INTERPRETATION OF 24-HOUR SAMPLING DATA: Methods for Deriving 24-Hour Reference Values for Comparison to 24-Hour Ambient Air Monitoring Data

(Workshop VI)
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1.0 Problem Formulation

The Texas Commission on Environmental Quality (TCEQ), a state regulatory agency, employs several interactive programs to ensure concentrations of air toxics do not exceed levels of potential health concern (Capobianco et al. 2013): comprehensive air permitting, extensive air monitoring, and the establishment of Air Pollutant Watch List Areas if monitoring data indicate concentrations above levels of concern. This case study will focus on the air monitoring program and the need to evaluate 24-hr ambient air concentrations for potential health effects.

For chemicals evaluated in the TCEQ ambient air monitoring network, acute 1-hr reference values (ReVs) and chronic ReVs have generally been derived to evaluate 1-hr measured concentrations of chemicals of interest or calculated annual average concentrations, respectively. These averaging times correspond to averaging times evaluated in air permitting. However, 24-hr ambient air samples (e.g., 24-hr canister samples collected every 3rd or 6th day) may be collected for special projects and also at permanent monitoring sites to calculate annual averages for comparison to chronic ReVs. A 24-hr sample is an acute exposure duration significantly longer than 1-hr. Toxic effects induced by 24-hr exposure may be governed by modes of action somewhat different than those influencing toxicity due to 1-hr or chronic exposure. It is not appropriate to use a short-term, 1-hr ReV or long-term ReV to evaluate a 24-hr ambient air sample. Thus, the development of a 24-h ReV would allow the TCEQ to fully evaluate 24-h data for possible health concerns and could be used for risk communication purposes.

Sometimes, members of the public will compare 24-hr measured air concentrations to chronic ReVs. It is often thought that if a chemical concentration measured in a 24-hr sample exceeds a chronic ReV, then adverse health effects will occur. A 24-hr ReV predictive of health effects that may occur due to a 24-hr exposure may provide useful information and important context for risk managers and the general population. This information can be an important part of the risk communication process. In addition, this information is helpful to risk assessors for performing health effects reviews when 24-hr air monitoring data exceed chronic ReVs.

The following case study concerns guidelines to develop 24-hr health-based ReVs for comparison to 24-hr ambient air data. A 24-hr ReV is derived for human health hazards associated with threshold dose-response relationships (typically effects other than cancer) and is defined as an estimate of an inhalation exposure concentration that is likely to be without an appreciable risk of adverse effects to the human population (including susceptible subgroups) for a single 24-hr exposure. However, exposure to chemicals may occur on an intermittent basis. The 24-hr ReV would be protective of intermittent 24-hr exposures at the ReV if the time period between intermittent exposures is sufficient for adequate toxicokinetic and toxicodynamic clearance such that a toxicologically significant accumulation of neither the particular causative
agent nor effect is expected. The 24-hour ReV is derived to evaluate a single 24-hour exposure. In order to determine if intermittent exposures that occur frequently at or below the 24-hour ReV would cause adverse health effects, chemical-specific information such as additional dose-response data (e.g., subchronic) and toxicokinetic/toxicodynamic information would have to be evaluated in the context of the specific exposure scenario, based on actual air monitoring data.

The methods described in the case study are useful for addressing the problem formulation because they present guidelines to calculate 24-hr ReVs based on MOA, toxicokinetics/toxicodynamics, and the dose-response relationship. Procedures used to develop 24-hr ReVs are similar to procedures used to develop 1-hr and chronic ReVs (TCEQ 2012).

2.0 Case Study Summary

This method involves development of guidelines to develop ReVs to evaluate measured 24-hr ambient air concentrations. It is an extension of the hazard identification and dose-response methods used to derive ReVs to evaluate air concentrations for a short-term 1-hr averaging time or long-term annual averaging time. An inhalation ReV is defined as 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. A 24-hr ReV is based on the most sensitive noncarcinogenic adverse health effect relevant to humans reported in the scientific literature. ReVs are derived by adjusting an appropriate point of departure (POD) with uncertainty factors (UFs) to reflect data limitations and to derive a value that is below levels where health effects would be expected to occur. Examples of PODs include the benchmark concentration lower confidence limit (BMCL) and the no-observed-adverse-effect-level (NOAEL).

Ideally, an acute study of 24-hr exposure duration would be used to develop a 24-hr ReV, but such toxicity studies are rare. Thus, this method is to provide guidelines on incorporation of information on mode of action (MOA), toxicokinetics/toxicodynamics, and the dose-response relationship to develop ReVs applicable for conducting a health effects evaluation for 24-hr ambient air monitoring data. Appendix A of the case study provides the draft guidelines developed by the TCEQ (TCEQ 2011a) for developing 24-hr ReVs. The TCEQ did not finalize the draft guidelines because the TCEQ wanted to test their utility through chemical-specific examples using available data as well as to submit chemical-specific 24-hr ReVs to the panel for additional review (Appendix B).

- Acrolein (Appendix B, Example 1) illustrates development of a 24-hr ReV for a chemical whose health effects are irritation of eyes and the upper respiratory tract, health effects that are mainly concentration dependent (based on additional analyses from TCEQ 2010).

- Benzene (Appendix B, Example 2) illustrates development of a 24-hr ReV based on a subacute study for a health effect with informative toxicokinetic and MOA data (based on additional analyses from TCEQ 2007).

- 1,3-Butadiene (BD) (Appendix B, Example 3) illustrates development of a 24-hr ReV using an intermittent reproductive/developmental study (6 hr/day; gestational day 6-15). The endpoint was judged to be concentration/duration dependent. There was limited
toxicokinetic and MOA information for acute effects (based on additional analyses from TCEQ 2008).

The purpose of this case study is to obtain comments from the panel on procedures to develop 24-hr ReVs, not on procedures to calculate the 1-hr or chronic health-protective ReVs.

3.0 Comparison of 24-Hr Ambient Air Monitoring Data to 24-Hr AMCVs -Considerations of Intermittent Exposures

Measured 24-hr concentrations of all chemicals were below their respective chemical-specific 24-hr AMCVs (as discussed below), especially for measured 24-hr concentrations of benzene and 1,3-butadiene, mainly due to comprehensive air permits reviews as discussed in Section 3.4 below. Since the procedure for developing 24-hr ReVs is specific to the exposure period and effect being considered, they may be used to conduct a health effects review. In order to address health concerns about intermittent (and longer) exposures, an exposure assessment of ambient air monitoring data and health effects review was conducted, as illustrated for 1,3-butadiene, acrolein, and benzene.
3.1 1,3-Butadiene

Figure 1 show the five sites in Texas with the highest 1,3-butadiene annual average concentrations (01/01/2010 to 12/31/2011). These measured 24-hr concentrations were almost two orders of magnitude below the 24-hr AMCV of 430 ppb based on decreased fetal body weight and maternal body weight gain. Adverse health effects would not be expected to occur.

It should be noted that 24-hour AMCVs are based on noncancer effects and are not relevant to a cancer assessment. However, as cancer is typically of some interest it is addressed here in the context of the data shown as solely a peripherally-related topic. When 24-hr measured concentrations were compared to the long-term AMCV for butadiene for 2010-2011 sampling data, there were no exceedances of the long-term AMCV of 9.1 ppb (based on a $1 \times 10^{-5}$ lifetime excess risk goal for leukemia).

