Integrating Mechanistic Evidence into TCEQ Toxicity Factor Assessments

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Declaration of Interests

- I have no conflicts of interest to declare.

Outline

- TCEQ toxicity factor derivation
- Example of mechanistic evidence integration: Chromium (VI)
- TCEQ systematic review guidelines
- Example of mechanistic evidence integration: Ethylene glycol
- Conclusions and future plans

TCEQ Toxicology Division

TCEQ Mission Statement:

The Texas Commission on Environmental Quality strives to protect our state's public health and natural resources consistent with sustainable economic development. Our goal is clean air, clean water, and the safe management of waste.

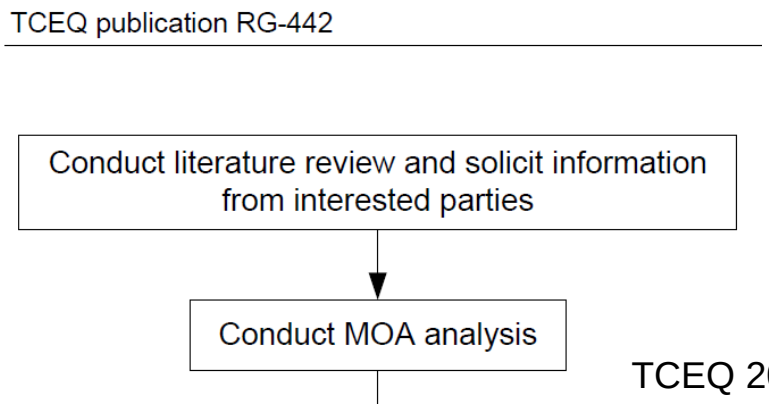
- 15 Toxicologists
- Toxicology Division supports different offices at the TCEQ
  - Air Monitoring
  - Air Permitting
  - Remediation
  - Water issues
- Other
  - Review of toxicological assessments from other agencies; emergency response; risk communication; communication with the public, press, regulatory community, regulated community, legislators, etc.
- Toxicity Factor development

TCEQ Toxicity Factor Development

- The Texas Clean Air Act specifically mandates that the TCEQ conducts air permit reviews of all new and modified facilities, including review of proposed emissions for both federal criteria and non-criteria pollutants
- Due to the comprehensiveness of this language, the TCEQ has developed Toxicity Factors for as many contaminants as possible, even for chemicals with limited toxicity data
- Along with air permit reviews, the TCEQ develops Toxicity Factors for analyzing air monitoring data and remediation activities
- The 2015 TCEQ Guidelines to Develop Toxicity Factors (Regulatory Guidance-442), originally published in 2006, is a technical guidance written and used by the TCEQ Toxicology Division to develop health- and welfare-based inhalation toxicity values, and health-based oral toxicity values

