INTERPRETATION OF 24-HOUR AIR MONITORING DATA:

Methods for Deriving 24-Hour Reference Values for Comparison to 24-Hour Ambient Air Monitoring Data

Roberta L. Grant, Allison Jenkins,
Joseph (Kip) Haney
Toxicology Division, Texas Commission on Environmental Quality, Austin, TX

Overview

* Problem formulation
* Definition of 24-Hr Reference Values (ReVs)
* Methods to Develop 24-Hr ReVs
* 24-Hr ReVs developed for example chemicals

Problem Formulation

* Acute 1-hr ReVs and chronic ReVs are used to evaluate 1-hr measured concentrations or calculated annual average concentrations, respectively.
* 24-hr ambient air samples (i.e., canister samples collected every 3rd or 6th day) are collected and used to calculate annual averages – the TCEQ does not have 24-h ReVs
* 24 hrs is an acute exposure duration significantly longer than 1-hr

Problem Formulation

* Development of 24-h values would allow the TCEQ to fully evaluate 24-h data for possible health concerns

* Some members of the general public compare 1 hr or 24-hr measured air concentrations to chronic ReVs

* If a concentration measured in a 24-hr ambient air sample exceeds a chronic ReV, they believe adverse health effects will occur

Problem Formulation

* Provide useful information for risk managers and the general population.

* An important part of the risk communication process

Definition of an Inhalation ReV

* An estimate of an inhalation exposure concentration for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse effects.

* Based on noncarcinogenic health effects

Definition of an Inhalation ReV

* ReV is the terminology used in our Guidelines and case study
* The ReV is used for review of ambient air monitoring data, and is called the Air Monitoring Comparison Value (AMCV)
* The AMCV = ReV

Methods to Develop 24-Hr ReVs

* Similar to procedures used to derive 1-hr and chronic ReVs (TCEQ 2012)
* Based on the most sensitive adverse noncarcinogenic health effect relevant to humans reported in the scientific literature.
* Duration and animal-to-human dosimetric adjustments
* Adjust an appropriate point of departure (POD_{HEC}) with uncertainty factors (UFs) to reflect data limitations

Methods to Develop 24-Hr ReVs

* Challenges
  * Selecting the critical study and critical health endpoint
    * Acute studies for a 24-hr exposure duration are rare, so may use acute, subacute, or subchronic studies to develop a 24-hr ReV
  * Duration Adjustment

Methods to Develop 24-Hr ReVs

* Duration adjustments for a 24-hr ReV must be considered on a chemical-by-chemical basis and the type of the chosen study
* Mode of action (MOA), toxicokinetics/ toxicodynamics, and the dose-response relationship are important to develop 24-hr ReVs

Strengths

* A 24-hr ReV may be used to conduct a hazard assessment in combination with 1-hr and annual ReVs or to evaluate data collected for special projects
* Cannot replace the 1-hr or annual ReVs
* Part of proposed Guidelines (TCEQ 2011a) that have been peer-reviewed (TERA 2011).
* Similar to guidance developed by OECD (2010).

Limitations

* Data- and resource-intensive
* If a measured concentration is close to the 24-hr ReV, it may cause an increase in the calculated annual average concentration
* The 24-hr air monitoring data do not provide information on short-term peak concentrations

Limitations

* Exposure to chemical peak concentrations may occur on an intermittent basis

* The 24-hr ReV would be protective of intermittent 24-hr exposures if the time period between peak intermittent exposures is sufficient for adequate toxicokinetic and toxicodynamic clearance such that a significant accumulation of neither the chemical nor toxic effect is expected

Limitations

* The 24-hr ReV is designed to evaluate a single acute exposure

* After 24-hr ReVs are derived, TCEQ toxicologists will conduct a health effects review of air monitoring data to evaluate whether repeated intermittent 24-hr exposure would result in adverse health effects.

* This determination is very chemical-specific and would depend on the toxicity study used to develop the ReV and duration adjustments

Example Chemicals

* Acrolein
* Benzene
* 1,3-Butadiene (BD)

Acrolein

* Highly reactive aldehyde
* Causes eye, nose, throat, and respiratory tract irritation that is mainly concentration dependent

Acrolein

* Several human acute and animal acute/subacute studies
* 1-hr ReV based on a human study, 1-hr exposure duration, with a LOAEL of 0.3 ppm based on mild eye, nose, and throat irritation and slight decrease in respiratory rate
* Study not justifiable for use in developing 24-hr ReV

Acrolein

* The key study for development of the 24-hr ReV was Dorman et al. (2008) (4 day interim histopathology)
* Male F344 rats exposed to 0, 0.02, 0.06, 0.2, 0.6, or 1.8 ppm acrolein for 6 hr/day for 4, 14, 30, or 65 days
* Rat subchronic study, with interim histopathology after exposure for 6 hr/day for 4 days
* A NOAEL of 0.2 ppm
* At the LOAEL of 0.6 ppm (6 hr/day for 4 days), mild respiratory epithelial hyperplasia was observed in the lateral wall of the nasal epithelium.
* This study was also used for development of the TCEQ's chronic ReV

Acrolein

Exposure Regimen Considerations

* The key study of Dorman et al. (2008) utilized an exposure regimen of 6 hours/day for 4 days.
* Total number of 24 hours equals the 24-hr exposure duration of interest:

6 hr/day + 6 hr/day + 6 hr/day + 6 hr/day = 24 hrs

Acrolein

* Since adverse effects of acrolein are largely concentration dependent, it was determined that the exposure regimen was sufficiently analogous to a continuous 24-hr exposure.
* The NOAEL of 0.2 ppm was consistent across all exposure durations up to 65 days.

