March 24, 2009

Dr. Jonathan Samet, Chair
Clean Air Scientific Advisory Committee
U.S. Environmental Protection Agency
c/o Dr. Holly Stallworth, Designated Federal Officer (DFO)
EPA Science Advisory Board (1400F)
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW.
Washington, DC 20460

Dear Dr. Samet

I am pleased to present HEI’s comments on the First Draft Integrated Science Assessment for Particulate Matter (PM ISA). As you know, HEI has produced, and is continuing to produce, a number of studies and an important literature review of traffic exposures and effects that are relevant to the development of this document. We are pleased to see in this first draft of the ISA that many HEI reports, and many comments provided by the HEI Review Committee, played an important role at key points in the document.

I provide a summary of our written comments here, including a few general thoughts and key findings of the newest HEI studies that can inform the next revision of the PM ISA.

General Comments

Overall, we found that the National Center for Environmental Assessment (NCEA) has done a very good job of reviewing a diverse new set of studies and placing them in the context of the larger literature. We are especially supportive of the effort, starting in Chapter 1, to identify a priori the Agency’s criteria for making judgments of causality, and adopting a uniform descriptive language for different levels of confidence in making such causality determinations. Having said that, we note in our detailed comments several areas where this language is vague, or not always consistently applied, and urge CASAC and EPA to address that in the second draft.

We also found that while the PM ISA in general was careful in presenting the evidence, and we appreciate the fact that the ISA frequently cites the Commentaries of the HEI Review Committee in interpreting the evidence, we found several areas where the document tends to emphasize the positive results from a study but does not place that in the context of other negative results. We note several of these areas relevant to HEI work in our detailed comments; one example is the citation of the article by McCreaor et al (2007) at 6-128 and 6-131, which is a paper drawn from the HEI Zhang study of asthmatics exposed to traffic and urban background in London and which HEI published in full form in February (Zhang et al. 2009). Although the ISA notes the effects reported in the McCreaor et al paper (which are also described in the fuller, Zhang HEI report) on some measures of lung function, it does not report that the McCreaor et al paper (and the Zhang HEI report) found few or no effects on some other measures of lung function, asthma symptoms, or medication use. It is critical that such findings (for these studies and all others) are placed in their full context. (I have attached the HEI Statement for the Zhang study)
HEI’s Newest Studies

In addition to the Zhang study, HEI has published and is publishing a number of studies that will be relevant to the next revision of the ISA. We focus on a few of those here:

- HEI has just published its Brunekreef Report (2009) *Effects of Long-Term Exposure to Traffic-Related Air Pollution on Respiratory and Cardiovascular Mortality in the Netherlands: The NLCS-AIR Study*. It reports the comprehensive results of analyses in the Dutch NLCS diet and health cohort; the investigators have estimated air pollution and traffic exposure in the full cohort, and analyzed the degree to which those exposures are associated with premature all-cause and cause-specific mortality. A summary of the results of this work is cited in the ISA from the paper by Beelen (Beelen et al. 2008a; Beelen et al. 2008b).

  This study finds, in the view of the HEI Review Committee and the investigators, one of the first small but relatively consistent associations of air pollution and traffic exposure with premature mortality in a carefully-studied European cohort. There are several aspects of how this work is currently cited in the ISA that could be enhanced in the next draft, as well as additional detailed analysis in the full report that could be incorporated. These include

  - Better delineating that the PM2.5 analyses are based on estimated PM 2.5, with substantial uncertainty surrounding the estimation procedure. In the HEI Review Committee’s view, although this does not change the overall finding of air pollution associations, it does affect the degree to which these estimates can be relied on for specific analysis of PM2.5.

  - Better emphasizing and including in its evaluation that these results, especially for measures of traffic exposure, are substantially lower than those previously found in the pilot study in this cohort published in 2002 (Hoek, 2002).

- HEI plans to publish its Krewski report *Extended Follow-Up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality* (Krewski 2009) in late April. This report contains a number of major updates and further analyses in this important cohort, including:

  - New *Nationwide Analyses* using extended follow-up and enhanced statistical models to more fully test possible spatial auto-correlation and additional confounders. These analyses, which in the view of the HEI Review Committee are innovative and well done, have reported higher relative risks than past analyses, and one of the first findings of an ozone-mortality relationship in this cohort (for longer term exposure to ozone season levels (May – September). Extended analyses of this latter finding were published recently in the New England Journal of Medicine (Jerrett et al. 2009).

