Benzene

CAS Registry Number: 71-43-2

Prepared by

Joseph T. Haney, Jr., M.S.

Toxicology Section

Chief Engineer's Office

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

Revision History

Original Development Support Document (DSD) posted as final on October 15, 2007.

Revised DSD September 14, 2015:

(1) the 24-hour reference value (ReV) was added to the Summary Tables, and the derivation of the 24-hour ReV was added as Appendix D. Refer to TCEQ 2015a for guidelines for deriving 24-hour ReVs

(2) the odor-based value was withdrawn because benzene does not have a pungent, disagreeable odor (TCEQ 2015b).

TABLE OF CONTENTS

Benzene
Page iv

LIST OF TABLES

LIST OF FIGURES

Chapter 1 Summary Tables

Table 1 provides a summary of health- and welfare-based values based on an acute and chronic evaluation of benzene. Table 2 provides summary information on benzene's physical/chemical data.

Table 1 Health- and Welfare-Based Values
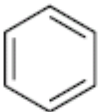
Short-Term Values	Concentration	Notes
^{acute}ESL [1 h] (HQ = 0.3)	170 µg/m^3 (54 ppb) **Short-Term ESL for Air Permit Reviews**	**Critical Effect(s):** Depressed peripheral lymphocytes and depressed mitogen-induced blastogenesis of femoral B-lymphocytes in C57BL/6J mice (male)
acute ReV [1 h] (HQ = 1.0)	580 µg/m^3 (180 ppb) [a]	Same as above
acute ReV [24 h] [c] (HQ = 1.0)	320 µg/m^3 (100 ppb) [a, c]	Same as above
^{acute}ESL$_{odor}$	---	aromatic; paint-thinner-like; sweet, solventy
^{acute}ESL$_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
^{chronic}ESL$_{nonlinear(nc)}$ (HQ = 0.3)	84 µg/m^3 (26 ppb)	**Critical Effect(s):** Decreased absolute lymphocyte count in occupationally exposed workers
chronic ReV (HQ = 1.0)	280 µg/m^3 (86 ppb) [a]	Same as above
^{chronic}ESL$_{linear(c)}$	4.5 µg/m^3 (1.4 ppb) [a, b] **Long-Term ESL for Air Permit Reviews**	Cancer Endpoint: Acute myelogenous and acute monocytic leukemia in occupationally exposed workers
^{chronic}ESL$_{veg}$	---	No data found

[a] Values that may be used for evaluation of ambient air monitoring data.

[b] unit risk factor (URF) = 2.2E-06 per µg/m^3 or 7.1E-06 per ppb.

[c] Appendix D

Table 2 Chemical and Physical Data of Benzene

Parameter	Value	Reference
Molecular Formula	C_6H_6	ATSDR 2005
Chemical Structure		ATSDR 2005
Molecular Weight	78.11 (g/mole)	TRRP 2006
Physical State	liquid	ATSDR 2005
Color	colorless	ATSDR 2005
Odor	aromatic [1];paint-thinner-like [2]; sweet, solvently [3]	[1] ATSDR 2005, [2] NRC 1995, [3] Ruth 1986
CAS Registry Number	71-43-2	ATSDR 2005
Synonyms/Trade Names	annulene, benzeen (Dutch), benzen (Polish), benzol, benzole, benzolo (Italian), coal naphtha, fenzen (Czech), cyclohexatriene, phene, phenyl hydride, pyrobenzol, pyrobenzole, Polystream [1]; benzol coal naphtha, benzine, motor benzol, mineral naphtha [2]	[1] ATSDR 2005 [2] WHO 1993
Solubility in water	1,770 mg/L	TRRP 2006
Low Kow	1.99	TRRP 2006
Vapor Pressure	95 mm Hg at 25°C	TRRP 2006
Vapor Density (air = 1)	2.7 g/L at 0° C and 1 atm	NRC 1995
Density (water = 1)	0.8765 g/cm^3 at 20° C	ATSDR 1995
Melting Point	5.5 ^{o}C	ATSDR 2005
Boiling Point	80.1 ^{o}C	ATSDR 2005
Conversion Factors	1 μg/m^3 = 0.31 ppb @ 20°C 1 ppb = 3.24 μg/m^3	ATSDR 2005

Chapter 2 Major Sources or Uses

The Agency for Toxic Substances and Disease Registry (ATSDR 2005) provides the following general information on benzene sources and uses: "Benzene was first discovered and isolated from coal tar in the 1800s. Today, benzene is made mostly from petroleum. Because of its wide use, benzene ranks in the top 20 in production volume for chemicals produced in the United States. Various industries use benzene to make other chemicals, such as styrene (for Styrofoam® and other plastics), cumene (for various resins), and cyclohexane (for nylon and synthetic fibers). Benzene is also used in the manufacturing of some types of rubbers, lubricants, dyes, detergents, drugs, and pesticides. Natural sources of benzene, which include gaseous emissions from volcanoes and forest fires, also contribute to the presence of benzene in the environment. Benzene is also present in crude oil and gasoline and cigarette smoke." The United States Environmental Protection Agency's (USEPA) 2001 National-Scale Air Toxics Assessment (NATA) of emissions from the 1996 National Toxics Inventory (NTI) indicates that statewide, benzene emissions from mobile sources (onroad and nonroad) accounted for approximately 65% of the NTI benzene emissions in Texas, with major facility sources and area/other sources (e.g., smaller facilities) comprising the remainder (USEPA 2001). See ATSDR (2005) and USEPA (2001) for additional source and use information.

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

3.1.1 Physical/Chemical Properties and Key Studies

3.1.1.1 Physical/Chemical Properties
Benzene is a clear, colorless volatile liquid with a moderately high vapor pressure. For inhalation exposure, it is treated as a vapor. The main chemical and physical properties of benzene are summarized in Table 2. At low concentrations, the health effects benzene produces are mainly remote effects and it is classified as a Category 3 Gas (USEPA 1994).

3.1.1.2 Essential Data and Key Studies
In both human and animal noncarcinogenic studies, data suggest the most sensitive endpoint for short-term (and long-term) exposure to benzene is hematotoxicity (e.g., bone marrow depression: leukopenia, pancytopenia, granulocytopenia, lymphocytopenia, thrombocytopenia, aplastic anemia). Bone marrow depression occurs in two stages – hyperplasia (increased synthesis of blood cells), followed by hypoplasia (decreased synthesis) (ATSDR 2005).

3.1.1.2.1 Human Studies
Human inhalation studies on the short-term (i.e., acute, subacute) hematotoxic effects of benzene are limited. Per ATSDR (2005), Midzenski et al. (1992) reported leukopenia, anemia,

thrombocytopenia, and increased mean corpuscular volume (MCV) in 15 male workers following subacute occupational exposure (mean of 5 days) at a Lowest-Observed-Adverse-Effect-Level (LOAEL) of 60 ppm. Dizziness and nausea were also reported in workers with more than 2 days of exposure. However, review of the study indicates that the reported sampling results (after exposure had ended) were "greater than 60 ppm" to 653 ppm (and could have been even higher due to sampling breakthrough), which does not allow for identification of a reliable LOAEL. Additionally, the study did not identify a No-Observed-Adverse-Effect-Level (NOAEL). The inability to identify a reliable LOAEL (or NOAEL) for Midzenski et al. (1992) precludes its use in the calculation of an acute Reference Value (acute ReV) and acute Effects Screening Level ([acute]ESL).

3.1.1.2.2 Animal Studies

Significantly more animal data than human data are available for identifying a NOAEL or LOAEL for use as a point of departure (POD) for deriving an acute ReV and [acute]ESL. Mice appear to be more sensitive to hematotoxicity from benzene than rats or rabbits (IARC 1982). While no acute (i.e., ≤ 1 day of exposure) mouse studies were identified for potential use in deriving an acute ReV and [acute]ESL, the weight-of-evidence from subacute (i.e., greater than 1 day up to a month of exposure) mouse studies suggests a NOAEL of approximately 10 ppm. See Table 3 below for information regarding subacute exposure mouse studies with a NOAEL of approximately 10 ppm (ATSDR 2005).

While the weight-of-evidence suggests a NOAEL of 10 ppm for the hematotoxic effects of benzene in subacute mouse studies, three subacute mouse studies identified approximately 10 ppm as the LOAEL. Rozen et al. (1984) reported depressed blood lymphocytes and depressed mitogen-induced blastogenesis of femoral B-lymphocytes in male C57BL/6J mice at a LOAEL of 10.2 ppm. Dempster and Snyder (1991) showed decreased erythroid progenitor cell colony forming units in male DBA/2J mice at a LOAEL of 10.3 ppm. Corti and Snyder (1996) showed decreased erythroid progenitor cell colony forming units in male Swiss Webster mice at a LOAEL of 10.2 ppm. No NOAELs were identified in these studies (Table 3).

Rozen et al. (1984), supported by Dempster and Snyder (1991) and Corti and Snyder (1996), was selected as the key study for deriving an acute ReV and [acute]ESL for the following reasons: (1) no reliable LOAEL (or NOAEL) can be identified for the Midzenski et al. (1992) study; (2) the acute animal database is significantly more robust than the human; (3) the LOAEL identified (~10 ppm) for this study (and the supporting two studies) is the lowest among these animal studies; (4) while this study (and the two supporting studies) shows hematotoxicity at a LOAEL lower than other studies, the LOAEL is supported by the weight-of-evidence NOAEL (10 ppm) for short-term mouse studies; and (5) existing studies indicate that benzene metabolism occurs along similar pathways in both humans and laboratory animals. Rozen et al. (1984) was also selected by ATSDR (2005) to derive the draft acute inhalation minimal risk level (MRL) and previous final acute MRL (ATSDR 1997).

Table 3 Summary of Subacute Mouse Inhalation Studies

Study	Mouse Strain	Exposure Duration	NOAEL (ppm)	LOAEL (ppm)	Response at LOAEL
Green et al. 1981a,b	CD-1 (male)	6 hs per day for 5 days	9.9	103	granulocytopenia, lymphocytopenia, and decreased marrow cellularity and polymorphonucleucytes
Dempster and Snyder (1991) [2]	DBA/2J (male)	6 hs per day for 5 days	---	10.3	decreased erythroid progenitor cell colony forming units
Rozen et al. (1984) [1]	C57BL/6J (male)	6 hs per day for 6 days	---	10.2	depressed blood lymphocytes, depressed mitogen-induced blastogenesis of femoral B-lymphocytes
Corti and Snyder (1996) [2, 3]	Swiss Webster (male)	6 hs per day for gestational days (GD) 6-15	---	10.2	decreased erythroid progenitor cell colony forming units
Rosenthal and Snyder 1985	C57BL/6 (male)	6 hs per day for 1-12 days	10	30	T- and B-lymphocyte depression and increased *Listeria monocytogenes* infection bacterial counts
Cronkite et al. 1985	C57B1/6BNL	6 hs per day, 5 days per week, for 2 weeks	10	25	lymphopenia
Toft et al. 1982	NMRI (male)	8 hs per day, 5 days per week, for 2 weeks	10.5	21	increased micronucleated polychromatic erythrocytes and decreased granulopoietic stem cells
Cronkite 1986	CBA/Ca and C57B1/6BNL	6 hs per day, 5 days per week, for 2 weeks	10	25	lymphopenia
Farris et al. 1997a,b	B6C3F1/CrlBR (male)	6 hs per day, 5 days per week, for 1-8 weeks	10	100	lymphopenia and other blood effects

[1] Key study

[2] Supporting study

[3] Effects were reported in male mice exposed as adults; no increased sensitivity shown in the developing organism.

3.1.2 Mode-of-Action (MOA) Analysis

Benzene-induced hematotoxicity is a complex process, which involves initial metabolism of benzene by cytochrome P-450 2E1 (CYP2E1) in the liver and may also involve metabolism in the bone marrow. Various metabolites have been proposed as possible contributors to benzene's toxicity (e.g., trans,trans-muconic acid, benzene epoxide, phenol metabolic pathway products catechol, hydroquinone, and p-benzoquinone). While the mechanism(s) of toxicity are poorly understood, proposed mechanisms involve protein and DNA adducts, genotoxicity, oxidative stress, and inhibition of cytokine formation. Peripheral blood abnormalities induced by benzene reflect a disruption at various levels of hematopoiesis in the bone marrow (e.g., bone marrow cellularity, stem cell compartments, granulocytic and erythropoietic progenitor cells, bone marrow macrophage) (USEPA 2002).

The following information on the metabolism of benzene was derived from ATSDR (2005): "Although the metabolism of benzene has been studied extensively, the steps leading to benzene toxicity are not yet fully understood. Cytochrome P-450 2E1 (CYP2E1) is important in benzene metabolism, and it is generally understood that both cancer and noncancer effects are caused by one or more reactive metabolites of benzene. Potential candidates include benzene oxide, phenolic metabolites (phenol, catechol, hydroquinone, 1,2,4-benzenetriol, and 1,2- and 1,4-benzoquinone), and *trans*,*trans*-muconaldehyde. Available data indicate that metabolites produced in the liver are carried to the bone marrow, the site of characteristic benzene toxicity. Benzene metabolism may occur, at least in part, in the bone marrow. Following inhalation, unmetabolized benzene is excreted primarily through exhalation, while urinary excretion is the major route for benzene metabolites." See ATSDR (2005) or Snyder and Hedli (1996) for additional information. Figure 1 below (which is Figure 3-3 from ATSDR 2005) shows metabolic pathways for benzene.
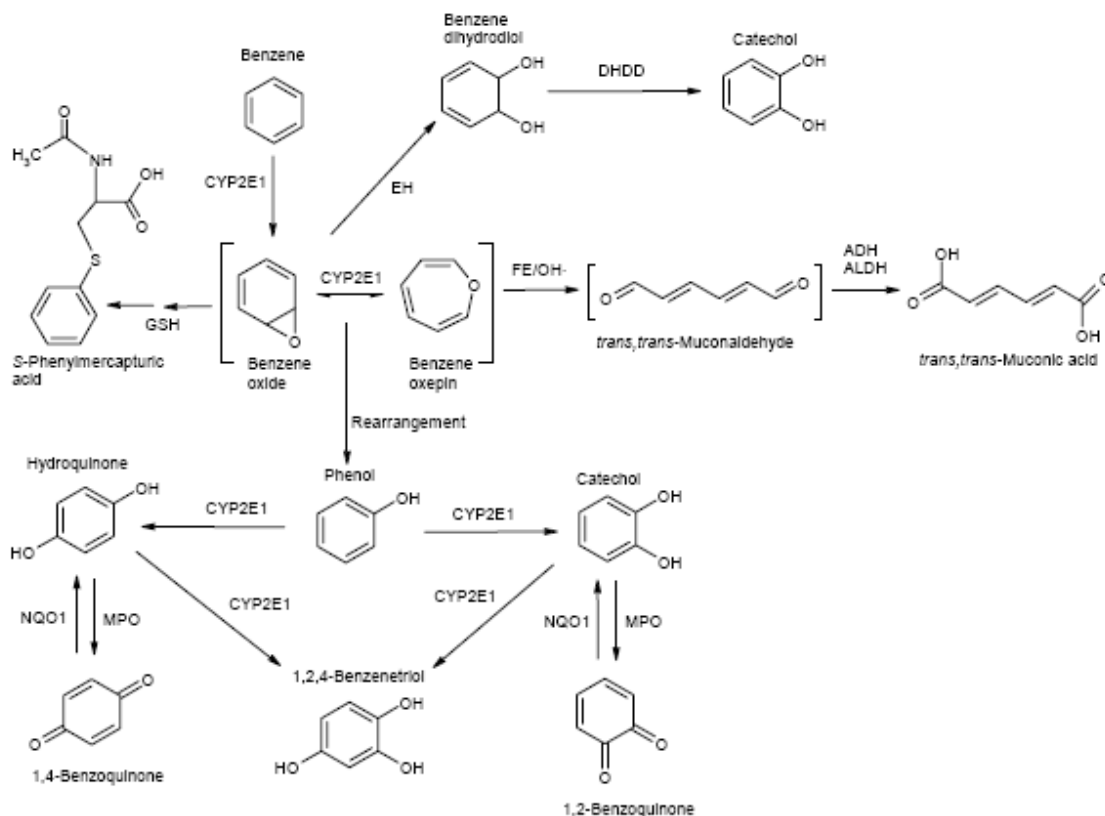
Adapted from Nebert et al. 2002; Ross 2000

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

Figure 1 Metabolic Pathways for Benzene

3.1.3 Dose Metric

In the key and supporting studies, data on exposure concentration of the parent chemical are available. Since data on other more specific dose metrics (e.g., blood concentration of parent chemical, area under blood concentration curve of parent chemical, or putative metabolite concentrations in blood or target tissue) are not available for these studies, exposure concentration of the parent chemical will be used as the default dose metric.

3.1.4 Points of Departure (PODs) for the Key and Supporting Studies

The LOAEL of 10.2 ppm (analytical concentration) based on 6 hs/day for 6 days (Rozen et al. 1984) was used as the key study POD. The LOAEL of 10.2 ppm from Corti and Snyder (1996) and the LOAEL of 10.3 ppm from Dempster and Snyder (1991) were used as PODs for the supporting studies.

3.1.5 Dosimetric Adjustments

3.1.5.1 Default Exposure Duration Adjustments

Default procedures discussed in TCEQ (2006) with n = 3 are used to adjust exposure duration from subacute studies (1-28 days) where both concentration and duration play a role in toxicity.

