Questions for Non-Member Consultants on the PM PA from Dr. Tony Cox

Technical Background for the Questions

Page 3-79 of the Draft Policy Assessment for PM NAAQS, dated 9-05-2019 (henceforth, the "PA") states that "Our consideration of estimated risks focuses on addressing the following policy-relevant questions:

- What are the estimated PM2.5-associated health risks for air quality just meeting the current primary PM2.5 standards?
- To what extent are risks estimated to decline when air quality is adjusted to just meet potential alternative standards with lower levels?
- What are the uncertainties and limitations in these risk estimates?"

The second of these questions – *how much would reducing PM2.5 air pollution levels reduce health risks?* – asks about the effect on health risks of reducing PM2.5 levels. This appears to me to be a question about manipulative or interventionist causality (https://plato.stanford.edu/entries/causation-mani/).

I seek your guidance on how well this causal question is answered by the techniques and models used in the PA. Specifically, the PA uses concentration-response (CR) regression models (Table C-1 of the PA) that describe the health risks associated with different levels of exposure to simulate effects on public health of changing PM2.5 standards. A key technical question is: ***Are the C-R models in Table C-1 appropriate, logically valid, and empirically well-validated, for answering the causal question of how changes in PM2.5 levels would change health risks?*** Both specific and general versions of this question are of interest:

- Are the specific regression models in Table C-1 known to produce valid predictions or simulations of how changing PM2.5 exposure would change population health effects or risks?
- In general, are such regression models appropriate for predicting how an intervention or manipulation that changes the value of a predictor (right-hand side variable) would cause the value (or frequency distribution) of the dependent variable to change? If certain conditions must hold for this to be an appropriate use of regression models, what are they, and has the PA shown that they are satisfied for the C-R regression models in Table C-1?

In more technical detail, Page C-38 of Appendix C states that "BenMAP-CE is an open-source computer program that calculates the number and economic value of air pollution related deaths and illnesses. The software incorporates a database that includes many of the concentration-response relationships, population files, and health and economic data needed to quantify these impacts. BenMAP-CE also allows the user to import customized datasets for any of the inputs used in modeling risk. For this analysis, CR functions developed specifically for this assessment were imported into BenMAP-CE (section C.1.1). The BenMAP-CE tool estimates the number of health impacts resulting from changes in air quality—specifically, ground-level ozone and fine particles." Page C-1 explains that "our general approach to *estimating PM2.5-associated human health risks* in this review utilizes concentration-response (CR) functions obtained from epidemiology studies to link ambient PM2.5 exposure to risk in the form of incidence (counts) of specific health effects. The derivation and use of this type of CR

function in modeling *PM2.5-attributable risk* is well documented both in previous PM NAAQS-related risk assessments (section 3.1.2 of U.S. EPA, 2010) and in Appendix C of the BenMAP-CE User Manual" (emphases added). In turn, the BenMAP-CE User Manual (pages C-1 to C-2, on "Deriving Health Impact Functions") states that "Epidemiological studies have used a variety of functional forms for C-R functions. Some studies have assumed that the relationship between adverse health and pollution is best described by a linear form, where *the relationship between y and PM is estimated by a linear regression* in which y is the dependent variable and PM is one of several independent variables. Log-linear regression and logistic regression are other common forms. … The relationship between Δx and Δy [change in PM2.5 concentration and change in population health response] can be derived from the CR function, as described below, and we refer to this relationship as a health impact function. Many epidemiological studies, however, do not report the C-R function, but instead report some measure of the change in the population health response associated with a specific change in the pollutant concentration. The most common measure reported is the relative risk associated with a given change in the pollutant concentration. *A general relationship between Δx and Δy can, however, be derived from the relative risk*." (Emphases added.) (www.epa.gov/sites/production/files/2015-04/documents/benmap-ce_user_manual_march_2015.pdf) Table E-1 of the BenMAP-CE User Manual ("Core Health Impact Functions for Particulate Matter and Long-Term Mortality") presents various expert estimates for "beta," which is defined and described as follows: "The coefficient for the health impact function. The value of beta (ß) typically represents the percent change in a given adverse health impact per unit of pollution. … Odds Ratios must be converted to beta coefficients to be used in BenMAP-CE." The notes on many of these beta values state "No causality included." Table C-1 of the PA ("Details regarding selection of epidemiology studies and specification of concentration-response functions for the risk assessment") presents the beta values used in the PA simulations, but has no column of notes indicating whether or how any of them addresses causality.