  - *Intraurban Analyses* for Los Angeles (which had been previously published (Jerrett et al. 2005)) and for the first time for New York City. These are important because while the Los Angeles study had reported substantially higher risk estimates than the national analyses, the New York City study found lower effect estimates than the national analyses (with the exception of ischemic heart disease mortality). The HEI Review Committee comments on this extensively in its Commentary and has prepared the figure below to illustrate that the wider confidence intervals for the two intraurban overlap the national analyses.
ACS Extended Analysis
Results for Cardiopulmonary Mortality

- Analyses of different Time Windows of Exposure and mortality associations.
- Education as an Effect Modifier. The new national analyses attempted to replicate the results of the original Reanalysis and other subsequent efforts suggesting that estimated risks were higher for those with lower education (and ostensibly lower socioeconomic status). However, the new analyses did not find the systematic modification of effects found in the earlier analyses; for one cause of death (ischemic heart disease) they found indications of a reverse relationship (with higher estimated risks for those with higher education). This may be due to a number of factors, but calls for a thoughtful inclusion in the discussion of socioeconomic status as an indicator of vulnerable populations at Page 8-17.

- The HEI Special Report A Critical Review of the Health Effects of Traffic-Related Air Pollution (HEI 2009) will be issued this spring. This report of an HEI-appointed expert panel has considered over 400 studies of exposure and health and their analysis of that literature and conclusions as to its strengths and weaknesses should be useful in the revised ISA, especially in the discussions in Chapters 6 and 7, of potential source-related effects.

In conclusion, we congratulate NCEA on a very good first draft ISA and hope that these comments – and HEI’s new studies – are helpful in crafting a better refined final draft ISA in the coming months. HEI stands ready to work with EPA to provide answers to questions and/or any additional assistance you might require.

Sincerely,

Daniel S. Greenbaum
President
REFERENCES


Health Effects of Real-World Exposure to Diesel Exhaust in Persons with Asthma

BACKGROUND

In the 1990s, results from several epidemiologic and controlled-exposure studies suggested an association between exposure to air pollution from traffic-derived particulate matter (PM) and increases in symptoms of airway diseases, including exacerbations of asthma. Some results also suggested that exhaust from diesel engines, used in a large fraction of vehicles worldwide and particularly in Europe, contributed to these effects. In response to HEI RFA 00-1, Effects of Diesel Exhaust and Other Particles on the Exacerbation of Asthma and Other Allergic Diseases, Dr. Junfeng (Jim) Zhang of the University of Medicine and Dentistry of New Jersey, proposed a study that would investigate how inhaling air with a high concentration of diesel exhaust from vehicular traffic while walking on a street in Central London, United Kingdom, might affect people who had either mild or moderate asthma. Dr. Zhang and his colleagues hypothesized that this exposure would exacerbate asthma symptoms, decrease lung function, and induce lung inflammation and oxidative stress responses. The HEI Research Committee recommended Dr. Zhang’s proposal for funding.

APPROACH

The investigators recruited 60 nonsmoking participants of both sexes between 18 and 55 years old, with mild or moderate asthma. Each subject participated in one 2-hour exposure session by walking along Oxford Street, a busy Central London thoroughfare where vehicles are predominantly diesel-powered, and one 2-hour session walking at a nearby control site, Hyde Park, where there is no traffic.

Before, during, and after each session, the investigators evaluated pulmonary function parameters (forced expiratory volume in the first second [FEV₁], forced vital capacity [FVC], and forced expiratory flow during the middle half of the FVC [FEF₂₅₋₇₅]) and asthma symptoms. At some time points Zhang and colleagues also evaluated bronchial reactivity (PC₂₀) and markers of airway inflammation and oxidative stress. These markers included exhaled nitric oxide, the pH of exhaled breath condensate (EBC), blood thiobarbituric acid reactive substances (TBARS), sputum interleukin-8 and myeloperoxidase (MPO). Participants kept a record of asthma symptom scores, peak expiratory flow rate (PEFR), and asthma reliever medication use during the 7 days before and after each session.

Pollutant samplers, placed on a cart that accompanied the participants during sessions, measured concentrations of PM₂.₅ (PM ≤ 2.5 μm in aerodynamic diameter), ultrafine particles (UFP; PM < 100 nm in aerodynamic diameter), elemental carbon (EC), and nitrogen dioxide (NO₂).

