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TCEQ Guidelines to Develop 24-Hour Inhalation Reference Values

Office of the Executive Director

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

Document Description and Intended Use

This document provides guidelines to develop chemical-specific 24-h reference values (ReVs). It is a supplement to the TCEQ Regulatory Guidance-442 (RG-442), *TCEQ Guidelines to Develop Toxicity Factors.*

For chemicals evaluated in the TCEQ ambient air monitoring network, acute 1-h ReVs and chronic ReVs have generally been derived to evaluate 1-h 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-h ambient air samples (e.g., 24-h 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-h sample is an acute exposure duration significantly longer than 1-hr. Toxic effects induced by 24-h exposure may be governed by modes of action somewhat different than those influencing toxicity due to 1-h or chronic exposure. Therefore, it is not appropriate to use a short-term, 1-h ReV or long-term ReV to evaluate a 24-h ambient air sample. Thus, the development of a 24-h ReV would allow the TCEQ to fully evaluate 24-h air monitoring data for possible health concerns and could be used for risk communication purposes. In addition, this information is helpful to risk assessors for performing health effects reviews when 24-h air monitoring data exceed chronic ReVs.

A 24-h 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-h exposure.

In the summer of 2011, the draft Guidelines (TCEQ 2011) underwent a letter peer review by an expert peer review panel organized by Toxicology Excellence for Risk Assessment (TERA 2011). Public comments were also submitted. The TERA (2011) final report can be obtained from TERA Final Report. Procedures to develop 24-h ReVs were included in the draft Guidelines (TCEQ 2011) as Chapter 4, and were reviewed by the expert peer review panel.

The TCEQ revised the 24-h guidelines based on peer review comments, which were favorable. One of the suggestions from one reviewer was to include chemical-specific examples for developing 24-h ReVs. In order for TCEQ staff to have the opportunity to derive chemical-specific 24-h ReVs, the section on deriving 24-h values was not included in the final RG-442 (TCEQ 2012).

In May 2012, the revised 24-h guidelines and examples of 24-h ReVs for acrolein, 1,3-butadiene, and benzene was presented as a case study to the panel at Workshop 6, Beyond Science and Decisions: From Problem Formulation to Dose-Response Assessment (May 28-30, 2013): *Workshop 6 website*. The guidelines to develop 24-h ReVs were revised based on the panel's comments.

In March 2014, the Guidelines were posted for a 90-day public comment period with proposed 24-h ReVs for benzene, 1,-3 butadiene, and formaldehyde, as example chemicals. The guidelines to develop24-h ReVs were revised based on public comments and posted as final June 16, 2014.

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FIGURE

Twenty-Four Hour Inhalation Reference Values

1 Problem Formulation

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

A 24-h 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-h exposure. However, exposure to chemicals may occur on an intermittent basis. The 24-h ReV would be protective of intermittent 24-h 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-h 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.

2 Analytical Steps to Develop 24-h ReVs

The same analytical steps used to derive acute 1-h ReVs and chronic ReVs are used to derive a 24-h ReV (TCEQ 2012).The critical step in deciding whether or not to derive a 24-h ReV is the availability of appropriate toxicity studies that provide meaningful information to evaluate a 24-h exposure duration. If there are inadequate data to derive a 24-h Rev, then a 24-h ReV will not be

developed. An evaluation of the mode of action (MOA), 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-h ReV (Figure 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-h ReV values (Chapters 3 and 4 of TCEQ 2012) and will not be discussed.

