



Development Support Document
24-Hour AMCV
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Benzene

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24-Hour Ambient Air Monitoring Comparison Value

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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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

1 **Chapter 1 Summary Tables**

2 Table 1 provides the health-based 24-hour Reference Value (ReV) from an acute evaluation of
3 benzene which is used as the 24-h Air Monitoring Comparison Value (AMCV) for evaluation of
4 24-hour ambient air monitoring data. The 24-hour AMCV was developed based on Guidelines
5 for Developing 24-Hour Reference Values (TCEQ 2014) and TCEQ Guidelines to Develop
6 Toxicity Factors (TCEQ 2012). Please refer to the Benzene Development Support Document
7 (DSD) (TCEQ 2007) for details on how other acute and chronic values in Table 1 used for
8 review of ambient air monitoring data were derived. Table 2 provides chemical/physical
9 properties.

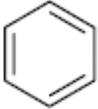
10 **Table 1. Air Monitoring Comparison Values (AMCVs) for Ambient Air**

Short-Term Values	Concentration	Notes
acute ReV [1 h]	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 h]	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

11 ^a TCEQ (2007)

12 ^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
13 100,000 excess cancer risk

1 **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

2 ^a Refer to TCEQ (2007) for references

3

1 **Chapter 2 Background**

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

18 Benzene is a VOC for which 24-hour canister data are collected. Additionally, as a known
19 human carcinogen that is ubiquitously-detected in the TCEQ ambient air monitoring network,
20 benzene is of significant agency and public interest. Therefore, benzene is a chemical for which a
21 24-hour, health-protective AMCV has been developed. The purpose of this document is to
22 summarize the main steps involved in the development of the 24-hour AMCV for benzene.
23 General steps discussed below for developing a 24-hour value include:

- 24 • identification of a point of departure for the critical effect(s) based on review of dose-
25 response data for relevant toxicity endpoints;
- 26 • consideration of an exposure duration adjustment;
- 27 • animal-to-human inhalation dosimetric adjustment;
- 28 • selection and application of applicable uncertainty factors; and
- 29 • derivation of the 24-hour AMCV.

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

32 **Chapter 3 Acute 24-Hour AMCV**

33 ***3.1 Potential Points of Departure***

34 Benzene can produce various toxic effects due to high short-term air exposure, including central
35 nervous system (CNS) depression, eye/respiratory tract irritation, developmental toxicity, and

1 hematotoxicity (e.g., bone marrow toxicity). These effects were considered for the basis of
 2 developing a 24-hour, health-protective AMCV. However, data from available short-term
 3 exposure studies suggest the most sensitive endpoint for this purpose is hematotoxicity (e.g.,
 4 bone marrow depression: leukopenia, pancytopenia, granulocytopenia, lymphocytopenia,
 5 thrombocytopenia, aplastic anemia) (ATSDR 2007). More specifically, as discussed in the
 6 following sections, dose-response data from subacute studies in laboratory animals (i.e., mice)
 7 provide the most conservative (i.e., lowest) point of departure (POD) for derivation of a 24-hour
 8 AMCV.

9 **3.1.1 Hematotoxicity**

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

14 **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 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

Study	Mouse Strain	Exposure Duration	NOAEL (ppm)	LOAEL (ppm)	Response at LOAEL
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/CrlBR (male)	6 hs per day, 5 days per week, for 1-8 weeks	10	100	lymphopenia and other blood effects

1 ¹ Key study

2 ² Supporting study

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

4 Three subacute mouse studies identified approximately 10 ppm as the LOAEL. Rozen et al.
5 (1984) reported depressed blood lymphocytes and depressed mitogen-induced blastogenesis of
6 femoral B-lymphocytes in male C57BL/6J mice at a LOAEL of 10.2 ppm. Dempster and Snyder
7 (1991) showed decreased erythroid progenitor cell colony forming units in male DBA/2J mice at
8 a LOAEL of 10.3 ppm. Corti and Snyder (1996) showed decreased erythroid progenitor cell
9 colony forming units in male Swiss Webster mice at a LOAEL of 10.2 ppm. No NOAELs were
10 identified in these studies. Rozen et al. (1984), supported by Dempster and Snyder (1991) and
11 Corti and Snyder (1996), was selected as the key study for deriving a 24-hour value because: (1)
12 the acute animal database is significantly more robust than the human; (2) benzene metabolism
13 occurs along similar pathways in both humans and laboratory animals; and (3) the LOAEL

1 identified (~10 ppm) for this study (and the supporting two studies) provides the most health-
2 protective POD among these animal studies.

