COMEAP

COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

Long-Term Exposure to Air Pollution: Effect on Mortality

A report by the Committee on the Medical Effects of Air Pollutants

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Foreword

This report is the first of a new series recording the results of our second visit to the difficult problem of quantifying the effects on health of exposure to air pollutants in the UK. Our first report, published in 1998, dealt only with the effects of short-term exposure to selected air pollutants. Quantitative data relating to the effects of long-term exposure were beginning to appear in the 1990s and we recognised that had we used these in estimating impacts on health in the UK a significantly larger estimate of effects would have been produced. But, at that time, we were uncertain about the applicability of these data to the UK and we limited the scope of our work accordingly. We returned to the problem in our second report published in 2001. In this we considered advances that had been made since 1998 and provided some provisional estimates of the effects of long-term exposure to particles in the UK.

The current report is an expansion and extension of our earlier work. We have been encouraged by the publication of studies from the UK and elsewhere in Europe and note that these have confirmed the findings of the US studies that we considered in our early reports. Our work has allowed estimates of benefits of reducing levels of air pollutants to be included in the Air Quality Strategy for the UK.

The effects of long-term exposure to air pollutants on mortality are well recognised and well studied. We know less of effects on morbidity, but this is also very important in terms of impact on public health. We are currently working on the second of this new series of reports: it will deal with effects of exposure to air pollutants on morbidity.

I am indebted to Members of the Subgroup who developed the report and, indeed, to all Members of the Committee. In particular, I wish to thank Fintan Hurley who has chaired the Subgroup with great skill and who has been responsible for developing the structure of our programme in this area. I should also like to thank the Secretariat: without their excellent work this report would not have been possible.

Professor Jon Ayres

Chairman of the Committee on the Medical Effects of Air Pollutants

Contents

Executive Summary

i The Committee on the Medical Effects of Air Pollutants (COMEAP) produced in 2001 a report on the long-term effects of particulate air pollution on mortality. Research in this field has progressed rapidly since then and we present in this report a summary of the new evidence and quantitative estimates of the impact of the long-term effects of particulate pollution on mortality.

ii We have looked in detail at the evidence linking long-term exposure to air pollutants and effects on mortality. In doing this we have assessed the possible effects of a range of factors that may affect or confound the reported associations. Whilst in this report we focus on effects on mortality, the effects of long-term exposure to air pollution on morbidity and the effects of short-term exposure to air pollution, including effects on infants, will be dealt with separately and are not covered by this report.

iii We are left with little doubt that long-term exposure to air pollutants has an effect on mortality and thus decreases life expectancy. In this report we have recommended coefficients which, when used in conjunction with methods developed for the Department of Health and the European Commission by the Institute of Occupational Medicine, will allow calculation of the potential impact on mortality and life expectancy of specified reductions in concentrations of air pollutants. We have not undertaken these calculations as part of the work reported here. These calculations will be undertaken at a later stage and presented as a supplementary paper to this report. This work will not involve the evaluation of specific policy interventions.

iv The evidence base regarding the effects of long-term exposure to air pollutants has strengthened since our 2001 report. This strengthening comprises both extensions to, and reanalysis of, the results of the studies we looked at in 2001 and publication of a number of European cohort studies and studies of the effects of policy initiatives. The evidence as a whole points strongly to an association between long-term exposure to particulate air pollution and effects on mortality. The evidence also points to $PM_{2.5}$ [1] as the most satisfactory index of particulate air pollution for quantitative assessments of the effects of policy interventions. The best studied effects and those which we recommend for use in quantification exercises are effects on all-cause mortality, on cardiopulmonary mortality and on lung cancer mortality.

v Evidence relating to the possible effects of long-term exposure to the common air pollutant gases (sulphur dioxide, nitrogen dioxide and ozone) is less well developed and we do not make any recommendations in favour of quantifying the effects of long-term exposure to these compounds. This may become possible if more evidence accumulates.