STATISTICAL METHODS

Zhang and colleagues used two main statistical approaches: comparative analyses between the exposure and control sessions that took advantage of the paired design of the study to compare within-subject responses, and pollutant-specific exposure–response analyses that estimated associations between the concentration of an individual pollutant and a change in a health endpoint from its baseline value. In one set of pollutant-specific exposure–response analyses, each of the four pollutants was used as a single covariate; a second set of analyses used two of the four pollutants as covariates. They analyzed responses for all subjects, and also analyzed responses separately for participants with either mild or moderate asthma.

RESULTS

The investigators found that participants were exposed to higher average pollutant concentrations...
during the exposure session than during the control session: approximately 5-fold higher EC, 4-fold higher NO\textsubscript{2}, 3.5-fold higher UFP, and 2-fold higher PM\textsubscript{2.5} mass.

FEV\textsubscript{1} and FVC were significantly lower after the exposure session compared with the control session (stratified analyses showed that these effects were dominated by responses in participants with moderate asthma). However, FEF\textsubscript{25–75} and PEFR did not differ significantly. Also not affected by exposure were asthma symptom scores, asthma medication use, PC\textsubscript{20}, and blood TBARS; some of these responses showed nonsignificant trends. A significant relative decrease in EBC pH of 2.0% (correlating with an approximate half-log change in pH) was noted one hour after the exposure session; this effect was also dominated by observations in subjects with moderate asthma. Of the sputum parameters evaluated, only the neutrophil-associated enzyme MPO differed significantly with a 5-fold increase after the exposure session compared with after the control session.

In one-pollutant exposure–response analyses, UFP and NO\textsubscript{2} were associated with changes in the most endpoints, EC with fewer, and PM\textsubscript{2.5} with fewer still. In two-pollutant models, several associations between the measured pollutants and changes in endpoints lost significance after the investigators controlled for other pollutants. Some associations, however, were unaffected by the inclusion of a second pollutant. Associations of UFP with endpoints were not affected by adjusting for other pollutants, except NO\textsubscript{2}. Adjusting for NO\textsubscript{2} generally appeared to reduce associations with the other pollutants.

**SUMMARY AND CONCLUSIONS**

The study by Zhang and colleagues, with an innovative approach, has provided interesting new findings. The effects with the most potential clinical significance were the relative decreases in FEV\textsubscript{1} (3.0%–4.1%) and FVC (3.1%–3.7%) during and several hours after the exposure ended. The magnitude of these decrements in lung function may be clinically relevant for patients with severe or uncontrolled asthma, whose lung capacity is severely diminished compared with healthy people.

Based on the statistically significant changes in one marker each of airway inflammation (MPO) and of airway acidification (EBC pH), and in conjunction with sputum findings of marginal statistical significance, results of this study suggest that the exposure session was associated with a mild increase in inflammatory response in the airways that was mediated by neutrophils.

Asthma symptoms and the use of asthma reliever medication increased only marginally after the exposure session. Thus, whereas exposure to a diesel-traffic–enriched environment may have produced changes in pulmonary function and inflammatory endpoints, the lack of significant changes in symptoms or the use of asthma reliever medication suggests that this single exposure did not affect the clinical status of asthmatic participants.

Analyses with stratification by the severity of asthma showed that changes in FEV\textsubscript{1}, FVC, and EBC pH were significant only in subjects with moderate asthma. Because the majority of subjects with moderate asthma were taking corticosteroids, it is possible that corticosteroid use may have blunted responses in this group. Though the background severity of asthma may be an important factor affecting responses to diesel traffic exposure, further work is needed to confirm or disprove this hypothesis.

Exploratory one- and two-pollutant analyses to identify associations between specific components of the pollutant mix and changes in endpoints found that UFP and NO\textsubscript{2} were associated with the most endpoints, EC with fewer, and PM\textsubscript{2.5} with fewer still. All these pollutants are constituents of traffic emissions and EC is frequently used as a marker of diesel emissions, but none is absolutely specific to diesel. Thus, because the pollutants measured are not specific to diesel emissions, the results are only suggestive of the effects of DE on the endpoints measured.

