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TECHNICAL MEMORANDUM
TOWN OF ERIE AIR QUALITY REVIEW

Prepared For:	Fred Diehl, Assistant to the Town Administrator
Prepared By:	Cynthia Ellwood, PH. D., CIH, Pinyon Environmental
Date:	February 4th, 2013
Re:	Town of Erie Air Quality Review (Pinyon Project # 1/12-695-02.8001)

Background

Pinyon understands that Town of Erie residents have raised concerns about potential public health effects that may be associated with increased oil and gas extraction facilities located in proximity to the Town. In early 2012, specific concerns had been raised about the reported concentrations of various volatile organic compounds as presented by Dr. Steven Brown from the National Oceanic and Atmospheric Administration's (NOAA) Earth System Research Laboratory to the Town of Erie Board of Trustees on February 21, 2012. NOAA concluded that propane was measured in concentrations approximately 10 times higher at the Erie tower than concentrations measured in Pasadena, California. NOAA also concluded that the benzene concentrations measured during the study were related to the natural gas wells in the area.

Pinyon Environmental prepared and submitted a technical memorandum on May 4, 2012. The memorandum presented toxicological information for propane and benzene in order for the Town of Erie Board of Trustees to understand potential health impacts of these two chemicals, independent of each other, at various exposure concentrations.

Pinyon also reported on the limitations of the NOAA study. In summary, NOAA conducted an atmospheric processes and pollution formation study. The NOAA study was not designed to measure potential pollutant concentrations that may represent exposures of the general public. Pinyon further noted that the NOAA study design did not include methodologies that would enable the data set to be used to discuss impact on human health without limitations on conclusions drawn from the data.

In July and August 2012, the Colorado Department of Public Health and Environment (CDPHE) conducted air sampling adjacent to natural gas well completion activities in Erie, Colorado. As stated in the CDPHE report (dated December 5, 2012), the purpose of the sampling was to measure air emissions that may be associated with well completion activities. Unlike the NOAA study, the CDPHE study did consider exposure potential at a distance of approximately six feet above the ground, which may be defined as typical breathing zone height. Air sampling measurements obtained from this height are considered breathing zone samples, which are samples representative of air passing by the mouth and nose of humans. As such, the air sample results can be used to gain further understanding of the general public exposure potential from adjacent natural gas well completion activities.

Two sampling locations (E1CO and E2CO) were identified based on proximity of wellheads to residential housing, schools, and land owned by the Town of Erie. The E1CO monitor was placed approximately 1,650 feet south/southwest of a group of wellheads. The E2CO monitor was placed approximately 850 feet southeast of the wellheads. These locations were placed in areas likely to be downwind from the wellheads.

Purpose

The purpose of this report is to present toxicological information for the primary constituents reported in the July and August 2012 CDPHE study, which include methane, ethane, propane, butane, isobutane, toluene and benzene. The information in this report is prepared in order for the Town of Erie Board of Trustees to understand potential health impacts of these chemicals, independent of each other, at various exposure concentrations.

In conducting the toxicological review and Pinyon followed basic scientific principles and only used information from United States federal health databases and peer-reviewed scientific journals and references.

Methodology

The toxicological review of ethane, propane, methane, butane, isobutene, toluene and benzene included health-based data from the following sources:

1. The Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) human health assessment program database and the U.S. Department of Health and Human Services' Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profiles for benzene and toluene [1, 2] Information about the IRIS and ATSDR databases is discussed in Appendix A.

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[1] http://www.epa.gov/iris/index.html
[2] http://www.atsdr.cdc.gov/substances/index.asp

2. The United States National Library of Medicine, Toxicology Data Network (TOXNET) Hazardous Substances Database (HSDB) and the Household Products Database for the above listed chemicals. [3,4]
3. The American Conference of Governmental Industrial Hygienists (ACGIH) Documentation of Threshold Limit Values for benzene, toluene, methane, ethane, propane, butane, and isobutane. [5,6,7]
4. The industrial hygiene and toxicology reference *Patty's Toxicology* for toluene and benzene [8]

Information from the toxicological review was used to extract known human and some animal health effects related to known or estimated inhalation exposure concentrations for the above listed chemicals.

The 2012 CDPHE study data, as presented in the CDPHE report titled, *Air Emission Case Study Related to Oil and Gas Development in Erie, Colorado*[9] was reviewed to evaluate applicability of the volatile organic compound concentration measurements to estimate health risk to the Town of Erie residents.

Benzene (CAS 71-43-2)

Benzene is a monocyclic aromatic hydrocarbon and the simplest single-ring aromatic hydrocarbon compound. When one methyl group (CH_3) is attached to the ring, toluene is formed.

Benzene in the air comes from both natural and man-made (anthropogenic) sources. Natural sources include gas emissions from volcanoes and forest fires, and the chemical is a constituent in crude oil and coal tar. Benzene is also released to the air from building fires. Man-made sources include vehicle exhaust, vehicle fuels (gasoline and diesel), aviation fuels, tobacco

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[3] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

[4] http://hpd.nlm.nih.gov/

[5] American Conference of Governmental Industrial Hygienists: Benzene. In: Documentation of Threshold Limit Values and Biological Exposure Indices, 7th Ed. ACGIH, Cincinnati, OH (2001).

[6] American Conference of Governmental Industrial Hygienists: Aliphatic Hydrocarbon Gases: Alkanes [C_1-C_4]. In: Documentation of Threshold Limit Values and Biological Exposure Indices, 7th Ed. ACGIH, Cincinnati, OH (2004).

[7] American Conference of Governmental Industrial Hygienists: Toluene. In: Documentation of Threshold Limit Values and Biological Exposure Indices, 7th Ed. ACGIH, Cincinnati, OH (2001).

[8] Henderson, Rogene, F: Aromatic Hydrocarbons—Benzene and Other Alkylbenzenes. In: Patty's Toxicology, 5th ed., E. Bingham, B. Cohrssen, C. H. Powell, editors, John Wiley & Sons, Inc. (2001)

[9] Colorado Department of Public Health and Environment, Air Emission Case Study Related to Oil and Gas Development in Erie, Colorado, Air Pollution Control Division, Technical Services Program, December 5, 2012.

smoke, and industrial emissions. Household products that contain benzene include automobile products, wood refinishing products, paints and window and door sealants.

Because of the natural sources of airborne benzene and the prevalence of anthropogenic sources, benzene is ubiquitous in the atmosphere. On a national level, industrial emissions and vehicle exhaust accounts for 20 percent of our total exposure to benzene. The cited references report, on average, that tobacco smoke accounts for about half of the total U.S. population exposure to benzene. In addition to tobacco smoke, sources of benzene in the home arise from using products that contain benzene. Benzene levels in the air have been shown to be higher in homes with attached garages.

People can also be exposed to benzene through food, beverages or drinking water, but these sources are small when compared to exposure through air.

The health effects resulting from exposure to benzene have been derived from animal studies, occupational epidemiology studies and clinical reports. It is important to note that several factors determine whether a harmful health effect will occur following exposure, as well as the type and severity of health effects. The two most important factors are the benzene exposure concentration and the length/duration of exposure. Exposures of very short duration but of very high concentration (10,000 to 20,000 parts per million,or ppm) can result in death. Brief exposures to lower concentrations (700 to 3,000 ppm) can result in dizziness, rapid heart rate, headaches and other central nervous system effects. Once exposure to these concentrations stop and individuals breathe uncontaminated air, symptoms quickly subside.

Another type of exposure is long-term exposure to low benzene concentrations. Most of the health effect information on long-term exposures comes from epidemiology studies of workers employed in industries that use or make benzene.

The health effects related to benzene exposure have been classified as noncancerous health effects and carcinogenic (cancer-causing) effects. Noncancerous health effects involve organ systems that include immunological, neurological, reproductive, and developmental. A summary of noncancerous health effects as presented in the Agency for Toxic Substances and Disease Registry (ASTDR) toxicological profile for benzene is available in Appendix B.

The ASTDR provides exposure level estimates that pose minimal risk to humans, which are called minimal risk levels (MRLs). An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. Three MRLs have been derived for three different exposure durations:

- Acute-duration inhalation exposure is 14 days or less
- Intermediate-duration inhalation exposure is 15 to 365 days
- Chronic-duration inhalation exposure is greater than 365 days

The United States Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) has developed an inhalation reference concentration (RfC) for chronic non-cancer health effects for benzene. As described in Appendix A, the Integrated Risk Information System is a human health assessment program that evaluates information on health effects that may result from exposure to environmental contaminants. When supported by available data, IRIS provides RfCs for chronic non-cancer health effects, and inhalation unit risks for carcinogenic effects. The RfC is an inhalation exposure concentration at or below which adverse noncancerous health effects are not likely to occur. EPA stresses that the RfC is not a direct estimator of risk, but rather a reference point to gauge the potential for health effects. At lifetime exposures increasingly greater than the reference exposure level, the potential for adverse health effects increases.

The noncancerous MRLs and RfC for benzene are listed below.

ASTDR Minimal Risk Level (MRL)	**ppm***	**ppb****	**µg/m^3**
Acute-duration inhalation exposure (14 days or less)	0.009	9	30
Intermediate-duration inhalation exposure (15 to 365 days)	0.006	6	20
Chronic-duration inhalation exposure (greater than 365 days)	0.003	3	10
IRIS Inhalation Reference Concentration (RfC)	**ppm***	**ppb****	**µg/m^3**
Chronic-duration inhalation exposure	0.009	9	30

*ppm, parts of benzene per million parts of air
**ppb, parts of benzene per billion parts of air
µg/m^3 - microgram per cubic meter

Regarding the carcinogenicity of benzene, occupational epidemiology studies have demonstrated a clear link between exposure to benzene and the occurrence of acute nonlymphocytic leukemia (ANLL), particularly the myeloid cell type (acute myelogenous leukemia, AML). The Environmental Protection Agency, Occupational Safety and Health Administration (OSHA), American Conference of Governmental Industrial Hygienists (ACGIH), National Institute for Occupational Safety and Health (NIOSH), and the National Toxicology Program (NTP) have classified benzene as a confirmed or known human carcinogen.

EPA has performed a risk assessment using various scientifically validated models to predict the lifetime risk of cancer when exposed to a lifetime of different air concentrations. Note that a lifetime exposure is measured at 70 years by EPA definition.