[1] $PM_{2.5}$: mass per cubic metre of particles passing through the inlet of a size selective sampler with a transmission efficiency of 50% at an aerodynamic diameter of 2.5 micrometres.

vi It is our view that the associations reported in the literature linking long-term exposure to particulate air pollution, represented by $PM_{2.5}$, and effects on mortality almost certainly represent causal relationships in respect of the air pollution mixture of which $PM_{2.5}$ forms part, and are highly likely to be causal in terms of particulate air pollution specifically. In saying this we note that there is a small possibility that some or all of the reported associations represent the effects of some as yet unidentified confounding factor or factors.

vii We think that the large American Cancer Society (ACS) cohort study of several hundred thousand people in metropolitan areas across the USA forms the best source of coefficients suitable for application in the UK. The results of this study have been exposed to the most searching examination and have been found to be robust to reanalysis. Recent extensions to the study have provided further data which we have found most helpful.

viii We accept that there may be variations in toxicity, per microgram per cubic metre ($\mu g/m^3$) of pollutant, between the various components of $PM_{2.5}$. However, we have not recommended the quantification of the effects of components of $PM_{2.5}$ separately. In particular, we have looked in detail at the case for treating particulate air pollution measured as 'sulphate' differently from $PM_{2.5}$ but have not been convinced that the available evidence warrants and enables this. We see 'sulphates', as measured, as representing the formation of toxicologically active species such as sulphuric acid from sulphur dioxide emissions from the burning of sulphur-containing fuel.

ix We have discussed the case for adjusting coefficients linking $PM_{2.5}$ and mortality for a variety of factors including sulphur dioxide, spatial autocorrelation and measurement error. We have also discussed the case for taking into account the higher coefficients found in studies at smaller spatial scales. Given the difficulty in distinguishing whether sulphur dioxide has a direct effect or whether it is acting as a marker for sulphur-related combustion sources, and our related decision not to attempt to quantify an effect of sulphur dioxide directly, we have not recommended adjustment for the possible effects of sulphur dioxide. We were unable to make a quantitative assessment of the combined impact of adjustment for the factors listed above because results from appropriate models were not available. However, in qualitative terms, adjustment for spatial autocorrelation reduces the coefficients and adjustment for finer spatial scale or measurement error is likely to increase the coefficients. We took this balance into account.

x We think that the ACS coefficients may be used to estimate the impact of policy initiatives on mortality in the UK within the range of annual average concentrations of 7–30 $\mu g/m^3$ expressed as $PM_{2.5}$, i.e. the range represented in the ACS study. This is the range of concentrations for cities included in the ACS study.

xi We have spent some time developing a method for expressing our joint perceptions of the uncertainty associated with the best estimate of the published coefficients. In the case of all-cause mortality we have moved away from the published 95% confidence interval (2–11%) for the relative risks (RR) associated with a 10 $\mu g/m^3$ increase in

$PM_{2.5}$ (Pope *et al,* 2002)[2] and have developed a plausibility distribution based on Members' consolidated views of the probability that hypothetical values of the coefficient are exceeded (see the figure below). This consolidated view indicated that the coefficient was 95% likely to fall between 0 and 15%. The extremes of this range were not considered probable and we have instead suggested, as more plausible 'low' and 'high' values, those coefficients (1 and 12%) that approximate, respectively, to the 12.5th and 87.5th percentiles of the probability distribution. To represent uncertainty, we recommend the use of Monte Carlo analysis to sample from the full plausibility distribution (see the figure below) but, if this is not possible, we suggest these coefficients (1 and 12%) for use in sensitivity analysis. We also recommend that the wider uncertainties (0 and 15%) discussed in this paragraph be described in any report on quantification, in addition to the sensitivity analysis.

xii In considering how rapidly the effects of a specified policy initiative are likely to appear we have not found it possible to give a precise estimate. However, we think that a noteworthy proportion of the total effect is likely to appear within the first five years.

xiii Our recommendations for the individual coefficients that express the relative risks associated with a 10 μg/m³ increase in $PM_{2.5}$ are:

For all-cause mortality:

Best estimate 1.06 with 95% confidence interval (CI) 1.02–1.11.

Our representation of the uncertainty regarding the coefficient linking the relative risk of death from all-causes to long-term exposure to $PM_{2.5}$ is given in the figure.

For the purposes of conducting impact assessments regarding all-cause mortality and assessing policy interventions designed to reduce levels of air pollutants, we have recommended that the full distribution of probabilities be used as an input into Monte Carlo analysis, the approach we favour. Alternatively, we suggest that the plausible 'low' and 'high' values of 1.01 and 1.12, respectively, based approximately on the 12.5th and 87.5th percentiles of the overall range of plausibility, could be used in sensitivity analysis.

