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Comments of the Health Effects Institute on "Strengthening Transparency in Regulatory Science" (Proposed Rule Docket Number: EPA–HQ–OA–2018–0259]

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The Health Effects Institute (HEI) is pleased to present these comments on Proposed Rule "Strengthening Transparency in Regulatory Science." (Docket No: EPA–HQ–OA–2018–0259)

HEI has a longstanding commitment to producing science of the highest integrity, quality, and transparency, built on a foundation of:

- Rigorous research and statistical design – subject to continuous oversight, data quality assurance audits, and more;
- Extensive efforts to test all findings against a wide range of different statistical techniques and assumptions,
- Intensive independent peer review, with *all* results published, and
- An active *Data Access Policy* for over 20 years to ensure access to underlying data for all HEI-funded studies.

Based on our extensive experience in producing, reviewing, reanalyzing, and interpreting science, we submit the following specific comments for your consideration:

Action to improve transparency should begin with review of the many existing efforts already in place.

In HEI's work to provide the highest quality, impartial and relevant science to inform decisions, we have seen reproducibility as a critical challenge for science: *can the results of important studies be reproduced*? But we would note that these issues are not new, and have been addressed now for over 15 years by administrations from both parties and by the scientific community. This has included the Guidelines for the Information Quality Act adopted by the Office of Information and Regulatory Affairs (OIRA) in 2002 (Federal Register / Vol. 67, No. 36 / Friday, February 22, 2002); numerous actions by the scientific community and journals to

enhance access to data and methods; and most recently the requirements for enhanced data access across the Federal Government promulgated by the Office of Science and Technology Policy (OSTP) in February 2013.

We would recommend that EPA carefully review the progress already made under these major initiatives prior to determining what if any additional action is needed to enhance transparency.

EPA should have the broadest possible range of science available for making decisions on risk, causality, and other important policy.

Based on our detailed knowledge of the underlying science, and our experience conducting rigorous systematic reviews of the scientific literature, HEI would recommend that EPA reconsider and not go forward with the provision in the proposed rule that would appear to in effect prohibit the use of otherwise high-quality and rigorously peer-reviewed studies if the data and models are not "publicly available in a manner sufficient for independent validation." Although HEI strongly supports making data and models available as widely as possible, and EPA can and has in the past made efforts to access data for important studies, there are several reasons why a blanket prohibition may interfere with EPA's ability to draw on and interpret the fullest range of scientific evidence for important decisions.

- First, EPA already has the ability and duty to assess the quality and robustness of results of a study even in cases where the data are not available, both by careful review of all of the methods and supplemental information presented, and by expert review by EPA scientific staff and scientific advisors. These steps can identify both the strengths and weaknesses of any such study in a manner that allows the proper weighing of that study in consideration of the weight of evidence for or against a specific health effect. To arbitrarily prevent the use of any such study has the potential to significantly weaken EPA's ability to make high quality judgments based on the full range of the available science.

- Second, in HEI's view the most effective way to test the reproducibility and validity of scientific results is not necessarily to simply reproduce the same results in the same data sets but rather to answer the question: Can the original results hold up when tested in new studies:

    - that use new and separate data bases not affiliated with the original studies?
    - have different investigators applying the same and/or different statistical techniques?
    - and test the sensitivity of the results against a wide range of possible other explanation, e.g. smoking behavior, socioeconomic status, and more?

  This broader assessment of the literature allows for an open and rigorous evaluation of an original study without the need for the data necessarily being available.

As there are multiple paths to assessing the integrity and validity of a study, we would recommend that EPA continue to fully evaluate *all available studies* for their strengths and weaknesses as it considers the weight of evidence for or against a specific health or policy decision.

Detailed and rigorous reanalysis may be appropriate in some cases, but it is costly if done correctly and reduces resources available for new, better-designed studies.

In a limited number of cases there may not be comparable studies available in other datasets, and it could be useful to gain access to the original study data and statistical approaches to allow for independent reanalysis that asks: Can the original results be replicated? And are they robust to a wide range of alternative assumptions, models and potential confounders? If such detailed, independent reanalysis has already been undertaken, it can significantly reduce the need for further independent validation of a specific study.