Rozen et al. 1984 (key study) and Corti and Snyder 1996 (supporting):
$$C_2 = [(C1)^3 \times (T1 / T2)]^{1/3} = [(10.2 \text{ ppm})^3 \times (6 \text{ hs}/1 \text{ h})]^{1/3} = 18.5 \text{ ppm} = POD_{ADJ}$$

Dempster and Snyder 1991 (supporting):
$$C2 = [(C1)^3 \times (T1 / T2)]^{1/3} = [(10.3 \text{ ppm})^3 \times (6 \text{ hs}/1 \text{ h})]^{1/3} = 18.7 \text{ ppm} = POD_{ADJ}$$

3.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

Benzene is moderately water soluble and can produce respiratory tract effects at relatively high concentrations. However, it produces remote effects at lower concentrations. Therefore, it is classified as a Category 3 gas. For category 3 gases:

$$POD_{HEC} = POD_{ADJ} \times ((H_{b/g})_A / (H_{b/g})_H)$$

where: $H_{b/g}$ = ratio of the blood:gas partition coefficient
$\quad$ A = animal
$\quad$ H = human

For benzene, the blood:gas partition coefficients for mice and humans are 17.44 and 8.12, respectively (Wiester 2002). 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 regional gas dose ratio (RGDR) (USEPA 1994).

Rozen et al. 1984 (key study) and Corti and Snyder 1996 (supporting):
$$POD_{HEC} = POD_{ADJ} \times ((H_{b/g})_A / (H_{b/g})_H) = 18.5 \text{ ppm} \times 1 = 18.5 \text{ ppm}$$

Dempster and Snyder 1991 (supporting):
$$POD_{HEC} = POD_{ADJ} \times ((H_{b/g})_A / (H_{b/g})_H) = 18.7 \text{ ppm} \times 1 = 18.7 \text{ ppm}$$

3.1.6 Critical Effect and Adjustments of the POD_{HEC}

3.1.6.1 Critical Effect

As indicated in Section 3.1.1.2, data from both human and animal noncarcinogenic studies suggest that hematotoxicity is the most sensitive endpoint for short-term exposure to benzene. The specific critical effect of benzene exposure in the key study (Rozen et al. 1984) is depressed

peripheral lymphocytes and depressed mitogen-induced blastogenesis of femoral B-lymphocytes in C57BL/6J mice (male). Supporting studies by Dempster and Snyder (1991) and Corti and Snyder (1996) also report hematotoxic effects.

3.1.6.2 Uncertainty Factors (UFs)

The MOA by which benzene may produce toxicity is discussed in Section 3.1.2. The default for noncarcinogenic effects is to determine a POD and apply appropriate UFs to derive a ReV (i.e., assume a threshold/nonlinear MOA). The POD_{HEC} of 18.5 ppm based on Rozen et al. (1984) was used and divided by the following UFs: 3 for extrapolation from a LOAEL to a NOAEL (UF_L), 3 for extrapolation from animals to humans (UF_A), 10 for intraspecies variability (UF_H), and 1 for database uncertainty (UF_D) (total UF = 100). The same UFs were applied to the supporting study POD_{HEC} values of 18.7 ppm based on Dempster and Snyder (1991) and 18.5 ppm based on Corti and Snyder (1996).

A UF_L of 3 was used because: (1) the LOAEL utilized for these noncancer effects is lower than that indicated in similar animal studies and in humans; (2) the LOAEL utilized is approximately equal to the weight-of-evidence NOAEL in mouse studies; (3) benchmark dose (BMD) modeling (Version 1.4.1) of lymphocyte count depression data read from Figure 1 in Rozen et al. (1984) indicates a benchmark dose low (BMDL) of approximately 4 ppm (standard deviation (SD) calculated from standard error (SE), benchmark response (BMR) of 1 SD, goodness of fit by visual inspection with goodness-of-fit p values > 0.1 and scaled residuals < 2) (see B1), which supports a UF_L of 3 as being sufficiently conservative; (4) lymphocyte count depression is a very sensitive sentinel effect that is not serious in and of itself (i.e., not a frank effect), and the decreased lymphocyte count in Rozen et al. (1984) at 10.2 ppm appears to be within the normal range (Jackson Laboratory 2007); and (5) 10.2 ppm is below levels at which a shift from more toxic (e.g., muconaldehyde, hydroquinone glucuronide) towards less toxic (e.g., phenylglucuronide, prephenylmercapturic acid) metabolites has been shown to occur in mice (e.g., between 50 and 600 ppm in Sabourin et al. 1989). Note that the BMDL referenced in (3) above could not be utilized as the POD in derivation of an acute ReV and [acute]ESL as the data used for BMD modeling were obtained by reading estimated numerical values off the graph in Figure 1 of Rozen et al. (1984) (as opposed to the plotted values being provided in tabular form in the actual study).

A UF_A of 3 was used because: (1) default dosimetric adjustments from animal-to-human exposure were conducted to account for toxicokinetic differences (2) existing studies indicate that benzene is metabolized along similar pathways in both humans and laboratory animals; (3) data suggests that mice are relatively sensitive laboratory animals in regards to the hematotoxic effects of benzene (e.g., relatively high respiratory and benzene metabolism rates) (USEPA 2002); and (4) some data suggest humans are more similar to rats (i.e., less sensitive than mice) in regards to benzene metabolism (Capel et al. 1972). A UF_A of 3 is thought to be conservative since the ratio of animal-to-human blood:gas partition coefficients used to adjust the POD_{HEC} was limited to 1, although the true ratio is approximately 2 and would increase the POD_{HEC},

acute ReV, and ^{acute}ESL accordingly (Section 3.1.5.2). A UF_A of 3 is in concordance with that used by ATSDR for derivation of the 2005 draft acute and intermediate MRLs (ATSDR 2005).

There is good experimental evidence to indicate that benzene-sensitive human subpopulations may exist (USEPA 2002), and available information supports use of a full UF_H of 10 when it is unknown whether a study population contained potentially sensitive subpopulations. Genetic polymorphisms associated with metabolic processes may confer variability in human susceptibility to benzene toxicity. For a more detailed discussion refer to ATSDR (2005) and USEPA (2002).

A UF_D of 1 was used because the overall toxicological database for benzene is extensive. The acute database contains numerous inhalation studies (mostly in animals) examining a wide variety of toxicological endpoints, both less and more serious in nature. Effects examined include, but are not limited to, mucous membrane and skin irritation, and hematological, cardiovascular, hepatic, immunological, neurological, reproductive, and developmental effects (sensitive/critical life stage). Several animal species/strains have been utilized (e.g., rats: Sprague-Dawley, Wistar, CFY; mice: BALB/c, Hale Stoner, C57BL/6BNL, CD-1, Swiss Webster, NMRI, CF-1; rabbits: New Zealand), including mice, which are particularly sensitive to benzene-induced hematological effects.

3.1.7 Health-Based Acute ReV and ^{acute}ESL

As discussed in the previous section, UFs are applied to the key study (Rozen et al. 1984) POD_{HEC} to derive the acute ReV.

Rozen et al. 1984 (key study) and Corti and Snyder 1996 (supporting):

acute ReV = POD_{HEC} / (UF_H x UF_A x UF_L x UF_D) = 18.5 ppm / (10 x 3 x 3 x 1) = 0.185 ppm

Dempster and Snyder 1991 (supporting):

acute ReV = POD_{HEC} / (UF_H x UF_A x UF_L x UF_D) = 18.7 ppm / (10 x 3 x 3 x 1) = 0.187 ppm

The acute ReV value was rounded to two significant figures at the end of all calculations. The rounded acute ReV was then used to calculate the ^{acute}ESL. Rounding to two significant figures, the 1-h acute ReV is 180 ppb (580 µg/m^3), and is supported by an identical value from Corti and Snyder (1996) and similar calculations based on Dempster and Snyder (1991). At the target hazard quotient of 0.3, the ^{acute}ESL is 54 ppb (170 µg/m^3) (Table 4).

Table 4 Derivation of the Acute ReV and [acute]ESL

Parameter	Summary
Study	Rozen et al. (1984), supported by Dempster and Snyder (1991) and Corti and Snyder (1996)
Study population	C57BL/6J mice (male)
Study quality	Medium-high
Exposure Methods	6 h per day for 6 days via inhalation from 0 to 301 ppm
LOAEL	10.2 ppm (average analytical concentration)
NOAEL	None
Critical Effects	Depressed peripheral lymphocytes and depressed mitogen-induced blastogenesis of femoral B-lymphocytes
POD	10.2 ppm (LOAEL)
Exposure Duration	6 h
Extrapolation to 1 h	TCEQ (2006) default procedures with n=3
POD_{ADJ} (extrapolated 1 h concentration)	18.5 ppm
POD_{HEC}	18.5 ppm (RGDR = 1)
Total Uncertainty Factors (UFs)	100
Interspecies UF	*3*
Intraspecies UF	*10*
LOAEL UF	*3*
Incomplete Database UF	*1*
Database Quality	*high*
acute ReV [1 h] (HQ = 1)	580 µg/m^3 (180 ppb)
[acute]ESL [1 h] (HQ = 0.3)	170 µg/m^3 (54 ppb)

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

Benzene is an aromatic with a paint-thinner-like or sweet, solventy odor (ATSDR 2005, NRC 1995, Ruth 1986). Nagata (2003), Leonardos et al. (1969), and Dravnieks (1974) have odor threshold information for benzene. Nagata (2003) lists a 50% odor detection threshold of 2,700 ppb (8,700 µg/m^3) for benzene, Leonardos et al. (1969) lists a 100% recognition threshold of

4,680 ppb (15,200 µg/m^3), and Dravnieks (1974) lists a 50% odor detection threshold of 380,000 µg/m^3 (117,000 ppb). Since benzene does not have a pungent, disagreeable odor, an ^{acute}ESL$_{odor}$ was not developed (TCEQ 2015b).

3.2.2 Vegetation Effects

No data found.

3.3. Short-Term ESL and Values for Air Monitoring Evaluation

The acute evaluation resulted in the derivation of the following values:

- acute ReV [1 h] = 580 µg/m^3 (180 ppb)

- acute ReV [24 h] = 320 µg/m^3 (100 ppb)

- ^{acute}ESL = 170 µg/m^3 (54 ppb)

The short-term ESL for air permit reviews is the health-based ^{acute}ESL of 170 µg/m^3 (54 ppb) (Table 1). The health-based ^{acute}ESL is only for air permit reviews, and is not for the evaluation of ambient air monitoring data. For the evaluation of air monitoring data, the acute ReV of 580 µg/m^3 (180 ppb) may be used for 1-h data and the acute ReV of 320 µg/m^3 (100 ppb) may be used for 24-h data (Table 1).

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties and Key Studies

Physical/chemical properties of benzene are discussed in Chapter 3. In both human and animal noncarcinogenic studies, data suggest the most sensitive endpoint for long-term exposure to benzene is hematotoxicity. Since relevant human studies are available, these studies were reviewed and used to develop the chronic ReV. The long-term effects of benzene in animals are discussed in ATSDR (2005).

Statistically decreased numbers of one or more circulating blood cell types (e.g., white blood cells, red blood cells, lymphocytes, platelets) are an early biomarker of benzene exposure (ATSDR 2005). As such, TCEQ considers decreases in blood cell counts to be the earliest indicator of benzene-induced hematotoxicity. Benzene-induced lymphopenia, for example, is the end result of decreases in lymphocyte counts over some time period, and restricting the definition of adverse hematological effects to clinically abnormal blood cell counts may reduce the sensitivity of studies to detect meaningful changes at the population level (ATSDR 2005).

The human occupational inhalation study by Rothman et al. (1996) was selected as the key study for derivation of the chronic ReV. Lan et al. (2004a, 2004b) was selected as a supporting study. Both the key and supporting study are well-conducted and provide dose-response relationships for hematological effects, which the scientific community considers to be the most sensitive of benzene-induced effects (USEPA 2002, ATSDR 2005). Data indicate that effects other than hematotoxicity (e.g., eye and nose irritation) occur at higher concentrations in humans (e.g., 33 and 59 ppm in Yin et al. 1987b).

The Rothman et al. (1996) study showed a dose-response relationship between benzene levels (dosimetry badge data) and five of the six hematological parameters measured (USEPA 2002). The hematological parameters measured were absolute lymphocyte count (ALC), white blood cell count (WBC), red blood cell count (RBC), hematocrit percent (HCT), platelet count, and MCV. The mean exposure duration was 6.3 +/- 4.4 (SD) years. Significant differences were identified for 22 workers exposed to an 8-h median of 31 ppm (high exposure group) in all six blood elements measured (i.e., ALC, WBC, RBC, HCT, and platelets decreased, MCV increased). In a group of 22 workers exposed to an 8-h median of 13.6 ppm (low exposure group), ALC, RBC, and platelets were significantly reduced. In a subgroup of 11 workers exposed to an 8-h median of 7.6 ppm (low exposure group subset), only ALC was significantly reduced, and was similar to the 13.6 ppm group. This study suggests that ALC is the most sensitive indicator of benzene hematotoxicity, representing a sentinel of a continuum of hematotoxic consequences of prolonged exposure to benzene below 31 ppm. It is one of the few occupational studies which provide a range of individual and workstation monitored benzene levels that encompass the likely POD for hematological effects based on data from larger-scale epidemiological studies (USEPA 2002). Additionally, measured urinary phenol levels showed good agreement with those expected based on monitored air benzene levels, median urinary metabolite levels (e.g., phenol, catechol, trans,trans-muconic acid, hydroquinone) correlated positively with 8-h benzene exposure category, exposure to other solvents was minimal, and age-/sex-matching of exposed and control subjects met adequate criteria (USEPA 2002). No NOAEL was identified. For reasons including those mentioned above, USEPA utilized the Rothman et al. (1996) study to derive the reference concentration (RfC) based on reduced ALC, which was designated as the critical effect since it was the only parameter for which there was a significant difference in all three exposure groups (i.e., high, low, low subset). The dose-response relationship between benzene levels and ALC is amenable to BMD modeling for purposes of developing a chronic noncarcinogenic ReV and ESL.

The Lan et al. (2004a) supporting study suggests that hematological effects may occur at lower exposure levels than Rothman et al. (1996). The study included 250 benzene-exposed workers and showed statistically significant decreases in the lowest exposure group (mean of 0.57 ppm, n=109) for the eight hematological parameters measured (i.e., WBC, granulocytes, monocytes, platelets, lymphocytes, and lymphocyte subsets: CD4+(T cells), CD4+/CD8+ ratio, B cells). The mean exposure duration was 6.1 +/- 2.9 (SD) years. Exposure to benzene (and toluene) was measured (dosimetry badge data) repeatedly up to 16 months before phlebotomy, and exposed

subjects were categorized into three groups based on the mean benzene concentration over the last month: < 1 ppm, 1 to < 10 ppm, and ≥ 10 ppm. Significant linear trends with benzene as a continuous variable were reported for platelets and all WBCs except monocytes and CD8+ (T cells). Total WBCs, granulocytes, lymphocytes, B cells, and platelets were also significantly decreased in workers exposed to a mean benzene level of less than 1 ppm based on data for the previous year of exposure (n = 60) and in workers exposed to less than 40 ppm-years lifetime cumulatively (n=50). Low benzene-exposed workers (mean of 0.36 ppm for previous year and 0.29 ppm for previous month) with reported negligible exposure to other solvents (n=30) also showed significantly decreased WBCs, granulocytes, lymphocytes, and B cells, however, means and standard deviations for these blood factors were not reported. For this group of 30 low-exposed workers, no measurements exceeded 1 ppm in the month prior to phlebotomy, and only 7.4% of the 337 measurements exceeded 1 ppm in the year prior (ranging from 1.01 to 1.74 ppm). No NOAEL was identified. Decreases in B cell count showed the highest magnitude of effect in this study (36% decrease in highest exposure group versus controls), and therefore was chosen as the critical effect for this supporting study consistent with ATSDR (2005). Exposure categorization based on the last year of exposure is relevant because the lifespan of RBCs and most WBCs is less than 180 days (Ward et al. 1996), more recent intensity of exposure may be more closely related to the risk of hematotoxicity than exposure duration (Dosemeci et al. 1996, Qu et al. 2002), cumulative lifetime exposure and years worked may not be more indicative of hematologic outcome (e.g., Qu et al. 2002), and blood cell counts may recover with reduced more recent exposure (e.g., Farris et al. 1997a, Cronkite et al. 1982, 1985, and 1989, Aksoy and Erdem 1978). The dose-response relationship between benzene levels and B cell decreases is amenable to BMD modeling for purposes of developing a supporting chronic noncarcinogenic ReV and ESL.