TCEQ Toxicity Factor Guidelines

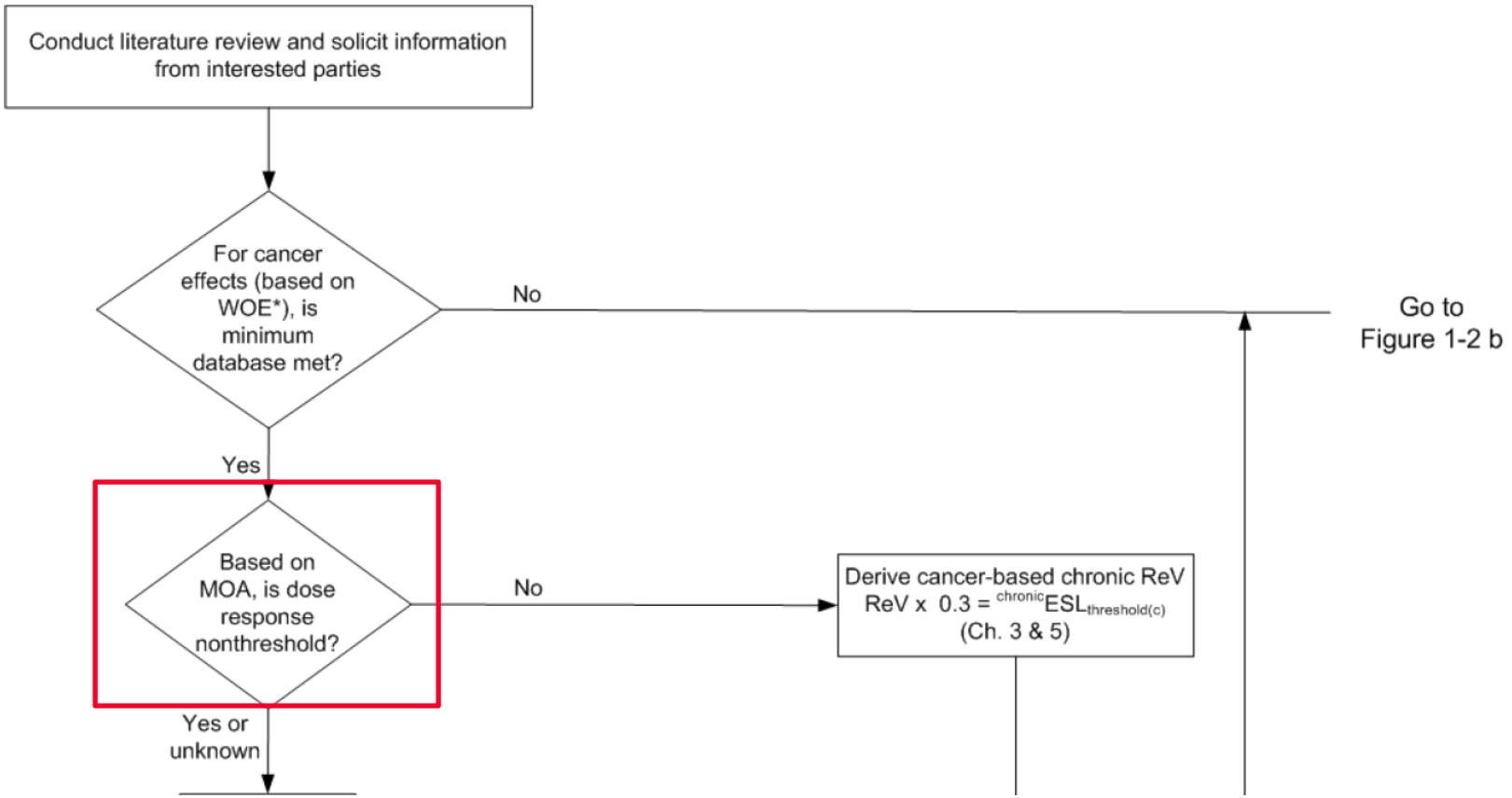
- Guidelines originally written in 2005
- Most updated revision published in 2015
- Subjected to two rounds of peer review and public comment



TCEQ 2015, Figure 1-1

- Mode-of-Action Analysis
  - key and obligatory steps in cellular or organ function that lead to toxicity
  - most appropriate dose metric for a dose-response assessment
  - threshold or non-threshold dose-response
  - relevance of an adverse effect to humans
  - sensitive subpopulations

