Appendix A

BRIEFING BOOK CONTENTS

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1. Excerpts from U.S. EPA's *Fourth External Review Draft of Air Quality Criteria for Particulate Matter (June, 2003)*: Volumes I and II **(FULL DOCUMENT AVAILABLE ON ENCLOSED CD)**

    a) Table of Contents
    b) Executive Summary
    c) Selected Tables from Main Document (Table 7-1a, 7-1b, 7-2a, 7-2b, 7-3, 7-4, 7-5a, 7-5b, 7-6, 7-7a, 7-7b, 7-9, 7-10, 7-12, 8-1, 8-2, 8-3, 8-4, 8-11, and 9-8)
    d) Appendix 8A - Short-term PM Exposure-Mortality Studies: Summary Table
    e) Appendix 9A - Key Quantitative Estimates of Relative Risk for Particulate Matter-Related Health Effects Based on Epidemiologic Studies of U.S. and Canadian Cities Assessed in the 1996 Particulate Matter Air Quality Criteria Document

2. Table: Examples of Effect Estimates for Total Mortality per 10 $\mu g/m^3$ and 1 $\mu g/m^3$ Changes in $PM_{2.5}$

3. Table of Contents for U.S. EPA's *Review of the National Ambient Air Quality Standards for Particulate Matter, OAQPS Staff Paper – First Draft* **(FULL DOCUMENT AVAILABLE ON ENCLOSED CD)**

4. *Health Aspects of Air Pollution with Particulate Matter, Ozone, and Nitrogen Dioxide*, Report of WHO Working Group, January 2003.

5. *Statement on Long-Term Effects of Particulates on Mortality* by the Committee of the Medical Effects of Air Pollutants (COMEAP), March 2001.

6. Kunzli, N; Medina S; Kaiser R; Quenel P; Horak F; Studnicka M. (2001). "Assessment of Deaths Attributable to Air Pollution: Should We Use Risk Estimates Based on Time Series or on Cohort Studies?" *American Journal of Epidemiology*. 153(11): 1050:1055.

7. Recently Published Articles Discussing PM Exposure and Mortality Not Included in June 2003 Draft of EPA's PM Criteria Document

    a) Brauer M; Brumm J; Vedal S; Petkau AJ. "Exposure misclassification and threshold concentrations in time analyses of air pollution health effects." *Risk Analysis*. December 2002, V22, N6: 1183-1193.
    b) De Leon S.F.; Thurston G.D.; Ito K. (2003). "Contribution of respiratory disease to nonrespiratory mortality associations with air pollution." *American Journal of Respiratory and Critical Care Medicine*. 167/8: 1117-1123.
    c) Devlin R B(a); Ghio A J; Kehrl H; Sanders G; Cascio W. (2003). "Elderly humans exposed to concentrated air pollution particles have decreased heart rate variability." *European Respiratory Journal*. May, 21 (Supplement 40): 76-80.
    d) Dominici Francesca; McDermott Aidan; Zeger Scott L; Samet Jonathan M. (2003). "Airborne particulate matter and mortality: timescale effects in four US cities." *American Journal of Epidemiology*. June 15, 157(12): 1055-65.

e) Dominici Francesca; McDermott Aidan; Zeger Scott L; Samet Jonathan M. (2003). "National maps of the effects of particulate matter on mortality: exploring geographical variation." *Environmental Health Perspectives*. January, 111 (1): 39-44.

f) Ibald-Mulli Angela; Wichmann H-Erich; Kreyling Wolfgang; Peters Annette. (2002). "Epidemiological evidence on health effects of ultrafine particles." *Journal of Aerosol Medicine*. Summer, 15 (2): 189-201.

g) Moolgavkar Suresh, H Fred Hutchinson. (2003). "Air pollution and daily mortality in two U.S. counties: season-specific analyses and exposure-response relationships." *Inhalation toxicology*. August, 15(9): 877-907.

h) Ramsay Timothy O; Burnett Richard T; Krewski Daniel. (2003). "The effect of concurvity in generalized additive models linking mortality to ambient particulate matter." *Epidemiology*. January, 14(1): 18-23.

i) Schlesinger R.B.; Cassee F. (2003). "Atmospheric secondary inorganic particulate matter: The toxicological perspective as a basis for health effects risk assessment." *Inhalation Toxicology*. March 1, 15/3: 197-235.

j) Schwartz J.; Laden F.; Zanobetti A. (2002). "The concentration-response relation between PMSUB2.5 and daily deaths." *Environmental Health Perspectives*. October 1, 110/10: 1025-1029.

k) Stieb D.M.; Judek S.; Burnett R.T. (2002). "Meta-analysis of time-series studies of air pollution and mortality: Effects of gases and particles and the influence of cause of death, age, and season." *Journal of the Air and Waste Management Association.* 52/4: 470-484.

l) Utell M.J.; Frampton M.W.; Zareba W.; Devlin R.B.; Cascio W.E. (2002). "Cardiovascular effects associated with air pollution: Potential mechanisms and methods of testing." *Inhalation Toxicology*. December 1, 14/12: 1231-1247.

m) Vedal S; Brauer M; White R; Petkau J. (2003). "Air pollution and daily mortality in a city with low levels of pollution." *Environmental Health Perspectives*. January, V111, N1: 45-51.

n) Zanobetti Antonella; Schwartz Joel; Samoli Evi; Gryparis Alexandros; Touloumi Giota; Peacock Janet; Anderson Ross H; Le Tertre Alain; Bobros Janos; Celko Martin; Goren Ayana; Forsberg Bertil; Michelozzi Paola; Rabczenko Daniel; Hoyos Santiago Perez; Wichmann H Erich; Katsouyanni Klea. (2003). "The temporal pattern of respiratory and heart disease mortality in response to air pollution." *Environmental Health Perspectives*. July, 111 (9): 1188-93.

8. Excerpts from *Estimating the Public Health Benefits of Proposed Air Pollution Regulations*, National Research Council: 2002. Summary and Chapter 5: Uncertainty.

9. U.S. EPA. *Latest Findings on National Air Quality: 2001 Status and Trends*. September 2002. **(LOCATED IN REAR POCKET OF BINDER)**

Appendix B

Elicitation Protocol

Elicitation Protocol
$PM_{2.5}$

Expert (circle one): A B C D E

Elicitors _____

Overview of the Day

1. Introduction
   - Objectives of elicitation
   - Definitions: variability vs. uncertainty
   - Methodology
   - Practice elicitation: feedback
2. Elicitation Questions: Preview
3. Preliminary Questions: Factors to Consider
4. Elicitation of quantitative judgments
5. Follow-up questions

I. Introduction

Objectives of the Study

In response to recommendations made in the NAS report, "Estimating the Public Health Benefits of Proposed Air Pollution Regulations," EPA is attempting to improve its characterization of uncertainty in its health benefits analyses that are part of its Regulatory Impact Analyses (RIAs). The purpose of this project is to provide a more complete characterization, both qualitative and quantitative, of the overall uncertainties associated with the relationship between changes in ambient $PM_{2.5}$ and premature mortality. The results will assist EPA in preparing RIAs for particular EPA proposed regulations (e.g., non-road rule, PM transport rule) and other benefit-cost and cost-effectiveness analyses over the next 1 to 2 years. The results of the current project will <u>not</u> be considered in making decisions about ambient standards in the ongoing review of the PM primary NAAQS, but may be used in the RIA for the NAAQS review.

To clarify our objectives for this elicitation, it may be helpful to examine briefly the current EPA methodology for estimating the potential benefits (reduction in premature mortality) associated with the reduction in $PM_{2.5}$ ambient concentrations. To estimate these benefits, for purposes of preparing RIA's, EPA must estimate the change in mortality within the exposed

population associated with changes in community level ambient concentrations of $PM_{2.5}$ (i.e., a concentration-response (C-R) function). Currently, separate C-R functions are used to calculate benefits based on long and short-term exposures. Each of the C-R functions is based on the Agency's selection of specific published studies.

To reflect the uncertainty surrounding predicted mortality changes resulting from the sampling uncertainty in the studies providing the C-R functions used, EPA's benefits models produce a *distribution* of possible incidence changes for each adverse health effect, rather than a single point estimate. To do this, the models use both the point estimate of the pollutant coefficient (β) in the C-R function and the standard error of the estimate to produce a normal distribution with mean equal to the estimate, and standard deviation equal to the standard error of the estimate. In other words, the standard error of the estimate is the only quantitative representation of uncertainty in the C-R function that is currently expressed.

Questions have been raised about this approach to characterizing uncertainty in the benefits of $PM_{2.5}$ reduction. A particular concern is how to characterize the uncertainty in the C-R relationship that is not captured in the β and standard error.

The purpose of this elicitation is to obtain your quantitative characterization your uncertainty in the relationship between exposure to PM2.5 and premature mortality, in the form of a probability distribution of the C-R relationship. This distribution should, specifically in the coefficient β reflect not just sampling error but other key sources of bias and uncertainty that you believe are important.

We plan to elicit your judgments in two steps:

1. Through a series of initial and follow-up questions, we will document your qualitative views on the evidence available to make inferences about the nature and magnitude of potential relationships between long-term and short-term exposures to $PM_{2.5}$ and premature mortality in the U.S., the strengths and weaknesses of that evidence, and the major factors that may be responsible for or could modify the relationships observed.

   This information will help both in the development of your quantitative judgments and in the design of more comprehensive analyses to be completed later.

2. We will elicit directly from you probabilistic judgments about the percent decrease in total non-accidental, premature mortality for adults associated with a 1) a permanent 1 $\mu g/m^3$ reduction in ambient annual average $PM_{2.5}$ concentrations and 2) a 10 $\mu g/m^3$ reduction in a single day's 24-hour average $PM_{2.5}$ concentration. The detailed questions will be presented in a later section.

It is important to recognize that your probabilistic judgments should ultimately reflect your state of knowledge about each of these quantities; they should be a function both of what you know and what you believe you do not know as a result of underlying uncertainties in the available evidence.

Your judgments, when viewed with those of other experts in the field, are intended to represent the group's view of the "state of knowledge" about the elicited quantities.

Use of Expert Elicitations

Your probabilistic judgments about each of these values will be presented in two ways 1) individually by expert (anonymously) and 2) as part of a combined distribution created using equal weights applied to the judgments of each of the five experts participating in the pilot project. The combined values will be used to develop probabilistic estimates of the C-R coefficients for short- and long- term exposures to $PM_{2.5}$, for input to EPA's benefits models.

Confidentiality Agreement

All information you provide as part of this assessment will be preserved through notes and a detailed summary. We will send you a copy of the summary of our discussions with you and your quantitative assessments for review and comment prior to finalization in a report or publication.

Your name, a summary of our discussions, and your quantitative judgments will all be publicly available; however, neither the summary nor your quantitative judgments will be associated with your name.

Definitions: Variability vs. Uncertainty

An important distinction that we need you to bear in mind while giving your judgments is that between variability and uncertainty. Although these two types of variation may exhibit similar mathematical properties, the distinction is important both for the clarity in the analysis and because they have different implications for decision making (Cullen and Frey, 1999).

> **Variability** – Variability expresses heterogeneity in a population or parameter. Variability in exposure, for example, may arise from geographical, seasonal, inter-individual differences, in types of homes, time activity patterns, and the like. Similarly, there may be variability in C-R functions describing the relationship between $PM_{2.5}$ and mortality across areas in the U.S. This variability does not itself imply uncertainty about the C-R functions in any specific area (although it may exist) but only that C-R functions may differ from one place to another reflecting differences in population, $PM_{2.5}$, etc. A

frequency distribution describes the frequency with which each value occurs in the population.

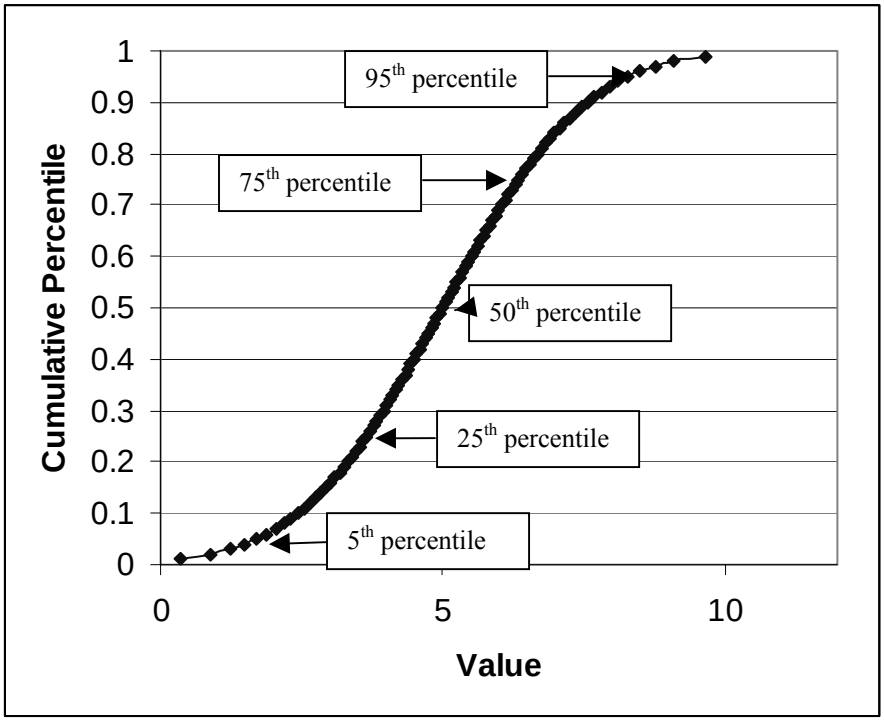
Uncertainty – Uncertainty refers to the lack of knowledge regarding the actual values of particular quantities such as model input variables (parameter uncertainty) and/or of physical systems or relationships – e.g. the shape of C-R functions (model uncertainty). Sources of uncertainty include various forms of measurement error, sampling error, extrapolation of one study population (or region or time period) to another, fundamental scientific disagreements, alternative model structures, etc. In principle, uncertainty can be reduced by improving the knowledge base (e.g. by increasing study sample size, developing more precise instruments or experimental designs) although in practice, it may not always be possible. We use the term probability distribution to describe variation due to uncertainty.

Introduction to the Elicitation Methodology

When we get to the quantitative elicitation, we will be asking you directly for your estimates in the form of a probability distribution using the following steps:

1. Provide clear definition of the quantity we are interested in.
2. Explore systematically how you think about the quantity, what factors you are considering and what data or other evidence you are utilizing in your response.
3. We will ask you to provide the 5, 25, 50, 75, and 95th percentiles of your uncertainty distribution. For example, assuming your uncertainty about a given quantity could be characterized by a normal distribution, the cumulative distribution would look something like the one depicted in Figure 1. We are asking you for particular quantiles of that distribution.

Figure 1



Illustrative Sample Question:

Please give us your probability distribution for the percent decrease in the annual mortality rate in the US population aged 65 and older from a 1 degree Celsius decline in the US mean summer temperature.					
Q#	5th %ile	25th %ile	50th %ile	75th %ile	95%
0					

If you answer in the following way:

Please give us your probability distribution for the percent decrease in the annual mortality rate in the US population aged 65 and older from a 1 degree Celsius decline in the US mean summer temperature.					
Q#	5th %ile	25th %ile	50th %ile	75th %ile	95%
0	**0%**	**1.5%**	**2.5%**	**3.5%**	**5.0%**

This probability distribution indicates that you think there is a 5% probability (1 in 20 chance) that the reduction in the true (but not perfectly known) mortality will be zero (i.e. there is no relationship between reduction of temperature and premature mortality); you think there is a 50% probability (fifty-fifty chance) that the true reduction is less than 2.5%; and you think there is a 95% probability (19 out of 20) that the true reduction is less than 5%.

Note: the percentiles are always increasing from left to right. The more uncertain you are about the percent reduction in premature mortality in this case, the larger will be the distance between your percentiles.

As part of this process, we will want to understand and record your rationale for estimating each quantity to the extent possible. This rationale may include your conceptual or mental model of the problem at hand, the key inputs to your estimate, the data or evidence you rely on, any limitations in the evidence, and any assumptions you are making in the application of the evidence in support of your probability distributions.

What does it mean to be a "good" expert?

In science-based decision support, it is desirable that subjective probability assessments be externally validated. In reality, external validation of subjective probability assessments can be difficult to achieve and we have not included validation methods in this phase of the study. Nonetheless it is important to bear in mind the characteristics of a good assessment and thus of a good expert.

