

Appendix 1

Peer Reviews on the Draft Report

The draft version of this report, published in 2007, was peer reviewed by the individuals listed below. This appendix provides a copy of each review.

1.1 Professor D Coggon

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1.2 Professor P K Hopke

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1.3 Dr M Krzyzanowski

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1.4 Dr B Ostro

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Readers may wish to note that the draft report, *Long-Term Exposure to Air Pollution: Effect on Mortality*, and all comments submitted to the Secretariat on the draft report between July and August 2007 are available on the Committee's website:

<http://www.advisorybodies.doh.gov.uk/comeap/index.htm>

1.1 Review by Professor D Coggon

Long-Term Exposure to Air Pollution: Effect on Mortality
Comments on Draft COMEAP Report, July 2007

David Coggon

This is a clear and well-structured report, making it easy to follow the arguments underpinning the Committee's conclusions.

My main concern scientifically relates to the assumptions that are made about relevant exposure periods. This is discussed on pages 35–36¹ and pages 54–55 of the draft report. Critical to the analysis of this issue is not only the latency of effects (i.e. the interval from exposure to first resultant elevation of risk), but also their duration. An effect may occur with a short latency and risk be reduced within a short time after reduction in exposure, but this alone does not exclude a long-term impact of exposure on risk. Thus, the last sentence of page 36, paragraph 1, is potentially misleading. What matters is not the lag between exposure and first effect, but that between exposure and last effect.

If effects on risk are persistent, even if occurring with short latency, then there may be major confounding by earlier higher levels of pollution, leading risk coefficients for PM_{2.5} to be seriously overestimated. The most relevant period of exposure might not be the earliest from which exposure data are available (page 36, paragraph 4), but perhaps even before that, when levels were still higher. Moreover, it is possible that cumulative exposure is a more relevant metric than the intensity of exposure in any single period. This is particularly plausible for effects on lung cancer, but could also apply to cardiovascular disease. What is the evidence that the effects of PM_{2.5} on risk of cardiovascular disease disappear within a few years after exposure?

I think this aspect of the report could usefully be developed further.

My other main comments are as follows.

Page 11, paragraph 3, refers to lack of control for spatial variations in mortality, but at this stage it is not clear to the reader what this means, or why there should be a need to control for spatial variation in mortality (spatial variation in mortality is after all the basis for risk estimation). Page 13, paragraph 2, then refers more explicitly to spatial autocorrelation, but still the term is not explained until later in the report. It might help to have a brief explanation of spatial autocorrelation at this early stage (perhaps in a footnote), with a reference to the later, more detailed discussion of its potential importance.

¹ Readers are asked to note that these and other page numbers cited in this appendix relate to the draft report published for comment in 2007. The draft report is available on the Committee's website: <http://www.advisorybodies.doh.gov.uk/comeap/index.htm>

Page 12, footnote 5. This definition of relative risk is useful and widely applied, but the Committee should be aware that some authors have assigned a more specific meaning to the term, distinguishing it, for example, from incidence density rate ratio.

Page 17, Table 2.1. It is unclear whether the time periods in this table refer to time of exposure measurement, time of mortality, or both.

Pages 17–18. In discussing causality, there should also be a consideration of carcinogenicity, and in particular, the strength of toxicological evidence indicating that PM_{2.5} can cause lung tumours. Is the effect on lung cancer thought to be a class effect of particles, or does it depend on the concomitant presence of PAHs?

Page 24, Table 3.1. The relative risks are said to take into account the relative concentrations of pollutants as they actually occur. This suggests that the ratios of their concentrations are similar at all levels of pollution. Is this correct?

Page 28, 3 lines from end. If there really is a direct effect of SO₂, what will be the effect of ignoring this when estimating the impact of reducing PM_{2.5}?

Page 31, Figure 3.3. It is unclear what implications this model has for assessment of the impact of reducing PM_{2.5}.

Page 33, paragraph 3. There is no mention here of the epidemiological findings on cancer risk in workforces occupationally exposed to sulphuric and other acid mists.

Page 34, last sentence. Are cause-specific analyses more precise (i.e. giving narrower confidence intervals) or less biased?