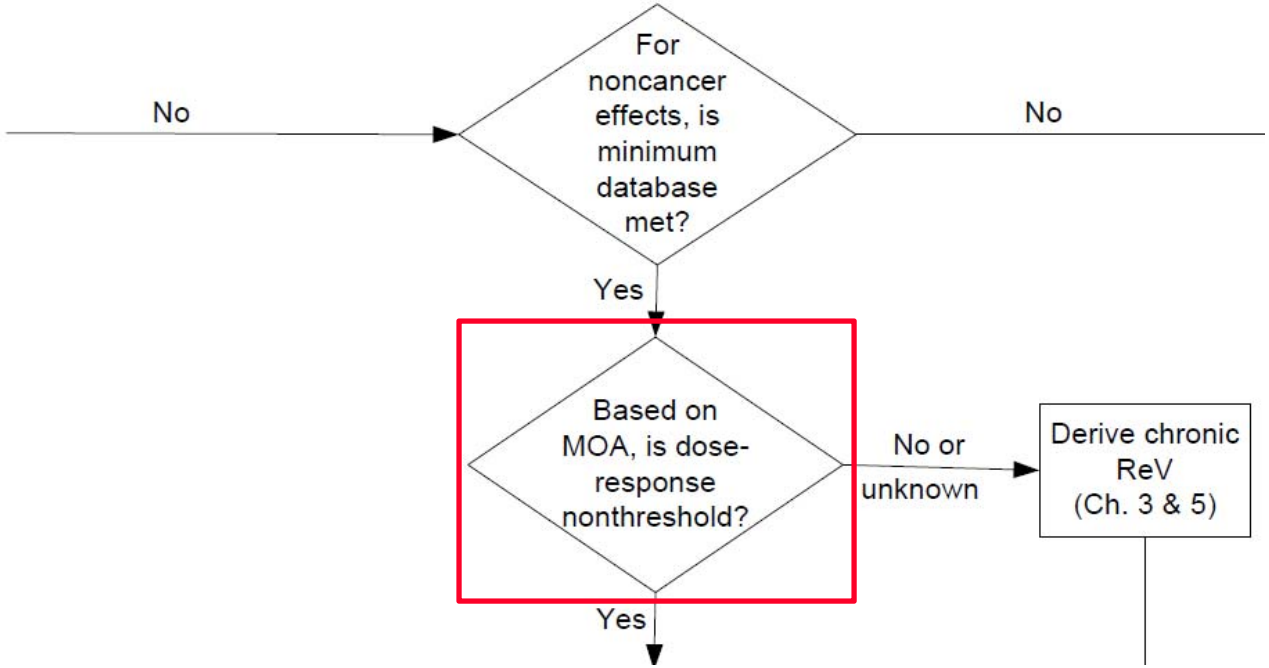
Carcinogen MOA Analysis



TCEQ 2015, Figure 1-2a

Non-Carcinogen MOA Analysis

From Figure 1-2 a



TCEQ 2015, Figure 1-2b

MOA Analysis Example: Chromium VI

- Oral CrVI administration (via drinking water) causes duodenal cancers in mice
- Questions:
  - How should the doses in mice be converted to human equivalent doses?
  - What kind of low-dose extrapolation method should be used to develop a human health-based toxicity factor for Cr(VI) in drinking water?

This example is based on work done by Joseph (Kip) Haney in our group and published in 2015:

- Haney, J., 2015a. Use of dose-dependent absorption into target tissues to more accurately predict cancer risk at low oral doses of hexavalent chromium. Regul. Toxicol. Pharmacol. 71, 93–100.
- Haney, J., 2015b. Consideration of non-linear, non-threshold and threshold approaches for assessing the carcinogenicity of oral exposure to hexavalent chromium. Regul. Toxicol. Pharmacol. 73, 834–852.
- Haney, J., 2015c. Implications of dose-dependent target tissue absorption for linear and non-linear/threshold approaches in development of a cancer-based oral toxicity factor for hexavalent chromium. Regul. Toxicol. Pharmacol. 72, 194–201

CrVI Oral Toxicity Factor

- Recently there has been a great deal of new research that informs the MOA for CrVI-induced carcinogenesis and to improve cross-species extrapolation (e.g., Thompson et al., 2011a, 2011b, 2012a, 2013a; Kirman et al., 2012, 2013; Proctor et al., 2012; Kopec et al., 2012a, 2012b; O'Brien et al., 2013; Suh et al., 2014; Thompson et al., 2015a, 2015c, 2017)