The findings of Rothman et al. (1996) are supported by other studies as well. For example, Qu et al. (2002, 2003) studied 130 benzene-exposed workers (51 age- and gender-matched controls) and identified a LOAEL of 2.26 ppm (4-week mean) for significantly reduced neutrophils and RBCs (ATSDR 2005). Qu et al. (2002) indicated that significant exposure-dependent decreases in total WBCs, neutrophils, and RBCs were associated with 4-week means, cumulative lifetime benzene exposure (ppm-years), and average exposure intensity (ppm per year). However, the study indicated that 4-week means may not be the most appropriate measure for correlation analysis with blood cell counts and that regression analysis indicated exposure intensity (mean annual benzene concentration) was a better predictor of bone marrow depression (e.g., depression of WBCs, RBCs, lymphocytes, and neutrophils) than exposure duration. Decreases in neutrophils and RBCs compared to controls were significant for the 4-week exposure group with a mean of 2.26 ppm (73 workers) (ATSDR 2005). Concurrent exposure to toluene was much more significant (i.e., higher) in this study as compared to Rothman et al. (1996) and the Lan et al. (2004a) subgroup which had negligible exposure to other solvents. The benzene levels associated with hematological effects in these studies (Qu et al. 2002, 2003) are within the range of those identified in the Rothman et al. (1996) and Lan et al. (2004a) studies. ATSDR (2005) indicated, however, that the Qu et al. (2002, 2003) studies are of limited value for derivation of a

chronic inhalation MRL due to discrepancies in the reported low-concentration results. Regarding supporting chronic animal studies, Baarson et al. (1984) for example, showed significant decreases in several endpoints (e.g., circulating lymphocytes and erythrocytes, marrow and splenic CFU-E in vitro) in C57BL mice exposed to 10.1 ppm for 178 days. Li et al. (1992) showed decreases in spleen weight and bone marrow myelocytes, premyelocytes, myeloblasts, and metamyeloblasts in a subchronic study of Kunming mice exposed to 12.5 ppm benzene for 30 days.

4.1.2 MOA Analysis

The MOA by which benzene may produce toxicity is discussed in Section 3.1.2.

4.1.3 Dose Metric

For the key and supporting hematotoxicity studies, data on exposure concentration of the parent chemical for occupationally exposed workers are available, whereas data on more specific dose metrics such as metabolites in blood or target tissue are not available. Therefore, exposure concentration of the parent chemical will be used as the default dose metric.

4.1.4 PODs for Key and Supporting Studies

USEPA (2002) performed benchmark concentration (BMC) modeling with EPA's Benchmark Dose Modeling (BMDM) Software (version 1.20) using the Rothman et al. (1996) data. A detailed discussion is available in Section 5.1.2 of USEPA (2002). However, Appendix B2 provides a summary of information for USEPA's approach using BMDM Software (Version 1.4.1). The results obtained using Version 1.4.1 in Appendix B2 are similar to results from USEPA (2002). Briefly, the Rothman et al. (1996) data for ALC were log-transformed so that a continuous linear BMC model fits the data. BMC modeling of the ALC data with a BMR of 1 SD from the control mean results in a benchmark concentration low (BMCL) of 7.2 ppm (Appendix B2). USEPA indicates that a BMR of 1 SD from control mean corresponds to an approximately 10% excess risk for individuals below the 2nd percentile or above the 98th percentile of the control distribution for normally distributed effects (USEPA 2000, 2002). The BMCL of 7.2 ppm represents USEPA's POD for derivation of their RfC (USEPA 2002), and TCEQ's POD for derivation of the chronic ReV.

Appendix B3 provides a summary of information used to perform BMC modeling on the B cell data from the supporting Lan et al. (2004a) study. Based on visual inspection with scaled residuals < 2 and the goodness-of-fit > 0.1 for model fit (test 4), the Hill model adequately describes the B cell data. Because means and standard deviations for B cell data from the subgroup exposed to 0.36 ppm over the previous year (0.29 ppm over the previous month) were not reported (see previous discussion on low-benzene exposed workers), this subgroup could not be included in the BMC modeling as a separate dose group. This subgroup was included in the lowest averaged mean concentration group of 0.57 ppm (Appendix B3). However, to take the effects reported for this subgroup into account, a BMR of 0.4 SD was utilized so that the

resulting BMCL would fall below the 0.36 ppm mean benzene level reported for this subgroup for the previous year. This was done so the POD obtained from BMC modeling would approximate a NOAEL. The resulting BMCL is 0.26 ppm (Appendix B3). ATSDR (2005) also performed BMC modeling using the Lan et al. (2004a) study. However, ATSDR used a BMR of 0.25 SD so the resulting BMCL would fall below the previous monthly average of 0.29 ppm for the subgroup, whereas a SD of 0.4 was selected here so the resulting BMCL would fall below the subgroup annual average of 0.36 ppm. TCEQ considered the annual average more relevant for selecting an appropriate BMR as it is more representative of a long-term average and the BMCL is being used in support of a chronic ReV.

4.1.5 Dosimetric Adjustments

Using the BMCLs from the key Rothman et al. (1996) study and the supporting Lan et al. (2004a) study, the occupational PODs (POD_{oc}) were adjusted to PODs applicable to the general population (POD_{HEC}) using the following dosimetric adjustments:

$POD_{HEC} = POD_{OC}$ x (VE_{ho}/VE_h) x (days per week$_{oc}$/days per week$_{res}$)

> where: VE_{ho} = occupational ventilation rate for an 8-h day (10 m^3/day)
> VE_h = non-occupational ventilation rate for a 24-h day (20 m^3/day)
> days per week$_{oc}$ = occupational weekly exposure frequency (study specific)
> days per week$_{res}$ = residential weekly exposure frequency (7 days per week)

Rothman et al. (1996) POD_{HEC} = 7.2 ppm x (10/20) x (5/7) = 2.6 ppm

Lan et al. (2004a) POD_{HEC} (supporting) = 0.26 ppm x (10/20) x (6/7) = 0.11 ppm

4.1.6 Critical Effect and Adjustments of the POD_{HEC}

4.1.6.1 Critical Effect

As indicated in Section 3.1.1.2, data from both human and animal noncarcinogenic studies suggest that hematotoxicity is the most sensitive endpoint for exposure to benzene. The specific critical effect for the key study (Rothman et al. 1996) is decreased ALC in benzene-exposed workers, supported by Lan et al. (2004a), which reported hematotoxic effects as well.

4.1.6.2 UFs

Section 3.1.2 discusses the MOA by which benzene may produce toxicity. Determining a POD and applying appropriate UFs (i.e., assume a threshold/nonlinear MOA) is the default for noncarcinogenic effects. Therefore, UFs were applied to the key study POD_{HEC} to derive the chronic ReV. The Rothman et al. (1996) POD_{HEC} was used with the following UFs: 1 for extrapolation from a LOAEL to a NOAEL (UF_L), 10 for intraspecies variability (UF_H), 1 for use of a subchronic (6.3 year) study (UF_{Sub}), and 3 for database uncertainty (UF_D) (total UF = 30).

The Lan et al. (2004a) supporting study POD_{HEC} was used with the following UFs: 1 for the UF_L, 3 for the UF_H, 1 for the UF_{Sub} (6.1 year), and 3 for the UF_D (total UF = 10). Choice of UFs is discussed below.

For the Rothman et al. (1996) POD_{HEC}, a UF_L of 1 was used because BMC modeling was used to derive the POD and the health endpoint that was modeled was a mild effect. As indicated by USEPA, decreased ALC is a very sensitive endpoint and not very serious in and of itself (i.e., not a frank effect), and there is no evidence that a decrease in ALC is related to any functional impairment at benzene levels near the BMCL (USEPA 2002). Additionally, although lymphocyte depression was observed at 13.6 ppm in the Rothman et al. (1996) study, lymphocyte count is still within the normal range (approximately the 15th percentile) (USDHHS 2005). For the supporting Lan et al. (2004a) POD_{HEC}, a UF_L of 1 was used because: (1) decreased B cell count is a sensitive endpoint; (2) the LOAEL from Lan et al. (2004a) is lower than that indicated in similar human studies; (3) a conservative BMR of 0.4 SD from control mean, versus the standard BMR of 1 SD, was utilized for BMC modeling; and (4) the reported changes are considered unlikely to have clinical consequences (Lamm et al. 2006).

A UF_H of 3 was selected for use with the supporting Lan et al. (2004a) study primarily because information that potential sensitive subpopulations were included in the actual study population was available (i.e., workers with genotypes which conferred greater sensitivity). A UF_H of 10 is justified for use with the Rothman et al. (1996) POD_{HEC} based on several considerations, including but not limited to: (1) available data on potentially greater sensitivity conferred by genetic polymorphisms; (2) no information is presented in Rothman et al. (1996) which indicates that the specific worker population evaluated in the study included potentially sensitive subpopulations (i.e., workers with genotypes which confer greater sensitivity); and (3) the larger worker populations in studies which evaluated polymorphisms (e.g., Rothman et al. 1997, Lan et al. 2005) may not necessarily be genetically representative of the workers in Rothman et al. (1996).

A UF_{Sub} of 1 was used for both the Rothman et al. (1996) and Lan et al. (2004a) studies since TS believes the mean exposure durations of 6.3 and 6.1 years, respectively, were sufficient in regards to observation of the response level for the hematotoxic effects evaluated (i.e., additional exposure time would likely not affect the response level).

The toxicological database for benzene is extensive. However, a UF_D of 3 was applied to both the Rothman et al. (1996) study and the supporting Lan et al. (2004a) study because of the absence of a two-generation reproductive/developmental toxicity study.

4.1.7 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

As discussed in the previous section, UFs are applied to the key study (Rothman et al. 1996) POD_{HEC} to derive the chronic ReV (Table 5).

Table 5 Comparison of UFs applied to the POD$_{HEC}$

POD$_{HEC}$	Subchronic-to-Chronic (UF$_{Sub}$)	Intra-Species (UF$_H$)	LOAEL-to-NOAEL (UF$_L$)	Incomplete Database (UF$_D$)	Total UF	Reference Value (ReV)
Key Study: Rothman et al. (1996) 2.6 ppm	1	10	1	3	30	86 ppb
Supporting Study: Lan et al. (2004a) 0.11 ppm	1	3	1	3	10	11 ppb

Rounding to two significant figures at the end of all calculations for the key study (Rothman et al. 1996) yields a chronic ReV of 86 ppb (280 µg/m^3). At the target hazard quotient of 0.3, the ^{chronic}ESL$_{nonlinear(nc)}$ is 26 ppb (84 µg/m^3) (Table 6). For the supporting Lan et al. (2004a) study, application of UFs yields somewhat lower supporting values for the chronic ReV (11 ppb or 36 µg/m^3) and ^{chronic}ESL$_{nonlinear(nc)}$ (3.3 ppb or 11 µg/m^3).

4.1.8 Comparison of Results

The chronic ReVs calculated based on the POD$_{HEC}$ values from the Rothman et al. (1996) and Lan et al. (2004a) studies are similar (less than one order of magnitude apart). The chronic ReV (86 ppb or 280 µg/m^3) based on Rothman et al. (1996) is expected to be health-protective and conservative since the levels of ALC decrement near the BMCL/POD$_{oc}$ are not expected to be associated with any functional impairment (USEPA 2002), and the chronic ReV is about 84 times lower than the BMCL/POD$_{oc}$ (the ^{chronic}ESL$_{nonlinear(nc)}$ is about 277 times lower). Additionally, many reports of clinical hematological abnormalities in chronic human studies are associated with much higher concentrations than the chronic ReV (86 ppb):

- 3,200-12,800 ppb for leukopenia in Doskin (1971);
- 6,000 ppb (mean) for leukopenia in Xia et al. (1995);
- 15,000-210,000 ppb for hematological abnormalities (e.g., leukopenia) in Aksoy et al. (1971);
- 15,000-640,000 ppb for pancytpoenia in Aksoy et al. (1972);
- 11,000-1,060,000 ppb for anemia and thrombocytopenia in Goldwater (1941);
- > 25,000 ppb for transient anemia and clinically increased MCV in Fishbeck et al. (1978);

- 150,000-650,000 ppb for pancytopenia in Aksoy and Erdem (1978).

Based on Rothman et al. (1996), the chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ are 86 ppb (280 µg/m^3) and 26 ppb (84 µg/m^3), respectively. As indicated in Lan et al. (2004a), confirmation of their findings of benzene-induced hematotoxicity at levels below 1 ppm (1,000 ppb) is needed in other studies.

USEPA (2002) calculated RfC-like values of 15.6 and 18.8 ppb based on the Ward et al. (1985) subchronic inhalation rodent study for comparison to the final RfC based on Rothman et al. (1996). Although based on an animal study, the use of which has uncertainties associated with extrapolation to humans, these values are similar to the $^{chronic}ESL_{nonlinear(nc)}$ (26 ppb) calculated based on Rothman et al. (1996). The $^{chronic}ESL_{nonlinear(nc)}$ is also similar to the CalEPA chronic recommended exposure limit (REL) of 20 ppb and the USEPA final RfC of 9 ppb.

Table 6 Derivation of the Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Parameter	Summary
Study	Rothman et al. (1996), supported by Lan et al. (2004a)
Study Population	44 benzene-exposed workers
Study Quality	high
Exposure Method	13.6 ppm median for low exposure group
Critical Effects	decreased ALC
POD (BMCL)	7.2 ppm at BMR of 1 SD from control
Exposure Duration	5 days per week , 6.3 years (mean)
Extrapolation to continuous exposure (POD_{HEC})	POD_{HEC} = 7.2 ppm x (10/20) x (5/7) = 2.6 ppm
Total UFs	30
Interspecies UF	*1*
Intraspecies UF	*10*
LOAEL UF	*1*
Subchronic to chronic UF	*1*
Incomplete Database UF	*3*
Database Quality	*high*
chronic ReV (HQ = 1)	280 μg/m^3 (86 ppb)
^{chronic}**ESL$_{nonlinear(nc)}$ (HQ = 0.3)**	84 μg/m^3 (26 ppb)

4.2 Carcinogenic Potential

It is not known whether a common mechanism is responsible for both benzene-induced hematotoxicity and carcinogenicity. Therefore, given the current state of knowledge on MOA, the noncancer and cancer health assessments cannot be integrated at this time (USEPA 2002).

4.2.1 Carcinogenic Weight-of-Evidence and MOA

Benzene is a known human carcinogen as evaluated by multiple sources (e.g., USEPA, the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), the American Conference of Governmental Industrial Hygienists (ACGIH), Germany's Commission for the Investigation of Health Hazards of Chemicals in the Work Area (MAK)). Epidemiologic and case studies provide clear and consistent evidence of a causal association between benzene exposure and acute myelogenous (nonlymphocytic) leukemia (AML or ANLL), the dominant leukemia type observed among benzene-exposed workers (USEPA 1998, Lamm 1989). To a lesser extent, benzene exposure may be associated with chronic myelogenous

(nonlymphocytic) leukemia and chronic lymphocytic leukemia, but studies have not yielded consistent results (USEPA 1998, Lamm 1989, Schnatter et al. 2005). AML is the only leukemia type shown to be definitely associated with benzene exposure. Acute monocytic leukemia is a subtype of AML, and is also derived from the myeloid or hematopoietic tissue of bone marrow (Lamm 1989). Information on different types of leukemia is provided in Appendix A.
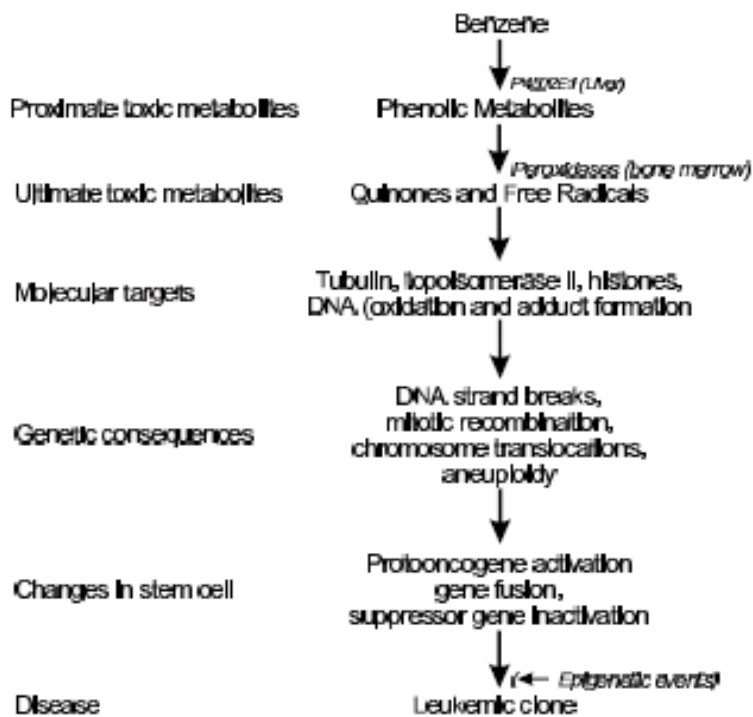
Figure 2. Schematic for mechanistic hypothesis of benzene pathogenesis (leukemognesis).

Source: Smith, 1996.

Figure 2 Proposed Mechanistic Hypothesis for Benzene-Induced Leukemogenesis

Development of leukemia is thought to be a multi-step process involving several independent genetic and epigenetic events, and evidence suggests that multiple mechanistic pathways are likely. The overall picture of benzene-induced leukemogenesis is an increased rate of genetic damage to hematopoietic cells occurring in the context of disrupted bone marrow function. While evidence supports the hypothesis that multiple toxic effects contribute to the leukemogenic process, data are insufficient to show exactly which effects (genotoxic or

otherwise) of benzene are critical for the induction of leukemia. The genotoxic effects involved in benzene-induced leukemogenesis most likely involve chromosomal damage rather than simple point mutations (USEPA 1998). Figure 2 below shows a proposed general schematic for benzene-induced leukemia taken from USEPA (1998).

4.2.2 Epidemiological Studies and Exposure Estimates

The most current USEPA review of scientific literature related to the derivation of an inhalation unit risk factor (URF) (USEPA 1998) indicates that a study of Pliofilm workers at three Ohio facilities (Rinsky et al. 1981, 1987) provides the best published set of data to evaluate human cancer risk from benzene exposure. USEPA (1998) also reviewed a cohort of Chinese workers (Hayes et al. 1997), but did not select this cohort based on several considerations (see USEPA 1998). Rinsky et al. (1981, 1987) (a.k.a. the Pliofilm cohort) has ample power, latency, relatively better estimates of later exposure to airborne benzene, and few reported co-exposures to carcinogenic substances relative to other studies (USEPA 1998).