![Figure 1. Five Texas Sites with the Highest 1,3-Butadiene Annual Average Concentrations (01/01/2010 - 12/31/2011)](image1.png)

3.2 Acrolein

Figure 2 shows acrolein samples collected every 6th day between 10/6/2011 and 10/30/2012 at two sites in Texas. The measured 24-hr values are well below the 24-hr AMCV of 1.2 ppb. Thus, no short-term adverse health effects would be expected based on an assumption of independent exposure to these individual 24-hour measurements.

For acrolein, there were only five occasions where the 24-hr measured concentrations were slightly above the chronic AMCV of 0.22 ppb (Karnack site). The annual average was below the...
chronic AMCV of 0.22 ppb. Thus, no chronic adverse noncancer health effects would be expected either regardless of assumed independence or frequency of exposure to these levels.

**3.3 Benzene**

Figure 3 shows the five Texas sites with the highest benzene annual average concentrations (01/01/2010 to 12/31/2011). The measured 24-hr concentrations were more than an order of magnitude below the 24-hr AMCV of 100 ppb based on hematotoxicity, a noncancer effect. Thus, no short-term adverse noncancer health effects would be expected based on an assumption of independent exposure to these individual 24-hour measurements. Additionally, they are significantly below even the chronic AMCV of 86 ppb based on hematotoxicity as well as chronic human hematotoxicity observed adverse effect levels (e.g., 7.2-13.6 ppm; Rothman et al. 1996). Actual representative long-term (e.g., annual) averages are even lower (< 1.4 ppb). Thus, no chronic adverse noncancer health effects would be expected either regardless of assumed independence or frequency of exposure to these levels.

Lastly, it should be noted that 24-hour AMCVs are based on noncancer effects and are not relevant to a cancer assessment. However, as cancer is typically of some interest it is addressed here in the context of the data shown as solely a peripherally-related topic. More specifically, although measured 24-hr concentrations (01/01/2010 to 12/31/2011) of benzene frequently exceeded the chronic (i.e., lifetime) AMCV of 1.4 ppb based on a $1 \times 10^{-5}$ lifetime excess risk goal for leukemia, excess lifetime cancer risk is evaluated by regulatory agencies using long-term
averages and the benzene annual averages for 2010 and 2011 at these top five sites did not exceed the chronic cancer-based AMCV of 1.4 ppb (see table, below).

Figure 3. Five Texas Sites with the Highest Benzene Annual Average Concentrations (01/01/2010 to 12/31/2011)

<table>
<thead>
<tr>
<th>Site</th>
<th>2010 Benzene Concentrations ppb-v</th>
<th>2011 Benzene Concentrations ppb-v</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corpus Christi Huisache</td>
<td>1.09</td>
<td>0.9</td>
</tr>
<tr>
<td>Galena Park</td>
<td>1.06</td>
<td>0.92</td>
</tr>
<tr>
<td>Channelview – Jacinto Port</td>
<td>1.03</td>
<td>0.91</td>
</tr>
<tr>
<td>Baytown- Lynchburg Ferry</td>
<td>1.11</td>
<td>0.91</td>
</tr>
<tr>
<td>La Porte – Shore Acres</td>
<td>0.81</td>
<td>0.89</td>
</tr>
</tbody>
</table>


3.4 Comprehensive Air Permit Reviews and Extensive Air Monitoring

Evaluation of monitoring data indicates that measured 24-hr concentrations of chemicals were below their respective chemical-specific AMCVs. There was a great margin between measured 24-hr concentration of benzene and butadiene and their respective AMCVs. The reason this occurs is because of comprehensive air permit reviews that evaluate potential health and welfare effects for both short-term (1-hr) and long-term (annual) averaging times (Capobianco et al. 2013).

Comprehensive air permit reviews conducted by the TCEQ are the foundation for ensuring ambient air concentrations of air toxics do not exceed a level of concern. In order to understand the program formulation for this case study, a brief description of the TCEQ air permitting review process is provided. One of the main objectives of the New Source Review program is to issue air permits that establish emission controls and limits based on applicable state and federal rules. Both short-term and long-term limits are established. A best available control technology (BACT) (TCEQ 2011b) and residual emissions impacts review (TCEQ 2009) are conducted. Thus, air permitting is one of the essential tools used by the TCEQ to ensure that authorized air toxic emission limits will be protective of human health and welfare. During the air permit review process, maximum emission rates are calculated for new and modified equipment, based on reasonable worst-case operating scenarios and the application of BACT on a chemical-by-chemical basis. Modeled maximum ground-level concentrations for both short-term (1-hr averaging time) and long-term (annual averaging time) are calculated and compared to health- and welfare-base Effects Screening Levels.

The TCEQ’s ambient air monitoring program is extensive and provides data to help assess the potential for adverse effects from all operational equipment in an area. The collection and evaluation of ambient air monitoring data enables the TCEQ to assess the potential impact of source or cumulative emissions on the general public and to characterize chemicals in the ambient air near industrial facilities. Ambient air monitoring data may indicate that there is a compliance problem such as a facility not operating consistent with its authorization (i.e., permitted emission limits).

References


Capobianco, T., S.M. Hildebrand, M. Honeycutt, J.S. Lee, D. McCant, and R.L. Grant. Impact of Three Interactive Texas State Regulatory Programs to Decrease Ambient Air Toxic Levels. J Air Waste Management Association, accepted for publication, 2013.


Appendix A: Guidelines to Develop Twenty-Four Hour Reference Values (ReVs)
Section 4 Twenty-Four Hour Reference Values (ReVs)

Short-term ReVs have generally been derived to evaluate 1-hr reported concentrations of chemicals of interest detected in the TCEQ ambient air monitoring network (Chapter 1, TCEQ 2012). In addition to 1-hr ambient air samples, 5-min to 24-hr ambient air samples may be collected. The use of a 1-hr ReV to evaluate monitoring data collected for exposure durations less than 1 hr is likely to be conservative and overestimate risk. However, a significant amount of ambient air data is collected over a 24-hr duration, which is an acute exposure duration significantly longer than 1-hr. It is not appropriate to use a short-term, 1-hr ReV or long-term ReV to evaluate a 24-hr ambient air sample. This is due to the fact that while the 24-hr data is an acute rather than a chronic exposure duration, toxic effects induced by 24-hr exposure may be governed by modes of action somewhat different than those influencing toxicity due to 1-hr or chronic exposure. Therefore, the derivation of chemical-specific 24-hr ReV values may be needed. For some chemicals, particularly those where the duration of exposure is a contributing factor in toxicity (e.g., chemicals with long clearance times, cumulative or sensitizing effects), derivation of a 24-hr ReV is needed if the evaluation of 24-hr air monitoring data is desired because the 1-hr ReV may be much higher than the 24-hr ReV. For chemicals where concentration is the primary contributing factor to toxicity, the 24-hr ReV may be similar to the 1-hr ReV, but the determination of a 24-hr ReV is still needed.

A 24-hr ReV is derived for human health hazards associated with threshold dose-response relationships (typically effects other than cancer) and is defined as an estimate of an inhalation exposure concentration that is likely to be without an appreciable risk of adverse effects to the human population (including susceptible subgroups) for a single 24-hr exposure. However, exposure to chemicals may occur on an intermittent basis. The 24-hr ReV would be protective of intermittent 24-hr exposures at the ReV if the time period between intermittent exposures is sufficient for adequate toxicokinetic and toxicodynamic clearance such that a toxicologically significant accumulation of neither the particular causative agent nor effect is expected. The 24-hour ReV is derived to evaluate a single 24-hour exposure. In order to determine if intermittent exposures that occur frequently at or below the 24-hour ReV would cause adverse health effects, chemical-specific information such as additional dose-response data (e.g., subchronic) and toxicokinetic/toxicodynamic information would have to be evaluated in the context of the specific exposure scenario, based on actual air monitoring data.

