

**COMMENTS OF THE HEALTH EFFECTS INSTITUTE
ON THE DRAFT INTEGRATED SCIENCE ASSESSMENT FOR
PARTICULATE MATTER AIR POLLUTION**

December 4, 2018

The Health Effects Institute (HEI) is pleased to have the opportunity to submit these comments to the Clean Air Scientific Advisory Committee (CASAC) on the new draft Integrated Science Assessment for Particulate Matter (PMISA). We are encouraged to see that the draft PMISA continues to adhere to the high standards of scientific quality and systematic review of the literature which has become a hallmark of EPA’s approach to meeting the requirements of Section 108 of the Clean Air Act. That section of the Act requires that such reviews “shall accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of such (*criteria*) pollutant in the ambient air.”

As you are aware, HEI has produced a large number of studies of air pollution and health to inform the review of the National Ambient Air Quality Standards (NAAQS) and we were pleased to see these studies – along with the independent Commentaries on the studies by the HEI Review Committee – cited in the draft PMISA. We will not review all of these specific studies (though we stand ready to answer any questions that CASAC might have on them). Rather we wanted to focus in these comments on:

1. The causality determinations in the draft PMISA, and
2. The status of several key HEI-funded studies of low levels of exposure to PM and ozone which are currently undergoing detailed HEI peer review.

1. Causality Determinations HEI has followed closely the development and application of EPA’s criteria for assessing causality of different air pollutants on particular health outcomes since they were first applied in the review of the NAAQS for NO_x in 2008. We have found that this approach has been a significant enhancement over previous reviews, especially because it includes:

- Well stated criteria for causality determination presented *a priori* in the Preface of each ISA;

- Careful evaluation of evidence from all strands of research: exposure assessment, toxicology, clinical studies, and epidemiology, rather than reliance on any one strand of evidence or solely on statistical causal analyses; and
- Explicit acknowledgement of the uncertainties attendant in each case.

The result of this process is an open presentation of the literature and assumptions applied, and the opportunity for both CASAC and the broader community to review and raise questions about those determination.

Given that opportunity, HEI has reviewed the latest determinations in the draft PMISA, which in general seem well and carefully done. We do have comments on the three determinations that appear to have changed to “likely to be causal” since the last review: long-term exposure to PM2.5 and lung cancer; long-term exposure to PM2.5 and nervous system effects; and long-term exposure to ultrafine particles (UFP) and nervous system effects.

- *Long Term PM2.5 and Lung Cancer* The literature on ambient PM2.5 and lung cancer has been growing in recent years, with several studies – including some supported and reviewed by HEI – finding robust associations of PM2.5 with lung cancer mortality, including in non-smokers. We had noted the recent determination by the International Agency for Research on Cancer (IARC 2016) that classified ambient PM2.5 as a Group 1 Known Human Carcinogen. But we agree with EPA that while the emerging evidence of this linkage is strengthening, it seems more appropriate at this stage – given the absence of formal dose considerations in the IARC review – to classify this relationship as “likely to be causal” rather than causal.
- *Long Term PM2.5 and Nervous System Effects.* HEI has also found that the literature on potential nervous system effects of long-term exposure to PM2.5 has been growing, and the HEI Research Committee has in recent years selected several new studies to undertake to further test this hypothesis. The review of causality in the draft PMISA relies heavily on the toxicological evidence – noting the limited epidemiologic evidence given the absence in many cases of assessment of the role of PM vs. other pollutants. While there continue to be significant uncertainties in this literature (which is why HEI is funding new studies) we could understand a determination by EPA that this is “likely to be causal,” although in view of the paucity of human evidence we would view this determination as being on the edge between “suggestive” and “likely.”
- *Long Term Ultrafine PM and Nervous System Effects.* While we could understand the determination for long-term PM2.5 and nervous system effects, we were surprised to see the elevation of exposure to UFP as “likely to be causal.” In contrast to the long-term PM2.5 evidence, this determination appears to be based primarily on high-dose exposures to animals from only six new studies, and considers only one epidemiology study which the PMISA draft notes is limited because they did not test for other pollutants. The doses administered in one of the toxicological studies are four-fold higher than even the highest

levels reported by EPA in the draft PM ISA (at p. 2-57); the doses in the other studies are 15- or more-fold higher than the highest ambient levels.

HEI conducted a detailed review of the UFP literature in 2013 (HEI 2013) that did not find conclusive evidence for independent effects of UFP. Recently, the Umweltbundesamt (the German EPA) commissioned a follow-on review (Ohlwein 2018) of the newest long-term evidence. That review concluded: “the evidence on health effects remains inconclusive or insufficient for most of the studied outcomes,” and even for those cardiovascular and pulmonary outcomes where there was some suggestion of effect, “the evidence for independence of effects remains limited here as well, as only few studies have adjusted for co-pollutants.”