Questions

1. *Are the beta coefficients in Table C-1 of the PA conceptually well defined?* That is, are their intended conceptual meanings and causal interpretations clear and unambiguous? If so, can the definition of beta be expressed using standard epidemiological terms (e.g., controlled direct effects, natural direct effects, total effects, indirect effects, and so forth?) (Petersen ML, Sinisi SE, van der Laan MJ. (2006) Estimation of direct causal effects. Epidemiology. May; 17(3):276-84; Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. Epidemiology 1992, 3:143-155; Tchetgen Tchetgen EJ, Phiri K. Bounds for pure direct effect. Epidemiology. 2014 Sep;25(5):775-6. doi: 10.1097/EDE.0000000000000154; VanderWeele TJ. Controlled direct and mediated effects: definition, identification and bounds. Scand Stat Theory Appl. 2011 Sep;38(3):551-563; Vansteelandt, Stijn; Bekaert, Maarten; Lange, Theis (2012). Imputation strategies for the estimation of natural direct and indirect effects. *Epidemiologic Methods*. **1** (1, Article 7).)
2. On the same topic of clear definitions, does the discussion of the BenMAP-CE beta coefficients in the PA and underlying documentation (described as typically representing "the percent change in a given adverse health impact per unit of pollution") unambiguously specify which of the following concepts the coefficients represent?
    a. Beta estimates the percent change in the conditional expected *observed* value of the health impact *associated with* a unit change in the *observed* value of the pollution variable. (This might be called the *regression interpretation* of the beta values.)
    b. Beta estimates the percent change in the mean value of the health impact variable *caused by* a manipulation or intervention that changes the value of the pollution variable by 1 unit (e.g.,

increasing concentrations at all times and locations by 1 microgram per cubic meter above what they otherwise would have been), while *holding the values of all other variables fixed* at the values they had before the intervention. (As concrete examples, the values of lagged daily high and low temperatures, humidity, and co-morbidities such as asthma in the weeks before a death would not be affected by the hypothetical (or counterfactual) change in the pollution variable for a beta coefficient that addresses the health impact on mortality risk of a change in pollution.) (This might be called the *natural direct effect* interpretation of beta.)

c. Beta estimates the percent change in the mean value of the health impact *caused by* a manipulation or intervention that changes the value of the pollution variable by 1 unit (e.g., increasing concentrations at all times and locations by 1 microgram per cubic meter above what they otherwise would have been), while *allowing the values all other variables to change* in response to the changes in pollution. (As concrete examples, the joint distribution of the values of lagged daily high and low temperatures, humidity, and co-morbidities such as asthma could be changed by conditioning on counterfactual changes in the pollution variable.) (This might be called the *total direct effect* interpretation of beta.)

d. Beta estimates the percent change in the mean value of the health impact *caused by* a manipulation or intervention that changes the value of the pollution variable by 1 unit (e.g., increasing concentrations at all times and locations by 1 microgram per cubic meter above what they otherwise would have been), while *holding the values of all other variables (e.g., co-exposures, co-morbidities, potential confounders or modifiers such as weather variables) fixed at the values they would be expected to have after the intervention.*

e. Beta means something different from any of the above (e.g., a controlled direct effect).

Do all of the beta values in Table C-1 refer to the same one of these concepts, or might they refer to different ones (or is the answer not clear)?

3. Similarly, *is the definition of "concentration-response (C-R) relationships" in the PA and its Appendices (cf p. C-38) adequately clear and unambiguous* to support simulation of well-defined causal effects of interventions that change pollution levels? For example, is it clear whether the term "C-R relationship" in the PA refers to natural direct effects of PM2.5 on mortality and other health outcomes, or to total effects, controlled direct effects, effects mediated by PM2.5, or simply slopes of estimated regression lines (associations), or perhaps something else?
4. The PA and BenMAP-CE documentation repeatedly refers to relative risks, odds ratios, attributable risks, and regression coefficients as bases for quantifying causal effects of changes in air pollution on changes in population health responses. Some epidemiology methodologists and experts in causal analysis have distinguished between association and causation (and between "seeing" and "doing") and have warned that relative risks, odds ratios, attributable risks, regression coefficients, and related concepts (e.g., population attributable fractions, probabilities of causation, etiologic fractions) address associations but not causation (including causal effects of interventions), because measures of statistical association do not address how changing one variable would change another (e.g., Pearl J, 2009 Causal inference in statistics: An overview. Statistics Surveys 3: 96-146; Greenland and Robins 2000, Epidemiology, justice, and the probability of causation; Maldonado G, Greenland S. Estimating causal effects. Int J Epidemiol. 2002 Apr;31(2):422-9.) *Do the beta coefficients in the PA overcome these methodological objections to using relative risks, regression coefficients, and related measures of association to predict (or simulate) effects of interventions?* If so, how were they overcome? If not, does this imply that the simulations in the PA are not necessarily reliable or valid predictors of the real-world effects on public health of reducing PM2.5? Why or why not?
5. On the same methodological issue, *which, if any, of these measures (relative risks, odds ratios, attributable risks, and regression coefficients) are currently generally accepted in contemporary*

causal analysis and epidemiology as valid measures of how changing one variable (e.g., exposure) will cause another (e.g., population health responses) to change? Please provide specific references if available, and identify whether any of these quantities are generally accepted now as valid measures of controlled direct, natural direct, indirect, total, or mediated causal effects.