The same analytical steps used to derive acute 1-hr ReVs and chronic ReVs are used to derive a 24-hr ReV (TCEQ 2012). The critical step in deciding whether or not to derive a 24-hr ReV is the availability of appropriate toxicity studies that provide meaningful information to evaluate a 24-hr exposure duration. If there are inadequate data to derive a 24-hr ReV, then a 24-hr ReV will not be developed. An evaluation of the mode of action, dose metric, and the toxicokinetics and toxicodynamics of the chemical of concern as well as exposure duration adjustments that are unique for the derivation of a 24-hr ReV (Figure 4.1) will be discussed in the following sections. However, animal-to-human dosimetric adjustments as well as application of UFs to the POD_{ADJ} to calculate a ReV are similar to the development of acute 1-hr ReV values (Chapters 3 and 4 of TCEQ 2012) and will not be discussed.
Section 4.1 Availability of Toxicity Studies

Available literature should be researched to determine if data are available to guide the derivation of a 24-hr ReV. Ideally, an acute study of 24-hr duration would be used to develop a 24-hr ReV, but such toxicity studies are rare. Many chemicals have a poor database, making the derivation of a 24-hr ReV at best difficult. In these instances, professional, scientific judgment must be used to decide whether sufficient data exist to support a scientifically-defensible 24-hr ReV.

For a data-rich chemical, it may be possible to perform PBPK modeling or categorical regression to extrapolate from studies that are conducted at other durations than 24 hr. For chemicals with limited data, a POD may need to be developed based on an acute study, subacute study or subchronic study and appropriate duration adjustments used to develop a 24-hr value. The best approach for developing a 24-hr ReV is to examine all available acute and subacute studies (and possibly subchronic studies) and develop an exposure response array (Chapter 3, TCEQ 2012). Then a consideration of physical/chemical parameters, MOA, toxicokinetics/toxicodynamics, etc. should be used to determine the most appropriate adverse effect relevant to humans for a 24-hr exposure duration. Development of several potential 24-hr ReV values based on different studies of different durations may be needed to aid in the decision-making process.

The acute key study used to develop the 1-hr ReV may or may not be appropriate to develop a 24-hr ReV based on the MOA, toxicodynamics, or toxicokinetics of a chemical, particularly if the 1-hr ReV is based on a key study with a 1-hr exposure duration or less. If data in the literature indicate that a key study other than the one used to derive the 1-hr ReV is the most appropriate study to derive a 24-hr ReV, which is expected to generally be the case, then a new POD_{HEC 24-hr} should be identified and new UF$s should be applied to this value. A literature search should always be conducted to identify a key study and adverse effect that is most appropriate for a 24-hr exposure duration. The following are some examples of toxicity studies that may be appropriate for derivation of a 24-hr ReV:

- acute toxicity studies (exposure durations 6-24 hr) where duration adjustments are defensible;
- acute or subacute toxicity studies may be used to derive a 24-hr ReV, particularly when data from subchronic and chronic studies indicate that longer exposure durations induce adverse effects unrelated to those expected to be caused by a 24-hr exposure duration;
- studies using exposure durations of less than 6 hr must be used cautiously, and may only be appropriate when available data indicate that the primary toxic effect induced by a chemical is irritation, the magnitude of which is generally determined by exposure concentration, and exposure to 24-hr would not be expected to have additional adverse effects other than the irritation;
- subacute toxicity studies (i.e., repeated or continuous exposure to a chemical > 1 day to 1 month or less) may be of greatest value for 24-hr ReV derivation because they may be more predictive of the effects expected due to 24-hr exposure when compared to acute studies of much shorter duration;
subchronic toxicity studies may be appropriate when acute or subacute studies are unavailable. However, use of a subchronic study to derive a 24-hr ReV may result in an unrealistic/unpredictive value. Section 4.4 provides appropriate adjustments that may be applied to aid in the generation of more realistic values;

chronic toxicity studies are usually not used for derivation of a 24-hr ReV, since the MOA for a chronic effect would generally be different than the one governing an effect induced by 24-hr exposure.

In some cases a subacute multi-day study may be more appropriate than an acute, single exposure study. Additionally, a subchronic study may be used for derivation of a 24-hr ReV if MOA and toxicokinetic/dynamic information support this application (e.g., chemicals with long toxicokinetic or toxicodynamic half-lives).

Section 4.2 Toxicokinetics/Toxicodynamics

Toxicokinetics and toxicodynamics are critical determinants of the key events that occur in a chemical-specific MOA. Toxicokinetics refers to how the body acts upon a chemical; this includes absorption, distribution, metabolism, and excretion. Toxicodynamics, on the other hand, refers to how the chemical affects the body. That is, the effect the chemical has on target tissue(s), including how the chemical damages tissue and how long it takes that tissue to repair itself. Both the toxicokinetics and toxicodynamics of a chemical can cause rate-limiting steps in a MOA that lead to the toxic effect (Rozman, 2000; Rozman and Doull, 2000; Rozman and Doull, 2001).

It is critical to carefully evaluate each step of a MOA, when known, and what the rate limiting steps may be for the toxic effects observed. An understanding of toxicokinetics and toxicodynamics of a chemical will help inform exposure duration adjustments as well as to determine whether an acute one-day exposure as opposed to a subacute repeat-dose study is more predictive of toxicity for a 24-hr exposure. For example, if a chemical is known to have a long toxicokinetic half-life or cause cumulative damage, subacute studies rather than a single-day (e.g., 6-hour) acute study may be more predictive of a 24 hr exposure because steady state condition may have been achieved after repeat exposures. Therefore, the POD from subacute studies may be more predictive of the toxicity expected to occur following a 24-hr exposure. On the other hand, for chemicals with a short toxicokinetic half-life or chemicals that do not cause cumulative tissue damage (e.g., chemicals causing concentration-dependent POE mild sensory irritation as a critical effect), acute or subacute studies may be appropriate to use as the key study, since intermittent exposures of the subacute studies may resemble a series of toxicologically-independent acute exposures (i.e., previous exposures may have little or no impact on the potential for current-day effects).

Section 4.3 Mode of Action and Dose Metric

An understanding of the chemical-specific MOA is critical to using available data to calculate a 24-hr ReV. Briefly, some questions that should be considered in this preliminary evaluation are:

- What are the critical steps or key events in toxicity?
- How severe are the adverse effects?
Section 4.4 Exposure Duration Adjustments

A variety of modeling approaches are available to identify the POD upon which a 24-hr ReV may be derived (PBPK or other optimized inhalation models and categorical regression). These approaches are discussed in Chapter 3 (TCEQ 2012) and in OECD (2010). If a PBPK model or categorical regression is used to derive a POD, these models can be used directly to perform exposure duration adjustments. Briefly, the model that may be chosen to identify the POD from a key study is dictated by the quantity and quality of the data available for a chemical of interest (Figure 4.1):

- a PBPK model may be used to identify a POD$_{ADJ}$ for a chemical based on an exposure duration of interest when such a model is available;
- exposure-response arrays may be generated as a means of estimating what a logical POD for a 24-hr ReV might be (OECD 2010);
- categorical regression is a valuable tool to assess toxicity across studies and exposure durations to identify an appropriate POD$_{ADJ}$, which may be used to derive a 24-hr ReV where duration adjustment is unnecessary (OECD 2010);
- when data are insufficient to apply any of the aforementioned approaches, benchmark concentration modeling or a NOAEL/LOAEL approach may be used to identify a POD. In these cases, exposure duration adjustments may be needed to calculate a POD$_{ADJ}$ for a 24-hr ReV.