A range of 2.2×10^{-6} to 7.8×10^{-6} is the increase in the lifetime risk of an individual who is exposed for a lifetime to 1 microgram per cubic meter ($\mu g/m^3$) benzene in air. One $\mu g/m^3$ is equivalent to 0.3 ppb or 0.0003 ppm.

The EPA has developed quantitative estimates of a lifetime of exposure to different air concentrations providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. These air concentrations at specific risk levels are presented below.

Risk Level	**Air Concentration**
1 in 10,000 (10^{-4})	4 to 14 ppb (0.004 to 0.014 ppm)
1 in 100,000 (10^{-5})	0.4 to 1.4 ppb (0.0004 to 0.0014 ppm)
1 in 1,000,000 (10^{-6})	0.04 to 0.14 ppb (0.00004 to 0.00014 ppm)

Before a comparison between the above-listed MRLs, RfCs and lifetime cancer risk estimates and the benzene concentrations reported by CDPHE from the air emissions case study can be presented, the CDPHE study limitations must be discussed.

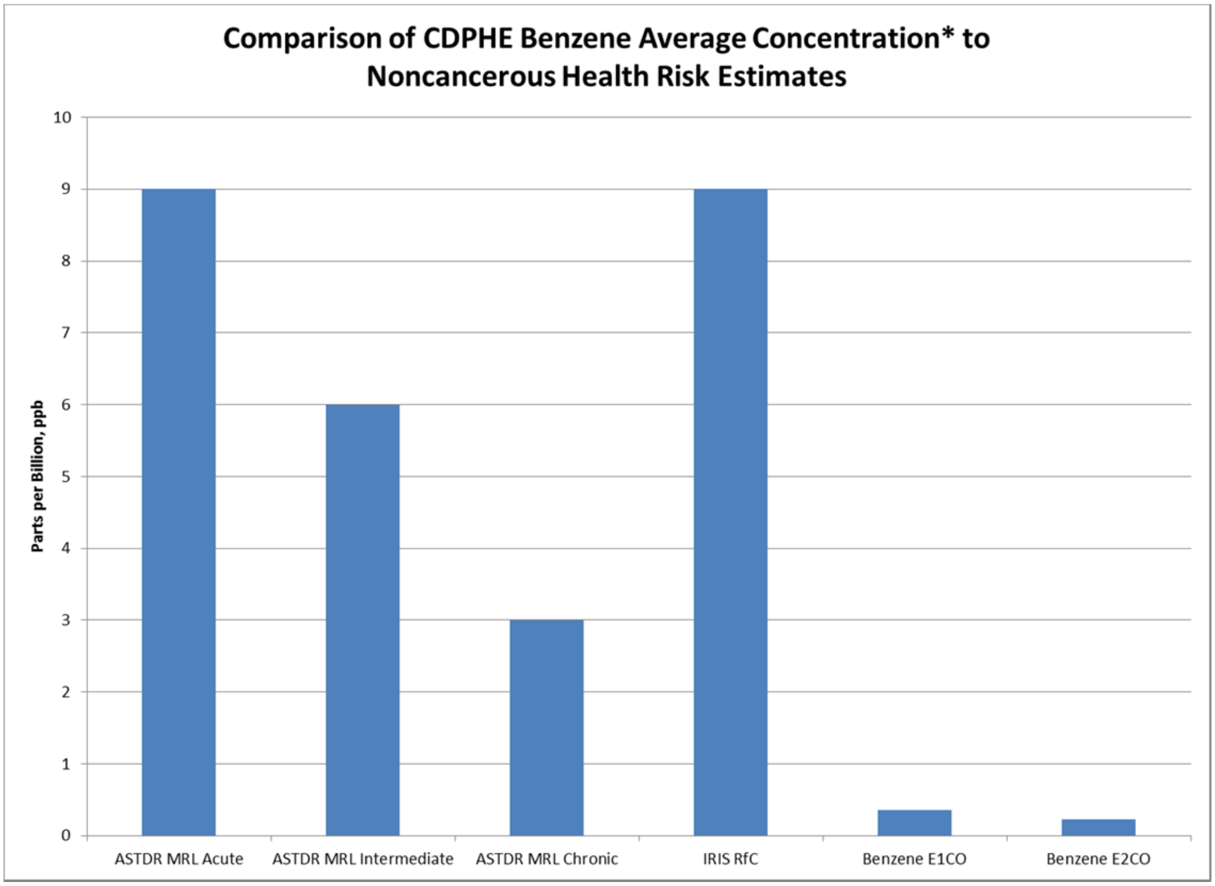
The authors of the CDPHE air emissions case study report clearly state the study is a snapshot in time and that the study only represents air samples collected near one well pad. The authors further state that limited data was collected, which may or may not be representative of conditions and potential emissions at other locations.

Based on the CDPHE information, and the understanding that the data set from the CDPHE study is limited in scope and quantity of data, the risk of Erie residents of experiencing an adverse health effect over a lifetime exposure to the CDPHE reported benzene concentrations is low.

Regarding cancer risk, the CDPHE study authors determine that if Erie residents were to continuously breathe air containing the CDPHE benzene concentration over an entire lifetime, the risk of cancer would be on the order of 5.7 to 8.7 in 1,000,000. EPA states that the results of risk estimates should not be used as an absolute measure of whether risks are acceptable. Rather, they should be used to focus or target more refined measurement and assessment activities.

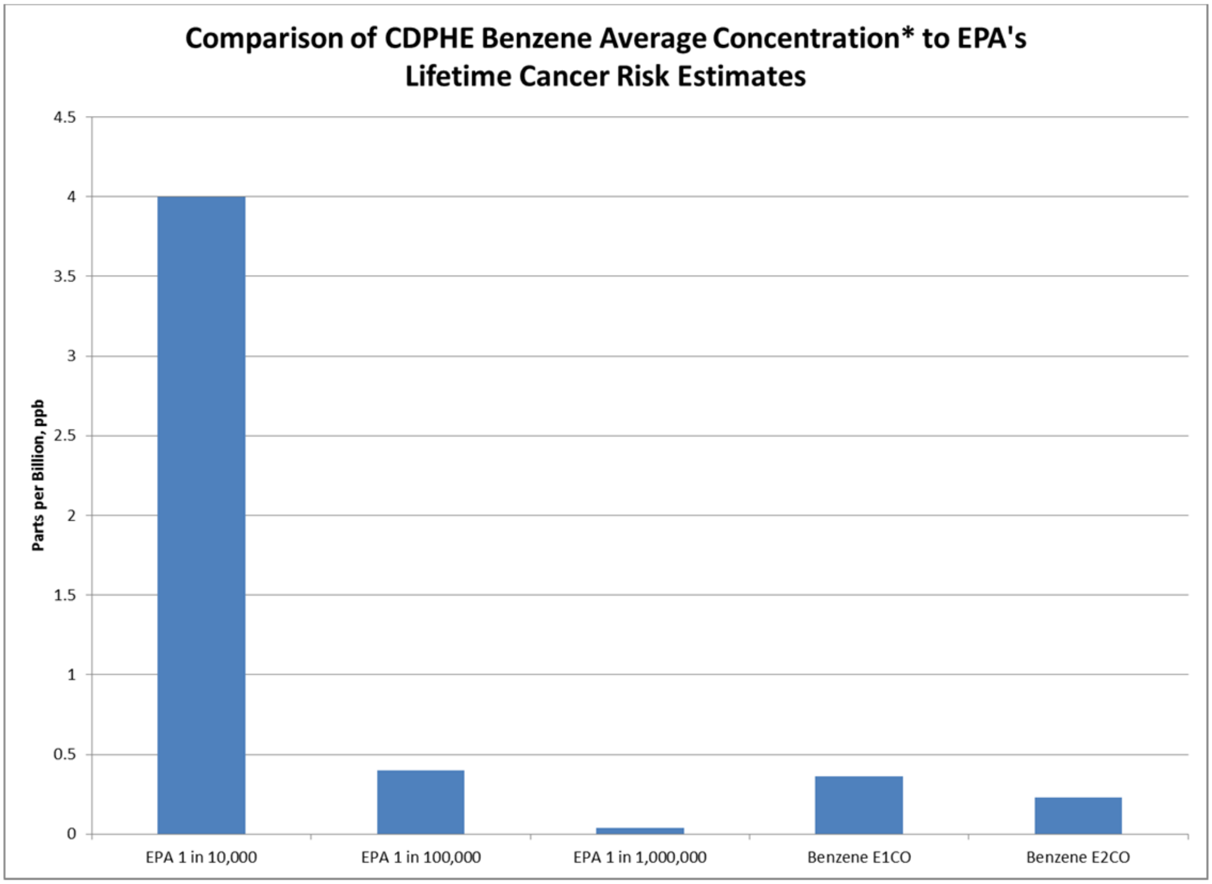
In order to put these risk estimates into perspective, it is helpful to compare the cancer risk identified in this assessment to lifetime cancer risk from all causes. Information extracted from the EPA estimates that approximately 1 out of every 3 Americans (or 336,000 in a million) will contract cancer in their lifetimes and about 570,000 out of the nearly 1.5 million cancer cases annually will die from their disease. Of these cancer deaths, almost one-third can be attributed to tobacco use alone, and another third can be related to lifestyle factors such as poor nutrition, physical inactivity, and obesity.

Figure 1
Benzene Concentrations at E1CO and E2CO compared to ASTDR MRLs and IRIS MRL, Noncancerous Risk Estimates



Note (*) that the benzene average concentration was calculated from Table 6, page 25 of the CDPHE report.

Figure 2
Benzene Concentrations at E1CO and E2CO compared to EPA Lifetime Cancer Risk Estimates



Note (*) that the benzene average concentration was calculated from Table 6, page 25 of the CDPHE report.

Toluene (CAS 108-88-3)

Toluene is a monocyclic aromatic hydrocarbon with one methyl group (CH_3) attached to the ring.