Acrolein

Animal to Human Dosimetric Adjustment

A Regional Gas Dose Ratio (RGDR) for a Category 1 gas of 0.187 was derived using study-specific body weight data for F344 rats. A ventilation rate was calculated using study-specific time-weighted average body weight data and a default ventilation rate for humans.

* Acrolein is classified as a category 1 gas (extrathoracic respiratory effects)
* For category 1 gases:
  * $POD_{HEC} = POD_A \times RGDR_{ET}$
    * = 0.2 ppm x 0.187
    * = 0.0374 ppm
  * A = animal
  * ET = extrathoracic

Acrolein

Applicable Uncertainty Factors (UFs)

* The default procedure for deriving health-protective concentrations for noncarcinogenic effects is to determine a POD and apply appropriate UFs
* The POD_{HEC} of 0.0374 ppm was divided by the following UFs: UF_A of 3, UF_H of 10, UF_L of 1, and UF_D of 1 (total UF = 30)

Acrolein

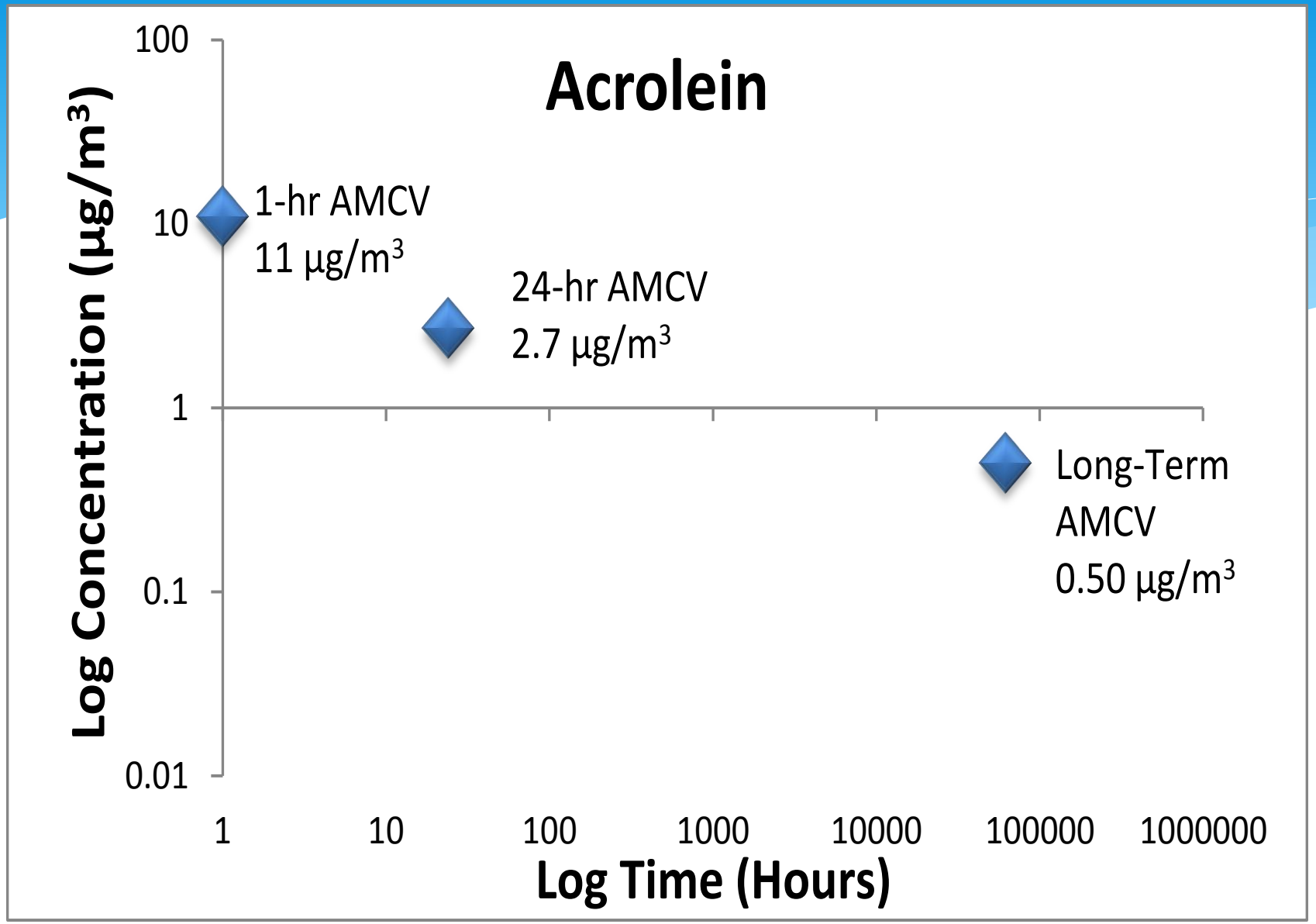
* 24-hr ReV Derivation:

* $POD_{HEC}/ (UF_H \times UF_A \times UF_L \times UF_D) =$

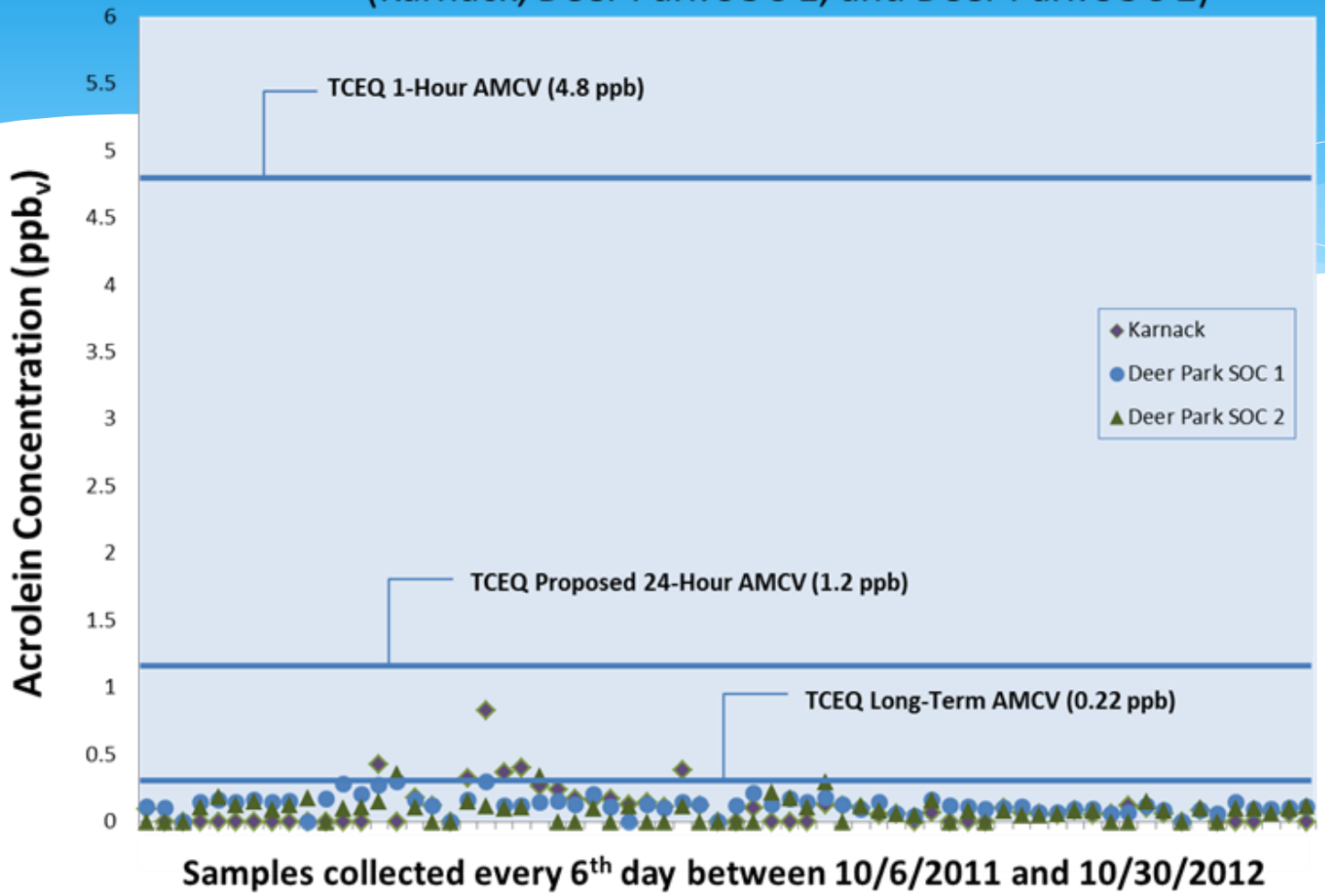
  0.0374 ppm /(10 x 3 x 1 x 1) = 0.0012 ppm

  (1.2 ppb)

  The rounded 24-hr, health-protective ReV for acrolein is 0.0012 or 1.2 ppb.


Acrolein
100
10
1
0.1
0.01
Log Concentration (µg/m³)
1-hr AMCV
11 µg/m³
24-hr AMCV
2.7 µg/m³
Long-Term
AMCV
0.50 µg/m³
1
10
100
1000
10000
100000
1000000
Log Time (Hours)

24-Hour Acrolein Canister Data Collected at Sites in Texas with Comparison Values (Karnack, Deer Park SOC 1, and Deer Park SOC 2)



Benzene

24-Hr ReV ultimately based on:

* Hematotoxicity in multiple-day, subacute study.
* Informative toxicokinetic and MOA data.

Benzene

Potential Points of Departure:

* Benzene can produce various toxic effects from high short-term exposure, including central nervous system (CNS) depression, eye/respiratory tract irritation, developmental toxicity, and hematotoxicity.

* These effects were considered for the basis of developing a 24-hr, health-protective inhalation comparison value.

Benzene

Point of Departure:

* Data from available short-term exposure studies suggest the most sensitive endpoint for this purpose is hematotoxicity (e.g., bone marrow depression).

* Dose-response data from subacute studies in mice provide the most conservative (i.e., lowest) point of departure (POD) for derivation of a 24-hr value.

Benzene

Point of Departure:

* The lowest lowest-observed-adverse-effect-level (LOAEL) among subacute animal studies demonstrating benzene-induced hematological effects (e.g., blood cell decreases) was used as the POD in the 24-hr ReV derivation.

Benzene

Point of Departure:

* Three subacute mouse studies identified approximately 10 ppm as the LOAEL, including the key study of Rozen et al. (1984) which 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.

Benzene

Exposure Regimen Considerations:

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-hr exposure duration of interest.