The approach used to identify the POD for a 24-hr ReV is highly dependent on the data available for a given chemical. While several approaches may be developed, the final approach used to derive a 24-hr ReV will be selected using best scientific judgment.

Section 4.4.1 Duration Adjustments for Acute Studies (< 24 hr)

If the above models are not available, there are several ways to perform exposure duration adjustments as discussed in Chapters 3 (Section 3.8) and 4 (Section 4.2) of TCEQ (2012). Studies evaluating 24-hr chemical exposures are not often available and a key study conducted for a different exposure duration may be the most appropriate key study used to derive the 24-hr ReV. In this case, Haber’s rule as modified by ten Berge (1986) can be used to calculate a POD to be used for the 24-hr ReV ($C^n \times T = K$). The same principles of performing duration adjustments discussed in Section 4.2 (TCEQ 2012) and used for a 1-hr ReV are generally applicable for exposure duration adjustments for a 24-hr ReV. The chosen method for exposure duration adjustments for the development of a 24-hr ReV should be dictated by available data and professional scientific judgment.
Haber’s rule is dependent on the assumption that log concentration and log time have a linear relationship or that a study employs experimental conditions wherein steady state toxicokinetics or toxicodynamics are achieved. This assumption, however, does not apply to chemicals that have rate-limiting critical steps in their MOA or experimental conditions that do not achieve steady state (Rozman and Doull 2001). There are many ways that a chemical’s MOA may have rate-limiting critical steps, including a very short or long toxicokinetic/dynamic half-life, zero order toxicokinetics, reduced elimination due to high apparent volume of distribution caused by compound or metabolite accumulation in the study organism’s body, or an MOA where tissue damage is particularly severe or irreversible as is the case with certain neuropathies (Rozman 2000, Rozman and Doull 2001, Witschi 1999).

Concentration-Dependent

In instances where the toxic effect appears to be modulated only by concentration, a horizontal line, a method called “flat-lining”, from the shortest duration through the response array may be used to identify a POD\textsubscript{ADJ}. An example of this type of chemical would be those that induce sensory irritation at the point of entry (OECD 2010).
Figure 4.1 Flowchart for Derivation of 24-hr ReV.

Concentration and/or Duration-Dependent Defaults

When a chemical’s MOA is poorly characterized, C\( ^n \) exponent, n (see Section 3.8 of Chapter 3 discussion, (TCEQ 2012) regarding Haber’s rule, C\( ^n \times T = K \)), is set equal to a default value of
1, which is considered to be conservative when performing a duration adjustment from a shorter exposure duration to a longer one.

### 4.42 Duration Adjustments for a Subacute Multi-Day Study

Subacute studies (> 1 day) may be used to derive a 24-hr ReV if an appropriate one-day acute study is not available. Typically, subacute studies are conducted for 6 h/day for up to 2 weeks. In these cases, the following adjustments will be made to the subacute POD to calculate a \( \text{POD}_{\text{ADJ}} \) appropriate for a 24-hr exposure duration.

- If it is reasonable to assume that steady state has been achieved, or toxicodynamics indicate that no additional toxic effect would be expected to occur with the subacute exposure duration, the POD from the subacute study can be used as the 24-hr POD. No duration adjustments will be made.
- If the chemical has a short dynamic half-life and each new day represents a toxic effect induced by an independent exposure, then a duration adjustment can be performed to derive the 24-hr ReV. The duration adjustment can be the traditional approach where a POD is derived from a key study or through an analytical method such as categorical regression.
- Alternatively, the OEHHA (2008) method for subchronic studies, which is described below, may be used to calculate a POD for a 24-hr exposure duration based on a subacute study.

### 4.43 Duration Adjustments for Subchronic Study

Subchronic studies may also be used to derive a 24-hr ReV if acceptable acute or subacute studies are not available or if the toxicokinetic or toxicodynamic half-life of the chemical is long. In those cases, the TCEQ uses the OEHHA (2008) default approach for a subchronic POD (\( \text{POD}_{\text{subchronic}} \)) to calculate a POD appropriate for a 24-hr exposure duration (\( \text{POD}_{24-hr} \)). The default approach to estimating an equivalent \( \text{POD}_{24-hr} \) from the \( \text{POD}_{\text{subchronic}} \) is summarized as:

\[
\text{POD}_{24-hr} = \text{POD}_{\text{subchronic}} \times (N \text{ hours}/24 \text{ hours}) \times (D \text{ days})
\]

where:

\( \text{POD}_{\text{subchronic}} = \) POD identified from key subchronic study

\( N = \) number of hours per day conducted in the key subchronic study

\( D = \) number of days per week conducted in the key subchronic study

### 4.44 Critical Evaluation of Duration Adjustment Procedures

When performing exposure duration adjustments using default procedures outlined in the above Sections, it is important to evaluate the reasonableness of the adjustment. Importantly, use of a default value of 1 for \( n \), where exposure concentration and duration are thought to contribute equally to the toxic effect of a chemical, may not result in a reasonable or predictive 24-hr ReV, particularly when exposure durations of less than 6 hr are used to calculate the 24-hr ReV. This is due to the fact that the product of this calculation may result in a number that is lower than the chronic ReV.
In addition, MOA(s) governing the toxic response following a shorter exposure may be unrelated to the MOA(s) that induces a toxic effect following a 24-hr exposure. To evaluate whether a 24-hr ReV derived using a default value of 1 for n and m generates a realistic value, compare where the potential 24-hr ReV falls on an exposure array generated for the chemical of interest. If the value for the 24-hr ReV is less than or equal to the 1-hr ReV and greater than the chronic ReV, it may be a reasonable and predictive value. If the 24-hr ReV appears to be an unreasonable value, a higher value for n, such as n = 2 or 3, may result in a more reasonable POD for derivation of the 24-hr ReV given what is known about the toxicity of the chemical. The OECD refers to this procedure as “interpolation.” Exposure-response arrays may be generated as a means of interpolating the POD_{ADJ} for a 24-hr ReV. Alternatively, an appropriate, chemical-specific “n” value may be derived via curve fitting on a log Concentration versus log Time plot (TCEQ 2012). Thus, it is always advisable to use scientific judgment to identify the most scientifically defensible approach for exposure durations used to derive the 24-hr ReV.

**Section 4.5 Conclusions**

This section describes a framework approach to derive a 24-hr ReV. The steps involved in the derivation of the 24-hr ReV are largely dictated by available, chemical-specific data, and include evaluation of the MOA, identification of rate limiting steps for the resultant toxicity, selection of an approach to derive a POD_{24-hr} (Figure 4.1 above), and selection of UF{s} to apply to that POD_{24-hr}. The OECD (2010) has proposed a similar approach for the derivation of acute reference concentrations (ARfCs) and has published a draft document wherein case studies detailing this approach may be found. Since a similar approach will be used by the TCEQ, these examples offer an illustration of how this approach can be successfully applied to model chemicals (OECD 2010).

