12-10-18 Preliminary Draft Comments from Members of the Clean Air Scientific Advisory Committee (CASAC). These preliminary pre-meeting comments are from individual members of the Committee and do not represent CASAC consensus comments nor EPA policy. Do not cite or quote.

Preliminary Comments from Members of the CASAC on

EPA's *Integrated Science Assessment for Particulate Matter (External Review Draft – October 2018)*

Received as of 12-10-18

Dr. James Boylan

General Comment

I recommend that EPA reconvene the PM Review Panel. I believe that a PM Review Panel would provide the 7-member chartered CASAC with additional insight and expertise to allow for a more thorough and in-depth review of the relevant science and policy documents. My experience on the most recent SO_2 Review Panel has shown me the importance and value of having multiple independent experts who are at the leading edge of research in their respective fields thoroughly reviewing each chapter.

The proposed review schedule is very aggressive and allows for one draft of the ISA and one draft of the PA. Also, EPA is planning to incorporate the REA analysis into the PA. EPA should recognize the possibility that second drafts of these documents might be necessary after CASAC and the public review the first drafts. In addition, the REA should not be included as part of the PA. Instead, the REA should be a stand-alone document that is reviewed by CASAC and the public prior to the release of the first draft of the PA. This will allow scientific review of risk and exposure metrics prior to developing policy recommendations. This review should not be strictly tied to the proposed schedule since getting high quality documents is more important than meeting the statutory deadline.

Executive Summary

The Executive Summary is intended to provide a concise synopsis of the key findings and conclusions of the PM ISA for a broad range of audiences. Please comment on the clarity with which the Executive Summary communicates the key information from the PM ISA. Please provide recommendations on information that should be added or information that should be left for discussion in the subsequent chapters of the PM ISA.

The Executive Summary did a good job of communicating the key information from the PM ISA. I have no recommendations for information that should be added or deleted.

Chapter 1 (Integrated Synthesis)

Chapter 1 presents an integrated summary and the overall conclusions from the subsequent detailed chapters of the PM ISA and characterizes available scientific information on policy-relevant issues. Please comment on the usefulness and effectiveness of the summary presentation. Please provide recommendations on approaches that may improve the communication of key findings to varied audiences and the synthesis of available information across subject areas.

What information should be added or is more appropriate to leave for discussion in the subsequent detailed chapters?

Chapter 1 provides a comprehensive overview of each chapter in the PM ISA and the policy-relevant issues. The summary tables in Section 1.7 (Tables 1-5, 1-6, and 1-7) are very useful for presenting the causality determinations in the current PM ISA and the previous PM ISA. I have no recommendations for information that should be added or deleted.

Chapter 2 (Sources, Atmospheric Chemistry, and Ambient Concentrations)

To what extent is the information presented in Chapter 2 regarding sources, chemistry, and measurement and modeling of ambient concentrations of PM clearly and accurately conveyed and appropriately characterized? Please comment on the extent to which available information on the spatial and temporal trends of ambient PM concentrations at various scales has been adequately and accurately described.

In general, Chapter 2 does a good job of presenting sources, chemistry, and measurements and modeling of ambient PM concentrations. The spatial and temporal trends of ambient PM concentrations have been accurately described.

Section 2.3 discusses primary sources of PM. Figures 2-2, 2-3, and 2-6 show the importance of various types of dust to total $PM_{2.5}$ and PM_{10} primary emissions based on the U.S. EPA 2014 National Emissions Inventory. However, when these emissions are used as inputs to CTMs, the modeled concentrations are significantly higher than the observed concentrations at the speciation monitors. The reason for the overprediction is that there is no adjustment for near-source removal due to small sub-grid scale turbulence and impaction on building and vegetative surfaces (Pouliot G., *et al*., Assessing the Anthropogenic Fugitive Dust Emission Inventory and Temporal Allocation Using an Updated Speciation of Particulate Matter, January 2012, DOI: 10.1007/978-94-007-1359-8_97). It is estimated that local source removal typically accounts for 75% of total removal of fine particulate matter nationally (T.G. Pace, "Methodology to Estimate the Transportable Fraction (TF) of Fugitive Dust Emissions for Regional and Urban Scale Air Quality Analyses", U.S. EPA, Research Triangle Park NC, August 2005, https://www.nrc.gov/docs/ML1321/ML13213A386.pdf). This removal factor is defined as a "capture fraction" and varies by location. The amount that is not removed is defined as the "transportable fraction." A discussion of capture fraction and transportable fraction should be included in this chapter to help place the importance of dust emissions into proper perspective.

Section 2.4.1 discusses the difference between FRM and FEM monitors and describes the three most widely used FEMs. FRMs typically measure 24-hour integrated samples every third day. Short time resolution automated FEMs can measure hourly samples every day. In the past, FEMs typically measured higher $PM_{2.5}$ concentrations than FRMs; therefore, some states were reluctant to switch to FEMs. However, the new Teledyne optical spectrometer FEMs are much more

accurate and many states are now converting their FRMs to FEMs. In July of 2017, Georgia EPD ran two regulatory FEMs. Currently, Georgia EPD runs nine regulatory FEMs and will be running twelve regulatory FEMs by June of 2019. A similar trend is occurring across many parts of the country which will produce significantly more $PM_{2.5}$ data at hourly resolution.

Section 2.4.7 does a good job of documenting the scientific advances in CTMs.

Figure 2-14 shows the 98th percentile 24-hour $PM_{2.5}$ concentrations for 2013-2015. The red monitor in southern Georgia appears to be Albany (13-095-0007). However, according to certified AQS data, the 24-hour 2013-2015 design value for Albany is 23 $\mu g/m^3$ (should be a blue dot, not red dot).

Figure 2-15 shows the 98th percentile PM_{10} concentrations for 2013-2015. There are no measurements shown in Georgia although Georgia has three PM_{10} monitors (13-089-0002, 13-121-0039, and 13-245-0091) with certified data in AQS from 2013-2015. The 98th percentile PM_{10} concentrations for all three PM_{10} monitors in Georgia are well below 75 $\mu g/m^3$ (blue dots).

Chapter 3 (Exposure to Ambient Particulate Matter)

Chapter 3 describes scientific information on exposure to ambient PM and implications for epidemiologic studies. To what extent is the discussion on methodological considerations for exposure measurement and modeling clearly and accurately conveyed and appropriately characterized? Please comment on the extent to which the discussion regarding exposure assessment and the influence of exposure error on effect estimates in epidemiologic studies of the health effects of PM has been adequately and accurately described.

In general, Chapter 3 does a good job of describing the latest scientific information on exposure to ambient PM and implications for epidemiologic studies, methodological considerations for exposure measurement and modeling, and the influence of exposure error on effect estimates in epidemiologic studies.

Section 3.3.1.2 and Table 3-1 discusses personal monitoring and error characteristics. Some personal samplers perform better than others. Before using personal sampling data to estimate exposure, a detailed evaluation of the sampler performance compared to FEMs should be performed. In some cases, the data may be better suited for looking at gradients in $PM_{2.5}$ exposure rather than directly using the measured $PM_{2.5}$ concentrations.

Table 3-2 contains a comparison of models used for estimating exposure concentrations or exposure. Under the column for "Dispersion", there is an "X" for Chemistry. However, it is stated on page 3-28 "Dispersion models…typically have limited ability to model chemistry (if any)." A footnote should be added to the table to indicate that many dispersion models do not account for chemistry.

Table 3-3 contains statistic measures used for air quality model performance evaluations. While the four performance measures listed are commonly used, the table should also include normalized mean bias (NMB) and normalized mean error (NME) since these are also commonly used and will show percent differences in addition to absolute differences (MB and ME).

Section 3.3.2.4 discusses "Mechanistic Models". The first paragraph is this section discusses CTMs, but does not mention dispersion models which are also discussed in this section (3.3.2.4.2).

In Section 3.3.2.4.1, additional information should be added to describe how Eulerian CTMs work (e.g., grid structures, finite difference, solving ADE).

On page 3-27, it is stated "Differential bias may also be observed across regions in space. Many such biases can be corrected for using adjustment factors based on comparisons of simulation results with observational data." However, it should be noted that arbitrarily adjusting modeling results to match observations can lead to the model getting the right answer for the wrong reasons. This is important if emission sensitivities or source apportionment is being used to look at control strategies since the model will not response appropriately to emission controls.

The bottom of page 3-27 discusses the Lagrangian trajectory model (which does not have any chemistry) by Stanier et al. (2014). Typically, Lagrangian models are not classified as CTMs, but rather they are classified as dispersion models. This discussion should be moved into Section 3.3.2.4.2.

Section 3.3.2.4.2 seems to mostly focus on using dispersion models for near-road modeling of mobile sources. However, dispersion models are much more widely used for modeling industrial point sources. Additional focus should be added for this aspect.

Section 3.3.2.4.2 should be updated to include Lagrangian dispersion models. The difference between a Lagrangian puff model and a steady-state plume model should be added. Under the section on Lagrangian puff models, a discussion on CALPUFF (limited chemistry), SCIPUFF (no chemistry), and SCICHEM (full chemistry) should be added.

Table 3-4 and other parts of Section 3.3.2.4.2 discuss model performance of dispersion models. Most published dispersion model performance evaluations are associated with using the model for compliance assessments. In these cases, the model's ability to capture the high end of the concentration distribution is evaluated with Q-Q plots where the highest data point from the model is compared to the highest data point from the observations even if they occur at different locations, time of day, and/or season of the year. When the model is being used to support health studies, spatial and temporal accuracy is much more important compared with compliance assessments. Therefore, dispersion modeling results need to be evaluated against observations

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paired in time and space, especially if they are being used as inputs to an exposure model such as SHEDS, APEX, or EMI.

Pages 3-32 to 3-34 discuss fusion of CTM predictions with surface observation data. This section does not discuss EPA's recommended approach to States for estimating ozone and $PM_{2.5}$ concentrations at unmonitored locations contained in their "Draft Modeling Guidance for Demonstrating Attainment of Air Quality Goals for Ozone, $PM_{2.5}$, and Regional Haze" (December, 2014) located at https://www3.epa.gov/scram001/guidance/guide/Draft_O3-PM-RH_Modeling_Guidance-2014.pdf. In this guidance document (pages 144-148), EPA discusses their "Modeled Attainment Test Software" (MATS). MATS will spatially interpolate data and adjust the spatial fields based on model output gradients (Abt Associates, Inc., 2014. Modeled Attainment Test Software: User's Manual. https://www.epa.gov/scram/photochemical-modeling-tools). EPA's MATS uses the Voronoi Neighbor Averaging (VNA) technique. This approach can be applied to $PM_{2.5}$ design values or 24-hour $PM_{2.5}$ values.

The last paragraph on page 3-34 states "Hybrid approaches can involve merging CTMs with dispersion and/or LUR models, merging CTMs with observational data, or some combination therein." However, there are no references showing how CTMs can be merged with dispersion models. Below are two examples that could be referenced:

- EPA's 2014 National Air Toxics Assessment (NATA) Technical Support Document (August, 2018) which merged CMAQ and AERMOD modeling results to determine cancer risks for HAPs and diesel PM (https://www.epa.gov/national-air-toxics-assessment/2014-nata-technical-support-document).

- K. Wesson, *et al*. (2010), A multi-pollutant, risk-based approach to air quality management: Case study for Detroit, Atmospheric Pollution Research 1, 296-304. This study merged CMAQ and AERMOD modeling results to determine exposure for HAPs, ozone, and $PM_{2.5}$. Data from the air quality modeling was used as input into the environmental Benefits Mapping and Analysis Program (BenMAP) and the Human Exposure Model-3 (HEM-3) to assess how the control strategies affect human health.

In general, I am in agreement with EPA's conclusions in Chapter 3:
- Exposure error tends to produce underestimations of health effects in epidemiologic studies of PM exposure, although bias in either direction can occur.
- New developments in PM exposure assessment methods have reduced bias and uncertainty in health effect estimates.
- High correlations of $PM_{2.5}$ with some gaseous copollutants necessitate evaluation of the impact of confounding on health effect estimates.

- There is typically more uncertainty for health effect estimates for exposure to $PM_{10-2.5}$ and UFP.

Dr. Tony Cox

Main Recommendations

The Draft ISA states on page ES-1 that it "is a comprehensive evaluation and synthesis of policy-relevant science aimed at characterizing exposures to ambient particulate matter (PM), and health and welfare effects associated with these exposures." To enable scientifically well-informed risk management and policy deliberations and decisions, the following changes and additions to the Draft ISA will be most valuable.

1. *Address preventable harm.* The ISA should provide quantitative estimates and uncertainty distributions for the amount of human health harm *preventable* by reducing PM exposures (e.g., reductions in mortality and morbidity numbers per year in the population or per capita-year for individuals in identified susceptible sub-populations). This is necessary to inform understanding of how changes in PM NAAQS would affect human health. It is an essential complement to the information already provided in the draft ISA about harm *associated* with PM. Questions that should be addressed to support scientifically well-informed decision-making include the following:

   a. *How large* is the fraction or number of adverse effects per year that could be prevented by a given reduction in PM exposures (e.g., how many cases of mortalities or morbidities per year in the US population, and per capita-year in identified sub-populations)?

   b. *What else,* other than PM, does the size of this preventable burden depend on (e.g., sociodemographic, meteorological, and co-pollutant factors)? Quantitatively, how does it depend on them? How do causal C-R curves for PM and various health risks change as these other factors change? What are the direct, indirect, and total effects of changes in PM exposure on changes in health risks? How heterogeneous are resulting risk reduction across individuals and sub-populations?

   c. *What changes are expected* over time in the other factors on which the preventable harm from PM depends (e.g., sociodemographic, meteorological, and co-pollutant factors), with and without different reductions in PM? What are the direct, indirect, and total effects of these changes on health risks associated with PM?

   d. *How sure are we* at present about the answers? How are they calculated, from what data, using what models and assumptions? How well validated are the models, assumptions, data, and calculations? What uncertainty bounds, intervals, or distributions should be attached to estimates of the adverse effects that would be prevented by different reductions in PM, taking into account model uncertainty as well as data uncertainty?

   The Draft ISA does not answer these questions, but the final ISA should do so.

2. *Describe and quantify causality and causal impacts of PM on human health more precisely throughout the ISA using modern epidemiological concepts, terms, and methods.* Use standard epidemiological terms and concepts (such as "controlled direct effect," "natural direct effect," and "mediated by PM2.5") in place of, or in addition to, more vague and ambiguous terms such as "causal relationship," "likely to be causal," and "concentration-response relationship." Currently vague, ambiguous, and undefined or imprecisely defined terms include the following:

   - "causal" (in phrases and classifications such as "likely to be causal")
   - "causal relationship"
   - "concentration-response relationship"
   - "effect"
   - "independent effect"
   - "adverse effect"
   - "evidence"
   - "result in"
   - "the relationship" between exposure and response

   If these terms continue to be used, quantitative definitions should be specified for the boundaries of descriptive categories. (For example, should a C-R association that is known to be 1% causal and 99% due to confounding or modeling choices be classified as "causal" or not?) Ideally, however, the final ISA should use standard, well-defined epidemiological concepts and terminology. It should also provide a glossary with clear definitions for all key terms used to communicate policy-relevant information.

3. *Discuss more relevant studies.* The Draft ISA omits many relevant studies that help to clarify real-world PM health effects caused by PM. The final ISA should include thoughtful discussions of high-quality accountability studies, natural experiments, intervention studies, and causal analyses for PM health effects. Its conclusions should synthesize lessons learned from these studies. Some specific examples of studies that are not discussed in the Draft ISA but that include relevant information for understanding how changes in PM affect changes in mortality rates include the following:

   - Health Effects Institute (2013). Did the Irish Coal Bans Improve Air Quality and Health? HEI Update, Summer, 2013.
     https://www.healtheffects.org/system/files/UpdateSummer2013.pdf. This study found that substantial reductions in ambient particulate air pollution (by up to 70% and several dozen $\mu g/m^3$) in Ireland were not found to cause reductions in all-cause or cardiovascular mortality rates despite strong, consistent, coherent etc. historical associations between levels of PM in air and levels of all-cause and cardiovascular mortality due to coincident historical trends. See also Dockery DW, Rich DQ, Goodman PG, Clancy L, Ohman-Strickland P, George P, Kotlov T; HEI Health Review Committee. Effect of air pollution control on mortality and hospital admissions in Ireland. Res Rep Health Eff Inst. 2013 Jul;(176):3-109.

- Health Effects Institute (2016) https://www.healtheffects.org/system/files/ZiglerRR187-Statement.pdf. This study found that "Contrary to expectations, their analysis suggested a reduction, on average, in mortality even in areas where their analyses reported that PM10 was not causally affected. The authors suggested that the observed causal effect of nonattainment designation on mortality, in the absence of a strong associative effect for PM10, may be due to causal pathways other than the one involving reduction of PM10. However, they suggested their results provide evidence that PM10 played a causal role in the reduction of hospitalization for respiratory disease, but again, not for cardiovascular disease. As the authors noted, all of the estimates from these analyses were accompanied by substantial uncertainty, indicated by broad posterior 95% confidence intervals that included zero. As a result, the HEI Health Review Committee thought the investigators generally overstated the average causal effects of nonattainment designation and the role of PM10 in this study." See also Zigler CM, Kim C, Choirat C, Hansen JB, Wang Y, Hund L, Samet J, King G, Dominici F; HEI Health Review Committee. Causal Inference Methods for Estimating Long-Term Health Effects of Air Quality Regulations. Res Rep Health Eff Inst. 2016 May;(187):5-49.
- Zhou M, He G, Fan M, Wang Z, Liu Y, Ma J, Ma Z, Liu J, Liu Y, Wang L, Liu Y. Smog episodes, fine particulate pollution and mortality in China. Environ Res. 2015 Jan;136:396-404. doi: 10.1016/j.envres.2014.09.038. This study examined the impacts on mortality rates of prolonged and severe smog episodes (PM2.5 hourly peak concentrations over 800 $\mu g/m^3$) in China in 2013, finding that "Without any meteorological control, the smog episodes are positively and statistically significantly associated with mortality in 5 out of 7 districts/ counties. However, the findings are sensitive to the meteorological factors. After controlling for temperature, humidity, dew point and wind, the statistical significance disappears in all urban districts. In contrast, the smog episodes are consistently and statistically significantly associated with higher total mortality and mortality from cardiovascular/respiratory diseases in the two rural counties." Thus study, and others like it, provide evidence of substantial geographic heterogeneity in estimated PM2.5-mortality associations.
- Zu K, Tao G, Long C, Goodman J, Valberg P. Long-range fine particulate matter from the 2002 Quebec forest fires and daily mortality in Greater Boston and New York City. Air Qual Atmos Health. 2016; 9:213-221. This study concluded that "substantial short-term elevation in PM2.5 concentrations from forest fire smoke were not followed by increased daily mortality in Greater Boston or New York City."

4. *Explain more explicitly how individual studies and evidence are selected, evaluated, combined or synthesized, and resolved when they conflict, in reaching the ISA's conclusions.* "Evidence" consisting of published results and conclusions from unverified or mistaken assumptions or models (e.g., with estimated exposures treated as true exposures, model uncertainty not quantified, effects of unobserved confounders and latent variables not tested for and quantified, etc.) is not necessarily valid evidence. Conclusions with unknown internal

and external validity should not be cited as facts. The Draft ISA does not independently and critically assess the validity of most of the conclusions that it cites or comment on the soundness of the methods that produce them. It leaves unclear exactly how studies were selected, why some apparently valuable ones were not, what makes evidence "sufficient to conclude" something, and how conflicting evidence should be presented and integrated. The final ISA should address each of these points and should be thorough in critically assessing the internal and external validity of the conclusions that it presents and synthesizes.

Comments on Preface and Executive Summary

"*To address these questions and update the scientific judgments in the 2009 PM ISA (U.S. EPA, 2009a), this ISA aims to:*
• Assess whether new information (since the last PM NAAQS review) further informs the relationship between exposure to PM and specific health and nonecological welfare effects?
• Inform whether the current indicators (i.e., PM2.5 for fine particles and PM10 for thoracic coarse particles), averaging times (e.g., 24-hour average, annual average), and levels of the PM NAAQS are appropriate?
In addressing policy-relevant questions, this ISA aims to characterize the independent health and welfare effects of PM, specifically PM2.5"

- The term "the relationship," as used here and throughout the draft ISA in contexts such as "the relationship between exposure to PM and specific health and nonecological welfare effects," is ambiguous. There are many quantitative relationships between exposure to PM and specific effects, including the following:
    - *Descriptive* relationships such as ratios of mean effects to mean exposure concentrations; ratios of differences in mean effects levels to differences in mean exposure concentrations; and regression coefficients for lines drawn through the mean values of estimated measures of exposures and effects
    - Various measures of statistical *association* (e.g., how much more frequently do exposure and effects tend to occur together than would be expected to by chance alone?)
    - Measures of statistical *information* (does knowledge of exposure help to predict effects better (e.g., with smaller mean squared prediction errors) than they could be predicted otherwise, and, if so, by how much?)
    - Measures of statistical *explanation* (how much of the variance in observed effects is explained by differences in exposures?), such as Pearson's or Spearman's rank correlations
    - Measures of various types of *causation* (e.g., by *how much* would changing exposure change effects (manipulative causation))
    - Measures of different types of causal *effects* (e.g., controlled direct, natural direct, indirect, mediated, and total effects).

Throughout the ISA, every reference to a "relationship" between exposure and response or PM concentration and response should clearly state *which* relationship, specifically, is being referred to.

- The term "independent effect" (as used in "independent health and welfare effects of PM") should be clearly defined. It is not self-evident that exposures have effects that are independent of all other factors (e.g., sociodemographic characteristics, co-morbidities, weather variables, etc.) For example, in the simple regression model

$$E(RISK \mid EXPOSURE, POVERTY) = 0.01*EXPOSURE*POVERTY + 0.5*POVERTY$$

where POVERTY is a binary (0-1) indicator variable with value 1 for people living in poverty and value 0 for others and RISK is a binary indicator variable with value 1 for people with an adverse health effect and 0 otherwise, how would the "independent effect" of exposure on risk be defined?

Table P-2: "Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures"

- The usage of the term "causal relationship" is ambiguous here and throughout the rest of the ISA. There are several distinct possible types of causal relationships between effects and exposures (e.g., associational, attributive, counterfactual, predictive, structural, manipulative, mechanistic, and but-for causation) as well as several types of causal effects (e.g., controlled direct, natural direct, indirect, total, mediated, etc. effects) (Cox LA Jr. (2018). Modernizing the Bradford Hill criteria for assessing causal relationships in observational data. Crit Rev Toxicol. 2018 Nov 15:1-31). A conclusion that "there is a causal relationship" leaves unclear *which* causal relationship(s), specifically, are being claimed. This matters because rational decision-making and policy deliberations require information specifically about manipulative causation (i.e., how would different choices affect the probability distributions of outcomes?) (Howard RA (1988). Decision analysis: Practice and promise. *Management Science* 34(6): 679-695). A declaration that "there is a causal relationship" does not help to inform normatively defensible decisions unless the type of causal relationship being asserted is manipulative. Most causal relationships discussed in existing air pollution health effects epidemiology are either associational or attributive, although there has been considerable recent enthusiasm for counterfactual causation based on potential outcomes and modeling assumptions (Cox LA Jr. (2017) Do causal concentration-response functions exist? A critical review of associational and causal relations between fine particulate matter and mortality. Crit Rev Toxicol. Aug;47(7):603-631. doi: 10.1080/10408444.2017.1311838). However, accountability studies, natural experiments, properly designed and analyzed quasi-experiments, and controlled human trials can all help to identify and quantify manipulative causal relationships between exposures and responses, given the levels of other causally relevant variables (e.g., sex, age, temperature, co-morbidities, etc.) (Dominici F, Greenstone M, Sunstein CR. Science and regulation. Particulate matter matters. Science. 2014 Apr 18;344(6181):257-9. doi: 10.1126/science.1247348; Pearl J, (2009) Causal inference in statistics: An overview. Statistics Surveys 3: 96-146, DOI: 10.1214/09-SS057.)

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- Throughout the ISA, every reference to a "causal relationship" between exposure and response or PM concentration and health or welfare effects should clearly specify *which type* of causal relationship is being referred to. These specifications should pass the clarity test used in decision analysis (Howard RA (1988). Decision analysis: Practice and promise. *Management Science* 34(6): 679-695).
- For supporting scientifically well-informed policy making, manipulative causal relationships are most relevant and valuable. Whenever a "causal relationship" is discussed, it should be made clear whether it is a manipulative causal relationship.
- Likewise, wherever "effects" of PM exposures are discussed, the specific *types* of causal effects being referred to should be clearly stated (e.g., controlled direct vs. pure direct vs. indirect vs. total, vs. mediated by biological responses to PM2.5 etc.)

P-12: "Table P-2 provides a description of each of the five causality determinations and the types of scientific evidence that is [sic] considered for each category for both health and welfare effects."

- To support scientifically well-informed risk management deliberation and decision-making, it is essential to augment these qualitative (category) determinations with corresponding *quantitative* determinations of the fraction of each adverse effect caused by exposure that would be prevented if exposure were reduced or eliminated.
- If this fraction is uncertain for a particular effect, then its probability distribution should be estimated.
- If this fraction depends on other factors (e.g., sex, age, income, education, ethnicity, co-exposures, co-morbidities, recent daily temperatures, etc.) then the conditional probability distribution for its value given the values of other variables on which it depends should be estimated. Technical methods for characterizing the dependence of adverse health effects on exposures in the presence of other causal factors include partial dependence plots and conditional probability tables or models in causal graph models or Bayesian networks and influence diagrams. Relevant technical references for these methods include the following:
  o Cox LA Jr. (2018). Modernizing the Bradford Hill criteria for assessing causal relationships in observational data. Crit Rev Toxicol. 2018 Nov 15:1-31
  o Howard RA. Decision analysis: Practice and promise. Management Science, Vol. 34, No. 6. (Jun., 1988), pp. 679-695. Stable URL: http://links.jstor.org/sici?sici=0025-1909%28198806%2934%3A6%3C679%3ADAPAP%3E2.0.CO%3B2-M.
  o Greenwell BM. (2017) pdp: An R Package for Constructing Partial Dependence Plots. The R Journal. Jun 9(1): 421-436. ISSN 2073-485).
- Table P-2 offers as a definition for its "Causal relationship" category determination that "Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. That is, the pollutant has been shown to result in effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence." But an observed association between exposure and effects can be partly due to confounding, biases, coincident historical trends, and other non-causal factors and partly due to manipulative causation. An association should not be classified as wholly "causal" or wholly

not in such cases. Rather the *fraction* of effects that would be prevented by reducing or eliminating exposure (the manipulative causal fraction) should be estimated. For example, suppose that risk is causally related to exposure and poverty via the following structural equation:

$$RISK = 0.1*EXPOSURE + 0.5*POVERTY$$

(where RISK = probability of adverse effect) and that

$$EXPOSURE = 1*POVERTY.$$

Then the total association between EXPOSURE and RISK would be described by the equation

$$RISK = 0.6*EXPOSURE,$$

but the manipulative causal fraction would be only $0.1/(0.1 + 0.5) = 1/6$ of the total association. The total association between exposure and risk is neither "causal" nor "not causal" but is partially causal. *The discussion of Table P-2 should clarify how the definitions of the categorical causal determinations in Table P-2 should be applied to such cases of mixed causal and non-causal C-R associations.* For example, for the family of regression models

$$RISK = w*EXPOSURE + (1 – w)*POVERTY$$

with the confounding relationship EXPOSURE = 1*POVERTY and the weight w a number between 0 and 1, for what range of values of w should the relationship between exposure and risk be classified as "causal"? Is there a smallest positive value of w below which the relationship should not be classified as causal? If so, what is it? (If not, then classifying an association as "causal" would convey no decision-relevant information about how changing exposure would change risk.) Thus, definitional clarity is needed for how the categorical determinations in Table P-2 should be applied to quantitative mixtures of causal and non-causal C-R associations.

P-18 "Causal relationship: the pollutant has been shown to result in health and welfare effects at relevant exposures based on studies encompassing multiple lines of evidence and chance, confounding, and other biases can be ruled out with reasonable confidence."

- The meaning of "result in" and criteria for determining whether a pollutant "has been shown to result in effects" should be clearly defined.
- The definition given for "result in" should be applicable to the realistic case in which PM exposure and other factors that are correlated with PM exposure, including sociodemographic and weather variables, jointly cause or contribute to health effects. For example, if the simple regression model

$$E(RISK \mid EXPOSURE, POVERTY) = 0.01*EXPOSURE*POVERTY + 0.5*POVERTY$$

were found to describe data from several different studies with relevant exposures accurately and was not found to be inaccurate for any study, and if chance, confounding, and biases could be ruled out with reasonable confidence, would this provide an adequate basis to conclude that "the pollutant has been shown to result in health and welfare effects at relevant exposures?" Why or why not? If the answer is no, what else would have to be considered to

make such a determination? The ISA should address these conceptual and definitional issues in sufficient clarity and detail so that different scientists independently applying them to the same data and studies can independently reach the same conclusion.

- To support scientifically well-informed policy deliberations and decisions, the ISA should develop, state, and use definitions of the following core concepts and terms:
    - o "causal relationship"
    - o "result in"
    - o "the relationship" between exposure and response
    - o "concentration-response relationship."
- These and other terms could be listed and defined in a technical glossary in the final PM ISA, along with definitions of more refined terms, such as different types of causal relationships and causal effects that have been defined and distinguished in the epidemiological and risk analysis literature.
- All definitions should meet the *clarity test* often used in decision analysis (Howard RA (1988). Decision analysis: Practice and promise. *Management Science*, 34(6):679-695.)
- Several commentators have offered written public comments that express a high degree of comfort and satisfaction with previous practices and that note to the evolution and improvement of the causal determination framework in Table P-2 over the years with the help of previous CASAC committees. These commentators may see little or no need to clarify key concepts and definitions as recommended here. However, normative principles of decision analysis for supporting responsible science-informed decisions and policy deliberations require such clarity. Ambiguous, unstated, or conflicting definitions of these key concepts are not adequate to support scientifically well-informed decisions. Admittedly, informality and lack of clarity in core definitions and concepts may facilitate consensus-building and political or psychological comfort with resulting statements (especially about causality and effect) despite – or because of – their unclear meanings. But they are inadequate for sound scientific work and for scientifically well-informed deliberation and decision-making based on understanding of how changes in NAAQS are likely to change health outcomes. Therefore, clear definitions should be stated. This may require some new conceptual work to precisely define various types of "relationships" and "effects" when multiple causally relevant factors interact in jointly increasing the probability or frequency of undesirable effects.

Executive Summary

*ES-1: "**Purpose and Scope of the Integrated Science Assessment***
This Integrated Science Assessment (ISA) is a comprehensive evaluation and synthesis of policy-relevant science aimed at characterizing exposures to ambient particulate matter (PM), and health and welfare effects associated with these exposures."