Toluene in the air comes from both natural and anthropogenic sources. Natural sources include natural gas deposits and emissions from volcanos, forest fires and crude oil. Anthropogenic sources include vehicle exhaust (both gasoline and diesel), and volatilization of vehicle fuels, solvents and thinners. Toluene can be released to the environment through various waste streams during its production and use as an intermediate in the production of benzoic acid, benzaldehyde, explosives, dyes and many other organic compounds. Toluene is a major constituent of the gas phase of the mainstream smoke of unfiltered cigarettes, on the order of 20-60 micrograms (µg) per cigarette. Toluene is used in the production of cements, solvents, spot removers, fingernail polish, antifreezes, and inks, and in adhesive solvents used in plastic toys and model airplanes. Because of the natural sources of airborne toluene and the prevalence of anthropogenic sources, toluene is ubiquitous in the atmosphere

Like benzene, people can also be exposed to toluene through food, beverages or drinking water, but these sources are small when compared to exposure through air.

Information on the health effects resulting from exposure to toluene have been derived from animal studies, occupational epidemiology studies and clinical reports. As previously stated, it is important to understand that several factors determine whether a harmful health effect will occur following exposure, as well as the type and severity of health effects. The two most important factors are the toluene exposure concentration and the length/duration of exposure. Exposures of very short duration (of around an hour) and at very high concentration (4,000 parts per million, ppm) can result in death. Brief exposures to lower concentrations (75 to 100 ppm) can lead to fatigue, sleepiness, feelings of intoxication, headaches, reduced performance on mental tests and other central nervous system effects. Once exposure to these concentrations stop and individuals breathe uncontaminated air, symptoms subside.

Another type of exposure is long-term exposure to low toluene concentrations. Nearly all the health effect information resulting from long-term exposures comes from epidemiology studies of workers employed in industries that make toluene or use products containing toluene (e.g., painters, printers, shoe manufacturing, etc.).

The health effects related to toluene exposure have been classified as noncancerous health effects and involve organ systems that include neurological, reproductive, developmental, and visual. A summary of noncancerous health effects as presented in the ASTDR toxicological profile for toluene is available in Appendix C. Toluene is not classified as a carcinogen.

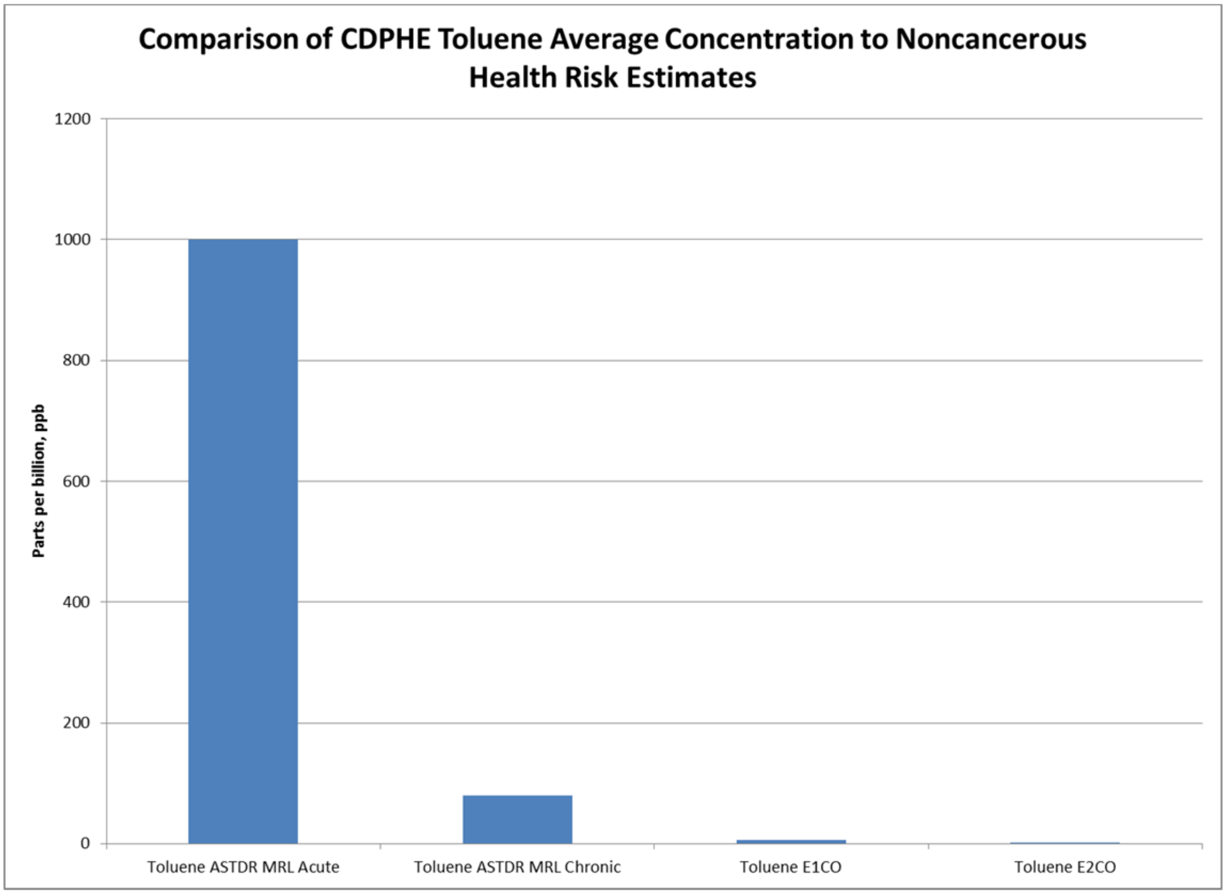
The noncancerous MRLs and RfC for toluene are listed below.

ASTDR Minimal Risk Level (MRL)	**ppm***	**ppb****
Acute-duration inhalation exposure (14 days or less)	1	1,000
Intermediate-duration inhalation exposure (15 to 365 days)	NE	NE
Chronic-duration inhalation exposure (greater than 365 days)	0.08	80
IRIS Inhalation Reference Concentration (RfC)	**ppm***	**ppb****
Chronic-duration inhalation exposure	1.32	1,320

*ppm, parts of benzene per million parts of air
**ppb, parts of benzene per billion parts of air
NE - Not established

A direct comparison of the toluene concentrations reported by CDPHE to the ASTDR Minimal Risk Levels and EPA's inhalation reference concentrations is presented in Figure 3. Understanding that the data set from the CDPHE study is limited in scope and quantity of data, the risk of Erie residents experiencing an adverse health effect over a lifetime exposure to the CDPHE reported toluene concentrations is low.

Figure 3
Toluene Concentrations at E1CO and E2CO compared to ASTDR MRLs and IRIS MRL, Noncancerous Risk Estimates



Note (*) that the toluene average concentration was obtained from Table 5, page 15 of the CDPHE report.

Methane (CAS 74-82-8), Ethane (CAS74084-0), Propane (CAS 74-98-6), Butane (CAS 106-97-8), Isobutane (CAS 75-28-5)

Methane, ethane, propane, butane and isobutane belong to the group of hydrocarbons called alkanes, due to the single covalent bond joining the hydrogen and carbon atoms. These gases are commonly referred to as C_1 to C_4 alkane hydrocarbons, are colorless and highly flammable, and all occur naturally in petroleum and natural gas.

There are other natural sources of methane. Methane is an end product of the anaerobic decay of organic material and as such is released to the environment as natural emissions from microbes and animal waste. Other important sources of methane are the rumen of domestic animals (especially cattle), from volcanos and emissions during the growing of rice.

Man-made sources of methane include emissions from automobiles and turbines, and diesel exhaust. Methane is also use as a fuel for illumination and cooking.

The gases ethane, propane, butane and isobutene are a constituent in the paraffin fraction of crude oil and natural gas. Anthropogenic sources of these gases include emissions from oil, gasoline, diesel and natural gas or propane fuel fired equipment and vehicle emissions. The combustion of gasoline is a major mechanism for the release of these gases.

Propane, n-butane and isobutene are used in refrigerants and as an aerosol propellant. Historically, isobutane in was used in cosmetics as the propellent in underarm deodorants, at a concentration of 50 percent. Many household products continue to contain these gases primarily as a propellant. Propane is also used as a cooking fuel. Of the 107 million households in the U.S., 9.4 million depend on propane for one use or another with 53 percent of these households relying on propane for their primary heating fuel.[10] Because of the natural sources of these gases and the prevalence of anthropogenic sources, these gases are ubiquitous in the atmosphere.

Methane, propane and ethane are simple asphyxiants. Simple asphyxiants displace atmospheric oxygen below concentrations that are required for normal tissue respiration. At low concentrations these gases are essentially physiologically inert, and have practically no physiological action under normal conditions of exposure (i.e., cooking). These gases affect the central nervous system (CNS) acting as a narcotic at the following predicted concentrations:

- Methane – 300,000 ppm
- Ethane – 130,00 ppm

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[10] DOE Energy Information Administration National Energy Information Center. Propane Prices. What Consumers Should Know. DOE/EIA-X04. May 2006. http://www.eia.doe.gov/bookshelf/brochures/propane06/propane.pdf

- Propane – 47,000 ppm
- Butane – 17,000 ppm
- Isobutene – 24,000 ppm

Due to the physiologically inert nature of the C_1 to C_4 alkane hydrocarbons at low concentrations, ASTDR and IRIS have not developed exposure risk estimates for the general population.

Occupational exposure limits have been developed by OSHA and NIOSH for some of these gases as presented below.

Gas	OSHA permissible exposure limit (ppm)	NIOSH recommended exposure limit (ppm)
Methane	NA	NA
Ethane	NA	NA
Propane	1,000	1,000
Butane	NA	800
Isobutane	NA	800

The American Conference of Governmental Industrial Hygienists proposed a TLV at 1,000 ppm for the aliphatic hydrocarbon gases, alkanes C_1 to C_4, which include methane, ethane, propane, butane, isobutene and liquefied petroleum gas.

The CDPHE study reported average concentrations for methane, ethane, propane, butane, isobutene, as presented in the below table.

Gas	E1CO		E2CO	
	ppm*	ppb**	ppm*	ppb**
Methane	1.73	1,730	1.80	1,800
Ethane	0.0247	24.7	0.0219	21.99
Propane	0.0149	14.9	0.0139	13.89
Butane	0.0068	6.84	0.0064	6.46
Isobutane	0.0029	2.90	0.0027	2.67

*ppm, parts of gas per million parts of air
**ppb, parts of gas per billion parts of air

Understanding that the data set from the CDPHE study is limited in scope and quantity of data, the risk of Erie residents of experiencing an adverse health effect over a lifetime exposure to the CDPHE reported concentrations of these gases is low.