Good subjective probabilistic assessments have two features which are analogous to the concepts of accuracy and precision;

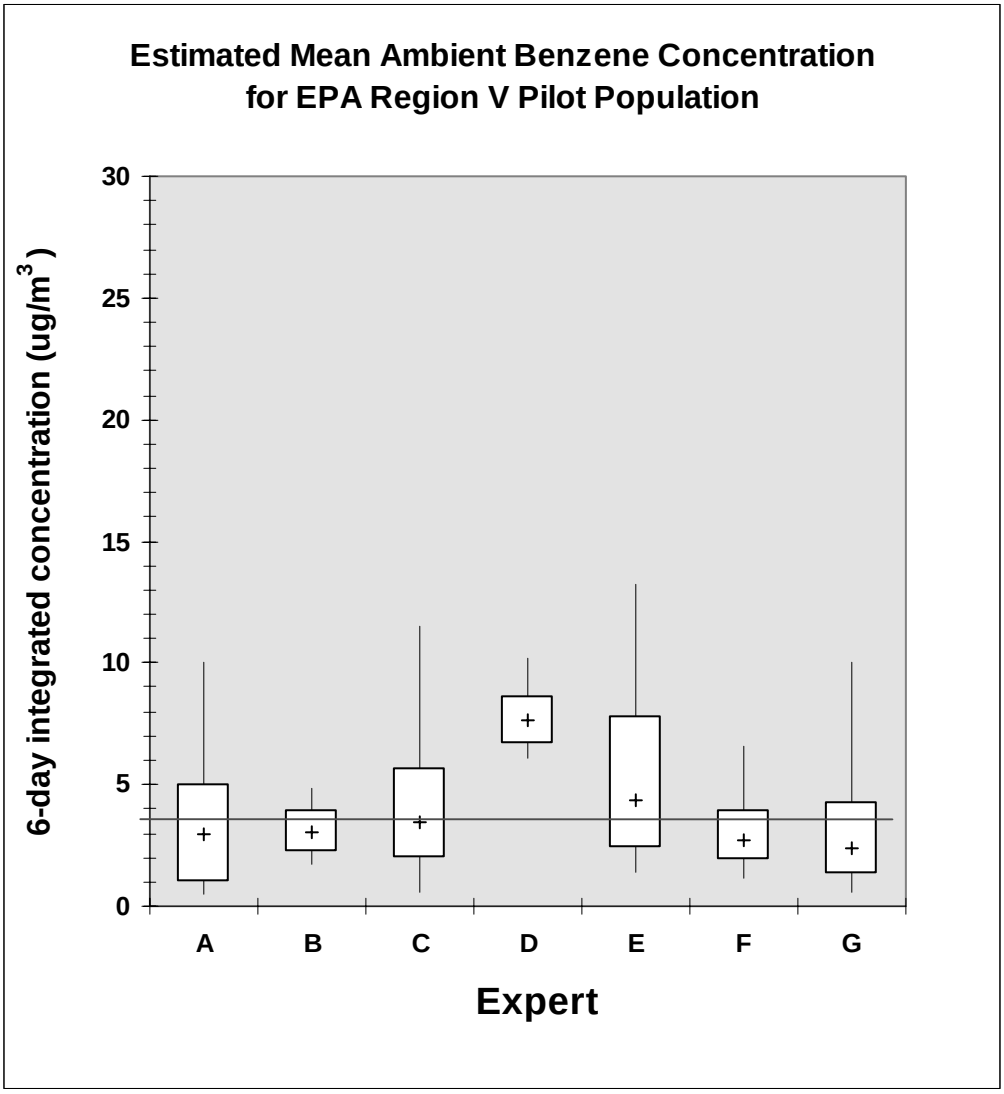
1. They "capture" the true values in the inter-percentile intervals with the appropriate relative frequencies. For example, if you were to provide your 90% "credible" or confidence intervals for 100 quantities, 90% of the time, the true values should fall between the 5th and 95th percentile and 50% of the time, the true value should fall below the 50th percentile. The process by which this property is measured is called *calibration*; and it is measured as statistical likelihood according to standard statistical practice. The calibration score is a measure of accuracy
2. They are informative (i.e. the confidence intervals are not "too wide" in a relative sense, One measure of informativeness is that used by Cooke et al. 1991 in Experts in Uncertainty, Shannon relative information, which is the customary dimensionless measure of spread, and is a measure of precision. Highly informative assessments are valuable *only if* they are well calibrated.

Figure 2 provides results from a study in which experts' probabilistic judgments were obtained about the expected benzene concentrations in ambient air from a USEPA National Human Exposure Assessment Survey (NHEXAS) pilot study in Region V (Walker et al. 2003). Seven experts were asked to predict the median, interquartile range, and 90% confidence intervals for the mean and the 90^{th} percentiles of the distributions of ambient, indoor and personal air benzene concentrations from the study. Their judgments were calibrated using the results of the NHEXAS study which became available in the next year. The red line indicates the actual mean detected by the study.

The figure illustrates some the attributes of good judgments. One expert, D, showed evidence of poor calibration. His 90% confidence interval about the mean level of ambient benzene in the Region V pilot did not contain the value subsequently reported by the study. His judgment, in this and other estimates, showed evidence of over-confidence (he thought he knew more than he did); though the estimate appeared highly informative (i.e. narrow confidence intervals) it was biased high and thus inaccurate. As is generally the case, experts who provided less informative (i.e. broader confidence intervals expressing greater uncertainty) were generally better calibrated. Those experts appropriately characterized what they knew and what they were uncertain about, although some experts were more informative than others.

Advice on giving probability judgments (sent as separate document) - Please make sure to review this document prior to our discussions.

Figure 2
Expert Judgments about Mean Ambient Benzene Concentrations in NHEXAS Region V Pilot Study Compared to Study Findings (Red line) (Walker et al., 2003)



Practice exercise: Calibration feedback

In order to give you some experience at providing quantitative judgments, we have prepared a set of questions which we would like you to answer to the best of your ability. Please take the next 15 minutes to fill out the questionnaire that will be given you during the interview. Following completion of the questionnaire, we will assess your performance using a methodology developed by Dr. Roger Cooke (author of Experts in Uncertainty) and his colleagues at Delft University in the Netherlands and discuss your results with you.

Part 2. Elicitation Questions: Preview

Before we spend the next few hours discussing your qualitative views on the factors that contribute to understanding of the relationship between $PM_{2.5}$ and premature mortality, we'd like you to read carefully the questions you will be asked to respond to with your quantitative probability distributions.

These questions can be found on pages 27 to 43. Following a review of the questions, we will return to the qualitative questions beginning on this page.

Part 3. Preliminary Questions: Factors to Consider

To assist you in providing quantitative probability judgments, we want to help you bring to mind the relevant evidence so that you may consider it systematically. With each question, you need to think about the relevant evidence, and consider any sources of uncertainty, error or bias that might influence your interpretation of the evidence. Also, in order to help us to interpret your judgments, we would like to ask you to discuss briefly your interpretation of various aspects of the literature.

We have identified several categories of questions that we would like you to consider:

- ***evidence for the short-term and long-term impact of PM exposure on the risk of premature mortality***
- ***mechanisms***
- ***cause of death***
- ***thresholds***
- ***concentration response function***
- ***lag/cessation period, or more simply, the time course of effects***
- ***relative effect of PM components***
- ***relative effect of PM sources***
- ***exposure issues***
- ***effects of confounding***
- ***effect modification***
- ***other _____***

We want to explore each of these, but the order here is not indicative of relative importance. You may specify a different order if you wish. If there are other important topics we have missed, please specify them.

A. Theoretical Construct for Long- and Short-term Exposure Effects on Premature Mortality

Because we want ultimately to obtain your quantitative estimates separately for the effects of long- and short term exposures on premature mortality, we want to begin by developing a conceptual framework for distinguishing these effects.

If you prefer, we can begin this discussion with an exploration of mechanisms. If so, we'll start with Questions B and C. **Continue/ Start with mechanisms**

Kunzli et al. (2001) have used Venn diagrams to describe the relationship between the deaths attributable to long-term and short-term exposure to fine particles. They define four categories of deaths attributable to air pollution:

Category of Cases	Impact of Air Pollution	
	Underlying frailty due to air pollution	Occurrence of death (event) triggered by air pollution
A	Yes	Yes
B	Yes	No
C	No	Yes
D	No	No

Where (from Kunzli et al., 2001):

A: Air pollution increases both the risk of underlying diseases leading to frailty and the short-term risk of death among the frail. For example, patients with chronic bronchitis that has been enhanced by long-term air pollution exposure may be hospitalized with an acute air pollution-related exacerbation of their illness leading to death shortly afterward.

B: Air pollution increases the risk of chronic diseases leading to frailty but is unrelated to timing of death. For example, a person's suffering from chronic bronchitis may be enhanced by long-term ambient air pollution exposure but the person may die due to acute pneumonia acquired during a clean air period.

C: Air pollution is unrelated to risk of chronic disease but short-term exposure increases mortality among persons who are frail. For example, a person with diabetes mellitus may be susceptible to heart attacks due to long-standing coronary disease; in such a case, an air pollution episode may trigger the fatal infarction leading to death.

D: Neither underlying chronic disease nor the event of death is related to exposure to air pollution.

Figure 3 depicts several possible relationships between A through D, one of which is the original Kunzli representation.

Do the categories A-D make sense to you as a way of defining long- and short-term effects of $PM_{2.5}$? **Yes/No**

If not, how would you alter them?
A

B

C

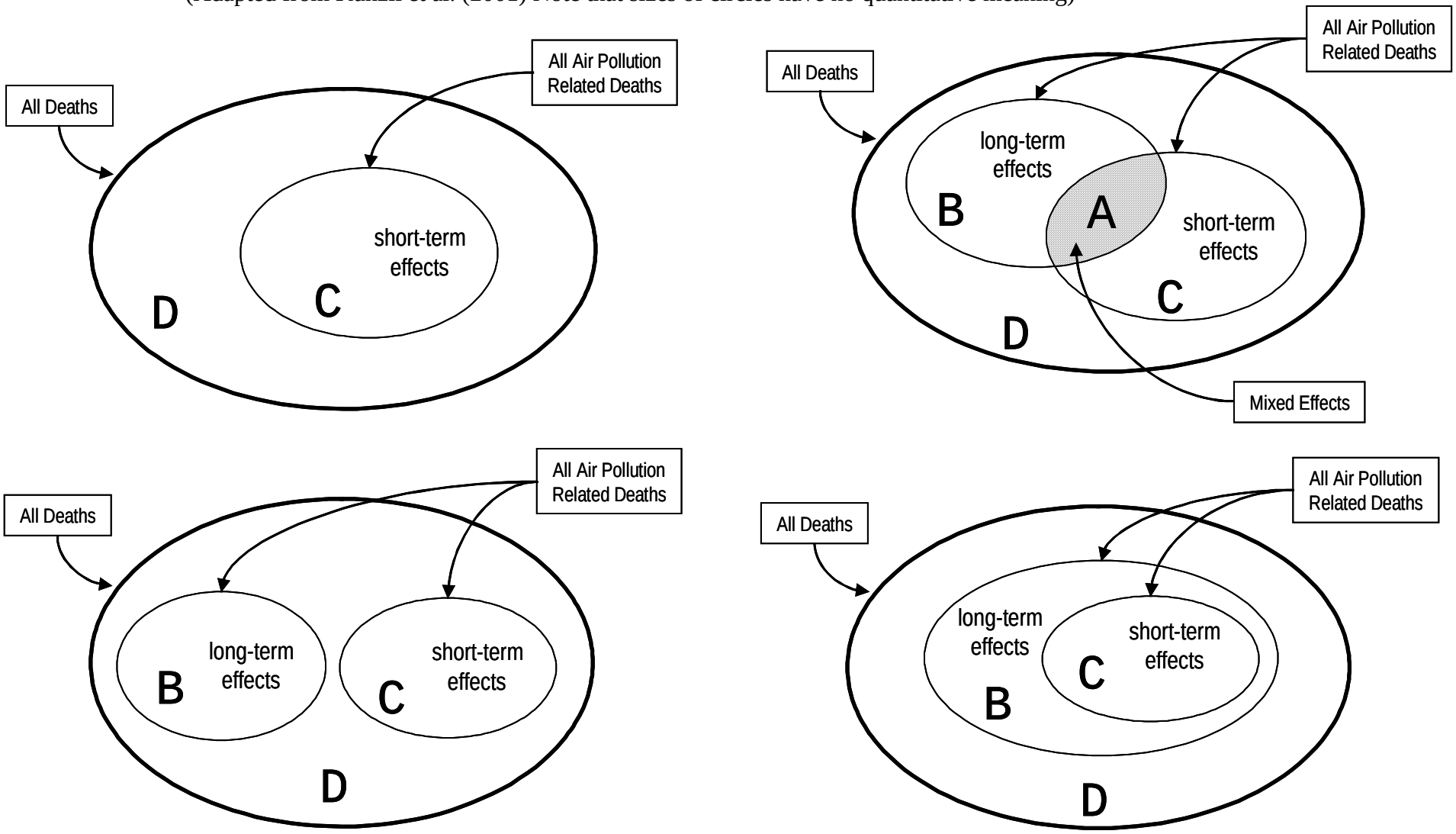
D

Does a Venn diagram adequately represent the relationships between these types of cases? **Yes/ No**

If yes, please draw for us or choose from the samples shown, the representation that best represents your views.

If not, please describe your views schematically or mathematically.

Figure 3 **ALTERNATIVE MODELS OF DEATHS ATTRIBUTABLE TO AIR POLLUTION**
(Adapted from Kunzli et al. (2001) Note that sizes of circles have no quantitative meaning)



Alternate Diagram or Conceptual Model

B. Mechanism for Effects from Long-Term Exposure

B1. What do you believe to be the major causes of death associated with long-term exposure to $PM_{2.5}$?

B2. What are your views concerning potential causal mechanisms for relationships between long-term exposure to $PM_{2.5}$ and premature mortality for each of these causes of death?

B3. What studies and/or evidence are most influential in informing your views about potential mechanisms?

C. Mechanism for Effects from Short-Term Exposure

C1. What do you believe to be the causes of death associated with short-term exposure to $PM_{2.5}$?

C2. What are your views concerning potential causal mechanisms for relationships between short-term exposure to $PM_{2.5}$ and premature mortality for each of these causes of death?

C3. What studies and/or evidence are most influential in informing your views about potential mechanisms?

D. Impact of Long-term Exposures to $PM_{2.5}$ on Premature Mortality

D1. Tell us which of the studies or groups of studies you find most informative for your judgments about the estimated reduction in non-accidental, premature mortality related to a reduction in ambient $PM_{2.5}$ concentrations? Please give the reasons for your choices. (To assist us with our records, please refer to studies by author, date rather than using general terms (e.g. by cohort).

What role do foreign vs. U.S. studies play in your considerations?

In addition, are any recent epidemiological studies, not published in the draft PM CD relevant to your judgments? If so, please discuss them.

D2. Please discuss the relative strengths and weaknesses of the cohort epidemiology studies in forming your judgments about the long-term impact of a change in ambient $PM_{2.5}$ on non-accidental, premature mortality?

D3. Can you tell us how likely you think it is that there is a causal relationship between **long-term** exposure to PM2.5 and premature mortality? Specifically, do you believe a causal relationship is:

- highly unlikely,
- somewhat unlikely,
- somewhat likely, or
- highly likely ---

at levels of exposure currently experienced in the US?

Please provide the quantitative range you associated with the qualitative term that you chose (e.g., if you chose "somewhat likely," does this mean more that 50% chance or 60 to 75% chance?)

D4. What is the underlying basis or rational for your response?

E. Impact of Short-Term Exposure to $PM_{2.5}$ on Premature Mortality

E1. Tell us which studies or groups of studies you find most useful in terms of their implications for judgments about the estimated reduction in non-accidental, premature mortality related to a reduction in daily ambient $PM_{2.5}$ concentrations? Why? Again, please use author, date format in your response.

Are any recent epidemiological studies, not published in the fourth external review draft PM CD relevant to your judgments and if so, please discuss them?

E2. Discuss the relative strengths and weaknesses of the time-series epidemiology studies in forming your judgments about the short-term impact of a change in ambient $PM_{2.5}$ on non-accidental, premature mortality?

E3. Can you tell us how likely you think it is it that there is a causal relationship between **short-term exposure** to $PM_{2.5}$ and premature mortality? **Yes/ No**

Specifically, do you believe a causal relationship is:

- highly unlikely,
- somewhat unlikely,
- somewhat likely, or
- highly likely

at levels of exposure currently experienced in the US?

Please provide the quantitative range you associated with the qualitative term that you chose (e.g., if you chose "somewhat likely," does this mean more that 50% chance or 60 to 75% chance?)

E4. What is the underlying basis or rational for your response?

F. Impact of Epidemiological Study Design

For the purpose of policy analysis, the true underlying impact of exposures to air pollution would ideally be separable into those impacts due solely to short-term fluctuations and those due solely to long-term exposure. However, we recognize the cohort and time-series designs (or existing studies) may have difficulty in completely distinguishing these two types of effects. Bearing in mind your earlier discussion of the mechanisms underlying effects of long-term and short-term exposures and the conceptual framework (e.g. Venn diagrams) you may have used to characterize the relationships between the different types of effects, we would now like you to characterize the degree of overlap you believe exists between the types of effects the cohort and time series studies conducted to date actually capture.

What evidence exists to support your judgments?

Please use a diagram, if necessary to explain the rationale for your responses.

F1. What proportion (i.e. X percent or X-XX (min,max) percent) of the mortality effects identified in the cohort studies do you believe represents short-term exposure effects?

____%

F2. What additional mortality impact (i.e. X percent more or X-XX (min,max) percent, etc.) due to short-term exposures is not captured by the mortality impact identified in the cohort studies, if any?

____ %

G. Thresholds

G1. Discuss for a moment your concept of a threshold for health effects related to $PM_{2.5}$?
- in theory (e.g. individual, population thresholds, other factors)
- in practice (e.g. in the context of epidemiological or other scientific studies)

G2. In your judgment, what information does the existing literature provide on population thresholds for $PM_{2.5}$-related mortality at current ambient $PM_{2.5}$ concentrations?