USEPA (1998) reviewed the benzene exposure estimates for the Pliofilm cohort from Rinsky et al. (1981, 1987), Paustenbach et al. (1992), and Crump and Allen (1984). Paustenbach et al. (1992) exposure estimates are generally higher than those of both Crump and Allen (1984) and Rinsky et al. (1981, 1987), and result in a lower estimate of carcinogenic potency (i.e., URF). While Crump (1994) indicates that the Paustenbach et al. (1992) exposure matrix was based on a much more detailed investigation than that by Crump and Allen (1984) and is likely to provide a better representation of exposures in the cohort, other investigators have reservations concerning the Paustenbach et al. (1992) exposure estimates (Utterback and Rinsky 1995). Therefore, based on a review of the reservations, the Paustenbach et al. (1992) estimates were not used to derive the $^{chronic}ESL_{linear(c)}$. Studies of hematologic surveillance data (e.g., WBC and RBC counts) from the Pliofilm cohort workers (e.g., Cody et al. 1993, Kipen et al. 1988, 1989) support exposure estimates that incorporate relatively higher benzene levels in the 1940s relative to subsequent decades. For example, Kipen et al. (1989) showed a correlation coefficient of 0.76 between the Crump and Allen (1984) exposure estimates and WBC count worker data from 1940-1948, while the correlation coefficient was only 0.05 for the Rinsky et al. (1987) exposure estimates. Since changes in blood cell counts (e.g., WBC) may be used as a biomarker of benzene exposure and worker hematologic data did not correlate well with the Rinsky et al. (1987) exposure estimates, the Rinsky estimates were not used to derive the $^{chronic}ESL_{linear(c)}$. Additionally, while USEPA did not endorse a particular set of exposure estimates in the 1998 update, USEPA's response to peer review comments on the draft indicates that USEPA considers the Crump and Allen (1984) exposure estimates to be the least biased (USEPA 1997). Cancer potency estimates based on the Crump and Allen (1984) exposure matrix are utilized in this assessment for calculation of the URF and $^{chronic}ESL_{linear(c)}$ as in the absence of more definitive information, it is reasonable that the exposure estimates which correlate best with hematotoxicity (WBC) data in the same cohort provide the most reliable exposure estimates for use in quantitative risk assessment.

4.2.3 Dose-Response Assessment

4.2.3.1 Potency Estimates Based on Observed Data

In the 1998 update, USEPA indicated that there is insufficient evidence to reject the USEPA default assumption of linearity and utilized linear low-dose extrapolation to derive a risk range of 7.1E-03 to 2.5E-02 per ppm (URFs of 2.2E-06 to 7.8E-06 per µg/m^3), within which any calculated unit risk estimate would have equal scientific validity. These unit risk estimates were taken from Crump (1994), and the lower and upper ends of the range are based on the Paustenbach et al. (1992) and Crump and Allen (1984) exposure estimates, respectively.

Similar to USEPA (1998), this assessment utilizes the linear model risk analyses of Crump (1994). Crump (1994) indicates that acute myelogenous and monocytic leukemia (AMML) was the only cancer response clearly related to benzene exposure, and that a dose response for all leukemia was not apparent if AMML was excluded. For this assessment, AMML was selected as the cancer endpoint of interest, with supporting calculations for all leukemia. A linear multiplicative risk model was selected because it fit the Pliofilm cohort data better than a linear additive risk model (Crump 1994).

Both the cumulative exposure and weighted cumulative exposure metrics fit the data well, therefore results from both exposure metrics were used in this assessment. Corresponding cancer potency estimates (β) and standard error (SE) values were obtained from Table 3 of Crump (1994), and 95% upper confidence limits (95% UCLS) on the β values were calculated using reported SEs as summarized in Table 7.

Table 7 Beta (β), Standard Error (SE), and 95% UCL β Values [a]

Leukemia Type	Exposure Metric	β	SE	95% UCL β [b]
AMML	Cumulative	4.5E-02	1.8E-02	7.5E-02
AMML	Weighted Cumulative	2.3E+00	8.9E-01	3.8E+00
All	Cumulative	1.7E-02	6.8E-03	2.8E-02
All	Weighted Cumulative	8.4E-01	3.4E-01	1.4E+00

[a] Units are in ppm-years

[b] 95% UCL = β + (1.645 x SE)

4.2.3.2 Dosimetric Adjustments

Consistent with TCEQ (2006), occupational concentrations were converted to environmental concentrations for the general population using the following equation:

$$\text{Concentration}_{HEC} = \text{Concentration}_{OC} \times (VE_{ho}/VE_h) \times (\text{days per week}_{oc}/\text{days per week}_{res})$$

> where:
> VE_{ho} = occupational ventilation rate for an 8-h day (10 m^3/day)
> VE_h = non-occupational ventilation rate for a 24-h day (20 m^3/day)
> days per week$_{oc}$ = occupational weekly exposure frequency (default of 5 days per week)
> days per week$_{res}$ = residential weekly exposure frequency (7 days per week)

4.2.3.2 Extrapolation to Lower Exposures

4.2.3.2.1 Calculation of Air Concentrations at 1 in 100,000 Excess Cancer Risk and the $^{chronic}ESL_{linear(c)}$

Air concentrations based on extra risk were calculated as opposed to added risk, and resulted in insignificantly lower calculated air concentrations at a cancer risk of 1 in 100,000. URFs and benzene air concentrations at 1 in 100,000 excess cancer risk were calculated with life-table analyses using the BEIR IV approach (NRC 1988) and the following mortality and survival rates (Appendix C):

- US mortality rates for 2000-2003 for all leukemia (Surveillance, Epidemiology, and End Results database (SEER 2006));
- US survival rates for 2000 (Arias 2002);
- Texas-specific mortality rates for 1999-2003 for AMML and all leukemia, US mortality rates for AMML for 1999-2003, and Texas-specific survival rates for 2003 were kindly provided by the Texas Department of State Health Services, Cancer Epidemiology and Surveillance Branch, Texas Cancer Registry.

Since Crump (1994) used a lag time of 5 years to conduct modeling using the cumulative exposure metric, an exposure lag time of 5 years was used in the cumulative exposure assessment to calculate air concentrations. Utilizing the data and inputs described above, air concentrations corresponding to the target excess cancer risk of 1 in 100,000 were calculated based on lifetime exposure of 70 years, the default used by TCEQ for exposure analysis. As can be seen from Table 8 below, there were no differences in the use of Texas versus US background AMML and all leukemia mortality rates and survival rates except for all leukemia with the weighted cumulative exposure metric, where use of Texas-specific data results in slightly lower calculated acceptable air concentrations. Therefore, air concentrations calculated with US rates are used in all subsequent discussions.

Table 8 Air Concentrations Corresponding to 1 in 100,000 Excess Leukemia Risk

Leukemia Type	Background Rates	Exposure Metric	Air Concentration @ 1 in 100,000 Excess Risk using β central estimate (ppb)	Air Concentration @ 1 in 100,000 Excess Risk using β 95% UCL (ppb)
AMML	US	Cumulative	1.4	0.9
AMML	US	Weighted Cumulative	2.3	1.4
AMML	TX	Cumulative	1.4	0.9
AMML	TX	Weighted Cumulative	2.3	1.4
All	US	Cumulative	1.6	1.0
All	US	Weighted Cumulative	2.7	1.6
All	TX	Cumulative	1.6	1.0
All	TX	Weighted Cumulative	2.6	1.5

As indicated previously, AMML was the only cancer response clearly related to benzene exposure (Crump 1994). *Therefore, AMML was selected as the cancer endpoint of interest (with calculations for all leukemia used as supporting data).* Based on AMML, air concentrations corresponding to the target excess cancer risk of 1 in 100,000 using the central estimate β ranged from 1.4 ppb (0.9 ppb for 95% UCL β) for cumulative exposure to 2.3 ppb (1.4 ppb for 95% UCL β) for weighted cumulative exposure. However, the best-fitting linear model for AMML from Crump (1994) was that based on weighted cumulative exposure as the exposure metric. *Therefore, weighted cumulative exposure was the preferred exposure metric for use in the linear model.* The weighted cumulative exposure metric used by Crump (1994) gives progressively less weight to exposures which occurred in the distant past and was more predictive of risk than simple cumulative exposure, which gives equal weight to all exposures regardless of when they occurred in the past (e.g., 10 years ago versus 50). The particular human epidemiological data available are considered when selecting an appropriate β estimate (central estimate or 95% UCL). The 95% UCL β should be used when estimates of mortality are available rather than incidence and mortality does not reflect incidence for the cancer evaluated (TCEQ 2006). For AML, incidence and mortality appear to differ by approximately twenty percent (American Cancer Society 2005). Additionally, considering other factors (e.g., the uncertainty inherent in exposure estimates and the dose-response modeling for benzene), TS believes use of the 95% UCL β is justified. *Therefore, the 95% UCL β value was used instead of the central estimate β value because potency estimates were derived from mortality data, not incidence data (i.e., to*

protect against developing leukemia), and in consideration of other factors as well.

Based on the best-fitting linear model for AMML (weighted cumulative exposure) and the more conservative 95% UCL β value, the air concentration at the target risk is 1.4 ppb. *Therefore, the* $^{chronic}ESL_{linear(c)}$ *is 1.4 ppb.* This would correspond to a URF of 7.1E-06 per ppb (2.2E-06 per µg/m^3), which is within the URF range of 2.2E-06 to 7.8E-06 per µg/m^3 suggested by USEPA based on the 1998 update. The value of 1.4 ppb falls within the range of air concentrations of 1.0-1.6 ppb based on the 95% UCL β values for all leukemia, which did not have an apparent dose-response relationship if AMML were excluded (Crump 1994).

USEPA (1998) states that the agency is fairly confident that the risk of leukemia increases at 40 ppm-years of occupational benzene exposure based on Rinsky et al. (1981, 1987) and recent studies, and that this equates to a lifetime (i.e., 24 hs per day for 76 years) exposure level of 120 ppb. Hence, lifetime exposure at the $^{chronic}ESL_{linear(c)}$ of 1.4 ppb would be approximately 86 times less than the cumulative exposure level identified by USEPA as being associated with elevated leukemia risk.

4.2.3.3 Evaluating Susceptibility from Early-Life Exposures

USEPA (2005) provides default age-dependent adjustment factors (ADAFs) to account for potential increased susceptibility in children due to early-life exposure when a chemical has been identified as acting through a mutagenic MOA for carcinogenesis. However, benzene is not a chemical which is currently identified by USEPA as having a mutagenic MOA, and data are not sufficient to determine which of the various documented effects (genotoxic or otherwise) are critical for leukemogenesis (USEPA 1998, Cox 1991). Benzene has generally yielded negative results in gene mutation assays in bacteria or *in vitro* mammalian cell systems (USEPA 1998), although some studies report an increase in gene mutation (e.g., Ward et al. 1992, Mullin et al. 1995). Benzene exposure results in a variety of structural and numerical chromosomal damage and increased frequency of micronuclei in human cells exposed *in vitro* to various metabolites/metabolite combinations (USEPA 1998). DNA adducts of phenol, hydroquinone, or benzoquinone have been reported in various *in vitro* systems, and DNA damage was reported using the comet assay in mice exposed to benzene *in vivo* and cultured human lymphocytes exposed to benzene and several metabolites *in vitro* (USEPA 1998). Although chromosomal rearrangements are detected in leukemia and following benzene exposure, such effects are only part of the leukemogenic process (USEPA 1998). Additionally, while there are no direct observational data on potential benzene-induced leukemia in children as with benzene-exposed workers, there is scientific literature available describing chemotherapy-induced AML in children, which may be a relevant surrogate. This information suggests that children are not more sensitive than adults following leukemogenic chemical exposure (e.g., Pyatt et al. 2005, 2006), and a few studies appear to indicate that younger children may have somewhat decreased susceptibility to chemotherapy-related AML (as discussed in VCCEP 2006). Available data on the maximum tolerated dose of anti-neoplastic agents also suggest that children are somewhat less susceptible to therapy-induced hematopoietic toxicity (VCCEP 2006). While not

determinative, available information on chemotherapy-induced AML in children lends support to the determination that as the MOA for benzene-induced leukemia has not been determined to be mutagenic by the scientific community, consistent with TCEQ guidance (TCEQ 2006), URF adjustment factors will not be applied. This issue will be reevaluated periodically as new scientific information on benzene's carcinogenic MOA becomes available. In the interim, TCEQ believes the use of several conservative factors (i.e., multiplicative versus additive risk model, extra versus added risk, 95% UCL β versus the central estimate β) results in a health-protective $^{chronic}ESL_{linear(c)}$.

4.3. Welfare-Based Chronic ESL

No data were found regarding vegetative effects.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

The chronic evaluation resulted in the derivation of the following values:

- $^{chronic}ESL_{linear(c)}$ = 4.5 µg/m^3 (1.4 ppb)
- URF = 2.2E-06 per µg/m^3 (7.1E-06 per ppb)
- chronic ReV = 280 µg/m^3 (86 ppb)
- $^{chronic}ESL_{nonlinear(nc)}$ = 84 µg/m^3 (26 ppb)

The long-term ESL for air permit reviews is the $^{chronic}ESL_{linear(c)}$ of 4.5 µg/m^3 (1.4 ppb) as it is lower than the $^{chronic}ESL_{nonlinear(nc)}$ (Table 1). For the evaluation of long-term ambient air monitoring data, the $^{chronic}ESL_{linear(c)}$ of 4.5 µg/m^3 (1.4 ppb) is the lowest chronic comparison value, although both the $^{chronic}ESL_{linear(c)}$ and chronic ReV will be used for the evaluation of air data (Table 1).

Chapter 5. References

5.1 References Cited in the Development Support Document

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. Toxicological profile for benzene.

Agency for Toxic Substances and Disease Registry (ATSDR). 2005. Toxicological profile for benzene.

Aksoy M, Dincol K, Akgun T, et al. 1971. Haematological effects of chronic benzene poisoning in 217 workers. Br J Ind Med 28:296-302.

Aksoy M, Dincol K, Erdem S, et al. 1972. Details of blood changes in 32 patients with pancytopenia   associated with long-term exposure to benzene. Br J Ind Med 29:56-64.

Aksoy M, Erdem S. 1978. Follow up study on the mortality and the development of leukemia in 44 pancytopenic patients with chronic benzene exposure. Blood 52:285-292.

American Cancer Society. 2005. Cancer facts and figures. Available at www.cancer.org/downloads/STT/CAFF2005f4PWSecured.pdf.

Arias E. 2002. United States life tables, 2000. National Vital Statistics Reports. 51(3): p. 3, Table B.

Baarson KA, Snyder CA, Albert RE. 1984. Repeated exposures of C57B1 mice to inhaled benzene at 10 ppm markedly depressed erythropoietic colony formation. Toxicol Lett 20:337-342.

Capel ID, French MR, Millburn P, et al. 1972. Fate of [14C]-phenol in various species. Xenobiotica 2:25-34.

Cody RP, Strawderman WW, Kipen HM. 1993. Hematologic effects of benzene: job-specific trends during the first year of employment among a cohort of benzene-exposed rubber workers. J Occup Med 35(8):776-782.

Corti M, Snyder CA. 1996. Influences of gender, development, pregnancy and ethanol consumption on the hematotoxicity of inhaled 10 ppm benzene. Arch Toxicol 70:209-217.

Cox LA. 1991. Biological basis of chemical carcinogenesis: Insights from benzene. Risk Anal 11(3):453-464.

Cronkite EP, Inoue T, Carsten AL, et al. 1982. Effects of benzene inhalation on murine pluripotent stem cells. J Toxicol Environ Health 9:411-421.

Cronkite EP, Drew RT, Inoue T, et al. 1985. Benzene hematotoxicity and leukemogenesis. Am J Ind Med 7:447-456.

Cronkite EP. 1986. Benzene hematotoxicity and leukemogenesis. Blood Cells 12:129-137.

Cronkite EP, Drew RT, Inoue T, et al. 1989. Hematotoxicity and carcinogenicity of inhaled benzene. Environ Health Perspect 82:97-108.

Crump KS, Allen BC. 1984. Quantitative estimates of risk of leukemia from occupational exposure to benzene. Prepared for the Occupational Safety and Health Administration by Science Research Systems, Inc., Ruston, LA.

Crump KS. 1994. Risk of benzene-induced leukemia: A sensitivity analysis of the pliofilm cohort with additional follow-up and new exposure estimates. J Toxicol Environ Health 42(2):219-242.

Dempster AM, Snyder CA. 1991. Kinetics of granulocytic and erythroid progenitor cells are affected

differently by short-term, low-level benzene exposure. Arch Toxicol 65(7):556-561.

Dosemeci M, Yin SN, Linet M, et al. 1996. Indirect validation of benzene exposure assessment by association with benzene poisoning. Environ Health Perspect 104:1343-1347.

Doskin VA. 1971. Effect of age on the reaction to a combination of hydrocarbons. Hyg Sanit 36:379-384.

Dravnieks A. 1974. A building-block model for the characterization of odorant molecules and their odors. Ann. NY Acad. Sci. 237: 44-163.

