Memorandum

SUBJECT: **December 12-13 Chartered CASAC Meeting on the PM ISA**

FROM: Dr. Tony Cox, Chair
CASAC

TO: Chartered CASAC Members

The Chartered Clean Air Scientific Advisory Committee (CASAC) will meet on December 12-13, 2018, in Arlington, Virginia, to conduct its peer review of the *Integrated Science Assessment for Particulate Matter (External Review Draft)*. The purpose of this memo is to review our preparations and follow-on actions for the peer review of this document. Attached to this memo are the link to the HERONET version of the PM ISA, the charge questions, and the Preamble to the ISA.

The Agency's National Center for Environmental Assessment, Research Triangle Park, NC (NCEA-RTP), within EPA's Office of Research and Development (ORD), has prepared charge questions for the Panel's review of the Draft PM ISA. You will also be receiving a link to download the HERONET version of the PM ISA, which contain hyperlinks to full-text articles of the studies referenced within the document. Instructions on how to access the HERO database will also be provided. Please note that the version of the PM ISA on our public website will only link to abstracts (not full-text articles). You need to use the HERONET version of the PM ISA to access the full-text articles.

For a peer review, consensus responses to the charge questions are developed as part of the letter/report to the Administrator in addition to the individual comments appended to the letter/report. I would like each of you to co-lead the discussions as indicated by the assignments below. The first-named (underlined) individual(s) will act as lead author and is responsible for capturing the consensus responses for the respective charge questions for the report. If you think that you are more suited to serve as a discussant for another topic than the one I designated for you, please let me know as soon as possible and we can try to adjust the assignments. However, all members are free to discuss and provide written comments on any of the charge questions. Each member is asked to submit preliminary, individual comments on the Draft PM ISA to both me and Aaron Yeow (Designated Federal Officer) by **Friday, December 7, 2018.**

Following our meeting, I request that the lead authors work with the other lead discussants to write the consensus responses.

Draft PM ISA Assignments

- **Executive Summary and Chapter 1 – Integrated Summary:** Dr. Tony Cox, all CASAC Members
- **Chapter 2 – Sources, Chemistry and Measurement and Modeling of Ambient Concentrations of PM:** Dr. Corey Masuca
- **Chapter 3 – Exposure to Ambient PM:** Dr. James Boylan
- **Chapter 4 - Dosimetry:** Drs. Sabine Lange, Mark Frampton, Steve Packham
- **Chapters 5-11 - Health Effects of Exposure to PM:** Drs. Mark Frampton, Sabine Lange, Steve Packham
- **Chapter 12 - Populations and Lifestages Potentially at Increased Risk for Health Effects Related to PM Exposure:** Drs. Steve Packham, Mark Frampton, Sabine Lange
- **Chapter 13 – Non-ecological Welfare Effects:** Dr. Timothy Lewis

At our December meeting, I would like us to be ready to discuss the following specific methodological and technical issues.