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

12 **3.1.2 Toxicokinetic Considerations**

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

20 In regard to clearance of benzene and its metabolites from the mouse at doses relevant to the key
21 study, results from Sabourin et al. (1987) suggest that around 48-56 hours is required to
22 eliminate most of a 6-hour mouse inhalation dose to 11 ppm [¹⁴C]benzene or an oral mouse
23 [¹⁴C]benzene dose (equivalent to a 11 ppm mouse exposure for 6 hours). Regarding elimination
24 from the target tissue (i.e., bone marrow) specifically, hematotoxicity-implicated metabolites
25 hydroquinone glucuronide and catechol (as well as muconic acid) have been detected in the bone
26 marrow of mice exposed to 50 ppm [³H]benzene for 6 hours (Sabourin et al. 1988), and data
27 indicate that appreciable amounts of these metabolites have been retained (perhaps ≈66-75%)
28 and not cleared from mouse bone marrow 24-hours following exposure (Greenlee et al. 1981).
29 This suggests the toxicokinetic half-life of these proposed contributors to benzene toxicity may
30 be greater than 24 hours at the target tissue. A relatively long half-life for benzene metabolites in
31 bone marrow is consistent with bone marrow/blood concentration metabolite ratios in rodents
32 ≈400 (Irons et al. 1980), and twice daily subcutaneous doses of [³H]benzene increasing
33 metabolites in the bone marrow of mice an average of ≈29-fold over a 6-day period (Snyder et al.
34 1978).

35 Collectively, these data suggest:

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

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

7 Thus, available data suggest the toxicokinetic half-life of the putative hematotoxic metabolites in
8 the bone marrow is sufficiently long to support use of a 6-day study for derivation of a 24-hour,
9 health protective AMCV. Consequently, the POD for hematotoxicity is based on the LOAEL of
10 10.2 ppm from Rozen et al. (1984).

11 **3.1.3 CNS Effects**

12 In regard to CNS depression, it is expected that mild CNS effects will be the first noticeable
13 effects of sufficiently high acute benzene exposure and that irritation occurs only at higher
14 exposures or is due to co-exposure to other substances (NAS 2009). However, acute human
15 studies relevant to CNS effects would provide a higher POD than subacute animal hematotoxicity
16 studies. For example, Srbova et al. (1950) provides a free-standing, no-observed-effect-level
17 (NOAEL) of 110 ppm for CNS effects for a 2-hour human exposure. Extrapolation of a 2-hour
18 free-standing NOAEL to a 24-hour exposure duration for the basis of deriving a health-
19 protective concentration involves appreciable uncertainty given the relatively large extrapolation
20 and the unknown relationship to actual CNS effect levels. Additionally, using a Haber's Law
21 "n" value of 1 similar to NAS (2009) may result in an overly conservative temporal extrapolation
22 considering that health effects were not mentioned even for human volunteers exposed to up to
23 125 ppm for 6-8 hours (Hunter and Blair 1972 as cited by NAS 2009). Nevertheless, this
24 extrapolation results in a NOAEL-based POD_{HEC} of 9.2 ppm for potential CNS effects. By
25 contrast, subacute mouse studies provide a 6-hour, multiple-day (e.g., 6-day) LOAEL for
26 hematotoxicity of 10.2 ppm (Rozen et al. 1984), which when adjusted to a human equivalent
27 concentration (HEC) not expected to be associated with adverse effects (using a LOAEL-to-
28 NOAEL UF of 3) results in a lower estimated NOAEL-based POD_{HEC} of 3.4 ppm. Thus, a 24-
29 hour AMCV which protects against hematotoxicity is also expected to be health-protective
30 against potential CNS effects (and irritation).

