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

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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 Supplemental Integrated Science Assessment for Particulate Matter (Supplemental PMISA). We are encouraged to see that the draft Supplemental PMISA continues to adhere to the high standards of scientific quality and careful 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 SPMISA. 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 consideration of causality in the draft SPMISA, and
2. The results, now in press, of one of several key HEI-funded studies of low levels of exposure to PM and ozone: the study in 68.5 million US Medicare recipients.

1. Considering Causality HEI has followed closely the development and application of EPA's criteria for assessing causality of different air pollutants on diverse health outcomes since they were first applied in the review of the NAAQS for NOx in 2008 and updated in the ISA Preamble in 2015. 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. In our view, this latest Supplemental PMISA continues that multidisciplinary consideration with detailed review and consideration of a number of key factors that may affect the confidence that can be placed in the body of evidence, including careful review of the range of newer evidence on cardiovascular and other endpoints; testing of the evidence on major uncertainties such as potential pollutant confounding; and examination of whether there is evidence of plausible underlying biological mechanisms (e.g., the well-described new mechanistic controlled human exposures study of Wyatt et al 2020). EPA has also examined the most recent evidence on concentration-response relationships and considered the latest well-designed and implemented "accountability" studies testing whether there have been measurable health changes as a result of efforts to reduce air pollution exposures (e.g. Henneman et al. 2019).

2. The Results of the Latest Report of HEI's Low-level Exposure Studies. While HEI has supported extensive work on all of these topics, we have focused especially closely in recent years on testing the concentration-response relationships at the lowest levels of exposure. We were pleased to see at page 3-81 in the Supplemental PMISA explicit consideration of HEI's program to address low level exposures to air pollution in populations in the U.S., Canada, and Europe:

> "While (*earlier studies added*) to the total body of evidence supporting a relationship between long-term PM2.5 exposure and mortality, key questions that often arise in the assessment of the evidence are (1) Do associations persist at low concentrations? and (2) Is there a point below which there is less confidence in that relationship? This led to the Health Effects Institute (HEI) initiating two recent research efforts with a main focus on examining the relationship between long-term PM2.5 exposure and mortality at low concentrations. One of these studies conducted in the U.S., referred to as the HEI Medicare study, focused on using a cohort of Medicare beneficiaries 65 years of age or older (Dominici et al., 2019), while another study conducted in Canada, referred to as the Mortality-Air Pollution Associations in Low Exposure Environments (MAPLE) study, relied on respondents from multiple years of the long-form Canadian Census Health & Environment Cohorts (CanCHEC) and/or participants from multiple years of the Canadian Community Health Survey (CCHS) (Brauer et al., 2019). A third study was conducted in Europe, using data from the European Study of Cohorts for Air Pollution Effects (ESCAPE) but is beyond the scope of this Supplement. Both of these research efforts conducted extensive analyses to further inform the PM2.5-mortality relationship in a series of studies, with a focus on examining associations at low PM2.5 concentrations, which are often considered as below the level of the current annual PM NAAQS of 12.0 μg/m3."

HEI published Phase 1 reports of the US and Canadian studies in November 2019. Now the primary work[1] of all three studies has been completed and subjected to independent peer review by the HEI Low-Exposure Epidemiology Studies Review Panel of the HEI review Committee, chaired by Dr. Sverre Vedal of the University of Washington. The European ELAPSE Study was

[1] HEI has provided additional funding to the three teams to conduct comparative analyses across the three studies which will be completed in

published in September 2021 (Brunekreef et al. 2021) and the Canadian MAPLE study is in the last stages of review.

The report of the third team, led by Francesca Dominici and conducting analyses in some 68.5 million US Medicare recipients - *Assessing Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Pollution: Implementation of Causal Inference Methods* – has now been completed, intensively reviewed, and accepted for publication; it is in press at HEI (Dominici 2021). While portions of this work were reported previously in a peer-reviewed journal article (Wu et al 2020), which is cited in the Supplemental PMISA, this is the first comprehensive review of all of the results of the analysis, including the extended and detailed commentary prepared by the HEI Low-Exposure Epidemiology Studies Review Panel of the HEI Review Committee. We would hope that CASAC and EPA could consider and include this overall report in the final Supplemental PMISA when it is completed in 2022.

In brief, the main findings of the HEI report are:

First, the investigators presented results from three newly developed causal inference approaches using generalized propensity scores and from two traditional regression approaches. As shown in Figure 1 below, their findings from the new approaches were generally consistent with those from the traditional approaches.