Explanations for the effects observed, other than exposure to DE, also need to be borne in mind. One is that participants were almost certainly concurrently exposed to air pollutants not associated with diesel-powered engines, such as pollutants derived from tailpipe emissions of gasoline-powered cars on streets that cross Oxford Street, as well as particles not derived from tailpipe emissions — such as those generated by tire and brake wear and roadway dust produced by all vehicles. In addition, concentrations of several traffic-associated pollutants (including CO, organic carbon compounds, and particles in the coarse size range) were not measured in the current study and may be associated with the endpoints evaluated. Furthermore, the exposure
and control sites differed in other, unmeasured characteristics, particularly in noise levels and the amount of stress experienced by the subjects.

Although the findings of the current study indicate that lung function is slightly decreased and some markers of airway inflammation are increased in people with asthma who are exposed to ambient urban air in a roadside environment dominated by diesel vehicles, the study does not provide direct evidence that DE itself causes these effects. Additional studies would be needed to address that question, and to identify specific components of DE that might be responsible for any observed health effects. A final consideration is that since the study was completed, more stringent emissions and fuel standards have been implemented and new engine technologies introduced in both the United States and Europe. As older vehicles are replaced in the fleet, decreases in most traffic-related pollutant concentrations can be anticipated. The health impact of these changes will need to be assessed; this study may serve as a baseline analysis for future studies on the effects of such changes.
Dr. John Vandenberg, Director
National Center for Environmental Assessment - RTP
U.S. Environmental Protection Agency
USEPA Mailroom - Mail Code: B243-01
Research Triangle Park, NC 27711

Dear Dr. Vandenberg:

Comments on Docket EPA-HQ-ORD-2007-0517

We are pleased to submit HEI’s comments on the First Draft Integrated Science Assessment for Particulate Matter (PM ISA). As you know, HEI has produced, and is continuing to produce, a number of studies and an important literature review of traffic exposures that are relevant to the development of this document. We are pleased to see in this first draft of the ISA that many HEI reports, and many comments provided by the HEI Review Committee, played an important role at key points in the document.

In these comments we provide some general comments first, and then discuss key findings of the newest HEI studies that we hope will be valuable to the next revision of the PM ISA. Finally, we attach some detailed comments on the ISA and especially how it interprets HEI’s previous work.

General Comments

Overall, we found that the National Center for Environmental Assessment (NCEA) has done a very good job of reviewing a diverse new set of studies and placing them in the context of the larger literature. We are especially supportive of the effort, starting in Chapter 1, to identify a priori the Agency’s criteria for making judgments of causality, and adopting a uniform descriptive language for different levels of confidence in making such causality determinations. Having said that, there were several areas where we thought this effort could be enhanced:

- First, the actual language describing the process and criteria in Chapter 1 could benefit from a careful review to tighten and make some of the language less vague; as currently constructed, there is some overlap in the different sections, which obscures the true hierarchy for decision making that EPA is applying.

- Second, in the discussion of evidence, there are appropriate discussions of both direct clinical evidence and time series and cohort epidemiology, but no discussion of the role of panel studies (which may, if well designed, combine elements of both) to the determinations of causality.

- Finally, in the actual application throughout the document, the descriptions of causality are generally consistent, but some differences in language do creep in, and the use of the
“causality” language appears very frequently in some sections (i.e. for each subsidiary step toward an overall determination of causality) and much less frequently in other sections. This adds confusion to judging the relative quality of the judgments being made and should be reviewed for consistency.

We also found that while the PM ISA in general was careful in presenting the evidence, and we appreciate the fact that the ISA frequently cites the Commentaries of the HEI Review Committee in interpreting the evidence, we did find some areas where the document tends to emphasize the positive results from a study but does not place that in the context of other negative results. We note several of these areas relevant to HEI work in the attachment; one example is the citation of the article by McCreanor et al (2007) at 6-128 and 6-131, which is a paper drawn from the HEI Zhang study of asthmatics exposed to traffic and urban background in London and which HEI published in full form in February (Zhang et al. 2009). Although the ISA notes the effects reported in the McCreanor et al paper (which are also described in the fuller, Zhang HEI report) on some measures of lung function, it does not report that the McCreanor et al paper (and the Zhang HEI report) found few or no effects on some other measures of lung function, asthma symptoms, or medication use. It is critical that such findings (for these studies and all others) are placed in their full context.