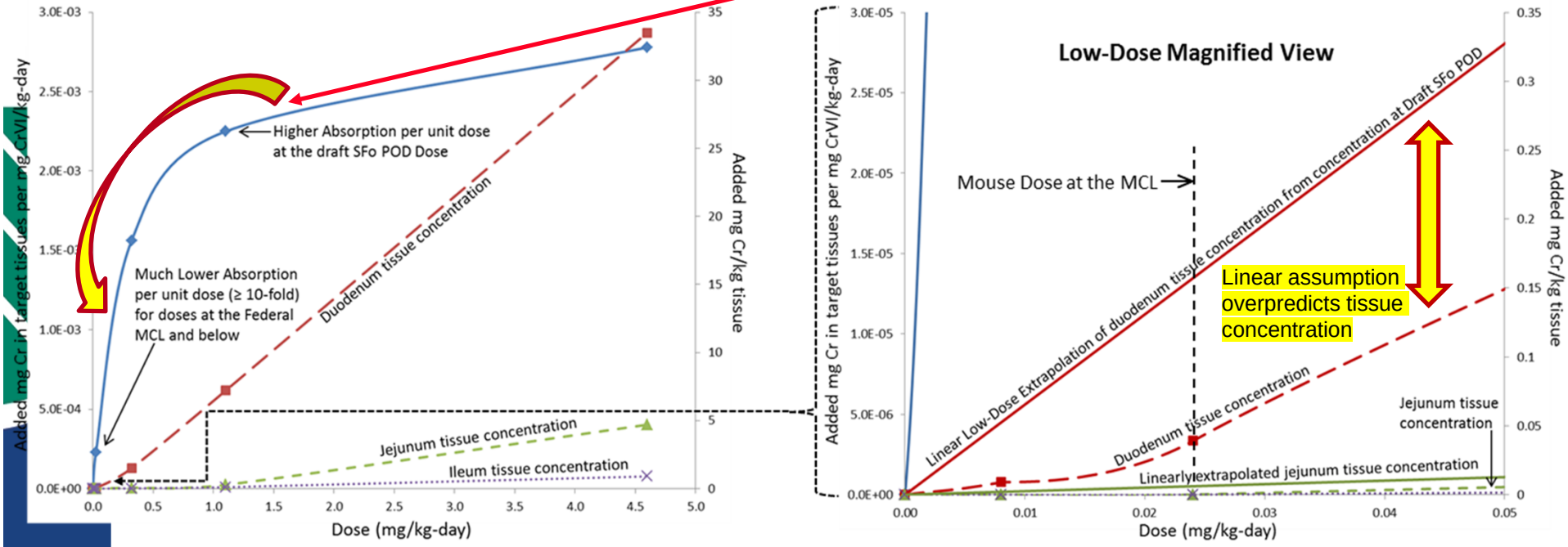
- These data specifically inform the carcinogenic MOA operating in rodent studies (e.g., NTP, 2008) and CrVI toxicokinetics following oral exposure

- This data could allow a toxicologically-predictive method for extrapolating high oral dose rodent study results to environmentally-relevant human doses

CrVI Toxicokinetic Implications

- The *relationship between oral dose and target tissue dose is non-linear* across doses of interest..

Figure 1: Dose-Dependent Changes in Mouse Target Tissue Absorption per Unit Dose and Low-Dose Nonlinearity in Absorbed Tissue Concentration versus Dose



Haney (2015c)

CrVI Toxicokinetic Implications

- Recent analyses of CrVI toxicokinetic (TK) data (Kirman et al., 2012) revealed *appreciable dose-dependent differences in target tissue absorption* (Haney, 2015a, 2015b).
- That is, *the dose fraction absorbed* (CrVI absorbed by target tissues per unit dose) *progressively decreases with decreasing oral dose*.
- Separate from MOA considerations, *any toxicity factor that assumes linearity* between oral dose and target tissue dose or risk such as the SFo *cannot account for the non-linear target tissue TK* resulting from the dose fraction absorbed progressively decreasing with decreasing oral dose.
- Therefore, using an appropriate TK conversion from high dose to low dose is crucial for accurate prediction of the human dose from typical drinking water ingestion concentrations

CrVI Toxicokinetic Implications

- Implication of dose-dependent CrVI target tissue absorption for use of a SFo: *overestimating risk* (exacerbated more so considering the MOA data).

Figure 2: Potential Human Excess Risk versus Lower Dose Adjusted for Dose-Dependent Differences in Target Tissue Absorption