Page 40, paragraph 2. Paragraph 2 of page 138 refers to the non-availability of coefficients based on average exposure with incorporation of spatial smoothing. This presumably was a major consideration in the approach adopted by the Committee, but it does not come out clearly in the argument set out on page 40.

Page 46, paragraph 2. The meaning of this paragraph is unclear.

Page 38, paragraph 1. Is there a possibility of effect modification by smoking habits, which might differ between populations? Comparison of coefficients for men and women (whose smoking habits historically have been different) might shed some light on this.

Page 48, paragraph 2. The evidence as presented in this paragraph certainly supports an effect of PM_{2.5} on mortality, but I do not see how it supports translation specifically of the ACS coefficients.

Page 48, paragraph 3. This definition of a 95% CI is potentially misleading, in that it could be taken to imply that where a 95% CI has been derived from a study, there is a 95% probability that the true RR coefficient lies within the calculated range. Clearly this is incorrect, since just by chance, two studies estimating the same parameter could end up with non-overlapping confidence intervals, and there cannot be 95% probability that the true value for the parameter lies in each of two non-overlapping ranges. The confusion arises because in conventional frequentist statistical inference, probability statements can only be made about sample statistics

and not about population parameters. It would be more accurate to say that 95% confidence intervals are calculated in such a way that, in the absence of bias, on average 95% of such intervals will include the parameter that is being estimated.

Page 178. Presumably, the absolute decline in particulate air pollution has been greater in urban than rural areas. Have you considered looking at the declines in mortality in rural populations, as a crude way of trying to gauge the impact of factors other than air pollution on mortality trends?

In addition to these main comments, I have quite a number of other more minor suggestions for amendment or clarification of wording, and these have been marked on the attached pages copied from the draft report².

² These pages are available from the Secretariat upon request.

1.2 Review by Professor P K Hopke

Long-Term Exposure to Air Pollution: Effect on Mortality
Comments on Draft COMEAP Report, July 2007

Philip K Hopke

The report provides a good review of the basis for risk estimation for the long-term effects of airborne particulate matter starting from the ACS study values. The assumptions and logic behind the directions taken are clearly stated and the working papers provide the necessary details to understand how the values were obtained. However, it appears that an important publication on the follow-up of the Harvard Six Cities Study has not been included and it needs to be incorporated into this review. Laden *et al* (2006) report an 8-year follow-up on the original Six Cities analysis. During this interval, there has been a significant decrease in PM_{2.5} concentrations that provides clear evidence for the role of PM in mortality. These authors found RR values near the higher ends of the confidence intervals obtained from the ACS study. Thus, these results require some of the consideration of the feasibility analysis that moved the analysis away from the upper end of the range.

In spite of its use both in this analysis and in the United States, I find the elicitation of experts to be an approach that involves too much subjectivity and is likely to be unreliable. I would suggest one be very careful using the guesses of experts as the basis of policy decisions. We have seen many cases where new phenomena were discovered that substantially changed the view of the problem. A classic example is stratospheric ozone depletion by chlorofluorocarbon compounds. In the late 70s, experts were convinced they fully understood the system and we had many years to develop alternative compounds to replace the CFCs and before substantial effects would be observed. Then in the early 80s, direct observation of the ozone column at the South Pole revealed the substantial depletion of ozone (polar ozone hole). This finding catalyzed more rapid action through the Montreal Protocols. About the time the first real action was taken on CFC controls, the heterogeneous processes that caused the polar holes were identified. With the best of intentions and considerable skill, there are still real questions about expert judgement relative to data analyses and making explicit assumptions that can subsequently be evaluated. Were these judgements made prior to or subsequent to the Laden *et al* paper? Would that paper make a difference? I see this as a problem in trying to suggest the elicitation supports the values presents. There is circular logic here.

