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Revisions to Animal-to-Human Inhalation Dosimetric Adjustments

Prepared by the

Toxicology Division

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Revisions to Animal-to-Human Inhalation Dosimetric Adjustments

Background

The Toxicology Division (TD) of the Texas Commission on Environmental Quality (TCEQ) is amending Section 3.9.1, Default Dosimetry Adjustments for Gases in the October 2012 regulatory guidance document, *TCEQ Guidelines to Develop Toxicity Factors* (RG-442). This section is being updated to include information on animal-to-human inhalation gas dosimetric adjustments based on recommendations in the following USEPA documents:

- Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment (USEPA 2012).
- STATUS REPORT: Advances in Inhalation Dosimetry of Gases and Vapors with Portal of Entry Effects in the Upper Respiratory Tract (USEPA 2011).
- STATUS REPORT: Advances in Inhalation Dosimetry for Gases with Lower Respiratory Tract and Systemic Effects (USEPA 2009).

These three USEPA documents summarize new scientific developments and advancements in animal-to-human inhalation dosimetry for gases and vapors from those provided in USEPA's Reference Concentration (RfC) Methodology (USEPA 1994). Refer to Appendix A for Table 4-1 *Overview of major findings related to the state of the science for inhalation dosimetry of gases* (USEPA 2012).

The intent of interspecies dosimetric extrapolation is to adjust an externally applied inhalation animal exposure to achieve the same internal concentration in humans. According to Section 3.9 of the TCEQ's 2012 regulatory guidance document (RG-442), when species-specific data for dosimetric adjustment from animal data to humans are not available, simplified mathematical models can be used as conservative default adjustments. TCEQ (2012) directs readers to the 1994 USEPA's RfC Methodology for a thorough understanding of the default dosimetric adjustments for respiratory tract or systemic health effects. Since default inhalation interspecies dosimetric adjustments have been reviewed and updated by USEPA (2012), a corresponding review of the updated information was undertaken by the TD. The following recommendations are being incorporated as updated guidance for animal-to-human dosimetric adjustments.

Animal-to-Human Dosimetric Adjustments for Acute and Chronic Exposure

- A default dosimetric adjustment factor (DAF) of 1 will be applied when the critical effect is in the extrathoracic (ET) respiratory tract region (includes the nasal and oral passages, pharynx, and larynx). Internal dose equivalency in the ET region for rats (and other

laboratory animals) and humans is achieved through similar external air exposure concentrations, not one adjusted by the ratio of ventilation (VE) to surface area (SA).

- No change to dosimetric adjustments for the tracheobronchial (TB) and pulmonary (PU) regions. The USEPA (2012) review supported principles and default procedures outlined in the RfC Methodology (USEPA 1994) for the tracheobronchial (TB) and pulmonary (PU) regions.

- No change to dosimetric adjustments for systemic health effects. Modeling and partition coefficient information suggests that the default DAF of 1 is appropriate, although it may be conservative (USEPA 1994, 2012).

References

TCEQ. 2012. TCEQ guidelines to develop toxicity factors (Revised RG-442). Texas Commission on Environmental Quality. Office of the Executive Director. Available from: http://www.tceq.texas.gov/publications/rg/rg-442.html

U.S. EPA. (U.S. Environmental Protection Agency). (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. (EPA/600/8-90/066F). Research Triangle Park, NC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993

U.S. EPA. (U.S. Environmental Protection Agency). (2009) Status report: Advances in inhalation dosimetry of gases and vapors with portal of entry effects in the upper respiratory tract. (EPA/600/R-09/072). Research Triangle Park, NC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=212131.EPA 2011

U.S. EPA. (U.S. Environmental Protection Agency). (2011) Status report: Advances in inhalation dosimetry for gases with lower respiratory tract and systemic effects. (EPA/600/R-11/067). Washington, DC.

U.S. EPA. (U.S. Environmental Protection Agency). (2012) Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment (EPA/600/R-12/044) Washington, DC.

Appendix A Overview of Major Findings (USEPA 2012)

Table 4-1 Overview of major findings related to the state of the science for inhalation dosimetry of gases

	Extrathoracic (ET)	Tracheobronchial (TB)	Pulmonary (PU)	Systemic (SYS)
Basis for Default DAF (addresses PK only)	V_E / SA ratio in animals and humans	V_E / SA ratio in animals and humans	V_E / SA ratio in animals and humans	$H_{b/g}$ (blood:gas (air) partition coefficient) animal to human ratio
Assumptions for default	Uniform flow to SA, uniform deposition to SA	Uniform flow to SA, uniform deposition to SA	Uniform flow to SA, uniform deposition to SA	Human and animal exposure scenarios are equivalent. Human blood concentration integrated over time is ≤ animal, animal blood concentration = human equilibrium blood concentration
Default DAF	0.2 – 0.3	> 2	> 2	1
Models vs. DAF	Robust PK and CFD modeling database for a variety of chemicals shows dose metric in animals ≥ humans (i.e. DAF is ≥ 1 not 0.2)	Limited to 2. Shows equivalent animal and human dose. Other modeling information is descriptive and does not provide information for extrapolation purposes.	Limited to 1. Shows potential for greater dose in humans for specific chemical.	Fairly robust PK database shows modeled derived DAFs to be ≥ 1.
Current Evidence and Conclusions	Strong evidence indicating that in the absence of modeling the default DAF = 1. Uniformity of flow and deposition to SA assumptions not supported in studies examining airflow patterns, airflow and lesion correlation, nor by CFD modeling.	Limited evidence. The available information from airflow modeling suggests assumptions may hold or that there is not any compelling evidence that they do not.	Limited evidence. The available information from airflow modeling suggests assumptions may hold or that there is not any compelling evidence that they do not.	Modeling and partition coefficient information suggests that the default DAF may be conservative. However, there is no apparent pattern of the relationship between modeled derived DAFs/HECs, and PCs.
Source	*Status I Report (2009b)*	*Status II Report (2011b)*	*Status II Report (2011b)*	*Status II Report (2011b)*