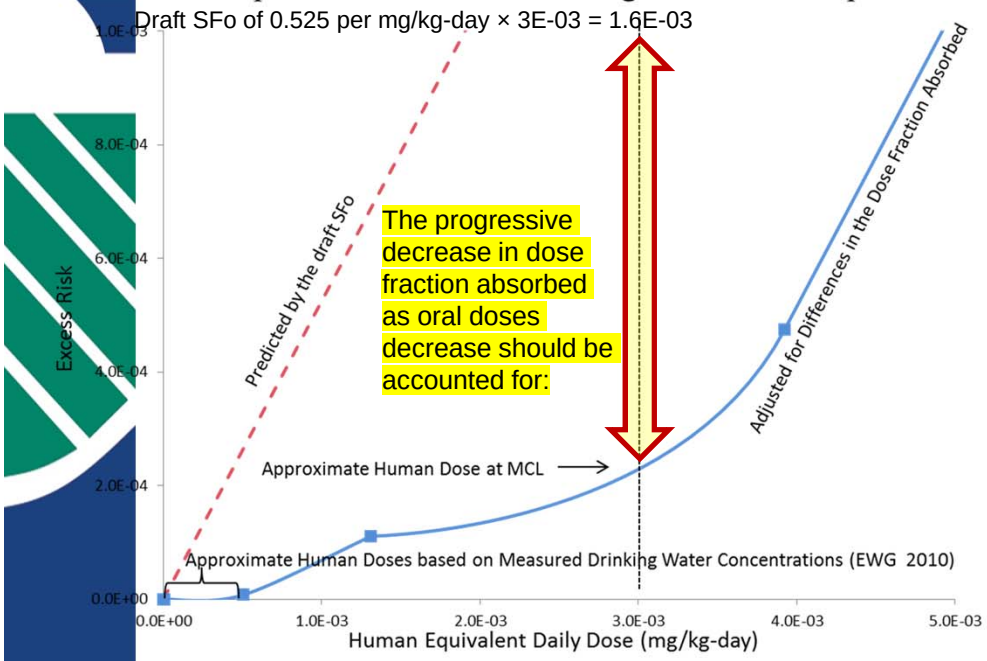
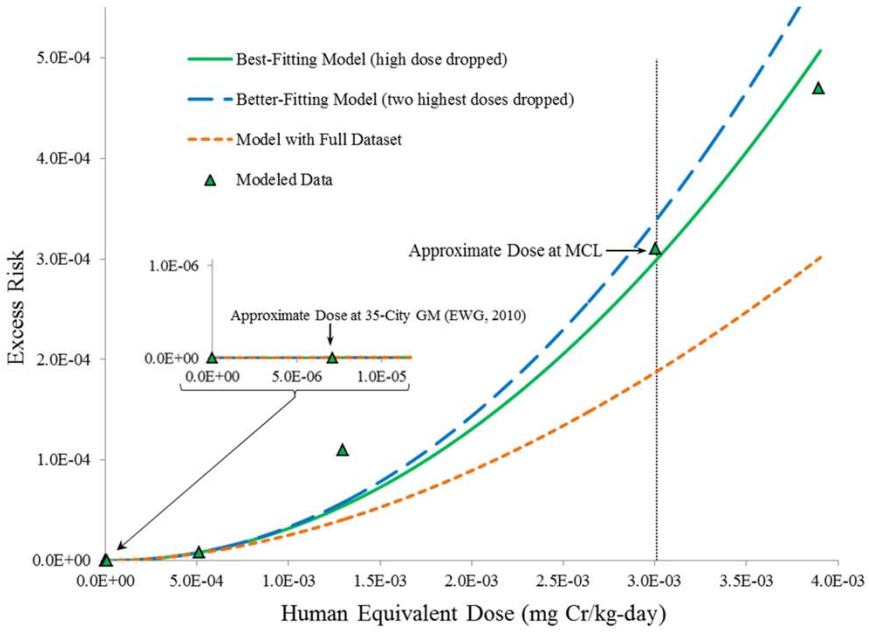


Figure 3: Non-Linear, Non-Threshold Model Fit for Potential Human Excess Risk versus Lower Dose Adjusted for Dose-Dependent Differences in Absorption



Haney (2015c)

CrVI Carcinogenic MOA

- Kip assessed the overall weight-of-evidence for the most scientifically-supported MOA
- While a detailed presentation of the relevant data is challenging for a PowerPoint presentation, Table 6 below shows the progression of responses with dose…

Table 6: Summary of Dose-Response Data Relevant to the MOA

Response [a]	Drinking Water Concentration mg SDD/L					
	0.3 (0.1 mg CrVI/L)	4 (1.4 mg CrVI/L)	14 (5 mg CrVI/L)	60 (20 mg CrVI/L)	170 (60 mg CrVI/L)	520 (180 mg CrVI/L)
Cr in Duodenum (villi)	✗	✗	✓	✓	✓	✓
Oxidative Changes	✗	✗	✓	✓*	✓*	✓*
Gene Expression Changes	✗	✗	✓*	✓*	✓*	✓*
Villus Toxicity	✗	✗	✗	✓	✓*	✓*
Crypt Hyperplasia	✗	✗	✗	✓	✓	✓*
K-ras Mutations	✗	✗	✗	✗	✗	✗
Crypt MN	✗	✗	✗	✗	✗	✗
Crypt DNA Damage (γ-H2AX)	NA	✗	NA	✗	NA	✗

[a] ✓=presence of response due to 90-day exposure, with "*" denoting that 7-day exposure also induced the effect; ✗=absence of response; NA=not assessed.

