Comments on the Integrated Science Assessment for Particulate Matter

First External Review Draft

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Comments of the American Lung Association on the U.S. Environmental Protection Agency’s First External Review Draft of the Integrated Science Assessment for Particulate Matter

Overview

The American Lung Association considers the review of the National Ambient Air Quality Standards (NAAQS) for particulate matter to be a top priority concern for the protection of public health, a position reinforced by the recent decision of the U.S. Court of Appeals. Particulate matter air pollution poses risks of serious respiratory and cardiovascular health effects, including premature death. The evidence in the last review indicated that adverse health effects ranging from respiratory problems to early death persisted at levels below both primary standards set in 2006. Newly available evidence reinforces this concern.

The Lung Association applauds the U.S. Environmental Protection Agency for significant improvements in the format, coverage of issues, criteria, and consistent framework for decision-making. The Lung Association urges EPA to incorporate a full review of the available research in the next draft of the integrated science assessment, particularly in light of the decision of the U.S. Court of Appeals. In particular, research into occupational exposure and traffic exposure, as well as international studies need to be included. **We believe that extensive new evidence that has emerged since the last review that strengthens the case for setting stringent short- and long-term standards for PM$_{2.5}$, PM$_{10}$, and PM$_{10-2.5}$**.

Developments since the previous review

Based on the health evidence presented in the last review, the American Lung Association supported 24-hour PM$_{2.5}$ standards of 25 µg/m$^3$ 99$^{th}$ percentile, coupled with an annual average PM$_{2.5}$ standard of 12 µg/m$^3$ or below.

The Lung Association favored establishment of a 24-hour PM$_{10-2.5}$ standard of 25 µg/m$^3$, 99$^{th}$ percentile, to apply nationally, without a special exemption for rural areas or for the mining and agriculture industries. In addition, we supported an annual average standard for coarse particles and opposed EPA action to revoke the PM$_{10}$ annual average standard.

The American Lung Association, Environmental Defense and a coalition of 18 states challenged the final 2006 PM standards in court.
On February 24, 2009, the U.S. Court of Appeals for the D.C. Circuit ruled in favor of most of the Lung Association’s challenges. The Court granted in part our petition for review of the 2006 primary annual fine particle standard.

“In sum, the EPA did not adequately explain why an annual level of 15 µg/m³ is sufficient to protect the public health while providing an adequate margin of safety from short-term exposures and from morbidity affecting vulnerable subpopulations. We therefore grant in part the petitions for review filed by the States and by the environmental petitioners (Nos. 06-1416 and 06-1411) and remand for reconsideration the primary annual NAAQS for PM_{2.5}.”

The Court specifically made note that several short-term studies are relevant to the setting of the annual standard:

“As both the CASAC and the staff reasoned, the studies of Eight Canadian Cities, of Santa Clara County (CA) and of Phoenix are relevant to setting an annual standard because each reports adverse health effects associated with short-term exposures in places where the annual PM_{2.5} concentration is below 15 µg/m³.”

In addition, with respect to studies of short-term exposures on children’s lung function, the Court discusses the significance of the Gauderman et al¹ study and the Raizenne et al² 24-Cities study cited in the Criteria Document to consideration of the annual standard.

The Court specifically agreed with our arguments that the Administrator must review and address evidence that the CASAC and the EPA staff had provided that showed the harm of mid-range exposure to PM, at levels well below the peak levels. The Court understood and agreed with the logic of the previous recommendations from CASAC and the staff that the two standards for PM_{2.5} were complementary components of a holistic approach to reducing particulate matter exposures.

Further, the Court upheld the Lung Association’s position and rejected the industries’ challenge to the coarse particle standards, arguments founded in their desire for a special exemption for agriculture and mining.

This court decision provides strong impetus for EPA to revise the annual average standard for PM_{2.5} to protect public health with an adequate margin of safety, including the health of sensitive populations such as children.

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Scope of the Document

The format of this first draft document is greatly improved from earlier Criteria Document versions. In the main, EPA has done a good job covering the major topics and the major issues, and applying a more consistent framework for the evaluation of the evidence. We recognize the complexity of the task facing EPA in producing an integrated science assessment for PM. The assimilation of hundreds of new studies with previous science assessments is a daunting task which is complicated by the continuous publication of new studies that must be assessed.

The document needs to include a clear statement of what scientific studies are included and excluded from the review, and why. First, the introduction to the ISA needs to set out the dates of article publication (or acceptance for publication) that will be included in the scope of this review. Second, the document needs to state the specific selection criteria for the inclusion of studies, as well as the rationale for exclusion of studies, if any.

Additional Categories of Studies Should Be Included in the Next Draft

Our perusal of the document reveals several key categories of studies that are relevant to the review and should be included in the next draft ISA. Some have previously been excluded in the past, but the growing body of evidence shows that they must be considered in this review.

Our concerns about the omitted research lead us to ask two questions:

- First, if studies of the adverse effects of air pollution are not considered here where will they be considered? Repeatedly, they have been excluded from the most recent reviews of the criteria pollutants.
- Second, have other studies of “air pollution” pertinent to the evaluation of the evidence for other health endpoints been excluded?

Occupational health studies (coarse particles and diesel)

In comments on the 2006 standards, the Lung Association raised concerns about the systematic exclusion of occupational health studies from the Criteria Document. These studies are of particular relevance to the assessment of fine particle health effects from diesel exposures, and to the consideration of coarse particle exposures, especially from agriculture and mining sources. We note that without examining the studies, it is impossible to support a claim that exposure levels associated with adverse health impacts in occupational settings are irrelevant for community exposures. Below we point to several reasons why they should be included in the next draft ISA.