**Section 4.6 References**


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Rozman, KK. 2000. The role of time in toxicology or Haber’s c x t product. Toxicology 149:35-42.

Rozman, KK and Doull, J. 2001. The role of time as a quantifiable variable of toxicity and the experimental conditions when Haber’s c x t product can be observed: implications for therapeutics. Perspectives in Pharmacol 296:663-668.


APPENDIX B: Chemical-Specific Examples of 24-Hr ReVs
Example 1: Development of a 24-Hour Reference Value (Air Monitoring Comparison Value) for Acrolein

Acrolein (Example 1) illustrates development of a 24-hr ReV for a chemical whose health effects are irritation of eyes and the upper respiratory tract, health effects that are mainly concentration dependent (based on additional analyses from TCEQ 2010).

Allison Jenkins, Texas Commission on Environmental Quality, Austin, TX

Abstract

Acrolein is of national and state interest because it is ubiquitous, is difficult to analyze in ambient air, and concentrations causing eye and respiratory irritation are low. The Texas Commission on Environmental Quality (TCEQ) has previously derived 1-hr and chronic health-protective Reference Values (ReVs) for acrolein in order to evaluate air monitoring data. The ReV is used as the Air Monitoring Comparison Values (AMCVs). In order to evaluate the 24-hr data collected at two permanent monitoring sites in Texas, the TCEQ has developed a proposed 24-hr AMCV to better evaluate any potential for adverse health effects. Acrolein’s toxicity is mainly concentration dependent and levels causing adverse effects are very similar in humans and animals. The same rat study used to develop the chronic AMCV was selected as the critical study for derivation of the 24-hr AMCV since interim histopathology was performed after various exposure durations (e.g., 6 hr/day for 4, 14, 30, and 65 days) which encompassed the 24-hr duration of interest. A no-observed-adverse-effect level of 200 ppb was identified from the key study for all exposure durations based on the absence of nasal epithelial hyperplasia. Based on a mode-of-action analysis, no duration adjustment was necessary. After correcting for animal-to-human dosimetric differences, the 24-hr human equivalent point of departure was 37.4 ppb. Total uncertainty factors of 30 were applied to calculate the proposed 24-hr AMCV of 1.2 ppb. In comparison, the 1-hr AMCV for acrolein is 4.8 ppb and its chronic AMCV is 0.22 ppb.

Introduction

The Texas Commission on Environmental Quality (TCEQ) has historically developed 1-h 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-h autoGC data or every sixth-day 24-h canister results. However, the TCEQ has not historically developed 24-h, health-based AMCVs for comparison to individual 24-h canister results from its monitoring network.

Only a limited evaluation of the reported 24-h levels is possible without 24-h AMCVs because 1-h and chronic (i.e., lifetime) AMCVs are of limited utility and largely inappropriate for this purpose. Regarding use of 1-h AMCVs for comparison, while a 24-h VOC concentration
exceeding a conservative 1-h AMCV would be indicative of a potential health concern requiring further evaluation, a 24-h level less than a 1-h AMCV could still be of potential concern if exposure duration is a primary determinant of toxicity and the 1-h AMCV is not sufficiently conservative (i.e., below 24-h 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-h level would be of dubious toxicological significance and thus still require an entirely different and appropriate evaluation. Thus, the development of 24-h AMCVs is necessary for the best possible health effects evaluation of individual 24-h canister VOC results, and would significantly complement the 1-h and chronic evaluations of chemicals of interest.

Acrolein is a VOC for which 24-h canister data are collected. Additionally, it is frequently detected in the TCEQ ambient air monitoring network and is of significant agency and public interest. Therefore, acrolein is a chemical for which a 24-h, health-protective AMCV has been developed. General steps discussed below for derivation of a 24-h acrolein’s 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, selection and application of applicable uncertainty factors, and derivation of the 24-h AMCV value.

**Key Study**

**Critical Study**

Four studies were evaluated for use in deriving the 24-hr AMCV (Weber-Tschopp et al. 1977, Dorman et al. 2008, Cassee et al. 1996, and Roemer et al. 1993). The Dorman et al. 2008 study was chosen as the key study because it investigated both duration and concentration effects and included several exposure groups and exposure durations. Dorman et al. (2008) exposed male F344 rats (whole-body exposure) to concentrations of 0.02, 0.06, 0.2, 0.6, or 1.8 ppm acrolein for 6 hr/day for 4 days. The POD from the key study was the NOAEL of 0.2 ppm (absence of critical effect - nasal respiratory epithelial hyperplasia). The effects were not amenable to benchmark dose modeling. Interim histopathology was performed after various exposure durations (e.g., 6 hr/day for 4, 14, 30, and 65 days). The NOAEL for all exposure durations was 0.2 ppm.

**Duration Adjustment**

No duration adjustment was performed, as adverse effects of acrolein are mainly concentration dependent. Acrolein is a highly reactive aldehyde that is strongly irritating to mucous membranes, especially the eyes and upper respiratory tract (TCEQ 2010). The health effects produced by acrolein are respiratory tract effects in the extrathoracic region of the respiratory tract.

**Dosimetric Adjustments**

Dosimetric adjustments were performed as a Category 1 gas and as such, the POD was multiplied by the regional gas dose ratio (RGDRr) of 0.187 (TCEQ 2010). The RGDRr is the ratio of regional gas dose in rats to that of humans. The resulting POD_{HEC} was 0.0374 ppm.

**Uncertainty Factor**
Total uncertainty factors (UF) of 30 (interspecies UF of 3, intraspecies UF of 10, database UF of 1) was applied to the POD_{HEC} to result in the proposed 24-hr AMCV of 0.0012 ppm (1.2 ppb) (TCEQ 2010).

24-Hour AMCV Derivation

As discussed in the previous section, UFs are applied to the key study (Dorman et al. 2008) POD_{HEC} to derive the 24-h value:

\[
\text{POD}_{\text{HEC}} / (30) = 0.0374 \text{ ppm} / 30 = 1.2 \text{ ppb or 2.7 } \mu\text{g/m}^3
\]

This value falls between the TCEQ acute 1-h ReV of 4.8 ppb (11 µg/m³) (TCEQ 2010) and the chronic noncarcinogenic ReV of 0.22 ppb (0.50 µg/m³) (TCEQ 2010) (Figure 1-1).

Figure 1-1 Comparison of Acrolein AMCVs developed to evaluate different averaging times

24-Hr Acrolein Canister Data Collected at Sites in Texas with Comparison Values

There are two sites in TX which collect 24-hr carbonyl canister samples of ambient air approximately every sixth day, including acrolein. Those sites are located in Karnack (in East Texas) and in Deer Park (near Houston). A comparison of the proposed 24-hr AMCV for acrolein to the improved ("verified") acrolein 24-hr data was conducted. Verified acrolein data are those data that have been collected and analyzed using USEPA’s improved acrolein analysis methodology. Concentrations of acrolein collected at the sites using the improved sampling method implemented in October 2011 have not exceeded the 24-hr AMCV (Figure 1-2, below).
Conclusion

- The proposed 24-h, health-protective AMCV for acrolein is 1.2 ppb (2.7 µg/m³).

- This value falls between the TCEQ acute 1-h ReV of 4.8 ppb (11 µg/m³) (TCEQ 2010) and the chronic noncancerous ReV of 0.22 ppb (0.50 µg/m³) (TCEQ 2010), and is less than the ATSDR acute (14 days or less) MRL of 3 ppb (6.9 µg/m³) (1-hr study).