We also recommend that the wider interval of 0 to 15% (relative risk 1.00 and 1.15) be included in any report on quantification of risks from long-term exposure to particulate air pollution represented by $PM_{2.5}$.

For cardiopulmonary mortality:

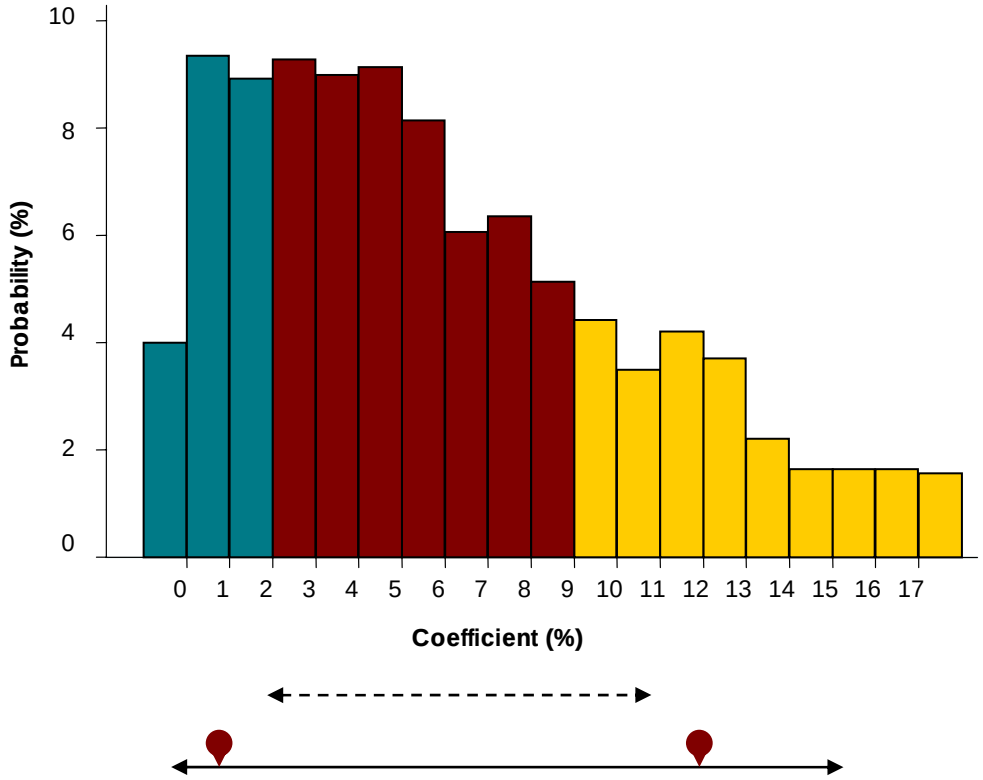
Best estimate 1.09 with 95% confidence interval (CI) 1.03–1.16; we did not assess a range of plausibility.

For lung cancer mortality:

Best estimate 1.08 with 95% confidence interval (CI) 1.01–1.16; again, we did not assess a range of plausibility.

[2] Pope, C.A., III., Burnett, R.T., Thun, M.J., Calle, E.E., Krewski, D., Ito, K., and Thurston, G.D. (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA.* **287,** 1132–1141.

Distribution of Members' aggregate probabilities (calculated as the arithmetic mean of the individual responses) of the uncertainty regarding the coefficient linking all-cause mortality and an increase in long-term exposure to $PM_{2.5}$



The first bar represents the probability of the coefficient being 0 or less (no adverse effect) and the last bar of it being more than 17%.

The coloured areas of the histogram indicate the quartiles of the distribution:

blue – the 1st quartile, regarded as the 'low' band of the distribution;
red – the 2nd and 3rd quartiles, regarded as the 'middle' band of the distribution;
yellow – the 4th quartile, regarded as the 'high' band of the distribution.

The coefficients indicated on the abscissa refer to the relative risks discussed in the text, i.e. a coefficient of 5% corresponds to a relative risk of 1.05.