Cohort studies?

Time-series studies?

Other disciplines or study types? Please identify

G3. Do you think it is likely that thresholds for $PM_{2.5}$-related premature mortality for the population
a) exist?
-for long-term exposures **Yes/ No**
-for short-term exposures **Yes/ No**

b) that are detectable?
-for long-term exposures **Yes/ No**
-for short-term exposures **Yes/ No**

G4. Does the information available allow selection of a particular threshold level or range of levels for total non-accidental mortality exist for the population? If yes, what information is most important for you in determining such a level?

For the effects of short-term exposure? **Yes/ No**

For the effects of long-term exposure? **Yes/ No**

G5. If you don't think it is likely that population thresholds exist for premature mortality at current ambient $PM_{2.5}$ concentrations, why not?

H. Concentration-Response Function

Most epidemiological studies of long-term exposures assume /demonstrate a log-linear or linear relationship between total non-accidental, premature mortality and exposures to $PM_{2.5}$. However, we are interested in whether you think there is reason to believe that the "true" relationship may differ from those assumptions or observations.

H1. Please discuss what the scientific evidence leads you to believe about the true, but unknown C-R function might be (mathematical form, existence of thresholds, etc.) and over what range. We will be asking you to use a sketch or equation to represent your ideas for the quantitative questions in Part 4 of this elicitation, but you may also present your ideas on the following page (Graph paper will be provided).

H2. Please identify the studies and/or evidence that you are relying on?

H3. Please answer the same questions but in regards the effects of short-term exposures to $PM_{2.5}$.

I. Latency Period and Cessation Lag for Long-term Exposures

Latency is defined as the delay between exposure and effect. Likewise, reductions in long-term average $PM_{2.5}$ levels may not result in an immediate reduction in mortality risk or an immediate reduction to a new equilibrium risk level. The term "cessation lag" refers to this period between the reduction in $PM_{2.5}$ and the achievement of a new steady state level of mortality risk. The cessation lag may assume any form, for example, some mortality risk reduction may occur in the first year with further reductions over a 10 year period until risk stabilizes at a new level at the end of the tenth year. Or, no risk reductions may occur until after two years, but the new risk level stabilizes immediately after the second year.

I1. Please discuss your views on the length of the cessation lag, (i.e., time period between a reduction in ambient $PM_{2.5}$ concentrations and reductions in non-accidental mortality).

I2. What studies and/or evidence do you rely on most strongly for these judgments?

J. Effects of PM Components/Sources

J1. What are your views concerning the relative contributions of individual $PM_{2.5}$ components (such as sulfates, nitrates, metals, organics, etc) to the observed premature mortality that has been associated with total $PM_{2.5}$ gravimetric mass?

J2. Do your judgments on this topic vary between long-term and short-term exposures? **Yes/ No**
If so, discuss separately.

J3. What are your views concerning the relative contributions of $PM_{2.5}$ components from different source types (for example gasoline powered mobile sources, diesels, utilities, industrial sources, bioaerosols, windblown dust) to the observed premature mortality that has been associated with total $PM_{2.5}$ in the literature?

Please discuss those studies and/or evidence that are most influential in informing your views on this topic.

J4. Can you identify certain components or sources that are relatively more important in terms of the magnitude and shape of C-R functions for total non-accidental premature mortality? **Yes/ No**

Please discuss those studies and/or evidence that are most influential in informing your views on this topic.

K. Exposure Issues

K1 What influence, if any, do concerns and/or questions about exposure misclassification or exposure error have on your judgments concerning the form, magnitude and uncertainty in the C-R functions for $PM_{2.5}$-related premature mortality?

- long-term exposures?
-

- short-term exposures?

K2 What evidence is most important to you in this regard?

L. Confounding and Effect Modification by Co-pollutants, Other Factors

L1. What are your views on the impact of potential confounding and effect modification in the $PM_{2.5}$ -- premature mortality relationship within the context of the cohort studies conducted to date (e.g., co-pollutants, weather/climatic factors, population characteristics)? Specifically,

What are the major sources of confounding and/or effect modification?

How would you characterize the impact of each source in terms of bias? Of uncertainty?

What evidence or studies are most influential in informing your views on this topic?

L2. What are your views on the impact of potential confounding and effect modification in the $PM_{2.5}$ -- premature mortality relationship within the context of time-series studies (e.g., co-pollutants, weather/climatic factors, population characteristics)? Specifically,

What are the major sources of confounding and/or effect modification?

How would you characterize the impact of each source individually in terms of bias? On uncertainty?

What evidence or studies are most influential in informing your views on this topic?

PART 4. ELICITATION OF QUANTITATIVE JUDGMENTS

Consider that, under ideal conditions, infinite resources etc, the answers to these questions could be known exactly. In reality, we must rely on imperfect evidence provided by epidemiologic and other scientific studies.

The elicitation has two parts:

1. *Elicitation of the percent reduction in annual average mortality associated with a decrease in long-term $PM_{2.5}$* ***exposure alone (i.e. excluding any effects of short-term exposures).***
2. ***Elicitation of percent reduction in daily mortality associated with a decrease in short-term $PM_{2.5}$ exposure alone (i.e. excluding any mortality effects of long-term exposures).***

These questions both assume that a reduction from a unit decrease in $PM_{2.5}$ will have the same absolute value per unit increase in $PM_{2.5}$

1. Air Pollution Mortality Estimates from Long-term Exposures

The specific goal of this question is to obtain your probabilistic judgment about the true, but unknown, percent reduction in annual, non-accidental, premature mortality in U.S. adults (approximately age 25 and older) associated with a permanent (1 $\mu g/m^3$) reduction in ambient annual average $PM_{2.5}$ concentrations for annual average $PM_{2.5}$ in the range typical for the United States (approximately 8-20 $\mu g/m^3$). The reduction in $PM_{2.5}$ related to the regulatory action is assumed to be immediate and permanent (see Figure 4).

For the purpose of this elicitation, , we are assuming that the "true" percent reduction in mortality per unit reduction in long-term $PM_{2.5}$ exposures for the adult U.S. population could be known exactly if the $PM_{2.5}$ exposures and mortality experience of all U.S. residents, across all regions, were to be measured perfectly and followed for an appropriate period of time. In essence, this relationship might be considered as a single, national average C-R function that could be applied throughout the United States in a benefits analysis.

We recognize this is likely a simplification; it is possible that there is not just one C-R function that applies everywhere, but rather multiple C-R functions specific to different places or different times, as PM and population characteristics vary over space and time. If there is, in fact, variability in the parameters of the C-R function from one location to another within the U.S., then the national average C-R function we are asking you to consider would represent a population-weighted mean effect of $PM_{2.5}$ exposure on mortality across geographic areas in the U.S.

We also recognize that any change in mortality resulting from a reduction of $PM_{2.5}$ may take several years to appear. We are asking about the change in risk after the baseline risk for the population reaches a new steady state (see schematic representation in Figure 5). We are not asking you to characterize quantitatively the time sequence of any changes although we will be asking your qualitative views about it.

Figure 4

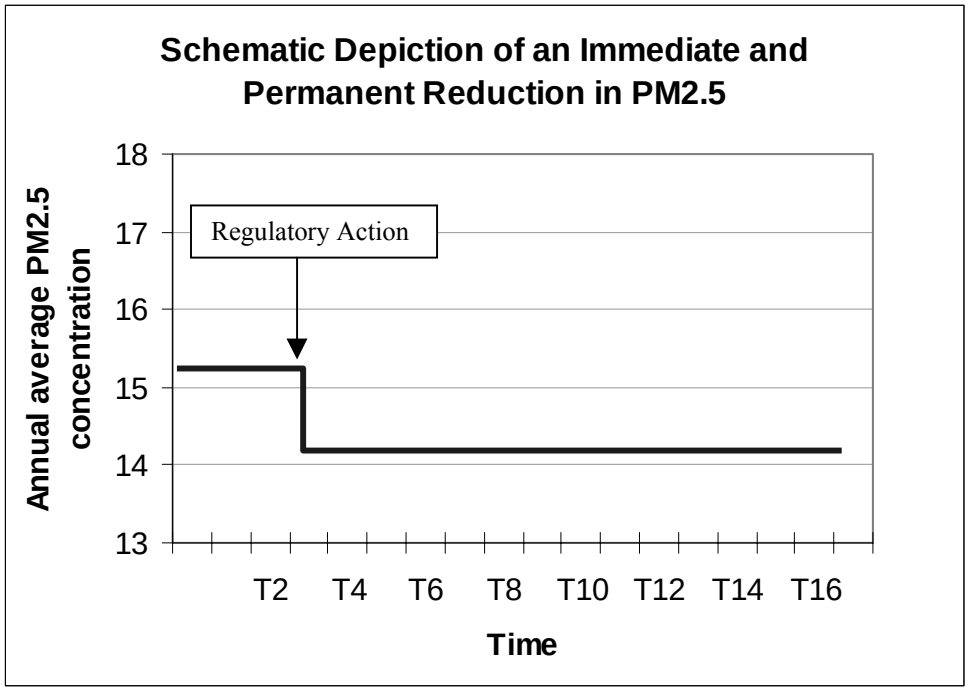
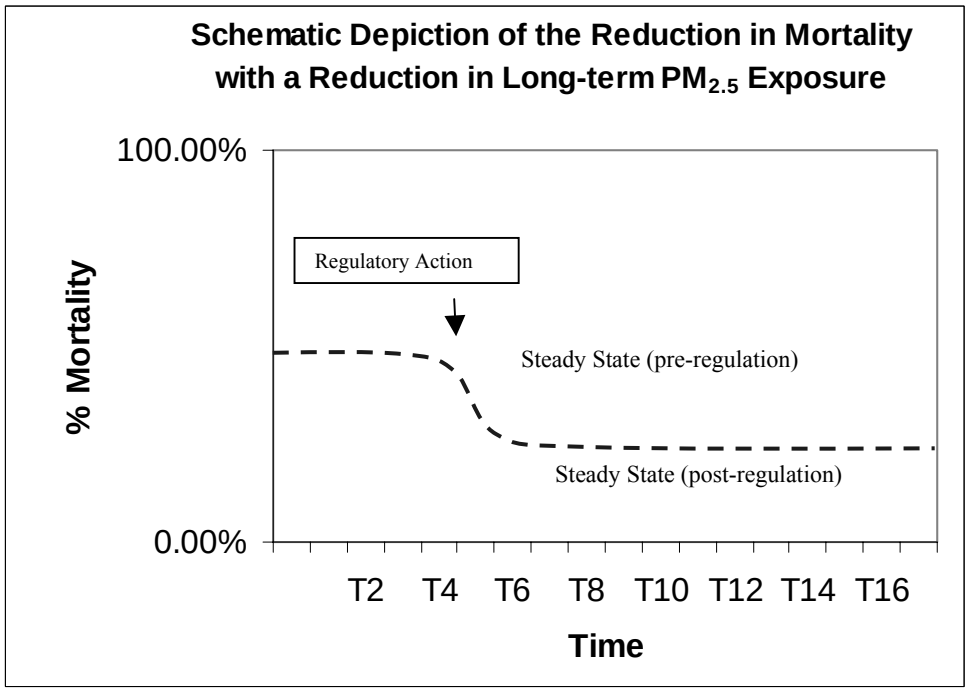


Figure 5



Assumptions on which your judgments should be conditioned:

- The C-R function over the range of $PM_{2.5}$ assumed in this study.

  In developing your quantitative estimates, we want you to rely on your understanding and beliefs about the true C-R function describing the relationship between $PM_{2.5}$ exposure and non-accidental, premature mortality. We will discuss your understanding of the C-R relationship as part of our elicitation.

  We recognize that many epidemiologic studies assume either a log-linear or linear relationship. If you were to believe that the shape of the C-R curve were consistently log-linear over the range of $PM_{2.5}$ exposures we are asking about in this study, the slope, β, could be derived from the reported relative risk for a change in PM concentration.

$$\beta = \frac{\ln(RR)}{\Delta PM}$$

  If the C-R function is linear, the relationship between a relative risk and the coefficient, β, is not as straightforward and the coefficient is usually reported directly. It may also be estimated from the change in health endpoint (e.g. non-accidental, premature mortality (deaths per 1000), M) and the PM differential:

$$\beta = \frac{\Delta M}{\Delta PM}$$

  If you do not think that the relationship is linear or log-linear over the range we are asking about in this study, you will have an opportunity to discuss other approaches.

- The reduction will affect all areas, not just non-attainment areas.

- Regulatory implementation:
  - the regulatory strategies implemented to achieve this reduction in $PM_{2.5}$ could include several specific measures that would likely focus largely on measures to reduce NOx, SOx, and primary $PM_{2.5}$. (For example, impacts might range from reduced diesel PM associated with the non-road rule to an across the board decrease in a variety of PM sources for the PM transport rule, or other measures designed for the purpose of meeting the $PM_{2.5}$ NAAQS.)
  - the impact of the regulatory action on co-pollutant concentrations is not known/specified and thus remains a source of uncertainty.
- Population: U.S. adult population (25 years and older)
- Pattern of exposure:

  - the pattern of daily concentrations is the same as recent ambient $PM_{2.5}$ concentrations in the U.S. (see Chapter 3, draft PM CD for characterization of $PM_{2.5}$ air quality distributions in the U.S.).
  - the specified change in ambient $PM_{2.5}$ concentrations (i.e. a 1 $\mu g/m^3$ reduction in annual average) occurs proportionally in the entire distribution of ambient daily concentrations (i.e., the overall pattern of daily ambient $PM_{2.5}$ is unchanged).
- Exposure History: Past exposures are as they existed in the United States over the last 30 years. (See Chapter 3 of the draft PM CD for characterization of past ambient levels)
- Ambient Conditions: Assume temperature and relative humidity conditions to be those that typically occur currently throughout the U.S.
- Other Pollutants:
  - the baseline concentration distributions of other pollutants, such as nitrogen dioxide, sulfur dioxide, ozone, and carbon monoxide and other pollutants are as they currently exist. (See EPA's Air Quality and Trends Report, 2002 for characterization of levels of these other pollutants)
  - prior ambient concentration levels of other pollutants were as they existed over the last 30 years in the U.S. (See EPA's Air Quality and Trends Report, 2002 for characterization of levels of other pollutants over last 30 years).

Do you have any questions or concerns regarding the specification of this problem?
Notes:

Q1: Long-term Exposures:

What is your estimate of the true, but unknown percent reduction in total annual, non-accidental mortality (excluding any short term effects) in the adult U.S. population resulting from a long-term 1 μg/m^3 reduction in annual average $PM_{2.5}$ (ranging from about 8 to 20 μg/m^3) across the U.S. (e.g. the population-weighted mean effect)? To express the uncertainty associated with the C-R relationship, please provide the 5th, 25th, 50th, 75th, and 95th percentiles of your estimate.

Q1. Graphical Representation

Q1A Before we work on your quantitative response, we would like to begin by having you sketch, in as much detail as possible, the overall C-R function for the range of $PM_{2.5}$ and other conditions we have specified in this question. For example, do you think the function is the same over the whole range, over some range, etc. Whether you are assuming an underlying linear, log-linear, or other concentration response function or you prefer to think initially about the difference in mortality rates, relative risks, or percent differences in excess mortality, it is critical in answering this question that we are both clear about the basis for your calculation. (Graph paper will be made available at the interview).

Q1B. If you have indicated a non-linearity in your graphical approach, please state the range of annual average $PM_{2.5}$ to which this estimate applies:

_____to _____ $\mu g/m^3$

Q#	5^{th} %ile	25^{th} %ile	50^{th} %ile	75^{th} %ile	95%ile
1					

Bearing in mind the qualitative discussion we have just completed, and using as much detail as feasible, tell us how you think about approaching/structuring a response to this question. You may find it useful to sketch an influence diagram or other conceptual model (use additional paper as necessary).

For example, what studies/and or evidence are you most relying on?

- ***What is the highest value you think it could be? Tell us, for example, what data you might use to bound this estimate.***
- ***How do you approach estimating the 95%ile?***
- ***What is the lowest value it could be?***
- ***How do you then approach the 5%ile?***
- ***… the median?***
- ***… the interquartile range?***

As part of this process, we want to understand what you believe to be the key sources of potential bias and uncertainty in the data available to estimate these quantities and how you have used them in arriving at your estimates. Another way to think of this is to ask what factors you would most want to know more about in developing your estimate.*((For reference purposes, a number of factors that have been raised as potential issues in the literature, many of which we may have discussed earlier in the elicitation, are listed in Table 1.)*

Please identify and discuss the top 5 factors that influence your estimates for:

Bias, the central tendency of your response
1.
2.
3.
4.
5.
uncertainty
1.
2.
3.
4.
5.

Q1C. Please state the range of annual average $PM_{2.5}$ to which this estimate applies (if you have indicated a non-linearity in your graphical approach):

_____to _____ $\mu g/m^3$

Q#	5th %ile	25th %ile	50th %ile	75th %ile	95%ile
1					

Bearing in mind the qualitative discussion we have just completed, and using as much detail as feasible, tell us how you think about approaching/structuring a response to this question.

For example, what studies/and or evidence are you most relying on?