Occupational exposures are not limited to workers. Increasingly, the evidence shows that the former distinctions between “occupational” and “community” exposures do not reflect real-world experiences. Occupational exposures and community exposures are likely to overlap particularly for the agriculture, mining, and diesel transport sectors, because the activities associated with production of PM from these sectors commonly take place in the open along highways, ports or other locations which are often in close proximity to residences.
Occupational studies bear directly on the question of carcinogenicity of PM. While the integrated health assessment includes toxicology studies of diesel, it does not include a comprehensive assessment of epidemiologic studies. Evaluation of the epidemiologic studies, many of which are of occupational cohorts, is essential to the assessment of the carcinogenicity of diesel emissions. Diesel pollution is such an important component of fine particle exposure that this ISA cannot adequately evaluate this issue without including these diesel studies. In light of the diesel evidence, we find a conclusion that the evidence is “inadequate” for a causal determination of the long-term effects of PM$_{2.5}$ on cancer is untenable.

EPA’s 2002 diesel health assessment no longer represents the most current review of diesel research. There is a long string of diesel epidemiology studies that were not included in past PM NAAQS reviews. It was presumed that these studies had been evaluated as part of EPA’s diesel health assessment, which was finally completed in 2002. Subsequently, there have been a number of studies demonstrating increased risk of cancer, lung disease, and COPD from occupational exposure to diesel. These studies imply that people who live near highways or commute in heavy diesel traffic, or who live near truck stops, ports, and bus depots face higher risk from diesel pollution as well. An additional occupational study provided evidence of increased risk for ischemic heart disease in Swedish male constructions workers due to diesel exhaust.

Occupational studies provide critical evidence about effects of coarse particles. Additional recent occupational exposure studies not considered in the ISA are relevant to the assessment of coarse particles. For example, a study of occupational exposure to mineral dusts in Indian stone crushers found that people exposed to mineral dust in childhood and early adult life had excess symptoms and reduced vial capacity without airflow obstruction, compared to control subjects. Another study investigated signs of airway inflammation in underground miners exposed to inhalable dust and diesel exhaust.

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Traffic related air pollution studies

Since EPA’s last review of the PM standard, a large number of studies have been published relating traffic air pollution to a variety of health endpoints. Indeed this has been the major new development in air pollution research over the last several years. Many of these studies have been funded by EPA through the PM Centers research program. These studies the growing use of studies based on geographic information systems to assess the effects of air pollution. They show that people who live near roads with heavy traffic are at increased risk of adverse health effects from roadway pollution.

EPA appears to have excluded from this review studies of traffic related air pollution that did not include ambient measurements of particulate matter, such as distance to roadways studies. Similarly, distance to roadway studies were excluded from consideration in the ongoing review of the nitrogen dioxide standard.

Traffic studies need to be included in a criteria pollutant review. We are concerned that a large body of studies of the effects of traffic pollution exposure measured as distance to roadway may not be reviewed and evaluated under either the gaseous or the particle pollution reviews. This would sidestep one of the purposes of the periodic reviews -- to ensure that standards reflect the latest scientific evidence of the effect of air pollution on public health.

Traffic studies explore critical exposures. The traffic studies have particular relevance to the question of the effects of long-term exposures, because they evaluate residency in proximity to major roadways. This is one of the key policy issues facing EPA in the current review of the PM standards. Many of the new studies of long-term exposures that are available since the last review fall under the umbrella of traffic studies.7

We appreciate that studies with quantitative measures of pollutant concentrations which have been included in the draft ISA have direct relevance to selecting a standard level. However, studies based on residence near major roads may provide information on novel health endpoints and add to the evaluation of strength of evidence and causality for certain effects. The studies may also inform the selection of the indicator pollutant such as for ultrafines. They are directly relevant to source attribution questions.

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We urge EPA not to prejudge the utility of these traffic studies without a thorough and objective review and assessment through inclusion in the ISA. Given the proximity of specific at risk groups such as children and lower socioeconomic populations to traffic sources, these studies are important from an environmental justice and children’s health perspective.

**Other studies of undifferentiated air pollution**

Other studies that evaluated exposure to undifferentiated air pollution may have relevance to this review but appear to have been excluded. For instance, the evaluation of neurologic effects appears to exclude a number of key studies that have bearing on the overall causal determination for this category of health endpoints. These studies include animal and human studies conducted in Mexico City in comparison to cleaner air areas. We suspect that the studies have been excluded from the discussion of neurologic effects because they dealt with undifferentiated air pollution, i.e. comparing the brains of dogs exposed to heavy air pollution to those that lived in cleaner air areas.

**International Studies**

EPA appears to have excluded from the ISA a number of international studies of potential significance to the consideration of coarse particles. We cite these below in our discussion of the coarse particle research. We have not checked to see if this exclusion has also been applied to studies of PM\textsubscript{2.5} or PM\textsubscript{10} or other measures of particulate air pollution such as ultrafines, diesel or black smoke. EPA has not supplied a justification for any exclusion of international studies. The international studies should be reviewed and evaluated.

The American Lung Association urges that all studies of air pollution pertinent to the evaluation of the evidence for all health endpoints, from all countries, from all relevant sources and research be included to arrive at the best understanding of the science. The complexity of the issues and the enormity of the health implications require this approach.

**Chapter 1: Criteria for Evaluation of Evidence**

The Clean Air Act demands precautionary action to protect public health with an adequate margin of safety. In keeping with that requirement, the EPA should set air quality standards that provide broad protection against effects that are not limited to those where a causal relationship is established or where there is likely to be a causal relationship. EPA should provide protection against effects found to be “suggestive of a causal relationship.”

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The Act’s mandate requires that in considering uncertainty EPA must err on the side of caution in terms of protecting human health and welfare. As the D.C. Circuit held in reviewing the last round of NAAQS revisions, “The Act requires EPA to promulgate protective primary NAAQS even where … the pollutant's risks cannot be quantified or ‘precisely identified as to nature or degree.’” Am. Trucking Assoc. v. EPA, 283 F.3d 355, 369 (D.C. Cir. 2002) (quoting Particulate Matter NAAQS, 62 Fed. Reg. 38653); id. (citing Ozone NAAQS, 62 Fed. Reg. 38857 (section 109(b)(1)’s “margin of safety requirement was intended to address uncertainties associated with inconclusive scientific and technical information ... as well as to provide a reasonable degree of protection against hazards that research has not yet identified”)).

