Comments by the Texas Commission on Environmental Quality
Regarding the Updated Problem Formulation and Protocol for the Inorganic Arsenic IRIS Assessment in May 2019

EPA Docket ID No. EPA–HQ–ORD–2012–0830

I. Summary of Proposed Action

On May 28, 2019, the United States Environmental Protection Agency (EPA) published in the *Federal Register* (84 FR 102) notice of the availability and public comment period for the Updated Problem Formulation and Protocol for the Inorganic Arsenic IRIS Assessment.

The EPA's Updated Problem Formulation and Protocol for the Inorganic Arsenic IRIS Assessment summarizes the EPA's needs for the assessment and presents a refined focus based on problem formulation activities conducted since the last assessment plan released to the National Academy of Sciences, Engineering, and Medicine (NASEM) in 2015. The public comment period precedes a July 16, 2019 NAS ad hoc committee meeting to review and determine whether the proposed methods are appropriate to synthesize the scientific evidence and develop conclusions.

II. General Comments

- The EPA proposes to consider new data regarding inorganic arsenic exposure and health impacts and refined methods for hazard assessment and exposure- and dose-response analysis that have emerged since the previous Inorganic Arsenic IRIS assessment (1995). In the assessment protocol, the EPA plans to categorize evidence based upon various health end points. They also describe a detailed process for systematic review and evidence integration. The TCEQ applauds the EPA for identifying and characterizing data in a more transparent, efficient, and systematized manner. The TCEQ also supports the EPA's intention to apply mode-of-action (MOA) data in a more global manner throughout the assessment, particularly to inform model systems chosen, modeling assumptions selected, and coding and mathematical expressions used to inform dose-response relationships.

- In Table 5-1. Rating criteria for inorganic arsenic exposure- or dose-response data sets for prioritizing studies for dose-response analysis, the EPA presents rating criteria for prioritizing studies for dose-response analysis. While the use of a system to rate studies is recommended, this particular figure is very data dense and ambiguous with regard to whether the rating should be associated with a form of scoring. This table would benefit from being broken into more columns to provide greater clarity for readers and users regarding study quality criteria. Further, if this rating system is based upon the development of a score or other numerical system, it should be communicated to make it clear what the end-product from this exercise should be.

- The TCEQ supports the EPA's plan to use probabilistic dose-response modeling approaches, particularly meta-regression of multiple studies. However, the EPA notes in Section 5.5 Dose Response Modeling Approaches, that "[t]he hierarchical Bayesian approach encompassed in the meta-regression method will be the focus of the assessment. The logistic model used thus far for modeling epidemiologic data in the meta-regression approach makes no assumption regarding the shape of the dose-response curve (linear vs. nonlinear) or whether a threshold exists in the dose-response relationship, meaning it can adequately describe threshold and non-threshold dose-response curves. However, it does not allow for a change in the dose-response direction (e.g., "J"- or "U"-shaped dose-response curves). Also, using multiple epidemiologic studies consisting of different populations and life stages with different levels and magnitudes of susceptibilities tends to linearize the dose-response relationship in the low-dose region." The EPA transparently acknowledges the possible drawbacks and artifacts that may be the outcome of the Bayesian (Markov Chain Monte Carlo) modeling approach. Further, the EPA intends to expand its modeling approach via application of a fractional logistic model in the Bayesian framework, which should enable the model to more accurately capture nonmonotonic dose-response curves. The TCEQ supports the application of modeling approaches that investigate the behavior of the dose-response curve that best characterizes the data itself and does not confine the shape of the dose-response curve to parameters within the model that ultimately limit the analysis to conventional, monotonic curve forms. Section 5.5 Dose Response Modeling Approaches may benefit from the addition of more information that discusses what modeling approaches can been considered to increase model flexibility to capture possible nonmonotonic dose-response curves or references that direct readers to studies where these modeling approaches have been used in comparable cancer assessments. The TCEQ encourages the EPA to be vigilant in ensuring that the data, rather than the modeling assumptions, inform the final dose-response model.

- Generally, no single approach is applicable or appropriate for modeling non-linear (threshold, U- or J-shaped) dose response relationships. It is not clear from this protocol description what possible models or dose response analyses were considered for use in this assessment. Given the many modes-of-action by which arsenic causes it toxic effects that are likely governed by non-linear dose-response relationships, the step of modeling dose-response is a highly important part of this assessment. Section 5.5 Dose-Response Modeling Approaches is brief and not particularly detailed. If the EPA conducted some form of systematic review for modeling approaches for non-linear dose-response assessment, that review should be discussed. If various modeling approaches were considered, the approaches chosen and the reasons why those approaches were selected need further documentation. For the sake of transparent communication and scientific documentation, the TCEQ recommends that the EPA consider expanding the section discussing dose-response modeling approaches, perhaps even adding this discussion as a separate appendix.

- The EPA performed a very comprehensive literature review and the Appendix A provides useful tables that present the various modes-of-action (MOA) identified and characterized in a transparent and practical manner. However, it is unclear how these MOA parameters and conclusions will be integrated into modeling exercises and/or assumptions.

III. Specific Editorial Comments

- Figure 4-2 "Metabolism pathways described in the literature" is blurry in the pdf version of this document. The addition of a higher resolution figure should be considered for ease of viewing the metabolic pathway.

- Figure A-1 "Hypothesized mode of action for effects mediated by oxidative stress," and Figure E-2 "Metabolism pathways describe [*sic*] in the literature" also have low resolution that makes the figures difficult to view.

- Is the MIE box of Figure A-2 supposed to have more bullets (e.g., bullet point in front of increase in oxidative stress)?

IV. Additional References for the EPA's Consideration

The TCEQ encourages the EPA to consider the following papers in its problem formulation and protocol:

Furukawa, K., Misumi, M., Cologne, J.B., Cullings, H.M. 2016. A Bayesian Semiparametric Model for Radiation Dose-Response Estimation, *Risk Analysis* 36:1211-1223, https://doi.org/10.1111/risa.12513.

Lu, D., M. Ye, and Hill, M.C. 2012. Analysis of regression confidence intervals and Bayesian credible intervals for uncertainty quantification, *Water Resour Res* 48: W09521, https://doi.org/10.1029/2011WR011289.

May, S. and Bigelow, C. 2005. Modeling nonlinear dose response relationships in epidemiologic studies: statistical approaches and practical challenges, *Dose-Response* 3:474-490, https://doi.org/10.2203/dose-response.003.04.004. Available at: https://scholarworks.umass.edu/dose_response/vol3/iss3/6

Royston, P., Ambler, G., Sauerbrei, W. 1999. The use of fractional polynomials to model continuous risk variables in epidemiology, *International Journal of Epidemiology* 28:964-974, https://doi.org/10.1093/ije/28.5.964. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10597998