Farris GM, Robinson SN, Gaido KW, et al. 1997a. Benzene-induced hematotoxicity and bone marrow compensation in B6C3F1 mice. Fundam Appl Toxicol 36(2):119-129.

Farris GM, Robinson SN, Wong BA, et al. 1997b. Effects of benzene on splenic, thymic, and femoral lymphocytes in mice. Toxicology 118(2-3):137-148.

Fishbeck WA, Townsend JC, Swank MG. 1978. Effect of chronic occupational exposure to measured concentrations of benzene. J Occup Med 20:539-542.

Goldwater LJ. 1941. Disturbances in the blood following exposure to benzol. J Lab Clin Med 26:957-973.

Green JD, Snyder CA, LoBue J, et al. 1981a. Acute and chronic dose/response effects of inhaled benzene on multipotential hematopoietic stem (CFU-S) and granulocyte/macrophage progenitor (GMCFU-C) cells in CD-1 mice. Toxicol Appl Pharmacol 58:492-503.

Green JD, Snyder CA, LoBue J, et al. 1981b. Acute and chronic dose/response effect of benzene inhalation on the peripheral blood, bone marrow, and spleen cell of CD-1 male mice. Toxicol Appl Pharmacol 59:204-214.

Hayes RB, Yin SN, Dosemeci M, et al. 1997. Benzene and the dose-related incidence of hematologic neoplasms in China. J Natl Cancer Inst 89(14):1065-1071.

International Agency for Research on Cancer (IARC). 1982. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 29: Some industrial chemical and dyestuffs. Benzene. Lyon, France: World Health Organization, International Agency for Research on Cancer, 93-148.

Jackson Laboratory. 2007. Hematology measurements involving C57BL/6J mice. http://phenome.jax.org/, accessed May 7, 2007.

Kipen HM, Cody RP, Goldstein BD. 1988. Hematologic effects of benzene: A thirty-five year longitudinal study of rubber workers. Toxicol Ind Health 4:411-430.

Kipen HM, Cody RP, Goldstein BD. 1989. Use of longitudinal analysis of peripheral blood counts to

validate historical reconstructions of benzene exposure. Environ Health Perspect 82:199-206.

Lamm SH, Walters AS, Wilson R, et al. 1989. Consistencies and inconsistencies underlying the quantitative assessment of leukemia risk from benzene exposure. Environ Health Perspect 82:289-297.

Lamm SH, Grunwald HW. 2006. Letter on benzene exposure and hematotoxicity. Science 312:998-9; author reply 998-9.

Lan Q, Zhang L, Li G, et al. 2004a. Hematotoxicity in workers exposed to low levels of benzene. Science 306:1774-1776.

Lan Q, Zhang L, Li G, et al. 2004b. Hematotoxicity in workers exposed to low levels of benzene: Supporting online material. Science 306:1774-1776.

Lan Q, Zhang L, Shen M, et al. 2005. Polymorphisms in cytokine and cellular adhesion molecule genes and susceptibility to hematotoxicty among workers exposed to benzene. Cancer Res 65(20):9574-9581.

Li L, Sun W, Gong Z, et al. 1992. Effect of low benzene exposure on neurobehavioral function, AChE in blood and brain and bone marrow picture in mice. Biomed Environ Sci 5(4):349-354.

Leonardos G, Kendall D, and Barnard N. 1969. Odor threshold determination of 53 odorant chemicals. J Air Pollut Control Assoc 19:91-95.

Midzenski MA, McDiarmid MA, Rithman N. 1992. Acute high dose exposure to benzene in shipyard workers. Am J Ind Med 22:553-565.

Mullin AH, Rando R, Esmundo F, et al. 1995. Inhalation of benzene leads to an increase in the mutant frequencies of a *lacI* transgene in lung and spleen tissues of mice. Mutat Res 327:121-129.

Nagata Y. 2003. Measurement of odor threshold by triangular odor bag method. Odor Measurement Review, Japan Ministry of the Environment. pp. 118-127.

National Research Council (NRC). 1988. Health risks of radon and other internally deposited alpha-emitters. Committee on the biological effects of ionizing radiation. Biological effects of ionizing radiation IV (BEIR IV). Washington DC: National Academy Press.

National Research Council (NRC). 1995. Prudent practices in the laboratory: handling and disposal of chemicals. Committee on the study of prudent practices for handling, storage, and disposal of chemicals in laboratories. Washington DC: National Academy Press.

Paustenbach DJ, Price PS, Ollison W, et al. 1992. Reevaluation of benzene exposure for the pliofilm (rubberworker) cohort (1936-1976). J Toxicol Environ Health 36(3):177-231.

Pyatt D, Hays S, Cushing C. 2005. Do children have increased susceptibility for developing secondary

acute myelogenous leukemia? Chemico-Biological Interactions 153-154:223-229.

Pyatt D, Hays S. 2006. Is age an independent risk factor for chemically induced acute myelogenous leukemia? In press.

Qu Q, Shore R, Li G, et al. 2002. Hematological changes among Chinese workers with a broad range of benzene exposures. Am J Ind Med 42(4):275-285.

Qu Q, Shore R, Li G, et al. 2003. Appendix A. Analyses of the combined data for year 1 and year 2: validation and evaluation of biomarkers in workers exposed to benzene in China. Boston, MA: Health Effects Institute, 1-54. Research number 115.

Rinsky RA, Young RJ, Smith AB. 1981. Leukemia in benzene workers. Am J Ind Med 2:217-245.

Rinsky RA, Smith AB, Hornung R, et al. 1987. Benzene and leukemia: An epidemiological risk assessment. N Eng J Med 316:1044-1050.

Rosenthal GJ, Snyder CA. 1985. Modulation of the immune response to *Listeria monocytogenes* by benzene inhalation. Toxicol Appl Pharmacol 80:502-510.

Rosenthal GJ, Snyder CA. 1987. Inhaled benzene reduces aspects of cell-mediated tumor surveillance in mice. Toxicol Appl Pharmacol 88:35-43.

Rothman N, Li Gl, Dosemeci M, et al. 1996. Hematotoxicity among Chinese workers heavily exposed to benzene. Am J Med 29(3):236-246.

Rothman N, Smith MT, Hayes RB, et al. 1997. Benzene poisoning, a risk factor for hematological Malignancy, is associated with the NQ01 [609] forward T mutation and rapid fractional excretion of chlorzoxazone. Cancer Res 57(14):2849-2842.

Rozen MG, Snyder CA, Albert RE. 1984. Depression in B- and T-lymphocyte mitogen-induced blastogenesis in mice exposed to low concentrations of benzene. Toxicol Lett 20:343-349.

Ruth JE. 1986. Odor Thresholds and Irritation Levels of Several Chemical Substances: A Review. American Industrial Hygiene J. 47: A142-A151.

Sabourin PJ, Bechtold WE, Griffith WC, et al. 1989. Effect of exposure concentration, exposure rate, and route of administration on metabolism of benzene by F344 rats and B6C3F1 mice. Toxicol Appl Pharmacol 99:421-444.

Schnatter AR, Rosamilia K, Wojcik NC. 2005. Review of the literature on benzene exposure and leukemia subtypes. Chem Biol Interact 153-154:9-21.

Snyder R, Hedli CC. 1996. An overview of benzene metabolism. Environ Health Perspect 104(Suppl 6):1165-1171.

Surveillance, Epidemiology, and End Results (SEER). 2006. Crude total US mortality rates, leukemia, for 1998-2003 by race and sex. www.seer.cancer.gov.

Texas Commission on Environmental Quality (TCEQ). 2006. Guidelines to develop effects screening levels, reference values, and unit risk factors. Chief Engineer's Office. RG-442.

Texas Commission on Environmental Quality (TCEQ). 2015a.TCEQ Guidelines to develop toxicity factors. RG-442. Office of the Executive Director. Austin, TX.

Texas Commission on Environmental Quality (TCEQ). 2015b. Approaches to derive odor-based values. Texas Commission on Environmental Quality. Office of the Executive Director, Austin, TX.

Texas Risk Reduction Program (TRRP). 2006. Chemical/physical properties table. www.tceq.state.tx.us/assets/public/remediation/trrp/trrptoxchph_2006.xls.

Toft K, Olofsson T, Tunek A, et al. 1982. Toxic effects on mouse bone marrow caused by inhalation of benzene. Arch Toxicol 51:295-302.

U.S. Department of Health and Human Services (USDHHS). 2005. Hematological and Iron-Related Analytes - Reference Data for Persons Aged 1 Year and Over: United States, 1988-94. Series 11, Number 247.

U.S. Environmental Protection Agency (USEPA). 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Washington, DC: U.S. Environmental Protection Agency. EPA/600/8-90/066F.

U.S. Environmental Protection Agency (USEPA). 1997. Response to peer review comments on the carcinogenic effects of benzene: An update. Washington, DC: U.S. Environmental Protection Agency. EPA600P97001A.

U.S. Environmental Protection Agency (USEPA). 1998. Carcinogenic effects of benzene: An update. Washington, DC: U.S. Environmental Protection Agency. EPA600P97001F.

U.S. Environmental Protection Agency (USEPA). 2000. Benchmark dose technical guidance document (external review draft). Washington, DC: U.S. Environmental Protection Agency. EPA/630/R-00/001.

U.S. Environmental Protection Agency (USEPA). 2001. National-Scale Air Toxics Assessment (NATA) for 1996 (Draft). Washington, DC: U.S. Environmental Protection Agency. EPA/453/R-01/003. Associated NATA emissions data available at http://www.epa.gov/ttn/atw/nata/tablemis.html.

U.S. Environmental Protection Agency (USEPA). 2002. Toxicological review of benzene (noncancer effects). Washington, DC: U.S. Environmental Protection Agency. EPA/635/R-02/001F.

U.S. Environmental Protection Agency (USEPA). 2005. Supplemental Guidance for Assessing

Susceptibility from Early-Life Exposure to Carcinogens. Washington, DC: U.S. Environmental Protection Agency. EPA/630/R-03/003F.

Utterback DF, Rinsky RA. 1995. Benzene exposure assessment in rubber hydrochloride workers: A critical evaluation of previous estimates. Am J Ind Med 27(5):661-676.

Voluntary Children's Chemical Evaluation Program (VCCEP). 2006. Report of the peer consultation meeting on benzene. Submission by American Chemistry Council Benzene, Toluene, and Xylenes Consortium.

Ward CO, Kuna RA, Snyder NK, et al. 1985. Subchronic inhalation toxicity of benzene in rats and mice. Am J Ind Med 7:457-473.

Ward JB, Ammenheuser MM, Ramanujam VMS, et al. 1992. The mutagenic effects of low level sub-acute inhalation exposure to benzene in CD-1 mice. Mutat Res 268(1):49-57.

Ward E, Hornung R, Morris J, et al. 1996. Risk of low red or white blood cell count related to estimated benzene exposure in a rubberworker cohort (1940-1975). Am J Ind Med 29(3):247-257.

Wiester MJ, Winsett DW, Richards JH, et al. 2002. Partitioning of benzene in blood: Influence of hemoglobin type in humans and animals. Environ Health Perspect 110(3):255-261.

World Health Organization (WHO). 1993. International Programme on Chemical Safety, Environmental Health Criteria 150: Benzene. World Health Organization, Geneva.

Xia Z-L, Xi-Peng J, Pei-Lian L, et al. 1995. Ascertainment corrected prevalence rate (ACPR) of leukopenia in workers exposed to benzene in small-scale industries calculated with capture-recapture methods. Biomed Environ Sci 8:30-34.

Yin SN, Li GL, Hu Y, et al. 1987b. Symptoms and signs of workers exposed to benzene, toluene or the combination. Ind Health 25:113-130.

5.2 Other Studies and Documents Reviewed by the TS

Aksoy M. 1989. Hematotoxicity and carcinogenicity of benzene. Environ Health Perspect 82:193-197.

Agency for Toxic Substances and Disease Registry (ATSDR). 2005. Disposition of peer review comments for toxicological profile for benzene.

American Thoracic Society. 2000. What constitutes an adverse health effect of air pollution? Am J Respir Crit Care Med 161:665-673.

Baarson K, Snyder CA, Green J, et al. 1982. The hematotoxic effects of inhaled benzene on peripheral blood, bone marrow, and spleen cells are increased by ingested ethanol. Toxicol Appl Pharmacol 64:393-404.

Belson M, Kingsley B, Holmes A. 2007. Risk factors for acute leukemia in children: a review. Environ

Health Perspect 115:138-145.

Bird MG, Greim H, Snyder R, et al. 2005. International symposium: recent advances in benzene toxicity. Chem Biol Interact 153-154:1-5.

Bogadi-Šare A, Zavalić M, Trošić I, et al. 2000. Study of some immunological parameters in workers occupationally exposed to benzene. Int Arch Occup Environ Health 2000:397-400.

Bond GG, McLaren EA, Baldwin CL, et al. 1986b. An update of mortality among chemical workers exposed to benzene. Br J Ind Med 43:685-691.

Brown EA, Shelley ML, Fisher JW. 1998. A pharmacokinetic study of occupational and environmental benzene exposure with regard to gender. Risk Anal 18(2):205-213.

Buckley JD, Robison LL, Swotinsky L, et al. 1989. Occupational exposure of parents of children with acute nonlymphocytic leukemia: A report from the Children's Cancer Study Group. Cancer Res 49:4030-4037.

Clark SC, Kamen R. 1987. The human hematopoetic colony stimulating factors. Science 263:1229-1237.

Collins JJ, Ireland BK, Easterday PA, et al. 1997. Evaluation of lymphopenia among workers with low level benzene exposure and the utility of routine data collection. J Occup Environ Med 39(3):232-237.

Crump KS. 1996. Risk of benzene-induced leukemia predicted from the pliofilm cohort. Environmental Health Perspect 104(Suppl 6):1437-1441.

Davis FA. 1989. Taber's cyclopedic medical dictionary, 17th Edition. Philadelphia, PA: FA Davis Company.

Dempster AM, Snyder CA. 1991. Kinetics of granulocytic and erythroid progenitor cells are affected differently by short-term, low level benzene exposure. Arch Toxicol 65(7):556-561.

Dosemeci M, Li GL, Hayes RB, et al. 1994. Cohort study among workers exposed to benzene in China: II. Exposure assessment. Am J Ind Med 26(3):401-411.

Duarte-Davidson R, Courage C, Rushton L, et al. 2001. Benzene in the environment: An assessment of the potential risks to the health of the population. Occup Environ Med 58(1):2-13.

Glass DC, Gray CN, Jolley DJ, et al. 2003. Leukemia risk associated with low-level benzene exposure. Epidemiology 15(5):569-577.

Glatt H, Padykula R, Berchtold GA, et al. 1989. Multiple activation pathways of benzene leading to products with varying genotoxic characteristics. Environ Health Perspect 82:81-89.

Hayes RB, Yin SN, Dosemeci M, et al. 1996. Mortality among benzene-exposed workers in China.

Environ Health Perspect 104(Suppl 6):1349-1352.

Hayes RB, Songnian Y, Dosemeci M, et al. 2001. Benzene and lymphohematopoietic malignancies in humans. Am J Ind Med 40(2):117-126.

Huff JE, Haseman JK, DeMarini DM, et al. 1989. Multiple-site carcinogenicity of benzene in Fischer 344 rats and B6C3F$_1$ mice. Environ Health Perspect 82:125-163.

Infante-Rivard C, Siemiatycki J, Lakhani R, et al. 2005. Maternal exposure to occupational solvents and childhood leukemia. Environ Health Perspect 113:787-807.

Institute for Health and Consumer Protection. 2007. European Union risk assessment report for benzene, C$_{10-13}$ alkyl derives. European Chemicals Bureau. Available at http://ecb.jrc.cec.eu.int/documents/Existing-chemicals/RISK_ASSESSMENT/REPORT/

Keller KA, Snyder CA. 1986. Mice exposed in utero to low concentrations of benzene exhibit enduring changes in their colony forming hematopoietic cells. Toxicology 42:171-181.

Keller KA, Snyder CA. 1988. Mice exposed *in utero* to 20 ppm benzene exhibit altered numbers of recognizable hematopoietic cells up to seven weeks after exposure. Fundam Appl Toxicol 10:224-232.

Kelsey KT, Ross D, Traver RD, et al. 1997. Ethnic variation in the prevalence of a common HAD(P)H quinone oxidoreductase polymorphism and its implications for anticancer chemotherapy. Br J Cancer 76:852-854.

Khuder SA, Youngdale MC, Schaub EA. 1999. Assessment of complete blood count variations among workers exposed to low levels of benzene. J Occup Environ Med 41(9):821-826.

Kuna RA, Kapp RW. 1981. Embryotoxic/teratogenic potential of benzene vapor in rats. Toxicol Appl Pharmacol 57:1-7.

Lamm SH, Engel A, Byrd DM. 2005. Non-Hodgkin lymphoma and benzene exposure: a systematic literature review. Chem Biol Interact 153-154:231-237.

Larson DE. 1996. Mayo clinic family health book, 2nd Edition. New York, NY: William Morrow and Company, Inc.

Lin YS, Vermeulen R, Tsai CH, et al. 2007. Albumin adducts of electrophilic benzene metabolites in benzene-exposed and control workers. Environ Health Perspect 115:28-34.

Loh MM, Houseman EA, Gray GM, et al. 2006. Measured concentrations of VOCs in several non-residential microenvironments in the Unites States. Environ Sci Technol 40:6903-6911.

Maltoni C, Conti B, Cotti G. 1983. Benzene: A multipotential carcinogen: Results of long-term bioassays performed at the Bologna Institute of Oncology. Am J Ind Med 4:589-630.

