Preliminary Comments from Dr. Mark Frampton

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

Revised 12-12-18

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 occurence in COPD patients, and a major contributor to exacerbations. There is epidemiological, clinical, and toxicological evidence to support a 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".

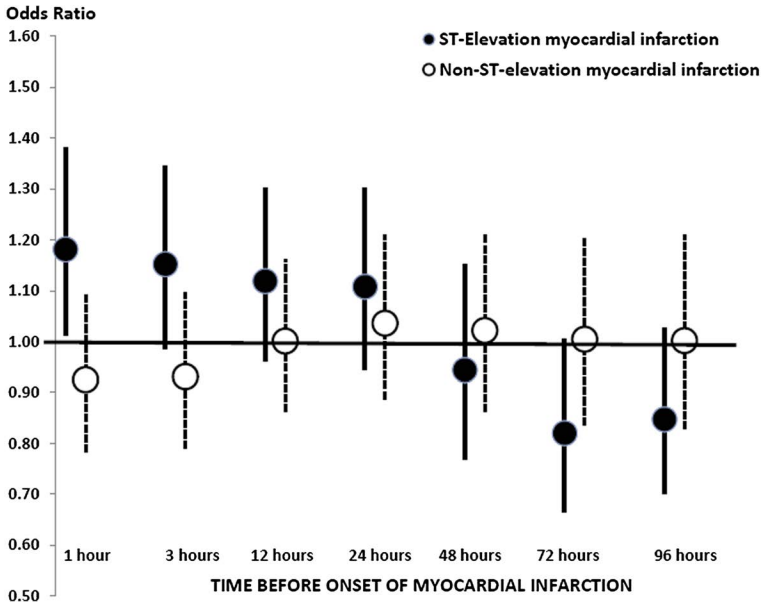
4. Page 6-14, line 18. "There were generally consistent results across recent studies looking specifically at MI, and registry studies, which are likely to reduce outcome misclassification, report evidence of positive associations with MI subtypes."

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%."

Page 6-283, line 26. "Weichenthal et al. (2014a) reported positive associations between 2-hour averages of NCs with SBP measurements taken 3 hours post-exposure, but associations with SBP were

null." This sentence is contradictory and needs clarification. Associations of UFP with SBP were not significant in this study.

Chapter 7, Metabolic Effects. A better distinction needs to be made between the potential metabolic effects of PM, and metabolic abnormalities as markers of susceptibility to CV effects of PM. These two issues are inappropriately thrown together here. Metabolic effects could include increased insulin resistance, blood glucose, hemoglobin A1c, and incidence of diabetes. Alternatively, having diabetes, obesity, or metabolic syndrome could render increased susceptibility to the CV effects of PM exposure. These are separate, important questions. However, the latter should not be described as "metabolic effects", but considered with other susceptibility factors.

It is unclear what is meant by "peripheral inflammation" in Figure 7-2 and the accompanying text, and would recommend not using this term. In reading section 7.1.3 (see below), peripheral inflammation seems to be referring to increased inflammation in adipose tissue in various organs, which could have important implications for obesity and metabolic responses. This should be stated more clearly.

Figure 7-2 is incomplete in several aspects. The text describes a potential pathway for metabolic effects involving the brain, but this important pathway is not represented in Figure 7-2. UFP have been shown in animal models to translocate to the brain via the olfactory nerves. This is a pathway different from the ANS effects of irritant nerve stimulation in the respiratory tract.

Section 7.1.3, Other Indicators of Metabolic Function, should be re-thought and re-organized. The subheading topics of systemic inflammation and blood pressure have already been reviewed as outcomes, and it is redundant to revisit them here. It is enough for the background to point out the interplay of inflammation in metabolic effects and in obesity, as well as hypertension as a clinical component of the metabolic syndrome, and reference the previous sections.

The biological plausibility section and Figure 7-2 **do not adequately address the distinctions and differences between type 1 and type 2 diabetes**.

Section 7.2.10, Metabolic Disease Mortality. The title of this section, and some of the text, are a bit misleading. People don't often die of "metabolic disease" (although there are certainly deaths from diabetic ketoacidosis). Their metabolic conditions increase risk for mortality from a variety of causes, from cardiovascular deaths to pneumonia and other infections. The Pope 2014 paper described in this section looks at cardiovascular mortality, and examines whether metabolic disease such as diabetes, contribute to the PM risk for CV mortality.

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.

Last sentence of 6.5.3. "However, relative to control animals, a toxicological study did not find an increase in markers consistent with cardiac damage following short-term exposure to PM10-2.5." PM10-2.5 is meant to be UFP here?

Page 7-12, line 2. "However, effects may be transient, so the upstream consequences are somewhat uncertain." Many of the outcomes discussed in this document are transient; it is not clear why the emphasis here. Also, it is not clear what is meant by "upstream" consequences. Did the author mean "downstream"? Perhaps "clinical consequences" would be more clear.

NFκβ should be NFκB.