Given the limitations in the evidence we would respectfully suggest that EPA re-consider this determination.

2. The status of several key HEI-funded studies of low levels of exposure to PM. The draft PMISA reviews a wide range of newer epidemiologic studies of PM_{2.5} exposure and health, including new analyses in existing cohorts such as the Harvard Six Cities and American Cancer Society studies as well as, importantly, a range of new studies finding associations in cohorts for which the underlying data is readily available.

One of the considerations now raised by some of these new studies is whether there are robust associations of PM_{2.5} exposure and health effects at levels of exposure below the annual PM NAAQS (i.e. 12 µg/m³). While there had been a few earlier studies finding such associations (e.g. Crouse et al., 2012), there were a relatively small number of studies, and questions remained about potential exposure measurement error at the lowest levels and the absence of information on potential confounders. This led the HEI Research Committee in 2016 to fund – after review of a large number of potential applications - three new comprehensive studies of potential associations of very low long-term exposure of PM with mortality and morbidity. These three studies – in 61 million US Medicare recipients, 10 million Canadian census participants, and over 35 million Europeans in several cohorts - are well underway, and the investigators have begun to publish some initial results in the peer-reviewed literature (e.g. Di, 2017; Di, 2017; Pinault 2017). Substantial additional work is underway in these studies to test causal inference models, examine exposure measurement error, and explore the role of various confounders.

Intensive HEI Peer-Review CASAC is likely familiar with the long-standing practice of HEI to subject comprehensive reports of HEI research to intensive peer-review by the HEI Health Review Committee. Recognizing the potential importance of these new studies to the current review of the NAAQS, HEI has asked the investigators of the US and Canadian studies to prepare Phase 1 reports of the work completed to date, and the HEI Review Committee has convened a special Expert Review Panel to intensively examine these studies, enabling HEI to publish comprehensive reports of the first phase of work, including an independent Commentary of the Review Panel, in timely fashion to inform this review. While we understand that the first

of the reports, to be published in April and presenting the work in the Medicare cohort, will be available after the normal window for literature review for the PMISA, *we respectfully request that CASAC, recognizing that this involves further intensive HEI review of studies already cited in the draft PMISA, would consider including this HEI research Report in its requests for the final version of the PM ISA, which is scheduled to be completed in December 2019.*

CONCLUSION

Thank you again for the opportunity to provide these comments. We would be pleased to provide any additional assistance to CASAC in its review process, and/or answer any additional questions you may have about these comments, or the range of other HEI Research Reports under consideration in the Draft PMISA.

References

- Crouse, DL; Peters, PA; van Donkelaar, A; Goldberg, MS; Villeneuve, PJ; Brion, O; Khan, S; Atari, DO; Jerrett, M; Pope, CA; Brauer, M; Brook, JR; Martin, RV; Stieb, D; Burnett, RT. (2012). Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. *Environ Health Perspect* 120: 708-714. <http://dx.doi.org/10.1289/ehp.1104049>
- Di, Q; Dai, L; Wang, Y; Zanobetti, A; Choirat, C; Schwartz, JD; Dominici, F. (2017a). Association of short-term exposure to air pollution with mortality in older adults. *JAMA* 318: 2446-2456. <http://dx.doi.org/10.1001/jama.2017.17923>
- Di, Q; Wang, Y; Zanobetti, A; Wang, Y; Koutrakis, P; Choirat, C; Dominici, F; Schwartz, JD. (2017c). Air pollution and mortality in the Medicare population. *N Engl J Med* 376: 2513-2522. <http://dx.doi.org/10.1056/NEJMoa1702747>
- HEI Review Panel on Ultrafine Particles. 2013. Understanding the Health Effects of Ambient Ultrafine Particles. HEI Perspectives 3. Health Effects Institute, Boston, MA.
- IARC (International Agency for Research on Cancer). (2016). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Outdoor air pollution [IARC Monograph]. (109). Lyon, France: World Health Organization.
- Ohlwein, S, Hoffmann, B, Kappeler, R, Kutlar Joss, M, Künzli, N. Health Effects of Ultrafine Particles: Systematic literature search and the potential transferability of the results to the German setting. Umweltbundesamt, Project No. 003777 7205 UKAGEP, Dessau-Roßlau, Germany (2018)
- Pinault LL, Weichenthal S, Crouse DL, Brauer M, Erickson A, Donkelaar AV, Martin RV, Hystad P, Chen H, Finès P, Brook JR, Tjepkema M, Burnett RT. Associations between fine particulate matter and mortality in the 2001 Canadian Census Health and Environment Cohort. *Environ Res.* (2017) 159:406-415. doi:10.1016/j.envres.2017.08.037