This is of course the approach that HEI applied in its independent, rigorous reanalysis of the Harvard Six Cities and American Cancer Society Studies. We have attached a summary description of the Reanalysis; the full reanalysis – which involved data audits, replication of the original results, and extensive testing of those results against a wide variety of alternate data, assumptions, and models, can be found at: https://www.healtheffects.org/publication/reanalysis-harvard-six-cities-study-and-american-cancer-society-study-particulate-air.

While this approach can – and did – provide comprehensive assurance of the integrity and validity of the original results, it is also a highly cost-intensive undertaking and should be considered only in those cases where there is not an ability to otherwise evaluate the results of a study.

"Depersonalized" data sets can be created, but in many instances they will not allow for full replication and reanalysis.

HEI has extensive experience with the careful and protected use of private medical information, which is critical to conducting high quality and reproducible air quality and health research. There are of course longstanding federal rules for protecting the privacy of individual medical information of the subjects of studies (e.g. the "Common Rule" mandating Institutional Review Board review of any use of personal data; confidentiality assurances provided to study participants; non-disclosure of personal information through HIPPA, and others) and it is important to adhere to these even as the valuable information contained in such records is applied in scientific research.

Fortunately, there *are* means available through a number of government agencies to make some such data available in detail to qualified researchers, conditional on their agreeing to a data use agreement that enables access to the data – but prohibits public disclosure of individual data. Many investigators have for example accessed the Medicare data set though application to the Center for Medicare Services (CMS). Alternatively, many agencies make the data available

through Federal Research Data Centers. While each of these options – and others – do contain some restrictions on the public disclosures, and will result in the incurring of costs, they can and have been used for an increasing number of air pollution and health studies. HEI does believe that there are improvements that could be made to those access options, e.g. easier access provisions for Federal Research Data Centers, and would urge EPA to work with its federal agency counterparts to accomplish that.

Some have argued that it should be possible to create a "depersonalized" data set by stripping all personal identifiers such as address, date of birth, etc. and making such a data set widely available. However, it is not possible to conduct a high-quality air pollution and health study without knowing the locations of those being studied, i.e. where they live, and what are the sources and levels of their air pollution exposure. And unfortunately, once that information is available at smaller spatial scale, it is possible to disclose extensive medical information for individual study subjects.

Since the goal should be to find ways to share data which enables full replication and sensitivity analysis of original studies, it is valuable to consider several aspects of large population air pollution studies that have moved them towards using data at smaller spatial scales:

- First, in response to valid criticisms that the earlier air pollution studies relied only on central air quality monitoring data to estimate exposure, investigators have increasingly sought to better estimate exposure employing land use regression models and other methods that can account for the distance of a subject's home from roadways, industrial facilities, and other sources of air pollution. They have also applied increasingly finer-grained community-level covariates (e.g. at the zip code level). While in the largest locations the application of these finer-grained data would likely not allow for identification of individual subjects, the national analyses in some of these studies include subjects from a wide range of community sizes, including smaller communities where identification could be possible.

- Second, as these types of studies have been reviewed intensively by the HEI Review Committee, the Committee has identified two potentially significant sources of uncertainty in their results: so-called "ecological confounding"[1] and "spatial autocorrelation."[2] To address both of these issues, one of the first steps that investigators have taken has been to use data at smaller scales which, while enhancing their ability to test for these two sources of uncertainties, also poses the potential in smaller communities for individuals and their personal information to be identified.

[1] Ecological confounding arises when some community-level variables, which are themselves risk factors for mortality, are also associated with air pollution levels

[2] Spatial autocorrelation is the tendency for variables to have similar values for people or areas that are geographically close, which can suggest that there are other mortality causes which are unaccounted for in the analysis or can distort the precision of risk estimates.

Taken together, these characteristics – which have in general enhanced the quality and the sensitivity of the studies – increase the difficulty of providing a fully "de-identified" data set while *also* enabling a different investigator to conduct a full replication and sensitivity analysis of the original study results. The other mechanisms discussed above – e.g. data use agreements, research data centers – fortunately would allow access to the more detailed data necessary to conduct such full new analyses while protecting the confidentiality of study subjects.