In the seminal case on the NAAQS, the court held that Congress “specifically directed the Administrator to allow an adequate margin of safety to protect against effects which have not yet been uncovered by research and effects whose medical significance is a matter of disagreement.”10 NAAQS must be set at levels that are not only adequate to protect the average member of the population, but also guard against adverse effects in vulnerable subpopulations, such as children, the elderly, and people with heart and lung disease.

For effects which are deemed “suggestive of causality,” EPA should include them in the quantitative risk assessment with appropriate consideration of uncertainty. We applaud that EPA discusses possible inclusion of birth related health endpoints in the draft Scope and Methods Plan, indicating that any quantitative risk assessment of these endpoints would need to appropriately characterize uncertainties. We further support characterization of coarse particle effects in the Scope and Methods Plan for the Risk Assessment.11

The Clean Air Act explicitly recognizes the uncertainty in scientific research in its requirements to periodically review the air pollution criteria and to err on the side of protection. This precautionary principle requires that EPA set air quality standards to protect against effects suggestive of causality.

### Chapter 2: Causal Findings

**EPA should discuss sub-daily findings**

The ISA should specifically discuss the evidence from new studies on the health impacts of sub-daily exposures. A number of studies have reported effects over shorter time periods than 24-hour averages, for instance, over periods of one or several hours, ranging down to periods of 10 minutes. Effects over shorter time periods may not be protected against by a 24-hour standard,

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9 Limited data are not an excuse for failing to establish the level at which there is an absence of adverse effect. To the contrary, as the D.C. Circuit has explained, “Congress’ directive to the Administrator to allow an ‘adequate margin of safety’ alone plainly refutes any suggestion that the Administrator is only authorized to set primary air quality standards which are designed to protect against health effects that are known to be clearly harmful.” Lead Indus. Ass’n, 647 F.2d at 1154-55.

10 Lead Industries Assn. v. EPA, 647 F.2d 1130, 1154 (D.C. Cir. 1980).

which averages out these peak exposures. EPA should critically examine these sub-daily studies because they are critical to the selection of the appropriate averaging times for the standards.

**EPA should find that a causal relationship exists between short-term PM$_{2.5}$ exposures and respiratory morbidity and mortality**

The Lung Association supports the draft ISA’s determination that there is a causal relationship with short exposures to PM$_{2.5}$ on cardiovascular morbidity. However, we urge reconsideration of the conclusion on respiratory morbidity and mortality. The Lung Association sees strong substantiation that short-term PM$_{2.5}$ exposure should be considered causally related to respiratory morbidity and mortality. Applying the research for both these health endpoints to the weight of evidence requirements from Table 1-3, we find that they appear to meet the test for a casual relationship as cardiovascular morbidity does.

**Respiratory morbidity**

The ISA cites the recent evidence of respiratory morbidity, noting that the epidemiological research demonstrates a consistent increase in effect on asthmatic children, and on older adults with respiratory diseases. Human clinical studies found increased markers of pulmonary inflammation, oxidative responses and exacerbation of allergic responses and sensitization in response to varying sources of PM$_{2.5}$. Toxicological studies also demonstrated respiratory effects. The discussion concludes that these findings represent “consistent and coherent results” with no evidence provided of any important uncertainties. Given those conclusions, the short-term exposures should be reclassified as having a causal relationship with respiratory morbidity.

**Mortality**

The ISA recognizes that the epidemiological studies show a consistent pattern of positive associations between PM$_{2.5}$ and mortality from all non-accidental, respiratory and cardiovascular causes. Only one study observed potential confounding by NO$_2$. Factors such as demographic and socioeconomic status were identified in studies as likely reasons for modified effects, but these are well-recognized as frequent modifiers of environmental effects. Although not discussed in this section, research has provided evidence of plausible biological mechanisms as well. Given the evidence from these studies, there appear to be no “important uncertainties” that remain. Therefore, we recommend that the short-term exposures be reclassified as having a causal relationship with mortality.

**Cardiovascular morbidity**

In addition to the studies evaluated in the draft ISA, a recently published study provides additional evidence in support of EPA’s determination that short-term PM$_{2.5}$ exposure is causally related to cardiovascular morbidity. This study points to adverse effects at levels below the 24-hour PM$_{2.5}$ standard. In a study of daily ischemic strokes and transient ischemic attacks

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(TIAs) in Corpus Christi, Texas, researchers observed associations with same day and previous
day PM$_{2.5}$ exposures. The 99$^{th}$ percentile 24 hour PM$_{2.5}$ concentration was 28 µg/m$^3$.$^{13}$

Moreover, especially in light of the recent court decision, it is critical that EPA consider the
studies of short-term exposures discussed in Chapter 6 in setting both short- and long-term
standards for PM$_{2.5}$.

**EPA should find that a causal relationship exists between long-term exposure to PM$_{2.5}$ and respiratory morbidity, cardiovascular morbidity and mortality**

EPA concludes that the evidence of long-term exposure to PM$_{2.5}$ on cardiovascular and
respiratory morbidity and mortality is likely causal. The Lung Association urges reclassification
of those conclusions to a causal relationship.

The strength of the evidence on the long-term effects of PM$_{2.5}$, especially regarding mortality,
has grown significantly since the last review. There are several new studies reporting effects at
lower concentrations than previously available. The rationale used for classifying these
outcomes as “likely to be causal” and not as causal seems to come from the absence of one of the
study types (epidemiological, toxicological or clinical), usually the clinical studies. However,
the description of the weight of evidence in Table 1-3 does not require evidence from all three.
The description recognizes instead that the absence of important uncertainty is the more critical
question. In each case, no important uncertainties are identified.

**Cardiovascular studies**

As discussed in the ISA, of particular significance is the Women’s Health Initiative study,
because it is one of the first to rely on direct measurements of fine particle concentrations. This
study reported increased risk of fatal and nonfatal cardiovascular events in women with
exposures to annual average PM$_{2.5}$ concentrations below the current standard.