2.1 Availability of Toxicity Studies

Available literature should be researched to determine if data are available to guide the derivation of a 24-h ReV. Ideally, an acute study of 24-h duration would be used to develop a 24-h ReV, but such toxicity studies are rare. Many chemicals have a poor database, making the derivation of a 24-h 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-h 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 will 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-h value. The best approach for developing a 24-h 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-h exposure duration. Development of several potential 24-h 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-h ReV may or may not be appropriate to develop a 24-h ReV based on the MOA, toxicodynamics, or toxicokinetics of a chemical, particularly if the 1-h ReV is based on a key study with a 1-h exposure duration or less. If data in the literature indicate that a key study other than the one used to derive the 1-h ReV is the most appropriate study to derive a 24-h ReV, which is expected to generally be the case, then a new human equivalent point of departure ($POD_{HEC\ 24\text{-}h}$) should be identified and new UFs 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-h exposure duration. The following are some examples of toxicity studies that may be appropriate for derivation of a 24-h ReV:

- acute toxicity studies (exposure durations 6-24 h) where duration adjustments are defensible;

- acute or subacute toxicity studies may be used to derive a 24-h 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-h exposure duration;

- studies using exposure durations of less than 6 h 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-h 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-h ReV derivation because they may be more predictive of the effects expected due to 24-h 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-h 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-h ReV, since the MOA for a chronic effect would generally be different than the one governing an effect induced by 24-h 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-h ReV if MOA and toxicokinetic/dynamic information support this application (e.g., chemicals with long toxicokinetic or toxicodynamic half-lives).

2.2 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-h 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 h 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-h 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).

2.3 Mode of Action and Dose Metric

An understanding of the chemical-specific MOA is critical to using available data to calculate a 24-h 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?
- Are the adverse effects reversible given the exposure duration?
- What is the appropriate dose metric (i.e., peak exposure versus area under the curve (AUC) and are there data available on dose at the target tissue?
- What is known about the metabolism and clearance of this chemical from the body?
- Is toxicological response proportional to the chemical dose/concentration?
- Is the exposure duration a key determinant of the toxic effect?
- Are the adverse effects seen relevant to humans?
- Are the adverse effects biologically plausible?

2.4 Exposure Duration Adjustments

A variety of modeling approaches are available to identify the POD upon which a 24-h 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 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-h 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-h 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-h ReV.

The approach used to identify the POD for a 24-h 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-h ReV will be selected using best scientific judgment.

2.4.1 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-h 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-h 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-h 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-h ReV are generally applicable for exposure duration adjustments for a 24-h ReV. The chosen method for exposure duration adjustments for the development of a 24-h 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).

2.4.1.1 Concentration-Dependent Defaults

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_{ADJ}. An example of this type of chemical would be those that induce sensory irritation at the point of entry (OECD 2010).

2.4.1.2 Concentration and/or Duration-Dependent Defaults

When a chemical's MOA is poorly characterized, the C 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.