McKinney PA, Alexandria FE, Cartwright RA, et al. 1991. Parental occupations of children with leukaemia in West Cumbria, North Humberside, and Gateshead. Br Med J 302(6778):681-687.

Medinsky MA, Sabourin PJ, Henderson RF, et al. 1989. Differences in the pathways for metabolism of benzene in rats and mice simulated by a physiological model. Environ Health Perspect 82:43-49.

Morgan GJ, Alvares CL. 2005. Benzene and the hemopoietic stem cell. Chem Biol Interact153-154:217-222.

Murray FJ, John JA, Rampy LW, et al. 1979. Embryotoxicity of inhaled benzene in mice and rabbits. Am Ind Hyg Assoc J 40:993-998.

Nakajima T, Okuyama S, Yonekura I, et al. 1985. Effects of ethanol and phenobarbital administration on the metabolism and toxicity of benzene. Chem Biol Interact 55:23-38.

Nebert DW, Roe AL, Vandale SE, et al. 2002. NAD(P)H:quinone oxidoreductase (NQO1) polymorphism, exposure to benzene, and predisposition to disease: A huGE review. Genet Med 4(2):62- 70.

Norpoth KH, Müller G, Schell CH, et al. 1996. Phenylguanine found in urine after benzene exposure. Environ Health Perspect 104(Suppl 6):1159-1163.

O'Conner SM, Boneva RS. 2007. Infectious etiologies of childhood leukemia: plausibility and challenges to proof. Environ Health Perspect 115:146-150.

Ott MG, Townsend JC, Fishbeck WA, et al. 1978. Mortality among workers occupationally exposed to benzene. Arch Environ Health 33:3-10.

Paxton MB, Chinchilli VM, Brett SM, et al. 1994a. Leukemia risk associated with benzene exposure in the pliofilm cohort: I. mortality update and exposure distribution. Risk Analysis 14(2):147-154.

Paxton MB, Chinchilli VM, Brett SM, et al. 1994b. Leukemia risk associated with benzene exposure in the pliofilm cohort. II. Risk estimates. Risk Anal 14(2):155-161.

Paxton MB. 1996. Leukemia risk associated with benzene exposure in the pliofilm cohort. Environ Health Perspect 104(Suppl 6):1431-1436.

Pazdur R. 1993. Medical Oncology: A Comprehensive Review. New York, NY: PRR Huntington Publishing Co.

Pui C, Hancock M, Raimondi S, et al. 1990. Myeloid neoplasia in children treated for solid tumours, Lancet 336:417–421.

Rickert DE, Baker TS, Bus JS, et al. 1979. Benzene disposition in the rat after exposure by inhalation. Toxicol Appl Pharmacol 49:417-423.

Rozen MG, Snyder CA. 1985. Protracted exposure of C57BL/6 mice to 300 ppm benzene depresses B- and T-lymphocyte numbers and mitogen responses. Evidence for thymic and bone marrow proliferation in response to the exposures. Toxicology 37:13-26.

Seaton MJ, Schlosser PM, Bond JA, et al. 1994. Benzene metabolism by human liver microsomes in relation to cytochrome P450 2E1 activity. Carcinogenesis 15:1799-1806.

Schnatter AR, Nicolich MJ, Bird MG. 1996a. Determination of leukemogenic benzene exposure concentrations: Refined analyses of the Pliofilm cohort. Risk Anal 16(6):833-840.

Schnatter AR, Armstrong TW, Thompson LS, et al. 1996b. The relationship between the low-levelbenzene exposure and leukemia in Canadian petroleum distribution workers. Environ Health Perspect Suppl 104:1375-1379.

Shaw G, Lavey R, Jackson R, et al. 1984. Association of childhood leukemia with maternal age, birth order, and paternal occupation. A case-control study. Am J Epidemiol 119(5):788-795.

Shu XO, Gao YT, Brinton LA, et al. 1988. A population based case-control study of childhood leukemia in Shanghai. Cancer 62:635-644.

Smith MT, Yager JW, Steinmetz KL, et al. 1989. Peroxidase-dependent metabolism of benzene's phenolic metabolites and its potential role in benzene toxicity and carcinogenicity. Environ Health Perspect 82:23-29.

Smith MT. 1996. The mechanism of benzene-induced leukemia: A hypothesis and speculations on the causes of leukemia. Environ Health Perspect 104:1219-1225.

Smith MT, Zhang L. 1998. Biomarkers of leukemia risk: Benzene as a model. Environ Health Perspect Suppl 106:937-946.

Snyder CA, Goldstein BD, Sellakumar A. 1978. Hematotoxicity of inhaled benzene to Sprague-Dawley rats and AKR mice at 300 ppm. J Toxicol Environ Health 4:605-618.

Snyder CA, Goldstein BD, Sellakumar AR, et al. 1980. The inhalation toxicology of benzene: Incidence of hematopoietic neoplasms and hematotoxicity in AKR/J and C57BL/6J mice. Toxicol Appl Pharmacol 54:323-331.

Snyder CA, Goldstein BD, Sellakumar A, et al. 1982. Toxicity of chronic benzene inhalation: CD-1 mice exposed to 300 ppm. Bull Environ Contam Toxicol 29:385-391.

Snyder CA, Sellakumar AR, James DJ, et al. 1988. The carcinogenicity of discontinuous inhaled benzene exposures in CD-1 and C57BL/6 mice. Arch Toxicol 62:331-335.

Snyder R, Kalf GF. 1994. A perspective on benzene leukemogenesis. Crit Rev Toxicol 24(3):177-209.

Sorahan T, Kinlen LJ, Doll R. 2005. Cancer risks in a historical UK cohort of benzene exposed workers.

Occup Environ Med 62:231-236.

Testa NG, Dexter TM. 1989. Long-term hematopoietic damage: concepts, approaches, and results relevant to the study of environmental toxins. Environ Health Perspect 82:51-56.

Tice RR, Luke CA, Drew RT. 1989. Effect of exposure route, regimen, and duration on benzene induced genotoxic and cytotoxic bone marrow damage in mice. Environ Health Perspect 82:65-74.

Tsai SP, Wen CP, Weiss NS, et al. 1983. Retrospective mortality and medical surveillance studies of workers in benzene areas of refineries. J Occup Med 25:685-692.

Tsai SP, Fox EE, Ransdell JD, et al. 2004. A hematology surveillance study of petrochemical workers exposed to benzene. Regul Toxicol Pharmacol 40:67-73.

Valentine JL, Lee SS, Seaton MJ, et al. 1996. Reduction of benzene metabolism and toxicity in mice that lack CYP2E1 expression. Toxicol Appl Pharmacol 141(1):205-213.

Vermeulen R, Li G, Lan Q, et al. 2004. Detailed exposure assessment for a molecular epidemiology study of benzene in two shoe factories in China. Ann Occup Hyg 48:105-116.

Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238:476-483.

Wells MS, Nerland DE. 1991. Hematotoxicity and concentration-dependent conjugation of phenol in mice following inhalation exposure to benzene. Toxicol Lett 56(1-2):159-166.

Witz G, Latriano L, Goldstein BD. 1989. Metabolism and toxicity of *trans,trans*-muconaldehyde, and open-ring microsomal metabolite of benzene. Environ Health Perspect 82:19-22.

Wong O. 1987. An industry wide mortality study of chemical workers occupationally exposed to benzene: II. Dose response analyses. Br J Ind Med 44:382-395.

World Health Organization (WHO). 2000. Air quality guidelines. 2nd ed. Geneva, Switzerland: World Health Organization.

Wynter E, Ploemacher RE. 2001. Assays for the assessment of human hematopoietic stem cells. J Biol Regul Homeost Agents 15:23-7.

Yin SN, Li GL, Tain FD, et al. 1987a. Leukemia in benzene workers: A retrospective cohort study. Br J Ind Med 44:124-128.

Yin SN, Li GL, Tain FD, et al. 1989. A retrospective cohort study of leukemia and other cancers in benzene workers. Environ Health Perspect 82:207-213.

Yin SN, Linet MS, Hayes RB, et al. 1994. Cohort study among workers exposed to benzene in China: I.

General methods and resources. Am J Ind Med 26(3):383-400.

Yin SN, Hayes RB, Linet MS, et al. 1996a. A cohort study of cancer among benzene-exposed workers in China: Overall results. Am J Med 29(3):227-235.

Yin SN, Hayes RB, Linet MS, et al. 1996b. An expanded cohort study of cancer among benzene exposed workers in China. Environ Health Perspect 104(Suppl 6):1339-1341.

Appendix A: Glossary of Terms

The following glossary of terms is intended to aid the reader in the understanding of this and other documents pertaining to the toxicity of benzene.

Acute Myelogenous (Nonlymphocytic) Leukemia - A malignant clonal proliferation of immature myeloid hematopoietic progenitor cells (i.e., myeloblasts; Pazdur et al. 1993), which are precursors to myeloid white blood cells (e.g., granulocytes: neutrophils, eosinophils, and basophils; Larson 1996); a neoplastic disease of the hematopoietic system in which there is diminished production of normal erythrocytes, granulocytes, and platelets, which leads to death by anemia, infection, or hemorrhage (ATSDR 1997).

Anemia - A decrease in the number of erythrocytes (i.e., red blood cells) (Davis 1989).

Aplastic Anemia - A more severe reduction in all three major blood cell types (i.e., erythrocytes, leukocytes, and thrombocytes) than pancytopenia in which the bone marrow ceases to function and stem cells never reach maturity. The depression in bone marrow function occurs in two stages: hyperplasia (increased synthesis of blood cell elements) followed by hypoplasia (decreased synthesis of blood cell elements). Bone marrow function progressively decreases until it is necrotic and filled with fatty tissue, a condition known as myeloblastic dysplasia. Aplastic anemia can progress to acute nonlymphocytic (myelogenous) leukemia (ATSDR 2005).

Blood Count - Enumeration of the red corpuscles and leukocytes per cubic millimeter of whole blood, normally: 5 million (male) and 4.5 million (female) average for erythrocytes, 5,000-10,000 leukocytes, 150,000-400,000 platelets. The differential blood count indicates the percentage of various white blood cells (WBCs), normally: 40-60% neutrophils, 1-3% eosinophils, 0.5-1% basophils, 20-40% lymphocytes, 4-8% monocytes (Davis 1989).

Chronic Lymphocytic Leukemia - A clonal expansion of mature lymphocytes (i.e., B- or T-cells) in the peripheral blood and bone marrow (Pazdur et al. 1993).

Chronic Myelogenous (Nonlymphocytic) Leukemia - A clonal expansion of pluripotent hematopoietic stem cells which do not mature normally (Pazdur et al. 1993).

Colony Forming Units – Colonies of recognizable mature cells which form from clonogenic progenitor cells, which produce large numbers of mature blood cells found in circulation and are the more developmentally restricted progeny of pluripotent stem cells (Wynter and Ploemacher 2001).

Cytopenia - A decrease in various cellular elements of the circulating blood which is a common clinical finding in benzene hematotoxicity and may manifest itself as pancytopenia and aplastic anemia or as unicellular cytopenias (e.g., leukopenia, anemia, thrombocytopenia) (ATSDR

1997).

Granulocyte - A granular/polymorphonuclear leukocyte (neutrophil, eosinophil, or basophil; Davis 1989).

Granulocytopenia - Abnormal reduction of granulocytes in the blood (Davis 1989).

Granulocytosis - Abnormal increase in the number of granulocytes in the blood (Davis 1989).

Hematocrit - The volume of erythrocytes packed by centrifugation into a given volume of blood expressed as the percentage of total blood volume, or as the volume in cubic centimeters of erythrocytes packed by centrifugation of blood. Normally: 47% average for men (40-54% range) and 42% for women (37-47% range) at sea level (Davis 1989).

Hematopoiesis – The production and development of blood cells from multipotent hematopoietic stem cells, which can become any type of cell in the blood system (Davis 1989).

Hematopoietic System - The blood-forming organs, especially bone marrow and lymph nodes (Davis 1989). See Clark and Kamen (1987) for an overview of hematopoietic development.

Hematotoxic - Toxic to blood cells (Davis 1989).

Hodgkin's Lymphoma - A malignant solid tumor of the lymphoreticular system, usually the lymph nodes, diagnosed by the presence of the Reed-Sternberg cell. Other cells present include lymphocytes, granulocytes, histiocytes, plasma cells, and fibroblasts (Davis 1989, Pazdur et al. 1993).

Leukemia - (1) An unregulated clonal proliferation of neoplastic stem cells of the hematopoietic system (i.e., blood-forming tissues such as the bone marrow) in which the neoplastic cells eventually replace the normal resident cells. Leukemia may be divided into acute and chronic forms, referring to the rapidity of the development of symptoms, signs, and complications of these two types. Acute leukemias are classified into two large groups, depending on whether the clonal population is lymphoid (immature B- and T-cells) or myeloid (immature erythrocytes, granulocytes, and platelets) in origin. Chronic leukemia is also divided into lymphoid (mature B- and T-cells) and myeloid (immature pluripotent hematopoietic stem cells) classes (Pazdur et al. 1993); (2) Cancers of the body's blood-forming tissues (including bone marrow and lymph system) resulting in high concentrations of abnormal white blood cells in the bone marrow, lymph system, and blood stream which can interfere with the functions of vital organs and overwhelm the production of normal white and red blood cells and platelets. Leukemia is classified as myelogenous or lymphocytic. Myelogenous leukemia is a cancer of the granulocytes (i.e., neutrophils, eosinophils, basophils), a type of white blood cell formed in the bone marrow. Lymphocytic leukemia involves the lymphocytes, a type of white blood cell produced in the lymph system and marrow. Myelogenous and lymphocytic leukemias may be

further divided into acute and chronic forms, referring to the rapidity of the development of symptoms, signs, and complications of these two types. Acute leukemia progresses rapidly with the proliferation of immature cells (i.e., blasts), while chronic leukemia progresses more slowly with the overproduction of mature and immature white blood cells (Larson 1996). Below is a classification table for malignant neoplasm of the hematopoietic and lymphatic tissue. See Lamm (1989) for additional information.

Leukemia/Lymphoma Type	International Classification of Disease
Leukemia	
Lymphoid	204
Acute (ALL)	204.0
Chronic (CLL)	204.1
Myeloid	205
Acute (AML)	205.0
Chronic (CML)	205.1
Monocytic	206
Other	207
Unspecified	208
Lymphoma	
Non-Hodgkins	200
Reticulosarcoma	200.0
Lymphosarcoma	200.1
Hodgkins	201
Others and Mixed (Hairy cell, histiocytosis)	202
Multiple myeloma (plasma cell origin)	203

Leukocytes – White blood cells which defend the body against infection and tissue damage. They include various cells from both myeloid and lymphoid lineages, and are often classified based on the presence or absence of staining granules in the cytoplasm: granulocytes (e.g., neutrophils, basophils, eosinophils) and agranulocytes (e.g., lymphocytes, monocytes) (Davis 1989).

Leukocyte Alkaline Phosphatase (LAP) - Increased LAP activity is an indicator of myelofibrosis and is associated with decreased WBC counts and changes in bone marrow activity (ATSDR 2005).

Leukopenia - A decrease in the number of white blood cells (leukocytes), which include granulocytes (e.g., polymorphonuclears: basophils, eosinophils, neutrophils) and agranulocytes (e.g., mononuclears: monocytes/macrophage, lymphocytes). Granulocytes and monocytes arise from the myeloid stem cell in the bone marrow, while lymphocytes arise from the lymphoid stem cells in the bone marrow which migrate to the thymus (T-cells), spleen and lymph nodes (B-cells) to mature. Synonyms include: granulocytopenia, leukocytopenia (Davis 1989).

Lymphomas – Non-Hodgkin's lymphoma is a group of malignant solid tumors of lymphoid tissues. Hodgkin's lymphoma usually begins in lymph nodes of the supraclavicular, high cervical, or mediastinal area (Davis 1989).

Lymphocytes - A subset of leukocytes consisting of several cell types which form from pluripotent stem cells in the bone marrow and travel between the blood and lymphatic tissue to provide the body's main means of immunity. *B lymphocytes* (B cells) provide *humoral immunity* by migrating to the spleen, lymph nodes, and other peripheral lymphoid tissue where they come into contact with foreign antigens to become mature functioning antigen-specific cells able to independently identify foreign antigens and differentiate into antibody-producing *plasma cells* (only source of antibodies) or *memory cells* (enable the body to quickly produce antibodies at a later date). Many immature B cells are found in the spleen, which due to high blood flows provides great opportunity for antigen exposure and subsequent B cell maturation. *T lymphocytes* (T cells) provide cell-mediated immunity (requires cell interactions) by migrating to the thymus to mature before circulating throughout the body to destroy or neutralize invading organisms. T lymphocyte subtypes include *helper/T4 cells*, *suppressor/T8 cells*, and two types of cytotoxic cells (i.e., *natural killer cells, cytotoxic T cells*). Helper/T4 cells, which control the activities of other T cells, are activated when a macrophage presents a foreign antigen on its surface next to a histocompatibility antigen (a.k.a. antigen processing) and secretes interleukin-1. Activated helper/T4 cells: secrete interleukin-2, which stimulates natural killer cells, cytotoxic T cells, and B-cells; secrete gamma interferon to inhibit virus growth and stimulate macrophage cytotoxicity and the processing of antigens; and activate suppressor/T8 cells after several days which inhibit T4 cells and B cells to prevent excessive lymphocyte activity (Davis 1989).