- Consider replacing "is a comprehensive evaluation" with "seeks to provide a comprehensive evaluation" or similar language to indicate that this is a goal for the ISA, not a declaration that it has yet been accomplished.
- **Accountability studies.** To provide a comprehensive evaluation and synthesis of policy-relevant science of health effects caused by PM exposures, the scope of the ISA should be expanded to add a thoughtful discussion of results and implications of *accountability studies* for the effects of observed changes in PM levels on observed health effect. Relevant references for accountability studies include the following:
  - Boogaard H, van Erp AM, Walker KD, Shaikh R. (2017) Accountability Studies on Air Pollution and Health: the HEI Experience.Curr Environ Health Rep. Dec;4(4):514-522. doi: 10.1007/s40572-017-0161-0.
  - Zigler CM, Kim C, Choirat C, Hansen JB, Wang Y, Hund L, Samet J, King G, Dominici F; HEI Health Review Committee. Causal Inference Methods for Estimating Long-Term Health Effects of Air Quality Regulations. Res Rep Health Eff Inst. 2016 May;(187):5-49.
  - Henneman LR, Liu C, Mulholland JA, Russell AG. (2017) Evaluating the effectiveness of air quality regulations: A review of accountability studies and frameworks. J Air Waste Manag Assoc. Feb;67(2):144-172. doi: 10.1080/10962247.2016.1242518.)
  - Health Effects Institute (HEI). 2013. Did the Irish Coal Bans Improve Air Quality and Health? HEI Update, Summer, 2013. https://www.healtheffects.org/system/files/UpdateSummer2013.pdf.

The new discussion should address the implications of the Irish Coal Bans accountability study for the following issues:
  - *C-R relationships for PM in different locations.* In Ireland, reducing ambient particulate air pollution by up to 70% and several dozen $\mu g/m^3$ was not found to cause reductions in all-cause or cardiovascular mortality rates despite strong, consistent, coherent etc. associations between levels of PM in air and levels of all-cause and cardiovascular mortality. Are (manipulative causal) C-R relationships for PM in Ireland expected to be different from those in the US? Why or why not?
  - *Testing and validation of causal determination methods.* Before the accountability study was done, would the methods used in the ISA to make causal determinations for health effects of PM exposures have determined that PM was a cause of increased all-cause and cardiovascular mortality risk in Ireland? Why or why not?
  - *Refinement of causal determination methods.* Are any refinements needed to the causal determination methods used in previous PM ISAs to adequately account for the results of recent accountability studies?

- **Natural experiments.** To provide a comprehensive evaluation and synthesis of policy-relevant science of health effects caused by PM exposures, the scope of the ISA should be expanded to add a discussion of the data and results from relevant natural experiments. Relevant references for natural experiments include the following:

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- o Alman BL, Pfister G, Hao H, Stowell J, Hu X, Liu Y, Strickland MJ. The association of wildfire smoke with respiratory and cardiovascular emergency department visits in Colorado in 2012: a case crossover study. Environ Health. 2016 Jun 4;15(1):64. doi: 10.1186/s12940-016-0146-8.
- o Elliott CT, Henderson SB, Wan V. Time series analysis of fine particulate matter and asthma reliever dispensations in populations affected by forest fires. Environ Health. 2013 Jan 28;12:11. doi: 10.1186/1476-069X-12-11.
- o Peters A, Breitner S, Cyrys J, Stölzel M, Pitz M, Wölke G, Heinrich J, Kreyling W, Küchenhoff H, Wichmann HE. The influence of improved air quality on mortality risks in Erfurt, Germany. Res Rep Health Eff Inst. 2009 Feb;(137):5-77; discussion 79-90.
- o Haikerwal A, Akram M, Del Monaco A, Smith K, Sim MR, Meyer M, Tonkin AM, Abramson MJ, Dennekamp M. Impact of Fine Particulate Matter (PM2.5) Exposure During Wildfires on Cardiovascular Health Outcomes. J Am Heart Assoc. 2015 Jul 15;4(7). pii: e001653. doi: 10.1161/JAHA.114.001653.
- o Hutchinson JA, Vargo J, Milet M, French NHF, Billmire M, Johnson J, Hoshiko S. The San Diego 2007 wildfires and Medi-Cal emergency department presentations, inpatient hospitalizations, and outpatient visits: An observational study of smoke exposure periods and a bidirectional case-crossover analysis. PLoS Med. 2018 Jul 10;15(7):e1002601. doi: 10.1371/journal.pmed.1002601.
- o Zhou M, He G, Fan M, Wang Z, Liu Y, Ma J, Ma Z, Liu J, Liu Y, Wang L, Liu Y. Smog episodes, fine particulate pollution and mortality in China. Environ Res. 2015 Jan;136:396-404. doi: 10.1016/j.envres.2014.09.038. .
- o Zu K, Tao G, Long C, Goodman J, Valberg P. Long-range fine particulate matter from the 2002 Quebec forest fires and daily mortality in Greater Boston and New York City. Air Qual Atmos Health. 2016;9:213-221.
  Although the Preface to the Draft ISA notes that "Studies that conduct an assessment of the PM effect from a source-based mixture (e.g., wood smoke, diesel exhaust, gasoline exhaust, etc.) are only included if they use filtration (e.g., a particle trap) or another approach to differentiate between effects due to the mixture and effects due to the particles alone," natural experiments involving long-range transport of PM from fires may also be useful in showing effects of elevated PM2.5 levels on human health, insofar as other components settle or volatilize out during long-range transport.

- **PM2.5 toxicology and biological mechanisms of adverse health effects.** To provide a comprehensive evaluation and synthesis of policy-relevant science of health effects caused by PM exposures, the ISA should add a discussion of recent advances in inflammation biology and toxicology for PM, such as the roles of the NLRP3 inflammasome in lung responses to PM2.5 exposures. The discussion should address implications of these advances for biologically realistic manipulative causal exposure concentration-duration-response functions. The ISA should specifically discuss evidence related to NLRP3 inflammasome activation by PM2.5 and exposure concentration thresholds and exposure duration thresholds

for NLRP3 inflammasome-mediated effects. Relevant technical references include the following:

- o Cevallos VM, Díaz V, Sirois CM. Particulate matter air pollution from the city of Quito, Ecuador, activates inflammatory signaling pathways in vitro. Innate Immun. 2017 May;23(4):392-400. doi: 10.1177/1753425917699864.
- o Du X, Jiang S, Zeng X, Zhang J, Pan K, Zhou J, Xie Y, Kan H, Song W, Sun Q, Zhao J. Air pollution is associated with the development of atherosclerosis via the cooperation of CD36 and NLRP3 inflammasome in ApoE-/- mice. Toxicol Lett. 2018 Jun 15;290:123-132. doi: 10.1016/j.toxlet.2018.03.022.
- o Xin L, Che B, Zhai B, Luo Q, Zhang C, Wang J, Wang S, Fan G, Liu Z, Feng J, Zhang Z. 1,25-Dihydroxy Vitamin D3 Attenuates the Oxidative Stress-Mediated Inflammation Induced by PM2.5 via the p38/NF-κB/NLRP3 Pathway.Inflammation. 2018 Nov 14. doi: 10.1007/s10753-018-0928-y.
- o Xu F, Qiu X, Hu X, Shang Y, Pardo M, Fang Y, Wang J, Rudich Y, Zhu T. Effects on IL-1β signaling activation induced by water and organic extracts of fine particulate matter (PM2.5) in vitro.Environ Pollut. 2018 Jun;237:592-600. doi: 10.1016/j.envpol.2018.02.086.
- o Zheng R, Tao L, Jian H, Chang Y, Cheng Y, Feng Y, Zhang H. NLRP3 inflammasome activation and lung fibrosis caused by airborne fine particulate matter. Ecotoxicol Environ Saf. 2018 Nov 15;163:612-619. doi: 10.1016/j.ecoenv.2018.07.076.

- **Advances in epidemiological and data science methods.** To provide a comprehensive evaluation and synthesis of policy-relevant science of health effects caused by PM exposures, the ISA should apply up-to-date methods for evaluating, interpreting, and synthesizing statistical and causal C-R relationships. Several useful technical methods for statistical analysis of epidemiological data have been developed and applied since 2009 to address statistical challenges that arise in most PM C-R epidemiological studies. These challenges and some references on recent technical methods for dealing with them include the following:
  - Unmeasured confounders
    - o 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
    - o Groenwold RH, Hak E, Hoes AW. Quantitative assessment of unobserved confounding is mandatory in nonrandomized intervention studies. J Clin Epidemiol. 2009 Jan;62(1):22-8. doi: 10.1016/j.jclinepi.2008.02.011.
    - o Kasza J, Wolfe R, Schuster T. Assessing the impact of unmeasured confounding for binary outcomes using confounding functions. Int J Epidemiol. 2017 Aug 1;46(4):1303-1311. doi: 10.1093/ije/dyx023.
    - o Pearl J. An introduction to causal inference. Int J Biostat. 2010 Feb 26;6(2):Article 7. doi: 10.2202/1557-4679.1203.

- o Streeter AJ, Lin NX, Crathorne L, Haasova M, Hyde C, Melzer D, Henley WE. Adjusting for unmeasured confounding in nonrandomized longitudinal studies: a methodological review. J Clin Epidemiol. 2017 Jul;87:23-34. doi: 10.1016/j.jclinepi.2017.04.022.
  - o VanderWeele TJ. Mediation Analysis: A Practitioner's Guide. Annu Rev Public Health. 2016;37:17-32. doi: 10.1146/annurev-publhealth-032315-021402.
  - o Zhang Z, Uddin MJ, Cheng J, Huang T. Instrumental variable analysis in the presence of unmeasured confounding. Ann Transl Med. 2018 May;6(10):182. doi: 10.21037/atm.2018.03.37.
- Other unmeasured (latent) variables
  - o Bobb JF, Claus Henn B, Valeri L, Coull BA. Statistical software for analyzing the health effects of multiple concurrent exposures via Bayesian kernel machine regression. Environ Health. 2018 Aug 20;17(1):67. doi: 10.1186/s12940-018-0413-y.
  - o Hu ZG, Wong CM, Thach TQ, Lam TH, Hedley AJ. Binary latent variable modelling and its application in the study of air pollution in Hong Kong. Stat Med. 2004 Feb 28;23(4):667-84.)
  - o Ma Z, Li D, Zhan S, Sun F, Xu C, Wang Y, Yang X. Analysis of risk factors of metabolic syndrome using a structural equation model: a cohort study. Endocrine. 2018 Aug 21. doi: 10.1007/s12020-018-1718-x.
  - o Shook-Sa BE, Chen DG, Zhou H. Using Structural Equation Modeling to Assess the Links between Tobacco Smoke Exposure, Volatile Organic Compounds, and Respiratory Function for Adolescents Aged 6 to 18 in the United States. Int J Environ Res Public Health. 2017 Sep 25;14(10). pii: E1112. doi: 10.3390/ijerph14101112.
  - o 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
  - o Strand M, Sillau S, Grunwald GK, Rabinovitch N. Regression calibration with instrumental variables for longitudinal models with interaction terms, and application to air pollution studies. Environmetrics. 2015 Sep;26(6):393-405.

- Errors in estimates and measurements of exposures and covariates
  - o Samoli E, Butland BK. Incorporating Measurement Error from Modeled Air Pollution Exposures into Epidemiological Analyses. Curr Environ Health Rep. 2017 Dec;4(4):472-480. doi: 10.1007/s40572-017-0160-1.
  - o Alexeeff SE, Carroll RJ, Coull B. Spatial measurement error and correction by spatial SIMEX in linear regression models when using predicted air pollution exposures. Biostatistics. 2016 Apr;17(2):377-89. doi: 10.1093/biostatistics/kxv048.
  - o Baxter LK, Wright RJ, Paciorek CJ, Laden F, Suh HH, Levy JI. Effects of exposure measurement error in the analysis of health effects from traffic-related

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air pollution. J Expo Sci Environ Epidemiol. 2010 Jan;20(1):101-11. doi: 10.1038/jes.2009.5.

- o Keller JP, Chang HH, Strickland MJ, Szpiro AA. Measurement Error Correction for Predicted Spatiotemporal Air Pollution Exposures. Epidemiology. 2017 May;28(3):338-345. doi: 10.1097/EDE.0000000000000623.
- o Silva R. (2016) Comments on "Causal inference using invariant prediction: identification and confidence intervals" by Peters, Buhlmann and Meinshausen. http://www.homepages.ucl.ac.uk/~ucgtrbd/papers/comment_peters.pdf

- Residual confounding
  - o Chen K, Wolf K, Hampel R, *et al* OP VII – 2 Does temperature confounding control influence the modifying effect of air temperature in ozone-mortality associations? *Occup Environ Med* 2018;**75:**A14. (Similar methods can be applied to PM2.5.)
  - o Flanders WD, Strickland MJ, Klein M. A New Method for Partial Correction of Residual Confounding in Time-Series and Other Observational Studies. Am J Epidemiol. 2017 May 15;185(10):941-949. doi: 10.1093/aje/kwx013.
  - o Groenwold RH, Klungel OH, Altman DG, van der Graaf Y, Hoes AW, Moons KG; PROTECT WP2 Adjustment for continuous confounders: an example of how to prevent residual confounding. CMAJ. 2013 Mar 19;185(5):401-6. doi: 10.1503/cmaj.120592. Epub 2013 Feb 11.
  - o Halonen JI, Blangiardo M, Toledano MB, Fecht D, Gulliver J, Ghosh R, Anderson HR, Beevers SD, Dajnak D, Kelly FJ, Wilkinson P, Tonne C. Is long-term exposure to traffic pollution associated with mortality? A small-area study in London. Environ Pollut. 2016 Jan;208(Pt A):25-32. doi: 10.1016/j.envpol.2015.06.036. Epub 2015 Jul 7. (Suggests the potential practical importance of uncontrolled confounding in C-R estimates, albeit for exhaust-related PM2.5.)

- Model uncertainty
  - o The main important recent advances for dealing with model uncertainty (e.g., initially unknown form of the C-R function) without relying on unverified modeling assumptions use non-parametric methods and nonparametric model ensembles (e.g., random forest). The following references discuss and illustrate these and other techniques and demonstrate their practical importance for various pollutants, covariates, and health effects.
  - o Pannullo F, Lee D, Waclawski E, Leyland AH. How robust are the estimated effects of air pollution on health? Accounting for model uncertainty using Bayesian model averaging. Spat Spatiotemporal Epidemiol. 2016 Aug;18:53-62. doi: 10.1016/j.sste.2016.04.001.
  - o Fang X, Li R, Kan H, Bottai M, Fang F, Cao Y. Bayesian model averaging method for evaluating associations between air pollution and respiratory mortality: a time-series study. BMJ Open. 2016 Aug 16;6(8):e011487. doi: 10.1136/bmjopen-2016-011487.

- o Smith AE, Glasgow G. Integrated Uncertainty Analysis for Ambient Pollutant Health Risk Assessment: A Case Study of Ozone Mortality Risk. Risk Anal. 2018 Jan;38(1):163-176. doi: 10.1111/risa.12828.
  - o Cox LA Jr.(2018). Modernizing the Bradford Hill criteria for assessing causal relationships in observational data. Crit Rev Toxicol. Nov 15:1-31. doi: 10.1080/10408444.2018.1518404;
- Time-varying C-R models, effects and lagged and time-varying interactions among variables
  - o Gass K, Klein M, Sarnat SE, Winquist A, Darrow LA, Flanders WD, Chang HH, Mulholland JA, Tolbert PE, Strickland MJ. Associations between ambient air pollutant mixtures and pediatric asthma emergency department visits in three cities: a classification and regression tree approach. Environ Health. 2015 Jun 27;14:58. doi: 10.1186/s12940-015-0044-5. The current Draft ISA mentions this study on p. 5-115. A result of the study is that "**No single mixture emerged as the most harmful**. Instead, the rate ratios for the mixtures suggest that all three pollutants drive the health association, and that the rate plateaus in the mixtures with the highest concentrations. In contrast, the results from the comparison model are dominated by an association with ozone and suggest that the rate increases with concentration. …Examination of the differences between the C&RT and comparison model results suggests that **the two approaches for modeling multipollutant exposures lead to different conclusions** regarding the roles of individual pollutants. In the comparison model, **joint effects are driven by O3 concentration**." (Emphases added.) It is not clear that these points are well captured by the ISA's summary of results from this and other studies, which reads as follows: "In summary, the studies that examined multipollutant mixtures that include PM2.5 indicate that mixtures encompassing days with high PM2.5 concentrations are often those mixtures with the highest risk estimates. Additionally, when comparing single-pollutant PM2.5 results with those based on mixtures, the risk estimate associated with the mixture is relatively similar and, in some cases, larger than that observed for PM2.5."
  - o Castner J, Guo L, Yin Y. Ambient air pollution and emergency department visits for asthma in Erie County, New York 2007-2012. Int Arch Occup Environ Health. 2018 Feb;91(2):205-214. doi: 10.1007/s00420-017-1270-7.
  - o Szyszkowicz M, Kousha T. Emergency department visits for asthma in relation to the Air Quality Health Index: a case-crossover study in Windsor, Canada. Can J Public Health. 2014 Jul 31;105(5):e336-41. (The current Draft ISA mentions this study on p. 5-115.)
  - o 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.)

- Correlations and dependencies among explanatory variables
  - Causal graph models, directed acyclic graph (DAGs) methods, structural equations models (SEMs) and related methods now provide excellent techniques for quantifying dependencies among explanatory variables (Cox LA Jr.(2018). Modernizing the Bradford Hill criteria for assessing causal relationships in observational data. Crit Rev Toxicol. Nov 15:1-31. doi: 10.1080/10408444.2018.1518404).
  - Pearl J. An introduction to causal inference. Int J Biostat. 2010 Feb 26;6(2):Article 7. doi: 10.2202/1557-4679.1203.
- Interindividual heterogeneity in C-R functions
  - Kim C, Daniels M, Li Y, Milbury K, Cohen L. A Bayesian semiparametric latent variable approach to causal mediation. Stat Med. 2018 Mar 30;37(7):1149-1161. doi: 10.1002/sim.7572
  - Li X, Xie S, McColgan P, Tabrizi SJ, Scahill RI, Zeng D, Wang Y. Learning Subject-Specific Directed Acyclic Graphs With Mixed Effects Structural Equation Models From Observational Data.Front Genet. 2018 Oct 2;9:430. doi: 10.3389/fgene.2018.00430).
  - https://cran.r-project.org/web/packages/ICEbox/ICEbox.pdf
- Generalization of study results
  - Section 1.5.3, p. 1-49, states that "conducting C-R and threshold analyses is challenging due to the "'(1) limited range of available concentration levels (i.e., sparse data at the low and high end); (2) heterogeneity of (at-risk) populations (between cities); and (3) influence of measurement error'." Important advances since 2009 in methods for valid extrapolation of C-R analyses that adjust for heterogeneity of at-risk populations between locations and that help to overcome some of the challenges of limited ranges of data include greatly improved theories and algorithms for transportability and transport formulas for generalizing study results. Relevant technical references include the following.
  - Bareinboim E, Pearl J. Causal transportability with limited experiments. In Proceedings of the 27th AAAI Conference on Artificial Intelligence, pp. 95-101, 2013. http://ftp.cs.ucla.edu/pub/stat_ser/r408.pdf
  - Hernán MA, Vanderweele T. On compound treatments and transportability of causal inference. *Epidemiology*. 2011; 22:368.
  - Lee S, Honavar V. (2013) m-Transportability: Transportability of a causal effect from multiple environments. Proceedings of the Twenty-Seventh AAAI Conference on Artificial Intelligence. www.aaai.org/ocs/index.php/AAAI/AAAI13/paper/viewFile/6303/7210
  - Schwartz S, Gatto NM, Campbell UB. Transportabilty and causal generalization. Epidemiology: Sep 2011 22(5): 745-6

A Suggested Checklist of Methodological Issues for Evaluating Studies and their Conclusions

For each study used in evaluating, synthesizing, and stating its conclusions about the policy-relevant science of health effects caused by PM exposures, the ISA should critically evaluate the *internal validity* of the study's conclusions (do they follow from the study design and data analysis presented?) and the *external validity* of its conclusions (have they been appropriately generalized and caveated for applications beyond the specific conditions of study?) For a comprehensive evaluation, the ISA should report how well each study has tested and corrected for each of the following potential threats to valid conclusions:

1. **Unmeasured confounders.** Did the study use appropriate designs and tests and corrections for effects of unmeasured confounders? For example, were minimum daily temperatures with lags out to at least 2 weeks considered as potential confounders of PM-health effect C-R associations, and was the omission of any lagged temperatures justified by conditional independence tests showing that they had no detectable effect on the C-R function being estimated?

2. **Other unmeasured (latent) variables.** Did the study use appropriate designs and tests and corrections for effects of unmeasured variables? For example, did it test and use invariance properties for causal dependencies, finite mixture distribution models, causal graph criteria (Pearl J. An introduction to causal inference. Int J Biostat. 2010 Feb 26;6(2):Article 7. doi: 10.2202/1557-4679.1203) or other techniques to quantify or bound their effects on the PM C-R function?

3. **Errors in estimates** and measurements of exposures and covariates. Did the study use appropriate errors-in-variables methods or other techniques to correct for differences between true and estimated exposure values and between true and estimated values of other variables? Did it quantify (or bound) the magnitudes and effects of errors in exposure estimates, e.g., using sensitivity analyses and uncertainty analyses?

4. **Residual confounding.** Were effects of residual confounding appropriately quantified, e.g., using bounds and sensitivity analyses?

5. **Model uncertainty.** Were conclusions (e.g., about the shapes of C-R functions) shown to hold with high confidence in the absence of unverified modeling assumptions, e.g., by using non-parametric model ensembles (such as partial dependence plots and individual conditional expectation plots)?

6. **Time-varying C-R models, effects and lagged and time-varying interactions** among variables. Were interactions and statistical dependences among variables for various lags quantified and displayed, e.g., using methods based on C&RT trees or dynamic Bayesian networks? Were lagged effects of covariates (e.g., of daily temperatures for out to at least several weeks during cold seasons) been adequately modeled? 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?

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7. **Modeling of interactions and dependencies among explanatory variables and between explanatory and risk variables.** Were dependencies among exposure and other causes of responses or health effects modeled explicitly so that direct, indirect, total, and other causal effects of exposure on risk (or of C on R in C-R models) could be isolated and displayed (e.g., using partial dependence plots)? Were formal tests performed for identifiability of the (manipulative causal) C-R functions from available data, and the results reported? Were confounding effects of socioeconomic gradients 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.) Were interactions among air pollution and other explanatory variables (such as noise, green space, income, and activity level) quantified and modeled so that the effects of air pollution could 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.)

8. **Interindividual heterogeneity** in C-R functions. Was interindividual heterogeneity in C-R functions quantified and visualized, e.g., using finite mixture distribution models or individual conditional expectation plots?

9. **Generalization of study results**. Were transportability tests and formulas used to appropriately generalize study results?

Throughout the ISA, conclusions from cited studies should not be presented as evidence until their internal and external validity have been carefully, critically, and independently evaluated and documented as part of the ISA process. Unwarranted, unsound, and unvalidated conclusions appear to be prevalent in this literature (Cox LA Jr. (2017) [Do causal concentration-response functions exist? A critical review of associational and causal relations between fine particulate matter and mortality.](#) Crit Rev Toxicol. Aug;47(7):603-631. doi: 10.1080/10408444.2017.1311838). Therefore it is important for the ISA not to passively repeat and summarize conclusions taken at face value, but to actively engage in critical evaluation and synthesis. The above checklist may help to quickly assess the methodological soundness of different studies and whether their conclusions are trustworthy or might instead result from unaddressed issues on this list.

ES-6: "In summary, exposure error tends to produce underestimation of health effects in epidemiologic studies of PM exposure, although bias in either direction can occur."

- Please add citations or explanations for this claim. It is not true in general. Instead, estimation errors typically lead to over-estimates of low-dose risks and under-estimates of high-dose risks if the true manipulative causal C-R function has a threshold or threshold-like nonlinearity. These two errors can cause the estimated C-R function to flatten and appear linear even if the true C-R function has a well-defined threshold (e.g., Cox LAT. [Effects of exposure estimation errors on estimated exposure-response relations for PM2.5.](#) Environ Res. 2018 Jul;164:636-646. doi: 10.1016/j.envres.2018.03.038).

ES-9: "As in the 2009 PM ISA, the current ISA concludes there is a "likely to be causal relationship" between short-term PM2.5 exposure and respiratory effects (Section 5.1)."
- The ISA should augment this qualitative determination with a quantitative discussion of what is currently known about the fraction of short-term respiratory effects that could be prevented by reducing or eliminating PM2.5 exposure.

ES-16: "An examination of the C-R relationship between short- and long-term PM2.5 exposure and health effects can inform both the shape of the C-R curve and whether there is a threshold (i.e., concentration level) below which there is no evidence of an effect of PM2.5 on health."
- This is not usually true when there is substantial estimation error for the concentrations to which individuals are exposed, as is the case for PM, and specifically for PM2.5 studies. Examining a C-R relationship estimated from data with individual exposure estimates containing unmodeled estimation errors does not in general reveal the shape of the true (error-free) C-R curve or whether it has a threshold (i.e., concentration level) below which exposure does not affect health. The draft ISA's discussion of concentration-response (C-R) relationships should be revised throughout to address effects of exposure estimation and measurement errors on estimated C-R functions and on uncertainty about the shapes of true C-R functions. Technical references on the effects of exposure estimation errors on estimated shapes of C-R functions include the following:
  - Rhomberg LR, Chandalia JK, Long CM, Goodman JE. (2011) Measurement error in environmental epidemiology and the shape of exposure-response curves.Crit Rev Toxicol. Sep;41(8):651-71. doi: 10.3109/10408444.2011.563420.
  - Cox LAT. Effects of exposure estimation errors on estimated exposure-response relations for PM2.5.Environ Res. 2018 Jul;164:636-646. doi: 10.1016/j.envres.2018.03.038
- The definition of "the C-R relationship" should be clearly stated using standard epidemiological terms such as controlled direct effect, natural direct effect, mediated effect, total effect, etc. There are many C-R relationships, and it is important to be clear about which one(s) are being discussed. Without such a clear specification, it appears that the draft ISA uses the same term, "the C-R relationship," to refer to both natural direct effects and total effects, and perhaps also some controlled direct effects; these should be separate curves. Technical references on different types of effects and how to estimate them include the following:
  - Pearl J. (2001) Direct and Indirect Effects. In Proceedings of the Seventeenth Conference on Uncertainty in Artificial Intelligence, San Francisco, CA: Morgan Kaufmann, 411-420.
  - 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.
  - TchetgenTchetgen EJ, Phiri K. Bounds for pure direct effect.Epidemiology. 2014 Sep;25(5):775-6. doi: 10.1097/EDE.0000000000000154.

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CASAC consensus comments nor EPA policy. Do not cite or quote.

- o VanderWeele TJ. Controlled direct and mediated effects: definition, identification and bounds.Scand Stat Theory Appl. 2011 Sep;38(3):551-563.
- It is not clear that any single C-R relationship exists that applies to different areas of the United States (e.g., both west coast and east coast cities). The ISA should address whether a single C-R relationship exists before estimating and applying such an assumed relationship to estimate changes in health risks caused by changes in PM concentrations. The hypothesis that a single manipulative causal C-R relationship exists can be tested using C-R data from different studies by testing whether the property of invariant causal prediction (ICP) holds across the studies. Relevant technical references include the following for testing whether ICP holds across multiple studies include the following:
  - o Cox LA Jr. (2018). Modernizing the Bradford Hill criteria for assessing causal relationships in observational data. Crit Rev Toxicol. 2018 Nov 15:1-31. The discussion of external consistency is particularly relevant.
  - o Heinze-Deml C, Peters J, Meinshausen N. 2017. Invariant causal prediction for nonlinear models. https://arxiv.org/pdf/1706.08576.pdf
  - o Peters J, Bühlmann P, Meinshausen N. Causal inference by using invariant prediction: identification and confidence intervals. Journal of the Royal Statistical Society Series B, 2016 78(5):947-1012

p. ES-20: "Epidemiologic studies that conducted copollutant analyses show that associations remain relatively unchanged when adjusting for gaseous pollutants and other particle size fractions (e.g., PM10−2.5), addressing a key uncertainty identified in the 2009 PM ISA."

- The ISA should address whether natural direct, controlled direct, and total manipulative causal effects of PM exposures on health outcome probabilites also remain relatively unchanged after adjusting for gaseous pollutants and other particle size fractions
- The ISA should also address whether natural direct, controlled direct, and total causal effects of PM exposures on health outcome probabilities remain relatively unchanged after adjusting for other risk factors such as sociodemographic factors and daily minimum and maximum temperatures over the two weeks preceding the adverse health effects(s) of interest?

p. ES-21: "Evidence continues to support a linear, no-threshold concentration-response relationship, but with less certainty in the shape of the curve at lower concentrations (i.e., below about 8 μg/m3)."

- The ISA should clearly distinguish throughout between *true* exposure concentrations, which are usually unknown, and *estimated* exposure concentrations, which usually contain estimation or measurement errors.
- Wherever the terms "exposure" or "concentration" are used in the ISA, it should be made clear whether the exposures and concentrations referred to are *actual* (true) or *estimated* values. For epidemiological studies, the answer is usually that they are estimated (often with large errors and uncertainties). Much of the epidemiological literature on air pollution health

effects, including for PM2.5 specifically, conflates actual and estimated values and ignores errors in estimates. The ISA should be meticulous in avoiding this conflation.

- Current evidence does not support a linear no-threshold (LNT) relationship between *true* concentration and response probability, but only a LNT relationship between *estimated* concentration and response probability. It is now known that even a sharp threshold in the true C-R function is compatible with LNT for the estimated C-R relationship, so evidence supporting LNT for the estimated C-R function does not constitute evidence supporting LNT for the true C-R function. Technical references include the following:
  - o Rhomberg LR, Chandalia JK, Long CM, Goodman JE. (2011) Measurement error in environmental epidemiology and the shape of exposure-response curves.Crit Rev Toxicol. Sep;41(8):651-71. doi: 10.3109/10408444.2011.563420.
  - o Cox LAT. Effects of exposure estimation errors on estimated exposure-response relations for PM2.5.Environ Res. 2018 Jul;164:636-646. doi: 10.1016/j.envres.2018.03.038
- This conclusion that "*Evidence continues to support a linear, no-threshold concentration-response relationship*" should be revisited and updated if necessary after the draft ISA's discussion of concentration-response (C-R) relationships is revised throughout to address effects of exposure concentration estimation and measurement errors on estimated C-R functions and on uncertainty about their true shapes.
- The ISA's discussion of evidence about LNT assumptions should be updated considering recent advances in understanding biological mechanisms of PM-induced lung inflammation, such as the role of the NLRP3 inflammasome, which involves several exposure concentration and duration thresholds for assembly, activation, and pyroptosis (Cox LAT Jr. Biological mechanisms of non-linear dose-response for respirable mineral fibers. *Toxicol Appl Pharmacol*. 2018 Jun 19. pii: S0041-008X(18)30282-5. doi: 10.1016/j.taap.2018.06.016).

Dr. Mark Frampton

General Comments

1. Need to re-appoint the CASAC PM review panel. Prior to the release of this draft PM ISA, and without consulting CASAC, EPA disbanded the expert PM review panel that had been previously appointed to assist CASAC in this important review. Over the past 30 years, NAAQS document reviews by CASAC have been assisted by expert review panels that supplement and expand the scientific expertise brought to bear. The seven chartered CASAC members by themselves do not have the breadth and depth of knowledge or expertise in many areas that is necessary to adequately advise the EPA, and to meet the statutory requirement for a thorough and accurate review.

In order to provide the needed expertise in the review process, EPA should immediately re-appoint the PM review panel, and convene an additional CASAC public meeting to review and discuss the panel's comments, before CASAC finalizes its advice on the current draft ISA.

Major Comments on the draft ISA

(My comments below are preliminary, and focus on chapters 5 and 6. I have not had sufficient time to complete my review.)

2. Possible pulmonary vascular effects of PM, and cardiopulmonary interactions. In general, the background sections of chapters 5 and 6 ignore the importance of inter-relationships between respiratory and cardiac function. The mechanistic figures showing potential pathways for PM pulmonary and cardiovascular effects should be modified to reflect these considerations. Acute PM-related effects on LV ischemia or function, or effects on pulmonary artery pressure, could present as respiratory effects, with dyspnea. This is especially true for COPD, where many patients have co-existing cardiac disease and/or pulmonary arterial hypertension, and acute exacerbations often have a major cardiac contribution.