Haney (2015c)

CrVI Carcinogenic MOA

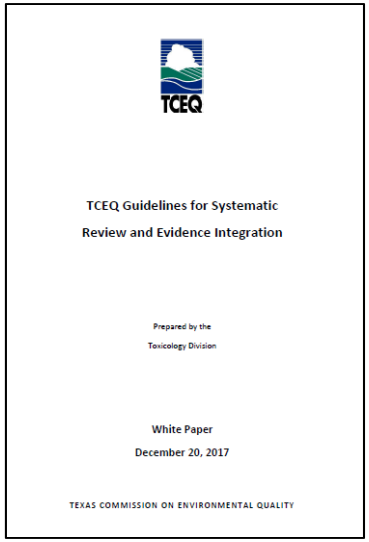
- Compensatory crypt enterocyte hyperplasia induced by chronic villous toxicity should be considered as required (not always sufficient) for CrVI-induced intestinal tumorigenesis.

- That is, *cytotoxicity-induced regenerative hyperplasia should be considered a key event in the carcinogenic MOA for oral exposure to CrVI.*

- Consequently, the threshold (i.e., RfD) approach should be adopted for assessing the potential intestinal carcinogenicity of oral exposure to CrVI.

TCEQ Systematic Review Guidelines

- Draft guidelines used during development of toxicity factors for Ethylene Glycol
- Whitepaper titled “TCEQ Guidelines for Systematic Review and Evidence Integration” proposed for public comment in July, 2017, finalized in December, 2017
- Published paper: Schaefer, H.R., Myers, J.L., 2017. Guidelines for performing systematic reviews in the development of toxicity factors. Regul. Toxicol. Pharmacol. 91, 124–141.
- Currently using these Systematic Review Guidelines for the development of toxicity factors for several other chemicals
  - Ethylene glycol – finalized February, 2016
  - Ethanolamines – finalized June, 2018
  - Diisocyanates
  - Ethylene oxide