**HEI’s Newest Studies**

In addition to the Zhang study, HEI has published and is publishing a number of studies that will be relevant to the next revision of the ISA. We focus on a few of those here:

- HEI plans to publish its Brunekreef Report (2009) *Effects of Long-Term Exposure to Traffic-Related Air Pollution on Respiratory and Cardiovascular Mortality in the Netherlands: The NLCS-AIR Study* later in March. It reports the comprehensive results of analyses in the Dutch NLCS diet and health cohort; the investigators have estimated air pollution and traffic exposure in the full cohort, and analyzed the degree to which those exposures are associated with premature all-cause and cause-specific mortality. A summary of the results of this work is cited in the ISA from the paper by Beelen (Beelen et al. 2008a; Beelen et al. 2008b).

This is an important study because it finds, in the view of the HEI Review Committee and the investigators, one of the first small but relatively consistent associations of air pollution and traffic exposure with premature mortality in a carefully-studied European cohort. However, there are several aspects of how this work is currently cited in the ISA that could be enhanced in the next draft, as well as additional detailed analysis in the full report that could be incorporated:

- Figure 7-8 at 7-104, includes a number of results of the Beelen study for PM2.5, but in a note to that figure or accompanying text it should be highlighted that this is based on estimated PM 2.5, with substantial uncertainty surrounding the estimation procedure. In the HEI Review Committee’s view, although this does not change the overall finding of air pollution associations, it does affect the degree to which these estimates can be relied on for specific analysis of PM2.5.

- Figure 7-8 and the discussion of these results at 7-110 reports appropriately note the small consistent associations found, but should emphasize and include in its evaluation
that these results, especially for measures of traffic exposure, are substantially lower than those previously found in the pilot study in this cohort published in 2002.

- The full HEI report also provides detailed additional analyses of other pollutants, as well as an analysis restricted to the three largest cities, all of which should be useful to EPA’s interpretation of these results in the final draft.

- HEI plans to publish its Krewski report *Extended Follow-Up and Spatial Analysis of The American Cancer Society Study Linking Particulate Air Pollution and Mortality* (Krewski 2009) in late April. This report contains a number of major updates and further analyses in this important cohort, including:
  - New *Nationwide Analyses* using extended follow-up and major enhanced statistical models to more fully test possible spatial auto-correlation and additional confounders. These analyses, which in the view of the HEI Review Committee are innovative and well done, have reported somewhat higher relative risks than past analyses, and one of the first findings of an ozone-mortality relationship in this cohort (for longer term exposure to ozone season levels (May – September). Extended analyses of this latter finding were published recently in the New England Journal of Medicine (Jerrett et al. 2009).
  - *Intraurban Analyses* for Los Angeles (which had been previously published (Jerrett et al. 2005)) and for the first time for New York City. These are important because while the Los Angeles study had reported substantially higher risk estimates than the national analyses, with the exception of ischemic heart disease mortality, the New York City study found lower effect estimates than the national analyses. The HEI Review Committee comments on this extensively in its Commentary and has prepared the figure below to illustrate that the wider confidence intervals for the two intraurban overlap the national analyses. We urge EPA to revise Figures 7-7 and 7-8 (on p.7-103) and the text beginning on Page 7-111 to incorporate and discuss these New York results and the HEI commentary on the two analyses.

*ACS Extended Analysis Results for Cardiopulmonary Mortality*

- **Intra-urban and national**

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<tr>
<th>Hazard Ratio per 10 mg/m3 PM2.5 (2000)</th>
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Analyses of different *Time Windows of Exposure* and mortality associations. The investigators conducted extensive analyses to determine whether certain time windows were more strongly associated with estimated risk. Though they were unable to find a clear signal, the analyses would significantly enhance the discussion in the ISA at 7-113.

*Education as an Effect Modifier.* The new national analyses attempted to replicate the results of the original Reanalysis and other subsequent efforts suggesting that estimated risks were higher for those with lower education (and ostensibly lower socioeconomic status). However, the new analyses did not find the systematic modification of effects found in the earlier analyses; for one cause of death (ischemic heart disease) they found indications of a reverse relationship (with higher estimated risks for those with higher education). This may be due to a number of factors, but calls for a thoughtful inclusion in the discussion of socioeconomic status as an indicator of vulnerable populations at Page 8-17.

The HEI Special Report *A Critical Review of the Health Effects of Traffic-Related Air Pollution* (HEI 2009) will be issued this spring. This report of an HEI-appointed expert panel has considered over 400 studies of exposure and health and their analysis of that literature and conclusions as to its strengths and weaknesses should be useful in the revised ISA, especially in the discussions in Chapters 6 and 7, of potential source-related effects.