Using data from the Women’s Health Initiative (WHI), an observational study of cardiovascular
disease in 66,000 women in 36 U.S. cities, researchers demonstrated that female residents of
cities and neighborhoods with higher levels of fine particulate matter experience higher rates of
death and infirmity from heart disease and strokes than residents of cleaner cities. In this study,
annual average PM$_{2.5}$ concentrations varied from 3.4 to 28.3 µg/m$^3$, with a mean concentration of
13.4 µg/m$^3$. Increased exposure to PM$_{2.5}$ was associated with increased risk of stroke, heart
problems, and death from heart disease. Adjustment for other pollutants did not alter the
findings for PM$_{2.5}$.

The figure below illustrates how the risk of death rose as the concentrations of the pollutant
increased, relative to a reference value of 11 µg/m$^3$. The current annual average standard for
PM$_{2.5}$ is 15 µg/m$^3$. This figure should be included in the ISA.

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$^{13}$ Lisabeth LD, Escobar JD, Dvonch JT, et al. Ambient Air Pollution and Risk for Ischemic Stroke and Transient
Researchers concluded that: “Our study provides evidence of the association between long-term exposure to air pollution and the incidence of cardiovascular disease. Our study confirms previous reports and indicates that the magnitude of health effects may be larger than previously recognized. These results suggest that efforts to limit long-term exposure to fine particulate pollution are warranted.”

Writing in an accompanying editorial, Dr. Douglas W. Dockery of the Harvard School of Public Health and Dr. Peter H. Stone of the Harvard Medical School note that this study established a stronger statistical association between fine particulate air pollution and death from coronary heart disease than found in earlier studies. The WHI study reported a 76 percent increased risk of death from cardiovascular disease for every increase of 10 µg/m³ in the mean PM$_{2.5}$ concentration, as compared to a 12 percent increase reported in the American Cancer Society cohort study. Referring to EPA’s last review of the NAAQS for particulate matter, they note: “Unfortunately for public health, the EPA failed to follow the recommendation of its science advisors and reduce the long-term standard for fine particles. The findings of the WHI study strongly support the recommendation for tighter standards for long-term fine particulate air pollution.”

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In addition, there are a number of studies extending the findings of the landmark cohort studies, the Harvard Six Cities Study and the American Cancer Society Cohort Study. As fine particle concentrations have come down with the implementation of pollution control programs, the extended analyses continue to report associations between contemporary concentrations of PM$_{2.5}$ and mortality. Thus, these studies provide important new evidence of the need to lower the annual average standard for fine particles. They are discussed in the ISA and briefly summarized here.

A study using Medicare data confirmed to assess the association between fine particulate air pollution (PM$_{2.5}$) on morality for the same geographic locations included in two landmark cohort studies and recent extensions of them: the Harvard Six Cities Study (SCS) (Dockery, et al 1993; Laden et al, 2006) and the American Cancer Society Study (ACS) (Pope et al. 1995, 2002). The analysis considered individual data on only age and sex, and was not adjusted for other individual risk factors. Mortality data and PM$_{2.5}$ data were collected for the period 2000-2002.

Risk estimates were comparable to the original studies.$^{16}$

### TABLE 2. Study Characteristics: Med-ACS, ACS, Med-SCS, and SCS

<table>
<thead>
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<th>Characteristics</th>
<th>Med-ACS</th>
<th>ACS</th>
<th>Med-SCS</th>
<th>SCS</th>
</tr>
</thead>
<tbody>
<tr>
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<td>110$^*$</td>
<td>50$^1$</td>
<td>6$^2$</td>
<td>6</td>
</tr>
<tr>
<td>No. subjects$^3$</td>
<td>7,333,040</td>
<td>295,223</td>
<td>341,099</td>
<td>8096</td>
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<tr>
<td>No. deaths$^4$</td>
<td>1,122,311</td>
<td>62,000</td>
<td>54,160</td>
<td>2732</td>
</tr>
<tr>
<td>PM$_{2.5}$ (μg/m$^3$); mean (SD)</td>
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<td>17.7 (3.7)</td>
<td>14.1 (3.1)</td>
<td>16.4$</td>
</tr>
<tr>
<td>Range</td>
<td>6.0–25.1</td>
<td>9–33.5</td>
<td>9.6–19.1</td>
<td>10.2–29.0$</td>
</tr>
</tbody>
</table>

$^*$ Counties identified by the Reanalysis team as being within the 50 metropolitan statistical areas included in the ACS.$^2$

$^1$ The 6 cities that include the 6 counties in the SCS.

$^2$ The number of subjects for the Med-ACS and Med-SCS datasets is the number of persons at risk in year 2000. For ACS and SCS, it is the number of persons enrolled at the beginning of the study period.

$^3$ Total deaths occurred during the entire study period. For ACS,$^5$ the number of deaths is approximately triple the number of deaths in the original ACS.$^2$

$^4$ Calculated based on Table 1 and Figure 1 from Laden et al.$^5$

SD indicates standard deviation.