Summary

The information provided in this report only documents research conducted by CDPHE in July and August 2012. Based on the understanding that the CDPHE study is limited in scope and quantity of data, the risk of Erie residents of experiencing an adverse health effect over a lifetime exposure to the CDPHE reported concentrations of the gases discussed in this report is low.

Appendix A

A Summary of EPA's Integrated Risk Information System (IRIS) human health assessment program database and the U.S. Department of Health and Human Services' Agency for Toxic Substances and Disease Registry (ATSDR)

EPA's Integrated Risk Information System (IRIS) is a human health assessment program that evaluates information on health effects that may result from exposure to environmental contaminants. Through the IRIS Program, EPA provides the highest quality science-based human health assessments to support the Agency's regulatory activities. The IRIS database contains information on more than 550 chemical substances containing information on human health effects that may result from exposure to various substances in the environment. The IRIS database is prepared and maintained by the EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD).

The heart of the IRIS database is its collection of searchable documents that describe the health effects of individual substances and that contain descriptive and quantitative information in the following categories:

- **Noncancer effects:** Oral reference doses and inhalation reference concentrations (RfDs and RfCs, respectively) for effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. In most instances, RfDs and RfCs are developed for the noncarcinogenic effects of substances.
- **Cancer effects:** Descriptors that characterize the weight of evidence for human carcinogenicity, oral slope factors, and oral and inhalation unit risks for carcinogenic effects. Where a nonlinear mode of action is established, RfD and RfC values may be used.

EPA's IRIS is a human health assessment program that evaluates quantitative and qualitative risk information on effects that may result from exposure to specific chemical substances found in the environment. The IRIS database contains information that can be used to support the first two steps (hazard identification and dose-response evaluation) of the risk assessment process. When supported by available data, IRIS provides oral reference doses (RfDs) and inhalation reference concentrations (RfCs) for chronic non-cancer health effects, and oral slope factors and inhalation unit risks for carcinogenic effects. Combined with specific exposure information, government and private entities use IRIS to help characterize public health risks of chemical substances in a site-specific situation and thereby support risk management decisions designed to protect public health.

More specifically, the reference dose (RfD) and reference concentration (RfC) provide quantitative information for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. The RfD (expressed in units of mg of substance/kg body weight-day) is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. An RfD can be derived from a no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL), or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. The inhalation RfC (expressed in units of mg of substance/m^3 air) is analogous to the oral RfD but provides a continuous inhalation exposure estimate. The inhalation RfC considers toxic effects for both the respiratory system (portal of entry) and effects peripheral to the respiratory system (extrarespiratory or systemic effects). Reference values may also be derived for acute (≤24 hours), short-term (>24 hours, up to 30 days), and subchronic (>30 days, up to approximately 10% of the life span) exposure durations, all of which are derived based on an assumption of continuous exposure throughout the duration specified. RfDs and RfCs are generally used in noncancer health assessments.

Cancer slope factors and unit risks are used to estimate the risk of cancer associated with exposure to a carcinogenic or potentially carcinogenic substance. A slope factor is an upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent by ingestion. This estimate, usually expressed in units of proportion (of a population) affected per mg of substance/kg body weight-day, is generally reserved for use in the low-dose region of the dose-response relationship, that is, for exposures corresponding to risks less than 1 in 100. A unit risk is an upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/L in water or 1 µg/m^3 in air. The interpretation of unit risk for a substance in drinking water would be as follows: if unit risk = 2×10^{-6} per µg/L, 2 excess cancer cases (upper bound estimate) are expected to develop per 1,000,000 people if exposed daily for a lifetime to 1 µg of the substance in 1 liter of drinking water.

A risk level of 1 in a million implies a likelihood that up to one person, out of one million equally exposed people would contract cancer if exposed continuously (24 hours per day) to the specific concentration over 70 years (an assumed lifetime). This would be in addition to those cancer cases that would normally occur in an unexposed population of one million people. Note that this assessment looks at **lifetime** cancer risks, which should not be confused with or compared to **annual** cancer risk estimates. If you would like to compare an annual cancer risk estimate with the results in this assessment, you would need to multiply that annual estimate by a factor of 70 or alternatively divide the lifetime risk by a factor of 70. A 1 in million lifetime risk to the public in 1996 was 250 cancer cases over a 70 year period.

A risk level of 1 in a million implies a likelihood that one person, out of one million equally exposed people, would contract cancer if exposed continuously (24 hours per day) to that specific concentration over 70 years (an assumed lifetime). This risk would be an excess cancer risk that is in addition to any cancer risk borne by a person not exposed to these air toxics.

What does EPA believe constitutes an acceptable level of risk?
Unlike other pollutants that EPA regulates, air toxics have no universally-applicable, pre-defined risk levels that clearly represent acceptable or unacceptable thresholds. However, EPA has made case-specific determinations and described certain general presumptions that apply to particular regulatory programs. The 1989 Benzene National Emission Standard for Hazardous Air Pollutants (NESHAP) rule set up a two-step, risk-based decision framework for the NESHAP program. This rule and framework are described in more detail in EPA's 1999 Residual Risk Report to Congress (PDF) (225pp, 2.3 MB). First, the rule set an upper limit of risk acceptability of about 1 in 10,000 (or 100 in 1 million) lifetime cancer risk for the most exposed individual. In the rule, we explained, "The EPA will generally presume that if the risk to that individual [the Maximum Individual Risk] is no higher than approximately 1 in 10 thousand, that risk level is considered acceptable and EPA then considers the other health and risk factors to complete an overall judgment on acceptability." Second, the rule set a target of protecting the greatest number of persons possible to an individual lifetime risk level no higher than approximately 1 in 1 million. These determinations called for considering other health and risk factors, including the uncertainty in the risk assessment, in making an overall judgment on risk acceptability. Unlike cancer risk, there currently is no framework for determining the acceptability of noncancer risks. Aggregate exposures equal to or below a hazard index (HI) of 1.0 derived using target organ specific hazard quotients likely will not result in adverse noncancer health effects over a lifetime of exposure and would ordinarily be considered acceptable. However, an HI greater than 1.0 does not necessarily suggest a likelihood of adverse effects nor does it imply an unacceptable level of effect. Instead, the acceptability of exceedances is evaluated on a case-by-case basis, considering such factors as the confidence level of the underlying health data, the uncertainties , the slope of the dose-response curve (if known), the magnitude of the exceedances, and the numbers or types of people exposed at various levels above the RfC.

An IRIS health assessment consists of the hazard identification and dose-response assessment steps. The information in the IRIS assessment is combined with site- or problem-specific exposure assessments to provide the scientific support for EPA risk management decisions.

EPA considers risk assessment information along with social and economic factors, public health impacts, and statutes and regulations, in deciding how best to protect public health and the environment. Examples of risk management actions include deciding how much of a substance a company may discharge into a river; deciding which substances may be stored at a hazardous waste disposal facility; deciding to what extent a hazardous waste site must be cleaned up; setting permit levels for discharge, storage, or transport; establishing levels for air emissions; and determining allowable levels of contamination in drinking water.

The Agency for Toxic Substances and Disease Registry (ATSDR), based in Atlanta, Georgia, is a federal public health agency of the **U.S. Department of Health and Human Services**. ATSDR serves the public by using the best science, taking responsive public health actions, and providing trusted health information to prevent harmful exposures and diseases related to toxic substances.

The agency's mission is to prevent harm to human health and diminished quality of life from exposure to hazardous substances found at waste sites, in unplanned releases, and in other sources of pollution present in the environment. ATSDR identifies communities where people might be exposed to hazardous substances in the environment. The agency also determines how hazardous a site is and recommends actions that need to be taken to safeguard the health of community members. ATSDR works with communities, environmental groups, tribal governments and local, state, and other federal agencies to protect the public health.

ATSDR does not:

- Conduct large-scale site- or release-related environmental sampling (responsibility of the Environmental Protection Agency and state environmental agencies);
- Enforce regulations (ATSDR is an advisory, nonregulatory public health agency);
- Provide medical treatment and health care services

Minimal risk level (MRL)

An ATSDR estimate of daily human exposure to a hazardous substance at or below which that substance is unlikely to pose a measurable risk of harmful (adverse), noncancerous effects. MRLs are calculated for a route of exposure (inhalation or oral) over a specified time period (acute, intermediate, or chronic). MRLs should not be used as predictors of harmful (adverse) health effects.

The MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse, non-cancer health effects over a specified duration of exposure. The information in this MRL serves as a screening tool to help public health professionals decide where to look more closely to evaluate possible risk of adverse health effects from human exposure.

Toxicological Profile Information

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described in the profile. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The focus of the profile is on health and toxicologic information. Therefore, each profile begins with a **Public Health Statement** that summarizes in nontechnical language, a substance's relevant properties.

Appendix B
ASTDR Toxicological Profile for Benzene
Chapter 2. Relevance to Public Health

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO BENZENE IN THE UNITED STATES

Benzene is widely distributed in the environment. The exposure scenario of most concern to the general public is low-level inhalation over long periods. This is because the general population is exposed to benzene mainly through inhalation of contaminated air, particularly in areas of heavy traffic and around gas stations, and through inhalation of tobacco smoke from both active and passive smoking. Smoking has been identified as the single most important source of benzene exposure for the estimated 40 million U.S. smokers. Smoking accounts for approximately half of the total benzene exposure of the general population. Individuals employed in industries that make or use benzene, or products containing benzene, are probably exposed to the highest concentrations of atmospheric benzene. In addition, benzene is a common combustion product, providing high inhalation exposure potential for firefighters. Of the general population, those residing around certain chemical manufacturing sites or living near waste sites containing benzene or near leaking gasoline tanks may be exposed to concentrations of benzene that are higher than background air concentrations. In private homes, benzene levels in the air have been shown to be higher in homes with attached garages, or where the inhabitants smoke inside the house.

Although low levels of benzene have been detected in certain foods, beverages, and tap water, these do not constitute major sources of exposure for most people. However, leakage from underground gasoline storage tanks and seepage from landfills and hazardous waste sites have resulted in significant benzene contamination of well water. People with contaminated tap water can be exposed from drinking the water or eating foods prepared with it. In addition, exposure can also occur via inhalation during showering, bathing, or cooking with contaminated tap water. Showering and bathing with benzene-contaminated water can also contribute significantly to dermal exposure.