Benzene

Exposure Regimen Considerations:

* However, factors such as toxicokinetics must be considered to determine 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-hr value.

Benzene

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).

Benzene

Toxicokinetic Considerations:

* 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, catechol, muconic acid) from the bone marrow as evidence suggests they are not readily excreted.

Benzene

Toxicokinetic Considerations:

* 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-hr mouse inhalation dose to 11 ppm [^{14}C]benzene or an oral mouse [^{14}C]benzene dose (equivalent to a 11 ppm mouse exposure for 6 hours).

Benzene

Toxicokinetic Considerations:

* Regarding elimination from the target tissue (i.e., bone marrow) specifically, hematotoxicity-implicated metabolites have been detected in the bone marrow of mice exposed to 50 ppm [^{3}H]benzene for 6 hours (Sabourin et al. 1988), and appreciable amounts of these metabolites have been retained (perhaps ≈66-75%) and not cleared from mouse bone marrow 24-hr following exposure (Greenlee et al. 1981).

Benzene

Toxicokinetic Considerations:

* This suggests the toxicokinetic half-life of these proposed contributors to benzene toxicity (e.g., hydroquinone glucuronide, catechol, muconic acid) may be greater than 24 hours at the target tissue.

Benzene

Toxicokinetic Considerations:

* 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).

Benzene

Toxicokinetic Considerations:

* 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;

Benzene

Toxicokinetic Considerations:

(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; and

(3) 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-hr ReV.

Benzene

Toxicokinetic Considerations:

* Consequently, the POD for hematotoxicity is based on the LOAEL of 10.2 ppm from Rozen et al. (1984).

Benzene

Consideration of Other Effects:

* Other effects (CNS , irritation, developmental) were also considered for the 24-hr ReV but provided higher PODs than hematotoxicity.

Benzene

Final POD:

* This evaluation of the dose-response data for relevant endpoints suggests that the most sensitive endpoint for derivation of a 24-hr ReV is hematotoxicity.

* Rozen et al. (1984) provides a conservative LOAEL-based POD of 10.2 ppm for derivation of a 24-hr, health-protective ReV.

Benzene

Potential Exposure Duration Adjustment:

* If a single day of exposure (6 hr) from Rozen et al. were being used to derive a 24-hr value, then a default duration adjustment from 6 to 24 hr would be conducted using a Haber's Law "n" value of 1 (i.e., POD x 6/24 hr) (TCEQ 2012).

Benzene

Potential Exposure Duration Adjustment:

* However, such a duration adjustment is judged to be unnecessary as 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.

Benzene

Animal-to-Human Dosimetric Adjustment:

* Benzene 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

Benzene

Animal-to-Human Dosimetric Adjustment:

* For benzene, the animal blood:gas partition coefficient is greater than the human blood:gas partition coefficient, so a default value of 1 is used for the regional gas dose ratio (RGDR) (USEPA 1994). Thus…

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

$$10.2 \text{ ppm} \times 1 = 10.2 \text{ ppm}$$

Benzene

Applicable 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 was divided by the following UFs: UF_L of 3, UF_A of 3, UF_H of 10, and UF_D of 1 (total UF = 100).

Benzene

24-Hr ReV Derivation:

* $POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_D) =$

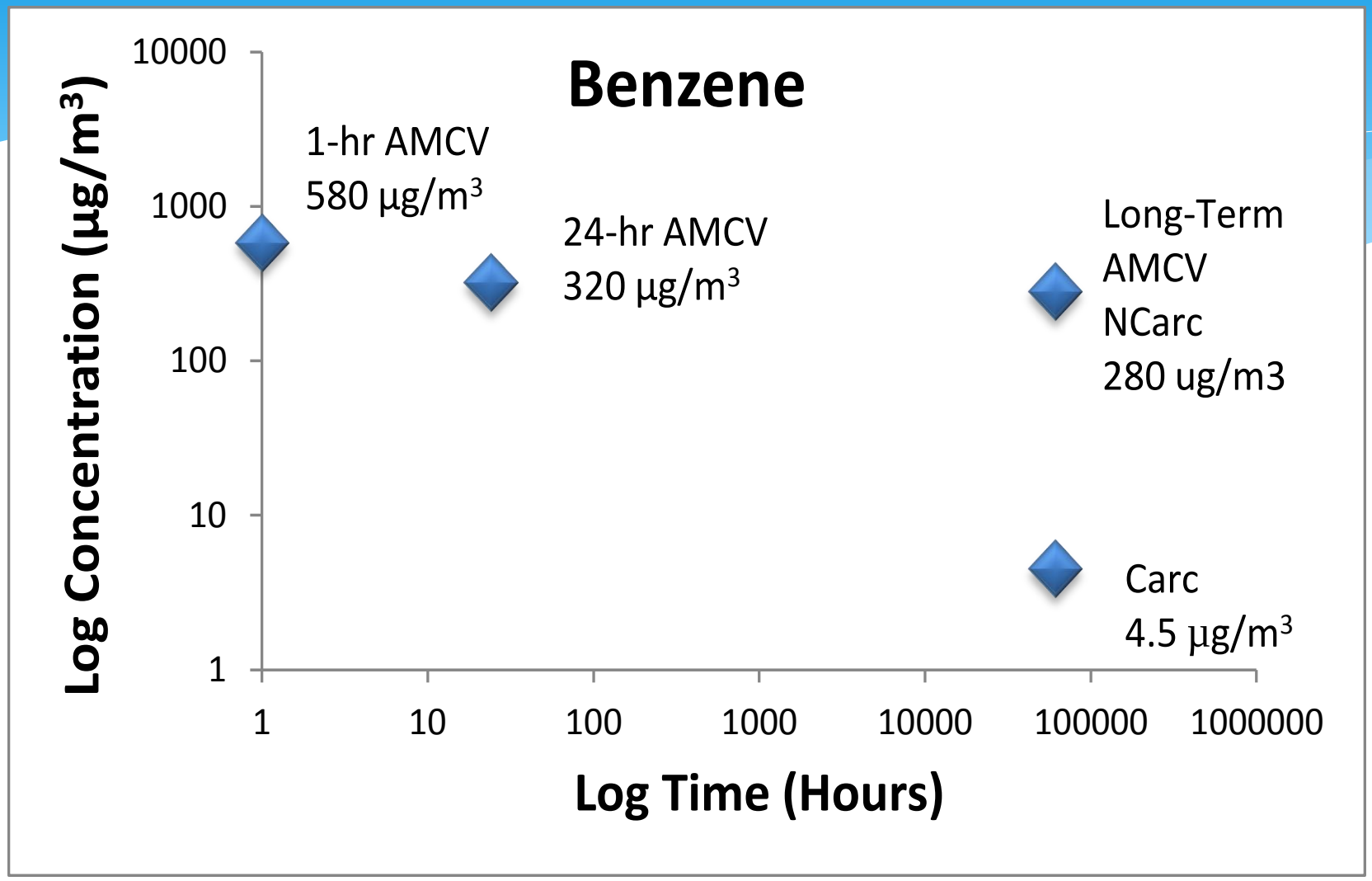
  $10.2 \text{ ppm} / (10 \times 3 \times 3 \times 1) = 0.102 \text{ ppm}$