Schwartz et al conducted an extended follow-up of the Harvard Six Cities Study explored the effect of dose and timing of dose on the association between PM$_{2.5}$ and survival. Their study found that the association between exposure to fine particles and increased risk of death continued well below 15 μg/m$^3$. The researchers reported finding little evidence for a threshold. While earlier time-series studies had found a similar association of daily particle levels with increased mortality, this was the first detailed examination of the question in a cohort study examining annual exposures. Additionally, the study reported that the deaths associated with

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exposure to fine particles occurred primarily within two years of exposure. This implies that reductions in air pollution can be expected to produce rapid improvements in public health.\(^{17}\)

An important 2003 study that was excluded from the last review specifically addresses one of the issues regarding interpretation of the long-term studies. Further analysis of the American Cancer Society data set demonstrates that the dose response relationship between long-term PM exposure and premature death continues below levels of 15 µg/m\(^3\) and is in fact strongest in that range. Abrahamowicz et al used a flexible regression spline model to more accurately examine the nature of the dose response relationship at different levels of exposure, and concluded that most of the increase in mortality risk from PM\(_{2.5}\) exposure occurs between the low end of the range (around 9.5 µg/m\(^3\) in this study) and 16 µg/m\(^3\).\(^{18}\)

Laden et al conducted further investigations into the extension of the Harvard Six Cities Study and provided evidence of increased risk of cardiopulmonary mortality at annual exposure levels well below the current standard of 15 µg/m\(^3\). Average PM\(_{2.5}\) concentrations during the 1990-1998 follow-up period ranged from 10.2 µg/m\(^3\) in Portage, WI to 22 µg/m\(^3\) in Steubenville, OH. Long-term average concentrations were at or below 13.4 µg/m\(^3\) in four of the six cities, lower in all cities than those that had existed during the original study period. Yet the linear dose-response association between PM\(_{2.5}\) concentrations and total mortality persisted even at the lower concentrations. Mean concentrations across the six cities in the second period of the study, from 1990 to 1998, were 14.8 µg/m\(^3\), with a standard deviation ± 4.2, suggesting a range of 10.6 to 19.0 where most effects occurred. The study reported that an average of three percent fewer people died for every one µg/m\(^3\) reduction in the annual average levels of PM\(_{2.5}\).\(^{19}\)

Evidence of short- and long-term health effects of PM\(_{10}\) demands re-evaluation of causality determinations

The American Lung Association strongly recommends that the EPA reconsider the conclusions of the health effects of PM\(_{10}\). Strong evidence shows that there is likely evidence of a causal relationship between PM\(_{10}\) and respiratory morbidity, cardiac morbidity and mortality. Indeed most of the early studies evaluated in the 1997 review were done using PM\(_{10}\) as the exposure metric, as the PM\(_{2.5}\) monitoring network was not yet deployed. The simple logic of the issue strikes us as hard to avoid: If PM\(_{2.5}\) causes or is likely to cause respiratory morbidity, cardiac morbidity and mortality, then how can PM\(_{10}\), which includes PM\(_{2.5}\) as well as other particle sizes, fail to create as much harm? Absent any evidence that the combination or of the PM\(_{10-2.5}\) fraction is so beneficial that it erases the harm from the fine particulates, we can see no reason that the EPA would not find PM\(_{10}\) to have similar effects to PM\(_{2.5}\).


Our comments focus on long-term PM\textsubscript{10} effects because we believe the evidence supports the need for reinstatement and strengthening of the annual average standard.

**Long-Term PM\textsubscript{10} Mortality**
The document concludes the effects of long-term exposure to PM\textsubscript{10} on mortality are merely suggestive. EPA should re-evaluate this conclusion and consider classification of PM\textsubscript{10} effects on mortality as likely causal, in light of the evidence. A number of new studies are available since the last review that report persuasive evidence of adverse effects of long-term exposures to PM\textsubscript{10}.

Many of these studies are reviewed in the draft ISA but we highlight them here because of the importance of reinstating and strengthening the annual average standard for PM\textsubscript{10}.

**Nurses’ Health Study**
The Nurses’ Health Study is an ongoing prospective cohort initiated in 1976, which follows 120,000 female registered nurses with biennial questionnaires on behavioral and lifestyle exposures and health outcomes. A new analysis of a subset of 66,000 of the nurses currently residing in 13 Northeastern metropolitan areas examined the association of chronic particulate exposures with death from all causes, heart attacks, and fatal coronary heart disease.

The study used a geographic information system to estimate particulate matter concentrations at every residential address for each nurse based on monitoring data and factors that affect air pollution such as population density, distance to roadways, elevation, urban land use, point-source emissions, precipitation, and wind speed. Information on lifestyle and behavioral risk factors were considered in the analysis.

Mean PM\textsubscript{10} values (12-month moving average) were 21.6 µg/m\textsuperscript{3}, with a standard deviation of 4.3. Increases in 12-month average exposures to PM\textsubscript{10} were associated with both all-cause mortality and fatal coronary heart disease. Overweight women who have never smoked were found to be at greatest risk of fatal coronary heart disease associated with PM\textsubscript{10}.

The study concluded: “Our findings add to a growing coherence of the literature across multiple time scales indicating that the public health benefits of reducing particle concentrations will be realized within years, not decades of the reduction. This study also suggests that measures taken to limit particulate air pollution should benefit population health over extended periods of time.”\textsuperscript{20}

**Medicare study**
Long-term exposure to particulate matter elevates the risk of mortality in people with chronic obstructive pulmonary disease (COPD) according to a new study of Medicare patients in 34 U.S. cities.

Zanobetti et al used hospital data to construct a cohort of people aged 65 and older that were discharged from a hospital with COPD, between 1985 and 1999. The study focused on residents of 34 cities with daily monitoring of PM$_{10}$, and examined temporal changes in pollution concentrations within the cities. The study found a relatively large effect of PM$_{10}$, compared to general population cohorts in early studies. The study also found that the effect was evident for exposure in the previous year, and higher when looking at effects over the previous 4 years. According to the study authors, the study “indicates that reductions in air pollution should be followed quickly by improvements in public health.”

**German cohort study**

This German study finds that chronic exposure to PM$_{10}$ pollution increases deaths from cardiopulmonary causes in a cohort of women.

Ghering et al followed 4,800 women living in industrial and nonindustrial areas of the Ruhr area of Germany who had been included in earlier studies to determine their cause of death relative to long term exposures to air pollution. Living within a 50-meter radius of a major road was associated with an increased risk of death from cardiopulmonary causes. Exposure to elevated levels of nitrogen dioxide and PM$_{10}$ (estimated from total suspended particulates) increased the risk of total morality and mortality due to cardiopulmonary causes. This study provides additional evidence that long-term exposure to air pollution increases the risk of early death, a finding previously reported in U.S. cohort studies.