The Benzene Subregistry Baseline Technical Report of the National Exposure Registry contains information on 1,143 persons who had documented exposure to benzene in their drinking water and were exposed for at least 30 days. No causal relationship has been proposed for health conditions identified in the base subregistry or continued follow-up of the population.

2.2 SUMMARY OF HEALTH EFFECTS

The carcinogenicity of benzene is well documented in exposed workers. Epidemiological studies and case reports provide clear evidence of a causal relationship between occupational exposure to benzene and benzene-containing solvents and the occurrence of acute myelogenous leukemia (AML). The epidemiological studies are generally limited by confounding chemical exposures and methodological problems, including inadequate or lack of exposure monitoring and low statistical power, but a consistent excess risk of leukemia across studies indicates that benzene is the causal factor.

In vivo and *in vitro* data from both humans and animals indicate that benzene and/or its metabolites are genotoxic. Chromosomal aberrations (hypo- and hyperdiploidy, deletions, breaks, and gaps) in peripheral lymphocytes and bone marrow cells are the predominant effects seen in humans.

Damage to both the humoral and cellular components of the immune system has been known to occur in humans following inhalation exposure. This is manifested by decreased levels of antibodies and decreased levels of leukocytes in workers. Animal data support these findings.

The most characteristic systemic effect resulting from intermediate and chronic benzene exposure is arrested development of blood cells. Early biomarkers of exposure to relatively low levels of benzene include depressed numbers of one or more of the circulating blood cell types. A common clinical finding in benzene hematotoxicity is cytopenia, which is a decrease in various cellular elements of the circulating blood manifested as anemia, leukopenia, or thrombocytopenia in humans and in animals. Benzene-associated cytopenias vary and may involve a reduction in one (unicellular cytopenias) to all three (pancytopenia) cellular elements of the blood.

Benzene also causes a life-threatening disorder called aplastic anemia in humans and animals. This disorder is characterized by reduction of all cellular elements in the peripheral blood and in bone marrow, leading to fibrosis, an irreversible replacement of bone marrow. Benzene has also been associated with acute non-lymphocytic leukemia in humans, and aplastic anemia may be an early indicator of developing acute non-lymphocytic leukemia in some cases.

Limited information is available on other systemic effects reported in humans and is associated with high–level benzene exposure. Respiratory effects have been noted after acute exposure of humans to benzene vapors. Cardiovascular effects, particularly ventricular fibrillation, have been suggested as the cause of death in fatal exposures to benzene vapor. Gastrointestinal effects have been noted in humans after fatal inhalation exposure (congestive gastritis), and ingestion (toxic gastritis and pyloric stenosis), of benzene. Myelofibrosis (a form of aplastic anemia) was reported by a gasoline station attendant who had been exposed to benzene by inhalation, and probably also through dermal contact. Myalgia was also reported in steel plant workers exposed to benzene vapors. Reports of renal effects in humans after benzene exposure consist of kidney congestion after fatal inhalation exposure. Dermal and ocular effects including skin irritation and burns, and eye irritation have been reported after exposure to benzene vapors. Swelling and edema have been reported to occur in a human who swallowed benzene. Studies in animals show systemic effects after inhalation exposure, including cardiovascular effects. Oral administration of benzene to animals has yielded information concerning hepatic effects. A study conducted in rabbits lends support to the finding that benzene is irritating and damaging to the skin and also shows that it is irritating and damaging to the eyes following dermal or ocular application.

Neurological effects have been commonly reported in humans following high-level exposure to benzene. Fatal inhalation exposure has been associated with vascular congestion in the brain. Chronic inhalation exposure has been associated with distal neuropathy, difficulty in sleeping, and memory loss. Oral exposure results in symptoms similar to inhalation exposure. Studies in animals suggest that inhalation exposure to benzene results in depressed electrical activity in the brain, loss of involuntary reflexes and narcosis, decrease in hind-limb grip strength and tremors, and narcosis, among other symptoms. Oral exposure to benzene has not been shown to cause significant changes in behavior. No neurological effects have been reported after dermal exposure to liquid benzene in either humans or animals.

Acute inhalation and oral exposures of humans to high concentrations of benzene have caused death. These exposures are also associated with central nervous system depression. Chronic low-level exposures have been associated with peripheral nervous system effects. Abnormalities in motor conduction velocity were noted in four of six pancytopenic individuals occupationally exposed to adhesives containing benzene.

Evidence of an effect of benzene exposure on human reproduction is not sufficient to demonstrate a causal association. Some animal studies provide limited evidence that benzene affects reproductive organs following inhalation exposure. Results from studies of benzene administered orally to rats and mice indicate no adverse effect on male or female reproductive organs at 17 weeks, but at 2 years, endometrial polyps were observed in female rats, preputial gland lesions were observed in male mice, and ovarian lesions were observed in female mice. Results are conflicting or inconclusive as to whether inhalation of benzene vapors reduces the number of live fetuses and/or the incidences of pregnancy. Other studies are negative for effects on reproductive competence.

Epidemiological studies implicating benzene as a developmental toxicant have many limitations, and thus, it is not possible to assess the effect of benzene on the human fetus. Results of inhalation studies conducted in animals are fairly consistent across species and demonstrate that, at levels >47 ppm, benzene is fetotoxic as evidenced by decreased fetal weight and/or minor skeletal variants. Benzene has also been shown to reduce pup body weight in mice. A persistent decrease in the number of erythroid precursors was found in mice exposed *in utero*. Benzene has not been shown to be teratogenic, but has been shown to be fetotoxic in animals at high concentrations that are maternally toxic.

Cancer. The strongest evidence for the leukemogenic potential of benzene comes from series of cohort mortality studies on workers exposed to benzene in Ohio (the Pliofilm study) and China (the NCI/CAPM study). The Pliofilm study investigated workers exposed to benzene in three rubber hydrochloride (‘Pliofilm’) manufacturing plants. Mortality from all leukemias was increased but declined after additional years of follow-up, suggesting that the excess risk diminished with time since exposure. Exposures in the most recent 10 years were most strongly associated with leukemia risk, and there was no significant relation between leukemia death and benzene exposures received more than 20 years previously. AML accounted for most of the increased leukemia, and the risk of AML increased with increasing cumulative exposure above 200 ppm-years.

The NCI/CAPM study, a collaboration between the National Cancer Institute and the Chinese Academy of Preventive Medicine, evaluated lymphohematopoietic malignancies and other hematologic disorders in 74,828 benzene-exposed workers employed in 672 factories in 12 cities in China. Findings included increased risks for all leukemias, acute nonlymphocytic leukemia (ANLL), and combined ANLL and precursor myelodysplastic syndromes. These risks were increased at average exposure levels of 10– 24 ppm and cumulative exposure levels of 40–99 ppm-years, and tended to increase with increasing average and cumulative levels of exposure.

The results of the Pliofilm and NCI/CAPM studies are consistent with epidemiologic studies and case reports showing increased incidences of leukemia in shoe factory and rotogravure plant workers exposed to high benzene levels during its use as a solvent. No significant increases in leukemia or other lymphohematopoietic malignancies were found in chemical industry workers or petroleum industry workers exposed to lower levels of benzene.

Possible associations between occupational exposure to benzene and non-Hodgkin's lymphoma (NHL) and multiple myeloma have been suggested. The risk for mortality from NHL increased with increasing level and duration of benzene exposure the NCI/CAPM study. The significance of this finding is unclear because NHL mortality was not significantly elevated in the cohort overall, concerns regarding the adequacy of the data have been raised, and increases in NHL were not found in other cohort mortality studies or in case-control studies of benzene-exposed workers.

The risk of mortality from multiple myeloma was increased in one of the early assessments of the Pliofilm cohort. The implication of this finding is unclear because the risk declined to non-significant levels in subsequent follow-up studies, and was not supported by the findings of other cohort mortality studies. Additionally, population-based and hospital-based case-control studies indicate that benzene exposure is not likely to be causally related to the risk of multiple myeloma. A meta-analysis of case-control studies found no significant association between occupational exposure to benzene and benzene-containing products and risk of multiple myeloma from sources categorized as benzene and/or organic solvents, petroleum, or petroleum products.

Animal studies provide supporting evidence for the carcinogenicity of benzene. Benzene has been shown to be a multiple site carcinogen in rats and mice following inhalation and oral exposure. Tumors that were increased in rats that were exposed to 200 or 300 ppm benzene by inhalation for 4–7 hours/day, 5 days/week for up to 104 weeks included carcinomas of the Zymbal gland and oral cavity. Mice that were exposed to 100 or 300 ppm benzene for 6 hours/day, 5 days/week for 16 weeks and observed for 18 months or life developed a variety of tumors, including thymic lymphomas, myelogenous leukemias, and Zymbal gland, ovarian, and lung tumors.

In oral bioassays conducted by the National Toxicology Program, benzene was administered to rats and mice by gavage at dose levels of 25–200 mg/kg/day on 5 days/week for 103 weeks. Tumors that were induced in the rats included Zymbal gland carcinomas and squamous cell papillomas and carcinomas of the oral cavity and skin. In the mice, benzene caused tumors that included malignant lymphomas, Zymbal gland carcinomas, lung alveolar/bronchiolar adenomas and carcinomas, Harderian gland adenomas, preputial gland squamous cell carcinomas, and mammary gland carcinomas. Similar effects occurred in rats exposed to 50–500 mg/kg/day benzene by gavage on 4–5 days/week for up to 104 weeks and observed for life; induced tumors included carcinomas of the Zymbal gland, oral cavity, forestomach, nasal cavity, and skin. Mice that were similarly exposed to 500 mg/kg/day for 52 or 78 weeks developed Zymbal gland carcinomas, mammary carcinomas, and lung adenomas.

Application of benzene to the skin of animals has not produced evidence of carcinogenicity, although most of the dermal studies were inadequate for cancer evaluation. Many dermal carcinogenicity studies of other chemicals used benzene as a vehicle and treated large numbers of control animals (mice) with benzene alone. None of these studies indicated that benzene induced skin tumors; however, all possible tumor sites usually were not examined.