31 **3.1.4 Developmental Effects**

32 A similar conclusion is reached for developmental effects. Although epidemiological studies
33 evaluating benzene as a developmental toxicant have many significant limitations, results of
34 multiple-day inhalation studies in laboratory animals are fairly consistent across species and
35 demonstrate that at LOAELs of 47-500 ppm, benzene has the ability to induce fetotoxicity as
36 evidenced by decreased fetal weight, skeletal minor variants or retardation, and/or delayed
37 skeletal ossification (ATSDR 2007). These LOAELs for developmental effects are higher than
38 the multiple-day LOAEL for hematotoxicity. For example, the lowest developmental LOAEL of
39 47 ppm (decreased fetal weight, skeletal retardation in Tatrai et al. 1980) is for 24-hour per day

1 exposure (for eight days) and is appreciably higher than the lowest hematotoxicity LOAEL of
2 10.2 ppm for 6-hour per day exposure (for six days), and the same would be true for the
3 associated POD_{HEC} values. Thus, similar to CNS effects, a 24-hour AMCV derived to protect
4 against hematotoxic effects is also expected to protect against potential developmental effects.

5 ***3.2 Critical Effect***

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

11 ***3.3 Potential Exposure Duration Adjustment***

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

20 ***3.4 Dosimetry Adjustments from Animal-to-Human Exposure***

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

$$24 \quad POD_{HEC} = POD_A \times ((H_{b/g})_A / (H_{b/g})_H)$$

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

26 A = animal

27 H = human

28 For benzene, the blood:gas partition coefficients for mice and humans are 17.44 and 8.12,
29 respectively (Wiester 2002). If the animal blood:gas partition coefficient is greater than the
30 human blood:gas partition coefficient, a default value of 1 is used for the regional gas dose ratio
31 (RGDR) (USEPA 1994).

$$32 \quad \text{Rozen et al. (1984): } POD_{HEC} = POD_A \times ((H_{b/g})_A / (H_{b/g})_H) = 10.2 \text{ ppm} \times 1 = 10.2 \text{ ppm}$$

1 **3.5 Uncertainty Factors (UFs)**

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

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

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

22 A UF_A of 3 was used because: (1) default dosimetric adjustments from animal-to-human
23 exposure were conducted to account for toxicokinetic differences; (2) existing studies indicate
24 that benzene is metabolized along similar pathways in both humans and laboratory animals; (3)
25 data suggests that mice are relatively sensitive laboratory animals in regards to the hematotoxic
26 effects of benzene (e.g., relatively high respiratory and benzene metabolism rates) (USEPA
27 2002); and (4) some data suggest humans are more similar to rats (i.e., less sensitive than mice)
28 in regards to benzene metabolism (Capel et al. 1972). [Note that the ratio of animal-to-human
29 blood:gas partition coefficients used to adjust the POD_{HEC} was limited to 1, although the true
30 ratio is approximately 2 and would increase the POD_{HEC} accordingly.]

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

35 A UF_D of 1 was used because the overall toxicological database for benzene is extensive. The
36 acute database contains numerous inhalation studies (mostly in animals) examining a wide
37 variety of toxicological endpoints, both less and more serious in nature. Effects examined
38 include, but are not limited to, mucous membrane and skin irritation, and hematological,
39 cardiovascular, hepatic, immunological, neurological, reproductive, and developmental effects.

1 Several animal species/strains have been utilized (e.g., rats: Sprague-Dawley, Wistar, CFY;
2 mice: BALB/c, Hale Stoner, C57BL/6BNL, CD-1, Swiss Webster, NMRI, CF-1; rabbits: New
3 Zealand), including mice, which are particularly sensitive to benzene-induced hematological
4 effects.

5 ***3.6 Derivation of the 24-Hour, Health-Protective AMCV***

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

$$\begin{aligned} 8 \quad & POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_D) = 10.2 \text{ ppm} / (10 \times 3 \times 3 \times 1) \\ 9 \quad & = 0.102 \text{ ppm or } 100 \text{ ppb} \end{aligned}$$

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

11

1 **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 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 24 h	Not applicable based on toxicokinetic considerations
POD _{ADJ} (extrapolated 24 h 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 ReV [24 h] (HQ = 1)	320 µg/m³ (100 ppb)

1 **3.7 Short-Term Values for Air Monitoring Evaluation**

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

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

6 In conclusion, the 24-hour, health-protective AMCV for benzene is 0.10 ppm or 100 ppb (320
7 $\mu\text{g}/\text{m}^3$). It is well below even chronic human hematotoxicity effect levels (e.g., 7.2-13.6 ppm)
8 (Rothman et al. 1996). This value is sufficiently conservative for the adequate protection of
9 public health for the exposure duration and adverse effects considered and would significantly
10 complement TCEQ health effect evaluations of ambient air data, which currently utilize 1-hour
11 and chronic (i.e., lifetime) health-protective and welfare-based (e.g., odor) AMCVs.

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