**Long-Term PM$_{10}$ Effects on Respiratory Morbidity**

The draft ISA concludes that long-term exposures to PM$_{10}$ are “likely to be causal” for respiratory morbidity. We concur with EPA’s assessment that the evidence is sufficient to conclude that the relationship between long-term PM$_{10}$ exposure and respiratory morbidity is likely to be causal. Several new studies supporting this conclusion are briefly reviewed below. These studies are highlighted because they indicate morbidity effects at levels below the current standards.

**Swiss Lung Function study**

In 2007, Downs et al documented evidence that a decline in PM$_{10}$ over time could attenuate the decline in lung function with aging.

This prospective study of 9,600 Swiss adults 18 to 60 years old included measurements of several measures of lung function at baseline and 11 years later. PM$_{10}$ concentrations declined over this same period. Downs et al reported: “Our data show that improvement in air quality may slow the annual rate of decline in lung function in adulthood. The finding suggests that important changes in the rate of decline in pulmonary function occur across the range of exposures seen in Switzerland, where particle concentrations are relatively low.”

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The strongest beneficial effects of a reduction in PM$_{10}$ were in the small airways. In its 2006 revisions to the National Air Quality Standards, EPA revoked the annual average PM$_{10}$ standard of 50 µg/m$^3$. The study authors suggest that: “further reductions in these standards are likely to improve pulmonary health.” “Our findings provide further support for a causal role of exposure to air pollution in respiratory health,” conclude the researchers. “Relatively small reductions in exposure to PM$_{10}$ have measurable benefits for lung function, suggesting that a decline in air pollution, even from low levels, may have positive consequences for public health.”

In an accompanying editorial, New York University School of Medicine Professor Morton Lippmann, noted that the rate of lung function decline with age is a well-established predictor of longevity. He argued that this study is significant because the decline in lung function was linear even at quite low concentrations, and suggests that the current U.S. EPA and World Health Organization annual average standards are not protective against such losses in lung function.

**German COPD study**

Schikowski et al studied a cohort of 4,800 55-year-old women in the Rhine-Ruhr Basin of Germany to focus on the impact of long-term exposures of nitrogen dioxide, PM$_{10}$, and traffic on lung function and exacerbation COPD. The prevalence of COPD and lung function declines were affected most strongly by long-term exposure to PM$_{10}$ and traffic related exposure. A 7 µg/m$^3$ change in five-year means of PM$_{10}$ was associated with a 33 percent increase in the prevalence of COPD, as defined by lung function. “The results of this study suggest that long-term exposure to air pollution from PM$_{10}$, NO$_2$, and living near a major road might increase the risk of developing COPD and can have a detrimental effect on lung function,” conclude study authors.

This German study is significant annual mean concentrations of PM$_{10}$ in this study were 44 µg/m$^3$, well below the level of the annual average standard revoked in 2006.

**Cystic Fibrosis Study**

Goss et al followed a cohort of more than 11,000 patients older than 6 years of age enrolled in the Cystic Fibrosis Foundation National Patient Registry for which medical information was available. Cystic fibrosis is a lifelong, hereditary disease that is the second most common inherited disorder occurring in childhood in the United States, behind sickle cell anemia. As the disease progresses, it is characterized by chronic and recurrent lung infections, inflammation, and a loss of lung function over time. Cystic fibrosis results in shortened life expectancy.

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Exposures were assessed based on air quality monitors correlated with the patients’ home zip codes. After controlling for confounders, annual average exposure to PM$_{10}$, PM$_{2.5}$ and ozone was associated with an increased risk of pulmonary exacerbations. The association was most pronounced for patients who experienced two or more exacerbations per year. PM$_{2.5}$ was also associated with a significant loss in lung function. Researchers speculate that the decline in lung function may be due to chronic exposure to air pollutants, which may be part of the causal pathway in the worsening prognosis of cystic fibrosis.

Researchers concluded: “Exposure to ambient PM$_{10}$, PM$_{2.5}$ and ozone may increase the risk for pulmonary exacerbations and increase the rate of change in lung function in the CF [cystic fibrosis] population. Ambient air pollution may also impact survival.”\textsuperscript{26}

**Long-Term PM$_{10}$ Effects on Cardiovascular Morbidity**

The draft ISA characterizes cardiovascular morbidity from long-term exposure to PM$_{10}$ as merely “suggestive”. Several new studies of cardiovascular effects point to a “likely to be causal” determination. However, we restate our argument that to provide a “margin of safety” requisite with the need to protect public health, we should include protections against effects that are strongly suggested by the evidence.

**Measures of Atherosclerosis**

Diez Roux et al examined the effect of 20-year exposures to PM$_{10}$ and PM$_{2.5}$ on atherosclerosis in a cohort of 6,800 residents of Baltimore, Chicago, Forsyth County, North Carolina, Los Angeles, New York and St. Paul. These individuals ranged in age from 44 to 84 and were free of heart disease at enrollment.

Diez Roux et al found some evidence of associations between particulate matter exposure and “carotid intimal-medial thickness,” an ultrasound measurement of the carotid artery commonly used to assess risk for atherosclerosis. No associations were reported for two other measures of subclinical atherosclerosis. There was no evidence that associations were stronger in subgroups such as women, older people, or diabetics. “Results are compatible with some effect of particulate matter exposures on development of carotid atherosclerosis,” concluded the researchers.\textsuperscript{27}

**Inflammatory Responses**

Annual average exposures to PM$_{10}$ have been linked to white blood cell count, a marker of inflammation, in a long term cross-sectional study of healthy adults using the NHANES III cohort. The association was observed after adjusting for demographics, socioeconomic factors, lifestyles, and residential characteristics. The study is of interest because of the potential role of inflammation in the development and progression of atherosclerosis and coronary heart disease. One-year average PM$_{10}$ exposures in the study were 36.8 µg/m$^3$. “This study provides the first epidemiological data linking inflammatory biomarkers to long-term PM exposure and supports


the hypothesized involvement of inflammation in the PM-mediated chronic cardiovascular effects,” conclude the researchers.