- ***What is the highest value you think it could be? Tell us, for example, what data you might use to bound this estimate.***
- ***How do you approach estimating the 95%ile?***
- ***What is the lowest value it could be?***
- ***How do you then approach the 5%ile?***
- ***… the median?***
- ***… the interquartile range?***

As part of this process, we want to understand what you believe to be the key sources of potential bias and uncertainty in the data available to estimate these quantities and how you have used

them in arriving at your estimates. Another way to think of this is to ask what factors you would most want to know more about in developing your estimate.*((For reference purposes, a number of factors that have been raised as potential issues in the literature, many of which we may have discussed earlier in the elicitation, are listed in Table 1.)*

If different, please identify and discuss the top 5 factors that influence your estimates of:

bias, the central tendency of your response
1.
2.
3.
4.
5.
uncertainty
1.
2.
3.
4.
5.

Table 1 --- Potential Sources of Bias and/or Uncertainty

- *Population variables:*
  - age,
  - SES, and educational profiles,
  - susceptible subpopulations
  - pre-existing diseases
  - population sampling errors
  - population representativeness
  - nutrition/diet
  - other (please name)_____
- *Physical-chemical variables:*
  - composition of the particulate mixture (ammonium nitrate, ammonium sulfate, primary inorganic, primary organic, secondary organic, etc.),
  - pH,
  - size distribution,
  - particle number, and/or presence of endotoxin
  - other pollutants
  - other_____
- *Mechanism related variables*
  - deposition in the lung
  - retention and clearance
  - effect on pulmonary system
  - effect on cardiovascular system
  - other_____
- *Region / exposure related variables*
  - meteorology
  - health delivery systems
  - exposure history
  - exposure patterns
  - exposure measurement/sampling error
  - time/activity patterns
  - housing characteristics
  - other
- *Physiological/toxicological variables*
  - Relative toxicity of PM components
  - thresholds
  - other
-

2: Air Pollution Mortality Estimates from Short-term Exposures

The specific goal of this elicitation is to obtain your probabilistic judgment about the true, but unknown, percent change in short-term, non-accidental, premature mortality alone (i.e. short-term mortality effects excluding effects of long-term exposure) for adults associated with a 10 $\mu g/m^3$ decrease in a single day's 24-hour average ambient $PM_{2.5}$ concentration across the United States.

Assume that baseline ambient daily average $PM_{2.5}$ falls in the range representative of the full range of average daily $PM_{2.5}$ concentrations in the U.S. (up to 60 $\mu g/m^3$). As a result of a change in emissions following regulatory action, there is a 10 $\mu g/m^3$ drop in the 24-hour average $PM_{2.5}$ concentration for a single day across the U.S.

We next want you to predict the percent change in short-term exposure non-accidental, premature mortality (short-term mortality effects only) in the adult population (25 years and older) resulting from that single-day decrease in $PM_{2.5}$. As in the question about long-term exposures, this is like asking about the true population-weighted mean effect of a vast study involving the full adult population of the U.S.

Assumptions on which your judgments should be conditioned:

- the concentration-response function you specify
- the short-term mortality effects from this one day drop in $PM_{2.5}$ are independent of those resulting from a change on any other day.
- the percent change in mortality should reflect deaths occurring shortly after the short-term excursion in $PM_{2.5}$ (e.g in the following week up to a few months).
- the percent change should not include deaths related to long-term exposures
- The reduction will affect all areas, not just non-attainment areas.
- Regulatory implementation:
  - the regulatory strategies implemented to achieve this reduction in $PM_{2.5}$ could include several specific measures that would likely focus largely on measures to reduce NOx, SOx, and primary $PM_{2.5}$. (For example, impacts might range from reduced diesel PM associated with the non-road rule to an across the board decrease in a variety of PM sources for the PM transport rule, or other measures designed for the purpose of meeting the $PM_{2.5}$ NAAQS.)
  - the impact of the regulatory action on co-pollutant concentrations is not known/specified and thus remains a source of uncertainty.
- Population: Adult U.S. population aged 25 and older.
- Pattern of exposure:

  - the pattern of daily concentrations is the same as recent ambient $PM_{2.5}$ concentrations in the U.S. (see Chapter 3, draft PM CD for characterization of $PM_{2.5}$ air quality distributions in the U.S.).
  - the specified change in ambient $PM_{2.5}$ concentrations (i.e. a 1 $\mu g/m^3$ reduction in annual average) occurs proportionally in the entire distribution of ambient daily concentrations (i.e., the overall pattern of daily ambient $PM_{2.5}$ is unchanged).
- Exposure History: Past exposures are as they existed in the United States over the last 30 years. (See Chapter 3 of the draft PM CD for characterization of past ambient levels)
- Ambient Conditions: Assume temperature and relative humidity conditions to be those that typically occur currently throughout the U.S.
- Other Pollutants:
  - the baseline concentration distributions of other pollutants, such as nitrogen dioxide, sulfur dioxide, ozone, and carbon monoxide and other pollutants are as they currently exist.(See EPA's Air Quality and Trends Report, 2002 for characterization of levels of these other pollutants)
  - prior ambient concentration levels of other pollutants were as they existed over the last 30 years in the U.S. (See EPA's Air Quality and Trends Report, 2002 for characterization of levels of other pollutants over last 30 years).

Do you have any questions or concerns regarding the specification of this problem?
Notes:

Short-term Exposures:

What is your estimate of the true, but unknown percent reduction in total annual, non-accidental premature mortality (excluding any long-term effects) in the adult U.S. population resulting from a one-day 10 μg/m^3 reduction in daily average $PM_{2.5}$ (ranging from background up to 60 μg/m^3) across the U.S. (e.g. the population-weighted mean effect)? To characterize the uncertainty in the C-R function, please provide the 5th, 25th, 50th, 75th, and 95th percentiles of your estimate.

Q2. Graphical Representation of C-R

Q2A Before we work on your quantitative response, we would like to begin by having you sketch, in as much detail as possible, the overall C-R function for the range of $PM_{2.5}$ and other conditions we have specified in this question. For example, do you think the function is the same over the whole range, over some range, etc? (Graph paper will be made available at the interview). Whether you are assuming an underlying linear, log-linear, or other concentration response function or you prefer to think initially about the difference in mortality rates, relative risks, or percent differences in excess mortality, it is critical in answering this question that we are both clear about the basis for your calculation.

Q2B. Please state the range of 24-hour average $PM_{2.5}$ concentrations to which this estimate applies (if you have indicated a non-linearity in your graphical approach, use an additional worksheet for other ranges):

_____to _____ $\mu g/m^3$

Q#	5th %ile	25th %ile	50th %ile	75th %ile	95%ile
2					

Bearing in mind the qualitative discussion of issues we have just completed, explain in as much detail as feasible how you think about approaching/structuring a response to this question. You may find it useful to sketch an influence diagram or other conceptual model.

For example, what studies/and or evidence are you most relying on?

- ***What is the highest value you think it could be? Tell us, for example, what data you might use to bound this estimate.***
- ***How do you approach estimating the 95%ile?***
- ***What is the lowest value it could be?***
- ***How do you then approach the 5%ile***
- ***… the median?***
- ***… the interquartile range?***

As part of this process, we want to understand what you believe to be the key sources of potential bias and uncertainty in the data available to estimate these quantities and how you have used them in arriving at your estimates. Another way to think of this is to ask what factors you would most want to know more about in developing your estimate.*(For reference purposes, a number of factors that have been raised as potential issues in the literature, many of which we may have discussed earlier in the elicitation, are listed in Table 1.)*

Are they different than those you identified in the discussion of long-term exposures?
If so, please identify and discuss the top 5 factors that influence your estimates of:

bias, the central tendency of your response
1.
2.
3.
4.
5.
uncertainty
1.
2.
3.
4.
5.

Q2C. Please state the range of 24-hour average $PM_{2.5}$ concentrations to which this estimate applies (if you have indicated a non-linearity in your graphical approach, use an additional worksheet for other ranges):

_____to _____ $\mu g/m^3$

Q#	5^{th} %ile	25^{th} %ile	50^{th} %ile	75^{th} %ile	95%ile
2					

Bearing in mind the qualitative discussion of issues we have just completed, explain in as much detail as feasible how you think about approaching/structuring a response to this question. You may find it useful to sketch an influence diagram or other conceptual model.

For example, what studies/and or evidence are you most relying on?

- ***What is the highest value you think it could be? Tell us, for example, what data you might use to bound this estimate.***
- ***How do you approach estimating the 95%ile?***
- ***What is the lowest value it could be?***
- ***How do you then approach the 5%ile***
- ***… the median?***
- ***… the interquartile range?***

As part of this process, we want to understand what you believe to be the key sources of potential bias and uncertainty in the data available to estimate these quantities and how you have used them in arriving at your estimates. Another way to think of this is to ask what factors you would most want to know more about in developing your estimate. ***(For reference purposes, a number of factors that have been raised as potential issues in the literature, many of which we may have discussed earlier in the elicitation, are listed in Table 1.)***

Please identify and discuss the top 5 factors that influence your estimates:

Bias, the central tendency of your response
1.
2.
3.
4.
5.
Uncertainty
1.
2.
3.
4.
5.

5. Follow-up Questions:

As a preliminary step to furthering our understanding of the uncertainties surrounding the relationship between changes in PM and changes in premature mortality, as well as for preparing for the full expert elicitation that we are considering conducting in the future, we have a few additional questions. All of these questions are based on the probabilistic judgments you have just provided us regarding estimates of percent decrease in premature mortality associated with an "across the board" reduction in ambient $PM_{2.5}$. However, we recognize that not all $PM_{2.5}$ components may have the same effects and that regulatory strategies may have differential impacts on particular $PM_{2.5}$ components.

The following questions relate to the relative mortality impacts of different components of $PM_{2.5.}$. As the proportion of sulfates, nitrates, transition metals, and other components of $PM_{2.5}$ vary regionally, please describe for us the assumptions that you made with respect to the C-R relationships for the impact of $PM_{2.5}$ on premature mortality.

As you deem appropriate, please indicate your response separately for long-term and short-term exposures.

M1. If we told you that the $PM_{2.5}$ mixture you were considering was much higher in sulfates than you had originally assumed, how would your judgment about the C-R relationship have changed?

M2. If we told you that the $PM_{2.5}$ mixture you were considering was much higher in black carbon (soot) associated with diesel emissions than you had originally assumed, how would your judgment about the C-R relationship have changed?

M3. If we had told you that the $PM_{2.5}$ mixture you were considering was much higher in nitrates than you had originally assumed, how would your judgment about the C-R relationship have changed?

M4. If we had told you that the $PM_{2.5}$ mixture you were considering was much higher in organics than you had originally assumed, how would your judgment about the C-R relationship have changed?

M5. If we had told you that the $PM_{2.5}$ mixture you were considering was much higher in ultra fine particles than you had originally assumed, how would your judgment about the C-R relationship distribution have changed?

M6. If we had told you that the $PM_{2.5}$ mixture you were considering was much higher in transition metals than you had originally assumed, how would your judgment about the C-R relationship distribution have changed?

M7. Would changing the $PM_{2.5}$ mixture in any other way have substantially changed your judgment about the C-R relationship distribution? If so, how and why?

Appendix C

Summary of Expert Responses to Preliminary Questions

In the following tables, we have developed brief summaries of the individual expert's responses to the preliminary questions. In a number of cases, experts' responses covered multiple questions where they felt the questions were inter-related. It made more sense in these cases to compose a single integrated discussion covering responses to the relevant questions (see for example, the mechanisms for the effects of long and short-term exposures on mortality). Experts did not always respond to every subpart of each question; nor did they respond in the same level of detail.

A	**Theoretical Construct for Long-and Short-term Exposure Effects on Premature Mortality**
	See discussion of F1 and F2 in text

B1.	**What do you believe to be the major causes of death associated with long-term exposure to $PM_{2.5}$?** ***(In order of importance)***
A	• Cardiovascular disease • lung cancer • Respiratory disease
B	• Cardiovascular disease • Respiratory disease • Not cancer – does not believe PM is likely to be a significant contributor to cancer risk
C	• Cardio-respiratory diseases probably constitute the bulk of the effects of PM but because cardiac deaths represent a very substantial portion of all deaths in the U.S. "But then our air pollution related effects are a very small part of that total." • "I think our data is highly uncertain with regard to the issue of lung cancer associated with contemporary levels of airborne particulate material and I think even more uncertain with regard to other cancers." • He thinks that PM exposure does not create a unique disease related to PM exposure. Instead, it "adds to the wear and tear of life."

D	• Broad Category of Effects: Cardio-respiratory deaths
	  • Heart Disease (CHD)
	  • COPD (particles likely contribute, but are not a major contributor)
	  • stroke, possibly
	• Cancer

E	• cardiovascular deaths • respiratory deaths (COPD, pneumonia, flu, infectious disease) • lung cancer

B2.	What are your views concerning potential causal mechanisms for relationships between long-term exposure to $PM_{2.5}$ and premature mortality for each of these causes of death?
A	Expert A believed there to be a growing body of evidence for plausible mechanisms by which cardiovascular and pulmonary disease might develop. He defined three general categories of mechanisms: circulatory and cardiac events (related to inflammatory, atherosclerotic changes), pulmonary and systemic inflammation, and disturbances of the cardiac-autonomic nervous system. He cited work showing increases in C-reactive protein, PM related increases in fibrinogen, and epidemiologic studies relating particles to coagulation, to plasma viscosity and to C - reactive protein (Ghio et al. 2000; Peters A. et al., 1997; Peters A., et al. 2000a; Peters A., et al., 2000b; Peters A, et al., 2001a; Peters A, et al., 2001; Seaton et al., 1999) These factors are indicators of injury and inflammation and can be predictors of subsequent heart disease and mortality. Although the studies have observed these effects following short-term exposures largely, Expert A felt that they are indicative of a mechanism that could also be a longer-term process. The conceptual model for the pulmonary and systemic inflammation mechanism is that deposition of smaller particles, in particular, to the deep lung can cause inflammatory responses that can amplify the injury and set another chain of mechanisms into play. For example, increased respiratory infections, hyper-responsiveness, and other markers of lung injury could precede chronic obstructive pulmonary disease (COPD). The Utah studies that exposed cell lines to concentrated air pollution particles both before and after the closure of the local steel mill and showed increased inflammatory responses are informative in this regard (e.g. Dye et al., 2001). Expert A also described a the third type of mechanism that involves impact on the nervous system, in particular, the cardiac- autonomic nervous system. Several studies (Gold, et al, 2000; Pope, et al, 1999; and Liao et al., 1999) have shown associations between PM exposures and heart rate variability and/or cardiac arrhythmias. The evidence from "defibrillator studies" showing associations between increased numbers of arrhythmias with increased particle concentrations is particularly strong since there is no reliance on recall by patients and the doctors downloading the defibrillator data are blind to the particulate concentrations (Peters et al, 2000a; Peters et al., 2001a).
B	Expert B also described the possible mechanism for PM-related cardiovascular disease as operating through the increased risk of atherosclerosis, resulting from chronic inflammation of the arteries. Inflammation might be the result of the particles directly or indirectly via various mediators, such as cytokines. Expert B discussed studies (epidemiological and laboratory) that showed increases in biomarkers of inflammation, c-reactive proteins, fibrinogen, conduction disturbances, and heart rate variability following exposure to fine particles. He found the Peters et al. (2000a,b; 2001a,b) work showing relationships between particulate exposure and cardiac arrhthymias and other irregularities intriguing as a mechanism for $PM_{2.5}$ to trigger cardiac events. Some recent laboratory data in healthy humans have shown

	direct reductions in oxygen diffusing capacity following exposure to ultrafine particles (citation). Although the studies cannot yet determine whether it is diffusing capacity across alveolar membranes or vascular membranes, he notes that this reduced flow of oxygen to the system could be a factor in cardiac problems, primarily in individuals with pre-existing disease. "[I]n the short term, if I had people who have underlying either pulmonary or cardiac disease, and I interfere with their gas exchange, I can see that having an acute effect. The reason people get arrhythmias is ultimately they don't get enough oxygen to the tissue. It isn't just that the tissue fires, there's something that happens that makes it fire. Hypoxia is a pretty good explanation. I want to be careful that I don't extrapolate too far, but I think that the animal and human studies have increased the plausibility of the acute toxicity. I'm not really convinced that we're there with the chronic studies, because we really don't have very good models (animal)." He believed fine particles to be the more likely explanation for the cardiovascular effects seen than coarse particles.
C	Expert C laid out a general conceptual framework for mechanisms of cardio-respiratory disease related to deposition of particles in the respiratory system, cytotoxicity, and " a cascade of events that take place both locally and may move beyond local effect to what I'll call a tissue effect…. We may have effects in terms of the tracheal bronchial tree [..] in terms of going down pathways of bronchitis and alterations in airway permeability." Much of his discussion, however, centered on concerns about disentangling the effects of $PM_{2.5}$ from those of other particulate fractions (i.e. $PM_{10\text{-}2.5}$) and the role of higher historical exposures in the etiology of underlying levels of frailty and rates of death observed in recent epidemiological studies. For cancer, he thought the mechanism would be that materials are deposited in respiratory tract and trans-located to other organs. But the data are "highly uncertain" and "the lung is not an efficient way to provide dose to the body."
D	Expert D described conceptually similar mechanisms for the impact of $PM_{2.5}$ on coronary heart disease and chronic obstructive lung disease as Expert A and B. However, he felt the plausible arguments existed mostly by analogy to smoking or higher levels of exposure to PM. He referred to tobacco smoke studies (from years ago), showing immediate sequestration of white cells in lungs of healthy individuals. There are lots of studies ranging from in vitro systems to whole animal exposures to the concentrated air pollution (CAP) studies. The postulated mechanism is that coronary heart disease and COPD are associated with inflammation and that particulate matter contributes to that inflammation. In some people, inhaled particles tip the balance toward inadequate inhibition of elastolitic and proteolitic enzymes…that seem to cause the damage that leads to COPD. Smoking studies provide a useful analogy except that the exposure to particles from smoking is extraordinary in comparison to exposure to particles through the air. Passive smoking is also associated at least with coronary heart disease in adults and has at least some effects on lung function in some studies

	(certainly in children). " A better example with particles [are] the animal studies with diesel;… it seemed that the observed diesel particle-lung cancer association in rats was a general phenomenon that happened in the overloaded lung with too much particles that caused inflammation. That is a mechanism that probably (for sure didn't) apply to the general population levels" "I think there are reasons to suspect particles as contributing to any increased risk of cancer…because of what they contain on the surfaces. Some are polycylic rich and contain some carcinogens; there are also radionuclides in power plant emissions that are alpha emitters and may contribute to cancer risk."
E	Expert E stated that he is not well versed in the relevant literature, although his reasoning was conceptually similar to that outlined by Expert A and B (i.e. that the mechanisms for increase risk of death from heart attack are related to ability of body to keep the heart well-oxygenated or to control heart rate). In addition, he speculated about what kind of weight should be given to hypotheses about the relationship between chronic disease in adults and early childhood, including fetal exposures. In general, he felt that the mechanistic models were not well-established and remain a source of uncertainty.