Pulmonary vascular effects are a likely pathway, in addition to inflammation and translocation, for both acute and long-term PM effects. Pulmonary hypertension and right sided heart failure are briefly discussed in section 6.2.5, under long-term effects, but there is additional evidence for pulmonary vascular and right heart effects not discussed. Also, the findings of the study cited dealing with diastolic dysfunction (Ohlwein et al., 2016) is related, because RV dysfunction can worsen LV diastolic dysfunction by encroachment on the LV, with impaired filling. This is a pathway leading to clinical findings of acute heart failure, but with preservation of LV systolic function. This is a very common occurrence in COPD patients, and a major contributor to exacerbations. There is epidemiological, clinical, and toxicological evidence to support a

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12-10-18 Preliminary Draft Comments from Members of the Clean Air Scientific Advisory Committee (CASAC).
These preliminary pre-meeting comments are from individual members of the Committee and do not represent
CASAC consensus comments nor EPA policy. Do not cite or quote.

pathway of pulmonary vascular effects for PM. Only one of the following studies (Aaron et al.) was cited in the ISA, in the context of heart failure in general.

1. Aaron CP, Chervona Y, Kawut SM, Roux AV, Shen M, Bluemke DA, et al. Particulate Matter Exposure and Cardiopulmonary Differences in the Multi-Ethnic Study of Atherosclerosis. Environ Health Perspect. 2016;124(8):1166-73. *Long-term PM2.5 exposures were associated with greater RV mass and RV mass/ end-diastolic volume ratio conditional on the LV.*

2. Grunig G, Marsh LM, Esmaeil N, Jackson K, Gordon T, Reibman J, et al. Perspective: ambient air pollution: inflammatory response and effects on the lung's vasculature. Pulm Circ. 2014;4(1):25-35.

3. Leary PJ, Kaufman JD, Barr RG, Bluemke DA, Curl CL, Hough CL, et al. Traffic-related Air Pollution and the Right Ventricle. The Multi-ethnic Study of Atherosclerosis. Am J Respir Crit Care Med. 2014;189(9):1093-100. *NO2 as marker of TRAP linked with increased RV mass. Accompanying editorial.*

4. Liu J, Ye X, Ji D, Zhou X, Qiu C, Liu W, et al. Diesel exhaust inhalation exposure induces pulmonary arterial hypertension in mice. Environ Pollut. 2018;237:747-55.

5. Park SH, Chen WC, Esmaeil N, Lucas B, Marsh LM, Reibman J, et al. Interleukin 13- and interleukin 17A-induced pulmonary hypertension phenotype due to inhalation of antigen and fine particles from air pollution. Pulm Circ. 2014;4(4):654-68.

6. Rich DQ, Freudenberger RS, Ohman-Strickland P, Cho Y, Kipen HM. Right heart pressure increases after acute increases in ambient particulate concentration. Environ Health Perspect. 2008;116(9):1167-71. *Panel study of patients with heart failure. Acute increase in PA pressure with PM2.5.*

7. Wauters A, Vicenzi M, De Becker B, Riga JP, Esmaeilzadeh F, Faoro V, et al. At high cardiac output, diesel exhaust exposure increases pulmonary vascular resistance and decreases distensibility of pulmonary resistive vessels. Am J Physiol Heart Circ Physiol. 2015;309(12):H2137-44. Human clinical study of diesel exhaust using echocardiography, with exercise testing and hypoxia.

3. Page 5-6, line 5. "Activation of sensory nerves in the respiratory tract can trigger local reflex responses resulting in lung irritation." "Lung irritation" lacks specificity, and may have different meanings for different people. The more accurate term is "airway irritant response" which refers to this whole sensory-mediated process, not just its result. Suggest replacing lung irritation in this sentence with "lung function decrements and airway inflammation". Elsewhere would replace "lung irritation" with "airway irritant response".
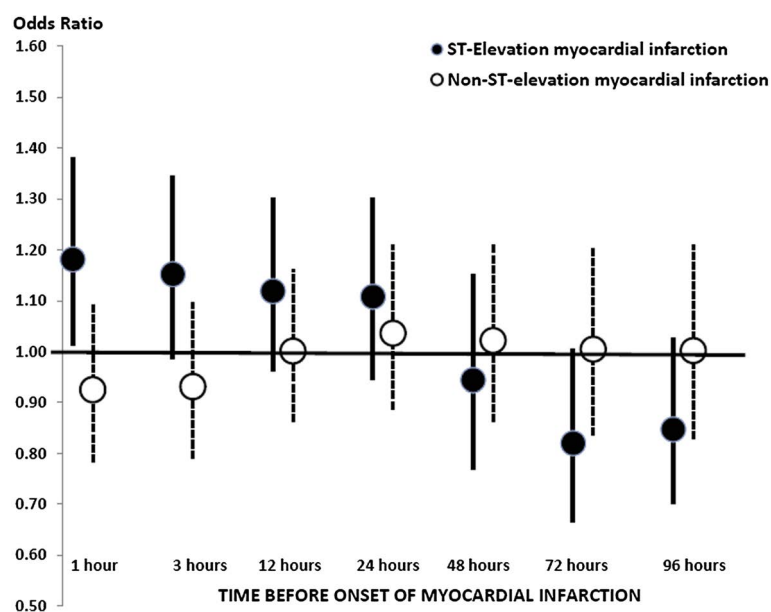
4. Page 6-14, line 18. "There were generally consistent results across recent studies looking specifically at MI, and registry studies, which are likely to reduce outcome misclassification, report evidence of positive associations with MI subtypes."

This sentence seems somewhat at odds with the first paragraph on this page, which indicates inconsistencies, especially in the European studies. The interpretation should be further clarified, with justification for disregarding the negative European studies.

5. Chapter 6, Figure 6-1. The potentially important role for NO and endothelins in PM effects on vascular function are not adequately covered in the figures or the mechanistic paragraphs. There is evidence that PM may act through both, with reduction in NO bioavailability and increased production of endothelins by a variety of cells. There is also the possibility that translocated particles or their components may directly injure the vascular endothelium.

6. Figure 6-2, page 6-13. The depiction of the associations with MI in the Gardner study appear to be incorrect. The ISA Figure shows minimal associations with very broad CIs, but the figure (below) and data from paper show a significant effect on STEMI with a 1 hr lag.

7. Section 6.2.6 is "Cardiac Electrophysiology and Arrhythmia", and section 6.2.11 is "Heart Rate (HR) and Heart Rate Variability (HRV)". These should be combined, retaining the electrophysiology and arrhythmia heading. Some would argue that cardiac electrophysiology encompasses HRV. They are all measured using ECG. Having widely separated sections is confusing. Similar for sections 6.1.4 and 6.1.10.

Page 6-196, line 31. In the description of the Wilker 2014 study, the ISA states, "Only hyperemic flow velocity was additionally associated with PM2.5 [-1.80 % change (95%CI: -3.45, -0.15)] These effects are relatively large given that normal ranges are between 5-10% (Järhult et al., 2009)."

The second part of this sentence is incorrect. The normal range for FMD% is 5-10, not for hyperemic flow velocity, which is expressed in the units of cm/s, not %. Second, it is not clear where the "-1.80% change" comes from. The Wilker 2014 abstract states: "An inter-quartile range difference in PM2.5 (1.99 mu g/m(3)) was associated with -0.16% (95% confidence interval [CI] -0.27%, -0.05%) lower flow-mediated dilation% and -0.72 (95% CI -1.38, -0.06) cm/s lower hyperemic flow velocity%."

Minor/Editorial Comments
P-18. List of definitions of causal relationships duplicates Table P-2, page P-12, could just reference that table. These 5 levels of causality are again listed on page ES-7. redundant.

Table 5-30, page 5-232. "Mild to moderate individuals with asthma" should be "Individuals with mild to moderate asthma".

Page ES-13, footnote 31. "Whole PM exposures" is a poor terminology for "exposures that contain both PM and gaseous pollutants". "Whole atmosphere" may be more descriptive.

There are several places in the ISA where "Section 0" is referenced. Presumably this is a placeholder that needs to be corrected/completed. Examples: Page 5-5, line 13; page 5-8, line 13; Table 5-49, page 5-310.

Variable Figure quality. See Fig. 5-4, page 5-25.

Some CHE studies have failed to find BP elevations.

Page 167, line 3. The study being referenced is missing here. Judging from the text, it seems to be Aaron et al., 2016.

Page 6-16, line 20. Provide the reference referred to here.

Section 6.1.5, Page 6-41. There should be a concluding sentence to the first paragraph indicating that there are new studies since the 2009 review.

Page 6-56, line 2. The reference should be "Gong Jr. et al.".

Page 6-56, line 31. "…although it was noted that assessing changes in blood pressure in the HF group is difficult given beta-blocker use." Assessing the changes is not difficult; the problem is that beta-blocker use may blunt the effect.

Page 6-60, line 18. "…animal toxicological studies that provide biological plausibility for these associations by demonstrating changes in hemodynamics (e.g., an increase in coagulation

factors) following short-term PM2.5 exposure…" "Hemodynamics" refers to blood circulation, including blood flow, pressure, and rheology, not levels of coagulation factors or other soluble blood components.

Page 6-79, line 14. HFn needs to be defined.

Page 6-91, line 5. "…increase the potential for an embolism." The major concern is the increased potential for thrombus formation obstructing blood flow, especially in diseased coronary arteries. That is the most common cause of acute MI.

Page 6-148, line 11. This sentence is incomplete and unclear.

Long-term CV effects sections, problems with missing words, incomplete sentences, grammatical errors. Document requires editorial review.

Page 6-176, line 3. "A study of newborns in Massachusetts found elevated SBP with higher PM2.5 averages over the 30-, but not 60- or 90-day periods before birth (van Rossem et al., 2015) while trimester specific associations between PM2.5 and increased SBP increased but confidence intervals were wide…" This sentence is run-on and needs clarification. The words "30 hours after birth" should be inserted after "elevated SBP".

Section 6.2.8, peripheral vascular disease refers to disease in the peripheral arterial system, but the discussion here is limited to venous thromboembolism. May be best not to lump PVD with venous TE disease; they have different etiologies, pathophysiology, and treatments.

Dr. Sabine Lange

General note for these comments: a reference list can be found at the bottom of this document for those studies that are not referenced in the PM ISA.

General Comments

Literature Review and Study Quality:
- EPA needs to provide specific details about how studies were chosen for this review. In the absence of this information it is very difficult to determine whether a comprehensive, unbiased review has been completed.
- The EPA states that other recent studies are not the focus of this evaluation because they did not address uncertainties and limitations in the evidence previously identified. So only studies that address uncertainties are included – does that mean only those with better methods, that consider copollutants and other confounders, etc were included? Looking at the listed studies, that doesn't seem to be the case. Which studies weren't included? Referencing 14000 studies in the HERO database is not helpful to see which studies were not discussed in the ISA.
- Similarly, a detailed explanation of how study quality criteria was applied to the reviewed studies should be described. These study quality criteria also need to be included in the discussion of the study results in the health effects sections, so that appropriate conclusions can be drawn that consider how the study was conducted.
- The quality of measured outcomes needs to be discussed in the health effects chapters, because not all measured outcomes are equally reliable.
- Why are Asian studies included? These studies are in environments with PM concentrations much higher than in the US, and with a much different combination of constituents.
- "Uncertainties" should be a column in each of the data tables, laying out the potential concerns with each study. This makes it easy for reviewers to see what gaps still need to be filled in the literature and helps them appraise whether those gaps may be substantial.
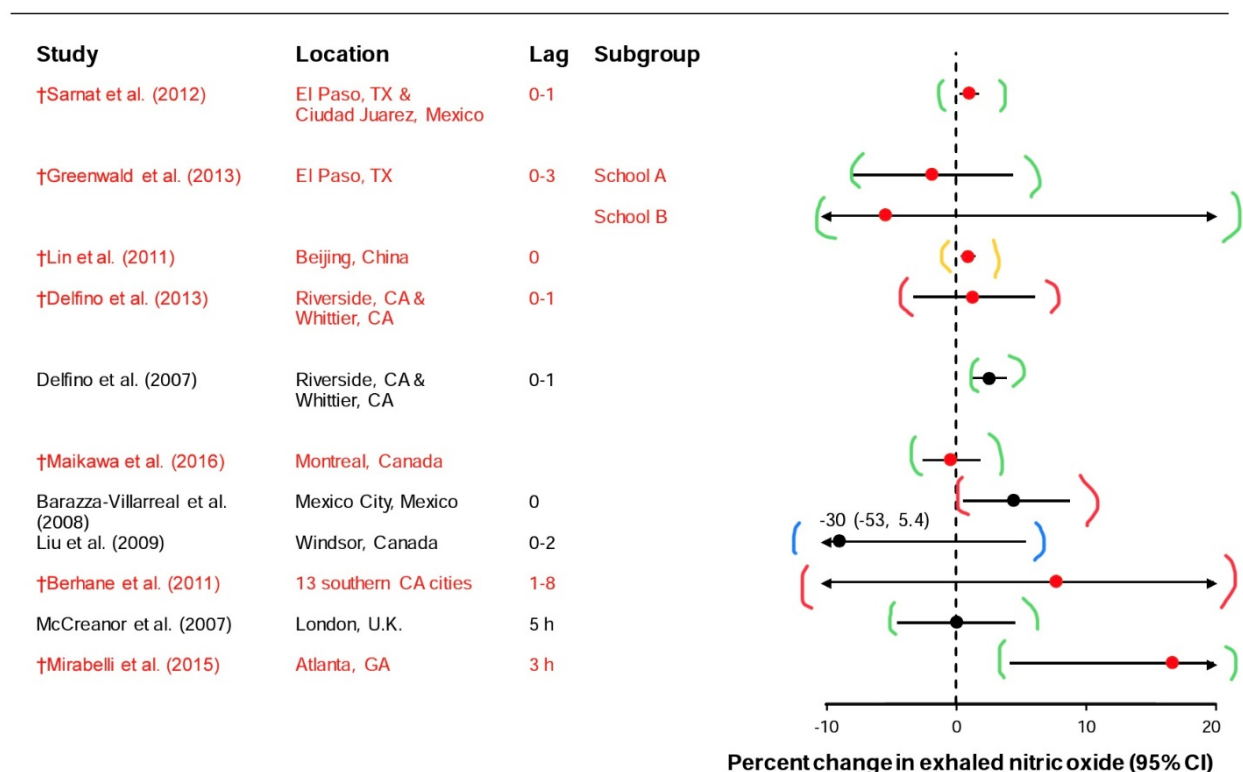
Evidence Integration:
- There should be a discussion at the beginning of this document about how the EPA addresses the combination of positive and null or negative studies. For example, in the biological plausibility sections, is a single paper showing some effect on an end-point of interest enough to conclude that the pathway is plausible? What if there are a lot of studies not showing that effect?
- EPA should hypothesis-test its conclusions. For example, if PM2.5 concentrations are causally related to total mortality, you might expect that PM2.5 only actually impacts

some subset of mortality types. If this is the case, then that mortality should have a larger more significant association with PM2.5 than total mortality. Similarly, if all these effects are occurring at the same concentrations, then you would expect the milder effects to be more common and more likely to show an association than the more serious effects (e.g. HA or mortality). You would also expect that long-term effects would occur at lower concentrations and would show stronger effects than short-term, because of the cumulative exposure (assuming that PM2.5 has an impact via cumulative exposure). In addition, EPA notes that increasing variability in exposure or outcome estimates can bias the health effect estimate towards the mean. Therefore, one would hypothesize that studies with better exposure or outcome measures would have higher, more precise estimates than studies with poorer exposure or outcome estimates. I completed a simple analysis of this type of hypothesis testing using data in several of the presented forest plots:

- o Figure 1 – this figure is a copy of Figure 5-5 from this ISA (associations between short-term PM2.5 exposures and exhaled nitric oxide in asthmatics), with marks around those effect estimates with more precise (green) or less precise (red) estimates of exposure; or with the highest (yellow) or lowest (blue) PM2.5 concentrations. No clear patterns are discernible demonstrating higher effect estimates with more precise exposure estimates or with higher PM2.5 concentrations.
- o Figure 2 - this figure is a copy of Figure 5-8 from this ISA (associations between short-term PM2.5 exposures and respiratory-related HA and ED visits), with marks around those effect estimates with more precise (green) or less precise (red) estimates of exposure. The effect estimates generated with more precise exposure estimates tend to be lower, but more precise, than those with less precise exposure estimates.
- o Figure 3 – this figure is a copy of Figure 11-1 from this ISA (associations between short-term PM2.5 exposures and all-cause mortality), with marks around those effect estimates with more precise (green) or less precise (red) estimates of exposure; or with the highest (yellow) or lowest (blue) PM2.5 concentrations. Concentration does not seem to impact the association. Mortality associated with studies using more precise effect estimates shows generally higher, although not more precise, risks for health effects.
- o Figure 4 – this figure shows the health effect estimates from forest plots in the short-term PM2.5 and respiratory effects section, with the range of effects representing the range of central estimates from each study. This does not show a clear pattern of increasing risk of health effects with decreasing effect severity.

- Noting whether a change in a biomarker or a subclinical effect in a pathway is adverse or is a substantial change (in terms of disease states) would be helpful for distinguishing effects. For example, what is the significance of the change in glomerular filtration rate associated with long-term PM2.5 concentrations (pg 6-180)?
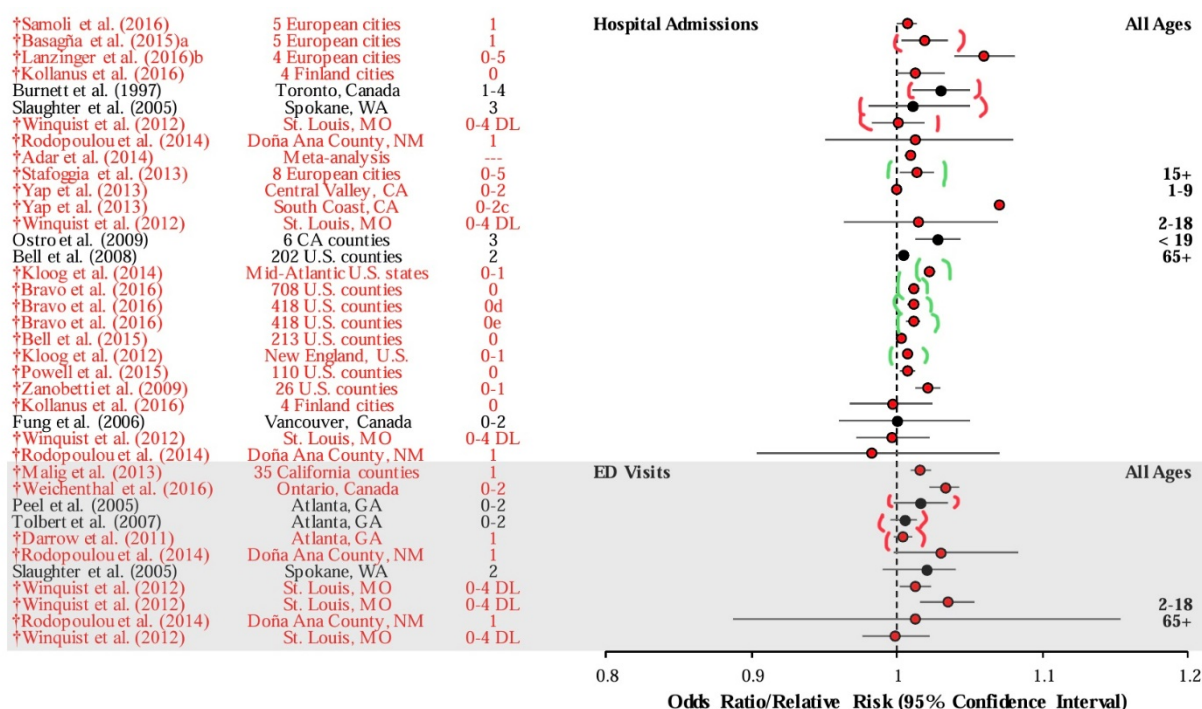
CI = confidence interval.

Note: Studies in red with a dagger are recent studies. Studies in black were included in the 2009 PM ISA. Effect estimates are standardized to a 10 µg/m³ increase in 24-hour average $PM_{2.5}$. Lag times reported in days. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-5   Summary of associations between short-term PM2.5 exposures and exhaled nitric oxide in populations with asthma.

Figure 1. Copy of Figure 5-5 from this ISA (associations between short-term PM2.5 exposures and exhaled nitric oxide in asthmatics), with marks around those effect estimates with more precise (green) or less precise (red) estimates of exposure; or with the highest (yellow) or lowest (blue) PM2.5 concentrations.
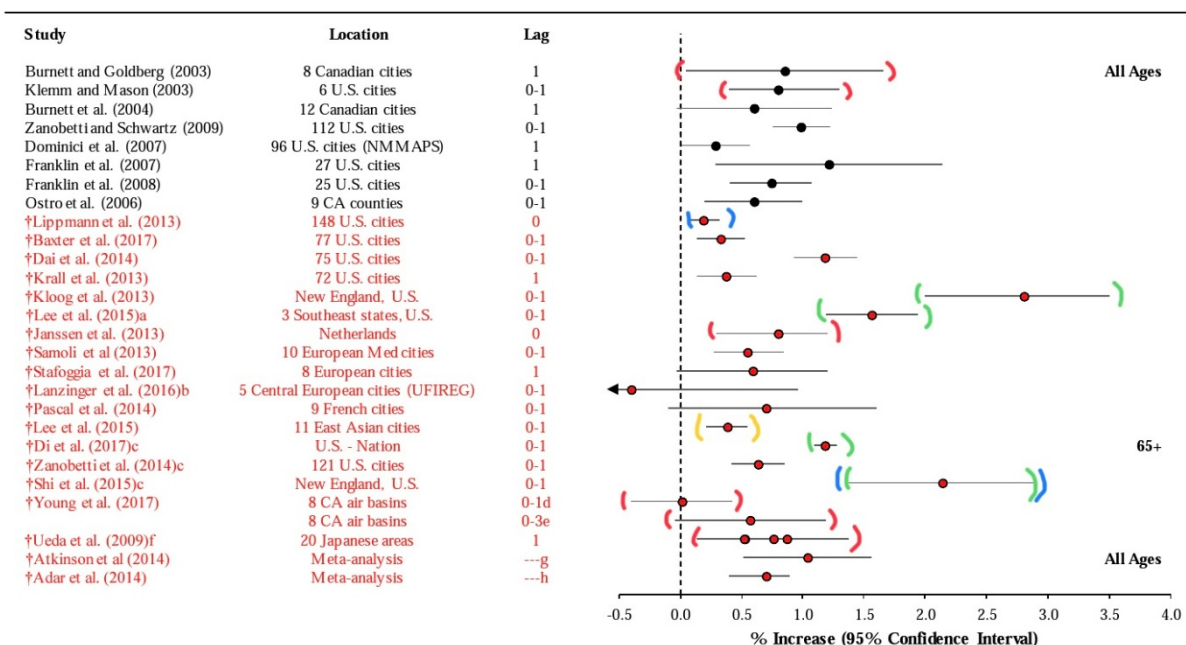
DL = distributed lag.

Note: †Studies published since the 2009 PM ISA. Black text: U.S. and Canadian studies included in the 2009 PM ISA. a = five European cities as part of the MED-PARTICLES project; b = only four of the five cities had $PM_{2.5}$ data; c = quantitative data for confidence intervals not reported, but above the null; d = monitoring data result; e = downscaler CMAQ, only counties and days with monitoring data. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-8   Summary of associations from studies of short-term PM2.5 exposure and respiratory-related hospital admission and emergency department (ED) visits for a 10 µg/m³ increase in 24-hour average PM2.5 concentrations

Figure 2. Copy of Figure 5-8 from this ISA (associations between short-term PM2.5 exposures and respiratory-related HA and ED visits), with marks around those effect estimates with more precise (green) or less precise (red) estimates of exposure.

NMMAPS = National Morbidity, Mortality, and Air Pollution Study; UFIREG = Ultrafine Particles—an evidence based contribution to the development of regional and European environmental and health policy.

[a]Results are from modeled $PM_{2.5}$ analysis, analysis focusing on measured $PM_{2.5}$ reported 1.21% (95% CI: 0.94, 1.47).

[b]Only four of the five cities measured $PM_{2.5}$.

[c]Shi et al. (2015) and Zanobetti et al. (2014b) only had data for all-cause mortality including accidental mortalities.

[d]Main model used in Young et al. (2017) included current and average of 3 previous days daily maximum temperature, daily minimum temperature, and maximum daily relative humidity.

[e]Sensitivity analysis in Young et al. (2017) focusing on only the San Fransisco Bay air basin, dropping out the maximum daily relative humidity term, where the shortest duration of lag days examined was 0−3 days.

[f]Ueda et al. (2009) presented results for three different modeling approaches, which are presented here: GAM, GLM, and case-crossover.

[g]Atkinson et al. (2014) primarily focused on single-day lag results.

[h]Adar et al. (2014) focused on single-day lag results, specifically lag 0, 1, or 2.

Note: †Studies published since the 2009 PM ISA. Black circles = U.S. and Canadian multicity studies evaluated in the 2004 PM AQCD and 2009 PM ISA. Red circles = Multicity studies and meta-analyses published since the completion of the 2009 PM ISA.

Corresponding quantitative results are reported in the Supplemental Material for this chapter, see (U.S. EPA, 2018a).

Figure 11-1   Summary of associations between short-term PM₂.₅ exposure and

Figure 3. Copy of Figure 11-1 from this ISA (associations between short-term PM2.5 exposures and all-cause mortality), with marks around those effect estimates with more precise (green) or less precise (red) estimates of exposure; or with the highest (yellow) or lowest (blue) PM2.5 concentrations.

Figure 4. Health effect estimates from forest plots in the short-term PM2.5 and respiratory effects section, with the range of effects representing the range of central estimates from each study.

Confounding:
- EPA should specifically look at studies that investigate confounding by known other causes of the effects of interest, such as allergens for asthma.
- This document needs more discussion in the epidemiology sections about confounders considered in the different studies and the evidence of their impact on associations.
- EPA states throughout this document that you can't reliably do a copollutant analysis if the copollutant is well correlated with the primary pollutant. But it is the correlation that makes the copollutant a potential confounder (if they aren't correlated, then it can't be a confounder, by definition). I see the problem with determining the difference between the two (whichever is measured more precisely will have the effect attributed to it) but that seems like something to directly address and develop an answer for.
- The incidence of many diseases (including cardiovascular disease, lung cancer, and asthma) have genetic components. In addition, it is not unusual for families to live in the same city or neighborhood. Therefore, family history is a potential confounder for PM effects (because it may be related to both the exposure and the effect, while not being a part of the possible causal pathway) that the EPA should consider when looking at incidence datasets.

Measurement Error, Statistics, and Concentration-Response:
- Measurement error and variability in epidemiology studies linearizes a non-linear relationship, and supra-linearizes a linear relationship (Rhomberg et al., 2011). It can also obscure a threshold. Therefore, should linear C-R curves be used as evidence that a non-linear C-R curve is actually present? I discuss this point more in my comments on the exposure chapter. Why aren't the animal and human studies used to determine a likely threshold – there is quite a lot of data for this.
- Is there an association between the likelihood for a positive and statistically significant result and sample size? Maybe there are no/few associations with the CVD subtypes because they have smaller sample sizes? This would suggest that the effects aren't mediated by actual health impacts of PM, but rather by n.
- Concentration needs to be considered whenever a result is discussed. For example, EPA states that mortality evidence provides coherence for a continuum of effects, without ever considering the concentrations at which these effects occur, or the proportions of the population (both of which could provide plausibility that mortality is occurring). Similarly, concentration plays a part in biological plausibility – is it plausible, based on what we know happens at low concentrations, that an extreme endpoint such as mortality occurs?

Editorial Comments:
- Most of the figures are hard to read, because they are low resolution.
- There is often reference made to Section 0 – there is no section 0.
- Most of the chapters require some copy-editing, particularly chapters 4 and 9.

- Much of the verbiage in the biological plausibility sections is recycled from one section to another – if the pathways are the same, these sections should be consolidated. Also, all the biological plausibility sections state that their intention is to show "how" PM causes the health effect. Why is "how" in quotation marks? This makes it sound like EPA doesn't take this important consideration seriously.
- The tables should specify what type of effect estimate was generated for a particular study (e.g. OR, HR, RR, % increase, etc).
- This document needs a list of figures and tables.
- At the beginning of every subsection on a particular health effect there should be a summary of EPA's conclusions about that health effect based on the new data. As it stands, some of them have these summaries, and others do not.
- What is the pattern for studies listed in the tables? E.g. studies in Tale 5-1 aren't alphabetical, by year, or by age, or by exposure type. These should be arranged in some way to make a particular study easier for the reader to find, or easier for patterns to be discerned.
- Different chapters have inconsistent organization – CNS has biomarkers of effects first, then diseases, where as the opposite is true with respiratory and CVD. The organization should be consistent between chapters.
- When including monitoring information in tables in this ISA, there should be inclusion of information about the monitoring sample schedule (e.g. 1 in 3-day, 1 in 6-day, a combination) – this can impact the information that can be gleaned from the study, and potentially the exposure measurement error. Similarly, any data interpolation that is done in a study (particularly the long-term) to estimate PM2.5 concentrations should be included in the tables. Also, the model fit if it was presented by the authors (and a note if the model fit was not presented by the authors).
- EPA should not present negative associations that aren't statistically significant as "near null" (e.g. pg 11-72), and positive associations that aren't statistically significant as "positive".
- In general, which estimate is chosen to present in the graphs, if there are multiple estimates presented in a study?

Chapter 3: Exposure to Ambient Particulate Matter

- There is very little discussion of the personal-exposure measurement literature, including some key systematic reviews published in 2010 (Avery et al., 2010a, 2010b) that described the variability in personal-ambient relationships, and stated that "The wide range in estimated correlations between personal and ambient PM2.5, as well as the associations with participant, study and environment characteristics, suggest that the potential for exposure misclassification can be substantial." This should be further discussed in this document and used to better inform interpretation of studies that assume a relationship between ambient and personal PM2.5 concentrations. The systematic review guidelines for TSCA lists study quality criteria for epidemiology studies (amongst

others). They state as a criterion for deeming a study unacceptable (and therefore for removal from the review) "There is evidence of substantial exposure misclassification that would significantly alter results." This needs to be seriously considered for studies that use ambient monitors as surrogates for personal exposure (US EPA, 2018).

- From Rhomberg 2011: "Overall, because of the prevalence of exposure measurement error in epidemiology data and lack of reliable error-mitigating techniques, conclusions about the linearity of the exposure-response curve must be examined carefully and treated with some skepticism."
    - o "Lipfert and Wyzga (1996 found that for a true PM10 threshold of up to 150 µg/m3, an underlying "hockey-stick" risk model would appear consistent with linear (no-threshold) models in the presence of independent variable error."
        - ▪ From Lipfert and Wyzga: "If the variables that we are forced to work with (from fixed ambient monitors) already contain a lot of exposure error, no amount of analysis of this type can provide a remedy since the error cannot be removed. In such situations (which may include most of the PM studies), even sophisticated statistical analysis cannot impart real meaning to the data." (Lipfert and Wyzga, 1996)
    - o For Watt (1995), "Using the same data and parameters from Lioy et al., (1990) as Lipfert and Wyzga (1996) but a slightly different computational approach in which individual exposures were assumed to be lognormally distributed around the central/ambient exposure, they also showed that error can mask a true threshold function." (Lioy et al., 1990; Watt et al., 1995)
    - o Description of results from Brauer 2002: "From both sets of figures, it is evident that when surrogate measures (ambient concentrations) are not highly correlated with personal exposures, a threshold can be masked at the population level even if there is a clear, common threshold at the individual level (individual risk function). Furthermore, even if the threshold is not completely masked, it is likely to be biased." (Brauer et al., 2002)
- For the general conclusion that exposure measurement error biases towards the null, evidence suggests that this is only true if: the following assumptions hold: 1) the concentration-response is linear (Fuller, 1987); 2) the measured concentrations are a good surrogate for ambient concentrations (not a valid assumption for PM, as noted above); 3) it is a single-pollutant model; and 4) the differences between measured concentrations and personal concentrations are constant (Zeger 2000). If any of these assumptions are false, then the estimated effect of PM on health could either be an under-estimate of the true effect, or it could reveal an effect that is not due to ozone concentrations.