The study observed differential inflammatory responses across individuals with different degrees of metabolic abnormalities, supporting the hypothesis that metabolic syndrome may impart greater susceptibility to PM cardiovascular effects. 28

Blood Clots in the Legs
A novel study found an association between PM10 pollution and enhanced risk of deep vein thrombosis, blood clots in the thighs or legs. Bacarelli et al assessed exposure to PM10 among 80 patients who had been diagnosed with deep vein thrombosis in Lombardy, Italy between 1995 and 2005. These patients, along with 1,210 control subjects who did not have deep vein thrombosis, were assigned to one of nine geographic regions based on their residence. Researchers used average concentration of particulate matter from 53 monitors to estimate the level of exposure over the year before the diagnosis.

Those with the blood clot condition had a higher exposure to PM than the controls. After adjusting for other environmental and health factors, an increase of 10 µg/m³ increased the risk of blood clots in the legs by 70 percent. In addition, a clinical test of those exposed to higher levels of particulate matter found that their blood took less time to clot.

“Given the magnitude of the observed effects and the widespread diffusion of particulate pollutants, our findings introduce a novel and common risk factor into the pathogenesis of DVT [Deep Vein Thrombosis] and, at the same time, give further substance to the call for tighter standards and continued efforts aimed at reducing the impact of urban air pollutants on human health.” 29

Taken together with the full range of evidence reviewed in the ISA, these studies suggest that PM10 cardiovascular effects are “likely causal.”

EPA should re-examine causal findings on coarse particles in light of additional studies

We identified a number of studies of coarse particles that apparently have not been included in the ISA. In addition, we report on a number of abstracts presented at scientific meetings on coarse particle studies. These studies may have bearing on the causal findings with respect to morbidity and mortality for PM10-2.5. Given the relatively small number of studies of coarse particles, EPA must be diligent in tracking down all relevant research and research in progress to provide for a complete evaluation of the evidence.

In addition to the occupational health studies discussed above, EPA should examine the following additional studies.

• A national, multi-city time series study of the acute effect of PM$_{2.5}$ and PM coarse on the increased risk of death for all causes, cardiovascular disease, myocardial infarction, stroke, and respiratory mortality for the years 1999-2005 was recently accepted for publication in *Environmental Health Perspectives*. The study reported a strong association of both fine and coarse particles with daily deaths. In a analysis of 47 cities, researchers reported significant associations between PM coarse with total mortality, stroke, cardiovascular disease, and respiratory mortality, which had the largest effects: a 1.2 percent increase for 10 µg/m$^3$ increase in PM coarse.$^{30}$

Two additional studies may be relevant:


Several international studies excluded from the ISA highlight the health risks of coarse particles.

• New evidence of the adverse effects of coarse particles on respiratory health among the elderly comes from a 2009 study in Helsinki, Finland.$^{31}$

• A 2007 Taiwanese study apparently not included in the ISA reported stronger effects of coarse particles (compared to other size particles) on reduction of heart rate variability in the elderly.$^{32}$

• A 2008 study conducted in Zonguldak, Turkey examined associations between various size fractions of PM and respiratory hospital admissions among children less than 15 years old. A bidrectional case-crossover design was used to calculate odds ratios for admissions adjusted for daily meteorological parameters. The highest association noted was an 18 percent rise in asthma admissions with a 10 µg/m$^3$ increase in PM$_{10-2.5}$ on the same day of admissions.$^{33}$

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$^{32}$ Chang LT, Tang CS, Pan YZ, Chan CC. Association of heart rate variability of the elderly with personal exposure to PM$_1$, PM 1-2.5, and PM 2.5-10. *Bull Environ Contam Toxicol* 2007; 79: 552-556.

$^{33}$ Tecer LH, Alagha O, Karaca F, Tuncel G, Eldes N. Particulate Matter (PM$_{2.5}$, PM$_{10-2.5}$, and PM$_{10}$) and Children’s Hospital Admissions for Asthma and Respiratory Diseases: A Bidirectional Case-Crossover Study. *J of Tox and Environ Health* 2008; Part A 71: 512-520.
• A study in Sin-Chung City, Taiwan reported that coarse particles are likely to contribute to the exacerbation of asthmatic conditions in children.34

• A study in Taipei, Taiwan found an association between Asian dust storm events and daily admissions to the hospital for pneumonia, one day after the event.35

Several abstracts presented at the 2008 Joint Annual Conference of the International Society for Environmental Epidemiology & International Society of Exposure Analysis are relevant to the assessment of coarse particle health effects.


• Abstract #1365: Associations Between the Ratio of Fine and Coarse Particles of Ambient Air and Daily Mortality in Seoul, Korea. Kim Y, Huh J, Hong Y, Yi S, Kim H.

• Abstract #1570: Chronic Fine and Coarse Particulate Exposure, Mortality and Coronary Heart Disease in the Nurses’ Health Study.

Additionally, some abstracts presented at the American Thoracic Society’s 2007 and 2008 Annual Conference report preliminary findings on coarse particles:

• 2008: Page A505: Transcriptional Indicators of Oxidative Stress within Coarse, Fine and Ultrafine PM in Human Airway Epithelial Cells. Karoly ED, Dailey LA, Schmitt MT, Graff DW, Devlin RB.

• 2007: Poster Board #120: Association between Coarse Particles and Asthma Emergency Department (ED) Visits in New York City. Ito, K, Thurston GD, Silverman RA.

• 2007: Poster Board #H1. Coarse Particles and Mortality, Barcelona (Spain). Perez L, Tobias A, Kunzli N, Querol X, Sunyer J.


EPA should ascertain if studies have progressed and have been accepted for publication.