1. **Treatment of exposure estimation errors.** Do key analyses distinguish clearly between estimated exposure levels and actual (true but uncertain) exposure levels? Have errors-in-variables methods been applied appropriately to quantify, bound, or correct for potential biases due to uncertainties in exposure and covariates? Are key conclusions (e.g., about low-dose linearity of estimated C-R functions) robust to corrections for errors and uncertainties in exposure estimates? Have methodological issues for estimation of nonlinear C-R functions in the presence of realistic measurement error (Rhomberg LR, Chandalia JK, Long CM, Goodman JE. Measurement error in environmental epidemiology and the shape of exposure-response curves. Crit Rev Toxicol. 2011 Sep;41(8):651-71. doi: 10.3109/10408444.2011.563420), e.g., due to interpolation among sensor stations) been adequately addressed?
2. **Adequacy of lags considered and of modeling for lagged effects**. Have lagged effects of covariates (e.g., of daily temperatures for out to at least a month during cold seasons) been adequately modeled? (See e.g., Zeng Q, Li G, Cui Y, Jiang G, Pan X. Estimating Temperature-Mortality Exposure-Response Relationships and Optimum Ambient Temperature at the Multi-City Level of China. Int J Environ Res Public Health. 2016 Mar 3;13(3). doi: 10.3390/ijerph13030279.) Have residual confounding (e.g., due to use of broad "season" indicators) and latent confounding (e.g., due to omitted lagged values) been adequately controlled for and their effects quantified or bounded?
3. **Control for latent variables.** Have effects of unmeasured individual-level variables and components of PM2.5 been adequately modeled and any substantial biases corrected for (or bounded quantitatively, e.g., via sensitivity analyses)? (See e.g., Salway R, Lee D, Shaddick G, Walker S. Bayesian latent variable modelling in studies of air pollution and health. Stat Med. 2010 Nov 20;29(26):2732-42. doi: 10.1002/sim.4039; Best N, Hansell AL. Geographic variations in risk: adjusting for unmeasured confounders through joint modeling of multiple diseases. Epidemiology. 2009 May;20(3):400-10. doi: 10.1097/EDE.0b013e31819d90f9; Hu ZG, Wong CM, Thach TQ, Lam TH, Hedley AJ. Binary latent variable modelling and its applicationin the study of air pollution in Hong Kong. Stat Med. 2004 Feb 28;23(4):667-84.)
4. **Modeling of interactions and dependencies among explanatory variables and between explanatory and risk variables.** For example, have confounding effects of socioeconomic gradients been adequately modeled? (Milojevic A et al.. Socioeconomic and urban-rural differentials in exposure to air pollution and mortality burden in England. Environ Health. 2017 Oct 6;16(1):104. doi: 10.1186/s12940-017-0314-5.) Have interactions among air pollution and other explanatory variables (such as noise, green space, income, and activity level) been adequately quantified and modeled so that the effects of air pollution can be distinguished from the effects of other variables? (Cole-Hunter T et al. Estimated effects of air pollution and space-time-activity on cardiopulmonary outcomes in healthy adults: A repeated measures study. Environ Int. 2018 Feb;111:247-259. doi: 10.1016/j.envint.2017.11.024.)
5. **Treatment of manipulative causality** (as opposed to associational, attributive, counterfactual, predictive, structural, or mechanistic causality). Does the ISA clearly distinguish among different concepts of causality, e.g., among associational causality (such as Hill considerations, IARC criteria, WoE), attributive causality (e.g., burden of disease calculations, attributable risk calculations), predictive (Wiener or Granger) causality, manipulative causality, structural (Simon-Iwasaki) causality, and mechanistic causality? Do the main conclusions clearly address manipulative causality? Do they provide information for decision-makers that is specifically about manipulative causal C-R functions and that is clearly distinguished from other types of causality? (See e.g., Pearl J. Causal inference in statistics: An overview. Statistics Surveys Vol. 3 (2009) 96–146; Campaner R Mechanistic causality and counterfactual-manipulative causality: recent insights from philosophy of science. J Epidemiol Community Health. 2011 Dec;65(12):1070-4. doi: 10.1136/jech.2011.134205.)
6. **Clear definition and quantification of direct, mediated, and total causal effects for causal C-R functions.** Have estimated C-R functions been developed for clearly specified natural direct, controlled direct, indirect, mediated, and total causal effects of changes in PM2.5 concentrations on

changes in human health risks? Which of these different causal effects have been quantified to inform decision makers? How have errors and uncertainties in mediators been accounted for in quantifying causal C-R functions? (See e.g., Richiardi L, Bellocco R, Zugna D. Mediation analysis in epidemiology: methods, interpretation and bias. Int J Epidemiol. 2013 Oct;42(5):1511-9. doi: 10.1093/ije/dyt127. Vanderweele TJ, Vansteelandt S, Robins JM. Effect decomposition in the presence of an exposure-induced mediator-outcome confounder. Epidemiology. 2014 Mar;25(2):300-6. doi: 10.1097/EDE.0000000000000034. Blakely T, McKenzie S, Carter K. Misclassification of the mediator matters when estimating indirect effects. J Epidemiol Community Health. 2013 May;67(5):458-66. doi: 10.1136/jech-2012-201813.)

7. **Treatment of inter-individual variability and heterogeneity in causal C-R functions.** Are inter-individual variability and heterogeneity in individual-level C-R functions appropriately characterized and quantified? Have appropriate techniques such as individual conditional expectation plots been used to quantify and visualize the extent of inter-individual heterogeneity in causal C-R functions? (See e.g., Zhao Q, Hastie T. Causal interpretations of blackbox models. 2017.)
8. **Uncertainty characterization.** Are uncertainties about individual-level and population-level causal C-R functions fully and clearly characterized? Are appropriate techniques (e.g., non-parametric model ensembles) used to quantify model uncertainties for causal C-R functions? Does the uncertainty characterization integrate exposure uncertainties, C-R function uncertainties, and uncertainties in other (measured and latent) variables that can mediate or confound the exposure-response C-R function?

Thank you all very much. I look forward to a productive meeting. In the interim, please contact me or contact Aaron at phone: 202-564-2050, or via at e-mail: yeow.aaron@epa.gov, if you have any questions or comments.

Sincerely,

Tony Cox
Chair
CASAC