EPA, IARC, and the Department of Health and Human Services have concluded that benzene is a human carcinogen. The Department of Health and Human Services determined that benzene is a known carcinogen based on human evidence showing a causal relationship between exposure to benzene and cancer. Two studies classified benzene in Group 1 (carcinogenic to humans) based on sufficient evidence in both humans and animals. EPA classified benzene in Category A (known human carcinogen) based on convincing evidence in humans supported by evidence from animal studies. Under EPA's most recent guidelines for carcinogen risk assessment, benzene is characterized as a known human carcinogen for all routes of exposure based on convincing human evidence as well as supporting evidence from animal studies. Based on human leukemia data, EPA derived a range of inhalation unit risk values of $2.2\text{x}10^{-6}$ – $7.8\text{x}10^{-6}$ $(\mu\text{g/m}^3)^{-1}$ for benzene. For risks ranging from $1\text{x}10^{-4}$ to $1\text{x}10^{-7}$, the corresponding air concentrations range from 13.0–45.0 $\mu\text{g/m}^3$ (4–14 ppb) to 0.013–0.045 $\mu\text{g/m}^3$ (0.004–0.014 ppb), respectively.

The consensus conclusion that benzene is a human carcinogen is based on sufficient inhalation data in humans supported by animal evidence, including the oral studies in animals. The human cancer induced by inhalation exposure to benzene is predominantly acute nonlymphocytic (myelocytic) leukemia, whereas benzene is a multiple site carcinogen in animals by both the inhalation and oral routes. Due to the lack of oral carcinogenicity data in humans, as well as the lack of a well-demonstrated and reproducible animal model for leukemia from benzene exposure, EPA extrapolated an oral slope factor from the inhalation unit risk range. The oral slope factor ranges from $1.5\text{x}10^{-2}$ to $5.5\text{x}10^{-2}$ $(\text{mg/kg/day})^{-1}$, and for cancer risks from 1x10^{-4} to 1x10^{-7}, the corresponding dose levels are 6.7x10^{-3}–1.8x10^{-3} to 6.7x10^{-6}–1.8x10^{-6} mg/kg/day, respectively.

Hematological Effects. Both human and animal studies have shown that benzene exerts toxic effects on various parts of the hematological system. All of the major types of blood cells are (erythrocytes, leukocytes, and platelets). In the less severe cases of toxicity, specific deficiencies occur in individual types of blood elements. A more severe effect occurs when there is hypoplasia of the bone marrow, or hypercellular marrow exhibiting ineffective hematopoiesis so that all types of blood cells are found in reduced numbers. This is known as pancytopenia. A biphasic response (i.e., a hyperplastic effect in addition to destruction of the bone marrow cells) has been observed. Severe damage to the bone marrow involving cellular aplasia is known as aplastic anemia and can occur with prolonged exposure to benzene. This condition can lead to leukemia.

Numerous earlier studies of benzene-exposed workers demonstrated that chronic exposure to benzene air concentrations of 10 ppm or more resulted in adverse hematological effects, which increased in severity with increasing benzene exposure levels. Animal studies support the findings in humans. Significantly reduced counts for all three blood factors (white blood cells [WBCs], red blood cells [RBCs], and platelets); and other evidence of adverse effects on blood-forming units (reduced bone marrow cellularity, bone marrow hyperplasia and hypoplasia, granulocytic hyperplasia, decreased numbers of colony-forming granulopoietic stem cells and erythroid progenitor cells, damaged erythrocytes and erythroblast-forming cells) have been observed in animals at benzene concentrations in the range of 10–300 ppm and above.

Several more recent epidemiological studies have demonstrated hematological effects (including significant reductions in WBC, RBC, and platelet counts) in workers chronically exposed to benzene levels below 10 ppm, and even as low as 1 ppm or less. Results of one of these studies served as the basis for a chronic-duration inhalation MRL for benzene. Other reports demonstrated the lack of clinical signs of hematotoxicity following long-term, low-level occupational exposure to benzene levels below approximately 0.5 ppm (8-hour time-weighted average [TWA]). These investigators utilized a defined range of clinically normal hematological values and compared the prevalence of abnormal results between benzene-exposed workers and unexposed controls. The normal range for certain hematological parameters is necessarily broad due to large interindividual differences in clinical status. Restricting the comparison of benzene-exposed and nonexposed populations to only those values considered clinically abnormal or adverse may reduce the sensitivity of a particular study to detect meaningful changes at the population level.

Only one study was found that described hematological effects in humans after oral exposure to benzene. No reports describing hematological effects in humans following direct dermal exposure to benzene were found. However, intermediate- and chronic-duration animal studies show that loss of blood elements occurs in animals exposed to benzene in drinking water or by gavage at doses as low as 8–25 mg/kg/day.

Based on information found in the literature, it is reasonable to expect that adverse hematological effects might occur in humans after inhalation, oral, or dermal exposure, since absorption of benzene through any route of exposure would increase the risk of damage to blood elements. Studies show that the hematological system is susceptible to chronic exposure at low levels, so people living in and around hazardous waste sites that may be exposed to contaminated air, drinking water, soil, or food may be at an increased risk for adverse hematological effects. Deficiencies in various types of blood cells lead to other disorders, such as hemorrhagic conditions from a lack of platelets, susceptibility to infection from the lack of leukocytes, and increased cardiac output from the lack of erythrocytes.

Immunological and Lymphoreticular Effects. Benzene has been shown to have adverse immunological effects in humans following inhalation exposure for intermediate and chronic durations. Adverse immunological effects in animals occur following both inhalation and oral exposure for acute, intermediate, and chronic durations. The effects include damage to both humoral (antibody) and cellular (leukocyte) responses. Human studies of intermediate and chronic duration have shown that benzene causes decreases in the levels of circulating leukocytes in workers at low levels (30 ppm) of exposure and decreases in levels of circulating antibodies in workers exposed to benzene at 3–7 ppm. Other studies have shown decreases in human lymphocytes and other blood elements after exposure; these effects have been seen at occupational exposure levels as low as 1 ppm or less. Animal data support these findings. Both humans and rats have shown increases in leukocyte alkaline phosphatase activity. No studies regarding effects from oral or dermal exposure in humans were located. However, exposure to benzene through ingestion or dermal contact could cause immunological effects similar to those seen after inhalation exposure in humans and inhalation and oral exposure in animals.

Animal studies have also shown that benzene decreases circulating leukocytes and decreases the ability of lymphoid tissue to produce the mature lymphocytes necessary to form antibodies. This has been demonstrated in animals exposed for acute, intermediate, or chronic periods via the inhalation route. This decrease in lymphocyte numbers is reflected in impaired cell-mediated immune functions in mice following intermediate inhalation exposure to 100 ppm of benzene. The impaired cellular immunity after benzene treatment was observed both *in vivo* and *in vitro*. Mice exposed to 100 ppm for a total of 100 days were challenged with 10^4 polyoma virus-induced tumor cells (PYB6). Nine of 10 mice had reduced tumor resistance resulting in the development of lethal tumors. In the same study, lymphocytes were obtained from spleens of benzene-treated mice and tested for their immune capacity *in vitro*. The results showed that two other immune functions, alloantigen response (capacity to respond to foreign antigens) and cytotoxicity, were also impaired. Similar effects were noted in mice exposed to benzene via the oral route for intermediate time periods, and in rats and mice exposed for chronic time periods. A decrease in spleen weight was observed in mice after acute-duration exposure to benzene at 25 ppm, the same dose levels at which a decrease in circulating leukocytes was observed. Similar effects on spleen weight and circulating leukocytes were observed in mice exposed to 12 ppm benzene 2 hours/day for 30 days. The acute-duration inhalation MRL was based on a study showing decreased mitogen-induced blastogenesis of B-lymphocytes following exposure of mice to benzene vapors at a concentration of 10 ppm, 6 hours/day for 6 days. The intermediate-duration inhalation MRL was based on a study showing delayed splenic lymphocyte reaction to foreign antigens evaluated by *in vitro* mixed lymphocyte culture following exposure of mice to benzene vapors at a concentration of 10 ppm, 6 hours/day, 5 days/week for a total of 20 exposures.

Based on information found in the literature, it is reasonable to expect that adverse immunological effects might occur in humans after inhalation, oral, or dermal exposure, since absorption of benzene through any route of exposure would increase the risk of damage to the immunological system. Studies show that the immunological system is susceptible to chronic exposure at low levels, so people living in and around hazardous waste sites who may be exposed to contaminated air, drinking water, soil, or food may be at an increased risk for adverse immunological effects.

Neurological Effects. In humans, results of occupational studies indicate that there is a cause-andeffect relationship between acute inhalation of very high concentrations of benzene and symptoms indicative of central nervous system toxicity. These symptoms, observed following both acute nonlethal and lethal exposures, include drowsiness, dizziness, headache, vertigo, tremor, delirium, and loss of consciousness. These symptoms are reversible when symptomatic workers are transferred from the problem area. Comparable toxicity in humans has been reported following ingestion of benzene at doses of 125 mg/kg and above. Occupational exposure to benzene has also been reported to produce neurological abnormalities in humans. Electromyographical and motor conduction velocity examinations were conducted on six patients with aplastic anemia, all of whom worked in environments where adhesives containing benzene were used (in one case, air concentrations bracketed around 210 ppm).

Abnormalities in motor conduction velocity were noted in four of the six pancytopenic individuals and were thought to result from a direct effect of benzene on the peripheral nerves and/or spinal cord.

In its acute stages, benzene toxicity appears to be due primarily to the direct effects of benzene on the central nervous system, whereas the peripheral nervous system appears to be the target following chronic low-level exposures. In addition, because benzene may induce an increase in brain catecholamines, it may also have a secondary effect on the immune system via the hypothalamus-pituitary-adrenal axis. Increased metabolism of catecholamines can result in increased adrenal corticosteroid levels, which are immunosuppressive.

Animal studies provide additional support that benzene affects the nervous system following acute inhalation and oral exposures, albeit at extremely high acute exposure levels. Effects reported include narcosis, nervous system depression, tremors, and convulsions. Acute and intermediate inhalation exposures have also been reported to produce adverse neurological effects in animals including a reduction in hind-limb grip strength and evoked electrical activity in the brain, and behavioral disturbances. Effects of benzene on learning were investigated in male hooded rats of the Sprague-Dawley strain given 550 mg/kg of benzene in corn oil or corn oil without benzene, intraperitoneally, on days 9, 11, and 13 postpartum. The rats exposed to benzene exhibited a significantly impaired learning ability when tested on problems of the closed-field, maze-learning task. This sign of neurotoxicity was not observed in control animals. In another study, 47-day-old juvenile cotton rats were maintained on one of two isocaloric diets containing either 4 or 16% crude protein for a 26-day experimental period. Animals were treated intraperitoneally with either 0 (corn oil), 100, 500, or 1,000 mg/kg benzene in corn oil for 3 consecutive days. The first dose was administered on days 15– 17 of the experimental period. Animals were terminated on day 27. During the experimental period, severe loss of coordination was observed in some rats on the low protein diet immediately after exposure to benzene, but this subsided.