- 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-h and chronic (i.e., lifetime) health-protective and welfare-based (i.e., odor, vegetation) AMCVs.
References


Example 2: Development of a 24-Hour Reference Value (Air Monitoring Comparison Value) for Benzene

Benzene (Example 3) illustrates development of a 24-hr ReV (Air Monitoring Comparison Value (AMCV)) based on a subacute study for a health effect with informative toxicokinetic and MOA data (based on additional analyses from TCEQ 2007).

J. Haney, Texas Commission on Environmental Quality (TCEQ), Austin, TX.

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., RfC-like values for noncancerous 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. 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. 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 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 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, a 24-hour VOC concentration exceeding a conservative 1-hour AMCV would be indicative of a potential health concern requiring further evaluation. Additionally, a 24-hour level that is 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 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.

**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 observed-adverse effect-level (LOAEL) among the studies for use as a POD in derivation of a 24-hour, health protective AMCV.

### Summary of Subacute Mouse Inhalation Studies

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

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

The key study of Rozen et al. (1984) utilized an exposure regimen of 6 hours per day for 6 days. Thus, the total number of 36 exposure hours exceeds the 24-hour exposure duration of interest. However, factors such as toxicokinetics and toxicodynamics 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-hour value. This is opposed to it being 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. Available data suggest the former 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 $[^{14}\text{C}]$benzene or an oral mouse $[^{14}\text{C}]$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 $[^{3}\text{H}]$benzene for 6 hours (Sabourin et al. 1988). More specifically, data indicate that appreciable amounts of these metabolites have been retained (perhaps $\approx$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 $\approx$400 (Irons et al. 1980), and twice daily subcutaneous doses of $[^{3}\text{H}]$benzene increasing metabolites in the bone marrow of mice an average of $\approx$29-fold over a 6-day period (Snyder et al. 1978). Collectively, these data suggest two important findings for this 24-hour ReV derivation.
• First, 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.

• Second, 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$_{HEC}$ 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).

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. These studies 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.

**Conclusion on 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 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.

**Potential Exposure Duration Adjustment**

If a single day of exposure (6 hours) from Rozen et al. was being used to derive a 24-hour AMCV, then a default duration adjustment from 6 to 24 hours would be conducted using a Haber’s Law “n” value of 1 (i.e., POD x 6/24 hours) (TCEQ 2012). However, as discussed above, 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. Consequently, 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:

\[
\text{POD}_{\text{HEC}} = \text{POD}_A \times \left(\frac{(H_{bg})_A}{(H_{bg})_H}\right)
\]

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).

Rozen et al. (1984): \(\text{POD}_{\text{HEC}} = \text{POD}_A \times \left(\frac{(H_{bg})_A}{(H_{bg})_H}\right) = 10.2 \text{ ppm} \times 1 = 10.2 \text{ ppm}\)
Uncertainty Factors (UFs)

The default procedure for deriving health-protective concentrations for noncancerous effects is to determine a POD and apply appropriate UFs (i.e., assume a threshold/nonlinear MOA) (TCEQ 2012). The POD\textsubscript{HEC} 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\textsubscript{L}), 3 for extrapolation from animals to humans (UF\textsubscript{A}), 10 for intraspecies variability (UF\textsubscript{H}), and 1 for database uncertainty (UF\textsubscript{D}) (total UF = 100).

A UF\textsubscript{L} of 3 was used because:

(1) the LOAEL utilized for these noncancerous 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\textsubscript{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\textsubscript{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\textsubscript{HEC} was limited to 1, although the true ratio is approximately 2 and would increase the POD\textsubscript{HEC} accordingly.

Available information supports use of a full UF\textsubscript{H} of 10. 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 (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.

**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 [Note: UFs of 3 are usually treated by regulatory agencies as square root of 10 values in deriving toxicity factors such that $3 \times 3 = 10$].

$$\text{POD}_{\text{HEC}} / (\text{UF}_H \times \text{UF}_A \times \text{UF}_L \times \text{UF}_D) = 10.2 \text{ ppm} / (10 \times 3 \times 3 \times 1) = 0.102 \text{ ppm} (0.32 \text{ mg/m}^3)$$

The proposed 24-hour, health-protective AMCV for benzene is 0.10 ppm or 100 ppb (320 µg/m³). It is between the 1-hr AMCV of 180 ppb (580 µg/m³) (TCEQ 2007), and the long-term AMCVs of 86 ppb (280 µg/m³) (noncarcinogenic effects) and 1.4 ppb (4.5 µg/m³) (carcinogenic effects) (TCEQ 2007) (Figure 2-1).

![Figure 2-1 Comparison of AMCVs developed to evaluate different averaging times](image)

**Ambient Air Monitoring Data from 24-Hr Canister Samplers from 2010-2011**

Figure 2-2 shows 2010-2011 ambient air monitoring data for benzene from 24-hr VOC canister samples at monitoring sites with the highest annual averages across the state (Corpus Christi Huisache, Galena Park, Channelview – Jacinto Port, Baytown – Lynchburg Ferry, and La Porte –
Shore Acres) (5 out of a total of 47 sites 24-hr canister VOC samplers). The detected 24-hr benzene peak values were frequently above the long-term AMCV of 1.4 ppb (4.5 µg/m³), but were well below the 24-hr AMCV of 100 ppb (320 µg/m³).

Figure 2-2 Five Texas Sites with the Highest Benzene Annual Average Concentrations (01/01/2010 to 12/31/2011)

**Conclusion:**

- The 24-hour, health-protective AMCV for benzene is 0.10 ppm or 100 ppb (320 µg/m³). It is between the 1-hr AMCV of 180 ppb (580 µg/m³), and the long-term AMCVs of 86 ppb (280 µg/m³) (noncarcinogenic effects) and 1.4 ppb (4.5 µg/m³) (carcinogenic effects) (Figure 2-1).

- 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 (i.e., odor, vegetation) AMCVs.

References


Example 3: Development of a 24-Hour Reference Value (Air Monitoring Comparison Value) for 1,3-Butadiene

1,3-Butadiene (BD) (Example 3) illustrates development of a 24-hr ReV using an intermittent reproductive/developmental study (6 hr/day; gestational day 6-15). The endpoint was judged to be concentration/duration dependent. There was limited toxicokinetic and MOA information for acute effects (based on additional analyses from TCEQ 2008).

R.L. Grant and R.E. Jones, Texas Commission on Environmental Quality (TCEQ), Austin, TX

ABSTRACT

The TCEQ develops AMCVs, which are considered safe concentrations of chemicals in air, to determine whether 1-hour (hr) or annual average chemical concentrations in ambient air exceed levels of potential concern for adverse health effects. Previously for 1,3-butadiene (BD), a 1-hr AMCV of 1,700 ppb was derived based on a mouse developmental study (6 hr/day exposures, gestational days 6-15). A chronic AMCV of 9.1 ppb was derived based on a 1 in 100,000 excess risk for leukemia mortality from an epidemiological study in styrene-butadiene workers. To calculate annual ambient air concentrations, the TCEQ collects a significant amount of 24-hr monitoring data that are not directly comparable to the 1-hr or chronic AMCV. Therefore, the TCEQ has developed a 24-hr AMCV for BD to evaluate the potential for health effects from 24-hr exposure. The same mouse study used for the 1-hr AMCV was judged to be the critical study for the 24-hr AMCV based on mode-of-action and toxicokinetic data. The 6-hr human equivalent point of departure (POD-HEC) of 51,300 ppb was duration adjusted (Haber’s rule with n = 1) to calculate the 24-hr POD-HEC of 12,800 ppb. The proposed 24-hr AMCV is 430 ppb (950 µg/m³) after application of total uncertainty factors of 30.