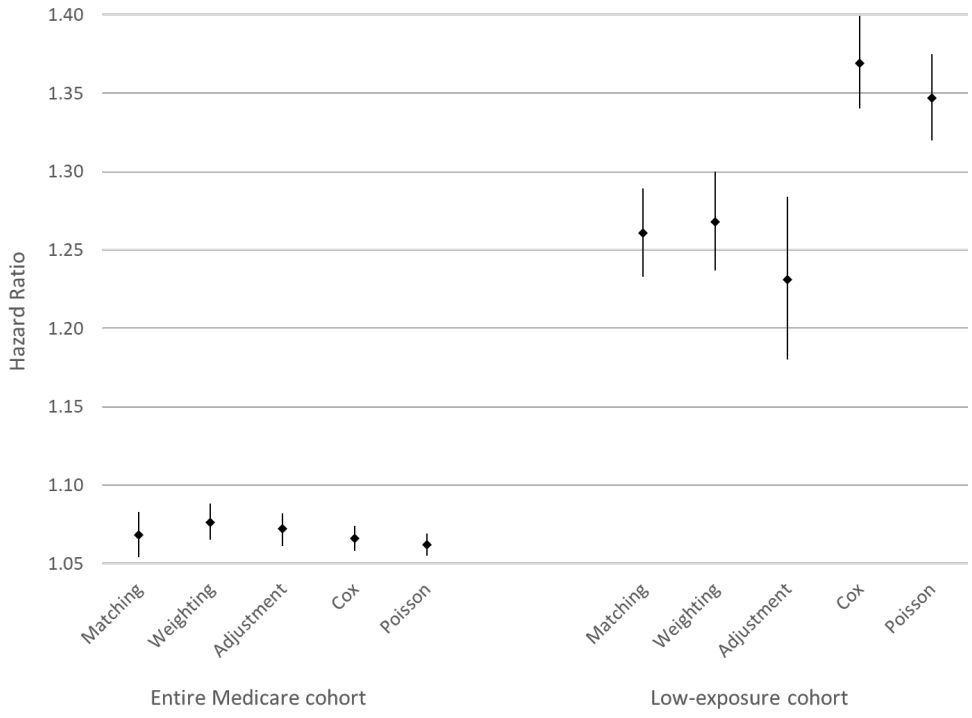

Figure 1. Associations between longer-term exposures to $PM_{2.5}$ and all-cause mortality among enrollees in the full Medicare cohort (left side) and in the low-exposure cohort (right side). Data shown are HRs and 95% CIs. The HRs were estimated under five statistical approaches: three causal inference approaches using generalize propensity scores (matching, weighting, and adjustment) and two traditional approaches (Cox and Poisson regression). The HRs were calculated per 10-$\mu g/m^3$ increase in $PM_{2.5}$ exposure. Results are presented for fully adjusted models.

Second, the investigators reported increased risks of all-cause mortality of 6% to 8% per 10 µg/m^3 increase in $PM_{2.5}$ across the five approaches, with stronger associations at the lowest levels of exposure below the current annual national standard of 12 µg/m^3 even when adjusting for potential confounding from other pollutants (See Figure 2).

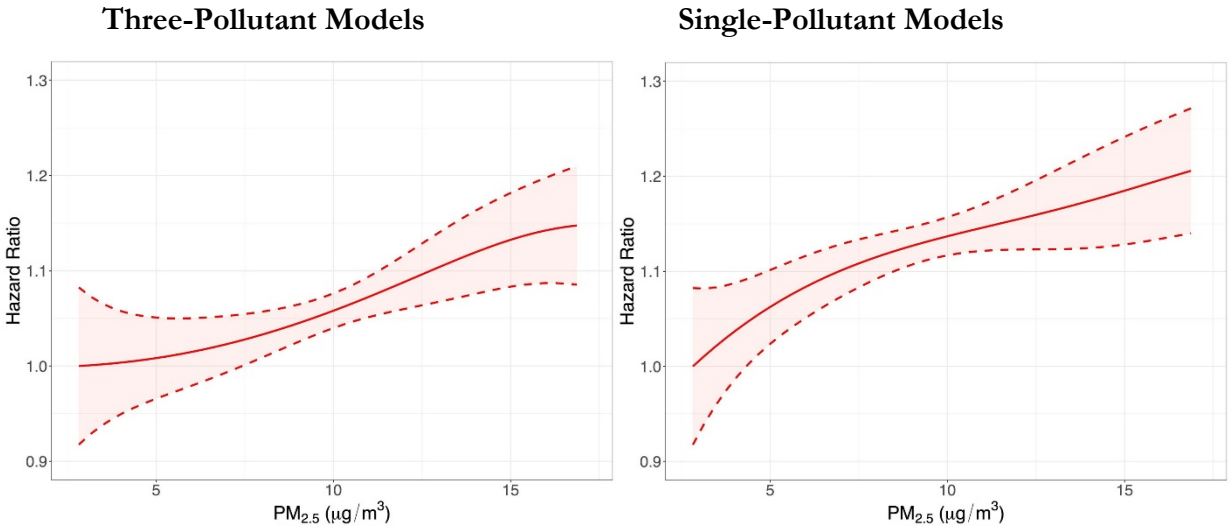

Figure 2. Estimated ER functions relating $PM_{2.5}$, NO_2, and O_3 to all-cause mortality among Medicare enrollees (2000–2016) with and without adjustment for co-pollutants. Data shown are HRs with 95% CIs obtained using a generalized propensity score matching approach. The left panels show the ER functions associating long-term exposure to $PM_{2.5}$ with all-cause mortality, adjusted for NO_2 and O_3 as potential confounders. The right panels show the ER functions for single-pollutant models without adjusting for the other two pollutants.

Overall, the HEI Low-Exposure Epidemiology Studies Review Panel of the HEI Review Committee appreciated the substantial strengths of the study, including provisions to make all of the data and methods accessible. At the same time, they noted several continuing uncertainties, including (1) the likely greater error in estimating rural concentrations due to the relative paucity of ground monitors for evaluation and training of exposure models in those areas, (2) the exposure measurement error from using zip-code aggregated exposure estimates, and (3) the effects of using aggregated covariates (at several spatial scales) in adjusting for confounding. Ultimately, the Panel considered a major contribution of this study that using several different approaches, the investigators produced findings of associations across their several analytic approaches that were generally consistent with each other, and with those of previous studies.

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We hope that the addition of these results and Commentary can help CASAC and EPA strengthen is current draft Supplemental PMISA and stand ready to answer any additional questions that CASAC might have.

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