B3.	**What studies and/or evidence are most influential in informing your views about potential mechanisms?**
A-D	*See Question B2*

C1.	What do you believe to be the causes of death associated with short-term exposure to $PM_{2.5}$?
A	• Cardiovascular disease • Respiratory disease
B	• By interfering with the gas exchange, PM has an acute effect on people who have underlying pulmonary or cardiac disease • PM exposure creates conduction disturbances and effects heart rate variability and fibrinogen
C	• He thinks that PM exposure probably makes diseases worse than they would be otherwise. This is similar to harvesting, but analytically distinct.
D	• Deaths in individuals who are already frail from cardio-respiratory diseases
E	• Cardiovascular deaths (myocardial infarction) • Pneumonia, influenza exacerbated by compromised lung function

C2.	What are your views concerning potential causal mechanisms for relationships between short-term exposure to $PM_{2.5}$ and premature mortality for each of these causes of death?
A	See Question B2
B	See Question B2
C	Although he felt the term "harvesting" has been over-interpreted and too narrowly used, he did state that, in terms of short term effects, "there is a susceptible population and the individuals who do have a burden in terms of respiratory disease is fairly substantial." "It can be a signal there and it will play itself out over a period of days to perhaps weeks. [W]e've got to keep in mind that it is a very small signal played out on top of a lot of variability attributed to other factors."
D	For the effects of short-term exposures, the mechanism probably involves processes that further injure the lung, presumably inflammatory, or other systemic processes that affect the heart (heart rhythm, possibility of congestive heart failure, ischemia). These affect individuals who are already in a state of frailty. However, in discussing how well we understand these mechanisms he says, "We don't understand yet, believe it or not, what makes people with COPD die…. We can postulate what might be affected by particles, but I don't think anyone can yet say with a high degree of certainty that, yes, this is the process. We have mechanisms proposed by no support for a particular mechanism."
E	See Question B2

C3.	What studies and/or evidence are most influential in informing your views about potential mechanisms?
A-E	See Question B2

D1 and D2	Tell us which of the studies or groups of studies you find most informative for your judgments about the estimated reduction in non-accidental, premature mortality related to a reduction in ambient $PM_{2.5}$ concentrations? Please give the reasons for your choices. (To assist us with our records, please refer to studies by author, date rather than using general terms (e.g. by cohort)… What role do foreign vs. U.S. studies play in your considerations? In addition, are any recent epidemiological studies, not published in the draft PM CD relevant to your judgments? If so, please discuss them. Please discuss the relative strengths and weaknesses of the cohort epidemiology studies informing your judgments…
A	Expert A cited several studies from both the US and Europe, the analogy to smoking and environmental tobacco smoke as epidemiological evidence for the impact of long-term exposures to PM2.5 on increased mortality rates. The primary epidemiological studies he relied on were the original Six Cities and ACS studies, their re-analyses by Krewski et al., 2000, and Pope et al. (2002). The strengths of the Six Cities study included the recruitment of a representative sample of subjects, use of questionnaire specifically developed for studying effects of air pollution, and control over the location of air pollution monitors. Its weaknesses include the small sample size, limited number of cities, and a choice of cities that may not be representative of the U.S. While the PM2.5 concentrations in the cities may represent an appropriate range, the cities are largely located in the Eastern/Midwestern regions; important regions of the U.S. (e.g. the southwest, Midwest and California) are not represented. Although the Six Cities study results held up well upon reanalysis by Krewski et al., (2000), the small size and number of cities made it impossible to do some of the additional sensitivity analyses that were possible with the ACS study. He felt the ACS cohort provides the population size and the large number of cities with better geographical representation that the Six Cities study lacks. Air pollution characteristics in the cities also encompass a wide distribution of particle composition and chemistry, allowing for the additional sensitivity analyses conducted by Krewski et al. (2000) in their reanalysis. The questionnaire, though not developed for the purpose of studying the effects of air pollution, nonetheless provides a richer source of data on possible confounders and effect modifiers than the Six-City study. Its weaknesses include the method of recruitment for the study which favored higher income, education and a greater proportion of whites that is representative of the general U.S. population. Unlike the Six Cities, the ACS study had to rely on whatever monitors were available to the study which raises issues of quality control and representativeness of the exposures for the study population. Uncertainties about the residence history of subjects in both the Six Cities and ACS studies raise some questions about possible exposure

	misclassification. Expert A noted that Krewski has an ongoing study to examine the impact of residence history. He cited include lung function changes in children (e.g. LA childrens' study) traffic-related study conducted in the Netherlands (Hoek et al.) as other supportive evidence of a plausible effect of PM on morbidity and mortality, respectively. Overall, Expert A did not feel that the evidence against the findings of these studies was strong. The AHSMOG study showing increased mortality from lung cancer in males, but not other types of mortality. While Expert A felt this study was relatively unconfounded and had good residence history, it represents a healthier subject pool and is therefore not likely to be representative of the broader U.S. population. Its measure of exposure is also not ideal; for some of the years, it approximated PM10 levels from total suspended particles (TSP). Also, the sample size was relatively small. The McDonald et al. (JEAEE, 2000) study is a variant of AHSMOG (it uses a subset of people located within a given range of a local airport and FP is estimated from airport visibility, after correcting for humidity). For the subset of those living in higher density areas, an effect associated with estimated PM2.5 was found. Veteran's Cohort study (Lipfert et al., 1999) This study has not undergone a high level of peer review that would allow confidence to be placed in the results of this study. The analysis and results of this study are not very clear and the population is unrepresentative (veterans with high blood pressure).
B	The two studies that he felt represented the best evidence for a positive association were the Dockery et al. (1993) and Pope et al. (1995 and 2002) studies and their re-analyses by Krewski et al. (2000). (We also briefly discussed the Abbey et al, (1999), Brunekreef, and Lipfert et al (1999) studies). The major strengths of the Dockery et al. (1993) study cited was that the study was designed with the specific purpose of answering questions about the impact of air pollution (i.e. the prospective cohort study design with cities selected for variation in exposures). The potential concerns he raised regarded the relatively small size of the study, the potential for exposure misclassification (use of central monitors for personal exposures, population migration over a lifetime, etc), possible confounders ("lifestyle" (broader than socioeconomic variables capture), co-pollutants, occupational). The Pope et al. (1995) study's primary strength was its size and geographic distribution. He expressed some concern about possible selection bias in the ACS study, both the self-enrollment process and the reliance on a cohort selected for other purposes than air pollution impacts. We discussed the observation that most of the increased mortality reported in the ACS study appeared in the population with less than a high school education. The Lipfert et al. (1999) study was discussed briefly. Expert B expressed some concern about whether study design might have underestimated the true effect. At

	the same time, however, he felt that it provided some evidence on the weakness of the causal relationship.
C	Expert C cited the Six-Cities study, the ACS study, the VA study and the AHSMOG as the four studies most informative about PM2.5/ mortality relationships. • Six Cities Studies: "Its value is clearly the extensive efforts to characterize what the populations were exposed to, including the early measurements of several PM indicators." But a major weakness is the small sample size---8,000 individuals. • ACS Study: Major strength is the large sample size—over 500,000 individuals. A major weakness is that they individuals self-enrolled and they're probably biased toward individuals with a higher level of educational attainment and probably less representative of blue collar work. • Reanalysis by Krewski is interesting: Showed that educational attainment is important. • VA Study: Only included males. • Seventh Day Adventist study in southern California: Only included non-smokers; not a wide variety of air quality. • Neither of these studies includes sufficient information on individuals' exposure history prior to the time period when measurements were begun to ascertain exposure. • Neither VA nor ACS studies were originally intended to study the effects of air pollution (ACS study was designed to study cancer). • He points out that the vast majority of cardio-respiratory disease in the United States has associated with it cigarette smoking. As a result, studies need to take special care to control for cigarette smoking. The Six Cities study controls for smoking the best (although it was done better at the beginning of the study, not very well tracked during the study). The ACS study does not track smoking well (he thinks some people may not have accurately reported their smoking). • He thinks that the marginal effect of PM exposure on mortality may differ substantially geographically. Temperature, humidity, barometric pressure could all play a role. The current literature does not tease this out very well. • "Once we move out of the U.S., Canada- I don't attach a great deal of significance to those other studies." • "They may be generally helpful in telling us that air pollution is hazardous… but my personal experience is the nature of air pollution in different parts of the world is not always similar to the U.S. and air quality in the U.S. is in general substantially better than in most of the heavily populated areas of the world."
D	Expert D's overall assessment of the epidemiologic evidence for the effect of chronic exposures to PM2.5 on mortality was that it was limited. Only a handful of studies exist and their results have not been consistent (he notes that it is difficult to assess consistency with only 2 studies). Expert D believes the most informative studies to be the Six-Cities study (Dockery et al., 1993; Krewski et al.,

	2000) and the ACS studies (Pope et al., 1995; Krewski et al., 2000, and Pope, 2002). They provide reasonable evidence that there is some increased risk of mortality when exposed to PM. There's some consideration that's been given to confounding at the individual level, and some assessment of effect modification. One limitation lies in the studies' reliance on measurements of exposure at a single point in time to represent longer historical exposures. "[I]n fact in some cases, exposures were measured after people were dead." As a result, the "risk coefficients in these studies represent the consequences of some exposure on a time dimension that's not exactly clear, but it's sort of the long run." He argued that there is a fallacy in the strict quantitative interpretation of these coefficients; ideal measurements of exposure would involve lifetime personal exposure monitoring and follow-up but what we have is a measurement of air pollution in a community measured at some arbitrary time point in each individual's life. He suggested that such air pollution measurements are semi-quantitative measures of exposure, a kind of relative ranking, at best.
E	Epidemiological evidence cited: Krewski (2000) reanalyzes of ACS and Six-City studies • Both of these studies had large sample size, large number of cities, and adequate baseline information about people (including information on smoking history). • He did lay out a theory whereby the studies could be missing some confounding by important factors that affect premature mortality (diet, stress, etc) that are not somehow captured adequately in current measures of socioeconomic status. However, both ACS and Six Cities include a variety of potential confounders which probably account for the bulk of the socioeconomic impact on mortality. • He is concerned that the bulk of the affect of PM on premature mortality in the ACS study occurred among people without a high school education. He noted that this doesn't make a lot of biological sense—why the wide split among people with varying education levels? He doesn't think the VA study is credible (the wide differential between its results and the results of other similar studies). • He has more experience with the US studies than with foreign studies. Based on this experience, he has a high degree of confidence that the ACS and Six City studies reach statistically robust results. He has less confidence that the results of foreign studies are statistically robust. • The London Smog of 1952 plays a significant role in his decision-making process. He thinks that the smog provides compelling evidence that higher levels of particles cause people to die.

D3 and D4	**Can you tell us how likely you think it is that there is a causal relationship between long-term exposure to PM2.5 and premature mortality?** **Please provide the quantitative range you associated with the qualitative term that you chose (e.g., if you chose "somewhat likely," does this mean more that 50% chance or 60 to 75% chance?)** **What is the underlying rationale for your response?**
A	When asked to assign a percent likelihood to the causal relationship between long-term exposure to $PM_{2.5}$ and premature mortality, Expert A chose the category "highly likely". This corresponded to a quantitative estimate of about 85-90 (88 best estimate) percent probability. The residual doubt comes from questions about: (1) exposure metrics, (2) time/length of relevant exposure, (3) possibility of omitted variables, and (4) implications of short-term effects for long-term mortality. For example, he expressed concern whether the short term measures of impact (e.g. heart rate variability), done in studies that are essentially snapshots taken at a given point in time, are predictive of risk over long periods of time. There are a number of steps that must happen in between increased inflammation and death sometime in the future.
B	Although Expert B believed that the last 5 years have witnessed substantial progress in understanding the possible mechanisms underlying a relationship between PM and cardiovascular mortality, he did not feel that the data confirm a causal relationship. The data collectively support a plausible explanation but no individual study has been definitive. He thought a causal relationship is 'highly unlikely" assuming a healthy cohort but only "somewhat unlikely" assuming a typical cohort including smokers. He selected the category "somewhat unlikely" to represent his view on the likelihood of a causal relationship between long-term exposures to $PM_{2.5}$ and premature mortality for this project. This category reflected a judgment of roughly 40-50 percent likelihood of a causal relationship.
C	Expert C pointed out some implicit constraints resulting from framing of this question for the "levels of exposure currently experienced in the US" (i.e. 8-20 µg/m3 for annual average exposures). He argued that current exposures, or exposures measured in recent studies, may not be good indicators of historical exposures and also, that regional differences in exposures to $PM_{2.5}$ may be important. The six cities in the Dockery et al., 1993 study were not likely to be representative of the whole US in terms of exposures, weather (temperature, humidity, barometric pressure), and other factors. With regard to exposure, he thought Steubenville provided a high "anchor" for the Dockery et al. (1993) results. He ultimately placed 50 percent likelihood on a causal relationship, essentially "splitting the difference" between low levels of exposures where a causal relationship was unlikely to high PM levels (e.g. historical exposures in Steubenville) where he believed the likelihood of a causal relationship to be "very high."

D	When asked to evaluate the likelihood of a quantitative relationship between long-term exposures to PM2.5 and premature mortality, Expert D categorized his view as "somewhat likely" or about 50%. This judgment reflects the limited base of epidemiological evidence as well as uncertainty about the actual mechanisms that may be responsible. Some plausible arguments exist for possible mechanisms for PM contributing to atherosclerosis and chronic obstructive pulmonary disease, but they are mostly by analogy to smoking or higher levels of exposure to PM.
E	Expert E described a causal relationship between $PM_{2.5}$ and mortality from long term exposures as 'likely' (between the "somewhat likely" and "highly likely" categories specified in the protocol.) In quantitative terms, these categorical definitions translated into 80-98 percent likelihood with a modal value at 95 percent. His confidence derived in part from his view that the London Smog episode, in which large numbers of people died following acute exposures to smog, provided a kind of high dose experiment that lent support for a mechanistic relationship between PM and death in humans. Although he recognized that the episode was acute, he argued that increased death rates persisted over a sufficiently long period to also be picked up in chronic exposures studies. He had a residual concern that the Pope et al., 1995 study, though well-conducted, found so much of the mortality effect in the roughly 50 percent of the population without a high school education. He felt that such a finding did not make "biological sense".