There is relatively limited review of the role of particle composition in driving specific cause mortality. Although there are relatively few papers in the area, there now are several papers on source apportionment and mortality, including Laden *et al* (2000), Mar *et al* (2000), Ito *et al* (2006) and Mar *et al* (2006). There is only limited discussion of 'traffic' effects, and then leading to a more encompassing hypothesis. If oxidative stress to the system is the driving force that results in the chain of events leading to death, then should not the focus of attention move to chemically reactive materials that would drive such stress? There have been suggestions of the formation of endogenous reactive oxygen species (ROS) that drives the oxidative stress. We have seen the effect of metals in ROFA that could produce ROS, but ROFA is hardly representative of PM_{2.5}. Also why in NMMAPS are the RR values so similar across the US

when there are such large differences in the particle composition? Thus, it may not be what is in the particles, but rather what is on the particles. There has been limited work showing the presence of ROS on particles (Venkatachari *et al*, 2005; 2007). Sarnat *et al* (2005) found that ozone was a better surrogate for personal PM exposure than measured ambient PM. Is this because ozone is an indicator of the level of photochemical reactions in the atmosphere? The Southern California Childrens' Health Study, the Hoek *et al* and related work, etc., have shown that proximity to heavily traveled roads is important and diesel emissions are likely to be more important than spark-ignition. Is this because there are reactive free radicals in the exhaust in both the gas and particle phases that disperse and are quenched over distance from the source region? Thus, there needs to be more focus on species we have difficulty measuring, but may be much more related to driving chemistry in the respiratory tract and outward into the rest of the body. Continuing to focus on the toxicology and epidemiology of particle composition measured long after collection and thus long after the chemically reactive species are gone, is likely to miss key species. This report continues lines of very conventional thinking with regard to the mechanisms of causality by particles. How can one really think ammonium sulfate or ammonium nitrate will start a catastrophic chain of events leading to death? There needs to be more creative thinking as to the causal factors in particles or the whole aerosol with an emphasis on those constituents that are likely to drive reactions. This will require new techniques for sampling and analysis of the ambient PM as well as creative ways to mimic the reactive chemistry in the lab so that controlled toxicological studies can be conducted. However, major reports like this one needs to start recognizing we are continuing to plow the same old ground and it is time to strike off in new directions if we are to make additional progress.

I understand that the primary purpose of this report is to provide numerical long-term exposure risk coefficients for policy analysis use, but there needs to be a better framework of what we know, what we can hypothesize, and how that should drive the directions we will need to take to get a better basis for such risk coefficients in the future.

In summary, it seems that the values provided are reasonable although may need to be adjusted depending on how much weight the new Six Cities results are given. The range and nature of the uncertainties are outlined appropriately. However, it may be useful to provide more discussion of the heterogeneous nature of PM and the potential role of compositional differences in driving health effects particularly with respect to our currently limited ability to fully characterize particle constituents.

References

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- Venkatachari, P., Hopke, P.K., Grover, B.D., and Eatough, D.J. (2005) Measurement of particle-bound reactive oxygen species in rubidoux aerosols. *J. Atmos. Chem.* **50**, 49–58.
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1.3 Review by Dr M Krzyzanowski

Long-Term Exposure to Air Pollution: Effect on Mortality
Comments on Draft COMEAP Report, July 2007

Dr Michal Krzyzanowski

The report presents an analysis of several most important aspects regarding association between ambient levels of particulate matter and mortality. Scientific evidence on this association is still developing, has gaps and recognized uncertainties. However the estimates of burden of disease, based on the conclusions from this evidence, indicate very significant public health impacts and have important policy implications. Therefore careful assessment of these uncertainties and decisions concerning interpretation of the existing knowledge require careful and systematic evaluation of the available evidence and balanced scientific judgment.

The report demonstrates that the analysis of the evidence was done in a very careful and systematic way. Questions formulated to guide the analysis cover the most important aspects of the evaluated area and the conclusions reached by the Committee are well supported by the background papers. Former assessments are considered and the conclusions of the report are fully in line with the assessments conducted by the expert groups convened by WHO^{1,2}. The report also provides an innovative approach to illustrate the uncertainty of the risk coefficient based on the range of expert opinions concerning the real magnitude of risk. The central estimate of the risk coefficient, proposed by the review, agrees with the value used in the burden of disease assessment performed for the Clean Air for Europe programme. This is a reassuring result, increasing confidence both in the CAFE assessment and in the COMEAP review.

Specific comments

Page 33³, 2nd para. on epidemiology and Working Paper 4 should include recent paper by Ostro *et al* [The effects of components of fine particulate air pollution on mortality in California: Results from CALFINE, *Environ. Health Perspect.* **114**,13–19 (2007)].