1.06 (1.02–1.11) relative risk of death of all-cause mortality and 95% statistical sampling confidence interval (CI) per 10 µg/m³ increase in $PM_{2.5}$ (as published by Pope *et al,* 2002).

1.06 (1.00–1.15) relative risk of death of all-cause mortality and Members' 95% plausibility interval per 10 µg/m³ increase in $PM_{2.5}$.

These indicate the typical 'low' (1%) and 'high' (12%) values suggested for use in sensitivity analysis. They represent the 12.5th and 87.5th percentiles of the overall plausibility distribution.

Chapter 1
Introduction

Studies in the USA (Dockery *et al*, 1993; Pope *et al*, 1995) have shown that individuals living in less polluted cities live longer than those living in more polluted cities. After adjustment for other factors, an association remained between ambient annual average concentrations of fine particles (represented by $PM_{2.5}$)[1] and age-specific risks of mortality, implying shorter life expectancy in more polluted cities. In its 1998 report (Department of Health, 1998), the Committee on the Medical Effects of Air Pollutants (COMEAP) did not recommend that these studies should be used as a basis for quantifying the effects on health of long-term exposure to particulate air pollution in the UK. However, it was noted that, had these studies been used, the assessment of the overall impacts of particulate air pollution would have been considerably increased.

COMEAP Report 2001

In 2001, COMEAP published a report on the long-term effects of particles on mortality (Department of Health, 2001). This considered two studies (Health Effects Institute, 2000; Institute of Occupational Medicine, 2000) which provided further analysis of the earlier results of the US studies. The Committee concluded that it was more likely than not that a causal association existed between long-term exposure to particles and mortality. The findings were considered transferable to the UK, although it was noted that the coefficients linking pollution and effects might not be the same in the UK and in the USA. The Committee considered it was preferable to assess the size of the possible effect and comment on it rather than to ignore it, but emphasised that there were uncertainties which needed to be made clear.

The key uncertainties were whether the results could be explained by undetected confounding, whether high exposures in the past had led to an overestimation of the effect, what lag times and what duration of exposure were required for the effect and a lack of understanding of the underlying mechanisms.

Bearing these uncertainties in mind, Members of the Committee developed a series of estimates of the expected gains in life years for a sustained 1 $\mu g/m^3$ reduction in $PM_{2.5}$ with comments on their confidence in them. The calculations were based on an illustrative scenario of the population of England and Wales alive in 2000 followed until all would have died (105 years). The range of reductions in mortality rate was based on Pope *et al* (1995) and the HEI Reanalysis (Health Effects Institute, 2000). The estimates are shown in Table 1.1.

[1] $PM_{2.5}$: mass per cubic metre of particles passing through the inlet of a size selective sampler with a transmission efficiency of 50% at an aerodynamic diameter of 2.5 micrometres.

Table 1.1: Reductions in mortality rate from a unit reduction in fine particles

% reduction in mortality rate	Total life years gained (millions)	COMEAP comments
Rough comparison based on PM_{10} effect in time-series studies	0.007–0.02	Estimate* considered highly likely to be at least this large. Time-series studies well replicated. Represents the possibility that the apparent long-term effect of particles is actually explained by unknown confounders
0.1% from lower adjusted RR in the HEI report	0.2–0.5	Estimate considered most likely to be around this size. This takes account of the small number of confounding factors that substantially reduced the relative risks in the HEI Reanalysis
0.3% from lower CI 1.09 (ACS)	0.6–1.4	Estimate considered reasonably likely but higher than predicted by some of the adjusted relative risks in the HEI Reanalysis
0.6% from RR of 1.17 (ACS)	1.2–2.8	Estimate considered less likely. In most cases, factors examined in the HEI Reanalysis did not markedly affect the relative risk but some did and there may also be unknown confounders. Higher exposures in the past may also lead to an overestimation of the risk at current levels
0.9% from upper CI 1.26 (ACS)	1.8–4.1	Estimate considered implausibly large for the reasons given above and in comparison with other risks or total changes in life expectancy in recent years

* The term 'estimate' refers to the coefficients listed in the first column. These coefficients can be seen as estimates of the true coefficient linking long-term exposure to fine particles and all-cause mortality.