Lymphocytopenia/Lymphopenia - A deficiency of lymphocytes (i.e., B- and T-cells) in the blood (Davis 1989).

Mean Corpuscular Volume – The average volume of individual red blood cells in cubic millimeters, which can be calculated by dividing the hematocrit (volume of packed red blood cells per 1,000 mL blood) by the red blood cell count (red blood cell count in millions per cubic millimeter) (Davis 1989).

Mitogen-Induced Blastogenesis - A mitogen is a protein used to stimulate cells to divide (i.e., induce mitosis), and mitogens are frequently used to study the proliferation of lymphocytes *in vitro* (Davis 1989). Blastogenesis refers to the proliferative ability of cells (e.g., the

transformation of small lymphocytes into large, undifferentiated cells capable of mitosis) (Rozen 1984). Therefore, mitogen-induced blastogenesis is a measure of the proliferative ability of cells in response to mitogen stimulation (e.g., the number of colony-forming cells).

Myeloblastic Dysplasia - A condition resulting from the progression of aplastic anemia in which bone marrow function progressively decreases until necrotic and filled with fatty tissue (ATSDR 1997).

Myelocyte - A large cell in red bone marrow from which leukocytes are derived (Davis 1989).

Myelodysplastic Syndromes (a.k.a. preleukemia) – see definition for preleukemia.

Myeloma - A tumor originating in cells of the hematopoietic portion of the bone marrow. Multiple myeloma is a neoplastic disease characterized by the infiltration of bone and bone marrow by myeloma cells forming multiple tumor masses (Davis 1989).

Pancytopenia - Reduction in the number of all three major cell types of blood cells, erythrocytes (red blood cells), thrombocytes (platelets), and leukocytes (white blood cells), which results from a reduction in the ability of red bone marrow (vertebrae, sternum, ribs and pelvis) to produce adequate numbers of mature blood cells from its immature multipotent myeloid stem cells (ATSDR 2005).

Preleukemia - A group of nondiagnostic physical and blood abnormalities that may indicate that leukemia will develop later. They include: anemia, neutropenia, sometimes a relative lymphopenia, marked monocytosis, purpura, susceptibility to infections, and slow healing of skin and mucous membrane lesions (Davis 1989). Signs include loss of leukocytes and other blood elements, bone marrow histopathology, and enlarged spleen (ATSDR 2005). Myelodysplastic syndromes are preleukemic (USEPA 1998).

Reticulocyte - A red blood cell containing a network of granules or filaments representing an immature stage in development; normally about 1% of circulating red blood cells (Davis 1989).

Reticulocytosis - Increase in the number of reticulocytes in circulating blood, which is indicative of active erythropoiesis in red bone marrow (Davis 1989).

Thrombocytopenia - A decrease in the number of blood platelets (i.e., thrombocytes) (Davis 1989).

Appendix B: Benchmark Dose Modeling Results

Appendix B1: Rozen et al. (1984)

Results from the benchmark dose modeling of lymphocyte count depression data read from Figure 1 in Rozen et al. (1984) using USEPA Benchmark Dose Software (Version 1.4.1) are presented below. The benchmark dose low (BMDL) of approximately 4 ppm at 1 standard deviation (SD) from the control mean supports a LOAEL-to-NOAEL UF of 3 as being sufficiently conservative. Goodness of fit to the Hill model was by visual inspection with scaled residuals < 2 and goodness-of-fit p values > 0.1.

Rozen (1984) Modeled Data

Dose Group	Dose (mean ppm)	Estimated Mean Cell Number	Estimated SE	Estimated SD	Number of Subjects
controls	0	8604	690	2182	10
	10.2	5621	414	1309	10
	31	5621	690	2182	10
	100	3052	828	2618	10
	301	2500	414	1309	10

Estimated lymphocyte values read from Figure 1 of Rozen (1984)
Estimated standard deviation (SD) calculated using the formula SD = SE * ((n)^0.5)
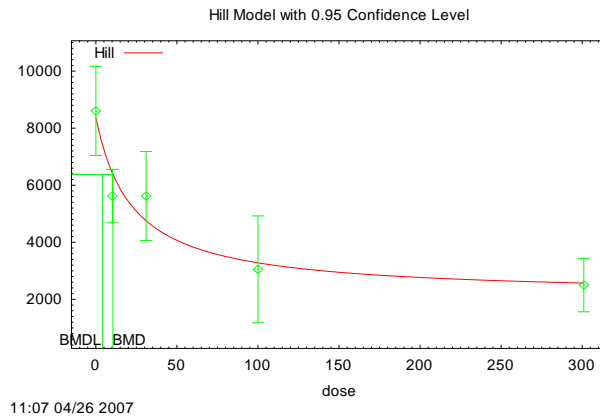
Benchmark Dose Computation:

Homogeneous variance

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

 BMD = 10.532 ppm

 BMDL = 4.03205 ppm

Hill Model with 0.95 Confidence Level

11:07 04/26 2007

Appendix B2: Rothman et al. (1996)

USEPA (2002) performed BMD modeling with EPA's BMDM Software (version 1.20) using the Rothman et al. (1996) data. A detailed discussion is available in Section 5.1.2. *Benchmark Dose Modeling* of USEPA (2002). A summary of results from the benchmark dose modeling of absolute lymphocyte count data from Rothman et al. (1996) using USEPA BMDM Software (Version 1.4.1) are presented below and are similar to values and results derived by USEPA (2002). Exposure concentrations were log-transformed using the equation in USEPA (2002) of $d'=\ln(d+1)$. The BMDL at 1 SD from the control mean using the continuous linear model is 2.1, which transformed back to the original exposure scale is 7.2 ppm.

Rothman (1996) Modeled Data

Dose Group	Dose (Median 8-hr TWA ppm)	Transformed Dose (d'= ln(dose + 1))	Mean (cell number x1000)	SD	Number of Subjects
controls	0.02	0.0198	1.9	0.4	44
low	13.6	2.68	1.6	0.3	22
high	91.9	4.53	1.3	0.3	22

Benchmark Dose Computation:
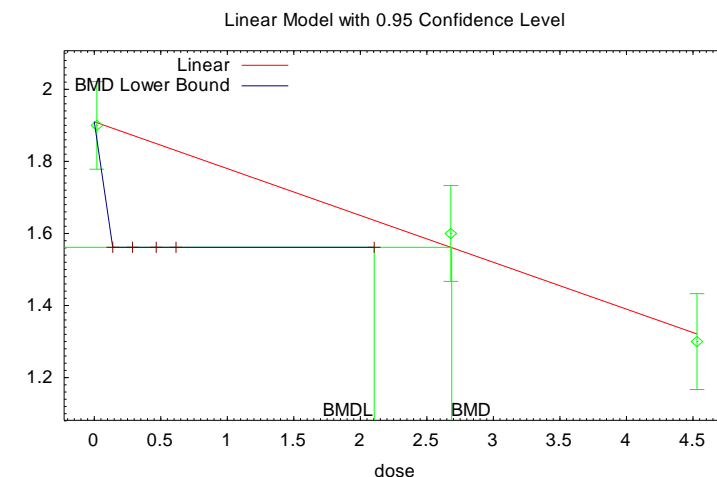
Homogeneous variance

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level =   0.95

BMD = 2.68656 ppm (transformed value)

BMDL = 2.1042 ppm (transformed value) = 7.2 ppm on the original exposure scale

11:11 04/26 2007

Appendix B3: Lan et al. (2004a)

Results from the benchmark dose modeling of lymphocyte count (B-cell) depression data read from Lan et al. (2004a) using USEPA Benchmark Dose Modeling Software (Version 1.4.1) are presented below. The BMCL is approximately 0.26 ppm at 0.4 SD from the control mean. A benchmark response of 0.4 SD was utilized so that the resulting BMDL would fall below the 0.36 ppm mean benzene level reported for a subgroup which could not be included in benchmark dose modeling but was reported to have significantly decreased WBCs, granulocytes, lymphocytes, and B cells. Goodness of fit to the Hill model was by visual inspection with scaled residuals < 2 and the goodness-of-fit > 0.1 for model fit (test 4).

Lan et al. (2004a) Modeled Data

Dose Group (ppm)	Dose (mean ppm)	Mean (B cell number)	SD	Number of Subjects
controls	0	218	94	140
< 1	0.57	186	95	109
1 to < 10	2.85	170	75	110
>= 10	28.73	140	101	31

Benchmark Dose Computation:
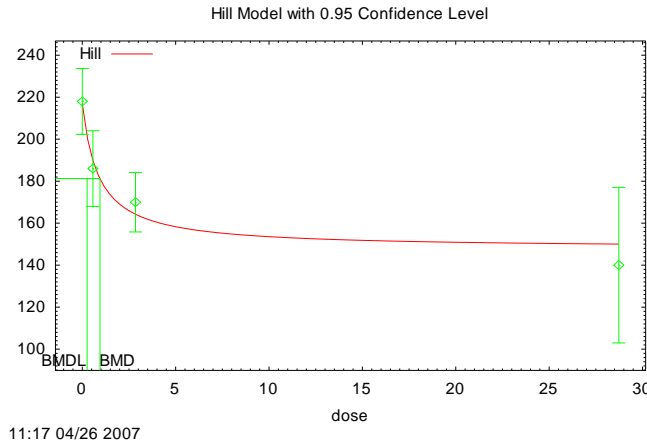
Homogeneous variance

Specified effect = 0.4

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.948615 ppm

BMDL = 0.260685 ppm

Hill Model with 0.95 Confidence Level

11:17 04/26 2007

Appendix C: US and Texas Survival, AMML, and All Leukemia Mortality Rates

Survival Rates			Acute Myeloid and Monocytic Leukemia (AMML) Mortality Rates			All Leukemia Mortality Rates		
Age (years)	US (2000)	Texas (2003)	Age (years)	US (1999-2003)	Texas (1999-2003)	Age (years)	US (2000-2003)	Texas (1999-2003)
0	1	1	0	0.2	0.3	0	0.7	0.9
1	0.993	0.993	01-04	0.3	0.4	01-04	0.9	0.9
5	0.992	0.992	05-09	0.2	0.1	05-09	0.7	0.6
10	0.991	0.991	10-14	0.2	0.2	10-14	0.8	0.9
15	0.990	0.990	15-19	0.4	0.3	15-19	1.1	1.3
20	0.987	0.987	20-24	0.4	0.4	20-24	1.2	1.5
25	0.982	0.982	25-29	0.5	0.4	25-29	1.1	1.1
30	0.977	0.977	30-34	0.5	0.5	30-34	1.3	1.4
35	0.971	0.972	35-39	0.7	0.7	35-39	1.6	1.5
40	0.963	0.964	40-44	0.9	0.7	40-44	2.0	1.8
45	0.952	0.952	45-49	1.3	1.3	45-49	2.9	3.4
50	0.935	0.935	50-54	2.0	1.8	50-54	4.4	4.2
55	0.911	0.911	55-59	3.3	3.5	55-59	7.5	8.4
60	0.875	0.876	60-64	5.5	5.7	60-64	12.9	13.2
65	0.821	0.824	65-69	8.8	9.0	65-69	20.8	21.3
70	0.746	0.751	70-74	13.1	13.2	70-74	33.0	31.8
75	0.642	0.651	75-79	17.5	17.1	75-79	47.0	43.4
			80-84	20.2	19.1	80-84	63.2	65.5
			85+	18.8	16.8	85+	81.5	81.3

Appendix D: Derivation of the 24-hour Reference Value for Benzene

The 24-hour ReV for benzene was finalized June 16, 2014

D.1 Background

The Texas Commission on Environmental Quality (TCEQ) reviews air concentration data collected from its monitoring network from a health effects perspective, that is, for the potential to cause adverse health effects (and welfare effects as well). The TCEQ has historically developed 1-hour health-protective and welfare-based (i.e., odor, vegetation) Air Monitoring Comparison Values (AMCVs) for comparison to 1-hour autoGC data collected from its ambient air monitoring network as well as for comparison to other data (e.g., 30-minute Summa canister results). The TCEQ also develops chronic (i.e., lifetime) health-protective and welfare-based (i.e., vegetation) AMCVs for comparison to long-term means (i.e., annual averages or longer) based on 1-hour autoGC data or every sixth-day 24-hour canister results. However, the TCEQ has historically not developed 24-hour, health-based AMCVs for comparison to individual 24-hour canister results from its monitoring network. Consequently, only a very limited evaluation of the reported 24-hour levels is possible without 24-hour AMCVs because 1-hour and chronic (i.e., lifetime) AMCVs are largely inappropriate for this purpose. Thus, the development of 24-hour AMCVs is necessary for the best possible health effects evaluation of individual 24-hour canister VOC results, and would significantly complement the 1-hour and chronic evaluations of chemicals of interest (TCEQ 2014; 2015).

Benzene is a VOC for which 24-hour canister data are collected. Additionally, as a known human carcinogen that is ubiquitously-detected in the TCEQ ambient air monitoring network, benzene is of significant agency and public interest. Therefore, benzene is a chemical for which a 24-hour, health-protective AMCV has been developed. The purpose of this document is to summarize the main steps involved in the development of the 24-hour AMCV for benzene. General steps discussed below for developing a 24-hour value include:

- availability of appropriate toxicity studies that provide meaningful information to evaluate a 24-h exposure duration;

- identification of a point of departure for the critical effect(s) based on review of dose-response data for relevant toxicity endpoints;

- consideration of an exposure duration adjustment;

- animal-to-human inhalation dosimetric adjustment;

- selection and application of applicable uncertainty factors; and

- derivation of the 24-hour AMCV.

Please refer to Section 3.1.1.1 and Table 2 for detailed information on physical/chemical properties. Refer to Section 3.1.2 for mode of action information.

D.2 Potential Points of Departure

Benzene can produce various toxic effects due to high short-term air exposure, including central nervous system (CNS) depression, eye/respiratory tract irritation, developmental toxicity, and hematotoxicity (e.g., bone marrow toxicity). These effects were considered for the basis of developing a 24-hour, health-protective AMCV. However, data from available short-term exposure studies suggest the most sensitive endpoint for this purpose is hematotoxicity (e.g., bone marrow depression: leukopenia, pancytopenia, granulocytopenia, lymphocytopenia, thrombocytopenia, aplastic anemia) (ATSDR 2007). More specifically, as discussed in the following sections, dose-response data from subacute studies in laboratory animals (i.e., mice) provide the most conservative (i.e., lowest) point of departure (POD) for derivation of a 24-hour AMCV.

D.2.1 Hematotoxicity

The following summary in Table 9 of subacute animal data demonstrating benzene-induced hematological effects (e.g., blood cell decreases) was used to identify the lowest lowest-observed-adverse effect-level (LOAEL) among the studies for use as a POD in derivation of a 24-hour, health protective AMCV.

Table 9 Summary of Subacute Mouse Inhalation Studies

Study	Mouse Strain	Exposure Duration	NOAEL (ppm)	LOAEL (ppm)	Response at LOAEL
Green et al. (1981a,b)	CD-1 (male)	6 hs per day for 5 days	9.9	103	granulocytopenia, lymphocytopenia, and decreased marrow cellularity and polymorphonucleucytes
Dempster and Snyder (1991) [2]	DBA/2J (male)	6 hs per day for 5 days	---	10.3	decreased erythroid progenitor cell colony forming units
Rozen et al. (1984) [1]	C57BL/6J (male)	6 hs per day for 6 days	---	10.2	depressed blood lymphocytes, depressed mitogen-induced blastogenesis of femoral B-lymphocytes
Corti and Snyder (1996) [2, 3]	Swiss Webster (male)	6 hs per day for gestational days (GD) 6-15	---	10.2	decreased erythroid progenitor cell colony forming units
Rosenthal and Snyder (1985)	C57BL/6 (male)	6 hs per day for 1-12 days	10	30	T- and B-lymphocyte depression and increased Listeria monocytogenes infection bacterial counts
Cronkite et al. (1985)	C57B1/6BNL	6 hs per day, 5 days per week, for 2 weeks	10	25	lymphopenia
Toft et al. (1982)	NMRI (male)	8 hs per day, 5 days per week, for 2 weeks	10.5	21	increased micronucleated polychromatic erythrocytes and decreased granulopoietic stem cells
Cronkite (1986)	CBA/Ca and C57B1/6BNL	6 hs per day, 5 days per week, for 2 weeks	10	25	lymphopenia
Farris et al. (1997a,b)	B6C3F1/CrlBR (male)	6 hs per day, 5 days per week, for 1-8 weeks	10	100	lymphopenia and other blood effects

[1] Key study
[2] Supporting study
[3] Effects were reported in male mice exposed as adults; no increased sensitivity shown in the developing organism.

Three subacute mouse studies identified approximately 10 ppm as the LOAEL. Rozen et al. (1984) reported depressed blood lymphocytes and depressed mitogen-induced blastogenesis of femoral B-lymphocytes in male C57BL/6J mice at a LOAEL of 10.2 ppm. Dempster and Snyder (1991) showed decreased erythroid progenitor cell colony forming units in male DBA/2J mice at a LOAEL of 10.3 ppm. Corti and Snyder (1996) showed decreased erythroid progenitor cell colony forming units in male Swiss Webster mice at a LOAEL of 10.2 ppm. No NOAELs were identified in these studies. Rozen et al. (1984), supported by Dempster and Snyder (1991) and Corti and Snyder (1996), was selected as the key study for deriving a 24-hour value because: (1) the acute animal database is significantly more robust than the human; (2) benzene metabolism occurs along similar pathways in both humans and laboratory animals; and (3) the LOAEL identified (~10 ppm) for this study (and the supporting two studies) provides the most health-protective POD among these animal studies.