Page 45, 1st para. The analysis of plausibility would profit from discussion of the reduction of cause-specific mortality, in particular of cardiovascular mortality, in addition to that presented

¹ Air Quality Guidelines. Global Update 2005. Copenhagen, WHO Regional Office for Europe, 2006: <http://www.euro.who.int/Document/E90038.pdf>

² Health Relevance of Particulate Matter from Various Sources. Report on WHO Workshop, Bonn, Germany, 26–27 March 2007, Copenhagen, WHO Regional Office for Europe, 2007: <http://www.euro.who.int/Document/E90672.pdf>

³ Readers are asked to note that this and other page numbers cited in this appendix relate to the draft report published for comment in 2007. The draft report is available on the Committee's website: <http://www.advisorybodies.doh.gov.uk/comeap/index.htm>

for total mortality. Assuming that the CVD effects of long term exposure to PM are more specific than those for the total mortality, and that the CVD mortality classification has not changed in the last decades in the United Kingdom, comparison of the changes expected due to the PM reduction with the observed mortality trends (not explained by smoking) would reduce the impact of the changing mortality structure.

Page 45, 2nd para: the text in line 5 is unclear: state clearly that it is the decline predicted with the coefficient of 17%.

1.4 Review by Dr B Ostro

Long-Term Exposure to Air Pollution: Effect on Mortality
Comments on Draft COMEAP Report, July 2007

Dr Bart Ostro

General comments

This report provides an excellent review of many of the important issues concerning the use of long-term exposure studies for estimating the impacts of changes in air pollution. It also provides a very transparent and complete discussion of the thinking, empirical aspects and necessary judgments that go into generating these estimates. I particularly appreciate the question and answer approach that has been used quite effectively here. Nevertheless, I will argue below that there is substantial evidence for using a higher coefficient than that suggested by this assessment. In addition, if you intend to use the results of the elicitation of Members, you need to more fully document the interview process, selection and expertise of Members, questions asked, biases addressed, sources used, peer review and complete results.

In California, we also have focused some attention on how to use the long-term exposure studies for calculating the current costs of air pollution or, stated somewhat differently, the potential benefits of improving air quality. We may have benefited from having a later closing date for the studies than you did. Nevertheless, there is some important information that should be included in your assessment including new studies and some expert elicitation efforts. This includes the review paper by Pope and Dockery (2006) and the new cohort results reported by Laden *et al* (2006) and Miller *et al* (2007).

In 2006, US EPA and its consultant, Industrial Economics Inc., conducted an expert elicitation exercise. This was a response to a report to the US Congress entitled *Estimating the Public Health Benefits of Proposed Air Pollution Regulations* by the National Research Council (2002). The NRC recommended that a better characterization of the uncertainty be performed for regulatory impact analyses, including estimating premature death associated with exposures to PM_{2.5} levels. As a result, the US EPA convened a panel of twelve experts to assess the reduction in premature death in the adult US population resulting from a long-term reduction in annual average PM_{2.5}. In their assessment, the experts considered all published literature, from both short- and long-term studies as well as toxicology, on the subject. Twelve experts were selected through a two-part peer nomination process and included experts in epidemiology, toxicology, and medicine. The peer nomination process was designed to obtain a balanced set of views and remove any EPA influence from the process. It is not clear how this elicitation compares to your own elicitation that is summarized in the report.

The following twelve individuals made up the panel of experts:

- Doug Dockery, Ph.D., Professor of Environmental Epidemiology
Department of Environmental Health, Harvard School of Public Health
- Kaz Ito, Ph.D., Assistant Professor of Environmental Medicine
New York University of Medicine

