



Development Support Document
24-Hour AMCV
Final, June 16, 2014

Benzene

CAS Registry Number: 71-43-2

24-Hour Ambient

Air Monitoring Comparison Value

Prepared by

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

Toxicology Division

Office of the Executive Director

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

TABLE OF CONTENTS

LIST OF TABLES	I
ACRONYMS AND ABBREVIATIONS	II
CHAPTER 1 SUMMARY TABLES.....	1
CHAPTER 2 BACKGROUND	3
CHAPTER 3 ACUTE 24-HOUR AMCV	4
3.1 POTENTIAL POINTS OF DEPARTURE	4
3.1.1 Hematotoxicity	4
3.1.2 Toxicokinetic Considerations	6
3.1.3 CNS Effects.....	7
3.1.4 Developmental Effects.....	7
3.2 CRITICAL EFFECT	8
3.3 POTENTIAL EXPOSURE DURATION ADJUSTMENT.....	8
3.4 DOSIMETRY ADJUSTMENTS FROM ANIMAL-TO-HUMAN EXPOSURE	8
3.5 UNCERTAINTY FACTORS (UFs)	9
3.6 DERIVATION OF THE 24-HOUR, HEALTH-PROTECTIVE AMCV	10
3.7 SHORT-TERM VALUES FOR AIR MONITORING EVALUATION	12
4 REFERENCES	12

LIST OF TABLES

Table 1. Air Monitoring Comparison Values (AMCVs) for Ambient Air	1
Table 2 Chemical and Physical Data.....	2
Table 3. Summary of Subacute Mouse Inhalation Studies	4
Table 4. Derivation of the Acute 24-Hour AMCV	11

ACRONYMS AND ABBREVIATIONS

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
ADH	aldehyde dehydrogenase
AEGL	Acute Exposure Guideline Levels
ATSDR	Agency for Toxic Substances and Disease Registry
⁰ C	degrees centigrade
BMR	benchmark response
CNS	central nervous system
ConA	Concanavalin A
CRO	crotonaldehyde
DSD	development support document
EC ₅₀	Effective concentration at a 50% response level
ESL	Effects Screening Level
^{acute} ESL	acute health-based Effects Screening Level for chemicals meeting minimum database requirements
^{acute} ESL _{generic}	acute health-based Effects Screening Level for chemicals not meeting minimum database requirements
^{acute} ESL _{odor}	acute odor-based Effects Screening Level
^{acute} ESL _{veg}	acute vegetation-based Effects Screening Level
^{chronic} ESL _{threshold(c)}	chronic health-based Effects Screening Level for threshold dose response cancer effect
^{chronic} ESL _{threshold(nc)}	chronic health-based Effects Screening Level for threshold dose response noncancer effects
^{chronic} ESL _{nonthreshold(c)}	chronic health-based Effects Screening Level for nonthreshold dose response cancer effects
^{chronic} ESL _{nonthreshold(nc)}	chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects
^{chronic} ESL _{veg}	chronic vegetation-based Effects Screening Level

Acronyms and Abbreviations	Definition
EU	European Union
GC	gas chromatography
GLP	good laboratory practice
hr	hour
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human
HEC	human equivalent concentration
HQ	hazard quotient
HSDB	Hazardous Substance Data Base
IARC	International Agency for Research on Cancer
IC ₅₀	Inhibitory concentration at a 50% response level
IL	interleukin
IPCS	International Programme on Chemical Society
IRIS	USEPA Integrated Risk Information System
kg	kilogram
LC ₅₀	concentration causing lethality in 50% of test animals
LD ₅₀	dose causing lethality in 50% of test animals
LPS	lipopolysaccharide
LOAEL	lowest-observed-adverse-effect-level
LTD	Limited toxicity data
MW	molecular weight
μg	microgram
μg/m ³	micrograms per cubic meter of air
mg	milligrams
mg/m ³	milligrams per cubic meter of air
min	minute

Acronyms and Abbreviations	Definition
MOA	mode of action
n	number
NAC	National Advisory Committee
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NRC	National Research Council
OAEL	Observed adverse effect level
OSHA	Occupational Safety and Health Administration
PBPK	physiologically based pharmacokinetic
POD	point of departure
POD _{ADJ}	point of departure adjusted for exposure duration
POD _{HEC}	point of departure adjusted for human equivalent concentration
ppb	parts per billion
ppm	parts per million
RD ₅₀	50% reduction in respiration rate
ReV	reference value
RGDR	regional gas dose ratio
ROS	Reactive oxygen species
RP	Relative potency
RP _{GM}	Geometric mean of relative potency endpoints
SA	surface area
SD	Sprague-Dawley
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
UF	uncertainty factor

Acronyms and Abbreviations	Definition
UF _H	interindividual or intraspecies human uncertainty factor
UF _A	animal to human uncertainty factor
UF _{Sub}	subchronic to chronic exposure uncertainty factor
UF _L	LOAEL to NOAEL uncertainty factor
UF _D	incomplete database uncertainty factor
USEPA	United States Environmental Protection Agency
V _E	minute volume

Chapter 1 Summary Tables

Table 1 provides the health-based 24-hour Reference Value (ReV) from an acute evaluation of benzene which is used as the 24-h Air Monitoring Comparison Value (AMCV) for evaluation of 24-hour ambient air monitoring data. The 24-hour AMCV was developed based on Guidelines to Develop 24-Hour Inhalation Reference Values (TCEQ 2014) and TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2012). Please refer to the Benzene Development Support Document (DSD) (TCEQ 2007) for details on how other acute and chronic values in Table 1 used for review of ambient air monitoring data were derived. Table 2 provides chemical/physical properties.