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Chapter 6 and 7 Summary Tables

We commend the authors for the inclusion of summary tables and figures providing key information for critical studies. Chapters 6 and 7 and the Annex contain numerous tables characterizing the ambient PM concentrations in various groups of studies, for instance hospital admission studies, or respiratory symptoms studies for either short-term or long-term exposure. Information on ambient concentrations in studies is crucial to the evaluation of the studies for standard-setting purposes. However, we note that the information on ambient concentrations provided in these tables is not necessarily consistent from table-to-table, nor do all the tables provide the type of complete information on ambient concentrations that is needed to evaluate the studies with respect to standard-setting.

We draw from examples of several Tables to illustrate our point:

- Table 6-1 summarizing epidemiologic/panel studies of PM and changes in heart rate variability, for example, provides information on the mean ambient concentration for various species of interest and the Standard Deviation (SD), when available. Information on the standard deviation around the mean is very useful in the evaluation of exposures, because the adverse health effects occur not only at the mean concentration, but also above and below the mean. As EPA pointed out in the last review, looking at mean concentrations plus or minus on standard deviation “may reasonably be used to characterize the range over which the evidence of association is strongest.”\(^{36}\) About 70 percent of the data are within the mean plus and minus one SD, and the regression results are driven by the bulk of the data. Therefore, it follows that the results demonstrating adverse health effects are driven by this range. The results are not just driven by concentrations at the mean and above. Effects are also triggered by concentrations below the mean.

- Table 6-2 on studies of ventricular arrhythmia in patients with implantable cardioverter defibrillators, for instance, provides information on daily median or mean ambient concentration, but not on SD.

- Table 6-6, on hospital admissions and ED visits for cardiovascular disease includes mean concentrations where available, and upper percentile concentrations. We assert that the range of exposures should be reported, the minimum as well as the maximum concentrations. As stated above, adverse effects do not just occur at the mean, or at the upper concentrations, but also at concentrations below the mean.

- Tables 6-7, 6-11, 6-13 include similar information to Table 6-6, that is only the mean and upper percentile concentrations are reported.

- The same is true for Tables 7-1, 7-2, 7-3, 7-4, 7-5, 7-6, and 7-8 in Chapter 7 on long-term exposures.

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\(^{36}\) Staff Paper pp. 5-22.
We commend EPA for including more complete information on pollutant concentrations including min and max, or 25th, 50th, and 75th percentiles in the more complete study summaries in the Annex. With pollutants such as PM for which there are no apparent thresholds, it is important to know the full range of concentrations in the studies. We strongly urge EPA to bring the information on SD around the mean, minimum and maximum concentrations and low percentile concentrations forward to the tables in the main document that summarize the most relevant studies, as this is the information that will carry forward into the policy assessment.

Chapter 8: Public Health Impacts

More complete discussion of public health impacts needed

Chapter 8, entitled Public Health Impacts is a disappointment because it does not actually discuss studies assessing the public health impacts of PM. Instead, it restricts itself to a discussion of the shape of the concentration-response function and potential populations at risk.

The dose-response discussion should reference the expert elicitation exercise undertaken by EPA. The views of 12 of the world’s leading experts on air pollution health effects exhibited substantial agreement regarding the nature and cause of mortality associated with PM$_{2.5}$, the likelihood of a causal connection between exposure and premature death, the shape of the concentration-response function, and the central estimate of the mortality impact. There were differences in the experts’ opinions of the relative importance and size of potential sources of uncertainty.

This chapter must be bolstered by a discussion of risk and benefit analysis studies such as the peer-reviewed California Air Resources Board PM benefits analysis published in October 2008. This analysis reported that PM$_{2.5}$ air pollution is associated with about 18,000 premature deaths annually in California. Taking into account the uncertainty interval, estimates could range from 5,600 to 32,000 deaths, based on 2004-2006 air quality data.

In addition, this chapter should include discussion of several recent intervention studies that demonstrate the positive impact on public health of reductions in particulate air pollution.

- In a stunning new study published in the New England Journal of Medicine, Pope et al find that average life expectancy in U.S. cities has increased nearly three years over recent decades, and approximately five months of that increase, or 15 percent, came because of reduced fine particle air pollution. The study by researchers at Brigham Young University and the Harvard School of Public Health examined changes in air pollution in 51 cities across the nation between 1980 and 2000 and residents’ life

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expectancies during that period. The scientists applied advanced statistical techniques to account for other factors that could affect average life spans, such as smoking, income, and education. For every decrease of 10 micrograms per cubic meter of particulate pollution in a city, the residents’ average life expectancy increased by more than seven months. The study found improvements in life expectancy even in cities that initially had relatively cleaner air, suggesting that further improvements in air quality will yield important public health benefits. “There is an important positive message here that the efforts to reduce particulate air pollution concentrations in the United States over the past 20 years have led to substantial and measurable improvements in life expectancy,” said study co-author Douglas Dockery, of the Harvard School of Public Health.

In an editorial commenting on the study, Dr. Daniel Krewski of the University of Ottawa wrote: “The strength of the study by Pope et al. resides in its ability to demonstrate an increase in life expectancy resulting from actual reductions in particulate air pollution. This finding provides direct confirmation of the population health benefits of mitigating air pollution and greatly strengthens the foundation of the argument for air quality management.”

- A Swiss study reported that reductions in particle levels over an 11 year period resulted in a measurable and significant reduction in people with regular cough, chronic cough or phlegm, and wheezing with breathlessness.

- A recent study reported that after a week away from urban air pollution, children with mild persistent asthma begin to show dramatic changes in their respiratory health. The study found that just seven days after a group of school-age children left the city for a rural area, airway inflammation went down and lung function increased.

In conclusion, the American Lung Association welcomes the improvements in the format, coverage of issues, criteria, and consistent framework for decision-making contained in this Integrated Science Assessment. The Lung Association urges EPA to incorporate a full review of the available research, as well as a reassessment of the causality findings, in the next draft.

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40 Brigham Young University News Release. “BYU-Harvard SPH study shows that Americans owe five months of their lives to cleaner air”. Undated, downloaded at http://byunews.byu.edu/archive09-jan-pope.aspx