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In closing we appreciate the opportunity to present these comments. We firmly believe that there is ample opportunity to enhance transparency and reproducibility in science to inform decisions, in many respects taking advantage of existing rules and methods and would welcome the opportunity to assist EPA in making these improvements. Should the Agency have any further questions, please feel free to contact Dan Greenbaum, President, Health Effects Institute, dgreenbaum@healtheffects.org, (617) 488-2331.

HEALTH EFFECTS INSTITUTE

STATEMENT

Synopsis of the Particle Epidemiology Reanalysis Project

BACKGROUND

Epidemiologic work conducted over several decades has suggested that long-term residence in cities with elevated ambient levels of air pollution from combustion sources is associated with increased mortality. Subsequently, two prospective cohort studies, the Six Cities Study (as reported in Dockery et al 1993) and the American Cancer Society (ACS) Study (as reported in Pope et al 1995) estimated that annual average all-cause mortality increased in association with an increase in fine particles (all particles less than 2.5 µm in median aerodynamic diameter [$PM_{2.5}$]).

As part of the Six Cities Study, Dockery and colleagues (1993) had prospectively followed a cohort of 8,111 adult subjects in northeast and midwest United States for 14 to 16 years beginning in the mid-1970s. The authors found that higher ambient levels of fine particles and sulfate (SO_4^{2-}) were associated with a 26% increase in mortality from all causes when comparing the most polluted to the least polluted city, and that an increase in fine particles was also associated with increased mortality from cardiopulmonary disease. The relative risks in all-cause mortality were associated with a difference (or range) in ambient fine particle concentrations of 18.6 µg/m^3 and a difference of ambient sulfate concentrations of 8.0 µg/m^3, comparing the least polluted city to the most polluted city.

In the much larger ACS Study, Pope and colleagues (1995) followed 552,138 adult subjects in 154 US cities beginning in 1982 and ending in 1989 (3 cities did not overlap between the 151 and 50 cities studied, resulting in a total of 154 cities). Again, higher ambient levels of fine particles were associated with increased mortality from all causes and from cardiopulmonary disease in the 50 cities for which fine particle data were available (sampled from 1979 to 1983). Higher ambient sulfate levels were associated with increased mortality from all causes, cardiopulmonary disease, and lung cancer in the 151 cities for which sulfate data were available (sampled from 1980 to 1982). The difference between all-cause mortality in the most-polluted city and the least-polluted city was 17% and 15% for fine particles and sulfate, respectively (with a range of 24.5 µg/m^3 for fine particles and of 19.9 µg/m^3 for sulfate).

Both of these studies came under intense scrutiny in 1997 when the EPA used the results to support new National Ambient Air Quality Standards for fine particles and to maintain the standards for particles less than 10 µm in median aerodynamic diameter (PM_{10}) already in effect. Members of Congress and industry, the scientific community and others interested in regulation of air quality scrutinized the studies' methods and their results. Some insisted that any data generated using federal funding should be made public. Others argued that these data had been gathered with assurances of confidentiality for the individuals who had agreed to participate and that the concept of public access to federally funded data did not take into account the intellectual property rights of the investigators and their supporting institutions. To address the public controversy, Harvard University and the ACS requested that the Health Effects Institute organize an independent reanalysis of the data from these studies. Both institutions agreed to provide access to their data to a team of analysts to be selected by HEI through a competitive process.

APPROACH

To conduct the reanalysis, the HEI Board of Directors, with support from the EPA, industry, Congress, and other stakeholders, appointed an Expert Panel chaired by Dr Arthur Upton from the University of Medicine and Dentistry of New Jersey and former Director of the National Cancer

This Statement, prepared by the Health Effects Institute, is a summary of a research project conducted by the Reanalysis Team, led by Dr Daniel Krewski at the University of Ottawa. The following Special Report contains the detailed Investigators' Report (Summary, Introduction, and Parts I and II), Commentary on the project prepared by a special panel of the Institute's Health Review Committee, and Comments on the Reanalysis Project by the Original Investigators (Drs Douglas W Dockery, C Arden Pope III et al).

Institute. The Expert Panel selected competitively a Reanalysis Team—led by Dr Daniel Krewski of the University of Ottawa—and oversaw all aspects of the team's work. They were assisted in their oversight efforts by a broad-based Advisory Board of knowledgeable stakeholders and scientists who, in the project's early stages, provided extensive advice to the Expert Panel on the key questions to be analyzed. The final results of the Reanalysis Team were intensively and independently peer reviewed by a Special Panel of the HEI Health Review Committee, which was chaired by Dr Millicent Higgins of the University of Michigan.