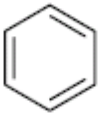
Table 1. Air Monitoring Comparison Values (AMCVs) for Ambient Air

Short-Term Values	Concentration	Notes
acute ReV [1 hour]	580 $\mu\text{g}/\text{m}^3$ (180 ppb) ^a 1-h Short-Term Health	Critical Effect(s): Depressed peripheral lymphocytes and depressed mitogen-induced blastogenesis of femoral B-lymphocytes in C57BL/6J mice (male)
acute ReV [24 hour]	320 $\mu\text{g}/\text{m}^3$ (100 ppb) 24-h Short-Term Health	Critical Effect(s): Depressed peripheral lymphocytes and depressed mitogen-induced blastogenesis of femoral B-lymphocytes in C57BL/6J mice (male)
acute ^c ESL _{odor}	8,700 $\mu\text{g}/\text{m}^3$ (2,700 ppb) ^a Odor	50% detection threshold
acute ^c ESL _{veg}	---	No data found
Long-Term Values	Concentration	Notes
chronic ReV (HQ = 1.0)	280 $\mu\text{g}/\text{m}^3$ (86 ppb) ^a Long-Term Health	Critical Effect: Decreased absolute lymphocyte count in occupationally exposed workers
chronic ^c ESL _{linear(c)}	4.5 $\mu\text{g}/\text{m}^3$ (1.4 ppb) ^{a, b} Long-Term Health	Cancer Endpoint: Acute myelogenous and acute monocytic leukemia in occupationally exposed workers
chronic ^c ESL _{veg}	---	No data found

^a TCEQ (2007)

^b Based on unit risk factor (URF) = 2.2E-06 per $\mu\text{g}/\text{m}^3$ or 7.1E-06 per ppb, and a risk level of 1 in 100,000 excess cancer risk

Table 2 Chemical and Physical Data

Parameter	Value	Reference ^a
Molecular Formula	C ₆ H 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, solventy 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 °C	ATSDR 2005
Boiling Point	80.1 °C	ATSDR 2005
Conversion Factors	1 µg/m ³ = 0.31 ppb @ 20°C 1 ppb = 3.24 µg/m ³	ATSDR 2005

^a Refer to TCEQ (2007) for references

Chapter 2 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.

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 the Benzene Development Support Document (TCEQ 2007) for detailed information on physical/chemical properties and mode of action information.

Chapter 3 Acute 24-Hour AMCV

3.1 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.

3.1.1 Hematotoxicity

The following summary 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 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 polymorphonucleocytes
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	Swiss	6 hs per day	---	10.2	decreased erythroid

Study	Mouse Strain	Exposure Duration	NOAEL (ppm)	LOAEL (ppm)	Response at LOAEL
Snyder (1996) ^{2,3}	Webster (male)	for gestational days (GD) 6-15			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 <i>Listeria monocytogenes</i> 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/CrIB R (male)	6 hs per day, 5 days per week, for 1-8 weeks	10	100	lymphopenia and other blood effects

¹ Key study² Supporting study³ 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.

3.1.2 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 [³H]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).

3.1.3 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 hematotoxicity 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).

3.1.4 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.

3.2 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.

3.3 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., $POD \times 6/24$ 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.

3.4 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 = animal

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).

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

3.5 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 2A 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.

3.6 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.

$$\begin{aligned}POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_D) &= 10.2 \text{ ppm} / (10 \times 3 \times 3 \times 1) \\ &= 0.102 \text{ ppm or } 100 \text{ ppb}\end{aligned}$$

Table 4 provides a summary of the major steps in deriving the 24-hour AMCV.

Table 4. 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
<i>Interspecies UF</i>	3
<i>Intraspecies UF</i>	10
<i>LOAEL UF</i>	3
<i>Incomplete Database UF</i>	1
<i>Database Quality</i>	high
Acute 24-hour ReV (HQ =1)	320 µg/m³ (100 ppb)
Acute 24-hour AMCV	

3.7 Short-Term Values for Air Monitoring Evaluation

The acute evaluation here and in TCEQ (2007) resulted in the derivation of the following values:

- acute 1-hr ReV = 580 $\mu\text{g}/\text{m}^3$ (180 ppb) (TCEQ 2007)
- acute 24-hour ReV = 320 $\mu\text{g}/\text{m}^3$ (100 ppb)
- ^{acute}ESL_{odor} = 8,700 $\mu\text{g}/\text{m}^3$ (2,700 ppb) (TCEQ 2007)

In conclusion, the 24-hour, health-protective AMCV for benzene is 0.10 ppm or 100 ppb (320 $\mu\text{g}/\text{m}^3$). 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.

4 References

- 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 (AEGs): Benzene. December 2008.
- Rothman N, Li GI, 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.
- 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). 2002. Toxicological review of benzene (noncancer effects). Washington, DC: U.S. Environmental Protection Agency. EPA/635/R-02/001F.

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. U.S. EPA. (U.S. Environmental Protection Agency). (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. (EPA/600/8-90/066F). Research Triangle Park, NC.