6. More generally, do the $\Delta y/\Delta x$ values calculated by BenMAP-CE have valid interpretations as *causal impacts* on y of *interventions* that change x? (If x represents daily ice cream consumption in a population and y represents daily cases of heat stroke, would the slope of an estimated regression line or C-R line relating them, β or $\Delta y/\Delta x$, necessarily provide valid predictions or simulations for how an intervention that changes ice cream consumption by 1 unit would change daily cases of heat stroke? Assuming the answer is no, how is the methodology of beta coefficients in Appendix C of the PA essentially different from this example?)
7. *Have the beta coefficients in the PA been empirically validated* as providing approximately correct or usefully accurate predictions or simulations of how interventions that change air pollution would change population health responses? A recent non-EPA review of the empirical evidence of health effects of interventions to reduce ambient PM air pollution did not conclude that there is strong evidence leading to confident rejection of the null hypothesis of no effect: rather, the authors concluded that "Most included studies observed either no significant association in either direction or an association favouring the intervention, with little evidence that the assessed interventions might be harmful. The evidence base highlights the challenges related to establishing a causal relationship between specific air pollution interventions and outcomes." (Burns J, Boogaard H, Polus S, Pfadenhauer LM, Rohwer AC, van Erp AM, Turley R, Rehfuess E. Interventions to reduce ambient particulate matter air pollution and their effect on health. Cochrane Database of Systematic Reviews 2019, Issue 5. Art. No.: CD010919. DOI: 10.1002/14651858.CD010919.pub2.) To what extent are such findings from actual interventions consistent with the assumptions, confidence intervals, and simulations in the PA?
8. Does the discussion of beta values in the PA, including the discussions of uncertainty, confidence intervals, and sensitivity analyses, adequately describe and discuss the extent (if any) to which their values reflect *potential omitted confounders* of the association between mortality risks and PM2.5 levels (e.g., lagged daily high and low temperatures and humidity in the weeks preceding mortality, if these contribute both to (possibly delayed) mortality and increased energy usage and PM2.5 pollution?)
9. Does the discussion of beta values in the PA, including the discussions of uncertainty, confidence intervals, and sensitivity analyses, adequately address the extent (if any) to which their values reflect *residual confounding* of the association between mortality risks and PM2.5 levels (e.g., by daily high and low temperatures and humidity in the weeks preceding mortality in models that only address seasonal, annual, or averaged temperatures)?
10. Does the discussion of beta values in the PA, including the discussions of uncertainty, confidence intervals, and sensitivity analyses, adequately address *model uncertainty* (e.g., the possibility that the linear no-threshold model specification is incorrect, e.g., because sufficiently low exposure concentrations do not cause pulmonary inflammation and adverse health effects that occur at higher concentrations)?
11. Does the PA's discussion of beta values, including the discussions of uncertainty, confidence intervals, and sensitivity analyses, adequately address *effects on the estimated values of the beta values of exposure uncertainties and estimation errors* (e.g., the possibility that individual exposure concentrations among people with adverse health responses tend to be higher than those among people who did not respond, even when they have the same estimated exposure values)?
12. Does the PA adequately assess *the suitability of the designs of the studies used to estimate beta values for purposes of valid causal inference and simulation? Does the PA's discussion of uncertainty and sensitivity analyses adequately address the internal validity and external validity (generalizability) of the estimated beta values* used to simulate the causal impacts on public health risks of changing PM2.5 levels?

(Campbell DT, Stanley JC (1963) *Experimental and Quasi-Experimental Designs For Research*. Houghton Mifflin. Boston, MA www.sfu.ca/~palys/Campbell&Stanley-1959-Exptl&QuasiExptlDesignsForResearch.pdf)

13. Does the PA's discussion of beta values adequately address *attribution of risk in the presence of joint causes?* For example, if a unit change in PM2.5 levels has different expected effects on mortality risk for a person below the poverty line and during extremely hot or cold weather than it would for an initially similar (exchangeable) person with higher income and no exposure to extreme temperatures, then how much of the statistical "effect" of PM2.5 on mortality risk, as reflected in the beta values in Table C-1, should be attributed to income and weather variables? Conversely, how well does the discussion in the PA make clear how much of the estimated beta value for PM2.5 is actually contributed by other variables (such as temperature extremes and poverty) that would not necessarily be changed by an intervention that reduces PM.5 levels?
14. Overall, does the PA and its underlying documents (e.g., the BenMAP-CE documentation) make a convincing technical case that its simulated health impacts of reductions in PM2.5 are trustworthy and usefully accurate? *How confident can policy analysts and decision makers be in the predictive validity of the simulated results?*
15. Are there other statistical or methodological issues that you would like to comment on that you believe might help the CASAC to assess the validity and soundness of the PA and its simulations for effects on health risks of changing PM2.5 levels, or that might help to improve the technical and scientific quality of the final PA?
16. How can techniques of formal causal modeling and analysis best be applied to improve the clarity of definitions and communication and scientific soundness of simulations, inferences, causal interpretations, generalizations, and policy-relevant conclusions in the PA? Please comment on whether any aspects of the following (or other) causal model formalisms can substantially improve the clarity and scientific soundness of the analyses and simulations in the PA: causal graph and DAG methods, conditional independence tests, intervention and interrupted time series analyses, other quasi-experimental methods, Wiener-Granger causality and transfer entropy, causal dynamic Bayesian networks (DBNs), other information-theoretic and graph methods, Simon-Iwasaki causal ordering , non-parametric structural equations models, mediation analysis.