* Thus, the rounded 24-hour, health-protective value for benzene is 0.10 ppm or 100 ppb.

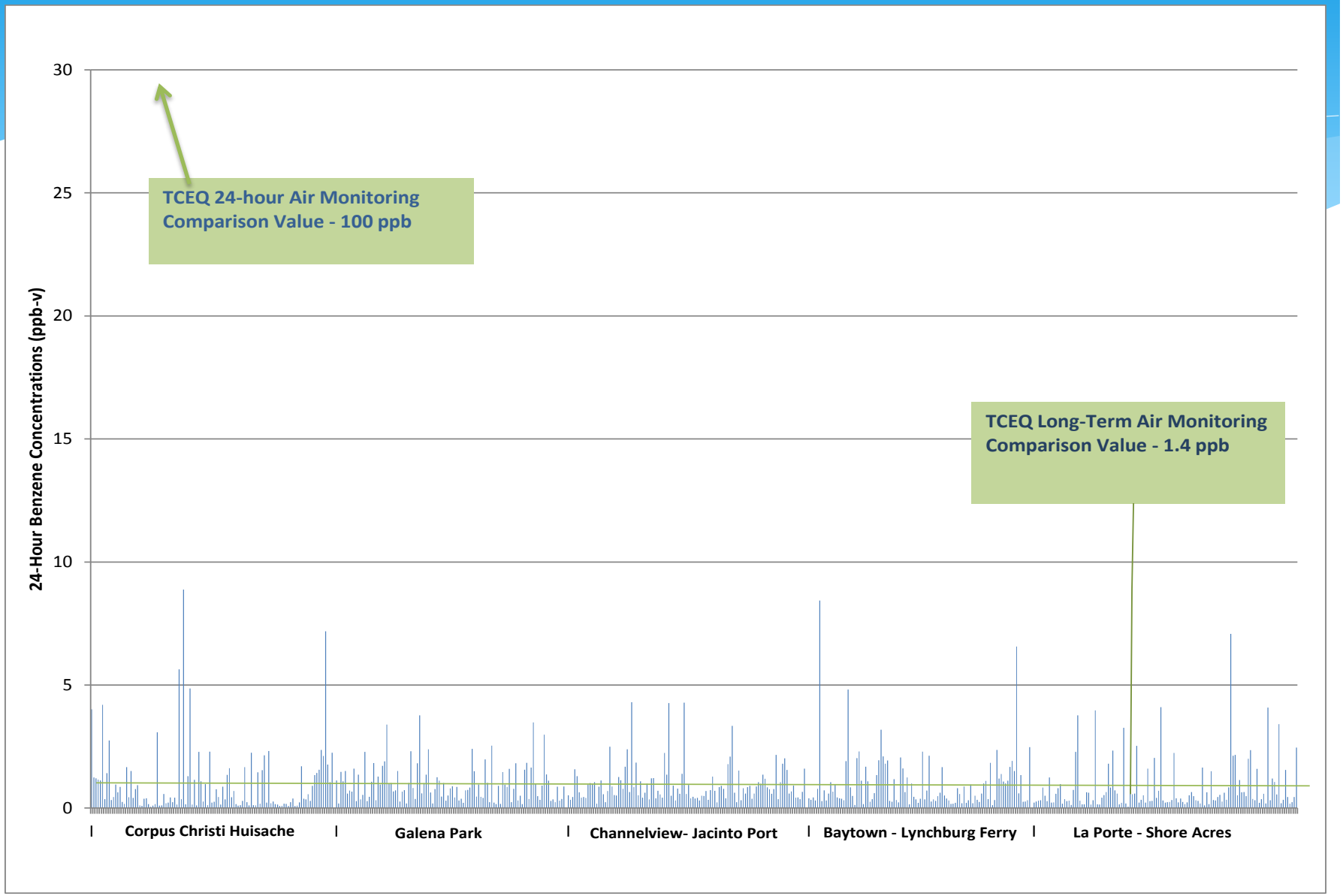
Benzene

24-Hr ReV :

* This 24-hr value of 100 ppb is well below even chronic human hematotoxicity effect levels (e.g., 7.2-13.6 ppm) (Rothman et al. 1996) so is expected to be sufficiently conservative for the adequate protection of public health.