In conclusion, we congratulate NCEA on a very good first draft ISA and hope that these comments – and HEI's new studies - are helpful in crafting a better refined final draft ISA in the coming months. HEI stands ready to work with EPA to provide answers to questions and/or any additional assistance you might require.

Sincerely,

Daniel S. Greenbaum
President

Attachment
REFERENCES


## ATTACHMENT

**HEI Detailed Comments on**

_The Integrated Science Assessment for Particulate Matter, First External Review Draft_

<table>
<thead>
<tr>
<th>ISA Pages</th>
<th>Line</th>
<th>Comment</th>
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<tr>
<td>3-102</td>
<td>11-20</td>
<td>In a discussion of the correlation between PM and gaseous pollutants, the ISA provides Bell (2007a) as a source of data on ozone; the citation is incorrect, as there are no ozone data in this paper. The reference may be to another work: Bell ML, Kim JY, Dominici F. 2007. “Potential confounding of particulate matter on the short-term association between ozone and mortality in multisite time-series studies.” <em>Environ Health Perspect</em>. Nov;115(11):1591-1595.</td>
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<tr>
<td>3-140-141</td>
<td>26-30, 1-2</td>
<td>In a discussion of source proximity as a surrogate for exposure, findings from Baxter et al. (2007a) are summarized as: “They found that PM2.5 was largely influenced by ambient PM2.5 while EC was more sensitive to local traffic source.” This diminishes the role of indoor air as it was described by Baxter et al.: “PM2.5 was influenced less by local traffic but had significant indoor sources, while EC was associated with local traffic and NO2 was associated with both traffic and indoor sources” (p. 6569).</td>
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<tr>
<td>3-152, passim</td>
<td>24</td>
<td>Mention of findings from the RIOPA study do not provide a citation for the underlying study publication; Weisel, Clifford P, Junfeng (Jim) Zhang, Barbara Turpin, Maria T Morandi, Steven Colome, Thomas H Stock, Dalia M Spektor, and Others, 2005. HEI Research Report 130-I, <em>Relationships of Indoor, Outdoor, and Personal Air (RIOPA). Part I, Collection Methods and Descriptive Analyses</em>, should be added to the ISA’s bibliography.</td>
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<tr>
<td>6-16</td>
<td>4</td>
<td>In section 6.2.1.2., “Human Clinical Studies,” findings are presented from Gong et al. (2003a) on increased parasympathetic stimulation of HRV following exposure to fine concentrated ambient particles. The ISA mistakenly summarizes the observation of an effect as “at 2-days post-exposure;” this should be corrected to read “1 day after the exposure.”</td>
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<tr>
<td>6-23</td>
<td>13-25</td>
<td>The ISA cites Dockery and colleagues’ study of arrhythmias using implantable cardioverter defibrillators (Dockery et al., 2005a and 2005b). An additional note on this work that should be made in the ISA is that, in reviewing the ECG for each ICD-detected arrhythmia, Dockery et al. (2005b) reported both ventricular and atrial</td>
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(supraventricular) arrhythmias. The HEI Review Committee’s Commentary on this report, in HEI Research Report 124, noted that “It is also the first in which a cardiologist attempted to distinguish the origin of the verified arrhythmia as ventricular or supraventricular” (Dockery et al., 2005b:135).

The same Commentary also provides a cautionary note missing in the ISA’s description of the associations between increases in individual pollutants and ventricular arrhythmias. As stated in the Commentary’s discussion: “The principal pollutant analyses—single-day, mean 2-day, and distributed lag models—indicated that nonfatal arrhythmic events were weakly and not significantly associated with ambient concentrations of PM2.5 or BC at any lag time up to 3 days before the event.” Moreover, the “Summary and Conclusions” section of the Dockery Commentary states “Overall, results of this study indicate that among patients who have an implanted ICD, ambient concentrations of PM2.5 or BC on the day of or up to 3 days before the event are only weakly, if at all, associated with the induction of nonfatal arrhythmias” (Dockery et al., 2005b:138).

6-50 13-16 In a discussion of toxicological studies looking at blood pressure effects and exposure to environmentally-relevant concentrations of PM, the ISA indicates that “no effect was observed” in Vincent, et al., 2001. Actually, the cited report found statistically significant elevations (P<0.05) of blood pressure on day 2 after exposure to Ottawa dust (EHC-93), although not with water-leached Ottawa particles.