Methodological Considerations:
- The conclusions of Pope 2009 and Zanobetti & Schwartz 2009 are cited, arguing that ambient monitors should continue to be used as exposure surrogates. One of these arguments is "The ambient monitor approach is the least data intensive approach among all exposure concentration estimation methods because it only requires data from a single

monitor to represent exposures to a large area (on the order of 100 km2)." Are the authors and the EPA suggesting that one monitor per square kilometer is adequate to capture exposure estimates for all of the individuals in that area? This is completely inconsistent with the personal exposure-ambient correlations, which show great variability in personal-ambient correlations, even using ambient monitors that are much closer than 100 km2 (Avery 2010a, b).

Exposure Assessment and Interpretation of Epidemiologic Study Results:

- EPA states that "If this occurs, the health effect related to PM exposure would be underestimated or potentially not detected. Positive correlation between PM and the copollutant and between the exposure measurement errors of PM and the copollutant can add more negative bias to the PM health effect estimate. Spatial variability of concentration differs among the particle size spectrum, and this may cause more exposure measurement error in PM10−2.5 or UFP compared with PM2.5 (Section 3.4.2.2). Hence, if PM2.5 is measured with less error than copollutants, it is likely that the effect will be attributed to PM2.5". This means that in copollutant models whichever pollutant is measure with the least error is most likely to be ascribed the positive effect. This makes interpreting copollutant models quite tricky and requires considerations of exposure measurement error for each component.
- Mcguinn 2017 shows that there is no difference in health effects estimates or reduction in CIs with different (presumably better) exposure estimates.

Chapter 4: Dosimetry of Particulate Matter

- This chapter provides very useful and up-to-date information about PM dosimetry in humans and model organisms. This information is crucial for interpreting doses caused by PM exposure, and should be an integral part of the interpretation of health effects studies in Chapters 5-11. One way to make this dosimetry more interpretable in the health effects chapters would be to include the exposure concentrations at which different patterns were observed. For example, the Miller 2017 study exposed people to particle numbers that are about 1000-times higher than ambient (compare 4.15 x 10E6/cm3 of ~4 nm particles, with Stanier 2004 study measuring 5.6 x 10E3 particles/cm3 for 3-10 nm particles cited in Ch 2 of the ISA on pg 2-32).
- The summary for this section captures the relevant conclusions from this chapter. However, the sentence "New dosimetric information shows that PM10 overestimates the size of particles likely to enter the human lung." Is somewhat confusing and could be reworded. I recommend using wording based on the summary in Chapter 1: PM10 uses a 50% cut-point at 10 μm, which provides a conservative (protective) overestimate of particles that reach the thoracic compartment of the lung.
- In general, this chapter needs to be copy-edited for grammar, punctuation, etc.

Structure and Function of the Respiratory Tract:
- To streamline this chapter so that it only includes necessary information, the paragraph reviewing the history of scientific views on post-natal alveolar development could be removed.

Ventilation Distribution:
- This section discusses ventilation distribution in dogs and horses, including pregnant Shetland ponies, and then concludes: "Thus, the position in which rats are exposed may influence the regional delivery and deposition of inhaled aerosols." Extrapolation of ventilation distribution to rats should probably be restricted to data that is more similar to rats (dogs and horses may be quite different), and if these species are relevant to rats, that should be explained.

Thoracic and Respirable Particles:
- I appreciate the inclusion of the information that PM10 was chosen as a cutpoint to over-represent the true penetration of particles into the thoracic region; and that penetration of 1 um particles into the human lower RT is more affected by route of breathing than by age, sex, activity level, or breathing pattern. This is very helpful for interpretation of human health effect studies and for assessment of at-risk populations.
- The discussion of translocation of insoluble versus soluble components provides good information. A great add-on to this would be providing some information about how big a contribution is made by soluble particles to total particles, because these particles could have a more direct or obvious linkage to the systemic effects than insoluble particle translocation (which occurs at a very low frequency).

Deposition Patterns:
- This section notes that inertial impaction at carinal ridges can result in concentrations at those locations that are hundreds to thousands of times higher. There may be very local responses at these sites of deposition that aren't captured by whole-lung washes. Would a reaction at these small sites be enough to mediate the health effects seen in toxicology and epidemiology studies?

Factors Modulating Deposition:
- Physical Activity - The last paragraph on page 4-26 provides important information about the impact of exercise on lung deposition of different sized particles. The clarity of this information summary would be improved by making a clear distinction between lung deposition fraction and total lung deposition. It seems that while lung deposition fraction may not change during exercise, because the individuals are breathing more air, more total particles are deposited in the lungs.

Particle Clearance:
- Interspecies clearance and retention – The information about the differences in particle clearance between animals and humans is very useful for the extrapolation of health effect results between species. It would be helpful if this section also included information about what concentrations and dose-rates in rats cause the inhibition of mucocilliary clearance, because that would provide information about what effects in rats may be more or less relevant to humans.

Particle Translocation:
- This section provides information that is used by the EPA to support biological plausibility in further chapters of this ISA. With this in mind there are several points that are worth emphasizing (perhaps summarizing at the beginning of this chapter) that will help readers apply this information to potential pathways of effect:
    - Translocation of particles < 200 nm may occur along the axon to the olfactory bulb may occur, although there is little data for this in humans. Because of a reduction in the foramina area in humans with age, there may be a decrease in this pathway.
    - Translocation to the olfactory has been demonstrated in animals with Mn from welding fumes. However, other poorly soluble metals in the fumes did not translocate to the olfactory bulb, suggesting that translocation may be component specific, or is due to soluble particles.
    - It has been difficult to determine how much translocation outside of the respiratory tract is caused by movement of insoluble particles, versus movement of soluble particle components. Because this translocation of particles to the blood and nervous system may contribute to health effects, it would be very valuable if the EPA provided some information about what fraction of particles are soluble, and perhaps what types of soluble components could cause certain types of health effects.
    - While olfactory particle translocation may happen, the human data is quite uncertain (the human autopsy studies published in 2010 and 2013 by Calderón-Garcidueñas et al. Do not provide definitive evidence because of problems with proper controls and determining the source of the UFPs found in brain tissue). However, even if there is translocation it is likely to be a very tiny fraction of particles, as estimated by Garcia et al. 2015, with only 0.001% of 20 nm particles being deposited on the human olfactory mucosa.
    - From Miller et al. 2017, about 0.03% of gold nanoparticles seem to have translocated from the respiratory tract to the blood in humans.
- In reference to the note made by EPA on page 4-59 that the "absolute numbers of particles reaching the olfactory bulb over time can be considerable (Figure 4-7)." More data should be provided to support this conclusion. Figure 4-7 provides the dose-rate of UFPs to the olfactory epithelium, which doesn't provide much explanation about the

absolute number of particles reaching the olfactory bulb, or whether it reaches a threshold that would be labeled "considerable".

- Many studies test the translocation of particles into the blood or olfactory apparatus using a label, typically a radio label. However, some of the label may be attached to a soluble subset of the tested chemical, causing a signal that may not be due to the insoluble particle. Therefore, when discussing these types of studies, it would be of value to the reader if EPA explicitly discussed that study's control for solubility, and whether the signal from the non-respiratory tissues was shown to be particle-bound (e.g. the discussion of the Geiser et al. (2005) results on page 4-59). The information provided can be similar to how EPA addressed the 99mTc-labeled particles discussed on page 4-60.

- Because Miller et al. 2017 is a central paper in this analysis, a discussion of solubility and potential ingestion of the gold particles should be provided. There should also be consideration of the doses used in Miller 2017 compared to ambient concentrations.

- There is a discussion in this chapter about the potential translocation of particles to the fetus. The only animal information available for this is from oral or IV routes of administration. The argument is made that the studies that provide these data are relevant despite the routes of exposure because "add biological plausibility for effects during pregnancy". However, a study does not add to the biological plausibility of an endpoint unless it provides relevant data. Given the tiny fraction of particles that translocated from lungs to blood, the tiny fraction of particles in the blood that reach the fetus (0.004-0.06% of gold NPs, depending on the size), and that the extra-pulmonary distribution of particles from inhalation are different than from IV or oral administration, the route and the dose both seem very relevant. I don't think that the EPA can or should use this data to provide biological plausibility of particle translocation to the fetus at relevant exposures via inhalation in humans.

Factors Modulating Particle Clearance:
- The discussion of particle overload in rats is very helpful for the extrapolation of rat data to humans, particularly for chronic effects of PM exposure. Providing data on what doses or dose-rates this occurs would aid further in applying this information to rat-human extrapolation. Are any of the doses or dose-rates used in the rat studies reviewed in the ISA likely to cause particle overload?

Summary:
- EPA states in the summary that "The fraction of nanoparticles translocating from the peripheral lung into circulation is generally low (less than a fraction of a percent) for larger nanoparticles (18−80 nm) but can approach several percent for extremely small particles (1.4−2.8 nm)." EPA should note here that while several percent of extremely small particles may translocate into the peripheral circulation in rodent studies with exposure by lung installation, there is no evidence that this much translocation occurs with exposure to even very small particles (4-5 nm) in humans.

- Similarly, when discussing results showing fetal translocation of particles, EPA should state that this was using oral or IV particle administration.

Chapter 5: Respiratory Effects

Short-Term Effects of PM2.5

Biological Plausibility:
- In this discussion of biological plausibility, the EPA does a good job of laying out the potential paths that particles may take to influence the respiratory system. In that summary EPA states that "Immune system responses due to the presence of particles in the interstitial space may contribute to respiratory health effects." What is the impact in the respiratory tract of particle translocation to the interstitial space and then movement to the lymph nodes? This is a method of removal, but is there direct evidence of its adversity? If particles activate the immune response in the lymph nodes, this could be added to the biological plausibility summary.
- The beginning of the biological plausibility pathway for all PM-induced health effects in this ISA is respiratory tract inflammation, oxidative stress, and injury. In this section EPA states that strong evidence for these effects is provided by human and animal studies. However, the human studies, which have exposed individuals at higher-than-ambient concentrations with exercise (healthy as well as vulnerable populations) show very little evidence for this (data summarized in the following bullet points).
- Inflammation in human controlled exposure studies of fine CAPs:
  - Ghio 2003, Gong 2003, Gong 2004, and Huang 2012 did not show an increase in inflammatory cell infiltration or soluble inflammatory mediators after exposure to fine CAPS from different locations, and Gong 2005 & Holgate 2003 did not show an increase in infiltration of immune cells. These studies were conducted on people who were healthy, asthmatic, elderly, or had COPD, and at concentrations up to 178 ug/m3. (Ghio et al., 2003; Holgate et al., 2003)
  - Ghio 2000 did show an increase in neutrophil infiltration with PM2.5 exposure, but no change in soluble inflammatory mediators. Urch 2010 showed an increase in soluble IL-6 at 3 hours after PM2.5 exposure in people exposed to concentrations higher than 100 ug/m3, but no change in inflammatory cell infiltration, and no change in soluble inflammatory markers when PM2.5 exposure was combined with 120 ppl ozone exposure.
  - Altogether, the evidence for PM2.5-induced respiratory inflammation in human controlled exposure studies is inconsistent and largely negative.
- Lung injury in human controlled exposure studies of fine CAPs:
  - Ghio 2000 showed a decrease in bronchial total protein, and Gong 2003 and 2005 found a decrease in sputum total or epithelial cells. This is the opposite direction of adversity, with lung damage usually manifesting in an increase in total protein

or cells. Behbod 2013, Gong 2004, Huang 2012, and Urch 2010 showed no increase in pulmonary damage markers with fine CAPs exposure.

- o Altogether these studies show evidence of a lack of pulmonary damage with higher than ambient PM2.5 concentrations in multiple populations.

- Most studies don't measure oxidative stress products with exposure to CAPs, but Mills 2008 (162-190 ug/m3 Edinburgh fine CAPS healthy and CHD elderly people) did show an increase in 8-oxo-pristane in exhaled breath condensate. (Mills et al., 2008)

- Similarly, this section says that there is evidence of lung function changes in humans, but most studies don't show this effect. No adverse pulmonary function effects of exposure to CAPs were shown in Brauner 2007, Ghio 2000, Gong 2003, Gong 2004, Huang 2012, Lay 2001, Sivagangabalan 2011, or Urch 2010, who used exposures up to 206 ug/m3 and in healthy younger and older subjects, and subjects with asthma or COPD. A few studies showed some lung function effects – Gong 2005 observed a decrease in FEF25-75 in healthy older adults with PM2.5 exposure, but not with PM2.5+400 ppb NO2, nor in individuals with COPD. Hazucha 2013 observed a decrease in FEV1 in smokers and ex-smokers. Altogether this is not compelling evidence that PM2.5 causes lung function deficits. How do you interpret the occasional positive study in light of many negative studies? (Bräuner et al., 2007; Lay et al., 2001)

- EPA conjectures that the ANS causes some of the changes, but they should include a discussion about whether the lack of FEV1 responses is consistent with an ANS or irritant response (usually an irritant/neural response in the lung triggers a decrease in FEV1, as with ozone).

- EPA states that PM2.5 caused changes in SaO2, FEV1, and tidal volume in human and animal studies with COPD. However, there was very little response in human studies (some evidence that CAPs cause less responsiveness in COPD people or maybe improvement in CB animals). Saldiva 2002 found less neutrophil density in CB rats with PM2.5 exposure, and Clarke 1999 found increases in TV and PEF (decreases would be adverse).

- Immune responses are cited as occurring subsequent to respiratory tract inflammation and oxidative stress and was blocked by anti-oxidants. However, this evidence comes from Whitekus 2002, a DEP study that only found effects with OVA treatment + 600 ug/m3 DEP and not with 2000 ug/m3 DEP alone. The OVA system is cited as being similar to human asthma, but a few sentences about how they are similar and different, and to what degree the severities are similar would be helpful (e.g. is this like severe asthma, or mild asthma?).

- For the pathway activation of sensory nerves, EPA notes that the previous ISA and this one demonstrated changes in respiratory rate and lung volumes (i.e. rapid shallow breathing). However, the Clarke 1999 paper demonstrated an increase in TV with CAPs in healthy or CB animals, and no increase in breathing rate. There is data that lung irritant responses are mediated by the vagus nerve and the parasympathetic nervous system. However, isn't this the opposite direction from the HRV responses cited in the next chapter? This needs to be addressed.

- EPA notes that Ghelfi 2008 found involvement of the TRP sensory nerve receptors in response to PM2.5 exposure, because TRP antagonists blocked PM2.5-mediated effects. This study lacks important study details (could be addressed with a study quality evaluation), but its data suggests parasympathetic ANS activation. However, Chiarella 2014 is also cited, and this study demonstrates activation of the sympathetic ANS with increased norepinephrine.

Asthma Exacerbations:
- HA & ED Visits – the EPA states on pg 5-7 that there is controlled human exposure and animal tox evidence for short-term PM2.5-induced allergic inflammation. However, I don't think that there is any human evidence for this, and there are no citations offered for this statement. If there is evidence, it should be cited, as well as discussed in the biological plausibility section. For animal toxicological studies, the Harkema 2009 and Wagner 2012 papers did not show evidence of CAPs alone inducing allergic inflammation, and only showed an enhancement of OVA-induced inflammation at higher CAPs concentrations from Detroit (not Grand Rapids).
  - Figure 5-2 – the confidence intervals are not presented for Yap 2013.
  - Most of the ED visit effect estimates are not statistically significant – how does this affect EPA's determinations about the conclusions from this data?
  - There needs to be discussion of other types of confounders besides copollutants, such as the aeroallergens presented in Hebern & Cakmak (2015). EPA states that there is evidence of seasonality, but it isn't clear if this is seasonality, or seasonal heterogeneity.
  - Several of the studies in Figure 5-3 have different years than the corresponding entry in Table 5-1.
- Asthma Respiratory Symptoms and Medication Use – most of the studies presented in Figure 5-4 show positive results, but almost none are statistically significant. This section states that the EPA has increased confidence in the results because recent evidence shows associations with PM2.5 measured outside of children's schools. However, the Spira-Cohen (2011) study showed that personal exposures were not associated with symptoms, and that outside concentrations were not good surrogates of personal exposure.
- Lung Function Changes in Asthmatics – the EPA states that lung function changes in asthmatics were only evaluated in epidemiology studies evaluated this, but Gong 2004 and Urch 2010 (both human controlled exposure studies) investigated effects of CAP exposures in asthmatics and found no effects on lung function. No summary figure or information is provided for the epidemiology studies, making study results difficult to interpret without looking up all of the papers individually. From looking at the studies, it is clear that the Spira-Cohen (2011) results weren't stat sig, and the Delfino (2008) paper only had associations with lag 0 for 1 or 8 hr max and it wasn't clear if the authors made sure that the maximum concentration occurred before the asthma lung function effect. Smargiassi (2014) found no effect of personal PM2.5 exposure on an array of lung

function effects. So again, there is considerable variability in the findings of these studies. Many of the studies summarized in Figure 5-4 are not present in the associated Table 5-2.

- Subclinical Asthmatic Effects – EPA focuses on a relationship with eNO (Figure 5-5). There is an even distribution of negative, null, and positive effect estimates. There are CAPs studies in asthmatics that have shown little or no effect of exposure to PM2.5 on lung function, inflammation, or damage (Gong 2003, Urch 2010). The Harkema (2009) paper does not show independent effects of 600 ug/m3 CAPs on pulmonary endpoints but does show that it can enhance OVA-induced bronchopneumonia. This did not happen with the animals exposed to 356 ug/m3 CAPs (8 Hrs per day for 3 days), demonstrating a threshold of effects. Wagner 2012 also showed that Grand Rapids CAPS at 600 ug/m3 actually diminished OVA-induced effects, showing a constituent-importance, and possibly a counter-intuitive protective effect.

COPD Exacerbation:

- HAs and ED Visits – A new meta-analysis is cited as providing positive (statistically significant) evidence of an association between PM2.5 and COPD exacerbation (Li 2016). Li (2016) conducted a systematic review and meta-analysis of 18 studies from North and South America (1 study), Europe, and Asia (3 studies). The heterogeneity statistic for PM2.5 and COPD HAs was 88%, meaning that these studies shouldn't have been meta-analyzed (should have been picked up on a study quality assessment). The mortality estimates were heavily weighted by the Santiago Chile study, and Taiwan studies weight the HA estimate.
- COPD Lung Function Changes – Ebelt (2006) and Trenga (2007) from the last review are cited as having found lung function effects in people with COPD. Both of these studies only showed positive associations with ambient monitors, and lesser non-significant associations with personal exposure. This isn't consistent with poorer exposure estimates biasing towards the null, or with biological plausibility of PM2.5 exposure causing the lung function effects. Two new American studies show no or inconsistent effects; the only significant effects presented are in studies in Mexico City or Asia. Controlled exposure studies that are cited (Gong 2004 and 2005) are noted as having decr in oxygen saturation in adults with COPD, but no changes in lung function. There were also no symptoms, and no evidence of pulmonary inflammation or damage in those studies.
- Subclinical COPD effects - The only new epi information provided is for Chinese studies. Two panel studies were cited as evidence of changes in eNO associated with PM2.5. One of these, Jansen 2005, showed no stat sig associations with fixed site monitors, and the association with indoor PM2.5 (which will be closer to personal), was null. EPA notes that Gong 2005 found a decrease in columnar epithelial cells with PM2.5 (more pronounced in healthy people than people with COPD). But this was a decrease in *sputum* epithelial cells – an increase in sputum epithelial cells suggests damage, but the authors couldn't explain the decrease in cells.

Respiratory mortality:
- There seems to be inconsistent evidence from new studies that there is an association between short-term exposure to PM2.5 and respiratory mortality: Figure 11-2 presents 7 new effect estimates from the US and Europe with a similar range of magnitude, but variable effects (3 statistically significantly positive, 2 non-statistically significantly positive, 2 non-statistically significantly negative). EPA noted that there was limited coherence with human controlled exposure and animal studies in the previous ISA, and presumably this is still the case.

Policy-Relevant Considerations:
- These are considered haphazardly in the individual sections as well – this section is not a separate component of the other end-points or exposures in this, why is it a separate section here?
- EPA notes that epidemiologic studies often conduct analyses to determine whether the observed effects are due to chance, bias, or confounding. However, there is essentially no discussion of chance in this chapter, despite its inclusion on this list. There is also very little on confounding that is not due to copollutants.
- Copollutant Confounding - EPA does present information from some studies showing that copollutants can attenuate risk estimates (sometimes become not statistically significant, particularly with NO2), but rarely do they change the direction of the association. In the figures the open and closed symbols need to be defined. Sometimes this section refers to a discussion of copollutant confounding in the relevant health effects section, and that section refers to this policy-relevant section (e.g. subclinical asthmatic effects section). The language in this section is confusing.
- Model Specification - EPA notes that degrees of freedom for temporal trends and weather variables mostly don't affect the results, and therefore that there is reduced uncertainty from model mis-specification. However, it seems like there are far more modeling options than just df for temporal trends and lags for weather variables. Two studies (Strickland 2010 and Sarnat 2015) look at the effect estimates for lag -1 day as a control. EPA notes that the results of the base model were similar to those for lag -1 day, but because the associations for lag -1 day were smaller (1.03 compared to 1.05 for lag 0-2; and 1.02 compared to 1.04 for lag 0-2), that potential confounders were adequately controlled in the model. But both show positive results, one borderline stat sig, for a lag -1. If those results were for lag 1 EPA would have considered them to be indicative of a positive association. This type of result needs to be considered when EPA takes any positive result as indicative of an effect. In general, Sarnat 2015 only saw associations between PM2.5 and ED visits for asthma/wheeze, not pneumonia, COPD, general respiratory disease, general CVD, IHD, arrhythmia, or CHD.
- Lag Structure - EPA notes that lag structure can be informative about whether PM2.5 has immediate, delayed, or prolonged effects. However, effects at inconsistent lags can place doubt on the veracity of the results. For example, Strickland 2010 showed early lag effects, and Kim 2012 showed 4-12-day lag effects. In addition, lag 0 is problematic

because it is not entirely clear if the effect occurs before or after the exposure. EPA notes a somewhat delayed lag of 0-5 days for respiratory morbidity, but a shorter lag of 0-2 for respiratory mortality – it seems that the opposite would be true – that more immediate concentrations would lead to less severe effects, while it would take more exposure to cause mortality.

- Season Effects – EPA notes that the 2009 ISA found some associations between PM2.5 and respiratory effects were stronger in the warm months, and for others they were stronger in the colder months. How is this heterogeneity interpreted? It can't all be attributed to sources. It is like EPA has said that they are using these sections to assess chance, bias, and confounding to determine the veracity of conclusions from the epi studies, when in fact they are skipping over those things, and assuming that the epi study results are true and moving on to try to figure out further patterns. Newer data that EPA presents demonstrates seasonal heterogeneity, with no clear pattern. Studies of aeroallergens (e.g. Hebern and Cakmak 2015) suggest that these could be important potential confounders and are a reminder that copollutants aren't the only confounder.

- Temperature – inconsistent results on respiratory mortality and morbidity. What would the EPA expect the effect of temperature (or season) to be on PM2.5-mediated respiratory effects? More effects in the cold season because of burning as a source of heat, during warm season because of interactions with allergens? EPA should generate some mechanism-based hypotheses for these effects, and then see if the data matches. For example, if you think that sulfate is an etiologic factor, then look at places with higher sulfate in certain seasons (even if it is not measured for the study, may have EI data or something like that), and see if that is when the effect is greater. This section is just summarizing data, and then generates a hypothesis afterwards.

- Concentration-Response and Threshold Analyses – EPA presents Figure 5-21 from Silverman and Ito (2010), and states that the authors found that the non-linear model wasn't any better at fitting the data than the linear model. However, Figure 5-21 presents a distinctly non-linear shaped curve. Evidence presented from Gleason 2014, showing positive estimates in the 5th quintile of PM2.5, no association in the 3rd and 4th quintiles, and the largest association in the 2nd quintile suggests a lack of evidence of any association. EPA concludes that there is some evidence for linearity, and some evidence for non-linearity. There is no discussion of MOA or results from experimental studies that would inform this decision.

Long-Term Respiratory Effects of PM2.5

Biological Plausibility:
- It would be helpful if the EPA could clarify how changes in the renin-angiotensin system could impact long-term respiratory function. In addition, since there is only a single study with information on this endpoint, a shorter discussion could be devoted to it.
- EPA states that long-term inhalation of CAPs increased levels of oxidized phospholipids in the BALF, and specific macrophage and T-cell subtypes in lung tissue. This came from

Deiuliis 2012, who exposed C57Bl6 mice from 24-28 weeks to 115 ug/m3 Columbus OH CAPs 6 hrs/day, 5 days per week. They found no histopathological changes or incr in total macrophages, but there was an about 2-fold increase in activated macrophages. There were increases in activated T cells and oxidized phospholipids in the lungs. There was little effect of PM on circulating T cell populations. Few inflammatory cytokines showed increased expression, and the authors suggest more of a TH1 than Th2 response. Kampfrath 2011 exposed C57Bl6 and Balb/c mice to an average of 92.4 ug/m3 fine Columbus Ohio CAPs for 6 hrs/day, 5 days per week for 20 wks. This group showed increased blood monocytes, evidence of systemic oxidative stress, and changes in the microvasculature.

- EPA states that there is evidence of Th2 immunity from Kim 2016a, however the cited Deiuliis 2012 suggested Th1 and not Th2, so the EPA should clarify why the Kim 2016a study provides more definitive evidence of the activated immune pathway. In addition, Kim 2016a used Penh as a marker of airway hyperresponsiveness (AHR), but this is generally acknowledged to be a poor marker for AHR in animals (Bates and Irvin, 2003).
- EPA cites studies showing increased oxidative stress, injury, inflammation, and morphologic changes in the nasal mucosa (Guo 2017 is cited twice). However, the relevance of nasal changes in rats and mice (obligate nasal breathers) to human effects is not clear and should be directly addressed.
- It would generally be useful to have concentrations and exposure conditions provided, with appropriate dosimetric adjustments to allow the reader to understand the comparison to human effects and doses.

Lung Function and Development:
- EPA states that PM2.5 effects on lung function and development are supported by several iterations of the Children's Health Study in California. They note that associations are supported by a multicity cohort in Taiwan, although the concentrations are considerably higher. Since they are reviewing these higher concentration Asian studies, it would be good if EPA noted if the associations were stronger or the effect estimates larger, as one would hypothesize (based on Figure 5-28, this doesn't seem to be the case). EPA states that pre-adolescent effects are uncertain (positive effects in a Chinese cohort, but not in the European PIAMA study). In general, it seems that the only real evidence comes from the CHS cohort, which is just studied over and over again.
- Table 5-19 shows that there are moderate to high correlations with many copollutants, which makes interpretation of the CHS study results problematic.
- EPA notes that they expect to have only low-to-moderate spatial heterogeneity for the CHS study, so that means that there is unlikely to be major exposure measurement error. This statement assumes that spatial heterogeneity is the only source of exposure measurement error.
- There seem to be animal toxicology studies only from Beijing and Sao Paolo looking at developmental effects of PM2.5. They show some evidence of effects, but interpretation is tricky because of the exposure locations.

Development of Asthma:
- Several longitudinal studies look at the relationship between new asthma and PM2.5. Many of them show positive associations, but most are not statistically significant (Gehring 2010 is non-statistically significant when adjusting for study region, and Gehring 2015, Yang 2016, McIntyre 2014 for ever asthma, McConnell 2010, Clarke 2010, and Nishimura 2013 aren't statistically significant). EPA notes that studies generally provide support for an association between asthma prevalence and PM2.5, though not all studies – Fuertes 2013b and Akinbami 2010. Why aren't these last two studies are shown in the summary Figure 5-30?

Long-Term PM10-2.5
- Table 5-30 and 5-31 are the same.

Short-Term Respiratory Effects of UFPs
- Biological Plausibility – For respiratory tract inflammation, Frampton 2004, Frampton 2006, and Gong 2008 didn't show any increase in immune cells or soluble inflammatory mediators after UFP exposure (with very high number concentrations, in the 10^5 to 10^6 range), and Samet 2009 say no immune cell infiltration, and only an increase in IL-8 at 0 hrs after exposure. Altogether this is not convincing of a respiratory tract inflammatory effect. In the inflammatory section when discussing evidence the EPA should be sure to note which species is being discussed (humans, rats, etc). (Frampton et al., 2006, 2004)
- There is a lot of discussion in the biological plausibility section about how UFPs can penetrate more deeply into the lungs, and maybe can translocate into the blood, but at some point in this section the EPA should address why the UFP results show less evidence of health effects than for PM2.5.
- There are few studies for short-term respiratory effects of UFPs, with essentially no statistically significant results for any of the analyzed endpoints (asthma HAs and ED visits, inflammation or pulmonary fxn changes in controlled human exposure studies, COPD exacerbation, respiratory infection, total respiratory HA or ED visits, healthy human controlled exposure studies). EPA should be clearer as to why this data merits a "suggestive" causality determination.
- Respiratory mortality incorrectly references Table 11-9, which is for PM10-2.5, not UFPs – should be Table 11-13.

Long-Term Respiratory Effects of UFPs

- EPA states that a paucity of data prevent the description of biological pathways that may underlie long-term respiratory effects of UFPs, and then they drew a diagram of those pathways (Figure 5-50). Is this a mistake, or was this pathway really drawn based on no data?

- Data present from Tyler 2016, Araujo 2008, Reed 2008, and Tanaka 2013a does not support pulmonary inflammation as a pathway, because there was no pulmonary inflammation observed.
- No association was demonstrated between UFPs and respiratory mortality in Ostro 2015.
- Incorrectly talks about PM10-2.5 in the summary and causal determination.