- Daniel Krewski, Ph.D., Director
R. Samuel McLaughlin Centre for Population Health Risk Assessment
University of Ottawa
- Nino Künzli, M.D., Ph.D., Associate Professor, Department of Preventive Medicine
University of Southern California Keck School of Medicine
- Morton Lippmann, Ph.D., Professor and Director of Aerosol Research Laboratory
New York University School of Medicine
- Joe Mauderly, DVM, Vice President and Senior Scientist
Lovelace Respiratory Research Institute
- Bart Ostro, Ph.D., Chief, Air Pollution Epidemiology Unit
California Environmental Protection Agency Office of Environmental Health Hazard
Assessment
- C. Arden Pope, III, Ph.D., Professor of Economics, Brigham Young University
- Richard Schlesinger, Ph.D., Biology and Health Sciences, Pace University
- Joel Schwartz, Ph.D., Professor of Environmental Health
Department of Environmental Health, Harvard School of Public Health
- George Thurston, Ph.D., New York University of Medicine
- Mark Utell, M.D., Professor of Medicine and Environmental Medicine
University of Rochester School of Medicine and Dentistry

The preparation process was very involved and included a pre-interview, a briefing book of the elicitation interview protocol, and a CD containing over 150 relevant papers. Ultimately, the main quantitative question asked each expert to provide a probabilistic distribution for the average expected decrease in US annual, adult, all-cause mortality associated with a 1 $\mu\text{g}/\text{m}^3$ decrease in annual average $\text{PM}_{2.5}$ levels. In addressing this question, the experts first specified a functional form for the $\text{PM}_{2.5}$ mortality C-R function and then developed an uncertainty distribution for the slope of that function (the mortality impact per unit change in annual average $\text{PM}_{2.5}$), taking into account the evidence and judgments discussed during the qualitative part of the interview. The interviewers asked each expert to characterize his distribution by assigning values to fixed percentiles (5th, 25th, 50th, 75th, and 95th).

Of note, while the Pope *et al* (2002) study that you have used for your estimates suggests a 6% change in mortality per 10 $\mu\text{g}/\text{m}^3$ change in $\text{PM}_{2.5}$, the median estimate of the experts was from 7 to 16% per 10 $\mu\text{g}/\text{m}^3$ change in annual average $\text{PM}_{2.5}$ concentration. Experts in this study tended to be confident that $\text{PM}_{2.5}$ exposure was causally associated with premature death. Ten of twelve experts believed that the likelihood of a causal relationship was 90% or higher. The remaining two experts gave causal probabilities of 35 and 70%. The results of Pope *et al* (2002), Jerrett *et al* (2005), Dockery *et al* (1993) and Laden *et al* (2006) were extensively used by the experts for both the central estimate and the uncertainty bounds. See US EPA website for more details on this procedure (www.epa.gov/ttn/ecas/ria.html).

Since there are several issues involved in determining how to use these results, it is prudent to conduct sensitivity analysis to investigate how robust the estimates are to alternative sampling. Among measures of central tendency, the median is the statistic least influenced by outlying observations. Therefore, it is reasonable as a first approximation to use the median to represent the point of central tendency among each expert's distribution of point estimates. Developing a range around this central estimate, of course, is not an easy task. Again, a simple approach is to

rely on empirical evidence to provide bounds for the central estimate. The two studies most widely cited in the literature and referenced by the experts in US EPA's elicitation are based on the American Cancer Society (ACS) and the Harvard Six Cities cohorts. These studies represent the most generalizable populations, have undergone rigorous scrutiny and peer review (Krewski *et al*, 2000), and can be used to develop a credible range of the PM-mortality relationship, with ACS as the lower limit and Harvard Six Cities as the upper limit.

There are several alternative approaches that could be used for developing the central estimate and low and high bounds. These include, for example:

- 1 Using the median of the experts' medians as the central estimate, but also the medians of the experts' 5th and 95th percentiles as the lower and the upper bound, respectively.
- 2 Pooling three studies, Pope *et al* (2002), Laden *et al* (2006), and Jerrett *et al* (2005) using equal weight – to treat the results from three studies equally. Though the Jerrett's analysis uses a subset of the ACS cohort analyzed by Pope *et al*, the methodology was different enough to be used as a separate estimate.
- 3 Pooling Pope *et al* (2002), Laden *et al* (2006) and Jerrett *et al* (2005) using inverse-variance weighting – to give more weight to studies with tighter confidence bounds than those with wider confidence bounds.
- 4 Pooling Pope *et al* (2002) and Laden *et al* (2006) using a random effects model.
- 5 Pooling all 12 expert distributions using random effects model.