E1 and E2	**Tell us which studies or groups of studies you find most useful in terms of their implications for judgments about the estimated reduction in non-accidental, premature mortality related to a reduction in daily ambient $PM_{2.5}$ concentrations? Why? Again, please use author, date format in your response. What role do foreign vs. U.S. studies play in your considerations? In addition, are any recent epidemiological studies, not published in the draft PM CD relevant to your judgments? If so, please discuss them.** **Discuss the relative strengths and weaknesses of the time-series epidemiology studies in forming your judgments about the short-term impact of a change in ambient $PM_{2.5}$ on non-accidental, premature mortality.**
A	The first set of studies he discussed were PM10 studies and included the APHEA2 study of 29 European cities (Katsouyanni, 2003), the body of evidence from single-city studies, and to a lesser extent the NMMAPS reanalysis. He placed greater weight on the single city studies than on NMMAPS. He argued that NMMAPS' use of a common methodology/set of assumptions across cities, while statistically appealing, might not be the best approach for estimating effects in individual cities, where weather and seasonal patterns might differ substantially and where optimization for particular cities would be warranted. NMMAPS on the other hand uses the same LOESS smoothers, spans and degrees of freedom for each smoother. He was concerned that they only were able to look at every 6th day data so they could not look at cumulative impacts. Expert A found the evidence for distributed lag effects compelling, noting that several (4-5) studies have been consistent in showing mortality effects of two to three times the single day effect. He cited in particular, the Schwartz (2000) (Schwartz J (2000) and Zanoebetti and Schwartz in 2003 HEI Time Series Reanalysis Report showing a doubling of the mortality effect related to PM10 when the analysis was extended out 30-40 days. He next discussed two PM2.5 multi-city studies by Burnett and Goldberg (2003) and Schwartz (2003). Expert A noted that both studies have limitations for extrapolation to a mortality effect for the whole U.S.; they are not representative of all cities and regions in the U.S. for example, lacking cities where people spend more time outdoors or use more air conditioning. (These considerations led him to generate a greater confidence intervals than in the Schwartz et al (1996) study.)
B	• NMMAPS despite it using PM10. • PM10 - coarse particles are bad for the lungs • PM2.5 - fine particles have more potential for vascular and cardiovascular toxicity as they are able to penetrate deeper. • NMMAPS is the strongest, most accurate study because it analyses numerous cities using a consistent methodology Are any recent epidemiological studies, not published in the fourth external review draft PM CD relevant to your judgments and if so, please discuss them? • Ozone study focusing on the lung growth in children • NYU Group trying to do a sub-chronic animal study, however lots of extrapolation

	is required • Extrapolation from animal to human and from short-term to long-term • National Academy is issuing a report looking at the progress of PM over the last five years • The animal and human studies increased the plausibility of acute toxicity
C	• He likes the NMMAPS study that used PM10 as an indicator. The study was "well-designed, well-executed, well-analyzed. "I am not as convinced [though] that it was well interpreted. I have some quarrels with it, particularly with the Bayesian analysis performed on it. But I think the study does give us some information in a sense in terms of $PM_{2.5}$." He does have reservations about the study, but due to the relevant dearth of PM_{10} studies, it's the gold standard for PM_{10}. • He also mentioned the Burnett 8- cities study and the 6 Cities time-series study. • He thinks the best individual city time series studies ar ethe ones Molgovkar did in terms of Chicago and L.A. because they use daily or near-daily measurements. Most studies are constrained by every six day monitoring day in terms of particulates.
D	• NMMAPS study • APHEA
E	• He thinks studies that only look at one city are not useful. Among other reasons, he thinks there is selection bias in the studies that get published (only studies that find associations get published). However, he thinks studies that use a consistent methodology to look at a large number of studies are useful. • The two most useful studies are the APHEA and NMMAPS projects (NMMAPS influences him the most). He also thinks the 8-Cities study is useful. Are any recent epidemiological studies, not published in the fourth external review draft PM CD relevant to your judgments and if so, please discuss them? • The London Smog of 1952 plays a significant role in his decision-making process. He thinks that the smog provides compelling evidence that higher levels of particles cause people to die.

E2	**Discuss the relative strengths and weaknesses of the time-series epidemiology studies in forming your judgments about the short-term impact of a change in ambient $PM_{2.5}$ on non-accidental, premature mortality?**
A	• It is important for studies to use a well specified time unit and to accurately deal with harvesting.
B	• Studies that look across multiple cities, allow for more confidence in the data. • This methodology removes the confounders of habits, previous exposure, etc. • Studies should not look to match the results with a lag timeframe that creates the largest effect. After 40 or so studies, it should be clear what the lag timeframe is. Therefore the studies should seek to determine whether the exposure lag fits within the constructed time frame • One result of this "fishing expedition" type research, is that it effects the relationship between PM and mortality in a positive direction; overestimation. • Future studies will and need to look more carefully at other pollutants (alternate explainers) • Samet, APHEA, and Moolgavkar looked at co-pollutants..
C	• For the most part, Expert C doesn't think individual city studies are very useful. • Ideally, time series studies should have multiple cities, longer time period, daily measurements of multiple pollutants, multiple indices for PM, good characterization of the weather. Heating and cooling practices (air conditioning etc) should also be controlled for.
D	• Time series studies, due to the nature of the smoothness, takes out any longer-cycle information • Single-city studies are not as informative as multi-city studies • Too much dependence on the characteristics of that individual city • The NMMAPS study did not use data for everyday which limited the ability to distribute lag approaches • A major issue in time-series studies is understanding the underlying phenomenon that are taking place, and how what is taking place biomedically effects the results
E	• It is difficult to accurately capture the effects of time lags. It's also difficult to capture seasonal effects, temperature effects, and air pollution effects. The seasonal effect is 10 times bigger than the air pollution effect, so it's extremely important to accurately incorporate it into your model.

E3 and E4	**Can you tell us how likely you think it is it that there is a causal relationship between short-term exposure to $PM_{2.5}$ and premature mortality?** **Please provide the quantitative range you associated with the qualitative term that you chose (e.g., if you chose "somewhat likely," does this mean more that 50% chance or 60 to 75% chance?)** **What is the underlying rationale for your response?**
A	He believed the likelihood of a causal relationship between short-term exposures to $PM_{2.5}$ and mortality to be slightly higher (90-95 percent, best estimate – 93 percent). Both the plausibly of the mechanistic data and the greater numbers of time-series studies, replicated in many places, lent substantial support to his judgment.
B	Expert B felt there was a somewhat stronger basis for a causal connection between short-term spikes in $PM_{2.5}$ and mortality. He believed that it was "somewhat likely" that there could be a causal relationship, corresponding to a probability of about 65 to 80 percent. The Peters et al. (2001a) defibrillator study was influential in this regard.
C	Expert C had the same concerns as he expressed for the long-term question about applying a likelihood of causality to the whole range of PM2.5 concentrations in this question. He placed causality between "somewhat unlikely and "somewhat likely," or about 50 percent, given concerns about having to make the statement for the whole US and "substantial" doubt about the extent to which weather-related variables (e.g., temperature, humidity) have been appropriately dealt with in the time-series studies. He thought that a major finding of the Health Effects Institute (HEI) reanalysis of the time-series studies was that weather, and its potential interactions with co-pollutants, had been accounted for in a "highly uncertain" manner.
D	Expert D said that he would categorize it as "somewhat likely or highly likely" or about 80-90%. There is a much greater wealth of complete data sets for the studies than for the cohort studies. Also, he does not think that these studies are as limited by the exposure data as the Six-City and ACS studies.
E	In discussions of the likelihood that short-term $PM_{2.5}$ exposure causes premature mortality, Expert E again chose the category "likely" with a best estimate of 95 percent and a range between 80 and 98 percent. Several factors influenced the high likelihood he placed on this relationship: historical evidence from the London smog episode; the large body of evidence from the time-series literature; and the robustness of the NMMAPS effects estimates despite rigorous control for numerous factors that have been suggested as possible explanations for the results.

F1 And F2	**What proportion (i.e. X percent or X-XX (min,max) percent) of the mortality effects identified in the cohort studies do you believe represents short-term exposure effects?** **What additional mortality impact (i.e. X percent more or X-XX (min,max) percent, etc.) due to short-term exposures is not captured by the mortality impact identified in the cohort studies, if any?**
A	Expert A offered the following conceptual model for considering what fraction of the deaths captured in the cohort studies might be considered to be the result of short-term, rather than long-term exposures. His basic premise was that the "short-term" deaths captured in the cohort studies are the non-"harvested" deaths, since "harvested" deaths, which involve little change in life expectancy, are unlikely to be captured in the cohort studies. On the basis of the Schwartz (2000c, 2001) studies showing that COPD deaths are more likely to be harvested than cardiovascular deaths, he assumed that 75 percent of the harvested deaths are COPD-related, with 25 percent related to other causes. He then estimated the percent of total non-accidental mortality due to COPD and cardiovascular causes in order to estimate the weighted average percent that are non-harvested (and thus likely to appear in the cohort studies). Based on NCHS data, roughly 90 percent of all cardiopulmonary, non-cancer deaths (this was the most important endpoint for cohort studies) are cardiovascular. Chronic respiratory disease accounts for most of the other 10 percent. Thus, he calculated that roughly 30 percent of the deaths are harvested (0.1 * .75+ .9*.25 = .30). If for a time-series effect, there is roughly a 1 percent increase in mortality per one-day increase of 10 $\mu g/m^3$ of $PM_{2.5}$, then there is a roughly 0.70 percent increase due to non-harvested deaths. Assuming a cohort effect of approximately a 6 percent increase in mortality per 10 μg/m3 increase in annual average exposures to $PM_{2.5}$, those non-harvested deaths represent about 12 percent (0.7/6) of the deaths captured in the cohort studies. If we assume a distributed lag model, the number of deaths from short-term exposures may be doubled leading to 24 percent being the proportion of deaths in the cohort studies that are the result of short term exposures. Under these assumptions, 30 percent of the time-series effect would not be captured by the cohort studies.
B	Expert B felt that the Kunzli et al. (2001) Venn diagrams and categories were useful conceptual constructs. However, consistent with his views on the likelihood of a causal relationship between long-term exposures and increased mortality, he was less certain about the size of the category of deaths (B) defined by Kunzli in which long-term air pollution exposures contributes to chronic frailty but the individual dies from something else. In general, he felt that people are more likely to die as a result of acute exposures to air pollution. "… [W]hen you're excluding accidental deaths, it's unusual that … some random person … is going to die the next day or the next week from air pollution. It's hard --- assuming that there is any relationship to air pollution---to

	say that it wasn't an acute effect. Most people are going die from cardiac deaths [and behind that, respiratory effects]. He estimated that 50 to as much as 85 percent of the cohort effects might be accounted for by short-term air pollution exposures. He estimated that only "a small number", maybe 10 percent, of the time-series effect was not picked up by the cohort studies.
C	Expert C found the Kunzli et al. (2001) paper a useful starting point although he wanted to see mortality broken out by cause of death with cardio-pulmonary deaths separated from cancer-related deaths (which he considered tentative). He ultimately did not feel that he had the data he would really like in order to answer this question, so he would be "somewhat guessing." He would like to see an appropriate comparison of the time-series and cohort results for the same data set (i.e. Six Cities). He also noted that his response to the question should really depend on the typical background $PM_{2.5}$ levels in the cities (i.e. the percentage of deaths due to short-term exposures might be higher in cities with higher background levels). Ultimately he estimated that the percent of the cohort effect due to short-term effects could be up to 50 percent. Expert C thought the percent of the time-series effect that would not be picked up by the cohort studies would be small. He estimated a 50 percent chance that it would be zero and 50 percent chance that it would be some small number, maybe 5-10 percent.
D	Expert D had mixed views on the value of the Kunzli (2001) framework. He said initially that the Kunzli framework is a "fine conceptual model", a two-compartment model in which air pollution might influence the rate at which you move into a frail pool and the rate at which you deplete the frail pool by dying. The problems arise when you have to think about a) "whether the underlying processes are such that the model is a reasonable reflection of what mechanisms are available to move you from healthy to frail (i.e. does air pollution contributed to chronic disease?) and b) once you are sick enough to be at risk of dying, does air pollution influence the timing of death?" He argued however that "we do not have and probably never will have cohort studies that truly go on for the long-term and reflect exposures across the life course where you can really separate out the effects of longer-term exposures versus short term." Ultimately, however, he seemed to argue against this two-compartment model. He viewed the processes by which individuals move to the frail pool as a result of pollution and the pollution-dependent timing of when individuals exit the frail pool to be different phenomena. "If you were to stop pollution today, then you would expect that whatever loss of life expectancy from earlier death, short-term would be removed so there would be some gain in life expectancy. But the longer-term, from the change in size of the frail pool, would take a long time to go away. .. [A]t least in the Kunzli model they're on different time domains and they should be overlapping. You could argue that they would overlap to the extent that short-term exposure and long-term exposure are going to be correlated so that one will pick up some of the other effect. I guess I worry most about the long term picking up some of the short term." Ultimately, he did not think that

	would be very important because "in the U.S. for the last 30 years or so, the way pollution has changed over that time, [means that there is] probably not likely to be a very high correlation between the long-term averages and the short-term variation. He argued, therefore, that there should be little overlap between the effects measured by the cohort and time-series studies. He estimated a small number, less than 10 percent of cohort effect would be attributable to a time-series effect, and that most of the time-series effect (90%) would be found outside the cohort effect.
E	Expert E thought the Kunzli et al. (2001) paper had provided important structure to what had been a very confused scientific discussion about the differences between cohort and time series, but he did want to point out that it is an oversimplification. People are not just frail or not frail but are part of a continuous distribution of degree of frailty. For individuals at any given point in time, their state of frailty is a cumulative function of their whole life history (including risk factors other than air pollution). He essentially laid out two possible models: one in which we have a frail subset of individuals who die as result of acute effects due to short-term exposure proximal (1-2 week time frame) to their death, and the other in which we have an increasing distribution of risk across a population (over time?). He argued for the latter model on the basis of research showing the same relative effects across multiple age groups, not just in the over 65 group which might suggest support for the very frail subset model. He noted that research has not shown a big effect modification by age. He saw the first question as asking "If we take our distributed lags model, which takes the whole lifetime of exposure and takes the total effect summed up over all the lifetime of exposure, what fraction of that total effect is the result of exposures that have occurred in the last week?" His response was that it would be about 10-20 percent. "The time series effect picks up the acute proximal effect, which is partially offset by what people call 'harvesting'. That is to say there are some people who would have died soon who die now, and so you do tend do see a little bit of a decrease in mortality subsequent to big air pollution events because there is a frail population that has been killed." He thinks there is some evidence of harvesting but that it does not explain away the time series effect. It might represent 10 to 20 percent of the time series effect. In other words, he believes that the cohort studies pick up about 80 percent of the time-series effect, which represents about 10-20 percent of the total cohort effect. The cohort studies miss about 20 percent of the time-series effect, which is probably due to harvesting.

G1	**Discuss for a moment your concept of a threshold for health effects related to $PM_{2.5}$?** - **in theory (e.g. individual, population thresholds, other factors)** - **in practice (e.g. in the context of epidemiological or other scientific studies)**
A	• "In general, the theory would be that on an individual level there are thresholds...but on a population level it would not be surprising to fail to detect a population level threshold, because you can always find someone who is exquisitely sensitive." • Studies show that there seems to be a linear/log-linear relationship with little evidence of a threshold. "There's no real evidence of leveling off at the lower levels."
B	• PM exposure, in theory, should exhibit a threshold level • The dose-response relationship should not go right through zero • Because thresholds can not be factored out from all of the noise, it does not dissuade Expert A from thinking biologically that thresholds do exist In practice: • The analyses done to date suggest PM may fall into a linear, no-threshold type of response, but biologically does not think that's true. • Ozone responses were not linear through zero and ozone standard was much more based on clinical studies. PM responses are based on epidemiological studies.
C	• He thinks that the risks associated with air pollution vary dramatically by subgroup. • Each subgroup may have a different relative risk and threshold. When you aggregate all the subgroups, it looks like there's no threshold when in reality there may very well be a threshold. This threshold is just very difficult to tease out statistically with available data.
D	• There would be some level below which no increased risk is observed (i.e. a threshold) In practice: • Few studies are precise enough to show the existence of a threshold, and few data sets are robust enough to generally tell us that there is or is not a threshold. • There is not evidence to think that there is a threshold for the kinds of carcinogens in the urban air mix.
E	• Generally speaking, almost all diseases have some threshold level of exposure/risk etc. But the precise threshold level is different for every person, so it's difficult to find a population threshold level for even well studied diseases…. As a result, Expert E does not think there is a population threshold level for PM.

G2	**In your judgment, what information does the existing literature provide on population thresholds for $PM_{2.5}$-related mortality at current ambient $PM_{2.5}$ concentrations?** - **Cohort studies?** - **Time Series studies?**
A	Cohort Studies? • Studies show that there seems to be a linear/log-linear relationship with little evidence of a threshold. "There's no real evidence of leveling off at the lower levels." • He cites Six Cities, Krewski, ACS, and Pope (2002). Time-series studies? • No evidence of a threshold. There are a variety of PM levels in the time series literature, which allows you to implicitly analyze whether there is a threshold by examining whether all the studies find an effect of PM on mortality. In fact, virtually all the studies find some effect of PM on mortality (even down to 2 micrograms), with the magnitude of the effect actually staying relatively constant. Other disciplines or study types? Please identify • The literature finds some evidence of a threshold for NO_x and Ozone… But, "even in those studies, if you found enough people you probably could find someone to respond."
B	Cohort studies? • Unsure, but the Six Cities study might exhibit a threshold effect. Time-series studies? • Unsure, but there would not be much of a threshold in a time-series study. Other disciplines or study types? Please identify • Animal studies are effective in teaching about thresholds.
C	• "I am of the opinion there are 'practical thresholds' such that when we get down into some of the levels that people have identified as being of regulatory concern, I have no confidence in the calculation of an excess level of risk." Cohort studies? • The sample size in the Six Cities study isn't large enough to offer any information regarding thresholds. Time-series studies? • He thinks the Schwartz study that defined the lowest level of risk at two micrograms is not credible. Two micrograms is lower than the background level of particulate matter in the air. • "When you're looking at cities with populations in excess of a million, and you're not able to detect a statistically significant [relationship between PM and mortality], then I think if you're going to present that data in terms of excess mortality, I think you have a responsibility to put the footnote that we were unable to detect an effect in this city based on the data that were here…. That's a practical threshold."
D	Time-series studies?