Chapter 6: Cardiovascular Effects

Short-Term PM2.5 Exposure and Cardiovascular Effects

Biological Plausibility:
- The first pathway starts with respiratory inflammation, leading to systemic inflammation. However, there was poor evidence of respiratory inflammation in CHE studies, and animal toxicology studies only showed respiratory inflammation when coupled with a strong allergen such as OVA, or SO2-damage to induce chronic bronchitis. Where does the systemic inflammation come from, in the absence of respiratory inflammation?
- Evidence for systemic inflammation in CHE studies shows some studies with increasing blood immune cells (neutrophils, monocytes, etc), but the types of cells are inconsistent, and other studies don't show increases. Behbod 2013 – shows increased leukocytes and neutrophils, but links these to endotoxin, not CAPs, and no increase in soluble inflammatory markers. Urch 2010 showed an increase in blood IL-6 at 3 hours after exposure to CAPs >100 ug/m3, but not with CAPs>100 + 120 ppb ozone; Brook 2009 – at 148.5 ug/m3 showed increased WBCs and neutrophils, but not soluble inflammatory mediators; Gong 2004 saw increased basophils in blood at 4 hrs after exposure to 167 ug/m3 in healthy older adults, but not in older adults with COPD. Studies that did not find changes in blood immune cells and/or soluble inflammatory mediators: Bellavia 2013, Devlin 2003 (or one of this group of studies), Gong 2003, Hazucha 2013, Hemmingsen 2015a, Huang 2012. Ghio 2003 saw a decrease in total blood leukocytes. Brauner 2008 saw no change in soluble inflammatory markers.
- Budinger 2011 is cited as evidence that PM induces inflammation in the lung, which increases systemic thrombosis. This group exposed mice to Chicago CAPs at 88.5 ug/m3 for 8 hrs per day for 3 days and saw a 2.5-fold increase in IL-6 mRNA, as well as TNF-alpha. These mice also had a 2.5-fold increase in blood thrombin-Antithrombin complexes and adipose PAI-1. They also intra-tracheally installed 200 ug of CAPs, and saw lung injury, decreases in clotting time (not dependent on PAI-1), and much higher increases in IL-6. This shows that increases in PAI-1 aren't necessary for changes in clotting time, and that the changes in the clotting parameters are not PM (or inflammation) dose-dependent. Unfortunately, the authors did not look at lung injury or clotting time in the inhalation-exposed mice. This evidence does not support that the inflammation in their respiratory tract is related to clotting effects, because when substantially more inflammation was induced (by intratracheal installation instead of inhalation, there was no further increase in blood thrombin-antithrombin complexes).

- EPA also references Xu 2013 to demonstrate an increase in systemic inflammatory mediators (although Xu 2012, discussed in the respiratory section, did not see this increase). Xu 2013 exposed mice to 143.8 ug/m3 Columbus OH CAPs for 6 hrs/day, 5 days per week for 5, 14, or 21 days. Adhesive leukocytes were increased at 14 days only and rolling leukocytes at 21 days only. Serum cytokine MCP-1 was increased at 5 days only, with no change in IL-6, IL-10, IL-12, TNF-alpha, or IFN-gamma. IL-6 expression was increased in epididymal fat at 5 days only. An increase in activated macrophages was seen in bronchial sections (but not BALF) with no change in neutrophils. The authors incorrectly conclude that there is a neutrophilic response. This is not convincing of a systemic inflammatory response.

- EPA state that there are CHE, epidemiology, and animal toxicology studies showing changes in thrombotic measures after PM exposure. The CHE studies they cite are Lucking 2011, Ghio 2000 and 2003, and Gong 2003 (incorrectly labeled as Jr. et al.). Ghio 2000 and 2003 both saw increased fibrinogen, but Gong 2003 saw a decrease in Factor VII, Gong 2004 and Huang 2012 saw no change in clotting factors, and Mills 2008 saw an increase in platelets. Lucking 2011 is a diesel exhaust paper. EPA cites Lucking 2011 to state that these increases in prothrombotic factors can increase thrombosis, but filtering particles out of the diesel exhaust in that study did not decrease the size of ex vivo thrombotic plaques.

- For the animal toxicology studies supporting changes in thrombotic measures, the EPA cites Kodavanti 2005, who studied the total results from 6 one-day CAPs exposures and 7 2-day CAPs exposures. There were no biological effects (pulmonary or systemic) in the SH rats exposed for 4 hrs to 1172-1765 ug/m3 CAPs. Two-day exposures (4 hrs each) to 144-2758 ug/m3 caused variable responses. No breathing parameters were different in the WKY rats, but the SH rats had decreased breathing frequency. The WKY rats had a decrease in total and macrophage cells in BAL, and an increase in neutrophils, but not on the day with the highest concentrations. No BALF changes were observed in the SH rats. There were increases in GGT (a damage marker) and fibrinogen in the SH rats, but not on the days with the highest PM. There was no correlation between any response and the PM mass, but some correlation with metals concentrations. This paper does not provide convincing evidence of PM2.5-induced inflammation or thrombotic effects.

- EPA cites changes in vascular function and blood pressure demonstrated in CHE, epidemiology, and animal studies. For the CHE fine CAPs studies investigating BP:
  - Bellavia 2013 showed increased SBP with exposure to 242 ug/m3 Toronto CAPs; Brook 2009 showed increased DBP (not SBP) with exposure to 148 ug/m3 Toronto CAPs; and Sivagangabalan 2011 showed increased DBP (not SBP) with exposure to 154 ug/m3 Toronto CAPs.
  - No effects on BP were seen with fine CAPs exposure in Brauner 2008, Brook 2002, Devlin 2003, Gong 2003, 2004, or 2005, Hemmingsen 2015a, Huang 2012, or Mills 2008. These studies exposed individuals who were healthy, elderly, overweight, with COPD, asthma, or CHD, to PM2.5 CAPs concentrations up to 207 ug/m3. (Brook et al., 2002)

- o Altogether, these don't appear to provide convincing evidence of an effect of CAPs on BP.
- EPA suggests that one of the pathways of effects of PM2.5 on the CV system is via activation of the sympathetic arm of the autonomic nervous system (ANS). However, this is the opposite arm of the suggested ANS pathway from the respiratory section.
- EPA notes that there can be resulting heart conduction abnormalities from PM2.5 exposure, as evidenced in CHE, epidemiology, and animal tox studies. However, the EPA does not reference or discuss the results from Langrish 2014 who showed with 12,500 hours of ECG recordings that there was no association between PM concentration and arrhythmia in CHE studies. (Langrish et al., 2014)
- One aspect of biological plausibility that doesn't seem to be considered here is that all of these pathways have to be activated in a single person for there to be movement form the initial exposure to the apical event. Therefore, citing one study for one aspect of the pathway, then another study for another part of the pathway does not prove that the whole thing could happen in one person. There are studies that look at many of the steps in a single analysis, and the the total results from these studies should be discussed, not single independent results. For example:
  - o Ghio 2000 and the other studies that published results from this dataset (Devlin 2003, Harder 2001, Holgate 2003) measured respiratory effects, and looked at systemic inflammation, BP effects and HRV. While increased pulmonary neutrophilia was observed, there was no increase in systemic inflammatory markers, and no change in BP or HRV. This study exposed healthy individuals to on average 120 ug/m3 Chapel Hill fine CAPs. (Harder et al., 2001)
  - o Gong 2003 exposed healthy and asthmatic individuals to 141 ug/m3 LA fine CAPs and observed no respiratory or systemic inflammation, and a decrease in heart rate and an increase in the high frequency HRV, both of which are indicative of parasympathetic activation. The lack of pulmonary or systemic inflammation suggests that this is not mediated by inflammation.
  - o Huang 2012 exposed healthy individuals to 90 ug/m3 Chapel Hill fine CAPs and did not observe any signs of pulmonary or systemic inflammation, nor changes in pulmonary function, clotting factors, BP, HR, or HRV.

Ischemic Heart Disease and Myocardial Infarction:
- This section notes a diminishment in concern about exposure measurement error from the last review because of better exposure modeling. However, there is no discussion about concern for copollutant confounding from the last review, although I don't see from the study summaries that the studies looked at copollutant confounding. Has this concern been addressed?
- Section 6.1.2.1 (ED visits and Has) concludes by saying that recent studies "continue to provide evidence for positive associations between short-term PM2.5 exposure and IHD ED visits and HA." However, in the paragraph before it there was discussion of one study with a positive but not statistically significant result (Bell 2015), one with a positive

statistically significant result (Kloog 2014), one with associations only in NYC but not the rest of the state (Hsu 2017), one with associations in 2 of 7 states (Talbot 2014), one with a negative association (Milojevic 2014), and two single city studies with opposite results (Kim 2012, Sarnat 2015). How does this add up to continuing to provide positive estimates? And where is the discussion of copollutant confounding?

- MI studies are even less consistent, although EPA concludes again that there is a generally positive association. Figure 6-2 shows studies on both sides of the "no-effect" line, and the majority aren't statistically significant. "Although not all studies observed positive associations, overall, recent administrative studies continue to provide evidence of a positive association between PM2.5 and MI, particularly for immediate lag periods (see Section 6.2)." What is your criteria for evidence of a positive association? This statement is also not supported by EPA's note that the MI registry-based studies, which have less outcome error than the administrative studies, show even less consistent results. If there is a real association, you would expect that studies with better outcome assessment would show more consistent, cleaner associations.
- Final statement: "Consistent, positive associations across multicity and single-city studies continue to provide strong evidence for the relationship between short-term PM2.5 and IHD that is unlikely to be driven by chance or systematic bias." However, only measurement error was even discussed in this section, although these studies didn't directly assess it. If you don't look for systematic bias (e.g. no discussion of copollutants), then you can't rule it out. Also, there weren't consistent, positive associations, as noted in the previous text, there were many null and negative associations.
- Panel Studies of ST-Segment Depression: Only two new studies, one with attenuated estimates in the copollutant model, and that other that was positive but not stat sig.
- Why aren't the CHE studies discussed here? ST-segment changes have been measured in several studies.

Heart Failure and Impaired Heart Function:
- Two of the studies in Table 6-3, published in 2015, are not marked as being published since the last ISA.
- Although the EPA again concludes that there is consistent positive evidence, similar heterogeneities are observed as were noted in the IHD section – some positive, some null, some negative. No discussion of copollutants or other biases.
- CHE: The EPA cite Vieira 2016 that shows decreased pulse O2 (a surrogate marker of ventricular stroke volume) in CHF patients with exposure to 325 ug/m3 DE for 6 minutes with submaximal exercise, but not when the particles were filtered out. This study is missing important details, like how the subjects were exposed, or when measurements were taken. This is a great example of the importance of study quality criteria.

Cardiac Electrophysiology, Arrhythmia, and Cardiac Arrest:
- This section concludes that there are inconsistent results for arrhythmia Has and ED visits, which is consistent with the data showing positive, negative, and null results.
- EPA notes that there were null results in the 2009 ISA for PM2.5 and out-of-hospital cardiac arrests (OHCA), but that there is positive newer data. It is not clear to me how reliable the classification for OHCA is. There seem to be copollutant models done, but that data is not discussed.
- Associations between PM2.5 and arrhythmia in panel studies was fairly inconclusive in the 2009 ISA, but there are more studies with less severe arrhythmia (e.g. atrial) in this ISA that the EPA considers as showing largely positive associations. As before, when looking at the details they are mostly positive but often not stat sig, and some are null or negative.
- Conclusion for conduction abnormalities: "Although evidence from recent studies is inconclusive, taken together these studies indicate a potential for cardiac depolarization and repolarization disturbances by PM2.5. These disturbances may increase the risk for malignant ventricular arrhythmias that could result in cardiac arrest." I think concluding that there is a "potential for polarization disturbances" is a better, more nuanced conclusion than stating something like "the data is generally positive".
- CHE Studies – EPA cites Gong 2000 and 2003 showing no effect on conduction, but Gong 2004 showing effects only in healthy adults (not COPD), and then Tong 2012, Kusha 2012, and Sivangangabalan 2011 as showing evidence of conduction changes. Not mentioned as showing no effect are Devlin 2003, Huang 2012, and a thorough review by Langrish 2014.
- Summary: "Most studies found at least some indication of conduction abnormalities as measured by ECG." How do you interpret the fact that many found no changes, and that the changes that were found were in different indicators?

Cerebrovascular Disease and Stroke:
- EPA notes that "Older age, female sex, smoking, obesity and prior stroke are known risk factors for stroke and should be considered in epidemiologic analysis." Therefore, these should be explicitly discussed in the following sections.
- Shouldn't there be a discussion in this section about the human and animal studies showing vascular effects of PM?

Blood Pressure and Hypertension:
- EPA notes in their summary that the epidemiological study results are inconsistent, but animal and human studies show some impacts of PM2.5 on blood pressure. I discuss the inconsistent human results for this endpoint in the biological plausibility section.
- HA and ED visit studies, and panel studies for BP, have had mixed and inconsistent results. Quasi-experimental studies generally did not show associations between PM2.5 and BP. However, EPA found that panel studies of older populations, particularly in nursing homes or assisted living facilities showed more consistent associations. This

makes some sense – you would expect older people, or those recovering from cardiac arrests, to be more sensitive. However, there was some variability in the presented studies.

- CHE studies – in the previous review there were inconsistent effects on BP. The EPA suggested then that longer follow up may be required to see changes in BP. However, several of the more recent CHE studies have shown BP changes only during, and not after, exposure. EPA lists some studies that show increases in exposure, and others that do not. Not included in the studies that don't show changes in BP are: Brauner 2008, Brooks 2002, Devlin 2003, Fahkri 2009, Gong 2003, 2004, 2005, Huang 2012, and Mills 2008. (Fakhri et al., 2009)

Peripheral Vascular Disease, Venous Thromboembolism, Pulmonary Embolism
- EPA considers the evidence for a connection between PM2.5 and PVD to be uncertain, despite evidence form CHE and animal toxicological studies showing changes in thrombotic factors. They present somewhat-consistent results in ED visit and HA studies.
- Why is there no discussion of the animal and human data?

Combined CV-Related Events
- EPA concluded from the 2009 ISA that there is strong evidence of associations between PM2.5 and total CVD HAs or ED visits, and that the more recent evidence adds to that conclusion. Does it make sense that most of the separate diseases have inconsistent evidence, but the total diseases have stronger evidence? Is this an indication that sample size is driving the association?
- Effect estimates for HA and ED visits are quite small (1.01-1.1), many are not stat sig, and some are null or negative. Some of the estimates in Figure 6-6 may be missing error bars.

Cardiovascular Mortality
- EPA concluded in their 2009 ISA that there were consistent positive associations between CV mortality and PM2.5, with a 0.47-0.94% increase in mortality per 10 ug/m3 increase in PM2.5. They note that more recent studies of total CV mortality are consistent with this conclusion, but that cause-specific mortality results are less consistent. That makes sense with the morbidity outcomes outlined above but doesn't provide a causal pathway. Most of the new studies showed positive effect estimates, but many weren't statistically significant.
- The ISA 2009 also concluded that there was coherence with CHE and animal tox studies, but this ISA doesn't say how the EPA arrived at that conclusion. Was mortality observed in the animal toxicological studies? There was no conclusion about CHE or animal toxicological studies from current data.

12-10-18 Preliminary Draft Comments from Members of the Clean Air Scientific Advisory Committee (CASAC).
These preliminary pre-meeting comments are from individual members of the Committee and do not represent
CASAC consensus comments nor EPA policy. Do not cite or quote.

Heart Rate and Heart Rate Variability
- EPA summarizes that there is additional evidence across disciplines that PM2.5 can impact HRV, but limited/inconsistent evidence that it can impact HR.
- Panel studies - The studies that EPA reports seem to show inconsistent results – some with NC in one HRV marker, but a change in another, and then the opposite in another study. EPA considers this to generally show that PM2.5 can lead to changes in HRV, but it is difficult to draw any conclusions beyond that. As usual, many of the effect estimates are not statistically significant, which is often not discussed.
- CHE – EPA notes a few recent studies that don't show any change in HR, and some that do. From my notes, ones that show changes in HR are Gong 2003 (decreased HR with PM2.5), but no change with Brook 2009, Fahkri 2009, Gong 2005, Huang 2012, Mills 2008, Sivangangabalan 2011, Urch 2005. EPA states that HR increased with CAPs in Gong 2003, but it actually decreased. Changes in HRV are noted in several studies, but EPA states that the lack of HRV effects found in Huang 2012 may be reflective of the lower exposure concentrations (89.5 ug/m3) – suggests some acknowledgement that there might be a threshold.
- EPA states that Brook 2009 showed reductions in time and frequency domain measurements of HRV. The paper states that "The changes in BAD (Table 4), BP, heart rate, and HRV measures (Tables S1 and S2) did not differ across the 4 different exposure conditions when measured at any time point outside the chamber", and from the supplemental tables there doesn't seem to be changes during exposure either. The EPA should revise their conclusions about this paper that clearly didn't show effects in HRV.
- CHE Conclusions: "Considered as a whole, the CHE studies discussed above provide some evidence of a change in HRV following PM2.5 CAP exposure, but not following exposure to DE." There are several studies that don't show an effect, not just the DE study.
- Animal Tox studies – They present some evidence that studies show some changes in HR, but it is inconsistent in direction. The HRV data is also inconsistent and in different directions – the EPA presents this as showing a pattern with diet or season, but it just seems to show heterogeneity and inconsistency in responses.

Systemic Inflammation and Oxidative Stress
- EPA notes that the evidence for inflammatory changes with PM2.5 remains limited, because some studies show increases in inflammatory mediators, while others don't. They note that there are a few more animal toxicology studies showing increases in oxidative stress markers.
- Panel studies – some positive studies, some negative. EPA presents that there is more evidence in older populations, but there is still a lot of inconsistent results in that population.
- CHE – EPA said that in the 2009 ISA there was essentially no evidence of systemic inflammation. For this ISA, they cite Behbod 2013 as having increased leukocytes at 0 hr, but not 3 hrs post-exposure. It is misleading to present the increase in leukocytes with

PM, but then to note that it wasn't statistically significant compared to filtered air (for Brook 2009). For the Urch 2010 study the increase in IL-6 was seen with the higher PM exposure, but not with PM + O3. EPA presents a considerable number of studies that do not show any effects. Despite this, they conclude "Overall, the evidence presented above is inconsistent. This is not unexpected however, given the variability in design and subjects across these studies (Table 6-24). Thus, it can still be concluded that the studies presented above provide limited evidence that short-term exposure to PM2.5 can result in an increase in inflammation. Moreover, these results also provide evidence that the amount of endotoxin present in PM2.5 exposure appreciably contributes to inflammatory potential." This is not justified by the data. EPA also did not find any evidence of increased oxidants in blood or urine but noted that different endpoints may have different results.

- Animal studies – again, inconsistent results, but EPA says there is evidence of some effects, and the study design can significantly impact the results.

Coagulation:
- EPA concludes that despite limited and inconsistent evidence in CHE and epidemiological studies, animal studies showing increased clotting factors in genetic mouse models, but not in rats, means that there is evidence of PM-induced clot formation. This data is not consistent with this conclusion – just mouse results in direct contrast to negative human data.
- Panel studies: EPA concludes that there is not strong evidence for an association between short-term exposures to PM and plasminogen, and studies for other biomarkers are limited (it seems like other biomarkers are also investigated in these studies, but maybe none so consistently as fibrinogen).
- CHE – For previous studies, EPA notes that Gong 2003 did not find any change in fibrinogen, or vWF or Factor VII. In fact, they observed a decrease in Factor VII. From the new studies there seems to be very little evidence of effect, and Tong 2015 shows evidence of an anti-thrombotic effect (as with Gong 2003). Again, EPA concludes that while the evidence is inconsistent, because of differences in subjects and study design that there is some evidence of PM2.5 promoting pro-thrombotic changes. What aspects of the study design and subjects do you suspect of causing the inconsistency? There are enough studies that EPA should be able to narrow down a particular culprit.
- Animal Tox – EPA cites studies that do not show any effect of PM2.5 pro-thrombotic effect in rats. In mice they cite Budinger 2011 and Chiarella 2014 as showing evidence of PM2.5-mediated pro-thrombotic effects. However, most of those studies are done with PM intratracheal installation, which induces far more damage and inflammation than the 3-day CAPs exposure. Interestingly, in Budinger 2011 despite the far greater damage and IL-6 expression with installation versus inhalation, the increase in plasma TAT complexes is almost identical, which doesn't speak to a dose-response or an inflammatory precursor. That most of the data comes from installation should be reflected in the EPA's discussion and Table 6-28.

Endothelial Dysfunction and Arterial Stiffness:
- Panel studies – EPA notes that the DEARS study in Detroit showed inconsistent associations between PM2.5 and measures of vascular constriction (FMD, BAD), and several Canadian studies showed no association with these endpoints. For digital vascular function, in the Framingham Heart Study Ljungman 2014 seemed to show an increase in microvessel dilation (I think that this is the opposite of the expected adverse direction). One panel study of arterial stiffness (measured by augmentation index) showed no association. EPA presents evidence from several studies that found associations between short -term PM2.5 and endothelial adhesion markers, and some that don't. Overall their conclusion is that PM2.5 could possibly affect adhesion markers, but the evidence is limited.
- CHE – EPA presents results from several studies that show vascular responses to PM2.5, but the responses aren't entirely consistent, nor are they clearly presented. Brook 2009 did not see a significant difference compared to FA control. Several studies saw increases in VEGF, which is a marker of vasodilation and is not consistent with the suspected direction of effects (vasoconstriction). This should be discussed before EPA comes to its conclusion of evidence that PM2.5 affects vascular function and that there is evidence for an increase in endothelial dysfunction markers in blood and urine. Also not mentioned is Mills 2008 who did not show any vascular dysfunction in older adults who were healthy or had CHD. There is no evidence of changes in arterial stiffness with PM2.5 exposure.
- Animal Tox – EPA reports consistent evidence of PM2.5 effects on vascular function, mostly based on ex vivo assays. They also report two studies that show a decrease in circulating endothelial progenitor cells, but don't make the implications of this decrease clear. Which direction is adverse, and is it consistent with the direction of effects in other studies?

Policy-Relevant Considerations:
- EPA focuses on copollutant confounding, temperature and season, and lag effects. For the respiratory section there were also considerations of model specification, averaging time, and shape of the C-R function. Were these not addressed in any of the CV studies? If so, that should be discussed at the beginning of this section.
- Temperature and Season- the 2009 ISA concluded that there was seasonal variability of PM2.5 associations with CV effects by season, and recent studies have continued to show that. This demonstrates heterogeneity in effect estimates that is not simply explained by sources. This section refers several times to Figure 6-6, which is not a figure showing seasonal effects, it shows ED visits and HAs for CV-related effects.
- Lagged Effects – EPA discusses how studies show effects at different lag periods, depending on the endpoint, or even within endpoints. Generally stronger effects are seen at lag 0 and 1, but some studies have shown delayed or prolonged effects. As I stated in the respiratory section, it seems that these results need to be considered not for what they say about the timing of PM effects, but whether there are effects at all given the heterogeneity of results.

PM2.5 Components and Sources:

- EPA generally concludes that studies that evaluated sources and species of PM showed inconsistent results. Does it make sense that there is only a "clear" association with PM mass, and not any of the components or sources (which would make more sense toxicologically?). Is it because there is more PM2.5 data, so you run into a sample size effect?
- EPA discusses two pathways for looking at components. They say that they don't use pathway 1 because it is typically used to look for heterogeneity in the PM2.5-CVD risk estimates. Even if that isn't useful for component analysis, that information seems like it would be very useful in other parts of the document to assess the heterogeneity in effect estimates.
- This section doesn't seem to assess results from CHE studies, although several have done component analysis compared to total mass. Those should be included, particularly because there is far less question about the causal inferences for the observed effects.
- Sources – EPA states that there is some evidence for associations between traffic PM, and wildfires, and CVD HA. Again, there is a lack of information from CHE and CAPs animal studies that can provide some source information.
- Section 6.1.15.7 – PM sources and components in diabetics is completely without context. There is no introduction, no discussion of diabetes or why this particular population was singled out, with a somewhat random table of studies that doesn't present effect estimates.
- EPA presents results from Chen 2010 which also describes the NPACT study, and notes that the mice were exposed for 6 months from May-Sept 2007. Although this is what the authors reported, it should be noted that May-Sept is only 5 months. EPA should also note that while this is a chronic study, the authors looked at acute effects during the day. No discussion of the opposite results at the two New York sites?
- Rohr et al present results for a 13-day exposure in Detroit in summer and winter to 518 ug/m3 ad 357 ug/m3 CAPs respectively. Most 8-hr HR and HRV effects weren't affected, but there were some elements associated with increased HRV and decreased HR. An explanation of the opposite response shown here compared to what is the direction of adversity would be helpful. A lot of these nuances aren't presented in the corresponding HRV section in the main text, which would provide more information for interpreting the weight of evidence. EPA also presents a summary analysis of the results but should also include a better explanation about what the results mean (counts, etc), and what the uncertainty in this integration method is. It should also be noted that the HEI review committee was skeptical of the authors' analysis and wasn't clear whether components or concentrations impacted the different results in different areas. Was there any evidence of increasing effects over time with PM exposure?

Summary and Causality Determination:

- EPA concludes that "A large body of recent evidence confirms and extends the evidence from the 2009 PM ISA (U.S. EPA, 2009) indicating that there is a causal relationship

between short-term PM2.5 exposure and cardiovascular effects." This skips over a whole host of uncertainties.

- This whole section emphasizes only the positive results (and often isolated, positive results from CHE and animal studies), making the literature seem cohesive and consistent, when in fact a much more nuanced and far less consistent picture is provided by the detailed data analysis. It doesn't seem like the CVD data is much stronger than the respiratory data – so why the difference in causality determinations?
- EPA notes that there is a coherence in the results from different endpoints, demonstrating the plausibility of an effect of PM2.5 on CVD effects. However, there is no discussion of concentration of effect, heterogeneity, or the type of hypothesis-testing that I recommend, which involves looking at the associations for patterns that would be expected of exposure to a toxicant in the population (e.g. increases in confidence in effect estimates that are more effect specific, and that are less severe). The opposite actually appears to be true – the more refined and less severe the effect, the less likely it is to be positively significantly associated, making these effects seem more like statistical artifacts. There is also no discussion in this section of bias, chance, or confounding, which could be impacting the effect estimates.
- Respiratory effects are broken down into sub-effects for the causal determination. Why is that not done here? There are a number of CV effects that do not have good supporting data, and these appear to be lumped together and not distinguished from those with more compelling data.

Long-Term PM2.5 Exposure and Cardiovascular Effects
- The long-term PM2.5 CVD section needs to be carefully copy-edited.

Summary:
- The previous determination was causal for long-term PM2.5 exposure and CV effects, with the strongest evidence coming from cohort studies associating PM2.5 with CVD mortality. I would hypothesize that the strongest evidence would come from milder or more specific effects, not from mortality.
- This document focuses on epidemiology studies conducted in areas with PM concentrations less than 20 ug/m3 (presumably not the case for the animal evidence), as well as those with copollutant confounding, different more specific health effects, and shape of the C-R function. Why 20 ug/m3?

Biological Plausibility:
- General pathway is respiratory inflammation (maybe particle translocation), then systemic inflammation, then thrombosis, hypertension and vascular dysfunction, then conduction abnormalities, heart disease, etc, then death. Most of the evidence comes from animal tox studies (concentrations not reported but are probably higher than 20 ug/m3). Another pathway is ANS activation, which can impact blood pressure and other factors.

Ischemic Heart Disease and Myocardial Infarction:
- Summary – Findings from epidemiology studies don't provide entirely consistent evidence of an association between long-term exposure to PM2.5 and IHD, with strongest evidence in people with pre-existing conditions (Chapter 12).
- EPA presents 11 effect estimates for long-term PM2.5 and IHD or MI – only one is statistically significant. Of the 6 US studies, 4 have substantial amounts of data from before the PM2.5 monitoring network was established. A meta-analysis of 11 European cohorts found a non-statistically significant HR of 1.13, and an almost statistically significant HR of 1.19 for PM2.5 concentrations <15 ug/m3. A separate study (Hoffmann 2015) that used physician-confirmed diagnoses did not report an association between PM and coronary events (but did with stroke) after considering noise and other cofactors. There is text missing at the sentence at the end of the paragraph, which ends with Koton (2013).
- EPA notes that data from cross-sectional studies does not provide consistent evidence of an association between long-term PM2.5 and IHD or MI.
- The summary paragraph at the end again emphasizes the positive results, even though throughout this section EPA has emphasized the inconsistent results. They also note that there is little information about copollutant confounding, and that copollutant correlations were generally moderate-to-high.

Cerebrovascular Disease and Stroke:
- Summary - while results aren't entirely consistent across subtype, epidemiology studies generally report an association between stroke and long-term PM2.5 exposure.
- Several of the epi studies did not have time concordance between PM2.5 measurements and outcome assessment (e.g.Lipsett 2011 – followup 1995-2000, PM2.5 – 1999-2005). How does this impact study interpretation? Of the 9 effect estimates presented, only one is maybe statistically significant (hard to tell – the Hoffmann 2015 study doesn't have an effect estimate, only an interval. If it is off the scale, perhaps the numeric value of the estimate can be put on the graph?). EPA notes that the Hartiala 2016 study showed an effect with wide CI, that was attenuated with consideration of various potential confounders (smoking, obesity, etc.). It seems that the unadjusted estimate is presented in the graph, but that the adjusted estimate should be presented.
- The graphs should provide information about which years are being specified – years where the PM2.5 concentration was measured, or years of followup/health effect analysis, because they are not always the same. The statement about the Hoffmann study (I think) in the text isn't referenced.

Atherosclerosis:
- Studies in the previous ISA were inconsistent, with null associations possibly explained by exposure measurement error, variations in baseline measurements, or lack of statistical power. Not mentioned was the option that there isn't an association between PM2.5 and atherosclerosis.

- What is the significance of observing changes in DNA methylation in circulating monocytes in the MESA-AIR cohort (Chi 2016b)? No explanation or justification of this result is offered. Also, the study results should be presented in the table, or in a figure.
- In general, it seems that there was a lack of evidence of association of PM2.5 with cIMT, and there was conflicting results for CAC.
- Animal Tox – atherosclerosis from PM2.5 has mostly been studies in the ApoE-/- mouse model of peripheral vascular disease. Lippman 2013 shows inconsistent effects of 60-138 ug/m3 CAPs on atherosclerotic plaque development after 3-6-month exposure, with effects in some areas and not others – may be due to constituents, may be concentration.

Heart Failure and Impaired Heart Function:
- Summary: recent epidemiology and animal toxicology data provides evidence for a role of long-term PM2.5 exposure in contributing to congestive heart failure and impaired cardiac function.
- Epidemiology studies – EPA notes several studies that show positive associations with CHF or HF and PM2.5, although not necessarily statistically significant. The cross-sectional study, To 2015, is not in Table 6-39.
- There were no positive statistically significant associations with various indices of CHF in the MESA-air study (one for right ventricle mass was positive). Another cross-sectional study (SALVIA) found positive associations between some CHF metrics and PM2.5. Again, effect estimates should be provided in the table or in a separate figure. The data seems insufficient and debatable to me, but EPA concludes that there is evidence of a possible relationship between PM2.5 and CHF and HF.
- Animal Tox – EPA presents evidence from multiple animal studies (although not consistent in all) of effects of CAPs exposure on cardiac wall thickness and heart function. No information is presented about whether any of the exposed animals experienced CHF or HF or died from the exposure. EPA also summarizes several studies that expose animals in utero and found cardiac changes. EPA says that "Tanwar et al. (2017) demonstrated that prenatal exposure alone was sufficient to produce heart failure in adulthood" from exposure to 74 ug/m3 Ohio State CAPs for 6 hrs/day throughout pregnancy. Did these animals experience heart failure? Also, Tanwar 2017 is listed twice in Table 6-40.

Cardiac Electrophysiology and Arrhythmia:
- Summary – lack of epi or animal tox evidence for 2009 ISA (no summary of current evidence – inconsistent structure of the document). They say that current animal tox evidence is still lacking, although it seems that a lot of animal studies did ECG Analysis, and likely presented some information about cardiac depolarization and repolarization.
- Epi studies – EPA presents two studies that show significant associations (OR about 1.2), and two that do not.