While this list is not meant to be exhaustive, it is used to demonstrate **two important findings**. **First, that the final estimates are robust to the technique used and, second, that the central estimate is always greater than that developed for COMEAP.** The results are detailed below.

Percentage change in mortality risk per 10- $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ exposure

Scenario	Low	Mean	High
Proposed credible range	4%	10%	16%
1 All medians from 12 experts	3%	10%	20%
2 3 studies, equal weight	2%	12%	26%
3 3 studies, inverse-variance weight	4%	11%	19%
4 2 studies, random effects pooling	3%	10%	20%
5 12 experts, random effects pooling	0%*	10%	21%

* Whenever the lowest value in an expert's distribution includes zero, a pooled result (including this expert) can have zero as a lower bound.

Note that the proposed credible range is not necessarily the 5th and 95th percentile but rather a more likely bound based on the original studies and informed by the expert judgments.

Are there reasons why these numbers might not apply to the UK?

One of the more important findings from the ACS and Harvard Six Cities studies is the effect modification by education, which is discussed in your own assessment. It is not clear, however, what 'education' *per se* is measuring in this context but there are several possibilities. These include: (1) low education and low income making individuals more susceptible due to related risks factors such as poor diet, obesity, low available and/or use of medical care; (2) greater exposure among individuals with lower socioeconomic status (SES); and/or (3) greater co-morbidity of those with lower SES. One reason to keep a lower coefficient for mortality (such as your suggested 6% per 10 $\mu\text{g}/\text{m}^3$) is if you believe that wealthier people live closer to the city center (which I have heard to be true anecdotally) and they will have little effect from PM and that others will not have much of an effect from exposure. However, evidence from Forastiere *et al* (2007) shows that (using a time-series study) even those with lower average exposure but also low SES have a demonstrated mortality effect from PM. It is also quite possible that overall exposures to combustion-related sources will be higher in the very urban parts of the UK due to greater proximity to roads and greater prevalence of diesels. Therefore, I have seen no compelling evidence presented to use a lower Pope *et al* (2002) estimate. As long as those with lower SES status in the UK have high co-morbidity and are exposed to reasonably similar concentrations of PM_{2.5} as in the US, one would expect the same effect as observed in the US. One reason to keep the risk estimates lower than that suggested by the empirical results indicated above (~10%) is if exposure alone is driving the result and low SES people in the UK are not being exposed. Note that the ACS cohort is non-representative of the US population and includes a higher income range than the population as a whole. Several of the experts in the elicitation process chose to weight the Pope *et al* (2002) upwards to account for the greater results (given the effect modification by education) if the ACS were more representative of the full population.

Comments on Executive Summary

Page 5¹: IV: I agree that the evidence base has increased dramatically since 2001. However, many of the new and important findings are not reflected in this report.

Page 5: V and VIII: I agree that there is no compelling basis at this time for generating estimates related to long-term exposure to the gaseous pollutants or to specific components of PM_{2.5}. However, there is a hint from several time-series mortality studies, that nitrates and sulfates (or their correlates) may be more toxic than generic PM_{2.5} mass. To date, most analyses using sulfates have produced positive, and often statistically significant, associations including studies conducted in Santa Clara County, CA (Fairley, 1999), eight Canadian cities (Burnett *et al*, 2000), and several urban areas on the east coast and in the Midwest (Schwartz *et al*, 1996). In addition, in a recent effort to compare results from alternative factor analysis methods to estimate the effects of sources of fine particles, the sulfate-related factor was most consistently significant in the cities studied (Thurston *et al*, 2005) In one of the few studies examining nitrates, a positive and significant association was detected (Fairley, 1999). Finally, a study of mortality in nine Californian counties suggests that nitrates and sulfates each have a higher risk

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estimate per $\mu\text{g}/\text{m}^3$ than does generic $\text{PM}_{2.5}$ mass (Ostro *et al*, 2007). If the cohort study results are merely a longer lag period extension of the time-series studies, these findings have relevance in terms of potentially calibrating the impact of constituents of $\text{PM}_{2.5}$.