	• We have enough cities and enough studies that we are getting some information about the dose-response relationship - (e.g. Mike Daniels' and Joel's meta-smoothing paper) Other disciplines or study types? Please identify • Radon study suggests there is no reason to think of thresholds
E	Cohort studies? • He doesn't think that any study supports the notion of a population threshold level.

G3	**Do you think it is likely that thresholds for $PM_{2.5}$-related premature mortality for the population** **a) exist?** **-for long-term exposures** **-for short-term exposures** **b) that are detectable?** **-for long-term exposures** **-for short-term exposures**
A	a) exist? • -for long-term exposures **No** • -for short-term exposures **No** b) that are detectable? • -for long-term exposures **No** • -for short-term exposures **No**
B	a) exist? • -for long-term exposures **Yes** • -for short-term exposures **Yes** b) that are detectable? • -for long-term exposures **Yes** • -for short-term exposures **Yes**
C	a) exist? • -for long-term exposures **Yes** • -for short-term exposures **Yes** b) that are detectable? • -for long-term exposures **Don't know, statistics are very shaky at very low exposure levels.** • -for short-term exposures **Don't know**
D	a) exist? • -for long-term exposures **Possible** • -for short-term exposures **Possible** b) that are detectable? • -for long-term exposures **Don't Know** • -for short-term exposures **No**
E	a) exist? • -for long-term exposures **No** • -for short-term exposures **No** b) that are detectable? • -for long-term exposures **No** • -for short-term exposures **No**

G4	**Does the information available allow selection of a particular threshold level or range of levels for total non-accidental mortality for the population? If yes, what information is most important for you in determining such a level?**
A	• For the effects of short-term exposure? **No** • For the effects of long-term exposure? **No**
B	• For the effects of short-term exposure? **No** • For the effects of long-term exposure? **No**
C	• For the effects of short-term exposure? **No** • For the effects of long-term exposure? **No**
D	• For the effects of short-term exposure? **No** • For the effects of long-term exposure? **No**
E	• For the effects of short-term exposure? **No** • For the effects of long-term exposure? **No**

G5	**If you don't think it is likely that population thresholds exist for premature mortality at current ambient $PM_{2.5}$ concentrations, why not?**
A	• There will always be some particularly sensitive people who respond to PM at any level.
B	
C	
D	
E	• "Because I don't think that individuals have strong thresholds. But even if I believed that individuals have strong thresholds, I do not think those thresholds are common across either biological systems or people (i.e., heterogeneity exists across populations)."

H1	**Please discuss what the scientific evidence leads you to believe about the true, but unknown C-R function might be (mathematical form, existence of thresholds, etc.) and over what range.**
A	He thinks that the bulk of the evidence suggests that there is a log-liner or linear relationship between total non-accidental, premature mortality and exposures to $PM_{2.5}$.
B	• Unsure what the relationship is, however strongly believes that the relationship does not pass through zero. • "whether we're looking at acute or long-term effects, it's hard for me to believe that it goes all the way to zero …[that] there's no level at which [a person] can be outdoors that doesn't put them at risk" • Beyond a certain threshold, there is clearly a dose relationship, although it is hard to know whether it is linear when various site-specific factors are taken into account. • Another factor making it hard to determine if a linear relationship exists is the fact that the components of the PM may be changing; therefore it is difficult to assume an increase in PM of X will equal an effect of a coefficient multiplied by X .
C	• "The shape of the concentration-response function is dictated primarily by the mathematical statistical methods used to derive the association between the indicator and the excess risk. It is, in my opinion, not necessarily well-grounded in any biological theory… It is not the result of our having rigorously looked at alternative methods." • He thinks that EPA should make more of the epidemiological data available to researchers so they can analyze alternative model specifications.
D	• Data sets are not robust enough in the long-term to be able to distinguish between linear and curvilinear relationships. In the short-term, however, linear seems reasonable (p.36) • The risk seems to increase with rising PM
E	• He thinks that the C-R function is probably monotonic, without a hard threshold. That's the only piece of the C-R Function puzzle to which he attaches a high degree of certainty. ("Because I use a log-linear model doesn't mean I think it's log-linear. It just means I think it's probably monotonic, without a hard threshold.")

H2	Please identify the studies and/or evidence that you are relying on?
A	• Doesn't mention any specific studies.
B	• Six Cities • Scott Letzke at Harvard ??
C	• Does not think any really rigorous studies have been conducted that examine alternative specifications.
D	• The ACS (long-term) data would be just as likely to fit a linear and non-linear dose-response function
E	• No evidence that any functional form or population risk level is "true"

H3	Please answer the same questions but in regards the effects of short-term exposures to $PM_{2.5}$.
A	• Because there have been many more studies conducted of the short term effects of exposures to $PM_{2.5}$ than the long-term effects, he is more confident that there is a log-linear or linear relationship between total non-accidental, premature mortality and short term exposures to $PM_{2.5}$.
B	
C	
D	• NMMAPS (short-term) data is consistent with a log-linear relationship
E	

I1	**Please discuss your views on the length of the cessation lag, (i.e., time period between a reduction in ambient $PM_{2.5}$ concentrations and reductions in non-accidental mortality).**
A	• "Some long-term deaths are related to short-term exposure. So that percent, whatever it is, you expect once the short-term exposure stops you would see immediate benefits. So the cessation lag would be very, very short… • For long-term deaths, some benefits would occur right away, and the rest of the benefits would be distributed over a 25-30 year time frame. Expert a declined to give a quantitative estimate of the distribution of the lag over that period. • The bulk of the mortality (90%) is due to cardiovascular disease, so this is the most important endpoint to understand. He thinks roughly half of cardiovascular benefits occur within 5 years.
B	• See E2 • Some of the variability in lag seen in studies may be accounted for by differences in diseases. For example, maybe cardiovascular effects occur with a lag of one day and respiratory effects would occur with three or four day lag • For end of point inflammation, it would be reasonably quick (within one year) between when an individual or population will have a reduction in exposure and when the benefits of that reduction are visible • With an ongoing inflammatory process, if the stimulus is reduced, a fairly rapid biologic response results.
C	• He thinks it's going to be over a period of years, but there really isn't any data to evaluate cessation lags at relatively low PM levels (8-20 micrograms)
D	• Nature does not create these arbitrary lag periods • There is not sufficient data to explore this issue • If we think there are long-term chronic effects of air pollution contributing to an underlying progression of disease, we will have to wait possibly several generations to see a reduction

E	• Cardiovascular risk: 1-5 years
	• Lung cancer risk: Decades
	• COPD and permanent lung dysfunction: 10 years
	• Overall cessation lag for total attributable years lost due to exposure:
	  • 10 percent from pollution over last two days
	  • 20 percent from pollution over last two weeks
	  • 50 percent from pollution over past two years
	  • 100 percent from pollution over past twenty years

I2	What studies and/or evidence do you rely on most strongly for these judgments?
A	• Toxicology studies; Heart study by Glantz (other first author, Loveland?)
B	• National Cancer Institute's study on smoking states that it takes 40 years (assuming a 1/2 pack a day for 10 or 15 years) before the risk of lung cancer for a smoker goes back to the level of a non-smoker
C	
D	• DOE, 1998, • Given current resources, the smoking studies are one of the best models to look at latency period and cessation lag • Monongraph series, National Cancer Institute, and Monograph 8
E	

J1	**What are your views concerning the relative contributions of individual $PM_{2.5}$ components (such as sulfates, nitrates, metals, organics, etc) to the observed premature mortality that has been associated with total $PM_{2.5}$ gravimetric mass?**
A	"Short term studies in general fail to indicate that there are notable differences between the different components."
B	• Expert B does not have an opinion as to which components are most important • There is no strong evidence that would put one component ahead of the other in terms of contribution. • A question that will emerge is "Are different components responsible for different diseases?" For example ultrafines are not going to easily explain lung respiratory effects, but they may explain cardiovascular effects. • Sulfate particulate that sits in lungs may put one at more risk for pulmonary disease; metals could interfere with conduction if they get into the bloodstream. • Ultrafine particles are a form of pollutant that would be plausible to link with cardiovascular effects. • Organics have interesting data looking at the stimulation of reactive oxygen species and the relationship with asthma and diesel..
C	• Not very much high-quality data or analysis regarding the effects of different PM components/sources. • We know that metals do bad things to cell and tissues at high concentrations. • We also know that high levels of certain organics and PAH's do bad things. • There is some evidence (Schlesinger) that sulfates may not be particularly bad.
D	• There is not good evidence to talk about the differences in PM components as indicated from Expert D's Report #4; some good leads but no answers • Some particles are polycyclic rich, and contain some carcinogens. Radionuclides in power plant emissions that are alpha emitters may contribute to cancer risk
E	• "I don't have the foggiest idea whether it's one component or another, and if you were to ask me what component you think causes people to die, I just say I don't know."

J2	Do your judgments on this topic vary between long-term and short-term exposures?
A	
B	• No
C	• Most studies are focused on short-term effects. There are very few high quality studies of long-term effects of different components.
D	• This is a very information-demanding question, and currently there is not enough data to answer this
E	• No, they don't vary.

J3	**What are your views concerning the relative contributions of $PM_{2.5}$ components from different source types (for example gasoline powered mobile sources, diesels, utilities, industrial sources, bioaerosols, windblown dust) to the observed premature mortality that has been associated with total $PM_{2.5}$ in the literature?**
A	• Some studies have found that emissions from mobile combustion sources tend to be a little more toxic. Also, elemental carbon seems to be more toxic than $PM_{2.5}$. • The effects of sulfate and PM are correlated. Not clear if they are independent. **Please discuss evidence influential in informing your views:** • Laden (2000); Schwartz and Laden (2003) both indicate that transportation sources are more toxic. • To a lesser extent: Oskynak and Thurnston (1987) and Turis and Mars study in Phoenix • The epidemiological literature does not provide very much evidence regarding the differential effects of sulfates and nitrates.
B	• Motor vehicles, diesel and non-diesel, are probably the most important source • Diesel engine emissions have changed dramatically over the past few years. The combustion now generates huge amount of ultrafine particles, but little to no mass. • If the utilities were more responsible, there would be a bigger problem in the East than in the West. **Please discuss evidence influential in informing your views:** • Regarding source types, the time-series studies where the same effects are found across the country and Canada are most influential. The one common source is automobiles.. • The Freunds California organic in vitro study. • Andy Sachs and Dia Sanchez organic diesel study.
C	• One series of studies tends to point toward mobile sources and roadways, but I think what we have is a very difficult kind of a problem in terms of trying to get a hold on it, because $PM_{2.5}$ is complex material coming from multiple sources…" Windblown dust could also be a factor. "I think these studies go both ways, but I would argue that by and large they show that crustal materials are probably not particularly potent."
D	• The Laden study that found a difference between mobile sources and non-mobile source is one that is very exploratory, but it is not enough to be making decisions based on it • Animal studies provide leads, no answers.
E	• "I don't know."

J4	**Can you identify certain components or sources that are relatively more important in terms of the magnitude and shape of C-R functions for total non-accidental premature mortality?** **Please discuss those studies and/or evidence that are most influential in informing your views on this topic.**
A	No
B	No • EPRI argues effectively, but not without issues, that sulfates are not an important component. (These issues are problems in terms of what the study was able to measure). • The NMMAPS studies, by showing the Northeast has a steeper dose-response curve, might suggest that power plant emissions are important, although some would argue that between Boston and Washington D.C. it is all one city with lots of people and automobiles.
C	The Schlesinger paper implies that sulfates are not a significant contributor to premature mortality. This implies that reducing SO2 emissions from power plants may not yield large marginal benefits.
D	
E	No

K1	**What influence, if any, do concerns and/or questions about exposure misclassification or exposure error have on your judgments concerning the form, magnitude and uncertainty in the C-R functions for $PM_{2.5}$-related premature mortality?**
A	Long-term exposures? • Period of exposure, age of initial exposure, and how well the monitors are representing people living in those areas. Short-term exposures? • The location of the monitors is important. If the measurement is too low the relative risk is going to be too high.
B	• Expert B is unsure if it is possible to determine the true relationship between PM and premature mortality without knowing what people have been exposed to throughout their life. • Studies have done a good job of understanding other factors which may affect the relationship, but are still unable to control for outside factors such as: • Occupational exposure, education, tobacco, obesity ,alcohol, diet • Exposure misclassification does not bias the data in one direction or another. In fact, some have argued that misclassification actually results in an underestimate of the risk. Exposure misclassification simply creates great uncertainty as to what the real exposure is). • Modeling is not what is going to resolve uncertainty. It is not that the models have been conducted poorly, it is that the models only corrects for some confounders..
C	
D	• Bottom line: we are probably not biasing anything upwards • It seems very doubtful, both in the short and long-term that exposure error could be leading us to upwardly bias estimates There are single time point classification issues, influenced by patterns of concentration in a town and residencies of the person, as well as spatial misclassification.
E	• Main sources of error: • Individuals who die and we don't know their individual average exposure (we use average pop. exposure as surrogate, but that's not quite right) • Errors probably lead to underestimate of PM effect.

K2	What evidence is most important to you in this regard?
A	
B	
C	
D	• Bob Stauffer
E	• He also referred to a paper “4 years ago” that was published in Environmental Health Perspectives.

L1	**What are your views on the impact of potential confounding and effect modification in the $PM_{2.5}$ -- premature mortality relationship within the context of the cohort studies conducted to date (e.g., co-pollutants, weather/climatic factors, population characteristics)? Specifically,** **What are the major sources of confounding and/or effect modification?** **How would you characterize the impact of each source in terms of bias? Of uncertainty?** **What evidence or studies are most influential in informing your views on this topic?**
A	• There is some confounding with other pollutants. But the main confounding pollutant is actually sulfates and since sulfates are part of particles, it shouldn't be a big problem (there's a particle effect either way). • Socioeconomic effects (including stress) are a bigger potential concern. One possibility is that the effect SO_2 is correlated with some socioeconomic factor that existing studies are not capturing. • Smoking and meteorological factors are other obvious confounding variables. How would you characterize the impact of each source (bias, uncertainty) • Weather, stress, socioeconomic variables are all likely to be sources of bias and/or uncertainty. What evidence or studies are most influential in informing your views on this topic? • The statistical results of the existing literature.
B	• Studies may overestimate the contribution of particulate matter towards mortality What are the major sources of confounding and/or effect modification? • Co-pollutants • Climatic factors • Education • Diet How would you characterize the impact of each source (bias, uncertainty) • Most sources would be considered uncertainties • Socioeconomic status could be a bias What evidence or studies are most influential in informing your views? • The ACS study suggests education is an important variable. • Stephaine Shorr in Boston looking at obesity in rats. • Dockery's work on diet and responsiveness to air pollution.
C	Long-term exposures? • Co-pollutants

	• Population characteristics: Smoking, occupation, diet, obesity, diabetes • No study has successfully controlled for all of these potential confounders. Short-term exposures? • Confounding by co-pollutants, weather, and climatic factors all tie together back into exposure misclassification. • "The thing they ought to do in both of these areas, put it in big letters, is population size, duration of study, number of pollutants measured."
D	He felt that the potential for residual confounding, by changes in smoking patterns over time in particular, is still a source of concern. Smoking patterns vary geographically as do patterns of cessation and air pollution. The incremental increases in mortality associated with air pollution are so small that it would not take much residual confounding to introduce associations of that magnitude. The reanalysis of the Six Cities data, taking into account time dependent changes in smoking, was somewhat reassuring as they did not find a substantial change in the effect estimate. Regarding general and vague claims of possible residual confounding that are levied against epidemiologic studies, Expert D stated that such claims are ill-informed (at best). They do not advance our understanding of the issues; a clear and systematic exploration of the role of confounding, effect modification by other pollutants, etc is both possible and preferable. • The major problems of confounding have been set aside by the co-pollutants. • The major question is not of confounding or effect modification, but rather causal pathway relationships of co-pollutants. What are the major sources of confounding and/or effect modification? • Smoking • Diet, obesity, level of activity How would you characterize the impact of each source (bias, uncertainty) • What evidence or studies are most influential in informing your views on this topic? • The ACS study has potential for confounding or modification of the extent of exposure, although it is difficult to determine which way the effects operate
E	• Smoking, socioeconomic status, general level of health (stress induced frailty, poor nutrition, poor exercise, obesity, general level of health). • Cultural differences that have to do with attention to health and preventive services. • There could also be some unidentified co-variation between pollution levels and some aspect of poor neighborhoods that is causing pollution to disproportionately affect poor people. What evidence or studies are most influential in informing your views on this topic? • ASC and Six Cities studies and logic

L2	**What are your views on the impact of potential confounding and effect modification in the $PM_{2.5}$ -- premature mortality relationship within the context of time-series studies (e.g., co-pollutants, weather/climatic factors, population characteristics)? Specifically,** **What are the major sources of confounding and/or effect modification?** **How would you characterize the impact of each source individually in terms of bias? On uncertainty?** **What evidence or studies are most influential in informing your views on this topic?**
A	What are the major sources of confounding and/or effect modification? • Seasonality and weather. • These have been controlled for pretty well, but there is still some residual uncertainty. • There's some evidence that air conditioning is a confounder. He notes a study by Nicole Jansen and a study by George Thurston on 8-cities. Both studies found an air conditioning effect. How would you characterize the impact of each source (bias, uncertainty) • He didn't give a precise quantitative estimate, but it seemed like he thought the existing estimates are relatively robust.
B	
C	•
D	• We are not being mislead by confounding What are the major sources of confounding and/or effect modification? • Weather, pollution, population characteristics What evidence or studies are most influential in informing your views on this topic? • NMMAPS explores the effect modification in the short-term in a robust way
E	What are the major sources of confounding and/or effect modification? • Seasonal variation and mortality. Seasonal variation comes from two main sources: • Temperature • Changing flora of infectious diseases • Generally speaking, there tend to be more deaths in the winter. • There also might some simultaneity—if people think air pollution is bad, they stay indoors. This results in downward bias in the effect of high air pollution levels.