Blood Pressure and Hypertension:

- Summary – EPA states that there are studies showing generally positive but small magnitude associations between long-term PM2.5 and blood pressure, but not in children.
- Some studies showed associations between long-term PM concentrations and some BP metrics, but not all studies. The changes were small – about 1 mm Hg. This seems like it is well-within the margin of error of BP measurements, so how significant is this result?
- Hypertension – EPA concludes that there is generally a positive association between long-term PM2.5 and hypertension, particularly supported by the Ontario hypertension study which has better outcome assessment. There are cross-sectional studies listed as being supportive, but no further discussion – why aren't these studies listed in Table 6-44?
- Gestational hypertension and preeclampsia – epi studies generally present inconsistent results. EPA noted that meta-analyses of PM2.5 and preeclampsia showed positive effects but had high heterogeneity scores so it may have been inappropriate to combine studies. This is good to note, and the EPA should strive to make sure that they assess this for all meta-analyses they include in assessments (e.g. Li 2016).
- Renal Function – one epi study observed an association between PM2.5 and reduced glomerular filtration rate. EPA should state whether the change observed was substantive and would be associated with adverse effects.
- Animal tox – studies in rodents showed increased BP with longer exposure to PM2.5 (85-375 ug/m3) as well as changes in the renin-angiotensin system. One study at 85 ug/m3 for 9 months (Wold 2012) showed increased blood pressure and decreases in pulse pressure (the difference between SBP and DBP). What is the expected adverse effect direction for changes in pulse pressure? EPA cites the RAS studies again, but the significance of these findings is uncertain, and isn't clarified by EPA.

Cardiovascular Mortality:

- Summary: the strongest evidence for effects of PM2.5 on CVD is the mortality data.
- Pope 2014 and Turner 2016 extended the ACS followup and showed associations between long-term PM2.5 and mortality from HF, cardiac arrest, CVD, and hypertensive disorder. EPA discusses the CanCHEC study, but the first set of results has no reference. The CanCHEC studies generally found associations with PM2.5 and IHD, diabetes, and MI, although one study (Weicenthal 2016a) showed that for people living within 5 km of a group monitor there was a null association (not consistent with the assumption that there is a bias towards the null with less precise exposure assessments).
- Figure 6-19 generally shows positive effect estimates (although not all), and generally stat sig (although not all). Why is Weicenthal 2016a not included here?
- Why is there no table providing details about these studies? Are they in the mortality chapter? This chapter says that more detail is provided in Section 6.2.10, but this is Section 6.2.10.

- In their summary EPA mentions the large European cohort meta-analysis Beelen 2014 study that showed no association of PM2.5 with CVD mortality except a positive but non-statistically significant association with CBVD. Why wasn't this discussed earlier, or included in the Figure? It doesn't fit with the discussion before it, which states that European studies generally show positive associations.

Heart Rate and Heart Rate Variability:
- The only epi data is from the MESA panel study (Park 2010), that shows non-statistically significant negative associations between 30-day or 60-day PM2.5 and rMSSD or SDNN, with higher effects in people with MetS. Does EPA's lack of consideration of statistical significance apply to panel studies as well?
- Animal Tox – The NPACT studies showed increases in HR in the early days in Manhattan but decreases in HR in the early days in Tuxedo, with no changes in CAPs from other studies (Lippman 2013a). No changes were observed in HRV with chronic exposure to CAPs from any location. Wold 2012 also showed an increase in HR with a 9-month exposure to 85 ug/m3. EPA concludes that there is some evidence of increased HR with long-term PM2.5 (although very inconsistent) but not of increased HRV. Without evidence of changes in HRV, how does this impact the ANS pathway in the biological plausibility section?

Systemic Inflammation and Oxidative Stress:
- Epidemiology studies – some studies showed associations between long-term PM2.5 and increases in CRP, whereas others did not, including the MESA study and the ESCAPE cohort. MESA did show a small increase in circulating IL-6, and it is not clear whether this was observed in other studies. Why is there no table or figure of results? There is a table for the animal studies.
- Animal Tox – EPA presents variable results for inflammatory markers in different animal studies. They note that while these results appear inconsistent, because it is difficult to compare inflammatory markers across study timing and design, this provides information for PM2.5-induced inflammation. Why is the default interpretation of a variable marker automatically on the side of showing an association? Why doesn't this just show that there is a lot of background variability in inflammatory markers that may not have any significance? Or perhaps it shows a threshold or other pattern of response? There is limited, inconsistent evidence of increased oxidative stress.

Coagulation:
- Summary: several recent studies show that long-term PM2.5 can impact fibrinogen, D-dimer, and platelet count. Why isn't this combined with the thrombosis section? How can you tell which direction of change is associated with pro-thrombosis? It seems that an increase in plasminogen could mean that more is being made in preparation for more clot formation, or that there is less fibrin formation. Similarly with D-dimer.

- Epidemiology studies – most summarized studies showed no effect of long-term PM2.5 on fibrinogen, and those that saw statistically significant effects were in opposite directions. Cross-sectional studies, and a meta-analysis of the ESCAPE cohort showed null effects. This does not in any way support EPA's statement that recent studies show impacts on fibrinogen, D-dimer, and platelet count.

Impaired Vascular Function and Arterial Stiffness:
- Epidemiology studies – the MESA Air and Framingham offspring studies showed small statistically significant negative associations with FMD, but no changes with BAD or several other markers. There was also a small statistically significant negative association with hyperemic flow velocity in the Framingham study. These studies showed changes of 0.5-1.8%, which the EPA says are large given that normal ranges are usually 5-10%. What does this mean? Normal ranges of normal function or variability? That doesn't make a 0.5% change seem large. Tallon 2017 showed associations with erectile dysfunction, which EPA says may be associated with vascular function. I would recommend removing this, unless a stronger connection is shown. Several studies showed no association of PM2.5 with arterial stiffness. Again, where is the evidence summary table?

Copollutant Confounding
- Is there a reason that the long-term exposure section doesn't have a separate policy-relevant considerations section, but there is one in the short-term exposure section?
- The beginning of this section notes "A change in the PM2.5 risk estimates, after adjustment for copollutants, may indicate the potential for confounding." How much of a change? This seems very subjective. A statistically significant change?
- EPA states that there are more studies looking at copollutant confounding for mortality, and fewer for morbidity, but those that are available generally remain unchanged. Can you make a final conclusion based on limited data? I would agree that the studies shown in Figure 6-20 mostly show no effects of copollutant confounding, but these also mostly don't show effects of PM2.5 either. There is a lack of labeling on the figure – are the filled circles the ones without copollutants?

Shape of the C-R Function
- Summary: some studies have suggested largely linear concentration-response functions, but in general there is a paucity of information, and cut-point analysis from other studies suggest non-linear C-R curves.
- Morbidity Studies - Kaufman 2016 used the MESA-AIR CAC data to look at the C-R function and found a somewhat supra-linear shape, whereas Dorans 2016 with the Framingham cohort showed a very odd C-R function shape. Cesaroni 2014 found similar HRs below and above a 15 ug/m3 cut-point for the ESCAPE cohort, and Chen 2014 showed an exponential-like C-R Function shape. This combination of data makes it difficult to draw any conclusions about the shape of the C-R function. As noted in the general section, there is evidence that variability and error in epidemiology study

estimates prevents one from determining the appropriate shape of the curve (Rhomberg 2011).

- Mortality – EPA concludes that most studies support a linear no-threshold response between long-term PM2.5 and CVD mortality, including studies with concentrations <12 ug/m3. Crouse 2012 showed higher risks for IHD mortality at concentrations <10 ug/m3 (although no departure from linearity) – similar in Jerret 2016 and Weicenthal 2014. Two studies by Pope (2009, 2011) showed that the risks at low PM concentrations were higher than the risks at higher concentrations associated with smoking, and so there could be a supra-linear relationship. EPA concludes that "This indicates the importance of considering the cause of death when characterizing the concentration-response relationship between long-term PM2.5 exposure and cardiovascular mortality." While I agree that all types of death shouldn't be lumped together, how does this conclusion follow from the statement about supra-linearity and cigarette smoke? Also, do the Pope analyses really make sense – that the risks from ambient PM are more than the risks from smoking? Shouldn't this call into question the PM results?

- Why isn't animal study data used to produce/inform the C-R function? At least it can be used for comparison to the epidemiology study results.

PM2.5 Components and Sources

- EPA states that Wolf 2015 showed positive associations with PM2.5 components in the ESCAPE cohort – which components? Information in this section is disjointed and needs to be better organized (or put back into the individual sections). From Figure 6-28 there seems to be more statistically significant associations with BC than with PM2.5 – what can be concluded from this?

- Regional Heterogeneity – this section (and Sources) should be numbered. EPA summarizes some data from studies showing evidence of regional heterogeneity in effect estimates. What conclusions do you draw from this? Are there any obvious areas that always (or never) show associations that can be used to draw conclusions? Why is there no regional heterogeneity section for short-term exposure, where there is more data about it?

- Animal Tox studies on components and sources – EPA discusses the Campen 2014 study at length, which exposed animals for 50 days to motor vehicle exhaust, particle-filtered exhaust, or sulfate, ammonium nitrate, or road dust particles at 300 ug/m3. Mostly there was very little biological response, with some evidence of vascular changes. Rohr et al 2011 showed inconsistent source associations between winter and summer CAPs exposures in Detroit. Conclusions from the animal tox studies?

Summary and Causal Determinations:

- The determination of "causal" in the 2009 ISA was mostly based on CVD mortality.

- EPA states that the evidence is stronger for long-term PM2.5 exposure and CVD mortality, with studies using variable exposure and statistical methods, were robust to copollutant confounding, and generally showed LNT C-R relationships.

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- For CVD morbidity there has been positive evidence from several cohorts, and although the results vary, this is expected based on the differences in the studies and the methods used.
- This section completely skates over the negative evidence and EPA's own "inconclusive" determinations for different endpoints.

Short-Term PM10-2.5 Exposure and Cardiovascular Effects

- What is EPA doing with all of the PM10 data? Or with the PM10 standard?
- EPA notes that there is only limited biological plausibility information from epi, CHE, and animal tox studies.

Biological Plausibility:
- EPA references section 5.2 to show that exposure to PM10-2.5 can cause respiratory tract inflammation. But section 5.2 is for long-term PM2.5 exposure. Section 5.3.1 is the PM10-2.5 biological plausibility section, and the evidence there for respiratory inflammation from coarse particle exposure in CHE studies are inconsistent.
- EPA cites Behbod 2013 as showing a potential increase systemic inflammation, even though there was no increase in soluble inflammatory mediators in the blood or respiratory tract – how does this inform the entire pathway? They also cite Graff 2009 as showing evidence of hemostasis effects because of a decrease in tPA, but don't mention that there was no change in platelets, Factor VII or IX, fibrinogen, PAI-1, vWF, protein C, prothrombin, plasminogen, or D-dimers. All of these tests make the tPA result seem like it might be spurious.
- For modulation of ANS, EPA cites Brooks 2014 for showing changes in HR and HRV with coarse particle exposure. However, these results were not concentration-responsive by regression analysis (subjects were exposed to a wide range of concentrations), and there was no pre-exposure measure, just a beginning of exposure measure for comparison. Byrd 2016 didn't show an effect on HRV. Very small changes in BP were seen in the referenced study, and different components of BP. Zhong 2015 is cited as showing BP changes, but it shows that endotoxin mediates this effect.

Systemic Inflammation and Oxidative Stress:
- EPA notes that the findings for systemic oxidative stress have been inconsistent, but given the transient nature of the effects, this is to be expected. This time they didn't go on to conclude that because of the transient effects, the few studies that showed effects must be showing a real effect.

Long-Term PM10-2.5 Exposure and Cardiovascular Effects

- Biological plausibility – EPA says that there is a plausible pathway connecting long-term exposure to PM10-2.5 and apical events, but then it offers almost no such data, and then

says that there are gaps in the pathway. If there are gaps in the pathway, then you don't have a plausible pathway.

- The summary on pg 6-272 talks about the inconsistency in the epi study results, the attenuation with PM2.5 copollutant analysis, the poor measurement method (subtraction), and the lack of biological plausibility information. How does this earn a "suggestive of causality" designation?

Short-Term UFP Exposure and Cardiovascular Effects

Biological Plausibility:
- The first step in one of the pathways is respiratory inflammation, but there is very little evidence in numerous human studies that this actually occurs (see respiratory section).
- Liu 2015a and Devlin 2014 are cited as showing increased systemic inflammation (but not cited for respiratory inflammation – didn't look for it or didn't see it?). From the other studies there seems to be a decrease in inflammatory cells and mediators in Frampton 2004, and no change in either for Gong 2008 or Samet 2009.
- EPA also cites Devlin 2014 as showing evidence for altered vascular function and hemostasis. However, Frampton 2004 and 2006, and Gong 2008 showed no increase in clotting factors (Frampton 2004 showed decreases) or increased expression of vascular adhesion molecules (Frampton 2004 showed decreases). Gong 2008 showed no changes in vascular function. The only evidence from these studies was an increase in D-dimers in Samet 2009 (but no change in platelets, fibrinogen, factor VII or IX, vWF, PAI-1, tPA, or plasminogen).
- Samet 2009 and Devlin 2014 are cited as showing changes in HRV. But Samet 2009 showed an increase in HF, which is usually associated with increased parasympathetic activity and is not in the direction that EPA suggests.
- EPA cites epidemiology panel studies as showing increases in BP, while not citing the human studies that show no changes in baroreflex (Frampton 2004 and 2006, and Gong 2008). EPA cites Samet 2009 and Devlin 2014 as showing evidence of conduction abnormalities and arrhythmia but didn't cite the Langrish 2014 review that showed no arrhythmia effects with 12,500 hours of ECG recordings in many types of PM exposure studies.
- EPA notes that the evidence to support most of the individual events in their biological plausibility pathway is quite limited.

Health Effects:
- EPA concludes that overall epidemiology studies do not support an association between short-term UFP exposure and IHD or MI. EPA discusses the paucity of panel studies showing ST-depression with short-term PM2.5 but should also note that there are two CHE studies (Frampton 2003, Gong 2008) who didn't find ST segment changes.

- HF and impaired HF – in the summary, EPA refers to findings from a PM10-2.5 study. Why are there tables with study information for the tox studies, but not for the epidemiology studies?
- Arrhythmia, Cardiac Arrest, Electrophysiology – The summary states that the 2009 ISA reviewed one epidemiology study of arrhythmia ED visits or HAs, and then in the epidemiology study section they say that there were no epidemiology studies of arrhythmia and ED visits or HAs. Which is it? This section references CHE studies showing a decrease in QT interval from Samet 2009 (this seems to be in the opposite direction of adversity), and an increase in GSTM1-null individuals in Devlin 2014. No mention of Frampton 2004 who also showed a decrease in QT, or Langrish who showed no change.
- CVD Mortality – there are only studies in Europe and China, and they suffer from serious exposure estimation problems. They show some positive effects, but most are not statistically significant. These studies are listed in Chapter 11 – EPA says table 11-9, but that is for PM10-2.5, not UFP.
- Generally, conclude that the evidence is suggestive by pointing out the few positive association studies. This isn't consistent with the details in individual sections.

Chapter 7: Metabolic Effects

Short-Term PM2.5 and Metabolic Effects

- What kind of metabolic effects could be caused by short-term exposure to PM2.5? These are usually only adverse or only develop in the long-term.

Biological Plausibility:
- EPA suggests that the activation of the ANS system by PM2.5 will cause an increase in output of norepinephrine (measured in an animal study, although not increased in at least one human study that looked at it – Graff 2009) and might also increase the output of glucose (not measured). There needs to be a better connection between a transient increase in glucose (which happens every day when you eat), and changes in homeostasis and disease. (Graff et al., 2009)
- EPA cites Kim 2015 as evidence of effects of PM2.5 on liver function in humans – it should be noted that this is an epidemiology panel study, not a CHE. In general, the evidence of respiratory and systemic inflammation is poor with short-term exposure to PM2.5 (discussed in previous comments), and so does not provide great support for metabolic effects. Also, as noted above, the species and circumstances of the exposure data should be part of the discussion of biological plausibility.

Glucose and Insulin Homeostasis:
- EPA notes that the effects of PM2.5 on glucose and/or insulin homeostasis may be transient.

- What is FBG? Please define all acronyms in the chapter, even if they have been defined earlier in the document.
- As noted elsewhere, it would be good to discuss the significance of changes in biomarkers – for example, a 0.8 ug/dL change in glucose levels – what is the clinical significance of that?
- Animal tox – some data indicating changes in metabolic parameters, but not consistent. There were also 5 papers in Table 7-4 that were not discussed in the text – is there a reason for that? These papers seem to be discussed in the following sections – the following sections should have references to this table.

Other Indicators of Metabolic Function:
- Inflammation – see comments in CVD chapter on systemic inflammation.
- Liver Effects – EPA cites a few epidemiology studies that show a change in CRP, and one animal study that does not. There is no mention of the human controlled exposure studies that show no change in CRP with exposure: Mills 2008, Huang 2012, Graff 2009, Gong 2008, Ghio 2003, Brooks 2009, Brauner 2008, Behbod 2013. In sections such as this that probably weren't included in the last ISA, how do you deal with studies that were previously published with potentially relevant markers, such as CRP?
- Blood Lipids – Not mentioned in the CHE studies section is Huang 2012, who showed no change in a lipid profile with Chapel Hill CAPs exposure, except for an increase in blood HDL (opposite direction of adversity).
- Blood pressure – EPA notes that there is limited evidence for changes in blood pressure with PM2.5 exposure (somewhat less confidence in this endpoint than was noted in the CVD chapter). Would one expect a change in the ANS without a change in HR and BP? My comments on CHE BP studies can be found in the CVD chapter.

Long-Term PM2.5 Exposure and Metabolic Effects

- Metabolic Syndrome – EPA shows a figure from Wallwork 2017 (Figure 7-4), that shows the shape of the C-R response in the Normative Aging Study cohort. However, this shows changes in hazard ratios (HR) with changing PM concentrations, which is generally not the way that HRs work in the Cox Proportional Hazards model – they remain the same over the entire period of the study. This is how the authors presented it, but it doesn't mean that they made the right choice. Perhaps they were looking at the Hazards, not the Hazard ratio. This is another demonstration of the importance of study quality evaluations.
- Glucose and Insulin Homeostasis – Presented are a number of changes in various glucose and insulin homeostasis measures, but it would be good if these could be placed in the context of normal levels or changes in those metrics, or changes that would be considered adverse. Figure 7-5 appears to show a non-linear C-R function. For Figure 7-7, it would be helpful if the exposure concentrations and times were added to the labels, to give the

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reader the chance to see if the responses were concentration or exposure-time dependent.
Animal studies are in Table 7-8, not 7-7.

- Incident Diabetes – EPA reports studies that mostly show null or non-statistically
  significant positive effects of PM2.5 on incident diabetes in adults, with variable effects
  of copollutants. There was also some evidence of non-linearity in the C-R functions. EPA
  rightly reports that most of the effect estimates CI intervals include the null – the first
  time I have run across this acknowledgement.
- Other Metabolic Effects – many animal study results are presented here. As before, it
  would be valuable to include concentrations (or, better, modeling to a HEC) in the
  discussion so as to put this in the context of human exposures. Also, some discussion of
  what the animals were exposed to would help – CAPs? Where were the CAPs generated?
  It seems that most of the studies were done in Columbus OH, which makes it difficult to
  translate study results to other locations or pollutant mixtures.
- Type I Diabetes – the two epidemiology studies that are compared seem to use different
  PM measures – Beyerlein 2015 uses PM2.5, and Rosenbauer 2016 uses PM10,
  supposedly as an attempt to repeat Beyerlein. Perhaps Rosenbauer 2016 isn't relevant for
  this section.
- Mortality – The summary in this section refers to a figure that summarizes the findings
  from the ACS and CanCHEC cohorts, but Figure 7-12 provides a C-R function, not a
  summary of effect estimates. The table where the summary information can be found
  from these studies should be referenced here. Also, if Chapter 11 has a summary figure,
  that should be referenced. If not, there should be a summary forest plot in this section. As
  with many of the other endpoints there are stronger/more consistent associations with
  mortality than with the less severe endpoints.

Long-Term PM10-2.5 and Metabolic Effects

- Biological Plausibility – as noted in previous sections in this chapter, the type of study
  and study population being discussed in this section should be noted. For example, Wolf
  2016 should be labeled as a cohort study.
- The causal determination is suggestive of causality, based on one epi study that showed a
  non-statistically significant positive association. This is not adequate data for this
  determination.

Short-Term UFP and Metabolic Effects

- EPA only cited one study in this section, showing some effects of 28-day exposure in a
  longitudinal epidemiology study. They didn't cite Samet 2009, who studied the effects of
  blood lipids with UF CAP exposure and saw decreases in TG and VLDL at 0 hrs after
  exposure.

Chapter 8: The Nervous System

Short-Term PM2.5 Exposure and Nervous System Effects

Biological Plausibility:
- The EPA asserts that PM2.5 exposure activates lung irritation receptors, which cause lung irritant responses and also signal to the ANS, causing HRV. However, lung/respiratory irritant responses are mild to non-existent in human studies (measured by symptoms, FEV1 changes, etc – I discuss the CHE studies in the respiratory chapter comments), so the data isn't consistent with this pathway. Is there evidence that you can activate the TRP sensory nerves and have systemic effects in the absence of local irritant effects?
- Further, the respiratory chapter presented evidence of activation of the parasympathetic ANS, whereas this chapter discusses activation of the sympathetic ANS. Can they be activated differentially? Is this a time-dependent occurrence? This discrepancy needs to be addressed (it is also relevant to the biological plausibility section in the CVD chapter).
- As noted before, there is little supportive data that shows respiratory tract inflammation, making this an unlikely upstream component. EPA notes that two studies show brain inflammation in the absence of respiratory or systemic inflammation, showing that PM may act directly on the brain (Tyler 2016, Bos 2012) – this may be true, but also contrasts the EPA's presented inflammation pathway. Bos 2012 seems to show a decrease in inflammatory mediators in the olfactory bulb, not an increase.
- EPA states that brain inflammation leads to particle uptake in the brain, citing Ljubimova 2013 – This paper doesn't show particles in the brain.
- The Fonken 2011 study showed some changes in behavior and cognition with 10-month Columbus CAPs exposure (95 ug/m3 6 hr per day 5 days per week). This paper is cited as a reference for the statement "Brain inflammation may be due to peripheral immune activation (Fonken et al., 2011)". It is not clear where the evidence is for peripheral immune activation in this study. It is also a chronic study cited in the acute section.
- EPA states that a CHE shows evidence of an impact of PM.5 on the blood-brain barrier (Liu 2017). This seems to be the only human study cited in this section – there is more human data for the earlier steps in the pathway, although it is often not supportive (but still informative). Liu 2017 doesn't show an increase in the BBB-related proteins S100B or UCHL1 with exposure to any of coarse, fine, or UFP CAPs, therefore there is not demonstration of a change in the BBB.

Activation of the SNS and Hypothalmus-Pituitary-Adrenal Stress Axis:
- CHE – the only study cited by EPA is Liu 2017, which shows no effects of PM2.5 exposure on the SNS or the HPA stress axis. I do appreciate that EPA cited this study and were upfront about the results.
- Animal Tox – EPA cites Balasubramian 2013 as showing effects of PM2.5 exposure on the SNS and HPA after 1 day of exposure, but not after 3 days of exposure. Firstly, this is

mis-represented in the text ("increased levels of norepinephrine in the paraventricular nucleus of the hypothalamus 1 day (p < 0.05), but not 3 days, after exposure") – the way this is written suggests that the effect wasn't seen 3 days after exposure (which would suggest a reversal), as opposed to the lack of effects after 3 days versus 1 day of exposure, which suggests adaptation to the stimulus. Secondly, EPA should offer some analysis of why this pattern is seen (or offer the authors' analysis of it).

Brain Inflammation and Oxidative Stress:
- CHE – EPA again cites Liu 2017, this time for an increase in blood ubiquitin C-terminal hydrolase L1, which they said is "related to blood-brain barrier integrity", and that BBB integrity impacts brain inflammation. Was the level of the bio marker enough/in a range to determine that this was an adverse effect? In addition, the study does not show a statistically significant increase in this marker – the p value is >0.05.
- Animal Tox – the results summarized from the Bos 2012 study seems to suggest in traffic-air exposed C57/Bl6 mice there was an up regulation in inflammatory genes in the hippocampus, but a down-regulation of inflammatory genes in the olfactory bulb, where presumably PM concentrations would be higher. How is this result explained? Did the authors look at protein expression, in addition to gene expression? Tyler 2016 shows a down-regulation of inflammatory markers in the hippocampus of WT C57/Bl6 mice but increases in ApoE-/- mice exposed to Chicago CAPs. Ljubimova 2013 saw no gene or protein expression changes in F344 rats exposed to Riverside CA air for 2 weeks (longer than the other studies). Bos 2012 had lower concentrations than Tyler, but for a longer duration. May also be the exposure conditions – for Bos 2012, the mice were actually in a roadway tunnel. How does a dampening of the response with increased exposure inform the biological plausibility pathways?

Disease of the Nervous System and Depression:
- Epidemiology studies show limited and somewhat conflicting associations. As in the other chapters, there should be some sort of summary at the end of each section, with a preliminary conclusion about the evidence presented in that section.

Summary and Causal Conclusions:
- It is not clear why the conclusion is "suggestive". There is some animal evidence, but no attempt is made to convert this to relevant human concentrations, or to discuss the evidence of differences in effects in rodents versus humans in dosimetry and deposition. In addition, there is evidence of an adaptive response, and no discussion of whether there was an overt, adverse effect of the gene expression and norepinephrine changes in the animals.

Long-Term PM2.5 Exposure and NS Effects

Biological Plausibility:
- In Figure 8-2, EPA draws a line from RAS activation to SNS activation. However, they state that there is animal evidence that PM2.5 activates the SNS, which then impacts blood pressure (a RAS-impacted pathway), so which is the proper directionality on this? Also, there is a lot of emphasis put on one group's demonstration of an impact on RAS.

Brain Inflammation and Oxidative Stress:
- Describing the specifics of the animal study results shows inconsistencies in the findings between different studies, even with similar types of exposures (Columbus OH CAPs). Do these studies demonstrate inflammation by means other than mRNA expression? Perhaps protein expression or changes in immune cells? The results are restricted to Columbus OH CAPs, except for a study on resuspended DEP that showed somewhat different results. The only rat study showed no effect – which of these factors is mediating the effects seen?

Cognitive and Behavioral Changes:
- Animal Tox – several studies showed behavioral changes with PM2.5 exposure – both from the Columbus OH group.

Neurodegenerative Diseases:
- Parkinson's Disease in epidemiology studies showed some positive associations, but mostly they weren't statistically significant, and they were lower and not statistically significant in the studies with better outcome assessment. Are these studies for PD incidence? Hospital admissions studies are particularly problematic for this endpoint, because it is hard to say what the reason for the HA was (noted in the Ozone workshop discussion).

Neurodevelopmental Effects:
- No consistent association of perinatal and childhood exposure with behavioral or cognitive effects, but some association with autism spectrum disorder.
- The type of effect estimate is not always labeled in this section.
- ASD – somewhat consistent positive associations, but often not statistically significant. What confounders were considered in these studies? The only animal study cited is Klocke 2017, who show various brain morphological effects from GD 0.5-16.5 exposure 6 hr/day to 93 ug/m3 NY CAPs. What is stated in the biological plausibility section, but not here, is that there was no evidence of cognitive or behavioral effects in this study.

Summary and Causal Determination:
- The conclusion that there is likely to be an effect on the CNS is not supported by the epidemiology studies that show largely null and inconsistent results. It may be supported

by the animal studies, but the appropriate dose modeling to compare to doses experienced in humans has not been done, and most of the animal studies that provide coherence were done by a single group in a single location.

Short-Term Exposure to PM10-2.5 and NS Effects

- Section 8.3 has the wrong section references in its summary section.

Biological Plausibility:
- the EPA cites an animal study showing coarse CAPs causing decrements in lung function as potential evidence of ANS activation. However, human CHE studies show no effect of coarse PM exposure on lung function (Gong 2004, Graff 2009). The EPA states that Liu 2017 supports an association between coarse PM and activation of the HPA axis. Liu is again referenced for showing changes in the blood brain barrier – they do not show changes in mRNA expression of the genes associated with BBB dysfunction, just Endotoxin, not PM coarse mass. This section notes that the rodent effects are likely nasal, but don't go all the way to using the available dosimetry data to extrapolate about whether this would be relevant for humans.
- The Fonken 2011 study showed some changes in behavior and cognition with 10-month Columbus CAPs exposure (95 ug/m3 6 hr per day 5 days per week). This paper is cited as a reference for the statement "Brain inflammation may be due to peripheral immune activation (Fonken et al., 2011)". It is not clear where the evidence is for peripheral immune activation in this study. It is also a chronic study cited in the acute section.

Activation of the SNS and Hypothalmus-Pituitary-Adrenal Stress Axis:
- Liu 2017 is the only paper cited here, and they note the $P<0.1$ effects of changing biomarkers of BBB integrity – this was not a significant response, and there were plenty of samples for statistical power for this endpoint. Also, EPA should explain or address the fact that although urine cortisol went up, blood cortisol went down – what does that say about activation of the HPA axis?

Long-Term Exposure to PM10-2.5 and NS Effects

- Section 8.4 has some wrong section references in its summary section.
- Biological Plausibility – This section states that there is not enough data to be sure of the biological plausibility pathways. If this is the case, then the EPA should not draw a biological plausibility pathway figure, which misleads the reader into thinking that there is good data to support the pathway.
- Brain inflammation – what are the Arc and Rac genes, and what do their gene products do? Do they promote inflammation?
- Cognitive and behavioral effects in adults – the text references Table 8-24 for study-specific information, but it should reference Table 8-25.

- Causality – how is this evidence suggestive? There is basically no data for mechanism or biological plausibility, and there are inconsistent epidemiology study results that don't account for copollutants.

Short-Term Exposure to UFPs and NS Effects

Biological Plausibility:
- The EPA cites Maher 2016 as showing that magnetite UFP, likely from combustion sources, is found in the brain. However, there is no evidence from that paper about where that UFP came from, or controls for people who would have been exposed to more or less UFP.
- Again, changes in lung function as an upstream indicator of ANS pathway activation is not very convincing, because of the lack of lung function changes observed in many CHE studies (Frampton 2004, Gong 2008, Samet 2009). The reference shouldn't be for Jr. 2008, it should be for Gong 2008, and there was no significant change in FEV1 observed with time (just a pattern).
- Again, Fonken 2011 is referenced for peripheral immune activation (not shown in the paper), and Ljubimova 2013 is referenced for uptake of particles into the brain (not shown in the paper).
- The Chang 2016 findings of inflammation, oxidative stress, and apoptosis in the olfactory epithelium may indeed by mediating the neuronal effects. But given the differences in rodent and human dosimetry, would this response be expected in humans?

Activation of the SNS and Hypothalmus-Pituitary-Adrenal Stress Axis:
- Again, there was not a stat-sig change in urinary excretion of VMA in UFP-exposed humans in the Liu 2017 study.

Brain Inflammation:
- As noted above, the Cheng 2016 study shows many olfactory effects of aerosolized UFP exposure, but is this a rodent specific effect?
- It should be noted when referencing the Tyler 2016 study that although they had a CAPS exposure that included more gases, the non-added gas exposure still had substantial concentrations of CO and NO2 (ppm levels).

Causality:
- Again, there is a lack of human evidence, and an inconsistency in animal evidence, that doesn't support a suggestive of causality conclusion.

Long-Term Exposure to UFPs and NS Effects

- Again, the citation of Maher 2016 shows no evidence of where the UFP came from, if it has any effects, or if it is mitigated by changes in external UFP concentrations.

12-10-18 Preliminary Draft Comments from Members of the Clean Air Scientific Advisory Committee (CASAC).
These preliminary pre-meeting comments are from individual members of the Committee and do not represent
CASAC consensus comments nor EPA policy. Do not cite or quote.