Estimated total gains in life years (millions) in the population of England and Wales in 2000, followed to extinction with a range of reductions in hazard rates in those aged 30 years and over. Total effects immediate, phasing in gradually or step function after up to 40 years based on a 1 $\mu g/m^3$ reduction in annual mean $PM_{2.5}$. (This is why the figures are given as a range in the second column of the table.) Estimate of effect in time-series studies based on a 1 $\mu g/m^3$ reduction in annual mean PM_{10} assuming a coefficient of 0.075%, a loss of life expectancy of 2 to 6 months per death brought forward and a similar effect on all ages.

RR, relative risk; CI, confidence interval; HEI, Health Effects Institute; and ACS, American Cancer Society study, Pope *et al* (1995).

Source: Department of Health (2001).

The Committee noted that the HEI Reanalysis (Health Effects Institute, 2000) had examined an expanded range of potential confounders such as the level of income, income disparity, poverty and unemployment and had found no marked impacts on the result. Level of education was found not to be a confounder, although it was an effect-modifier in that the effect was found to be greater in those with a lower level of education. However, adjustment for a small number of potential confounders such as population change and sulphur dioxide did reduce the relative risks substantially. The Committee noted that there could be other unknown confounders. Additionally, it was felt to be possible that some of the apparent effect of current or recent levels of particulate air pollution was, in fact, due to higher exposures in the past, leading to an overestimation of the effects.

For the above reasons, although opinions differed, the majority of the Committee preferred the estimate based on the 0.1% reduction in mortality rate per $\mu g/m^3$ $PM_{2.5}$. (The 0.1% was

derived from the relative risk of 1.03 (0.95–1.13)[2] per 24.5 μg/m^3 increase in $PM_{2.5}$ adjusted for sulphur dioxide in Table 37 of the HEI Reanalysis.) However, the Committee also considered that, given the uncertainties, it was unwise to give a single estimate and recommended use of the range of estimates shown in Table 1.1 in sensitivity analyses.

It was also considered possible, although unlikely, that there were no long-term effects, that is, if the results were caused by confounding by sulphur dioxide or by unknown confounders. If so, Members concluded, the only effect on mortality would be that of the short-term exposures detected by the time-series studies.

Evidence since 2001

Since publication of the COMEAP report in 2001 (Department of Health, 2001) new studies and reports of extensions to the American Cancer Society (ACS) study have appeared. These studies have reported important new findings. A number are discussed in more detail later in this report but a summary of the findings of the most important studies is given here as an introduction to more detailed considerations.

Pope *et al* (2002) have published an extension of the Pope *et al* (1995) study. This increased the statistical power of the study, with three times as many deaths as in the original study. This new paper also included further developments in analysis such as the incorporation of dietary variables (e.g. fat and vegetable consumption) and included various methods of control for spatial variation. Particulate pollution measured over two different time periods, and their average, was examined in relation to mortality.

The main results confirmed the previous findings for all-cause mortality[3]. The relative risk[4] for all-cause mortality for a 10 μg/m^3 increase in $PM_{2.5}$ (averaged over the two time periods) was 1.06 (1.02–1.11). The relative risk was slightly lower when the more distant time period (1979–1983) was used to represent exposure than when the more recent time period (1999–2000) was used. The authors reported that the effect estimates were not highly sensitive to adjustment for spatial variation.

The paper did not report a relative risk for $PM_{2.5}$ adjusted for sulphur dioxide, although a clear positive association between long-term average concentrations of sulphur dioxide and all-cause mortality was confirmed. The possible effect of adjustment for population change – which reduced the relative risk in the HEI Reanalysis (Health Effects Institute, 2000) – was not reported.

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[2] In this section, relative risks are given followed by the 95% confidence intervals (CI) in brackets.

[3] The relative risk for lung cancer mortality was increased and statistically significant in the study by Pope *et al* (2002) but was only slightly increased and was not statistically significant in the previous study with shorter follow-up (Pope *et al,* 1995). The results for cardiopulmonary mortality were confirmed as positive and statistically significant.

[4] In this report, risk refers to the probability of death at a particular age, assuming survival to that age. It can be thought of as the age-specific death rate, e.g. death rate at age 56 years. *Relative risk* (RR) is used here to compare age-specific death rates in two groups that differ in terms of exposure or other characteristics, e.g. in terms of their average annual exposure to $PM_{2.5}$. It is derived as the *ratio* of age-specific death rates in the two groups (assuming other factors are equal) because exposure is expected to increase age-specific death rates by some multiplicative factor, to be estimated from epidemiological studies. Relative risk is a measure of that factor.

