SUMMARY OF CASE STUDY

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. **Describe the problem formulation(s) the case study is designed to address. How is the method described in the case useful for addressing the 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. **Provide a few sentences summarizing the method illustrated by the case study.**

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 for 1,3-butadiene, acrolein, and benzene to the panel for additional review (Appendix B of the case study).

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 the1-hr or chronic health-protective ReVs.

3. **Comment on whether the method is general enough to be used directly, or if it can be extrapolated, for application to other chemicals and/or problem formulations. Please explain why or why not.**

The methods to develop 24-hr ReV are general enough to be used by others. They are based on guidance developed by OECD (2010) to develop an acute reference concentration (ARfC) and are derived using basic procedures for developing 1-hr and chronic ReVs (TCEQ 2012). The examples in the case study are for specific chemicals and are written specifically for evaluation of 24-hr ambient air data. This method can be used by others who need to communicate health risks with managers and the general public when 24-hr ambient air monitoring data exceeds chronic values. When conducting a health effects review, the monitoring data is reviewed to evaluate the possibility of accumulation of toxic moiety or effects due to high peak or repeated exposure in temporal proximity.

To the extent possible, determinations of 24-hr ReVs should have a reasonable degree of certainty associated with them. This method is not useful for chemicals with limited toxicity information.

4. **Discuss the overall strengths and limitations of the methodology.**

There are several overall strengths to this methodology. The procedures in Appendix A of the case study were a part of proposed guidelines (TCEQ 2011a) that have been peer-reviewed (TERA 2011). They are based on guidance developed by OECD (2010). Since the 24-hr ReV is specific to the exposure period and health effect being considered, they may be used toconduct a health effects review in combination with 1-hr and annual ReVs, although they cannot replace the 1-hr or annual ReVs.

The methods and approaches used to develop 24-hr values are similar to approaches used to derive 1-hr or chronic ReVs (TCEQ 2012). Ideally, an acute study of 24-hr would be used to develop a 24-hr ReV, but such toxicity studies are rare. Available literature should be researched to determine if data are available to guide the derivation of a 24-hr ReV. 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 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 if it can provide needed insight. Then a consideration of physical/chemical parameters, MOA, toxicokinetics/toxicodynamics, dose-response assessment 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. When 24-hr ReVs are developed, a narrative that discusses the uncertainties associated with the values should be included.

As with most methodologies there are also limitations. The following are considerations for the use of 24-hr ReVs:

- the methods to develop 24-hr ReVs are data- and resource-intensive.

- evaluation of only a 24-hr ambient air concentration would allow for some fairly high peak exposures for certain hours at a time, which could result from periodic high emissions or meteorological variation. Therefore, a 24-hr ReV may be used mainly for informational purposes and may have significant caveats depending upon the available information.

- exposure to chemicals may occur on an intermittent basis. The 24-hr ReV would be protective of intermittent 24-hr exposures 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. TCEQ toxicologists would conduct a health effects review of air monitoring data to evaluate whether repeated 24-hr peak exposure occur which would result in adverse health effects.

- intermittent exposure near to or at the 24-hr ReV may cause an increase in the calculated annual average concentration, which could cause the chronic ReV to be exceeded and suggest the potential for chronic health effects to occur. (Note: Throughout the year, TCEQ toxicologists calculate yearly rolling averages for chemicals of concern to evaluate whether the rolling average concentration may be near the chronic ReV. The yearly rolling average is compared to the yearly rolling averages from previous years to discover whether unusual patterns of high peak exposures occurred that would affect the annual average.)

- Twenty-four hour canister data is collected every 3rd or 6th day. Therefore, there is uncertainty about chemical concentrations on days where an air sample is not collected. The annual average based on 24-hr canister data compares well with annual averages calculated from data from 1-hr auto gas chromatographs. Therefore, 24-hr canister data are representative samples of typical 24-hr concentrations.

5. **Outline the minimum data requirements and describe the types of data needed.**

Development of 24-hr ReVs should be conducted for those chemicals with adequate toxicity information, not for chemicals with limited toxicity data. As mentioned previously, 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 if it can provide needed insight. 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 24-hr exposure duration. The minimum data requirements for developing 1-hr or chronic ReVs would apply to developing 24-hr ReVs (e.g. appropriate PODs for the critical effects should be available (i.e., the NOAEL, LOAEL or other appropriate points of departure ($BMCL_{10}$ and BMCL)); if an animal study is used, then data should be available to evaluate whether the effect in animals is relevant to humans, etc.)