M1	**If we told you that the $PM_{2.5}$ mixture you were considering was much higher in sulfates than you had originally assumed, how would your judgment about the C-R relationship have changed?**
A	• No change
B	• Stay the same.
C	missing
D	• Don't know
E	• No change

M2	**If we told you that the $PM_{2.5}$ mixture you were considering was much higher in black carbon (soot) associated with diesel emissions than you had originally assumed, how would your judgment about the C-R relationship have changed?**
A	• Probably higher. Maybe 1.5-2 times higher if it was all black carbon
B	• Stay the same.
C	• Missing – To be completed
D	• Don't know
E	• No change.

M3	**If we had told you that the $PM_{2.5}$ mixture you were considering was much higher in nitrates than you had originally assumed, how would your judgment about the C-R relationship have changed?**
A	• No change.
B	• Go down.
C	• missing
D	• Don't know
E	• No change.

M4	**If we had told you that the $PM_{2.5}$ mixture you were considering was much higher in organics than you had originally assumed, how would your judgment about the C-R relationship have changed?**
A	• No change.
B	• Stay the same.
C	• missing
D	• Don't know.
E	• No change.

M5	**If we had told you that the $PM_{2.5}$ mixture you were considering was much higher in ultra fine particles than you had originally assumed, how would your judgment about the C-R relationship distribution have changed?**
A	• No change.
B	• Increase or stay the same.
C	• missing
D	• Don't know
E	• No change.

M6	**If we had told you that the $PM_{2.5}$ mixture you were considering was much higher in transition metals than you had originally assumed, how would your judgment about the C-R relationship distribution have changed?**
A	• No change.
B	• Stay the same.
C	missing
D	• Don't know
E	• No change.

M7	**Would changing the $PM_{2.5}$ mixture in any other way have substantially changed your judgment about the C-R relationship distribution? If so, how and why?**
A	• Black carbon is the only particle for which there is evidence of a differential effect.
B	• No
C	• missing
D	• Don't know.
E	• No change.

Appendix D

Summary of Experts' Judgments about the Percent Increase in Total Non-Accidental Mortality Associated with Long- and Short-term Exposures to $PM_{2.5}$

Table D-1
Percent Increase in Annual Non-Accidental Mortality from a 1 μg/m^3 Increase in Long-term Exposure to $PM_{2.5}$

Percentiles	Expert				
	A	B[a]	C[b]	D	E
95th	0.9	0.86	0.28	1	1.6
75th	.7	0.29	0.16	0.6	1.2
50th	.5	0	0	0.3	0.7
25th	.275	0	0	0.1	0.4
5th	0	0	0	0	0
Minimum	0	0	0	0	0
Maximum	1	1.14	0.37	2	3
Mean (Estimated)[c]	0.48	0.20	0.08	0.41	0.81

a. Assumed a threshold (uncertain, range between 4 and 15 μg/m^3, with a modal value at 12 μg/m^3) and a log-linear relationship above the threshold (uncertainty distribution: min-0.0, 5th-0.0, 25th-0.0, 50th-0.0, 75th-0.5, 95th-1.5, max.- 2). The table shows the "effective" distribution for the full range estimated using Monte Carlo simulation (see text for full discussion of methodology).

b. Provided different distributions for different points in the range, 8-20 μg/m^3 (See Table D-2). This is the 'effective' distribution for the full range, estimated using Monte Carlo simulation (see text for full discussion of methodology).

c. The mean is estimated from by sampling from the distributions using Monte Carlo simulation (see text for full discussion of methodology). No mean values were elicited from the experts.

Table D-2
Percent Increase in Annual Non-Accidental Mortality from a 1 μg/m^3 Increase in Long-term Exposure to $PM_{2.5}$
Expert C Only

Percentiles	8 μg/m^3	10 μg/m^3	15 μg/m^3	20 μg/m^3
95th %ile	0.3	0.3	0.4	1.0
75th %ile	0.2	0.2	0.2	0.8
50th %ile	0.0	0.0	0.0	0.6
25th %ile	0.0	0.0	0.0	0.4
5th %ile	0.0	0.0	0.0	0.0
Minimum	0.0	0.0	0.0	0.0
Maximum	0.4	0.4	0.5	1.1

Table D-3

Percent Increase in Non-Accidental Mortality per 1 μg/m^3 Increase in Annual Mean $PM_{2.5}$ Concentrations For Range of Baseline $PM_{2.5}$ Concentrations from 8 to 20 μg/m3 – Combined Expert Distributions

Percentiles	Based on Population-Weighted Distribution of Baseline Annual Mean $PM_{2.5}$ Concentrations in U.S. (from BENMAP model)	Based on Uniform Distribution of Baseline Annual Mean $PM_{2.5}$ Concentrations
95th %ile	0.94	1.05
75th %ile	0.59	0.65
50th %ile	0.30	0.33
25th %ile	0.15	0.17
5th %ile	0.00	0.00
Mean (estimated)[b]	0.40	0.44
Minimum	0.00	0.00
Maximum	1.50	1.71

a. The combined values are averages across experts at each percentile. The method gives equal weight to each expert's distribution.
b. The mean is estimated by combining the distributions using Monte Carlo simulation (see text for full discussion of methodology).

Table D-4

Percent Increase in Annual Non-Accidental Mortality per 1 µg/m^3 Increase in Long-term Exposure to $PM_{2.5}$ at Specific Annual Average Baseline $PM_{2.5}$ Concentrations - Combined Expert Distributions[a]

Percentiles	8 ug/m^3	12 ug/m^3	15 ug/m^3	20 ug/m^3
95th percentile	0.82	0.99	1.08	1.2
75th percentile	0.56	0.61	0.64	0.76
50th percentile	0.30	0.30	0.30	0.42
25th percentile	0.16	0.16	0.16	0.24
5th percentile	0	0	0	0
Mean[b]	0.37	0.41	0.43	0.52
Minimum	0	0	0	0
Maximum	1.35	1.58	1.7	1.82

a. The combined values are averages across experts at each percentile. The method gives equal weight to each expert's distribution.

b. The mean is estimated from by combining the distributions using Monte Carlo simulation (see text for full discussion of methodology).

Table D-5

Sensitivity Analysis of Combined Results for Effects of Long-term $PM_{2.5}$ Exposure to Individual Expert Results

Percentiles	Combined Results All Experts[a]	Percent Change in Combined Results				
		Minus A	Minus B	Minus C	Minus D	Minus E
95th	0.94	-2%	-0.4%	15%	-4%	-20%
75th	0.59	-5%	13%	18%	-0.5%	-26%
50th	0.30	-19%	21%	21%	-3%	-35%
25th	0.15	-22%	21%	21%	5%	-41%
5th	0.00	0%	0%	0%	0%	0%
Mean (Estimated)[b]	0.40	-8%	10%	20%	-3%	-28%

a. The combined values are averages across experts at each percentile. The method gives equal weight to each expert's distribution. Combination method uses population-weighted distribution of annual mean $PM_{2.5}$ concentrations in U.S. (from BENMAP model).

b. The mean is estimated by combining the distributions using Monte Carlo simulation (see text for full discussion of methodology).

Table D-6
Percent Increase in Daily Non-Accidental Mortality
from a One-day 10 μg/m^3 Increase in 24-hour Average Exposure to $PM_{2.5}$

Percentiles	Expert				
	A	B[a]	C[b]	D	E
95th	2.95	0.82	0.74	1.2	2.4
75th	2.4	0.53	0.44	0.8	1.5
50th	2	0.30	0.11	0.5	1.2
25th	1	0.08	0.05	0.25	0.9
5th	0	0	0	0	0
Minimum	0	0	0.00	0	0
Maximum	3.2	1.64	0.89	N.S.	2.8
Mean (Estimated)[c]	1.84	0.36	0.25	0.55	1.21

a. Assumed a threshold (uncertain between 5 and 25 μg/m^3, with a modal value at 15) and a log-linear relationship above the threshold (uncertainty distribution: min-0, 5th-0, 25th-0.1, 50th-0.37, 75th-0.65, 95th-1, max.-2). The table shows the "effective" distribution for the full range estimated using Monte Carlo simulation (see text for full discussion of methodology).

b. Provided different distributions for different points in the range, background-60 μg/m^3 (See Table D-4). This is the 'effective' distribution for the full range estimated from the individual points in Table D-4 using Monte Carlo simulation techniques (see text for full discussion of methodology).

c. The mean is estimated from by sampling from the distributions using Monte Carlo simulation (see text for full discussion of methodology). No mean values were elicited from the experts.

N.S. Not specified and expert did not supply upon follow-up.

Table D-7
Percent Increase in Daily Non-Accidental Mortality
from a One-day 10 μg/m^3 Increase in 24-hour Average Exposure to $PM_{2.5}$
Expert C only

Percentiles	Back-ground[a]	20 μg/m^3	40 μg/m^3	60 μg/m^3
95th %ile	0.0	0.5	1.0	1.2
75th %ile	0.0	0.3	0.5	0.9
50th %ile	0.0	0.0	0.0	0.6
25th %ile	0.0	0.0	0.0	0.3
5th %ile	0.0	0.0	0.0	0.0
Minimum	0.0	0.0	0.0	0.0
Maximum	0.0	.6	1.2	1.4

a. Estimated at 4 μg/m^3 for the purposes of the study.

Table D-8
Combined Expert Distribution for Mortality Effects of Short-term $PM_{2.5}$ Exposures[a]

Percentiles	Percent Increase in Non-Accidental Mortality Per a One-day 10 μg/m^3 Increase in 24-hour Average $PM_{2.5}$ Exposure
95th %ile	1.69
75th %ile	1.14
50th %ile	0.82
25th %ile	0.52
5th %ile	0.00
Minimum	0.00
Maximum	2.24
Mean[b]	0.84

a. The combined values are averages across the percentile for each expert. The method essentially gives equal weight to each expert's distribution.
b. The mean is estimated from by combining the distributions using Monte Carlo simulation (see text for full discussion of methodology).

Table D-9

Percent Increase in Daily Non-Accidental Mortality per One-Day 10 µg/m^3 Increase in 24-hour Average Exposure to $PM_{2.5}$ at Specific Daily Average Baseline $PM_{2.5}$ Concentrations - Combined Expert Distributions[a]

Percentiles	8 ug/m^3	20 ug/m^3	40 ug/m^3	60 ug/m^3
95th percentile	1.34	1.58	1.71	1.75
75th percentile	0.96	1.11	1.17	1.25
50th percentile	0.74	0.80	0.81	0.93
25th percentile	0.43	0.45	0.45	0.51
5th percentile	0	0	0	0
Mean[b]	0.71	0.8	0.84	0.9
Minimum	0	0	0	0
Maximum	1.55	1.97	2.14	2.18

a. The combined values are averages across experts at each percentile. The method gives equal weight to each expert's distribution.

b. The mean is estimated from by combining the distributions using Monte Carlo simulation (see text for full discussion of methodology).

Table D-10

Sensitivity Analysis of Combined Results for Effects of Short-term $PM_{2.5}$ Exposure to Individual Expert Results

Percentiles	Combined Results All Experts[a]	Percent Change in Combined Results				
		Minus A	Minus B	Minus C	Minus D	Minus E
95th	1.69	-23%	12%	13%	6%	-12%
75th	1.14	-28%	13%	15%	7%	-8%
50th	0.82	-35%	16%	22%	10%	-11%
25th	0.52	-38%	25%	25%	15%	-15%
5th	0.00	0%	0%	0%	0%	0%
Mean (Estimated)[b]	0.84	-30%	14%	18%	8%	-11%

a. The combined values are averages across experts at each percentile. The method gives equal weight to each expert's distribution. Combination method uses uniform distribution of annual mean $PM_{2.5}$ concentrations in U.S.

b. The mean is estimated by combining the distributions using Monte Carlo simulation (see text for full discussion of methodology).

Appendix E

Potential Sources of Bias and Uncertainty in Estimates of the Impact of Long-term Exposures to PM2.5 on All-cause Mortality: Summaries

Expert A

	Sources of bias
1	Exposure misclassification (bias toward null)
2	Historical exposures likely higher, use of current exposures may bias current estimates upwards
3	Omitted covariates (weather, indoor/outdoor penetration rates)
4	Spatial auto correlation
5	Representativeness
	Sources of uncertainty
1	Representativeness of studies for U.S.
2	Omitted variables
3	Exposure misclassification: Impact of commuting/ within city exposures
4	Methodological issues
5	Lifestyle factors (anxiety/stress), how well the variables measure a pattern over 30 years
6	Averting behavior (staying inside during high air pollution episodes)

Expert B

	Sources of bias	Direction of bias relative to true effect	Adjustment to expert judgment
1	Confounding by "lifestyle"/personal factors	up	down
2	Selection bias in ACS cohort leading to overall healthier, better educated population than the general population.	down	up
3	Co-pollutants	?	?
4			
5			
	Sources of uncertainty		
1	Exposure misclassification (use of central site monitors, movement of study subjects during lifetime.) Likely to be random misclassification	--	
2	Differences in PM2.5 components mix across cities: random misclassification?	--	
3		--	

Expert C

	Sources of bias	Direction of bias relative to true effect	Adjustment to expert judgment
1	Historical exposures higher than exposures at time of Six City and ACS studies and were responsible for increased risk	up	down
2	Ascertainment of smoking status - only at beginning of study		
3	Non-representativeness of exposures in the Six cities study of non-LA basin west and midwest	up	down
4			
5			
	Sources of uncertainty		
1	Self enrollment in the ACS study - higher effect seen in portion of cohort with less than high school education	--	
2		--	
3		--	

Expert D

	Sources of bias
1	Confounding by smoking
2	
3	
4	
5	
	Sources of uncertainty
1	• Use of current exposures to represent past exposures. Changes in o Concentrations, mix o Patterns of air conditioning use o Housing construction • Other exposure misclassification issues
2	Differences in underlying age structure of the cohort populations versus the U.S. population
3	Independent effects of other pollutants
4	Relative toxicity of PM components and their role in determining PM effects

Expert E

	Sources of bias	Direction of bias relative to true effect	Adjustment to expert judgment
1	Residual confounding: -seasonality? -time dependent personal factors (smoking, SES)	Upward	downward
2	Measurement error: -ambient v. indoor exposure -ambient v. personal exposure	Downward	upward
3	Investigator, publication bias	Upward	downward
4	Selection bias in ACS study: -why does all of the effect come from 50% of population without a high school education	Downward	upward
5			
	Sources of uncertainty		
1	Questions about causality	--	
2	Heterogeneity among published studies reflecting true effect	--	
3	Confounding – "cultural" factors	--	
4	Confounding due to other socioeconomic factors	--	
5	Confounding due to smoking	--	

Appendix F

Potential Sources of Bias and Uncertainty Affecting Existing Estimates of the Impact of Short-term Exposures to PM2.5 on All-cause Mortality: Summaries

Expert A

	Sources of bias
1	Measurement error
2	Treatment of weather (big role (Burnett), small role (Schwartz))
3	Modeling approach and specification
4	Treatment of seasonality
5	
	Sources of Uncertainty
1	Use of smoothers
2	Modeling approach
3	Particle composition and chemistry
4	Activity patterns/ patterns in air conditioning use/patterns in socioeconomic status
5	Indoor/outdoor penetration, differences in housing characteristics across regions

Expert B

	Sources of bias
1	Absence of analysis for "distributed lag" effects in one-day lag studies; underestimate total impact on mortality
2	Analytical bias (small in NMMAPS, larger in single city studies); statistical modeling assumptions favor positive results (results biased upward)
3	
4	
5	
	Sources of Uncertainty
1	Infectious diseases (role of?)
2	Role of co-pollutants
3	Over correction for seasonality in NMMAPS Uncertainty or bias?
4	Exposure misclassification (use of central site monitors for personal exposure)

Expert C

	Sources of bias
1	Investigator bias (Schwartz studies primarily)
2	Weather (confounder) Well-controlled in Burnett studies
3	Co-pollutants (confounder)
4	Temperature/seasonality (increase in temperature increase adverse effects)
5	
	Sources of Uncertainty
1	Paucity of data
2	Role of PM10-2.5 versus PM2.5 in disease
3	
4	
5	

Expert D

	Sources of bias
1	
2	
3	
4	
5	
	Sources of Uncertainty
1	Independent effects of other air pollutants
2	Relative toxicity of PM components and their role in determining PM effects
3	
4	
5	

Expert E

	Sources of bias
1	Over-stringent control for seasonality in NMMAPS study; biases results downward
2	Lack of accounting for distributed lag effects in NNMAPS; underestimates total impact on mortality
3	Adjustment of effect for PM10 to PM2.5
4	
5	
	Sources of Uncertainty
1	Causality, residual concerns
2	Statistical and residual confounding
3	Measurement error
4	
5	