Hoek *et al* (2002) published the results of a cohort study in Europe. Although of a different design (exposure to black smoke and nitrogen dioxide were measured at a smaller spatial scale than used in the ACS study, taking account of the proximity of an individual's home address to a major road), this study provided confirmation that effects of long-term exposure to particles can be found with the air pollution mixture found in Europe. The relative risk for all-cause mortality was 1.32 (0.98–1.78) per 10 $\mu g/m^3$ increase in black smoke (this is not directly comparable with the Pope *et al* (2002) study as it refers to a different particle metric with a different spatial distribution). The possible long-term effects of sulphur dioxide were not examined in this study.

Jerrett *et al* (2005) reported a study of the association between air pollution and mortality using estimates of small-scale exposure in Los Angeles (California). The purpose of this work was to explore the possibility that metropolitan-area-scale estimates of exposures, as used in the ACS study (Pope *et al,* 2002), may have underestimated the coefficient linking air pollution and mortality. The use of a smaller spatial scale may improve the link between measured concentration and population exposure, and thus reduce measurement error. Jerrett *et al* (2005) extracted data on 22,905 subjects from the ACS cohort (1982–2000, 5856 deaths in all). Pollutant concentrations were measured at 25 sites for $PM_{2.5}$ and 42 sites for ozone within Los Angeles. Forty-four covariates were controlled for. The coefficient linking mortality and pollution was found to be considerably higher than that reported from the ACS study (Pope *et al,* 1995, 2002). Expressed as the relative risk (RR) of deaths (all-cause mortality) per 10 $\mu g/m^3$ increase in $PM_{2.5}$, the RR was 1.17 (1.05–1.30). With maximal control for confounding this fell to 1.11 (0.99–1.25).

World Health Organization recommendations

The European Commission has asked the World Health Organization (WHO) for advice on the health effects of particles. The WHO response (World Health Organization, 2003) included an overview of the studies, available at that time, of the effects of long-term exposure to particles on mortality. The WHO noted the extensive scrutiny that had been applied in the HEI Reanalysis (Health Effects Institute, 2000) and the fact that this had corroborated and extended the findings of the original two US cohort studies (Dockery *et al,* 1993; Pope *et al,* 1995).

The WHO report (World Health Organization, 2003) mentions the major concern that spatial clustering of air pollution and health data in the ACS study made it difficult to disentangle air pollution effects from those due to the underlying spatial autocorrelation[5] of the mortality data. The report goes on to note that the ACS study (Pope *et al,* 2002) did not reveal statistically significant spatial autocorrelation[6].

Concern about the role of sulphur dioxide was also noted as inclusion of sulphur dioxide in multi-pollutant models decreased the PM effect estimates considerably in the HEI Reanalysis

[5] Spatial autocorrelation of a variable (e.g. mortality), also called spatial clustering, is a tendency for values from nearby locations to be more similar than those from more distant locations. See Chapter 3, question ix, and Working Paper 7 for further details.

[6] This conclusion was based on a general test for the presence of statistically significant spatial autocorrelation in the survival data. However, the coefficients did decrease with adjustment for spatial autocorrelation. This is discussed further in Chapter 3, question ix.

(Health Effects Institute, 2000). This adjustment applies to models with and without spatial adjustment. This point was not further addressed in the extension of the ACS study (Pope *et al,* 2002). The WHO, quoting from the HEI Reanalysis (2000), noted that spatial adjustment may have over-adjusted for (i.e. reduced) the estimated effects of regional pollutants such as $PM_{2.5}$ compared with more local pollutants such as sulphur dioxide.

The WHO response described a small number of other studies of long-term exposure to particles and mortality including the Dutch cohort study mentioned above (Hoek *et al,* 2002). The abstract by Jerrett *et al* (2004) and the subsequent paper (Jerrett *et al,* 2005) were not published at the time of the WHO work.