The overall objective of what became the Particle Epidemiology Reanalysis Project was to conduct a rigorous and independent assessment of the findings of the Six Cities and ACS Studies of air pollution and mortality. This objective was met in two parts. In *Part I: Replication and Validation*, the Reanalysis Team sought to replicate the original studies via a quality assurance audit of a sample of the original data and to validate the original numeric results. In *Part II: Sensitivity Analyses*, they tested the robustness of the original analyses to alternate risk models and analytic approaches.

RESULTS AND IMPLICATIONS

PART I: REPLICATION AND VALIDATION

- An extensive audit of the study population data for both the Six Cities and ACS Studies and of the air quality data in the Six Cities Study revealed the data to be of generally high quality with a few exceptions. In both studies, a few errors were found in the coding and inclusion of certain subjects; when those subjects were included in the analyses, they did not materially change the results as originally reported. Because the air quality data used in the ACS Study could not be audited, a separate air quality database was constructed for the sensitivity analyses described in Part II.
- The Reanalysis Team was able to replicate the original results in both studies using the same data and statistical methods as used by the Original Investigators. The Reanalysis Team confirmed the original point estimates: For the Six Cities Study, they reported the relative risk of mortality from all causes associated with an increase in fine particles of 18.6 $\mu g/m^3$ as 1.28, close to the 1.26 reported by the Original Investigators. For the ACS Study, the relative risk of mortality from all causes associated with an increase in fine particles of 24.5 $\mu g/m^3$ was 1.18 in the reanalysis, close to the 1.17 reported by the Original Investigators.

PART II: SENSITIVITY ANALYSES

Once the original results of the studies had been validated, the Reanalysis Team sought to test an array of different models and variables to determine whether the original results would remain robust to different analytic assumptions.

- First, the Reanalysis Team used the standard Cox model used by the Original Investigators and included variables in the model for which data were available from both original studies but had not been used in the published analyses (eg, physical activity, lung function, marital status). The Reanalysis Team also designed models to include interactions between variables. None of these alternative models produced results that materially altered the original findings.
- Next, for both the Six Cities and ACS Studies, the Reanalysis Team sought to test the possible effects of fine particles and sulfate on a range of potentially susceptible subgroups of the population. Although different subgroups did show some variation in their estimated effects, the results were not statistically significant with one exception. The estimated effects of fine particles did appear to vary with educational level; the association between an increase in fine particles and mortality tended to be higher for individuals without a high school education than for those who had completed high school or for those with more than a high school education.
- In the ACS study, the Reanalysis Team tested whether the relationship between ambient concentrations and mortality was linear. They found some indications of both linear and nonlinear relationships, depending upon the analytic technique used, suggesting that the

issue of concentration-response relationships deserves additional analysis.