Benzene
Log Concentration (µg/m³)
10000
1000
100
10
1
1-hr AMCV
580 µg/m³
24-hr AMCV
320 µg/m³
Long-Term
AMCV
NCarc
280 ug/m3
Carc
4.5 µg/m³
1
10
100
1000
10000
100000
1000000
Log Time (Hours)

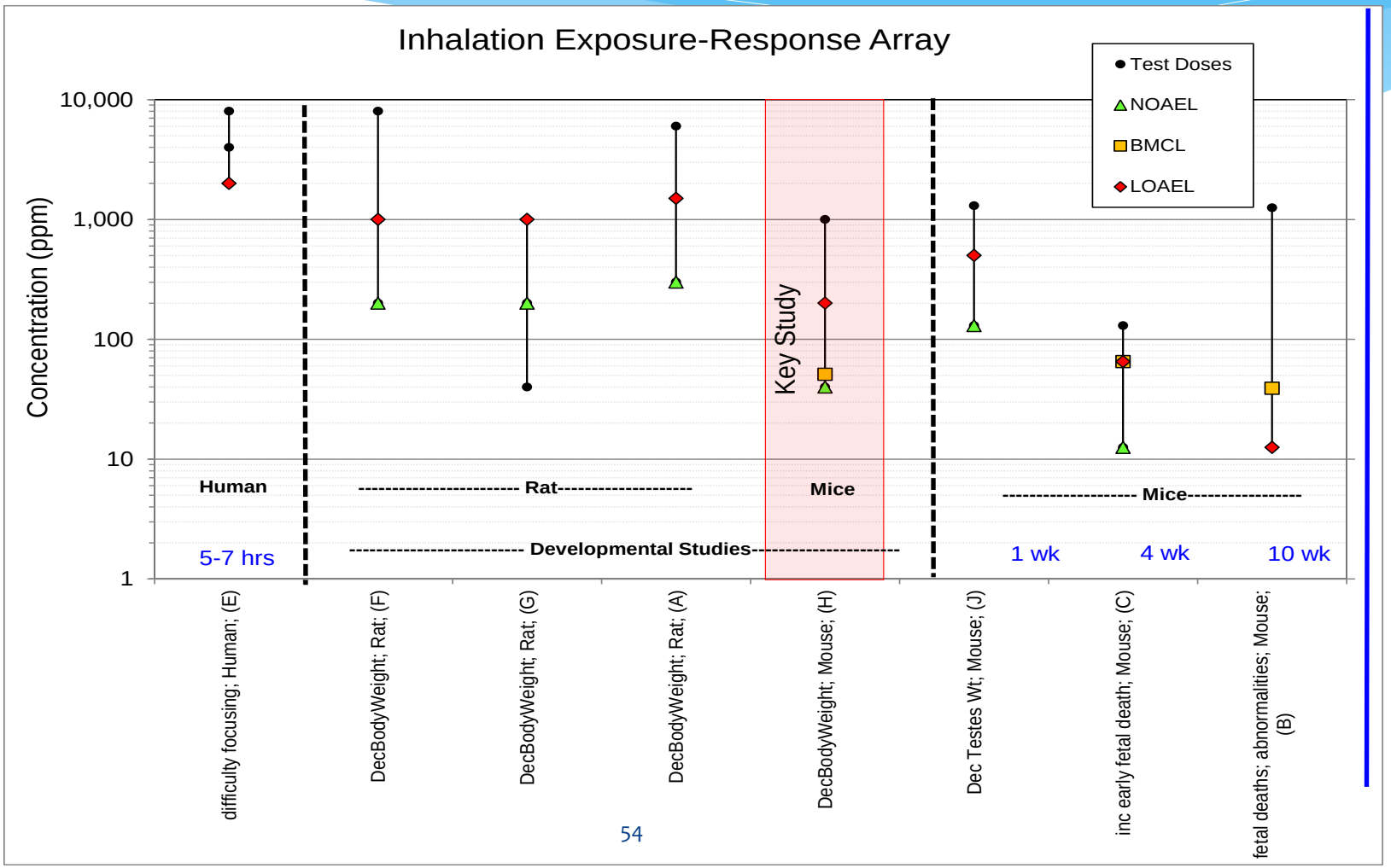
Benzene


30
25
20
15
10
5
0
24-Hour Benzene Concentrations (ppb-v)
TCEQ 24-hour Air Monitoring Comparison Value - 100 ppb
TCEQ Long-Term Air Monitoring Comparison Value - 1.4 ppb
Corpus Christi Huisache
Galena Park
Channelview- Jacinto Port
Baytown - Lynchburg Ferry
La Porte - Shore Acres

1,3-Butadiene (BD)

* Low acute toxicity
* Reproductive/developmental effects in mice
* Limited toxicokinetic and MOA information

1,3-Butadiene - Critical Study



1,3-Butadiene – Critical Study

* Reproductive/developmental effects in mice (Hackett *et al.* 1987b)
* Decrease in maternal extragestational weight gain and decrease in fetal body weight
* POD = 51.3 ppm ($BMCL_{1\ SD}$)
* 6 hr/day, Gestational Day 6-15

1,3-Butadiene - MOA

* BD produces toxicity when metabolized to reactive metabolites: 1,2-Epoxy-3-butene (monoepoxide) and 1,2:3,4-diepoxybutane (DEB - diepoxide)
* Diepoxide may induce ovarian atrophy and a decrease in serum progesterone levels
* Effects are concentration and duration dependent

1,3-Butadiene - Toxicokinetics

* Elimination of BD from tissues and blood was rapid, with 77% to 99% of the initial tissue burden being eliminated with half-times of 2 to 10 hr.