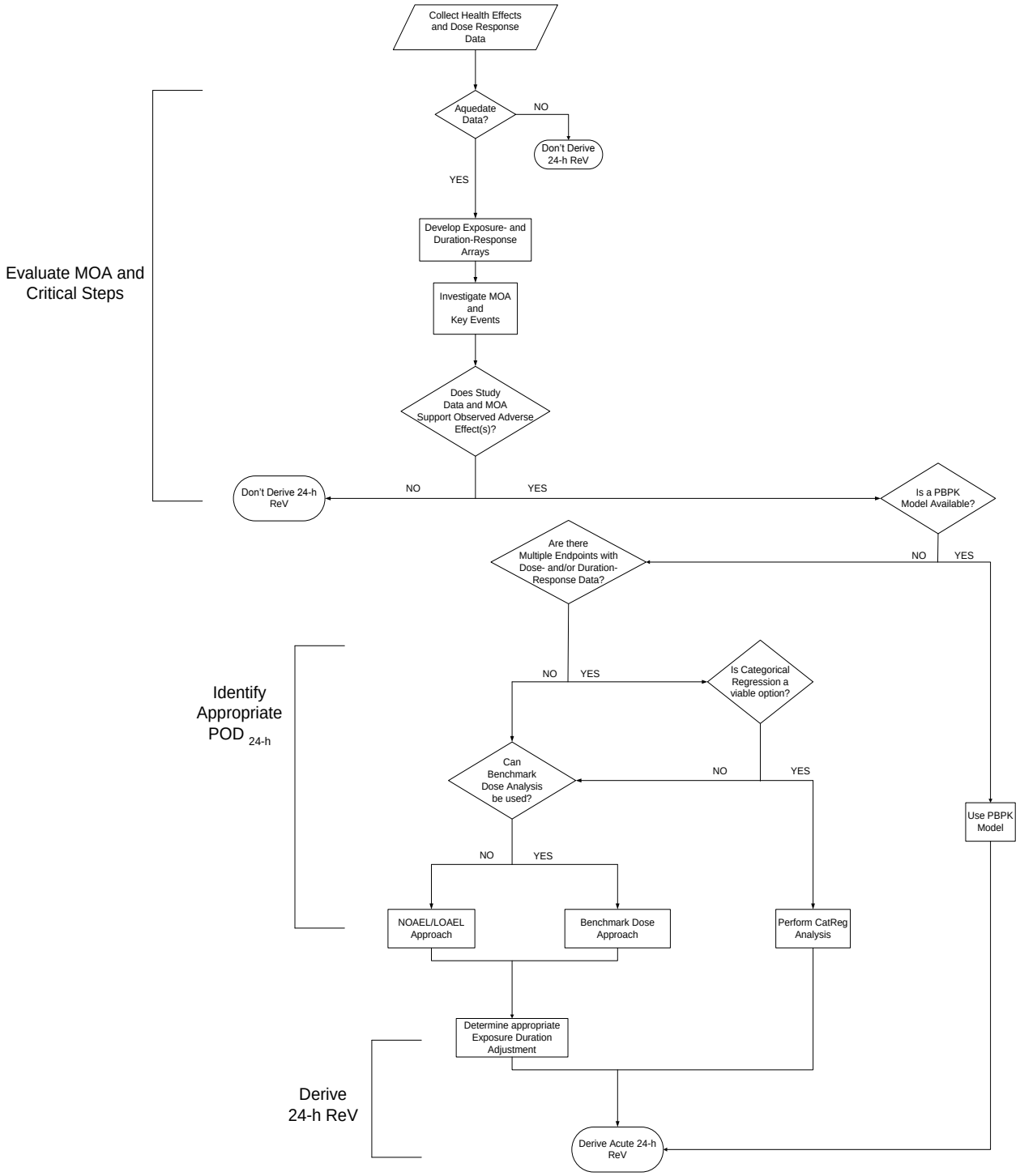

Figure 1 Flowchart for Derivation of 24-h ReV

2.4.2 Duration Adjustments for a Subacute Multi-Day Study

Subacute studies (> 1 day) may be used to derive a 24-h 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 POD_{ADJ} appropriate for a 24-h 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-h 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-h 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-h exposure duration based on a subacute study.

2.4.3 Duration Adjustments for Subchronic Study

Subchronic studies may also be used to derive a 24-h 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 ($POD_{subchronic}$) to calculate a POD appropriate for a 24-h exposure duration ($POD_{24\text{-}h}$). The default approach to estimating an equivalent $POD_{24\text{-}h}$ from the $POD_{subchronic}$ is summarized as:

$$POD_{24\text{-}h} = POD_{subchronic} \times (N \text{ hours}/24 \text{ hours}) \times (D \text{ days/week})$$

where:

$POD_{subchronic}$ = POD identified from key subchronic study

N = numbers of hour per day conducted in the key subchronic study

D = numbers of day per week conducted in the key subchronic study

2.4.4 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-h ReV, particularly when exposure durations of less than 6 h are used to calculate the 24-h 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-h exposure. To evaluate whether a 24-h ReV derived using a default value of 1 for n generates a realistic value, compare where the potential 24-h ReV falls on an exposure array generated for the chemical of interest. If the value for the 24-h ReV is less than or equal to the 1-h ReV and greater than the chronic ReV, it may be a reasonable and predictive value. If the 24-h 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-h 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-h 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-h ReV.

2.5 Conclusions

This section describes a framework approach to derive a 24-h ReV. The steps involved in the derivation of the 24-h 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 $POD_{24\text{-}h}$ (Figure 1 above), and selection of UFs to apply to that $POD_{24\text{-}hr}$. 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).

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