Intermediate oral exposures resulted in changes in the levels of monoamine transmitters in the brain without treatment-related behavioral changes. Mice exposed to 3 ppm for 2 hours/day for 30 days exhibited increased levels of acetylcholinesterase in the brain. *In vitro* studies suggest that benzene may have a direct effect on brain cells. Primary astrocyte cultures prepared from neonatal rat cerebella were treated with 3, 6, or 9 mmol/L benzene for 1 hour. ATPase and Mg^{2+}-ATPase activity were inhibited in a dose-related manner, and were detected at 78–92% of control values for ATPase, and 60–74% of control values for Mg^{2+}-ATPase.

These data suggest that humans exposed to benzene in the occupational setting for acute, intermediate, or chronic durations via the inhalation and oral routes are at risk of developing neurological effects. However, benzene levels in ambient air, drinking water, and at hazardous waste sites are lower and not likely to be of concern.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for benzene. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

- An MRL of 0.009 ppm has been derived for acute-duration inhalation exposure (14 days or less) to benzene.

The acute-duration inhalation MRL of 0.009 ppm was derived from a lowest-observed-adverse-effect level (LOAEL) value of 10.2 ppm for reduced lymphocyte proliferation following mitogen stimulation in mice (Rozen et al. 1984). The concentration was adjusted for intermittent exposure by multiplying the LOAEL (10.2 ppm) by 6 hours/24 hours to correct for less than a full day of exposure. The resulting adjusted LOAEL, 2.55 ppm, was then converted to a human equivalent concentration (HEC) according to

EPA (1994b) methodology for calculating a HEC for extrarespiratory effects of a category 3 gas (such as benzene) as follows:

$LOAEL_{HEC} = LOAEL_{ADJ} \times ([H_{b/g}]_A/[H_{b/g}]_H)$
where:

$LOAEL_{HEC}$ = the LOAEL dosimetrically adjusted to a human equivalent concentration

$LOAEL_{ADJ}$ = the LOAEL adjusted from intermittent to continuous exposure

$[H_{b/g}]_A/[H_{b/g}]_H$ = the ratio of the blood:gas partition coefficient of the chemical for the laboratory animal species to the human value

If the animal blood:gas partition coefficient is greater than the human blood:gas partition coefficient, a default value of 1 is used for the ratio. According to Wiester et al. (2002), blood:gas partition coefficients for benzene in mice and humans are 17.44 and 8.12, respectively. Therefore, the default value of 1 is applied, in which case, the $LOAEL_{[HEC]}$ is equivalent to the $LOAEL_{[ADJ]}$.

Therefore:

$LOAEL_{HEC} = LOAEL_{ADJ} = 2.55$ ppm

The resulting $LOAEL_{(HEC)}$ of 2.55 ppm was then divided by an uncertainty factor of 300 (10 for the use of LOAEL, 3 for extrapolation from animals to humans using dosimetric conversion, and 10 for human variability) to yield the MRL value of 0.009 ppm (see Appendix A). An increased number of micronucleated polychromatic erythrocytes (MN-PCEs), decreased numbers of granulopoietic stem cells (Toft et al. 1982), lymphopenia (Cronkite et al. 1985), lymphocyte depression, and increased susceptibility to bacterial infection (Rosenthal and Snyder 1985) are among the adverse hematological and immunological effects observed in several other acute-duration inhalation studies. The study by Rozen et al. (1984) shows benzene immunotoxicity (reduced mitogen-induced lymphocyte proliferation) at a slightly lower exposure level than these other studies. C57BL/6J mice were exposed to 0, 10.2, 31, 100, and 301 ppm benzene for 6 hours/day for 6 days. Control mice were exposed to filtered, conditioned air only. Lymphocyte counts were depressed at all exposure levels; erythrocyte counts were elevated at

10.2 ppm, equal to controls at 31 ppm, and depressed at 100 and 301 ppm. Femoral B-lymphocyte and splenic B-lymphocyte numbers were reduced at 100 ppm. Levels of circulating lymphocytes and mitogen-induced blastogenesis of femoral B-lymphocytes were depressed after exposure to 10.2 ppm benzene for 6 days. Mitogen-induced blastogeneses of splenic T-lymphocytes were depressed after exposure to 31 ppm of benzene for 6 days. In another study, mice exhibited a 50% decrease in the population of colony-forming granulopoietic stem cells (CFU-E) after exposure to 10 ppm benzene for 6 hours/day for 5 days (Dempster and Snyder 1991). In a study by Wells and Nerland (1991), groups of 4–5 male Swiss-Webster mice were exposed to 3, 25, 55, 105, 199, 303, 527, 1,150, or 2,290 ppm benzene for 6 hours/day for 5 days. The number of leukocytes in peripheral blood and spleen weights were significantly decreased compared with untreated controls at all concentrations >25 ppm. Therefore, 3 ppm was the no-observed-adverse-effect level (NOAEL) and 25 ppm was the LOAEL for these effects. These data support the choice of Rozen et al. (1984) as the study from which to derive the MRL.

- An MRL of 0.006 ppm has been derived for intermediate-duration inhalation exposure (15– 364 days) to benzene.

The intermediate-duration inhalation MRL of 0.006 ppm was derived from a LOAEL value of 10 ppm for significantly delayed splenic lymphocyte reaction to foreign antigens evaluated in *in vitro* mixed lymphocyte reaction following the exposure of male C57Bl/6 mice to benzene vapors 6 hours/day, 5 days/week for 20 exposure days (Rosenthal and Snyder 1987). The concentration was adjusted for intermittent exposure by multiplying the LOAEL (10 ppm) by 6 hours/24 hours to correct for less than a full day of exposure and by 5 days/7days to correct for less than a full week of exposure. The resulting adjusted LOAEL, 1.8 ppm, was then converted to a HEC according to EPA (1994b) methodology for calculating a HEC for extrarespiratory effects of a category 3 gas (such as benzene) as follows:

$$\text{LOAEL}_{\text{HEC}} = \text{LOAEL}_{\text{ADJ}} \text{ x } ([\text{H}_{\text{b/g}}]_{\text{A}}/[\text{H}_{\text{b/g}}]_{\text{H}})$$

where:

$\text{LOAEL}_{\text{HEC}}$ = the LOAEL dosimetrically adjusted to a human equivalent concentration

$\text{LOAEL}_{\text{ADJ}}$ = the LOAEL adjusted from intermittent to continuous exposure

$[H_{b/g}]_A/[H_{b/g}]_H$ = the ratio of the blood:gas partition coefficient of the chemical for the laboratory animal species to the human value

If the animal blood:gas partition coefficient is greater than the human blood:gas partition coefficient, a default value of 1 is used for the ratio. According to Wiester et al. (2002), blood:gas partition coefficients for benzene in mice and humans are 17.44 and 8.12, respectively. Therefore, the default value of 1 is applied, in which case, the $LOAEL_{[HEC]}$ is equivalent to the $LOAEL_{[ADJ]}$.
Therefore:

$LOAEL_{HEC} = LOAEL_{ADJ} = 1.8$ ppm

The resulting $LOAEL_{(HEC)}$ of 1.8 ppm was then divided by an uncertainty factor of 300 (10 for the use of LOAEL, 3 for extrapolation from animals to humans using dosimetric conversion, and 10 for human variability) to yield the MRL value of 0.006 ppm (see Appendix A).

Results of several studies support the choice of Rosenthal and Snyder (1987) as the basis for the intermediate-duration inhalation MRL for benzene (Baarson et al. 1984; Green et al. 1981a, 1981b), although the supporting studies employed a single exposure level, which precluded consideration as critical studies for MRL derivation. Exposure of C57BL mice to 10 ppm benzene for 6 hours/day, 5 days/week caused significant depressions in numbers of lymphocytes (ca. 30% lower than controls) as early as exposure day 32; this effect was also noted at the other scheduled periods of testing (exposure days 66 and 178) (Baarson et al. 1984). Splenic RBCs were significantly reduced (ca. 15% lower than controls) at exposure days 66 and 178. The failure of the erythrons of benzene-exposed mice to support normal red cell mass was illustrated by the significant reduction in peripheral red cell numbers in these animals at 66 and 178 days of benzene exposure. Green et al. (1981a, 1981b) exposed male CD-1 mice to benzene vapors at concentrations of 0 or 9.6 ppm for 6 hours/day, 5 days/week for 50 days and assessed the effects of exposure on cellularity in the spleen, bone marrow, and peripheral blood. Exposure-related effects included a 90% increase in numbers of multipotential hematopoietic stem cells (CFU-S) (Green et al. 1981a), approximately 25% increase in spleen weight and total splenic nucleated cellularity (Green et al. 1981b), and 80% increase in nucleated RBCs (Green et al. 1981b).

One intermediate-duration inhalation study reported increased rapid response to an electrical shock in mice at 0.78 ppm (Li et al. 1992). However, this study was not selected as the critical study for deriving an intermediate-duration inhalation MRL for benzene due to apparent discrepancies between reported and actual benzene exposure levels. Other animal studies identified neurological effects only at much higher exposure levels (Carpenter et al. 1944; Dempster et al. 1984; Evans et al. 1981; Frantik et al. 1994; Green et al. 1978).

- An MRL of 0.003 ppm has been derived for chronic-duration inhalation exposure (365 days or more) to benzene.

This MRL is based on statistically significantly decreased counts of B-lymphocytes in workers of shoe manufacturing industries in Tianjin, China (Lan et al. 2004a, 2004b), using a benchmark dose (BMD) analysis. The 250 benzene-exposed workers had been employed for an average of 6.1±2.9 years. Controls consisted of 140 age- and gender-matched workers in clothing manufacturing facilities in which measurable benzene concentrations were not found (detection limit 0.04 ppm). Benzene exposure was monitored by individual organic vapor monitors (full shift) 5 or more times during 16 months prior to phlebotomy. Benzene-exposed workers were categorized into four groups (140 controls, 109 at <1 ppm, 110 at 1–<10 ppm, and 31 at ≥10 ppm) according to mean benzene exposure levels measured during 1 month prior to phlebotomy. Complete blood count (CBC) and differential were analyzed mechanically. Coefficients of variation for all cell counts were <10%.