TCEQ

TCEQ Guidelines for Systematic Review and Evidence Integration

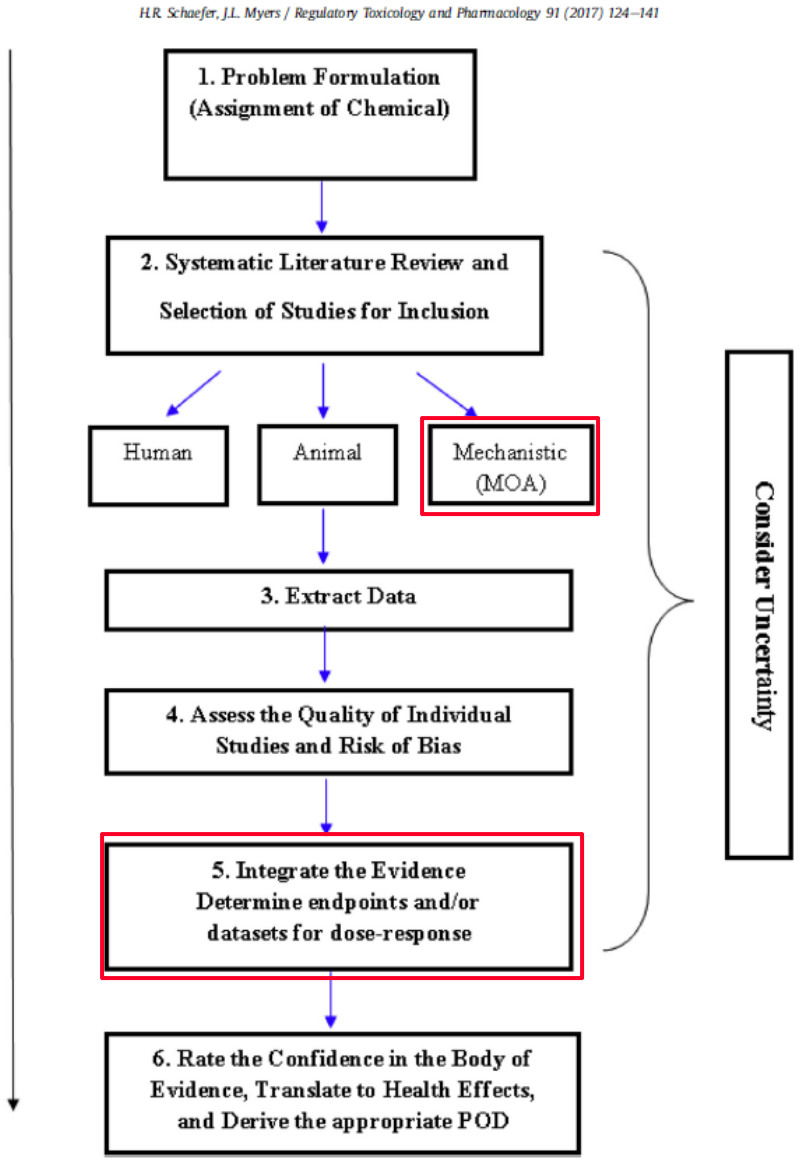
Prepared by the Toxicology Division

White Paper

December 20, 2017

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

TCEQ Systematic Review Guidelines



Ethylene Glycol Systematic Review

- Ethylene glycol chosen as a test chemical
  - Limited but sufficient data, no evidence of carcinogenicity or vegetative effects
- Questions used to structure the systematic review for EG:
  - What are the physical and chemical properties of EG?
  - What is the critical effect following exposure to EG?
  - Are there sensitive subpopulations?
  - **What is the mode of action (MOA)?**
  - Does route of exposure play a role?
  - Is EG carcinogenic, and if so, is it carcinogenic by a specific route of exposure?
  - Is EG a reproductive or developmental toxicant?

Ethylene Glycol Systematic Review

- Literature Review

Table 13. Search strings used in the literature review of EG

Search Term/String	PubMed Results
ethylene glycol	20205
“ethylene glycol”	18895
“ethylene glycol” [mesh]	2093
“ethylene glycol” [mesh] NOT “ethylene oxide”	2077
“ethylene glycol” [mesh] NOT “ethylene oxide” AND (inhal* OR air OR carc* OR onco* OR oral)	168
“ethylene glycol” [mesh] NOT “ethylene oxide” AND (inhal* OR air OR carc* OR onco*)	106

- 3 Categories of Studies:
  - Human studies
  - Animal studies
  - Mechanistic studies

Ethylene Glycol Mechanistic Studies

- Inclusion Criteria:
  - Complete study available for review
  - Exposure concentration is *environmentally relevant*
  - Study contains original data
  - Study examines effects related to chemical exposure
  - Study focused on the chemical of concern or active metabolites
- 5 Mechanistic studies were identified

Table A.7
Data extraction from mechanistic studies.

Reference	Model	Exposure Concentration	Exposure Duration	NOAEL	LOAEL	Notes
Capo et al. (1993)	Rat embryonic nerve cells	0.01, 0.1, 1, 10, 100 μM	24 h	–	0.01 μM (IC50 0.26 μM)	Neuronal degeneration, decrease in cell number
Carney et al. (1996)	Rat whole embryo culture	0.5, 2.5, 12.5, 25, 50 mM EG or GA	48 h	50 mM EG, 2.5 mM GA	12.5 mM GA	Inhibition of embryo growth and development
Carney et al. (2008)	Rabbit whole embryo culture	2.5, 6, 12.5, 25, 50 mM GA	48 h	50 mM GA	–	No significant adverse effects on developing embryos
Guo et al. (2007)	Human proximal tubule cells	0-25 mM EG or metabolites	6 h	25 mM EG	2 mM oxalate	Cytotoxicity and decreased cell viability
Klug et al. (2001)	Rat whole embryo culture	0-200 mM EG or metabolites	48 h	200 mM EG	0.1 mM GAl, 3 mM GA	Embryotoxicity, morphological changes

GA – glycolate, GAl - glycoaldehyde.