Introduction

For chemicals detected in the ambient air monitoring network, short-term AMCVs have generally been derived by the TCEQ to evaluate 1-hr reported concentrations and long-term AMCVs were derived to evaluate annual averages. Since a significant amount of ambient air data is collected over a 24-hr duration, the derivation of chemical-specific 24-hr AMCV values may be needed to better evaluate ambient 24-hr data. TCEQ believes using a short-term, 1-hr AMCV or long-term AMCV to evaluate a 24-hr ambient air sample is not appropriate because toxic effects induced by 24-hr exposure may be governed by modes of action somewhat different than those influencing toxicity due to 1-hr or chronic exposure. A 24-hr Reference Value is derived for human health hazards associated with threshold dose-response relationships (typically effects other than cancer) and is defined as an estimate of an inhalation exposure concentration that is likely to be without an appreciable risk of adverse effects to the human population (including susceptible subgroups) for a 24-hr exposure.

The critical step in deciding whether or not to derive a 24-hr ReV is the availability of appropriate toxicity studies that provide meaningful information to evaluate a 24-hr exposure duration. An evaluation of the mode of action, dose metric, and the toxicokinetics and toxicodynamics of the chemical of concern as well as exposure duration adjustments that are
unique for the derivation of a 24-hr ReV is conducted. The same analytical steps used to derive acute 1-hr ReVs and chronic ReVs (TCEQ 2012) are used to derive a 24-hr ReV. OECD (2010) also provides guidance applicable to the development of acute reference concentrations.

**Key Studies**

BD has very low acute toxicity (TCEQ 2008). The toxicity of BD is shown in Figure C-1 as an exposure response array for acute (less than 24 hr) and subacute studies which were considered for the development of a 24-hr ReV. Effects in humans (slight smarting of the eyes and difficulty in focusing) occurred at 2000 ppm after a 7-hr BD exposure (Carpenter et al. 1944). Animal studies show BD is a potential reproductive/developmental hazard to humans. The following studies were considered for the development of a 24-hr ReV:

- Developmental toxicity (decrease in maternal body weight gain and fetal body weight) occurs in mice, the most sensitive species, after BD exposure (6 hr/day, gestational day 6-15) with a lowest observed adverse effect level (LOAEL) of 200 ppm and a no-observed adverse effect level (NOAEL) of 40 ppm (Hackett et al. 1987b).

- In three different developmental studies in rats, the lowest critical effect is a decrease in body weight parameters. Toxicity occurs in rats at much higher concentrations than in mice. The LOAELs in rat studies ranged from 1000-1500 ppm and the NOAELS ranged from 200-300 ppm (IISRP 1982; Hackett et al. 1987a; ACC 2003).

- After a 6-hr/day, 5-day exposure in male mice, decreased testes weight was observed (LOAEL = 500 ppm; NOAEL = 130 ppm). There was a concentration/duration effect on male reproductive effects. After 4 weeks exposure in male mice, followed by mating, there was an increase in early fetal deaths with a LOAEL of 65 ppm. After 10 weeks exposure, a LOAEL of 12.5 ppm was observed for fetal deaths and sperm abnormalities.
Figure C-1 BD Exposure response array for acute (less than 24 hr) and subacute studies

<table>
<thead>
<tr>
<th>Citation</th>
<th>Key</th>
<th>Citation</th>
<th>Key</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al. (1996)</td>
<td>B</td>
<td>Hackett et al. (1987a)</td>
<td>G</td>
</tr>
<tr>
<td>Anderson et al. (1998)</td>
<td>C</td>
<td>Hackett et al. (1987b)</td>
<td>H</td>
</tr>
<tr>
<td>Carpenter et al. (1944)</td>
<td>E</td>
<td>Pacchierotti et al. (1998)</td>
<td>J</td>
</tr>
</tbody>
</table>
Critical Study

The TCEQ developed a 1-hr ReV in 2008 (TCEQ 2008) based on developmental toxicity in mice, the most sensitive species, after BD exposure (Hackett et al. 1987b). Reproductive/developmental effects may have been caused by only a single day’s exposure that occurred at a critical time during gestation. Therefore, this developmental study is relevant for derivation of a 24-hr ReV; this study has the lowest LOAEL and NOAEL (Figure 1). This study was also selected for development of the 24-hr ReV, based on the following toxicokinetic and mode of action analysis.

Toxicokinetics and Mode of Action

BD is a highly volatile, colorless gas with a mildly aromatic odor, and is only slightly soluble in water. Absorption through the lung is limited by blood flow to the lung. After absorption, BD is distributed throughout the body. For both rats and mice after exposure to $^{14}$C-butadiene, Bond et al. (1987) reported the following:

- Within 1 hr after the end of exposure, respiratory tissue, gastrointestinal tract, liver, kidneys, urinary bladder and pancreas contained higher concentrations of radioactivity than other tissues
- Tissues of mice attained significantly greater concentrations than did rats per µmole of BD inhaled, although there were no apparent differences between rats and mice in tissue depots of BD
- 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.

Research has shown that BD produces toxicity when metabolized to reactive metabolites. 1,2-Epoxy-3-butene (EB) and 1,2:3,4-diepoxybutane (DEB) are the two metabolites that are most reactive, after animals are exposed to BD (Figure 3-2).
P450 stands for cytochrome P450, EH stands for epoxide hydrolase, GST stands for glutathione transferase, and GSH stands for glutathione. The reactive metabolites are shown inside boxes. The urinary metabolites are numbered and listed in Table 3-1 of USEPA (2002).

There is a difference in the metabolism between mice and rats. The basis of the species differences may be related to the greater production of toxic intermediates and a lower capacity for detoxification of these intermediates in mice compared to rats (USEPA 2002). Humans are more similar to rats in the metabolism of BD. Humans produce much lower levels of DEB than mice as demonstrated by experimental data on DEB-specific pyr-Val Hb adducts (Swenberg et al. 2007; Georgieva et al. 2007; 2008) and urinary metabolites (Sabourin et al. 1992).

The specific mechanism of action for the maternal reproductive/developmental effects produced by BD is unknown after acute exposure, although the mode of action (MOA) may involve DEB-induced ovarian atrophy and a decrease in serum progesterone levels, as shown by Spencer et al. (2001) and Chi et al. (2002). Although the amount of DEB produced by humans is much lower than mice, reproductive/developmental effects were assumed to be relevant to humans (Kirman and Grant 2012). However, using a study in mice to predict toxicity in humans is conservative.

Based on toxicokinetic and MOA information, the reproductive/developmental effects in mice are considered to have a threshold and to be concentration and duration dependent.
Development of the 24-hr ReV (refer to Table 3-1)

Dose Metric
For the reproductive/developmental key study (Hackett et al. 1987b), the most appropriate dose metric for a 24-hr exposure is likely area under blood concentration curve of DEB or DEB concentration in target tissue; however, this data was not available. Therefore, data on the exposure concentration of the parent chemical was used as the default dose metric.