- In the Six Cities Study where data were available, the Reanalysis Team tested whether effect estimates changed when certain key risk factors (smoking, body mass index, and air pollution) were allowed to vary over time. One of the criticisms of both original studies has been that neither analyzed the effects of change in pollutant levels over time. In general, the reanalysis results did not change when smoking and body mass index were allowed to vary over time. The Reanalysis Team did find for the Six Cities Study, however, that when the general decline in fine particle levels over the monitoring period was included as a time-dependent variable, the association between fine particles and all-cause mortality dropped substantially, but the effect continued to be positive and statistically significant.
- Using its own air quality dataset constructed from historical data to test the validity of the original ACS air quality data, the Reanalysis Team found essentially the same results.
- Any future analyses using the sulfate data should take into account the impact of artifactual sulfate. Sulfate levels with and without adjustment differed by about 10% for the Six Cities Study. Both the original ACS Study air quality data and the newly constructed dataset contained sulfate levels inflated by approximately 50% due to artifactual sulfate. For the Six Cities Study, the relative risks of mortality were essentially unchanged with adjusted or unadjusted sulfate. For the ACS Study, adjusting for artifactual sulfate resulted in slightly higher relative risks of mortality from all causes and cardiopulmonary disease compared with unadjusted data. The relative risk of mortality from lung cancer was lower after the data had been adjusted.
- Because of the limited statistical power to conduct most sensitivity analyses for the Six Cities Study, the Reanalysis Team conducted the majority of its sensitivity analyses using only the ACS Study dataset with 154 cities. In that dataset, when a range of city-level (ecologic) variables (eg, population change, measures of income, maximum temperature, number of hospital beds, water hardness) were included in the analyses, the results generally did not change. Two exceptions were that associations for both fine particles and sulfate were reduced when city-level measures of population change or sulfur dioxide were included in the model.
- A major contribution of the Reanalysis Project is the recognition that both pollutant variables and mortality appear to be spatially correlated in the ACS Study dataset. If not identified and modeled correctly, spatial correlation could cause substantial errors in both the regression coefficients and their standard errors. The Reanalysis Team identified several methods for dealing with this, all of which resulted in some reduction in the estimated regression coefficients. The full implications and interpretations of spatial correlations in these analyses have not been resolved and appear to be an important subject for future research.
- When the Reanalysis Team sought to take into account both the underlying variation from city to city (random effects) and the spatial correlation between cities, only sulfur dioxide as a city-level variable continued to decrease the originally reported associations between mortality and fine particles or sulfate. This effect was more pronounced for sulfate.
- When the Reanalysis Team conducted spatial analyses of sulfur dioxide, the association between sulfur dioxide and mortality persisted after adjusting for sulfate, fine particles, and other variables.
- As a result of these extensive analyses, the Reanalysis Team was able to explain much of the variation between cities, but some unexplained city-to-city variation remained.

CONCLUSIONS

The Reanalysis Team designed and implemented an extensive and sophisticated series of analyses that included a set of new variables, all the gaseous copollutants, and the first attempts to apply spatial analytic methods to test the validity of the data and the results from the Six Cities Study and the ACS Study. Overall, the reanalyses assured the quality of the original data, replicated

the original results, and tested those results against alternative risk models and analytic approaches without substantively altering the original findings of an association between indicators of particulate matter air pollution and mortality.

At the same time, the reanalyses did extend and challenge our understanding of the original results in several important ways.

- The Reanalysis Team identified a possible modifying effect of education on the relation between air quality and mortality in that estimated mortality effects increased in the subgroup with less than high school education.
- The use of spatial analytic methods suggested that, when the analyses controlled for correlations among cities located near one another, the associations between mortality and fine particles or sulfate remained but were diminished.
- An association between sulfur dioxide and mortality was observed and persisted when other possible confounding variables were included; furthermore, when sulfur dioxide was included in models with fine particles or sulfate, the associations between these pollutants (fine particles and sulfate) and mortality diminished.

In reviewing these results, the Special Panel of the HEI Health Review Committee identified the following factors to consider when interpreting the results from the Reanalysis Team.

- The inherent limitations of using only six cities, understood by the Original Investigators, should be taken into account when interpreting results of the Six Cities Study.
- The Reanalysis Team did not use data adjusted for artifactual sulfate for most alternative analyses. When they did use adjusted sulfate data, relative risks of mortality from all causes and cardiopulmonary disease increased. This result suggests that more analyses with adjusted sulfate might result in somewhat higher relative risks associated with sulfate.
- Findings from spatial analyses applied to the ACS Study data need to be interpreted with caution; the spatial adjustment may have overadjusted the estimated effect for regional pollutants such as fine particles and sulfate compared with the effect estimates for more local pollutants such as sulfur dioxide.
- After the Reanalysis Team completed its spatial analyses, residual spatial variation was still noticeable; this finding suggests that additional studies might further refine our understanding of the spatial patterns in both air pollution and mortality.
- No single epidemiologic study can be the basis for determining a causal relation between air pollution and mortality.

In conclusion, the Reanalysis Team interpreted their findings to suggest that increased relative risk of "mortality may be attributed to more than one component of the complex mix of ambient air pollutants in urban areas in the United States". The Review Panel concurs. In the alternative analyses of the ACS Study cohort data, the Reanalysis Team identified relatively robust associations of mortality with fine particles, sulfate, and sulfur dioxide, and they tested these associations in nearly every possible manner within the limitations of the datasets. Future investigations of these issues will enhance our understanding of the effect of combustion-source air pollutants (eg, fine particles, sulfate, and sulfur dioxide) on public health.