



# Benzene: Development of a 24-Hour, Health-Protective Air Monitoring Comparison Value

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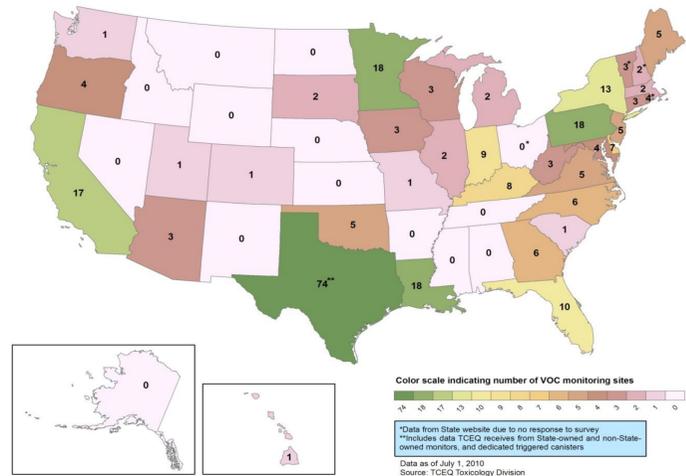
## Abstract

Texas has the most extensive volatile organic compound (VOC) ambient air monitoring network in the nation. As part of that network, the TCEQ collects 24-hour canister VOC data based on USEPA's every sixth-day schedule. These data are used to calculate annual averages for comparison to chronic, health-protective Air Monitoring Comparison Values (AMCVs) (i.e., RIC-like values for noncarcinogenic effects, 1E-05 excess risk levels for cancer effects). In regard to acute exposure durations, however, the TCEQ typically has only 1-hour AMCVs, which while conservative are not designed to evaluate 24-hour sample results. Thus, the development of 24-hour, health-protective AMCVs would allow the TCEQ to more fully utilize 24-hour VOC data for the evaluation of potential public health concerns. The TCEQ has developed a 24-hour AMCV for benzene since it is a ubiquitous VOC of both agency and public interest. Critical effect dose-response data for hematotoxicity from mouse studies indicate an effect level range of 10-100 ppm for subacute exposure (e.g., 6-8 hours per day, 5-10 days). A point of departure (POD) from these studies was used to develop the 24-hour value. The total number of exposure hours exceeds 24 hours for all these subacute studies and available toxicokinetic information indicates the time between the intermittent daily exposures would not allow for clearance of benzene's hematotoxicity-implicated metabolites (e.g., hydroquinone, hydroquinone glucuronide, catechol) from the bone marrow as evidence suggests they are not readily excreted. Using the same POD (LOAEL of 10.2 ppm) and uncertainty factors (total UF of 100) as the TCEQ used to derive its 1-hour AMCV (180 ppb) but without duration adjustment (based on toxicokinetic considerations) results in a conservative 24-hour, health-protective AMCV of 100 ppb. This value is well below even chronic human hematotoxicity observed adverse effect levels (e.g., 7.2-13.6 ppm). The 24-hour AMCV is considered sufficiently conservative for the adequate protection of public health and would significantly complement TCEQ health effect evaluations of ambient air data.

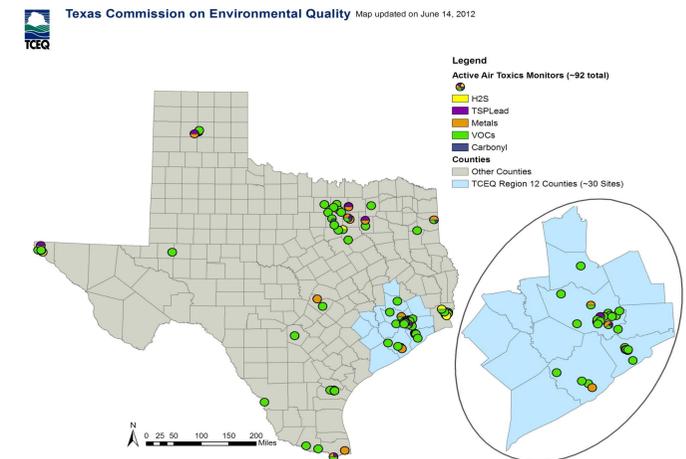
## Introduction

Texas has the most extensive ambient air monitoring network in the nation. The 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).