- Biological Plausibility section is 8.6.1, not 8.1.1.

Biological Plausibility:
- Evidence is applied inconsistently for supporting ANS and RAS between different chapters – in metabolism, the RAS was said to activate ANS (although evidence of the reverse was presented), and in this one, even though RAS activation is argued, no SNS activation is included in the chart.
- The Fonken 2011 and Ljubimova 2013 references again.
- The summary states that animal toxicology and CHE studies contributed to information about upstream and downstream events, but I didn't see any CHE studies cited, nor are they typically used to inform long-term effects.
- Again, if the information base is totally animal studies, then considerations of dosimetry, particularly in the olfactory compartment, must be considered.

Brain Inflammation:
- Again, the Tyler 2016 study should be interpreted with caution because there were significant gas concentrations in all the particle exposures. Also, Ljubimova did a 3- and 10-month exposure, which should be cited in this section, not the two week exposure.

Cognitive and Behavioral Effects:
- Were the behavioral effects seen in the animal studies consistent with the types of morphological changes seen with UFP exposure?

Neurodevelopmental Effects:
- Were the schools matched for other criteria besides SES to control for confounding? Were individual confounders considered?
- Animal Tox – it seems that Davis 2013 studied a lot of endpoints with prenatal exposure to UFPs and found very few changes. Are these significantly associated with any of the other pathways discussed in other parts of this section to show coherence of results? Or are they likely to be caused by the number of stat tests? While a number of papers are cited showing neurodevelopmental effects of UFP, there were actually only two studies, and they didn't show entirely consistent results.

Causality:
- Likely to be causal is not substantiated by the evidence. There are no supportive human studies, and there is no attempt made to show that the rodent effects aren't due to a difference between rodents and humans from the perspective of dosimetry and the part of the respiratory tract that is expected to be affected by UFP exposure. That type of information would make a far stronger case for this causality determination that is supposed to be applicable to humans at ambient concentrations.

- Again, the neurodevelopmental data isn't "extensive" – it is just two studies but subdivided into half a dozen papers.

Chapter 9: Reproductive and Developmental Effects

PM2.5 and Reproductive and Developmental Effects

Biological Plausibility:
- The introductory section repeats the information that insoluble and soluble particles from PM can translocate into systemic circulation 3 times. This needs to be cleaned up. It also relies on pulmonary and systemic inflammation at the beginning of the pathway, which has only been rarely demonstrated in CHE and animal studies.
- There needs to be some connecting evidence showing that, if present, systemic inflammation can cause all of these reproductive effects.
- It seems like all of the female evidence comes from one study – Veras 2009. Similarly, for testicular and sperm effects, only one study is really cited – Pires 2011.
- "Together, these mechanisms provide plausible pathways by which inhalation of PM2.5 could progress from the initial events noted above to altered fertility, fecundity, and reproduction." In the paragraph above this statement, it wasn't mechanisms that were presented, it was endpoints – saying that PM2.5 exposure affected sperm motility and increased time for successful mating does not tell you anything about "how" it happened – there is almost no discussion of how in this section.
- The very last paragraph in this section just repeats the same information over again several times, without providing any more detail about how PM2.5 could affect reproduction besides "inflammation and oxidative stress".

Male Reproduction:
- There should be a summary table providing details and results for the epidemiology studies that are presented in this section.

Female Reproduction:
- Epidemiology evidence – EPA states that "Gametes (i.e., ova and sperm) may receive higher exposures while outside of the human body, as occurs with assisted reproduction." Do they really? How are the gametes getting this exposure? They would be almost exclusively in closed containers and in protected environments to ensure sterility and viability. In the summary section, there should also be an acknowledgement of the studies that showed no effects. Summary table of these papers?
- Animal Tox – This endpoint should not be characterized as being supported by "multiple studies" – just two papers from the same group in Brazil, and not supported by the more recent study.

Pregnancy and Birth Outcomes:
- Biological Plausibility – The first step in the pathway, systemic inflammation (actually the second step, they didn't address how systemic inflammation would happen), is demonstrated by evidence of a change in CRP in an epidemiology study, and in a CHE study. However, the Devlin 2014 study is a UFP CAP study, and they don't reference all of the CHE studies that don't find a change in CRP (which is basically all of them – see my earlier comments on PM2.5 and CRP). A discussion of maternal toxicity versus direct fetal toxicity is important for this section.
- Maternal Health During Pregnancy – EPA cites a number of studies, but these should be summarized in a figure and in a table that is available for review (the supplementary information seems to be only available behind the HERO firewall, and not to the general public).
- In the fetal growth section, SGA and IUGR are defined, and the differences between them are noted (SGA is a small neonate, whereas IUGR is actually considered to be abnormal growth). But in the next sentence, EPA states that these terms are used interchangeably. Should they be? This should be clarified. In the paragraph describing the challenges of determining the effects of air pollution on adverse birth outcomes, the same text is repeated twice. These types of considerations, such as confounding and exposure, should be discussed when addressing the original studies. For the tox studies, one of the studies in the table didn't provide exposure concentrations (Gorr 2014). Also, there were more responses in the Blum 2017 study with exposure to Sterling Forest CAPs, than in the Klocke 2017 study with the same type of exposure, but at a lower concentration – perhaps a threshold effect? This type of thing should be discussed in this document. Was gestational time considered in the birth weight studies?
- Pre-term birth – the introduction notes that the mechanisms of pre-term birth are unknown, with multiple potential causes. What kinds of confounders were considered in these studies, and how were the outcomes assessed?
- Birth defects – table of study information?

Developmental Effects:
- It would make more sense if the summaries of developmental effects from other chapters followed the sequence of the other chapters – I.e. respiratory, cardiovascular, neurological, etc.
- For the neurodevelopmental section, the text states that the epidemiological data does not provide consistent evidence of positive associations. Then they say that this informs and contributes to the conclusion that there is likely to be a causal relationship. It does not seem like inconsistent evidence would contribute to that conclusion. It also says that these studies provide evidence that long-term PM2.5 exposure contributes to developmental effects – but it doesn't, because the data is inconsistent. I think this is a problem of copy-and-paste from text in other sections. For the animal tox section, when discussing the Klocke 2017 study, there should be reference to the fact that the study authors did not find any effect on behavioral or cognitive endpoints.

- Cardiovascular effects – the changes presented from the Gorr 2014 study is characterized in the ISA as "heart failure". But did these mice actually experience heart failure? The authors describe the effects as cardiovascular dysfunction, and incipient heart failure, but it isn't clear that there was actually death from this (which is what I assume is the outcome from failure of the heart).

Summary and Causality Determination
- I agree with the "suggestive" causality determination, although it is not clear to me why this endpoint received a "suggestive" determination, and others (such as long-term PM2.5 and CNS effects) received a "likely" determination.

UFP and Reproductive and Developmental Effects

Female Reproduction and Fertility:
- Table 9-13 incorrectly characterizes the doses the animals received for Li 2009 – they should be ug/m3, not g/m3.
- The lack of effects seen with low-dose DE in Li 2012 suggests that there may be a threshold for this effect.

Neurodevelopmental Effects:
- In the brain morphology section, the same information about ventriculomegaly being related to ASD is repeated twice in the same paragraph.

Chapter 10: Cancer

Introduction:
- The Smith (2016) 10 characteristics of carcinogens represent necessary but not sufficient conditions for carcinogenesis. While it is true that carcinogens display one or more than one of these characteristics, there are many chemicals that have those characteristics but are not carcinogens.

PM2.5 Exposure and Cancer

Biological Plausibility:
- This section discusses and emphasizes the Ames assay for mutagenicity, but also notes the drawback of the assays being conducted in bacterial cells. However, there are mammalian mutagenicity systems (particularly the in vivo assays), and EPA should emphasize results from those studies.
- This section discusses a lot of results from in vitro exposures, which is problematic for extrapolation to in vivo conditions. The in vivo results should be emphasized in this, and other, sections of this chapter.

- The discussion of the hallmarks of cancer is very vague. Also, while changes in telomerase activity is mentioned here, no data is provided to support changed telomerase activity.
- It is interesting and very informative to note that no animal toxicology studies have shown direct carcinogenicity from PM2.5 exposure.

Genotoxicity:
- It is alluded to in this section, but EPA should more clearly state that the mutagenicity studies done in vitro are hazard identifications only, and don't provide clear information about what might happen in vivo. A good example is provided by the mutation in the Salmonella strains to allow larger molecules across the cell wall – this would not be the case in an in vivo model.
- Where is the summary information for these studies?
- In the epidemiology studies, the Ma 2015 study is discussed as rating DNA damage as <40% or >40%. What does this mean? That 40% of the DNA contained damage? What kind of damage? If 40% of the DNA is damaged, then the cell is dead – the study authors may have not been excluding non-live cells. If EPA can't answer these questions, they shouldn't include the study in their discussion (the importance of study quality criteria).
- The summary fails to discuss the import of negative study results.

Epigenetic Effects:
- The Soberanes 2012 study showed increased methylation of the MMP2 promoter, but that would decrease the potential for tumor invasion, it would not increase tumorigenicity.
- When discussing genetic or epigenetic changes in non-in vitro studies, the EPA should specify what tissue was being tested.
- What do the NAS Panni 2016 results, presented as changes in "1, 1, or 10 CpG sites" mean? That kind of resolution is far beyond the realistic ability of these assays to measure, not to mention the inter- and intra-human variability. In fact, it would be useful to discuss the normal human variability in these biomarkers. Were they the same CpG sites in different people, or all over the genome, or could the authors even tell?
- Changes in expression of mir-21 are presented from Borgie 2015b. Is mir21 considered a tumor suppressive or promoting mir?

Lung Cancer Incidence, Mortality, and Survival:
- "ecological study design, estimation of PM2.5 concentrations for entire study duration from concentrations of other pollutants using conversion factors, and inadequate control for potential confounders are not the focus of this section. These studies are available at: https://hero.epa.gov/hero/particulate-matter." What do you mean by inadequate control for potential confounders? Because non-copollutant confounders are discussed so little in this document, it is difficult to tell what EPA would consider to be adequate or

inadequate control for confounders. In addition, there are plenty of studies used here that have ecological designs, why are they not OK here, but they are ok elsewhere?

- In Table 10-4, the exposure assessment for Lepeule 2012 is given as the average of the US EPA monitors for 1986-2009. This isn't the case – it is the EPA PM2.5 monitors for 1999-2009, but it is the EPA PM10 monitors with a conversion factor for 1986-1999.
- The R2 for the exposure model for Carey 2013 are pretty poor (0.23-0.71)
- The meta-analyses at the bottom of figure 10-3 should be included in the table (or in a separate table) with the relevant details.
- There is lots of variability in the effect estimates presented in Figure 10-3, with some negative estimates, and many that aren't statistically significant. From the perspective of exposure assessment, increasing the sophistication of the exposure assessment doesn't demonstrably impact the pattern of effect estimates as one would expect if there was bias towards the null with exposure error.
- With a better exposure assessment, one would expect to have higher exposure estimates and narrower CIs, but this is not what is observed with Jerret 2013 and Thurston 2013, compared to Krewski 2009 (particularly comparing Krewksi and Thurston, who looked at the same population). Similarly, Turner 2016 only looked at never-smokers, and if this is considered to be a more susceptible sub population, then it should have a higher, more precise estimate, which it does not (Table 10-5). Related to this, why are never smokers the group with higher incidence? Wouldn't you expect (based on biological plausibility) for it to be the smokers – I.e. for dose-response and pre-initiated reasons (like the urethane animal study)? And why is there such a big difference between Turner 2014's estimate for non-smokers (1.26) and 2016's estimate (1.04)? I understand that one is high versus low (presumably PM concentrations), but do these estimates correspond to one another when converted to a per 5 ug/m3 PM2.5 basis? It seems like they don't because the high versus low difference is less than 5 ug/m3.
- Table 10-5 says that Turner 2011 is the full cohort, but it should be never-smokers (appropriately specified in the text). Table 10-4 should also provide information about the sub-population analyzed, if there is one. In addition, the HR increases with the concentrations at the later time point (1999-2000), compared to the earlier time point (1979-1983). EPA should discuss how this could easily be the case for statistical reasons, and not because the risk is increasing in more recent times (it is because if you have the same number of deaths, but lower concentrations, then it makes the deaths per unit concentration look higher).
- Information about the H6C and CCHS cohorts presents the lag period as the 1-3 years of PM2.5 concentrations prior to cancer mortality. However, for standard cancer analyses for an agent that is considered to be carcinogenic, the cumulative exposure is the typical metric. By 1-3 years prior to death, the patient already has the disease, and likely is already undergoing treatment. So, is the EPA/study authors suggesting that PM2.5 exposure enhances mortality from lung cancer, but not its incidence? I understand that EPA is restricted to what the study authors have done, but there could be an emphasis on any studies that considered metrics that are consistent with the biological plausibility

argument, such as cumulative exposure. One of the "unacceptable" study criteria from the TSCA systematic review data quality criteria is "Exposures clearly fell outside of relevant exposure window for the outcome of interest." This seems relevant here.

- Related to the last point, Gradient presented information about temporality of PM2.5 exposure measurement and lung cancer mortality in Figure 5.1 of their comments on this ISA, which showed that many of the studies investigated exposures that were measured concurrently, *or after* the lung cancer mortality.

- With Wong 2016 conducted in Hong Kong (much higher concentrations of PM2.5), the effect estimate was about the same as the cohorts in the US and Europe – this is not consistent with the concept of a concentration-response.

- EPA notes at the beginning of this section that they don't include studies with "inadequate control for potential confounders". It seems that the Hart 2011 study, which does not consider smoking at all (a VERY important potential confounder for lung cancer), should not have been included in this section. It would be deemed unacceptable using the TSCA systematic review guidelines: "Confounding was demonstrated and was not appropriately adjusted for in the final analyses (NTP, 2015a)." Smoking should always be considered when looking at lung cancer.

- For the incidence studies, it is even more important to look at averaging time, with longer averaging times for PM2.5 concentrations obviously being more important. The idea of a one-month average of PM2.5 contributing to lung cancer (from the Gharibvand 2016 study) is ludicrous. Cancer is known to take decades to develop (look at the smoking data for comparison), and the idea of a one-month exposure to PM2.5 contributing to lung cancer is highly unrealistic.

- Figure 10-4, showing effect estimates from different types of exposure estimates (and the discussion in the text) shows that there is no difference with more precise exposure estimates (the prediction has been a bias away from the mean) and no difference in CIs. This paper also showed effects only in former smokers, not never smokers, which is inconsistent with the mortality data. However, this is more consistent with the idea of dose-response and pre-initiation that you would expect that PM2.5 may contribute to for lung cancer incidence.

- There seem to be fewer statistically significant positive studies for incidence than for mortality.

- C-R Function Shape – EPA cites Pope 2011, who combined smoking and SHS data with predicted PM2.5 concentrations from various studies and plotted them. A few concerns – what is the length of assumed exposure here (as noted above, longer exposure is usually necessary for cancer formation); also, the authors produce HR's, and then seemingly equate them to RRs, and plot the other results as RRs. These are NOT the same thing (Hernán, 2013; Stare and Maucort-Boulch, 2016; Sutradhar and Austin, 2017) and this isn't a comparable method. The authors also do this for CVD mortality, showing a much steeper D-R curve with ambient PM2.5 than smoking. Why does EPA/the authors think that gram for gram, PM2.5 is worse than smoking? Is there any basis for this? Perhaps both should consider the substantially different amounts of confidence in the exposure

metric? As before, the variability and error in these studies can prevent the identification of the appropriate shape of the C-R function, and the presence of a threshold.

- Cancer Survival – What confounders were considered in Xu (2013) and Eckel (2016)? Many factors can impact cancer survival that might be different between two cities, particularly with such variation as would be expected between LA and Honolulu, for example.

Summary and Causal Determination:

- The notes that PM2.5 components can be mutagenic in vitro, and that one study showed enhanced urethane-induced tumors, does not complete a pathway of biological plausibility of PM2.5 causing cancer. And it doesn't provide a plausibility pathway for mortality associated with relatively short-term PM2.5 exposure – months to several years. Those are two different things and should be separated out, because some genotoxicity in the years before cancer death aren't contributing to that cancer formation.
- Positive associations in never-smokers is cited several times, but there is no discussion of whether this makes sense – wouldn't an association in smokers, with their pre-initiated lung cells, make more sense?
- Again, no discussion of statistical significance (**chance**, bias, and confounding). And there are many other confounders that were not discussed in this section that could contribute to lung cancer mortality, particularly for this short a time-span.
- This lack of coherence does not suggest a likely causal relationship.

PM10-2.5 Exposure and Cancer

Biological Plausibility:

- Why is brain inflammation particularly emphasized in this figure (also for PM2.5 and UFP)? Is there substantial evidence of brain cancer? Or is there a pathway of systemic dysregulation thought to be caused by brain inflammation? If so, this should be discussed in this section.

Genotoxicity:

- For the Wessels 2010 study, the location from which the particles were collected should be included in the discussion. The single CHE study used as evidence here did not show a statistically significant change in 8-oxo-dG ($p < 0.1$ is not $p < 0.05$). The epidemiology study results were also not statistically significant.

UFP Exposure and Cancer

- Genotoxicity: there is a discussion of the results from Hemmingsen 2015, but that study focuses on PM2.5, and it seems that a lot of the mass concentration is higher than the 100 nm cut-off for UFP.

Chapter 11: Mortality

<u>Short-Term PM2.5 Exposure and Total Mortality</u>

- EPA states that "As detailed in the Preface, the focus of this section is on the evaluation of recently published studies that directly address policy-relevant issues, i.e., those studies where mean 24-hour average concentrations are less than 20 µg/m3 across all cities or where at least half of the cities have mean 24-hour average concentrations less than 20 µg/m3." Why 20 ug/m3? The 24-hr standard is 35 ug/m3. This statement references the Preface for the 2009 ISA – if it is important for this ISA, it should be in this ISA. This is also true of details about source apportionment in Section 11.1.11.2
- "The following sections provide a brief overview of the consistent, positive associations observed in recent studies of mortality and short-term PM2.5 exposures," Does this mean that the EPA is not including any studies that didn't provide consistent, positive associations? If not, then this should be restated.
- This same paragraph has a reference error (reference not found).
- The organization of this section, with a table at the beginning with all the relevant studies, is a better method than listing them over and over again in different sections, as is done in other chapters.

Biological Plausibility:
- EPA states in this section that "However, the evidence for how the initial events and subsequent endpoints could lead to the observed increases in respiratory ED visits and hospital admissions, for particularly chronic obstructive pulmonary disease (COPD) and asthma, is limited. Collectively, the progression demonstrated in the available evidence for cardiovascular morbidity (and to a lesser extent, respiratory morbidity) supports potential biological pathways by which short-term PM2.5 exposures could result in mortality." This seems to be a contradictory statement – the first sentence says that evidence is limited for how initial events can lead to HAs and ED visits, and the second states that the progression supports biological pathways. This needs to be clarified, and the plausibility of low concentrations of PM causing mortality after a short exposure (0-1 days) needs to be considered.
- I don't see any discussion of animal studies where mortality was an endpoint.

Total Mortality in All Year Analyses:
- When discussing the Lanzinger 2016 study, is EPA suggesting that the study size for the study is not high enough to discern a pattern between PM2.5 short-term exposure and mortality? Because only having 2 years of data won't affect short-term mortality associations (unlike long-term). Having the n in the summary Table 11-1 would help with this distinction.
- In the discussion of causal analytics papers, the EPA should include a discussion of whether the authors addressed the SUTVA assumptions.

Cause-Specific Mortality:
- Is it logical that respiratory mortality has higher effect estimates than CVD, but the evidence for morbidity is weaker?

Non-Copollutant Confounding of PM2.5 Effects:
- EPA states that "Recent multicity studies that assess the potential for copollutant confounding of the PM2.5-mortality relationship are limited to Europe and Asia" However, they then discuss Di et al. 2017, which is based in the US. It seems from Figure 11-3 that there is some attenuation of the risk estimate with copollutants, and some become non-statistically significant.
- None of the Sacks 2012 results (looking at different model specs for temp) were statistically significant.
- Seasonal analyses show heterogeneity of results, even with similar study types and all in the US. The EPA should offer some sort of explanation for this heterogeneity and lack of consistent pattern.
- For temperature patterns, the pattern seen by Dai 2014 (lower effects of PM at high and low temperatures) is not consistent with the (imprecise) results of Pascal 2014, who showed increased PM2.5 effects at high temperatures. Does EPA or the study authors have an explanation for this discrepancy? Similarly, Sun 2015, who shows more effects at lower temperatures is inconsistent with both Dai 2014 and Pascal 2014. And Li 2015 showed higher effects at both lower AND higher temperatures. These four studies have literally run the gamut of options and demonstrate unexplained heterogeneity in study estimates.
- City and Regional Heterogeneity – Two US studies conducted in similar ways did not show the same potential components as being responsible for the regional heterogeneity (Lippmann 2013a, Dai 2014). And in Boston Zanobetti 2014a reported that the strongest association was found on winter days with higher primary PM, even though EPA reports that the warm season has the strongest associations (in the seasonal section). Davis 2011, when looking for city-clustering by PM2.5 components, showed a North-South division, whereas the PM2.5-effects have typically shown an East-West division. Baxter 2013 also could not identify sources or components to explain the observed regional heterogeneity. All together it seems that despite multiple attempts, this heterogeneity is not explained by sources or PM components. It would be helpful if EPA could report the amount of PM2.5 effect estimate attributable to the various components reported from Lippmann 2013a and Baxter 2014 (I.e. the R2), as is done with Baxter 2017. The exposure section also shows a lack of ability to explain the heterogeneity in effect estimates for PM2.5.

Exposure Assessment Techniques
- Monitor representativeness wouldn't just provide information about regional heterogeneity (maybe), it would provide information about the biases and potential validity of epidemiology study results. EPA states that Di 2017 found a smaller association using the nearest monitor versus the modeled estimates, and that this was

consistent with Kloog 2013. But Kloog 2013 found a larger association with the nearest monitor method. Either there is a discrepancy here, or EPA needs to better explain what it is comparing to. There is also a substantial difference in effect estimates (0.8 % vs 4.5%). When discussing the differences between monitored and modeled data, it would be helpful if the EPA reported how well the study's model predicted monitored concentrations, as a measure of the accuracy of the model.

Timing of Effects and Exposure Metrics:
- A figure of the various lagged effects would be useful, particularly because many of the effect estimates are not presented elsewhere in the ISA. This would allow the readers to more easily understand the lagged patterns.

Concentration Response and Threshold Analyses:
- "2004 AQCD and 2009 PM ISA stated that conducting C-R and threshold analyses is challenging due to the "(1) limited range of available concentration levels (i.e., sparse data at the low and high end); (2) heterogeneity of [at-risk] populations [between cities]; and (3) influence of measurement error" (U.S. EPA, 2004). Even with these inherent limitations, studies have continued to examine the PM-mortality C-R relationship and whether a threshold exists." It isn't just challenging, it means that the results can be inaccurate or uninterpretable. Just because study authors did these analyses anyway, doesn't mean that the EPA has to take the results at face value, knowing that these problems exist. Rhomberg 2011 shows that you can't detect a threshold or nonlinear response with this much variability in the data, and a reviewer at the ozone workshop held in Oct-Nov 2018 said the same thing.
- For the Shi 2015 study (Figure 11-11), it doesn't look linear. Do the authors ever use the default as non-linear, and then test if linear fits any better than non-linear? (This has to do with your perspective and default assumptions). And if you have less confidence in the curve less than 5, you should also have less confidence in the curve at 10-15 ug/m3 – because the confidence interval widths are the same, down to about 2.5 ug/m3, and it certainly looks like a threshold at somewhere between 5 and 10 to me.
- It looks like the Di 2017a analysis forced the curve through the origin – if it did, how could it identify a threshold of no effect? Upon reading the text of that manuscript, it is not clear if they did force it through the origin or not – this should be clarified by EPA. What should also be clarified by EPA is the risk metric. Di 2017a presents the risk metric as a percent increase in relative risk (RR) per 10 ug/m3 PM2.5, which is a non-standard metric. Presumably this can be interpreted as a % increase in risk of total mortality per 10 ug/m3 PM2.5, but EPA should clarify this, so readers know that the results can be compared to other study results. Interestingly, the authors also present the absolute risk difference, per 1 million persons at risk. This is a very helpful metric, and shows that with the main analysis, there are 1.4 people with increased risk per 1 million at risk. This puts the risk in the context of other assessments, such as carcinogen assessments, and would allow the EPA to use similar frameworks for acceptable and unacceptable risk.

PM2.5 Components and Sources:

- In Figure 11-13, why is there no lag information in the orange boxes (null or non-statistically significant negative associations)? Also, why are some of the lag numbers in the boxes (primarily in the PM2.5 total row) bolder? This should be included in the legend.
- A forest plot would be useful in this section, to demonstrate whether or not the individual components had larger or smaller effect estimates than total PM2.5.
- It should be noted from Figure 11-14 of Lippmann 2013a, that the majority of the effect estimates weren't statistically significant, and many were negative. In addition, soil was more consistently positive than combustion products.

Summary and Causal Determination:

- While there are more studies on uncertainties like copollutant, C-R functions, regional heterogeneity, and PM2.5 components and sources, none of them really clarifies any of the underlying uncertainty. There are still unknowns with copollutants, C-R functions are still plagued by problems with innate variability that makes them difficult to interpret, there are studies showing completely inconsistent temperature relationships, none of the studies on regional heterogeneity adequately explained the reasons for the city-specific heterogeneity, and it is not clear what components or sources are causing the observed effects. At what point do you go back to your underlying assumptions and ask whether they are valid?
- "Collectively, recent studies indicate that the heterogeneity in PM2.5-mortality risk estimates cannot be attributed to one factor, but instead a combination of factors including, but not limited to, compositional and source differences as well as exposure differences." This statement is misleading – there is no data presented that looks at all of the possible components together to show that combined they impact the observed heterogeneity. What we do have is several studies that show almost no impact of composition, source, and exposure differences.
- "However, to date, studies have not conducted extensive analyses exploring alternatives to linearity when examining the shape of the PM2.5-mortality C-R relationship." It is hard to be confident that the shape of the C-R function is linear, when you haven't examined alternatives to linearity.

Long-Term PM2.5 Exposure and Total Mortality

- Again, why is the focus on 20 ug/m3 for long-term PM2.5 concentrations? This is above the current (and former) standard and shouldn't be equated to the 24-hour standard (which has a different form).
- "The evidence in this section will focus on epidemiologic studies because experimental studies of long-term exposure and mortality are generally not conducted." But long-term exposure studies in animals have been conducted, typically at higher-than-ambient

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concentrations – these studies could be investigated to explore whether animals have experienced increased mortality with exposure to PM2.5.

Associations between LT-PM2.5 and Mortality:

- Harvard 6 Cities and ACS Cohorts – The EPA notes that there are discrepancies between the findings of Pope 1995 for the early ACS (found a positive stat sig effect) and Enstrom 2017 (did not find a positive stat sig effect), but that there was a difference between the two in that Enstrom used 85 counties and Pope used 50 MSAs. However, the Enstrom study had a finer resolution, so one would guess that it had less exposure error and therefore possibly a greater effect estimate or one with narrower confidence intervals from Pope. As EPA notes, the many re-analyses of the ACS cohort present the opportunity to explore the effects of different types of exposure estimates. Instead of just saying that the results are generally consistent in magnitude and direction, EPA should take this opportunity to look for more patterns in the data, based on the assumptions that are made. For example, whether a better exposure estimate moves the effect away from the null or narrows the confidence intervals. From Figure 11-17, it doesn't seem that any of the investigated subtypes of mortality particularly show an increase in effect estimate, or a decrease in confidence interval, compared to total mortality. The regional estimate of mean PM2.5 concentration from Turner 2016 is shown as 0.5 in Figure 11-17. Is this right?

- Other North American Analyses – As with the H6S and ACS cohorts, Figure 11-19 shows that there is no increase in the association, or particular decrease in the effect estimate CIs, of CVD or respiratory mortality compared to total mortality. The Medicare cohort also offers the opportunity to compare results from different exposure models – the Shi 2015 study in New England used a sophisticated model, and Kioumourtzoglou et al. (2016) used fixed site monitors, and the effect estimate for Shi 2015 was smaller with about the same precision, so this does not support the hypotheses about improved exposure measurement techniques. The model accuracy of Thurston 2015 should be mentioned, because if it only uses a LUR model, these are known to be inaccurate in locations where they weren't specifically designed. The Crouse 2012 and 2015 results were somewhat inconsistent (IHD mortality in 2012 was 1.31, and in 2015 was 1.09) with the difference in studies being 5 more years of follow up. The EPA should offer some explanation or discussion of this result, if one was presented by the authors. Again, the same data between Lipsett 2011 and Ostro 2015, but Ostro had a better exposure estimate method, and the effect estimates were lesser for Ostro. European studies are discussed in this section, so I would recommend that the section be retitled "Other North American and European Analyses". Also, results from the European analyses should be included in the Forest plot for Figure 11-19, or their own forest plot.

- Causal Analysis – Did the studies cited adequately discuss whether the SUTVA assumptions were met in their studies? What about Tony Cox's other causality papers? What about the Greven 2011 and Pun 2017 papers that did a difference-in-difference

analysis to determine the effects of local changes in PM compared to national trends and found that there was no association between PM2.5 and mortality?

- Life Expectancy – what is a doubly-robust additive hazards model, and what kind of information does it provide that allows the authors to estimate 5400 fewer deaths from a decrease of 1 ug/m3 in annual average PM2.5? The authors (Wang 2017a) call it a causal analysis, but it is not clear why this "double robust" method is causal. Also, the effect estimate from Wang 2017b (upon which Wang 2017a is supposedly based) is pretty high – 1.021/1 ug/m3, whereas Di 2017c is 1.04/5 ug/m3. What kind of controls for confounding did Bacarelli 2016 use? Were the results comparable to the other life expectancy studies?

Potential Copollutant Confounding:
- What is the reference for the meta-analysis that only looked at copollutant models with r < 0.7?

Shape of the C-R Curve:
- EPA reports that many studies have shown evidence for LNT, some have shown supralinear shapes, and other studies have shown thresholds. As above, these likely aren't the best kind of studies to use to determine the shape of the C-R function, given the variability and errors in the estimates (Rhomberg 2011).

Factors that May Influence PM2.5 Associations:
- It is interesting that Lee 2011 showed that monitors are more accurate within a 98 km distance, but AOD is more accurate outside of that. That is a pretty bad track record, given the supposed resolution of satellite measurements.
- When discussing the Jerret et al. 2016 results, EPA should note that the effect estimate doesn't tell you how accurate the model is at estimating exposures.
- Results from the Hart 2015 study show that enhanced exposure estimate accuracy doesn't change the estimate, which would is not what would be predicted. They themselves show that a bias correction increases the effect estimate. Therefore, either the more sophisticated exposure estimate methods aren't actually more accurate, or there is some other reason for the observed association that is not impacted by the method used to estimate exposure.
- When talking about exposure windows, and specifically the Wong 2015 study, EPA noted that risks decrease (presumably from PM) in ages over 70 or 75. Is that just in the Wong 2015 study, or is it a general result? If it is a general result, that is not what would be expected for a population dying from CVD or respiratory illnesses and is not consistent with the hypothesis of a vulnerable population having enhanced mortality from PM2.5 exposure.

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PM2.5 Sources and Components:
- The Wolf 2015 results likely aren't useful, because of such poor LUR model performance.

Short-Term PM10-2.5 Exposure and Total Mortality

Associations with All-Year Mortality:
- While all of the associations presented are positive, few are statistically significant, and many have the added exposure error of estimating PM10-2.5 by subtracting PM10 from PM2.5 county-average measurements.
- CV and respiratory mortality may have somewhat higher effect estimates, but they have pretty wide CI's, so it is hard to tell.