Mean 1-month benzene exposure levels in the four groups (controls, <1 ppm, 1–<10 ppm, and ≥10 ppm) were <0.04, 0.57±0.24, 2.85±2.11, and 28.73±20.74 ppm, respectively. Hematological values were adjusted to account for potential confounding factors (i.e., age, gender, cigarette smoking, alcohol consumption, recent infection, and body mass index). All types of WBCs and platelets were significantly decreased in the lowest exposure group (<1 ppm), ranging in magnitude from approximately 8 to 15% lower than controls. Although similar statistical analyses for the mid- and high-exposure groups were not included in the study report, decreases in all types of WBCs and platelets were noted at these exposure levels as well; the decreases in the highest exposure group ranged in magnitude from 15 to 36%. Lymphocyte subset analysis revealed significantly decreased CD4+-T cells, CD4+/CD8+ ratio, and B cells. Hemoglobin concentrations were significantly decreased only within the highest (≥10 ppm) exposure group. Tests for a linear trend using benzene air level as a continuous variable were significant for platelets and all WBC measures except monocytes and CD8+-T cells. Upon restricting the linear trend analyses to workers exposed to <10 ppm benzene, excluding controls, inverse associations remained for total WBCs, granulocytes, lymphocytes, B cells, and platelets. In order to evaluate the effect of past benzene exposures on the hematological effects observed in this study, the authors compared findings for a group of workers who had been exposed to <1 ppm benzene over the previous year (n=60) and a subset who also had <40 ppm-years lifetime cumulative benzene exposure (n=50). The authors stated that the same cell types were significantly reduced in these groups, but did not provide further information of the magnitude (i.e., percent change) of the hematological effects observed. These data suggest that the 1-month benzene exposure results could be used as an indicator of longer-term, low-level benzene hematotoxicity. To demonstrate that the observed effects were attributable to benzene, significantly decreased levels of WBCs, granulocytes, lymphocytes, and B cells were noted in a subgroup of the <1-ppm group for which exposure to other solvents was negligible.

As shown in Table A-1 of Appendix A, exposure-response relationships were noted for several blood factors. Benzene-induced decreased B cell count was selected as the critical effect for BMD modeling because it represented the highest magnitude of effect (i.e., B cell count in the highest exposure group was approximately 36% lower than that of controls). A BMD modeling approach was selected to identify the point of departure because the critical study (Lan et al. 2004a, 2004b) identified a LOAEL in the absence of a NOAEL.

As discussed in detail in Appendix A, the BMD analysis selected a point of departure ($BMCL_{0.25sd}$) of 0.1 ppm, which was adjusted from the 8-hour TWA to a continuous exposure concentration ($BMCL_{0.25sdADJ}$) using the default occupational minute volume (EPA 1994b). The resulting $BMCL_{0.25sdADJ}$ of 0.03 ppm was divided by an uncertainty factor of 10 (for human variability) to yield the chronic-duration inhalation MRL value of 0.003 ppm.

Several recent epidemiological studies provide supporting information to the Lan et al. (2004a, 2004b) findings of hematotoxicity in workers chronically exposed to relatively low levels of benzene (Qu et al. 2002, 2003a, 2003b; Rothman et al. 1996a, 1996b; Ward et al. 1996). Qu et al. (2002, 2003a, 2003b) compared hematologic values among 105 healthy workers (51 men, 54 women) in industries with a history of benzene usage (Tianjin, China) and 26 age-and gender-matched workers in industries that did not use benzene. A LOAEL of 2.26 ppm was identified for significantly reduced total WBCs, neutrophils, and RBCs; there was also an indication of benzene-induced changes in some hematological values at exposure levels lower than the current industry 8-hour TWA of 1 ppm. Rothman et al. (1996a, 1996b) identified an 8-hour TWA LOAEL of 7.6 ppm for a group of 11 benzene-exposed workers in a cross-sectional study of 44 healthy workers in Chinese (Shanghai) industries with a history of benzene usage and age- and gender-matched workers in industries that did not use benzene. In a nested case-control study of a cohort of workers in the Pliofilm production departments of a rubber products manufacturer in Ohio (Ward et al. 1996), a strong exposure-response relationship was correlated with low WBC count. A weak positive exposure-response relationship was observed for RBCs, which was significant for cumulative exposure up until the blood test date. The study authors noted that there was no evidence for a threshold for hematologic effects and suggested that exposure to benzene levels <5 ppm may result in hematologic suppression.

Appendix C

ASTDR Toxicological Profile for Toluene

Chapter 2, subsection 2.5 Relevance to Public Health

2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

Adverse effects on the nervous system are the critical effects of concern from acute, intermediate, or chronic exposure to toluene. Acute exposure is associated with reversible neurological symptoms progressing from fatigue, headaches, and decreased manual dexterity to narcosis with increasing exposure levels. Reversible neurological impairment from acute exposure likely involves the direct interaction of toluene with nervous system membranes. Degenerative changes in white matter regions of the brain have been correlated with the severity of persistent neurological impairment in individuals who abused solvents and have repeatedly inhaled toluene at high exposure levels (4,000–12,000 ppm). Results from studies of groups of occupationally exposed workers suggest that chronic exposure to toluene at lower exposure levels (from about 50 to 200 ppm) can produce subtle changes in neurological functions including cognitive and neuromuscular performance, hearing, and color discrimination. Supporting data come from studies of toluene-exposed animals showing changes in behavior, hearing loss, and subtle changes in brain structure, electrophysiology, and levels of neurotransmitters. Case reports of birth defects in children of mothers who abused toluene during pregnancy suggest that exposure to high levels of toluene may be toxic to the developing fetus. However, results from animal studies indicate that toluene is not a teratogenic agent, but can retard fetal growth and skeletal development and adversely influence behavior of offspring at exposure levels that overwhelm maternal mechanisms protecting the developing fetus from exposure. Other adverse health effects, including cancer or effects on reproductive performance, do not appear to be of concern for persons who may experience low exposures to toluene by living or working near hazardous waste sites containing toluene.

Issues relevant to children are explicitly discussed in Section 2.7, Children's Susceptibility and Section 5.6, Exposures of Children.

Minimal Risk Levels for Toluene.

Inhalation MRLs.

- An MRL of 1 ppm (3.8 mg/m^3) has been derived for acute-duration (14 days or less) inhalation exposure to toluene.

This MRL is based on a study by Andersen et al. (1983) in which the effects of toluene on 16 healthy young subjects with no previous regular exposure to organic solvents were investigated (see Appendix A). Groups of 4 subjects were in a chamber for 6 hours a day on 4 consecutive days. The concentration of toluene was 0, 10, 40, or 100 ppm, with the subjects exposed to a different concentration each day. Physiological measurements were performed, including nasal mucociliary flow, and subjective measurements of discomfort. Eight different performance assessment tests were carried out. There was a statistically significant increase (P<0.05%) in the occurrence of headaches, dizziness, and feelings of intoxication during the 100 ppm exposure, but not during exposure to the other concentrations. No statistically significant effects of toluene occurred in the eight performance tests. For 3 of the tests, there was borderline significance (P<0.10%): the subjects felt that the tests were more difficult and strenuous during the 100 ppm exposure. No adverse effects were reported at the 10 and 40 ppm levels. The NOAEL of 40 ppm was adjusted to continuous exposure basis (40 ppmx5 days/daysx8 hour/24 hour=9.5 ppm) and divided by an uncertainty factor of 10 (to account for human variability) to derive the MRL of 1 ppm.

- No MRL has been derived for intermediate-duration (15–364 days) inhalation exposure to toluene.

No data were considered suitable for use in deriving an intermediate-duration MRL for inhalation exposures. ATSDR believes that the chronic inhalation MRL would also be protective for intermediate-duration exposures.

- An MRL of 0.08 ppm (0.3 mg/m^3) was derived for chronic-duration (365 days or more) inhalation exposure to toluene.

The chronic inhalation MRL is based on a LOAEL of 35 ppm toluene for color vision impairment in a group of toluene-exposed shoemakers studied by Zavalic et al. (1998a) and an uncertainty factor of 100 (10 for the use of a LOAEL and 10 to account for human variability). The study examined color vision abilities in three groups of workers: (1) 46 shoemakers exposed for an average of 16 years to a median toluene concentration of 32 ppm; (2) 37 rotogravure printing workers exposed for an average of 18 years to a median toluene concentration of 132 ppm; and (3) 90 control workers without any known exposure to solvents or neurotoxic agents. Average scores in a color confusion index (based on results of color vision tests and adjusted for age and alcohol intake) were significantly increased in the toluene-exposed shoemakers and printers compared with scores for control workers. The chronic LOAEL of 32 ppm is supported by observations of other subtle neurological effects in other groups of toluene exposed workers including altered visual-evoked brainstem potentials in printing press workers exposed to 50 ppm for 30 years (Vrca et al. 1995, 1996, 1997a, 1997b), altered auditory-evoked brainstem potentials in printers exposed to 97 ppm for 12–14 years (Abbate et al. 1993), hearing loss in printers exposed to 0.04–245 ppm toluene (Morata et al. 1997), changes in electro cardiographic R-R intervals in printers exposed to 83 ppm for 1–36 years (Murata et al. 1993), performance deficits in neurobehavioral tests in electronics workers exposed to 88–90 ppm (Boey et al. 1997; Foo et al. 1990), and increased incidence of self-reported neurasthenic symptoms in printers exposed to an average concentration of about 140 ppm over a 29-year period (Orbaek and Nise 1989).

Most of the data on health effects in humans exposed to toluene come from occupational studies or medical reports of solvent abusers. In both situations, concurrent exposure to other chemicals can limit the usefulness of the data for development of guidelines or standards. In addition, there are other confounding variables, especially in the occupational setting, such as alcohol consumption patterns, employment history, diet, use of medications, noise, and fluctuations in atmospheric toluene levels during different portions of the day, all of which complicate evaluation of dose-response patterns. These limitations were considered in selecting the studies for derivation of the MRLs.