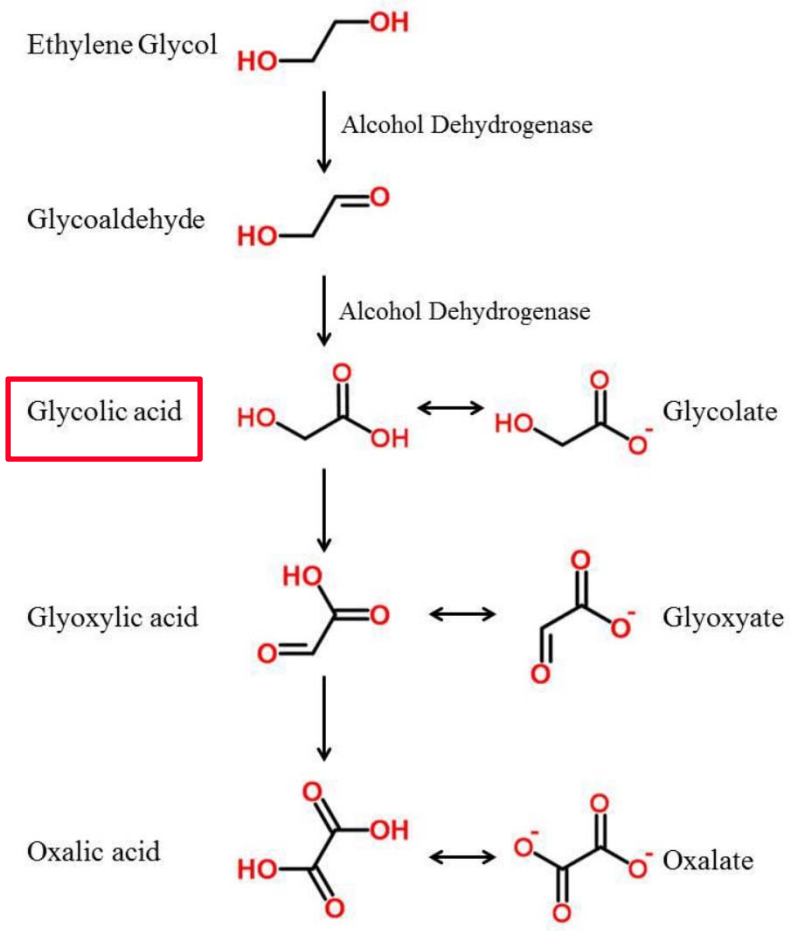
Ethylene Glycol Mechanistic Studies

- Study quality and risk of bias criteria

Table A.15
Study quality and ROB scoring for the selected EG mechanistic studies.

Study criteria	Capo 1993	Carney 1996	Carney 2008	Guo 2007	Klug 2001
General					
Original data	1	1	1	1	1
Applicable route of exposure	−1	−1	−1	−1	−1
Single route	1	1	1	1	1
Single chemical exposure	1	1	1	1	1
Range of doses/exposures	1	1	1	1	1
Exposure concentration known/measured	1	1	1	1	1
Blinded study	0	1	0	0	0
Health effects relevant to ReV development	0	1	1	0	1
Appropriate endpoints measured	0	1	1	1	1
Measured outcomes reported	1	1	1	1	1
Study design sufficient/clearly defined	0	1	1	0	1
Calculation of sample size	0	0	0	0	0
Confounding factors	0	0	0	0	0
Appropriate research practices	1	1	1	1	1
Mechanistic					
Concentration is relevant to human exposure	0	1	1	0	0
Dose is applicable to ReV development	0	0	0	0	0
Dose-response relationship	1	1	0	1	1
Reproductive/developmental					
Critical window for effects	–	1	1	–	1
Maternal and fetal toxicity	–	0	0	–	0
Total Points	**7**	**13**	**11**	**8**	**11**
Study Selection – Key, supporting, or informative	**I**	**I**	**I**	**I**	**I**
Acute or chronic	**A**	**A**	**A**	**A**	**A**

Ethylene Glycol Mechanistic Studies



- Review of MOA from Carney (1994)
- High oral EG exposure (from reviewed studies):
  - Glycolic acid metabolite causes developmental effects and metabolic acidosis
  - Oxalic acid causes renal effects
- Effects occur at saturation concentrations, which aren't achievable with inhalation exposure (inhalation critical effect is respiratory irritation)

Conclusions and Future Plans

- Mechanistic information is crucial for robust decision making when deriving toxicity factors
- Mechanistic data should be separately reviewed in the systematic review process, but must also be integrated into the choices made during the review, as well as the final conclusions
- Ongoing challenges:
  - When and how do you incorporate mechanistic information into the review?
  - Further development on study quality criteria is required
  - How do we use mechanistic data that was collected *in vitro*, which has difficult-to-extrapolate exposures and concentrations?