2010 VOC Monitoring Sites per State



There are more stationary monitor sites that measure volatile organic compounds (VOCs like benzene) in Texas than in any other state. For example, there are 17 VOC monitoring sites (20 monitors) in Harris County (i.e., Houston area) alone, which is equal to the number of VOC sites in the entire state of California.



The Texas Commission on Environmental Quality (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 not historically developed 24-hour, health-based AMCVs for comparison to individual 24-hour canister results from its monitoring network. Only a limited evaluation of the reported 24-hour levels is possible without 24-hour AMCVs because 1-hour and chronic (i.e., lifetime) AMCVs are of limited utility and largely inappropriate for this purpose. Regarding use of 1-hour AMCVs for comparison, while a 24-hour VOC concentration exceeding a conservative 1-hour AMCV would be indicative of a potential health concern requiring further evaluation, a 24-hour level less than a 1-hour AMCV could still be of potential concern if exposure duration is a primary determinant of toxicity and the 1-hour AMCV is not sufficiently conservative (i.e., below 24-hour effect levels). Additionally, while use of a chronic AMCV would be very conservative, exceedance of a lifetime average (i.e., chronic) comparison value by a 24-hour level would be of dubious toxicological significance and thus still require an entirely different and appropriate evaluation. 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. General steps discussed below for derivation of a 24-hour benzene AMCV include: 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 value.

## Potential Points of Departure

Benzene can produce various toxic effects from 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.

**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.

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) <sup>2</sup>	DBA/2J (male)	6 hs per day for 5 days	---	10.3	depressed erythroid progenitor cell colony forming units
Rozen et al. (1984) <sup>1</sup>	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) <sup>3</sup>	Swiss Webster (male)	6 hs per day for gestational days (GD) 6-15	---	10.2	depressed 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
Crankite et al. (1985)	C57B1/6BNL	6 hs per day, 5 days per week, for 2 weeks	10	25	lymphopenia
Idi 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
Crankite (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/CrBR (male)	6 hs per day, 5 days per week, for 1-8 weeks	10	100	lymphopenia and other blood effects

<sup>1</sup> Key study  
<sup>2</sup> Supporting study  
<sup>3</sup> 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 and toxicodynamics must be considered to determine whether this multi-day exposure is more analogous to an intermittent exposure wherein sufficient toxicokinetic and toxicodynamic 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.

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 [<sup>14</sup>C]benzene or an oral mouse [<sup>14</sup>C]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 [<sup>3</sup>H]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 [<sup>3</sup>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).

**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 a 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<sub>HEC</sub> 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<sub>HEC</sub> 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).

**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<sub>HEC</sub> 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.

**Critical Effect and POD:**  
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 data set. 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.

## Duration/Dosimetry Adjustments

### Potential Exposure Duration Adjustment

If a single day of exposure (6 hours) from Rozen et al. were 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, 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.

### 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:

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

where:  $H_{bg}$  = 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):

$$POD_{HEC} = POD_A \times ((H_{bg})_A / (H_{bg})_H) = 10.2 \text{ ppm} \times 1 = 10.2 \text{ ppm}$$

## 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<sub>HEC</sub> of 10.2 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<sub>L</sub>), 3 for extrapolation from animals to humans (UF<sub>A</sub>), 10 for interspecies variability (UF<sub>I</sub>), and 1 for database uncertainty (UF<sub>D</sub>) (total UF = 100). A UF<sub>I</sub> 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) 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 < absolute value of 2), which supports a UF<sub>I</sub> 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<sub>A</sub> 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<sub>HEC</sub> was limited to 1, although the true ratio is approximately 2 and would increase the POD<sub>HEC</sub> accordingly.] A UF<sub>I</sub> 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<sub>D</sub> 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.

## 24-Hour AMCV Derivation

As discussed in the previous section, UFs are applied to the key study (Rozen et al. 1984) POD<sub>HEC</sub> to derive the 24-hour value:

$$POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_D) = 10.2 \text{ ppm} / (10 \times 3 \times 3 \times 1) = 0.102 \text{ ppm}$$

### In Conclusion:

- The 24-hour, health-protective AMCV for benzene is 0.10 ppm or 100 ppb.
- This value is well below even chronic human hematotoxicity effect levels (e.g., 7.2-13.6 ppm) (Rothman et al. 1996).
- It 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 (i.e., odor, vegetation) AMCVs.

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