* Limited information on the half-time of EB and DEB in the target tissue

1,3-Butadiene – Default Duration Adjustments

* Point of departure

  51.3 ppm ($BMCL_{1\,SD}$)

* Extrapolation to 24 hr: Haber's rule with n = 1

* POD_{ADJ} = 51.3 ppm x 6 hr/24 hr = 12.8 ppm

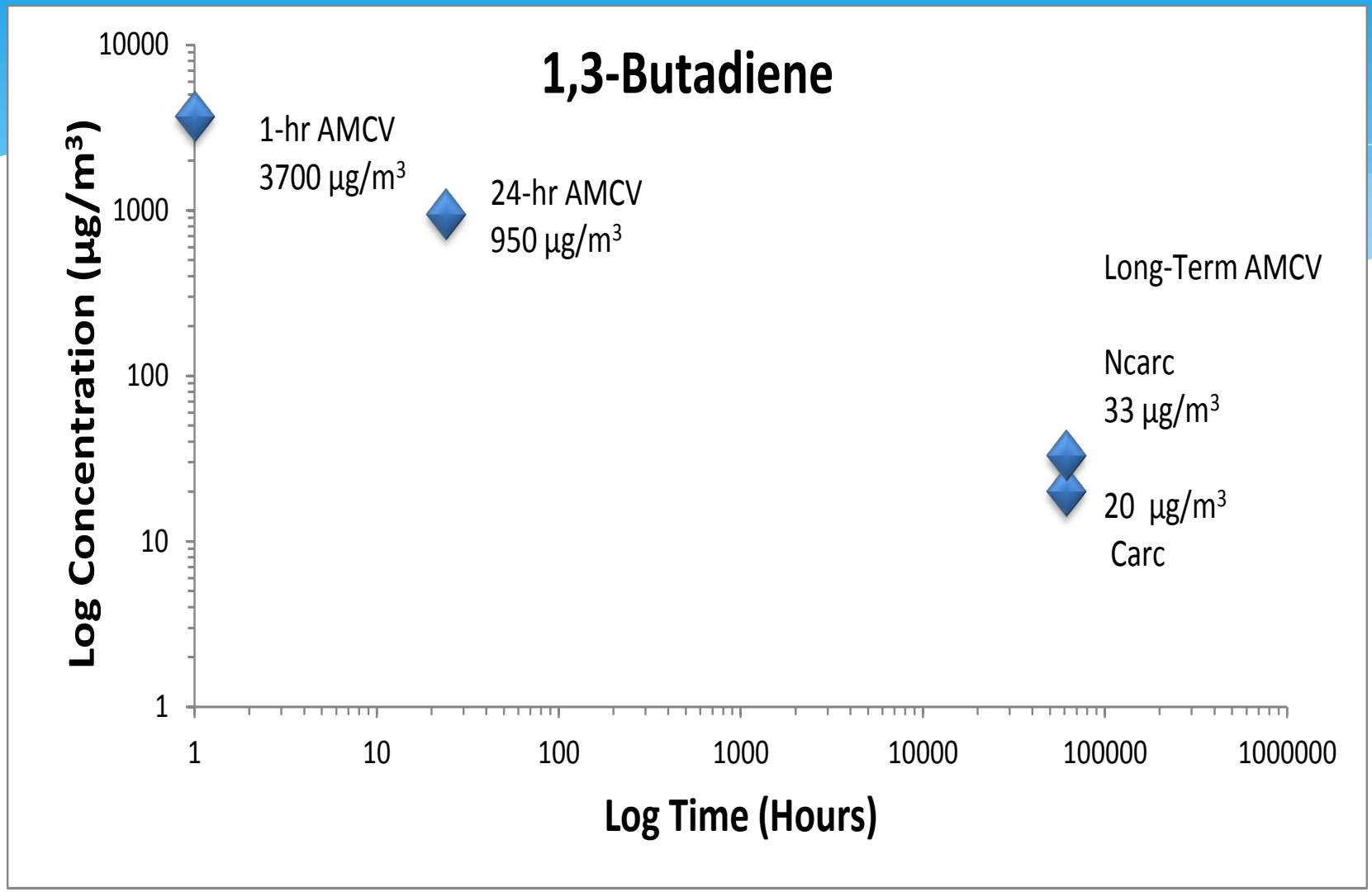
1,3-Butadiene – Animal-to-Human Dosimetric Adjustment

* Default Animal-to-Human Dosimetric Adjustment
* Gas with systemic effects, based on default RGDR = 1.0
  * $POD_{HEC} = POD_{ADJ} =$ 12.8 ppm

1,3-Butadiene – Uncertainty Factors

* Total UF = 30
  * UF_H of 10 was used to account for intraspecies variability.
  * A UF_A of 3 was used for extrapolation from animals to humans
  * A database UF_D of 1

