997 was reported as 4.4 per 100,000 (Alaska 2000a), suggesting no significant difference between the two. The report for the 1998 cancer registry provided more refined disease classification which allowed for a comparison of specifically AML, the disease of concern with benzene. The incidence of AML in 1998 in Alaska was 3.3 per 100,000 (95% CI: 1.7 – 5.9) and 2.8 in the U.S. for the years 1994 – 1998, again demonstrating no difference between the incidence of AML in Alaska and the U.S. There appears to be no difference in the incidence of leukemia (the subtypes of leukemia were not broken out in the Alaska report) between whites and Alaska natives (Alaska 2000b). AML incidence data for Alaska is not consistent with the hypothesis that Alaskan children are at higher risk due to increased benzene exposure.

As previously discussed, available epidemiological data strongly support that a threshold exists for benzene's hematopoietic toxicity, including the risk for developing AML. While the actual exposure/dose required for the development of AML is not universally agreed upon, the existence of a threshold for AML is consistent with clinical data obtained from secondary leukemia arising from ionizing radiation and/or chemotherapy and our current understanding of bone marrow patho-physiology and biology. For this reason, the cancer risk associated with benzene exposure was calculated with a MOS approach, predicated on a non-linear dose response relationship for the induction of AML. Additionally, clinical data on leukemia risk associated with the treatment of primary pediatric cancers do not support the hypothesis that children are at increased risk of developing chemically induced AML. As a result, a threshold for the development of AML in adults would likely be the same in children. Moreover, published data on the myelosuppressive/hematotoxic effects of various chemotherapy agents in children and adults do not support the existence of an age related difference in sensitivity. Therefore, additional uncertainty factors were not deemed necessary to adequately assess the risk of benzene associated adverse health effects in children.

Levels of benzene in the ambient environment have declined substantially over the past four decades and are anticipated to continue to decline. Therefore, the estimated margins of safety are anticipated to increase over the coming years and decades.

9.0 VCCEP TIER 2 DATA NEEDS ASSESSMENT

9.1 Hazard

Toxicity data on benzene are available for all the Tier 1 VCCEP endpoints and most of the higher tiered endpoints, including subchronic and chronic repeated-dose, reproductive and developmental toxicity, neurotoxicity, immunotoxicity, carcinogenicity and metabolism. In addition, there are extensive epidemiology and other human health data on benzene that have been used as the basis for human risk assessment for this VCCEP assessment and other existing assessments of benzene (IRIS, IARC, EU, ACGIH, etc.). These human and animal toxicology data are reviewed in Section 6 (Hazard Assessment).

For Tier 2, the VCCEP Federal Register Notice (Dec. 26, 2000) outlines six animal toxicity study types that could be considered:

- 90-day Subchronic toxicity in rodents
- Reproductive and fertility effects
- Prenatal developmental toxicity (two species)
- *In Vivo* mammalian bone marrow chromosomal aberrations OR *in vivo* mammalian erythrocyte micronucleus
- Immunotoxicity
- Metabolism and pharmacokinetics.

In determining whether any of these studies need to be conducted on benzene for purposes of the VCCEP program, the Consortium considered the existing study data for these endpoints and whether additional animal testing would significantly benefit the hazard/risk assessments and risk management for benzene.

As mentioned above, there are extensive hazard data for benzene that generally cover all of these possible Tier 2 tests. The one exception is the absence of a 2-generation reproduction toxicity study. Nonetheless, several existing studies evaluate benzene's effects on reproductive performance and fertility in animals, including studies evaluating female rat and mouse reproductive performance and studies in the rat and mouse evaluating male reproductive endpoints. Limited effects were observed in both female and male rat studies, though some effects on the testis were observed in male mice. While, some information on reproductive and developmental toxicity is available from the human literature, these data generally have significant methodology and other deficiencies which led the EU and OECD to recently conclude that they are "not sufficient to demonstrate a causal association" (OECD 2005).

While some additional animal toxicity information could be gained from a 2-generation reproduction study, its value would be quite limited. The Consortium does not believe that such a study could significantly benefit the existing risk assessments for benzene nor the extensive risk management programs and environmental controls in place and under development. The extensive human health effects database for benzene indicates that hematological endpoints and acute myelogenous leukemia (AML) are well established as critical effects for benzene risk assessment as has been concluded in several recent assessments by the U.S. EPA, the EU, and the OECD. Cancer risk concerns for benzene have led to extensive occupational and environmental regulations and risk management programs (see Section 4), which have resulted

in significant reductions in benzene emissions and exposure levels over the past decades (see Sections 5 and 7).

This downward exposure trend will continue as new programs and regulations are implemented. EPA has estimated that over 70% of ambient benzene exposure is from mobile sources, both gasoline emissions and combustion exhaust (see Section 7). As noted in Section 4, EPA has an ongoing mobile source rulemaking that targets benzene as a toxic of concern. This rulemaking will be completed long before a 2-generation reproduction study could be completed.

Finally, when the OECD (including the U.S. EPA) reviewed benzene in October 2005, it concluded that "further testing is not warranted" on benzene reproductive effects. Virtually all existing risk assessments and risk management actions for benzene are based on human data. For all of these reasons, the Consortium does not believe there is adequate rationale or justification to conduct a 2-generation reproduction study in experimental animals on benzene.

9.2 Exposure

For compounds, like benzene, that occur in many environments, additional exposure assessment work is always possible. The VCCEP sponsors believe, however, that the information presented in the Exposure Assessment (Section 7) is fully adequate to demonstrate exposures to benzene from anticipated sources. Benzene exposures have been declining for many years due to extensive environmental regulations (see Section 4), gasoline and product reformulations, emission control improvements for cars and trucks, smoking limitations in public buildings, and other factors. This downward exposure trend for benzene will continue with the introduction of additional regulations and controls, as such future exposure data will likely be lower then the data presented in this assessment.

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