C-R Relationships and Thresholds:
- Both the studies cited that looked at different concentration cut-points and the association between PM10-2.5 and mortality found that the highest concentrations and/or extreme events like dust-storms, had the lowest associations with PM10-2.5. Does this make sense? The EPA should address the lack of concentration response here.

Summary and Causal Conclusions:
- EPA states that "recent studies provide initial evidence that informs additional uncertainties and limitations identified in the studies evaluated in the 2009 PM ISA, specifically potential copollutant confounding; effect modification (e.g., temperature, season); and the shape of the C-R relationship and whether a threshold exists." However, most of these sections did not provide information that furthered informed the uncertainties in these areas. The studies looked at these potential limitation areas, but no real conclusions could be drawn about the results. Just because someone investigates a limitation in a study, doesn't mean that we come out of it more informed.
- Suggestive of causality doesn't seem supported here, because there were almost no statistically-significant effects, and many unaddressed uncertainties (bias, chance, confounding).

Long-Term PM10-2.5 Exposure and Total Mortality

- The EPA's final causal conclusion in this section is suggestive, but based on what? There is limited biological plausibility data, a number of epidemiology studies that show no effect, and those that do show effects are often attenuated when PM2.5 is included in the model, the exposure estimates are very uncertain (all used the subtraction model), and there is no other information about model specification, temperature, etc. There is one French study that shows positive effects, but is this enough (in the face of a lot of negative evidence) to call the endpoint suggestive?

Short-Term UFP Exposure and Total Mortality

- EPA references the preface for the last ISA again.

Long-Term UFP Exposure and Total Mortality

- What did the experts in Hoek et al. 2009 base their recommendations on, if there was no data for the endpoint? What is the point of asking experts for their advice on something without any information? I don't think that the Hoek study should be included in this review, because it is apparently based on opinion and not fact.
- This chapter generally requires editing.

Chapter 12: Populations and Lifestages Potentially at Increased Risk from PM Exposure

- The summary of this chapter should describe the conclusions for the chapter (I.e. the life stages or populations considered to be at increased risk), as is done with the other chapter summaries.
- "similar to the characterization of epidemiologic evidence in Chapters 5-11, statistical significance is not the sole criterion by which effect modification and evidence of increased risk is determined; emphasis is placed on patterns or trends in results across these epidemiologic studies." This is a mischaracterization of the method used in the other health effects chapters, where statistical significance wasn't used at all, let alone as the sole criterion. In this chapter it is also essentially never mentioned again, except for the occasional "wide confidence interval". The figures in the supplement do include notations for determination of whether there is a statistically significant difference between the two groups, and this should be incorporated into the main text.
- In the supplement the figure legends need to be changed so that they are endpoint-specific, and there needs to be an explanation of the up and down arrows in the colored boxes.

Pre-Existing Diseases/Conditions:
- CVD – The EPA concludes that there is only suggestive evidence of pre-existing CVD increasing the risk for PM2.5-mediated effects, but this isn't consistent with the hypothesis that those who are already vulnerable are the ones who would have more extreme effects from PM exposure (like mortality), or that PM2.5 targets the CV system. Does it make sense that there is a causal association between PM2.5 and CV effects, but only a suggestive association between PM2.5 and people with CVD? Is the EPA suggesting that PM2.5 is causing these effects de novo?
- Diabetes – I agree with the EPA that the evidence is insufficient to determine if diabetics have an increased risk from PM2.5 exposure. There was inconsistent evidence and issues with the studies, and this is the appropriate conclusion to derive from that combination of data.

- Obesity – The text is not clear as to why obesity gets a suggestive designation, whereas diabetes got an insufficient designation. Both have a fair number of studies showing mostly inconsistent associations. Similar with elevated cholesterol – why is that insufficient, and obesity is suggestive?
- Elevated cholesterol – similar to diabetes, I agree that there is insufficient data.
- Respiratory Diseases – it is unclear in this section whether data from Chapter 5 about asthma and COPD are being used to draw the suggestive conclusion here, or if it is the limited data presented where comparisons are made between people with and without the disease. In the introduction to this chapter the EPA specifies that the at-risk category is particularly in comparison to people without the potential risk factor, but the conclusions from this section seem to be mostly from the Chapter 5 conclusions.

Genetic Factors:
- The conclusion "the evidence is suggestive that individuals with variants in the glutathione pathway are at increased risk for PM2.5-related health effects compared to those without a variant genotype." should be more specific to which variant type – for example, to variants that reduce the ability for the glutathione pathway to reduce oxidant stress. There is also not much evidence presented for the glutathione pathway, and no information about the active or inactive or less active forms of the gene, and if those are related to PM2.5 health effects.
- There should be a description of the functional effect of the NFE2L2 rs1364725 allele. Does this allele decrease the function of the NFE2L2 protein? Were the people heterozygous for the allele (and therefore any effect would have to be dominant), or homozygous? Also, the referenced paper (Hampel 2010) used 16 sec ECG recordings, but my understanding is that there needs to be a longer duration of ECG recordings to get reliable variability data. In addition, that study did not see associations with the GSTM1 deletion allele. Similarly, the cited SNPs in GSTP1, TNF, and TLR4 – did those reduce the activity of the gene products? Just because it is a minor allele, doesn't make it less functional. The same with the micro-RNA processing gene GEMIN4 – if you don't know the effect of the SNP, then what does it tell you if there is an association?

Sociodemographic Factors:
- Children – To test the hypothesis that increased oral breathing in boys increases their risk of PM2.5-mediated effects, are there any studies that address the effects of PM2.5 in boys vs girls? This section also states that children tend to spend more time outdoors, but the exposure chapter section that discusses the CHAD database states that according to that data, children spend less time outdoors than adults (pg 3-65). So, either the CHAD database is flawed, or this statement is. This section states that "there has been little evidence from stratified analyses to demonstrate children being at increased risk of the health effects associated with PM2.5 exposure compared to adults. That is, positive effect estimates are often observed in stratified analyses of children, but these effect estimates are similar in magnitude to those observed for adults (Supplemental Table S12-7) (U.S.

EPA, 2018)." This doesn't seem consistent with the conclusion that there is adequate evidence that children are at increased risk from PM2.5 exposure. The conclusion seems to be based on the data showing positive associations in children for things that were only measured in children (e.g. lung function development), but that seems to go against what EPA said is the point of this section, which is comparison to a reference group. These aspects should be divided or specifically addressed.

- Older Adults – this document notes that there is no consistent evidence that older adults have greater health effects associated with exposure to PM2.5 than younger adults. This seems inconsistent with the general hypothesis that people with greater risk of the health effect are more susceptible to something that contributes to that health effect. It seems that there is actually evidence of no increased risk amongst older adults, not insufficient evidence – there is plenty of evidence.

- Race – in the summary section, the EPA concludes that there is adequate evidence demonstrating an increased risk of PM2.5-related effects in non-whites, in part due to disparities in exposure. However, in details of this section there is almost no discussion of whether the epidemiology studies tested whether the disparity was due to increased exposure, or due to other factors. This should be explicitly discussed in this chapter. If the conclusion is that the increased risk is due to some other non-exposure factor, there should be discussion of what that factor is.

Residential Location:
- Urban v Rural – There is a several page list of study results in this section, describing largely inconsistent results comparing urban v rural locations. However, there needs to be synthesis of all of these results – are there patterns? Why might you expect there to be higher associations in urban than rural locations, or vice versa? What would other data suggest? Did the authors control for the higher PM in urban locations? Just listing study results does not help the reader synthesize the conclusions.

- Proximity to roadway – again, why would you expect certain vulnerabilities, especially if there is no particular evidence that the PM concentrations are higher? Is it noise, or other SES factors, or other pollutants? Were these controlled for in the studies (proximity studies being notoriously problematic for drawing conclusions)? Both of the cited animal tox studies have interpretation issues – there may be other, non-PM related reasons why more effects were seen with animals closer to a major road (e.g. stress, noise) in Kleinman 2005, and the other cited study (Farraj 2006a, b) showed a concentration response, not a response to proximity to roadways (which the EPA says earlier does not increase PM2.5 concentrations).

Behavioural and Other Factors:
- Smoking – Lung cancer should be included as an endpoint in this section, because it is probably the best studied for differences between smokers and non-smokers, and EPA concluded that there was a likely causal association. From the summaries in Chapter 10, it seemed like there was more associations between PM2.5 and lung cancer in never

smokers than in ever or current smokers. In general, one would predict that PM2.5 would increase effects in smokers, because it would generally increase their dose, and because they already have a lot of the health effect precursors that are being attributed to PM (inflammation, CV changes, respiratory effects). Conversely, perhaps there is an adaptive process that protects the lungs of smokers from additional exposure. Either way, these are important issues to discuss in addition to just listing the study results.

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Dr. Timothy E. Lewis

- The PM advisory panel should be retained to enable more thorough review of this ISA.

General Comments on Chapter 13

There is no line numbering until Page 13-58.

The evaluation of welfare effects often lumps PM together as a whole without considering different size fractions. It is recommended that EPA perform more analyses for different size fractions to determine whether various effects on visibility, climate, and materials are observed.

Were there specific quality criteria set as targets for inclusion or exclusion of welfare effects studies? These should be articulated up front in each section. Studies are mostly descriptive with little reference to quality.

There is little discussion of how study findings that consist of different PM concentrations, different mixtures, different experimental design questions, and different ambient conditions apply directly to non-ecological welfare effects in the U.S.

I did not see a "Research Needs" section. I thought there used to be one in previous ISAs.

Visibility

A thorough discussion of the instrumentation used for measuring visibility is provided. It would be very useful if the instruments were shown in a table with the figures of merit associated with each, and how well each instrument provides the most policy relevant measurements.

Comparing perceived visibility impairment of urban versus more "bucolic" settings may have inherent biases. Some viewers of these scenes may not find urban viewscapes to be very appealing no matter how clear the image may be. Moreover, regional differences in perceived visibility may be due to societal differences. Westerners may have greater expectations of clear mountain vistas than Easterners.

The color maps, bar charts and other graphical data presentations are well done.

The uncertainty associated with the size fraction and visibility impairment needs to be stated clearly.

The document does a good job more firmly establishing a causal relationship between PM and

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visibility. The challenge I see for the Agency is how to tease out the complex nature of PM across the country and how the variation in PM composition affects visibility differently. Setting a secondary standard given such variability will be very difficult.

Does PM or perhaps other pollutants, such as the photochemical oxidant family of potent lachrymators known as the peroxyacyl nitrates, have a direct effect on visual acuity? Instruments would not be responsive to these eye irritants as the actual human eye.

The distinction between anthropogenic PM impairment versus natural PM impairment needs to be more clearly separated and explained. How this distinction can or will be dealt with for setting a secondary standard needs to be proposed.

Climate

An expert panel should be convened to more fully review the non-ecological welfare effects of PM on climate. There are many highly qualified scientists that would be able to provide sound review comments on this complex issue.

Uncertainty in the effects of complex aerosol composition on climate need to be better resolved.

I'm not in total agreement with moving the ecological effects of PM into the NOx/SOx ISAs. The interception of incoming solar radiation by PM on stream temperatures and forest productivity are due to more than just the N and S components of PM. These climate effects of PM on ecosystems should be discussed in this document.

Is there any new evidence that increased atmospheric turbidity is increasing cloud-to-ground lightning strikes and hence increased forest fires?

Materials

An expert panel should be convened to more fully review the non-ecological welfare effects of PM on materials. There are many highly qualified scientists that would be willing to provide sound review comments on this complex issue.

It is laudable that data from other countries were included in the assessment. Were sufficient meta data available to fully characterize the data quality attributes associated with these data?

Dr. Corey Masuca

2.2 Atmospheric Size Distributions

Atmospheric particle formation (secondary) nucleation, accumulation, and coarse modes

2.3 Primary Sources and Atmospheric Formation

Primary PM – source-derived

Secondary PM – gas-phase chemical compounds

2.3.1 – Primary PM2.5 Emissions
2.3.1.1 – National Scale Emissions

Uncertainties in emission estimates

Dust and fire – significant portion of PM2.5 2014 NEI

Dust includes agricultural and road dust, predominately

2.3.1.2. – Urban Scale Emissions

Great variability from city to city in PM2.5 primary emissions

Mobile sources are a major source of primary PM at urban scales

2.3.2 Secondary PM2.5 Formation

Secondary emissions account for a substantial fraction of PM2.5 mass with both natural and anthropogenic sources, forming by way of atmospheric photochemical oxidation reactions of both organic and inorganic gas-phase precursors.

2.3.2.1 Precursor Emissions

Ammonia plays important role in the formation of sulfate and nitrate PM. Oxidation of VOCs may also yield semi- and nonvolatile compounds that contribute to PM and the formation of new particles.

Sulfur dioxides emissions are mainly from electricity generation units (EGUs). Nitrogen oxides are emitted by a range of combustion sources, including various mobile sources

2.3.2.2 Secondary Inorganic Aerosols (SIA)

Particulate sulfate, nitrate, and ammonium formation processes help to form oxides of sulfur and nitrogen. Together, these PM2.5 components produced by secondary formation often account for the majority of PM2.5 mass.

Both H_2SO_4 and HNO_3 react with atmospheric ammonia. Atmospheric particulate NH_4NO_3 is in equilibrium with gas phase NH_3 and HNO_3. Lower temperature and higher relative humidity shifts the equilibrium towards particulate NH_4NO_3 because of the large sensitivity of the equilibrium constant to temperature.

2.3.2.3 Secondary Organic Aerosols (SOA)

In the presence of high NOx concentrations, the oxidation of biogenic hydrocarbons is observed to produce larger quantities of SOA. High ambient NOx concentrations in the atmosphere are typically due to anthropogenic emissions. Mixtures of both organic and anthropogenic precursors produce greater SOA yields than mixtures dominated by just one class of precursors.

2.3.3 Primary PM10-2.5 Emissions

Crustal materials dominate the PM10-2.5 fraction throughout the US and fugitive dust has been identified as the largest sources of measured PM10 in many locations in the western US. Mineral dust, organic debris, and sea spray have also been identified as mainly in the coarse fraction. Road and construction dust represent a mechanism for suspension of crustal material on paved and unpaved roads.

Any potential for secondary coarse PM formation?

2.3.4 Ultrafine Particles

Ambient UFP originate from two distinct processes: primary emissions and new particle formation (NPF). Primary UFP originate from a large variety of sources such as transportation (road, traffic, ships, and aircraft), power plants, municipal waste incineration, construction and demolition, vegetation fires, domestic biomass burning, cooking, and cigarette smoke.

2.3.4.1 Primary Sources

Motor vehicles are a major, if not the most important, source of UFP in urban environments.

Most of the particles emitted by marine and aircraft engines are in the ultrafine size range. Emissions of UFPs appears to be a strong function of fuel sulfur content, with reduced emissions from lower sulfur fuels.

Biomass burning is also a major source of UFP.

PM2.5 and PM10 have various degrees of inorganic metals such as chromium, cadmium, manganese, arsenic, etc.

No discussion of natural background concentrations or anthropogenic transport between cities/states/regions, etc. of primary PM

2.4 Measurement, Monitoring, and Modeling
2.4.1 PM2.5 and PM10

FRMs and FEMs

In practice, a large fraction of the FEM monitors in operation form PM are automated and designed to provide hourly data, while FRMs for PM2.5 PM10, and PM10-2.5 require sampling for 24-hours and provide a daily average PM2.5 concentration, including pre-and post sampling gravimetric laboratory analysis

41% reduction from 2000 through 2017 for PM2.5 – annual average

2.4.2 PM10-2.5

Although the PM10-2.5 FRM and FEMs were already discussed in the 2009 ISA, the state of technology for PM10-2.5 measured is reviewed here because the large data set of nationwide PM10-2.5 network measurements is reported for the here, in this document, for the first time. PM10-2.5 FRM and FEMs new used for routine network monitoring are considerably improved compared to methods (i.e., subtraction methods) used in the previous key analyses of PM10-2.5 sampling issues. New results reveal changing trends in PM2.5/PM10 ratios.

2.4.4 Chemical Compounds

Measurement of PM components is potentially useful for providing insight into what sources contribute to PM mass as well as for discerning differential toxicity. Sulfate, nitrate, ammonium, organic carbon and elemental carbon as well as a suite of elements are measured in national speciation monitoring networks and intensive field studies mainly by collection on filters.

2.4.5 Satellite Remote Sensing

Satellite instruments measure radiance (electromagnetic energy flux), that can then be used to provide information on the aerosol column amount, or the aerosol optical depth (AOD). Because PM2.5 is not directly measured, computational algorithms involving a range of assumptions must be applied to obtain estimates of PM2.5 concentrations. These inferred measurements involve potential errors that are not encountered with the FRM or other ground-based PM2.5 measurements.

Data cannot be collected when clouds and snow are present or from excessive amounts of smoke being mistaken for clouds.

The many factors that impact the relationship between AOD and PM2.5 concentrations lead to widely varying and sometimes relatively low, correlations when linear relationships are developed.

Limitations in accurately measuring PM concentrations

Any studies conducted to compare concentrations from satellite remote sensing with FRM/FEM monitoring?

2.4.6 Monitoring Networks

Extensive new PM monitoring efforts now complement long-standing networks by providing additional data supporting multiple objectives, including for PM research. These new monitoring efforts including Near-Road Monitoring for PM2.5 and the National Core (NCore) network for multipollutant measurements that are associated with special projects or are complementary to other networks, including particle number, black carbon, and continuous component monitoring.

Limitations of three to six day sample collection using FRM; FEM while continuous, not primary method

2.4.7 Chemistry-Transport Models

Key observations were that the largest errors in photochemical modeling were still thought to arise from the meteorological and emissions inputs to the model and that additional uncertainty was introduced by the parameterization of meteorological and chemical processes

No discussion of limitations and/or uncertainties of CTM

2.5 Ambient Concentrations
2.5.1.1 Variability Across the US
2.5.1.1.1 PM2.5

Both annual average and 98th percentile concentrations are generally lower than what was observed in the 2005-2007 period, continuing the downward trend.

The mean of annual average concentrations based on 24-hour samples across all sites during the 3-year period (2013-2015) was 8.6 micrograms/cubic meter. This compares to a mean of annual average concentrations of 12 micrograms/cubic meter from 2005 to 2007.

2.5.1.1.2 PM10

During the period from 2013-2015, the national average concentration was 21.1 micrograms/cubic meter, which is 15% lower than the average for 2005-2007

Summer concentrations appear to be typically higher than other seasons, with the highest average concentration as well as the highest concentrations at all percentiles up to the 95th percentile for summer. Winter concentrations are lower at all percentiles with average concentrations of 6 micrograms/cubic meter lower in winter than in summer.

2.5.1.1.6 PM2.5 Components

A major change in PM2.5 composition compared to the 2009 PM ISA is the reduction in sulfate concentrations, resulting in smaller sulfate contribution to PM2.5 mass in 2013-2015 compared to 2005-2007, especially in the Eastern US. As a result, at many locations sulfate has been replaced as the greatest single contributor to PM2.5 mass by organic material of nitrate.

2.5.2 Temporal Variability
2.5.2.1 Region Trends
2.5.2.1.5 Chemical Compounds

In the 2009 PM ISA, sulfate is described as the most abundant component of PM2.5 on a national average, with nitrate, particulate organic matter and sometimes crustal material also contributing substantially to PM2.5 mass.

Decreases in sulfate concentrations have led to decreases in PM2.5 concentrations since sulfates accounted for a large fraction of PM2.5 mass

12-10-18 Preliminary Draft Comments from Members of the Clean Air Scientific Advisory Committee (CASAC).
These preliminary pre-meeting comments are from individual members of the Committee and do not represent
CASAC consensus comments nor EPA policy. Do not cite or quote.

2.5.2.2 Seasonal Variations
2.5.2.2.1 PM2.5

Averaged over all locations and years from 2001 – 2006, seasonal average PM2.5 concentrations were approximately 12 micrograms/cubic meter in summer and winter, but declined to approximately 9 micrograms/cubic meter in the spring and fall.

Observations that the highest seasonal average concentrations occurred in the Eastern US and in winter in the Western US.

The observed reduction in summer PM2.5 concentrations in the East to the extent that summer is no longer the season with the highest national average PM2.5 concentrations is a major development, and is a predictable consequence of successful reduction of SO2 emissions.

2.5.2.2.4 PM Components

Sulfate and OC together accounted for the majority of PM2.5 mass in many metropolitan areas in the summer, while higher nitrate concentrations were observed in the winter.

2.5.2.3 Hourly and Weekday-Weekend Variability

A two-peaked diel pattern was observed in diverse urban locations and attributed to rush-hour traffic for the morning peak and a combination of rush hour traffic, decreasing atmospheric dilution, and nucleation for the afternoon/evening peak.

2.5.3 Common Patterns of Particulate Matter Characteristics in the US

Historically, PM2.5 has been highest in the summer and has been largely accounted for by sulfate over a large area that that encompasses most of the Eastern US, extending into the Great Plains.

At all of the locations reported sulfate was the most abundant component measured for the period 2003-2005, accounting for close to half of the overall average PM2.5 mass.

Ammonium nitrate and organic PM from diverse combustion sources are the main contributors to PM2.5 under winter conditions.

A common characteristic of PM in both California and the dryer areas of the Western US that contrasts with the Eastern US is higher fraction of PM10 accounted for by PM10-2.5, with PM10-2.5 accounting for the most PM10 mass in the West, but PM2.5 accounting for most PM10 in the East.

PM2.5 concentrations averaged over the 11-year period from 1998-2008 over the entire contiguous US were reported to be 2.6 micrograms/cubic meter higher on days under stagnant conditions than for non-stagnant days. When all US data over a multiyear period are considered, temperature is positively correlated with PM2.5.

Importance of confounding for temperature and/or relative humidity in either controlled human studies and/or epidemiological studies.

2.5.4 Background Particulate Matter

Missing discussion on regional (i.e., state-to-state) transport for both PM2.5 and PM10.

Background PM concentrations can be best characterized with chemical transport modeling simulations via source apportionment modeling or estimating what the residual PM concentrations would be were the US anthropogenic emissions entirely removed (i.e., "zero-out" modeling).

2.5.4.2 Intercontinental Transport

Transport at midlatitudes is dominated by westerly winds, which transport East Asian emission across the North Pacific Ocean to North America.

Observed trends in PM are usually more closely related to local emission trends than to long-range transport, and at monitoring sites throughout the US intercontinental influences are small.

Missing discussion on regional (i.e., state-to-state) transport for both PM2.5 and PM10.

Dr. Steven Packham

These Draft Consultative Comments (draft comments) are submitted in preparation for a meeting of the Clean Air Science Advisory Committee (CASAC) to peer review EPA's *Integrated Science Assessment (ISA) for Particulate Matter (External Review Draft – October 2018)* (PM draft ISA). They have been prepared in haste and do not reflect all thoughts and concerns held by this Member. Additional draft comments may be submitted later.

Comment: Relating to Chapter 4 Dosimetry of Particular Matter, *Overall Conclusions regarding the Dosimetry of Particulate Matter (PM)*, bullet 1.
- *New information, altering a conclusion in the last PM ISA, shows that particle translocation from the olfactory mucosa via axons to the olfactory bulb may be important in humans.*

I'm somewhat familiar with the particle translocation evidence. It would be helpful if the draft ISA could identify the adverse health effect(s) this particle translocation is suspected of causing.

Comment: Relating to 4.1 Introduction

The introduction is generally well written with a clear narrative and represents a thorough collection of referenced research. The NEROnet-linking functionality adds a significantly beneficial dimension to the PM draft ISA literature review process.

Comment: Relating to 4.1.2 Structure and Function of the Respiratory tract: 4.3.1.3 Alveolar Region, page 4-52, Line 20. "There is evidence that particle aggregates may disassociate once deposited in the lungs. This disassociation makes inhaled aggregate size the determinant of deposition amount and site, but primary particle size the determinant of subsequent clearance (Bermudez et al., 2002; Ferin et al., 1992; Takenaka et al.,1986)"
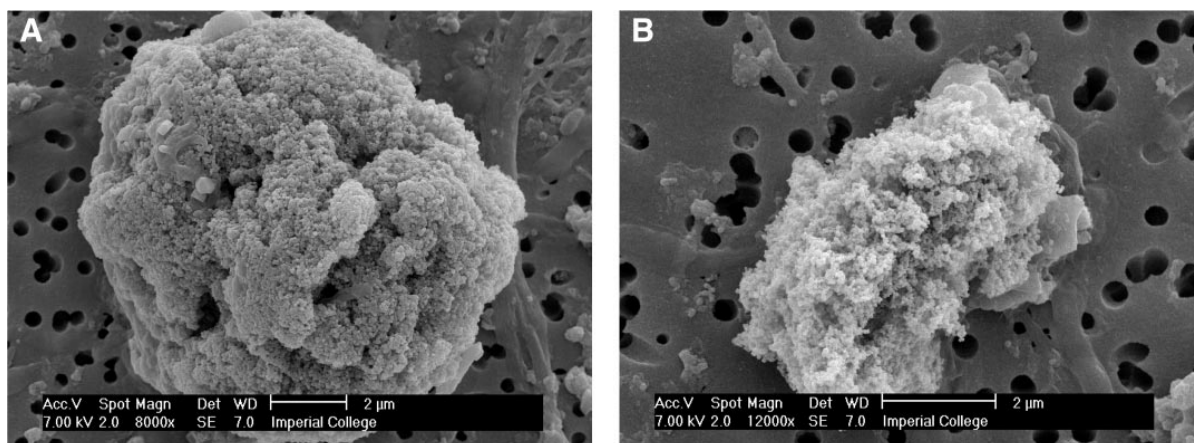
There may be more to the issue of particle disassociation than is mentioned in the draft PM ISA External Draft. Kendall, et al,[1] found that, *"...when PM2.5 is collected directly into normal lung lining liquid, the particles aggregate into larger (>5 um) dense structures compared with samples collected in air or into saline. The control showed that the agglomeration effects were not due to drying per se but were specifically associated with the protein-rich solution, which is in line with the AFM study that showed enhanced attraction between surfaces in BALF. The XPS*

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[1] KENDALL M,[1] TETLEY T D,[2] WIGZELL E.[1]HUTTON B,[3] NIEUWENHUIJSEN M,[1] AND LUCKHAM P[1]. Lung ling liquid modifies $PM_{2.5}$ in favor of particle aggregation: a protective mechanism. *Am J Physiol Lung Cell Mol Physiol*, 282: L109–L114, 2002.

studies of surface chemistry for urban and smoking PM2.5 showing significant modification by BALF together with the AFM findings of increased attractive and adhesive forces in BALF suggest that aggregation is enhanced by components of lung lining liquid."

Fig. 2. Densely agglomerated 35-nm particle conglomerates (>5 um) found in particle samples collected by sampling PM$_{2.5}$ directly into lung lining liquid. Samples were subsequently filtered onto 0.4 um Nucleopore filters for SEM analysis

Comment: Relating to 4.1.2.2. Breathing Rates

Tables like this provide pertinent information.

Human (male)	12[d]	625[d]	7,500[d]	3,300[d]	140[d]	73[d]
Human (female)	12[d]	444[d]	5,330[d]	2,700[d]	100[g]	60[d]

[d] ICRP (1994)

[g] Alveolar surface area of male scaled by ratio of total lung capacity, i.e., 4.97 ÷ 6.98.

Comment: relating to 4.1.2.1 Anatomy. This Yeh Model of Human Air Ways[2] should be added.

TABLE II
Typical Path Lung Model: Human-Whole Lung

n	Number of tubes	L (cm)	d (cm)	b (degrees)	g (degrees)	s (cm2)	v (cm3)	CV (cm3)
1	1	10	2.01	0	0	3.17	31.73	31.73
2	2	4.36	1.56	33	20	3.82	16.67	48.4
3	4	1.78	1.13	34	31	4.01	7.14	55.54
4	8	0.965	0.827	22	43	4.3	4.15	59.69
5	16	0.995	0.651	20	39	5.33	5.3	64.98
6	32	1.01	0.574	18	39	8.28	8.36	73.35
7	64	0.89	0.435	19	40	9.51	8.47	81.81
8	128	0.962	0.373	22	36	13.99	13.46	95.27
9	256	0.867	0.322	28	39	20.85	18,07	113.34
10	512	0.667	0.257	22	45	26.56	17.72	131.06
11	1024	0.556	0.198	33	43	31.53	17.53	148.59
12	2048	0.446	0.156	34	45	39.14	17.46	166.05
13	4096	0.359	0.118	37	45	44.79	16.08	182.13
14	8192	0.275	0.092	39	60	54.46	14.98	197.1
15	16,384	0.212	0.073	39	60	68.57	14.54	211.64
16*	32,768	0.168	0.06	51	60	92.65	15.57	227.21
17	65,536	0.134	0.054	45	60	150.09	20.11	247.32
18	131,072	0.12	0.05	45	60	257.36	30.88	278.2
19	262,144	0.092	0.047	45	60	454.81	41.84	320.04
20	524,288	0.08	0.045	45	60	833.84	66.71	386.75
21	1.048,576	0.07	0.044	45	60	1,594.39	111.61	498.36
22	2,097.15	0.063	0.044	45	60	3,188.78	200.89	699.25
23	4,194,304	0.057	0.043	45	60	6,090.97	347.19	1,046.44
24	8,388,608	0.053	0.043	45	60	12,181.95	645.64	1,692.08
25**	3 x 10^8	0.025	0.03	45	60	blank	3,871.80	5,563.88

*Terminal bronchioles
**Alvioi
n=generation number; L=airway segment length; d=segment diameter; b=branching angle
angle; g=gravity angle with 90° corresponding to a horizontal tube; S=cross-sectional area; V=volume; CV=cumulative volume.

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[2] Yeh, H. C., and Schum, F. G. M., Models of human lung airways and their application to inhaled particles deposition, Bull. Math. Biol., 42,461-480, 1980.

Comment: Relating to 4.1.2.3. Epithelial Lining Fluid

This Section should include studies substantiating the fetal development and the vital, life-long necessity of pulmonary surfactant's defense against oxidative stress from inhaled pollutants.

Comment: Relating to Section 4.3 Particle Clearance, Sub-section 4.3.3.2. Pulmonary Delivery, Membrane Translocation, paragraph 1, lines 7 – 23. Percentages of TiO_2 particles found in the luminal side of the airways in the epithelial and endothelial cells and the connective tissue and capillaries are given. The sum of these percentages obviously equal 100%.

The narrative states, "These studies effectively demonstrate that some inhaled ultrafine TiO_2 particles, once deposited on the pulmonary surfaces, can rapidly (≤1 hour) translocate beyond the epithelium and potentially into the vasculature."

Language be added to this conclusion stating: "These studies did not detect evidence of particle translocation beyond the vasculature."

In the absence of explicitly stating the limits of particle translocation observed, the draft PM ISA leaves the impression that these specific studies provide evidence that ambient PM could enter the blood stream; perhaps in dose amounts sufficient to explain short term exposure health effects.

The cited studies do not show that to be true, or even possible. If a statement is to be made that such a potential exists, then the draft ISA should lay out the physical and chemical facts substantiating its plausibility and suggest specific research study designs to test the hypothesis.

Extrapolative speculations in the absence of substantiating facts and reasoning are not a benign omission. They inevitably impose upon the reader a systemic suggestion that a conclusion can be fairly drawn in the absence of substantiating scientific observations and facts. Every effort should be made to closely examine the draft PM ISA in its entirety to assure CASAC that this and any other unsubstantiated, speculative statements relating to causation of adverse effects have been removed from the final PM ISA.