* 24-hr ReV = 12.8 ppm/ 30 = 0.430 ppm
* 24-hr ReV = **950 µg/m³ (430 ppb)**


1,3-Butadiene
Log Concentration (µg/m³)
10000
1000
100
10
1
1-hr AMCV
3700 µg/m³
24-hr AMCV
950 µg/m³
Long-Term AMCV
Ncarc
33 µg/m³
20 µg/m³
Carc
1
10
100
1000
10000
100000
1000000
Log Time (Hours)

1,3-Butadiene

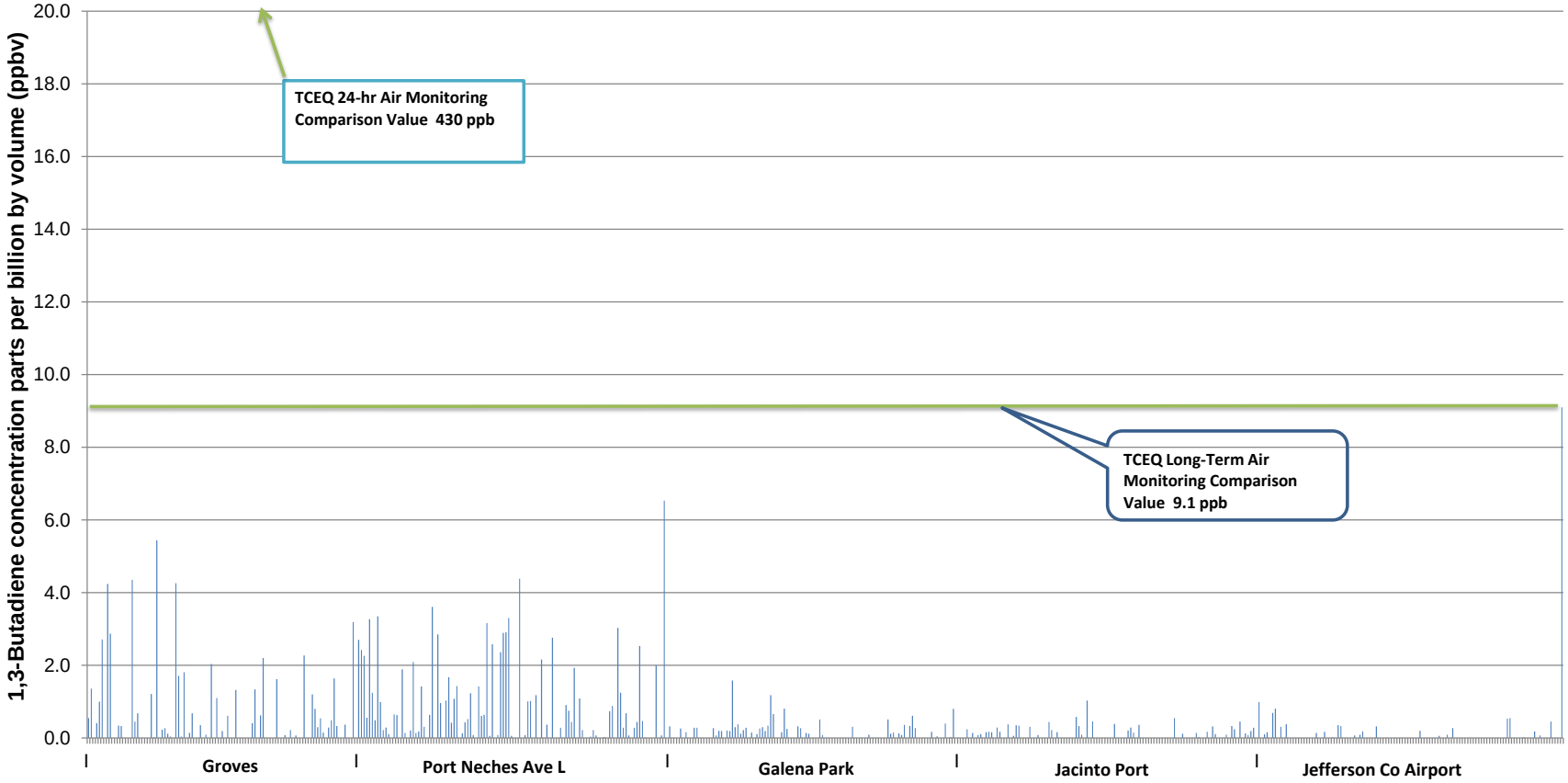


Figure 3-4 Top five sites with the highest 1,3-butadiene annual average concentrations (01/01/2010 - 12/31/2011)

Conclusions

* A 24-hr ReV would allow the TCEQ to fully evaluate 24-h data for possible health concerns

* Alleviate the concerns of the general public if a 24-hr measured air concentration exceed the chronic-based value

Conclusions

* Provide useful information for risk managers and the general population

* Risk communication

Conclusions

* 24-hr measured air monitoring concentrations are well-below 24-hr ReVs for the example chemicals (and are usually below the chronic value) during normal operations

* Air permitting procedures

Conclusions

* 24-hr air monitoring data may be measured above normal levels
  * Unplanned emission events
  * Maintenance/shut-down/start-up
* A 24-Hr ReV could be used to conduct a health effects review for these emission events

Contact Information

* Roberta Grant
  roberta.grant@tceq.texas.gov
* Allison Jenkins
  * allison.jenkins@tceq.texas.gov
* Joseph (Kip) Haney
  * joseph.haney@tceq.texas.gov