Dose-Response Modeling and Points of Departure (PODs)
The TCEQ (2008) performed benchmark concentration (BMC) modeling for numerous endpoints from Hackett et al. (1987b). The endpoint with the lowest relevant BMCL was decrease in maternal extragestational weight gain (BMCL_{1 SD} = 51.3 ppm with a BMC_{1 SD} of 723 ppm), followed by decrease in fetal body weight (BMCL_{05} = 54.7 ppm BMC_{05} of 65.8 ppm).

Duration and Default Dosimetry Adjustments
Table C-1 provides information on duration adjustments from a 6-hr exposure to a 24-hr exposure using Haber’s Rule as modified by ten Berge (1986) with “n” = 1. Default dosimetry adjustments from animal-to-human exposure were based on methods for Category 3 gases producing systemic effects (USEPA 1994; TCEQ 2012). For BD, the \( (H_{bg,A}) / (H_{bg,H}) > 1 \) (TCEQ 2008). When \( (H_{bg,A}) / (H_{bg,H}) > 1 \), a default value of 1 is used for the regional gas dose ratio (RGDR) (USEPA 1994). Table 1 compares the derivation of the 24-hr ReV to the derivation of the 6-hr ReV and a 24-hr ReV value based on a rat study (ACC 2003).

Uncertainty Factors
A full UF_H of 10 was used to account for intraspecies variability. There is experimental evidence that indicates BD-sensitive human subpopulations may exist due to metabolic genetic polymorphisms (USEPA 2002), although recent studies indicate that variability due to genetic polymorphisms is less than 10 based on metabolism of BD in humans with different genotypes. (Albertini et al. 2001, 2003).

A UF_A of 3 was used for extrapolation from animals to humans because default dosimetric adjustments from animal-to-human exposure were conducted, which account for toxicokinetic differences but not toxicodynamic differences. This approach is likely conservative, since existing studies indicate that mice are relatively sensitive laboratory animals in regards to the reproductive effects of BD.

A database UF_D of 1 was used because the overall acute toxicological database for BD includes acute inhalation studies in humans; two inhalation bioassays in different species investigating a wide range of endpoints; and several prenatal developmental toxicity studies in different species (USEPA 2002; TCEQ 2008). Both the quality of the studies and the confidence in the acute database is high.
Table 3-1: Derivation of the 1-Hr and 24-Hr ReV based on a Mouse study (Hackett et al. 1987b) and Alternate 24-Hr ReV based on a Rat study (ACC 2003)

<table>
<thead>
<tr>
<th>Study</th>
<th>Hackett et al. 1987b</th>
<th>ACC 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>CD-1 mice (18-21 pregnant mice per dose group)</td>
<td>Crl:CD® (Sprague-Dawley) IGS BR rats (12 male and 12 female rats per dose group)</td>
</tr>
<tr>
<td>Study quality</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Exposure Methods</td>
<td>0, 40, 200, and 1,000 ppm BD on gestation days (GD) 6-15 for 6 h/day</td>
<td>0, 300, 1,500, and 6,000 ppm BD (14 days prior to breeding, during gestation, and lactation) for 6 h/day</td>
</tr>
<tr>
<td>Critical Effects</td>
<td>Reduction in extragestational weight gain and fetal body weight; developmental toxicity</td>
<td>Persistent reductions in body weight parameters in F0 and F1 males and females</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6- hr Acute ReV mice</th>
<th>24 hr Acute ReV mice</th>
<th>24 hr Acute ReV rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>POD</td>
<td>51.3 ppm (BMCL1 SD)</td>
<td>51.3 ppm (BMCL1 SD)</td>
</tr>
<tr>
<td>Duration</td>
<td>6 h</td>
<td>6 h</td>
</tr>
<tr>
<td>Extrapolation to other durations</td>
<td>No adjustment to 1 hr because the critical effect was a maternal/developmental endpoint</td>
<td>Extrapolation to 24 hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51.3 ppm (BMCL1 SD) x 6/24</td>
</tr>
<tr>
<td>PODanimal</td>
<td>6 hr POD&lt;sub&gt;animal&lt;/sub&gt; = 51.3 ppm (BMCL1 SD)</td>
<td>24 hr POD&lt;sub&gt;mice&lt;/sub&gt; = 12.8 ppm (BMCL1 SD)</td>
</tr>
<tr>
<td>POD&lt;sub&gt;HEC&lt;/sub&gt;</td>
<td>6-hr POD&lt;sub&gt;HEC&lt;/sub&gt; 51.3 ppm (gas with systemic effects, based on default RGDR = 1.0)</td>
<td>24-hr POD&lt;sub&gt;HEC&lt;/sub&gt; 12.8 ppm (gas with systemic effects, based on default RGDR = 1.0)</td>
</tr>
<tr>
<td>Total UF</td>
<td>30</td>
<td>30</td>
</tr>
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<td>Interspecies UF</td>
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<td>3</td>
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<tr>
<td>Intraspaces UF</td>
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<td>10</td>
</tr>
<tr>
<td>LOAEL UF</td>
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<td>Not applicable</td>
</tr>
<tr>
<td>Database UF</td>
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<td>1</td>
</tr>
<tr>
<td>Database Quality</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>acute ReV</td>
<td>3,700 µg/m&lt;sup&gt;3&lt;/sup&gt; (1,700 ppb) [6 hr] mice</td>
<td>950 µg/m&lt;sup&gt;3&lt;/sup&gt; (430 ppb) [24 hr] mice</td>
</tr>
</tbody>
</table>
**Health-Based Acute ReVs**

The 24-hr ReV for BD is 430 ppb (950 µg/m³), whereas the 6-hr acute ReV is 1,700 ppb (3,700 µg/m³) (TCEQ 2008). These acute ReVs are considered to be conservative since pregnant mice exposed to BD and their offspring develop maternal/developmental toxicity much easier than similarly-exposed rats, available scientific information suggests mice are more sensitive than humans, and BD-induced reproductive/developmental effects have never been observed in humans (TCEQ 2008). Table 3-1 shows that if the highest quality rat study was used (ACC 2003), the 24-hr ReV would be 2,500 ppb (5,500 µg/m³); this value is more applicable to humans.

The 24-hr ReV of 430 ppb (950 µg/m³) falls between the TCEQ acute 1-h ReV of 1,700 ppb (3,700 µg/m³) and the chronic noncarcinogenic ReV of 15 ppb (33 µg/m³) and the carcinogenic value of 9.1 ppb (20 µg/m³) (TCEQ 2008) (Figure 3-3).

**Figure 3-3 Comparison of AMCVs developed to evaluate different averaging times**
**Ambient Air Monitoring Data from 24-Hr Canister Samplers from 2010-2011**

Figure 3-4 shows 2010-2011 ambient air monitoring data for BD from 24-hr VOC canister samples at monitoring sites with the highest annual averages across the state (Port Neches > Groves > Galena Park > Jacinto Port > Jefferson County Airport) (5 out of a total of 47 sites 24-hr canister VOC samplers). The detected 24-hr BD peak values were below the long-term AMCV of 9.1 ppb (20 µg/m³).

**Conclusion**

- The proposed 24-hour, health-protective AMCV for BD is 430 ppb (950 µg/m³).
- This value falls between the TCEQ acute 1-h ReV of 1,700 ppb (3,700 µg/m³) and the chronic noncarcinogenic ReV of 15 ppb (33 µg/m³) and the carcinogenic value of 9.1 ppb (20µg/m³).
- 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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