The key study of Rozen et al. (1984) utilized an exposure regimen of 6 hours per day for 6 days. Thus, the total number of 36 exposure hours exceeds the 24-hour exposure duration of interest. However, factors such as toxicokinetics must be considered to determine whether this multi-day exposure is more analogous to an intermittent exposure wherein sufficient clearance occurs following each day of exposure such that each day should be treated as an independent 6-hour acute exposure, or whether inadequate clearance occurs during the 18 hours between daily exposures such that the multiple-day exposure is sufficiently analogous to a continuous exposure for purposes of deriving a 24-hour value. Available data suggest the latter for the key subacute study.

D.2.2 Toxicokinetic Considerations

Metabolism of benzene to "active" metabolites is required for hematotoxicity to occur, and a good metric of the effective dose for benzene is the concentration of metabolites in the target tissue (i.e., bone marrow) (Sabourin et al. 1990). For the exposure regimen employed by Rozen et al. (1984), it appears the time between exposures (18 hours) would not allow for clearance of benzene's hematotoxicity-implicated metabolites (e.g., hydroquinone, hydroquinone glucuronide, benzoquinone, catechol, muconaldehyde, muconic acid) from the bone marrow as evidence suggests they are not readily excreted.

In regard to clearance of benzene and its metabolites from the mouse at doses relevant to the key study, results from Sabourin et al. (1987) suggest that around 48-56 hours is required to eliminate most of a 6-hour mouse inhalation dose to 11 ppm [14C]benzene or an oral mouse [14C]benzene dose (equivalent to a 11 ppm mouse exposure for 6 hours). Regarding elimination from the target tissue (i.e., bone marrow) specifically, hematotoxicity-implicated metabolites hydroquinone glucuronide and catechol (as well as muconic acid) have been detected in the bone marrow of mice exposed to 50 ppm [3H]benzene for 6 hours (Sabourin et al. 1988), and data indicate that appreciable amounts of these metabolites have been retained (perhaps ≈66-75%) and not cleared from mouse bone marrow 24-hours following exposure (Greenlee et al. 1981). This suggests the toxicokinetic half-life of these proposed contributors to benzene toxicity may

be greater than 24 hours at the target tissue. A relatively long half-life for benzene metabolites in bone marrow is consistent with bone marrow/blood concentration metabolite ratios in rodents ≈400 (Irons et al. 1980), and twice daily subcutaneous doses of [^{3}H]benzene increasing metabolites in the bone marrow of mice an average of ≈29-fold over a 6-day period (Snyder et al. 1978).

Collectively, these data suggest:

(1) the 18 hours between exposures in the key hematotoxicity study (Rozen et al. 1984) are expected to result in inadequate elimination of benzene metabolites from the target tissue; and

(2) the putative toxic metabolites of benzene would be expected to appreciably increase in mouse bone marrow with exposure duration over the six days of daily exposure in the key study such that it would be toxicokinetically inappropriate to treat each day as an independent acute exposure and more appropriate to view the exposure regimen as more toxicokinetically analogous to a continuous multiple-day exposure wherein dose to the target tissue increases daily with duration.

Thus, available data suggest the toxicokinetic half-life of the putative hematotoxic metabolites in the bone marrow is sufficiently long to support use of a 6-day study for derivation of a 24-hour, health protective AMCV. Consequently, the POD for hematotoxicity is based on the LOAEL of 10.2 ppm from Rozen et al. (1984).

D.2.3 CNS Effects

In regard to CNS depression, it is expected that mild CNS effects will be the first noticeable effects of sufficiently high acute benzene exposure and that irritation occurs only at higher exposures or is due to co-exposure to other substances (NAS 2009). However, acute human studies relevant to CNS effects would provide a higher POD than subacute animal hematotoxicty studies. For example, Srbova et al. (1950) provides a free-standing, no-observed-effect-level (NOAEL) of 110 ppm for CNS effects for a 2-hour human exposure. Extrapolation of a 2-hour free-standing NOAEL to a 24-hour exposure duration for the basis of deriving a health-protective concentration involves appreciable uncertainty given the relatively large extrapolation and the unknown relationship to actual CNS effect levels. Additionally, using a Haber's Law "n" value of 1 similar to NAS (2009) may result in an overly conservative temporal extrapolation considering that health effects were not mentioned even for human volunteers exposed to up to 125 ppm for 6-8 hours (Hunter and Blair 1972 as cited by NAS 2009). Nevertheless, this extrapolation results in a NOAEL-based POD$_{HEC}$ of 9.2 ppm for potential CNS effects. By contrast, subacute mouse studies provide a 6-hour, multiple-day (e.g., 6-day) LOAEL for hematotoxicity of 10.2 ppm (Rozen et al. 1984), which when adjusted to a human equivalent concentration (HEC) not expected to be associated with adverse effects (using a LOAEL-to-NOAEL UF of 3) results in a lower estimated NOAEL-based POD$_{HEC}$ of 3.4 ppm. Thus, a 24-hour AMCV which protects against hematotoxicity is also expected to be health-protective

against potential CNS effects (and irritation).

D.2.4 Developmental Effects

A similar conclusion is reached for developmental effects. Although epidemiological studies evaluating benzene as a developmental toxicant have many significant limitations, results of multiple-day inhalation studies in laboratory animals are fairly consistent across species and demonstrate that at LOAELs of 47-500 ppm, benzene has the ability to induce fetotoxicity as evidenced by decreased fetal weight, skeletal minor variants or retardation, and/or delayed skeletal ossification (ATSDR 2007). These LOAELs for developmental effects are higher than the multiple-day LOAEL for hematotoxicity. For example, the lowest developmental LOAEL of 47 ppm (decreased fetal weight, skeletal retardation in Tatrai et al. 1980) is for 24-hour per day exposure (for eight days) and is appreciably higher than the lowest hematotoxicity LOAEL of 10.2 ppm for 6-hour per day exposure (for six days), and the same would be true for the associated POD_{HEC} values. Thus, similar to CNS effects, a 24-hour AMCV derived to protect against hematotoxic effects is also expected to protect against potential developmental effects.

D.3 Critical Effect

This evaluation of the dose-response data for relevant endpoints suggests that the most sensitive endpoint for derivation of a 24-hour AMCV is hematotoxicity. Subacute mouse studies provide a reasonably robust hematotoxicity dataset. Most specifically, Rozen et al. (1984) provides a conservative LOAEL-based POD of 10.2 ppm for derivation of a 24-hour, health-protective AMCV.

D.4 Potential Exposure Duration Adjustment

If a single day of exposure (6 hours) from Rozen et al. was being used to derive a 24-hour AMCV, then a default duration adjustment from 6 to 24 hours would be conducted using a Haber's Law "n" value of 1 (i.e., POD x 6/24 hours) (TCEQ 2012). However, as discussed above in Section 2.1.1, the exposure regimen included a total exposure duration of 36 hours, and data suggest the time between exposures was insufficient for significant toxicokinetic clearance from the target tissue such that the putative hematotoxic metabolites of benzene would be expected to appreciably increase in mouse bone marrow over the six days of daily exposure. Therefore, such a duration adjustment is judged to be unnecessary.

D.5 Dosimetry Adjustments from Animal-to-Human Exposure

Although benzene can produce respiratory tract effects at relatively high concentrations, it produces remote effects (e.g., hematotoxicity) at lower concentrations. Therefore, it is classified as a category 3 gas. For category 3 gases:

$$POD_{HEC} = POD_A \times ((H_{b/g})_A / (H_{b/g})_H)$$

where: $H_{b/g}$ = ratio of the blood:gas partition coefficient

$$A = \text{animal}$$

$$H = \text{human}$$

For benzene, the blood:gas partition coefficients for mice and humans are 17.44 and 8.12, respectively (Wiester 2002). 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 regional gas dose ratio (RGDR) (USEPA 1994).

$$\text{Rozen et al. (1984):} \quad POD_{HEC} = POD_A \times ((H_{b/g})_A / (H_{b/g})_H) = 10.2 \text{ ppm} \times 1 = 10.2 \text{ ppm}$$

D.6 Uncertainty Factors (UFs)

The default procedure for deriving health-protective concentrations for noncarcinogenic effects is to determine a POD and apply appropriate UFs (i.e., assume a threshold/nonlinear MOA) (TCEQ 2012). The POD_{HEC} of 10.2 ppm based on Rozen et al. (1984) was used and divided by the following UFs:

- UF_L of 3 for extrapolation from a LOAEL to a NOAEL;
- UF_A of 3 for extrapolation from animals to humans;
- UF_H of 10 for intraspecies variability; and
- UF_D of 1 for database uncertainty.

A UF_L of 3 was used because: (1) the LOAEL utilized for these noncancer effects is lower than that indicated in similar animal studies and in humans; (2) the LOAEL utilized is approximately equal to the weight-of-evidence NOAEL in mouse studies; (3) benchmark dose (BMD) modeling of lymphocyte count depression data read from Figure 1 in Rozen et al. indicates a benchmark dose low ($BMDL_{1SD}$) of approximately 4 ppm (see Appendix B1 of TCEQ 2007), which supports a UF_L of 3 as being sufficiently conservative; (4) lymphocyte count depression is a very sensitive sentinel effect that is not serious in and of itself (i.e., not a frank effect), and the decreased lymphocyte count in Rozen et al. (1984) at 10.2 ppm appears to be within the normal range (Jackson Laboratory 2007); and (5) 10.2 ppm is below levels at which a shift from more toxic (e.g., muconaldehyde, hydroquinone glucuronide) towards less toxic (e.g., phenylglucuronide, prephenylmercapturic acid) metabolites has been shown to occur in mice (e.g., between 50 and 600 ppm in Sabourin et al. 1989).

A UF_A of 3 was used because: (1) default dosimetric adjustments from animal-to-human exposure were conducted to account for toxicokinetic differences; (2) existing studies indicate that benzene is metabolized along similar pathways in both humans and laboratory animals; (3) data suggests that mice are relatively sensitive laboratory animals in regards to the hematotoxic effects of benzene (e.g., relatively high respiratory and benzene metabolism rates) (USEPA 2002); and (4) some data suggest humans are more similar to rats (i.e., less sensitive than mice) in regards to benzene metabolism (Capel et al. 1972). [Note that the ratio of animal-to-human blood:gas partition coefficients used to adjust the POD_{HEC} was limited to 1, although the true

ratio is approximately 2 and would increase the POD_{HEC} accordingly.]

A full UF_H of 10 is supported by available information. There is good experimental evidence to indicate that benzene-sensitive human subpopulations may exist (USEPA 2002). For example, genetic polymorphisms associated with metabolic processes may confer variability in human susceptibility to benzene toxicity. For a more detailed discussion refer to USEPA (2002).

A UF_D of 1 was used because the overall toxicological database for benzene is extensive. The acute database contains numerous inhalation studies (mostly in animals) examining a wide variety of toxicological endpoints, both less and more serious in nature. Effects examined include, but are not limited to, mucous membrane and skin irritation, and hematological, cardiovascular, hepatic, immunological, neurological, reproductive, and developmental effects. Several animal species/strains have been utilized (e.g., rats: Sprague-Dawley, Wistar, CFY; mice: BALB/c, Hale Stoner, C57BL/6BNL, CD-1, Swiss Webster, NMRI, CF-1; rabbits: New Zealand), including mice, which are particularly sensitive to benzene-induced hematological effects.

D.7 Derivation of the 24-Hour, Health-Protective AMCV

As discussed in the previous section, UFs are applied to the key study (Rozen et al. 1984) POD_{HEC} to derive the 24-hour value.

$$POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_D) = 10.2 \text{ ppm} / (10 \times 3 \times 3 \times 1)$$

$$= 0.102 \text{ ppm or } 100 \text{ ppb}$$

Table 10 provides a summary of the major steps in deriving the 24-hour AMCV.

Table 10 Derivation of the Acute 24-Hour AMCV

Parameter	Summary
Study	Rozen et al. (1984), supported by Dempster and Snyder (1991) and Corti and Snyder (1996)
Study population	C57BL/6J mice (male)
Study quality	medium-high
Exposure Methods	6 hour per day for 6 days via inhalation from 0 to 301 ppm
LOAEL	10.2 ppm (average analytical concentration)
NOAEL	None
Critical Effects	depressed peripheral lymphocytes and depressed mitogen-induced blastogenesis of femoral B-lymphocytes
POD	10.2 ppm (LOAEL)
Exposure Duration	6 hour
Extrapolation to 24 h	Not applicable based on toxicokinetic considerations
POD_{ADJ} (extrapolated 24 hour concentration)	10.2 ppm
POD_{HEC}	10.2 ppm (RGDR = 1)
Total Uncertainty Factors (UFs)	100
Interspecies UF	*3*
Intraspecies UF	*10*
LOAEL UF	*3*
Incomplete Database UF	*1*
Database Quality	*high*
Acute 24-hour ReV (HQ =1) **Acute 24-hour AMCV**	**320 μg/m³ (100 ppb)**

D.8 Short-Term Values for Air Monitoring Evaluation

The acute evaluation resulted in the derivation of the following values:

- acute 1-hr ReV = 580 µg/m^3 (180 ppb) (TCEQ 2007)

- acute 24-hour ReV = 320 µg/m^3 (100 ppb)

In conclusion, the 24-hour, health-protective AMCV for benzene is 0.10 ppm or 100 ppb (320 µg/m^3). It is well below even chronic human hematotoxicity effect levels (e.g., 7.2-13.6 ppm) (Rothman et al. 1996). This value is sufficiently conservative for the adequate protection of public health for the exposure duration and adverse effects considered and would significantly complement TCEQ health effect evaluations of ambient air data, which currently utilize 1-hour and chronic (i.e., lifetime) health-protective and welfare-based (e.g., odor) AMCVs.

References for Appendix D

Agency for Toxic Substances and Disease Registry (ATSDR). 2007. Toxicological profile for benzene.

Capel ID, French MR, Millburn P, et al. 1972. Fate of [14C]-phenol in various species. Xenobiotica 2:25-34.

Greenlee WF, Sun JD, Bus JS. 1981. A proposed mechanism of benzene toxicity: formation of reactive intermediates from polyphenol metabolites. Toxicol Appl Pharmacol 59:187-195.

Hunter CG, Blair D. 1972. Benzene: pharmacokinetic studies in man. Ann Occup Hyg 15: 193-199.

Irons RD, Dent JG, Baker TS, et al. 1980. Benzene is metabolized and covalently bound in bone marrow in situ. Chem Biol Interact 30:241-245.

Jackson Laboratory. 2007. Hematology measurements involving C57BL/6J mice. http://phenome.jax.org/.

National Academy of Sciences (NAS). 2009. Interim acute exposure guideline levels (AEGLs): Benzene. December 2008.

Rothman N, Li Gl, Dosemeci M, et al. 1996. Hematotoxicity among Chinese workers heavily exposed to benzene. Am J Med 29(3):236-246.

Rozen MG, Snyder CA, Albert RE. 1984. Depression in B- and T-lymphocyte mitogen-induced blastogenesis in mice exposed to low concentrations of benzene. Toxicol Lett 20:343-

349.

Sabourin PJ, Chen BT, Lucier G, Birnbaum LS, Fisher E, Henderson RF. 1987. Effect of dose on the absorption and excretion of [14C]benzene administered orally or by inhalation in rats and mice. Toxicol Appl Pharmacol 87:325-336.

Sabourin PJ, Bechtold WE, Birnbaum LS, et al. 1988. Differences in the metabolism and disposition of inhaled [3H]benzene by F344/N rats and B6C3F1 mice. Toxicol Appl Pharmacol 94:128-140.

Sabourin PJ, Bechtold WE, Griffith WC, et al. 1989. Effect of exposure concentration, exposure rate, and route of administration on metabolism of benzene by F344 rats and B6C3F1 mice. Toxicol Appl Pharmacol 99:421-444.

Sabourin PJ, Sun JD, MacGregor JT, et al. 1990. Effect of repeated benzene inhalation exposures on benzene metabolism, binding to hemoglobin, and induction of micronuclei. Toxicol Appl Pharmacol 103:452-462.

Snyder R, Lee EW, Kocsis JJ. 1978. Binding of labeled benzene metabolites to mouse liver and bone marrow. Res Commun Chem Pathol Pharmacol 20(1):191-194.

Srbova J, Teisinger J, Skramovsky S. 1950. Absorption and elimination of inhaled benzene in man. Arch Ind Hyg Occup Med 2:1-8.

Tatrai E, Ungvary GY, Hudak A, et al. 1980. Concentration dependence of the embryotoxic effects of benzene inhalation in CFY rats. J Hyg Epidemiol Microbiol Immunol 24:363-371.

Texas Commission on Environmental Quality (TCEQ). 2007. Development Support Document Benzene CAS Registry Number: 71-43-2. Austin, TX.

TCEQ. 2012. TCEQ guidelines to develop toxicity factors (Revised RG-442). Texas Commission on Environmental Quality. Office of the Executive Director.

TCEQ. 2014. TCEQ guidelines to develop 24-hour inhalation Reference Values. Texas Commission on Environmental Quality. Office of the Executive Director.

TCEQ. 2015. TCEQ Guidelines to develop toxicity factors. RG-442. Office of the Executive Director. Austin, TX.

U.S. Environmental Protection Agency (USEPA). 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Washington, DC: U.S. Environmental Protection Agency. EPA/600/8-90/066F.