HOW THIS ASSESSMENT ADDRESSES ISSUES RAISED IN SCIENCE & DECISIONS:

A. **Describe the dose-response relationship in the dose range relevant to human exposure**?

Yes, to the extent possible. Procedures for calculation of 24-hr ReVs are for acute health effects that have a threshold dose-response relationship, not for chronic health effects that have a nonthreshold dose-response (typically carcinogens). Standard uncertainty factors (UFs) are used to extrapolate down to human exposure levels.

When human data are available for determination of 24-hr ReVs, the levels are more relevant to human exposure. When animal data are used as the basis of 24-hr ReVs, there is frequently uncertainty that the levels are relevant and predictive of effects in humans. Guidance discussed as part of an IPCS framework (e.g., MOA information, species sensitivity) should be considered to determine the extent to which 24-hr ReVs from animal studies are relevant and predictive for humans (Boobis et al. 2006, 2008). If MOA information is not available, then it is assumed as a default that responses in animals are relevant to humans.

B. **Address human variability and sensitive populations?**

Yes, to the extent possible. If human data are available in known or potentially sensitive subpopulations, those data should be used for determining 24-hr ReVs. Otherwise, an intraspecies uncertainty factor (UF_H) is used to address human variability and sensitive populations.

C. **Address background exposures and responses?**

These methods do not directly address background exposures or responses in people, but indirectly reflect background exposures and responses to the extent that they contributed to the effects observed in the key studies. The 24-hr ReVs are acute values, and are typically well above background exposures.

D. **Address incorporation of existing biological understanding of the likely mode of action (MOA)?**

MOA information is very useful for development of 24-hr ReVs. Since toxicity studies conducted at 24-hr are usually not available, MOA data can be used to more fully understand the relevance and/or predictiveness of toxicity studies conducted at shorter or longer durations as the basis of a 24-hr ReV. MOA information can inform the type of duration adjustment used to derive 24-hr ReVs. When animal data are used as the basis of 24-hr ReVs, MOA information should be considered to determine the extent to which levels from animal studies are relevant to humans (Boobis et al. 2006, 2008). MOA information is useful to understand the relevance and/or predictiveness of the 24-hr ReV when animal data from different species are available.

E. **Address other extrapolations, if relevant – insufficient data, including duration extrapolations, interspecies?**

Yes, the applicability of such extrapolations is considered and discussed. A 24-hr ReV should not be developed for chemicals with insufficient toxicity data. 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 if it can provide needed insight. 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.

A crucial decision for developing a 24-hr ReV is whether to adjust for duration, since toxicity studies are not typically conducted for 24 hrs. For duration extrapolations, a variety of modeling approaches are available to identify the POD upon which a 24-hr ReV may be derived. 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:

- 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).

- default approaches for duration adjustments as discussed in Chapter 3 of the TCEQ Guidelines (2012) and in OECD (2010) may be used.

- Appendix A, Section 4.4 of the case study provides a discussion of the use of subacute, subchronic, and chronic studies to derive a 24-hr value.

- Interpolation between 1-hr acute and chronic values is considered (Appendix A, Section 4.44 of the case study)

- It is important to evaluate the reasonableness of the duration adjustment, as discussed in Appendix A, Section 4.44 of the case study.

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.

F. **Address uncertainty.**

UFs are used to address uncertainty. The same UFs used to develop a 1-hr ReV (TCEQ 2012) are used to develop the 24-hr ReV.

G. **Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population?**

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 24-hr exposure. Risk estimates could not be calculated at environmentally-relevant concentrations.

H. Work practically? If the method still requires development, how close is it to practical implementation?

The procedures for calculation of 24-hr ReVs were included in proposed *TCEQ Guidelines to Develop Inhalation and Oral Cancer and Non-Cancer Toxicity Factors* (TCEQ 2011a) and have undergone a peer review (TERA 2011). They are based on guidance from OECD (2010) for ARfCs. They are practical and readily implemented by trained risk assessors. However, no 24-hr ReVs have been included in TCEQ Development Support Documents as of this time. As mentioned previously, 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.

This case study is designed to provide 24-hr ReVs for acrolein, benzene, and 1,3-butadiene as example chemicals to demonstrate the practical implementation of the method. After the scientific panels' review, the TCEQ plans to refine the guidelines on developing 24-hr values and submit the guidelines and the proposed 24-hr values for several chemicals for an additional public comment period.

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