6-63 9-13 In the section reviewing toxicological studies of blood coagulation, there is a mistaken reference to Nadziejko et al. (2002). The work by Nadziejko et al that reports findings for blood coagulation effects is: Nadziejko C, Fang K, Chen LC, Cohen B, Karpatkin M, Nadas A. Effect of concentrated ambient particulate matter on blood coagulation parameters in rats. Res Rep Health Eff Inst. 2002 Oct;(111):7-29; discussion 31-8. This reference would need to be added to the References section.

6-84 7-11 In section 6.2.10.4., “Acute Myocardial Infarction,” the ISA summarizes the findings of Peters et al., 2005 and Peters et al., 2004 from a study of patients hospitalized after surviving a myocardial infarction in Augsburg, Germany. The ISA correctly notes that no association between PM2.5 and MI risk was reported in the 2005 publication (although, there was a positive and statistically significant association with time spent in traffic). It should further note that Peters (2005), HEI Research Report 124, Part I. Air Pollution, Personal Activities, and Onset of Myocardial Infarction in as Case-Crossover Study, also measured ultrafine particle levels (at a site away from traffic, but with diurnal patterns influenced by traffic) and found no associations between ultrafines and MI induction.
In discussing PM and arrhythmias, the ISA makes use of Dockery (2005b): “Several additional analyses of this same cohort that examined different lags and pollutants have also reported increased risk of arrhythmia with PM2.5, BC and sulfate exposure” (Dockery et al., 2005a; 2005b). However, as noted above, the HEI Review Committee’s opinion for that study is that there was “little or no association” (p. 135) or that the association reported was “[weak], if at all.” (p. 138)

Discussions of findings of decreases in lung function in adults (FEV1, FVC, PEFR) associated with PM exposure make note of the positive observations in McCreanor et al. (2007). It should be noted that this publication also indicates that effects on asthma symptoms and on medication use were insignificant. The full report of the underlying study, HEI Research Report 138, Health Effects of Real-World Exposure to Diesel Exhaust in Persons with Asthma, also reports those findings, and, in addition, reports that there were no effects on PEFR.

The findings of Zhang et al reported in HEI Research Report 138, Health Effects of Real-World Exposure to Diesel Exhaust in Persons with Asthma (Zhang et al., 2009) will help the ISA’s discussion of pulmonary inflammation effects. The work finds that exposure to diesel traffic enhances airway inflammation (increased sputum myeloperoxidase levels) and airway acidification (increased exhaled breath condensate [EBC] pH). At the same time, the HEI Review Committee also cautioned that while diesel exhaust was a significant component of the Oxford Street exposure in this study, there were other important exposures as well. This information could be usefully inserted on page 6-128, Section 6.3.3. “Pulmonary Inflammation,” and specifically on page 6-131 in the section “Other Biomarkers of Pulmonary Inflammation.”

In a section of the ISA summarizing findings of studies of PM2.5 and PM10-2.5 and hospitalization or ED visits for respiratory diseases, observations in Bell et al., (2008a) are reported incorrectly. The ISA presents figures for increases observed during the winter in the Northeast “(1.05% [95% PI: 0.29-1.82], lag 0)” that are actually the national numbers; those the ISA summarizes as for the Southeast “(1.76% [95% PI: 0.60-2.93], lag 0)” are actually the numbers for the Northeast. (The Southeast was not significant.)

In sections summarizing toxicological studies of host defense mechanisms, the ISA makes note of findings in Harrod (2003). That report is partly based on an HEI-funded study that was not published. In the study, all animals were infected with RSV; thus there were no control groups that were exposed to diesel exhaust or air that were not infected with RSV. The HEI Review Committee commented that the study design made it difficult to disentangle whether the observed
changes in health endpoints were due to diesel exposure or RSV infection.