Page 5: VII: Given the above, I'm not sure I agree that the ACS is the best source of coefficients. This actually generates among the lower estimates and, as argued by Pope and Dockery (2006), has substantial exposure misclassification. As the exposure assessment improves, the risk estimates increase significantly.

Page 5: X: The Miller *et al* (2007) study using the Women's Health Initiative cohort includes concentrations as low as $3.5 \mu\text{g}/\text{m}^3$. Therefore, one could argue that the concentration-response function could be applied down to background concentrations or slightly above.

Page 6: The Monte Carlo results referred to here and summarized in Appendix 10 need to be presented in greater detail if they are to serve as the basis for the empirical estimates.

Page 6: From results I've seen, at least for developed economies, you get fairly similar estimates whether you use coefficients for all-cause or cardiovascular mortality (with higher coefficient but lower baseline mortality). Do you have different evidence?

Comments on Chapter 3 Discussion

(Note: If I didn't comment directly on the response to the questions, it signifies that I generally agreed with the line of thinking.)

Page 35, last para: Both current thinking (although not unanimous) and recent empirical results (Laden *et al*, 2006, and Miller *et al*, 2007) suggest that the more recent exposures (within the last two years) are biologically relevant. In turn, these studies suggest that the benefits of reductions will also be accrued fairly rapidly.

Page 38, para 3–5: There is now substantial evidence, as reviewed by Pope and Dockery (2006), that the reduction in exposure measurement error substantially increases the risk estimates. The improved exposure measurement in studies subsequent to Pope *et al* (2002) appears to greatly outweigh the potential impact of spatial autocorrelation. One could argue that one could more appropriately extrapolate the results for Los Angeles from Jerrett *et al* (2005) given the likely greater effects of nearby roadways (partially due to lower exposure misclassification and maybe diesels) in both LA and in many cities in the UK. The higher levels of elemental carbon (EC) in the UK (this should be discussed in some detail in the report) may also generate higher effects per $\mu\text{g}/\text{m}^3$ than generic $\text{PM}_{2.5}$. Of those few studies that have examined both $\text{PM}_{2.5}$ and EC, for example, most find greater effect estimates for EC.

Page 39, para 4: It may be, according to Pope, that there was less spatial autocorrelation in the later years of the cohort.

Page 40, para 2: I'm not sure I am convinced of the need to downward adjust the coefficient for spatial autocorrelation given the evidence of much stronger risk estimates in other studies, including those which adjust for autocorrelation.

Page 42, para 1: I don't think that these large and very expensive cohort studies are likely to be subject to publication bias.

Page 49, last para: If you intend to use the results of the elicitation of Members, you need to more fully document the process, selection of Members, questions asked, biases addressed, peer review and results. Regarding the selection of a midpoint and low and high estimate, please see my recommendations under "General comments". In short, I think the central estimate you have selected is too low given the results of several recent studies and of the EPA expert elicitation. These studies strongly suggest that as exposure misclassification is reduced, the risk estimates substantially increased. For example, the Harvard Six Cities study follow-up (Laden *et al*, 2006) uses a random and therefore more representative population, monitors specifically sited for the cohort study, and a very small spatially resolved catchment area for the participants (basically the community housing the monitor), resulting in significantly higher risk estimates than the national studies using the ACS.

Page 70: I support the Interim Statement of January 2006 regarding the likelihood of the estimate. Of course, the probability is greater that the true estimate will be closer to the central estimate than to the boundaries. I think the low and high estimates are often incorrectly interpreted by policymakers as equally likely as the central estimate. Attempts to disabuse this notion would be valuable.

Page 128 (WP 5): I agree with the recommendation for use of the combined sets of exposure data. However, if the effects are, in fact, due to fairly recent exposure, the more recent years will be less subject to misclassification.

Page 131 (WP 6): If different thresholds are considered, it would necessitate re-estimation of a concentration-response function which incorporates a similar presumed threshold, and consequently a higher slope.

Working Paper 7: Some very provocative work here. However, the actual model used for correction for the spatial autocorrelation was not clear. The authors should perhaps provide more information about the smoothing model or others used specifically to address this issue. It would be very informative to repeat some of the simulations and risk adjustments using some of the more recent studies (i.e. Laden *et al* and Miller *et al*) that presumably suffer from less spatial autocorrelation.

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