6-250

| 7 | The statement “In Gong et al. (2003a) the majority of the PM was in the thoracic coarse fraction,” appears to cite Gong’s work incorrectly; In Gong et al., (2003a), it is stated that “80% of CAP mass was….fine particles, < 10% was smaller (ultrafine) and > 10% was larger (coarse) particles.” Gong et al. (2004b) may have been the intended reference. |

7-87ff

| 1ff | The results from analyses of the NLCS cohort presented in Beelen, (2008a) are cited in the ISA’s review of findings of cancer effects. These include associations with PM2.5. The ISA’s incorporation of this data would be strengthened by including a note that the PM2.5 results did not come from measured values but were calculated from PM-10 through a chain of conversions from correlations between a few measurements and traffic counts from single paper sampling traffic and air quality at only a few locations at best. The HEI Review Committee, in its commentary on the forthcoming HEI Research Report 139 (Brunekreef 2009) of further analyses conducted on the Dutch cohort, points to the estimates of PM2.5 and notes that, while it does not change the overall findings, it does affect the degree to which they can be relied on for specific analyses of PM2.5 |

7-104

| n/a | Figure 7-8 has multiple listings of Beelen, 2008 results, but there is no discussion of the uncertainties in the PM2.5. As above, we suggest adding some discussion of the uncertainty (see Review Committee commentary of the Brunekreef group’s work in HEI Research Report No. 139, 2009). |

7-102

| 1ff | Section 7.62, reviewing findings from studies of the mortality effects of long-term exposure to PM2.5, would benefit from the inclusion of findings reported in Krewski (2009). This report presents the most recent extended analysis of ACS cohort data. Eighteen years of follow-up (1982-2000) data are analyzed with the application of statistical methods (Cox Random Effects Models) that have been extended to incorporate two levels of ecologic covariates (socioeconomic factors at zip-code and city levels) and two levels of spatial clustering in a single model. The nationwide analysis provides results for a cohort that is highly-controlled for confounding, adding to the epidemiological evidence for associations between long-term exposures to PM 2.5 and excess mortality. |

7-111

| 24ff | Section 7.6.6, “Within-City Effects of PM Exposure,” which considers investigations of within- vs. between-city effects of PM exposure, would be enhanced by a discussion of the Los Angeles and New York City intraurban analyses in Krewski (2009), which uses land use regression methods to assign exposure according to both monitored values and local emissions sources, such as traffic. The results found |
for New York City vary to a significant extent from previously the reported results for Los Angeles (Jerrett, 2005) which are considered in the ISA.

7-113 1ff Section 7.6.7, considering the time window over which the mortality effects of long-term pollution exposures occurred, should include a discussion of the recent ACS analysis (Krewski, 2009), which contains an extensive examination of “critical periods of exposure.”

7-115 1ff The Summary discussion in Chapter 7 cites Jerrett, (2005) to note that: “The results of new analyses from the Six Cities cohort and the ACS study in Los Angeles suggest that previous and current studies may have underestimated the magnitude of the association” between long-term PM2.5 exposure and mortality. The discussion can be enhanced by a consideration of the similarities and differences between that study and the most recent estimates using a different exposure assessment method presented in Krewski (2009).

8-15 9ff Section 8.2.1.10., which considers the relation of exposure to ambient PM on diabetes and obesity, would benefit from including findings reported in Krewski (2009), which includes a number of endocrine outcomes in its extended analyses of ACS Study cohort data.

8-17 18ff Results for nationwide analysis presented in Krewski (2009) were stratified for educational attainment – these show some effect modification by education level and could contribute to the discussion in this section, 8.2.4.

8-18 13 In a discussion of socioeconomic vulnerability characteristics, the ISA cites Kan (2008) to make note of a wide set of SES factors that may be associated with PM-related health effects; the proper citation for the observation should be Romieu I, Tellez-Rojo MM, Lazo M, Manzano-Patino A, Cortez-Lugo M, Julien P, et al. 2005. Omega-3 fatty acid prevents heart rate variability reductions associated with particulate matter. *Am J Respir Crit Care Med* 172(12): 1534-1540.

Sect. 6-2 n/a The ISA would benefit from consideration of *in vitro* studies of ultrafine particle effects on vascular endothelial cells. A recent HEI report (Kennedy, 2009) provides findings from a study on the effects of different ultrafine metal oxide particles on a vascular endothelial cell line. Given that occupational exposures to metal oxide particles may have significant cardiopulmonary effects and that inflammatory responses of the endothelium are considered critical in the development of atherosclerosis, the HEI Review Committee considered this a useful pilot study.
References Made to Publications Not in the ISA Bibliography


Weisel, Clifford P, Junfeng (Jim) Zhang, Barbara Turpin, Maria T Morandi, Steven Colome, Thomas H Stock, Dalia M Spektor, and Others, 2005. HEI Research Report 130-I, Relationships of Indoor, Outdoor, and Personal Air (RIOPA). Part I, Collection Methods and Descriptive Analyses. Health Effects Institute, Boston, MA.