The WHO has recommended a concentration-response function for estimating the impact of long-term exposure to $PM_{2.5}$ in Europe in a summary report prepared by the joint WHO/UNECE Task Force on the Health Aspects of Air Pollution (UNECE/WHO, 2003). It was proposed that the relative risk coefficient for all-causes of mortality for the average exposure level reported in the extension of the ACS study (Pope *et al,* 2002) should be used. (This is equivalent to a 0.6% increase in risk per $\mu g/m^3$ increase in $PM_{2.5}$.) The use of the average concentration-relative risk rather than the relative risk for the recent or earlier time period was discussed. It was suggested that a sensitivity analysis should be done using exposures from the earlier time period (equivalent to a 0.4% increase in risk per $\mu g/m^3$ increase in $PM_{2.5}$). There was also discussion of the fact that the ACS cohort had above-average educational status, compared with the US population generally, but that the long-term effects appeared to be greater in those with lower educational status. However, there was no reported discussion of spatial autocorrelation or of adjustment (or not) for possible effects of sulphur dioxide. A longer report on outdoor particles and health incorporating these views is now available (WHO, 2006).

Summary

COMEAP considered the issue of the long-term effects of particles on mortality in detail in 2001 and recommended the use of a range of coefficients with comments on the likelihood of the coefficients being good estimates of the actual coefficient linking long-term exposure to $PM_{2.5}$ and all-cause mortality. Further studies have been published since then and these are relevant to the expressed level of confidence in the various estimates discussed.

a There are now a larger number of cohort studies that report an association between long-term exposure to particles and mortality.

b The findings in the US cohort studies of associations between mortality and annual average concentrations of ambient particles have been broadly confirmed by European studies.

c The issue of whether or to what extent spatial correlation of mortality unrelated to air pollution is contributing to the apparent association with air pollution needs further debate.

d Some studies, conducted at a local scale, found larger relative risk coefficients than reported in the ACS study.

e The interpretation of the associations found with sulphur dioxide is not clear cut and needs further discussion as it has a major influence on the possible size of the association with particles.

In addition to these developments regarding the effects of long-term exposure to air pollution on mortality, there have also been developments in the evidence in other areas relating to air pollution and health. As a result, the Department of Health has asked COMEAP to update its 1998 report 'Quantification of the Effects of Air Pollution on Health in the United Kingdom' (Department of Health, 1998). A COMEAP Subgroup on Quantification of Air Pollution Risks (QUARK II) has been set up for this purpose. The primary objectives for this Subgroup are:

a to provide a methodology for estimating, as accurately and as completely as possible and in quantitative terms, the benefits to health in the UK of reductions in air pollution, as an aid to the development and assessment of policies, including through use of cost–benefit analysis;

b to use the methodology to quantify the health impact of the major air pollutants and to estimate the benefits to health expected to be associated with their reduction.

An important aspect of this work is the provision of concentration-response functions for individual pollutants for use in health impact assessment. This report is the first in a series of reports on quantification. The effects of long-term exposure to air pollution on morbidity and the effects of short-term exposure to air pollution, including effects on infants, will be dealt with separately and are not covered by this report. The aim of this report is to recommend a coefficient or coefficient(s) for use in the quantification of the effects of long-term exposure to air pollution on mortality, to discuss the basis of the recommendation and to discuss issues relating to the appropriate application of the coefficient, including the uncertainties involved.

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Chapter 2
Approach Adopted

We agreed that the American Cancer Society (ACS) study (Pope *et al*, 1995, 2002) should form the starting point for our work. It is the largest and most statistically powerful study in the field and has been exposed to more searching review and reanalysis than any other published study in this field. We also think that adopting the findings of the latest main ACS study (Pope *et al,* 2002) is the best starting point for a discussion of coefficients. To some extent we regard the other studies using ACS data published since the original study, both by the authors of the ACS study and by others, as most useful in shedding light on points raised by the ACS study.

In taking this position, we begin by reproducing the coefficients linking $PM_{2.5}$ and mortality reported by Pope *et al* (2002)[7]. These are presented in Table 2.1.

Table 2.1: Adjusted mortality relative risk [a] (with 95% CI) associated with a 10 μg/m³ increase in fine particles measuring less than 2.5 μm in diameter

Cause of mortality	1979–1983 [b]	1999–2000 [b]	Average
All-cause	1.04 (1.01–1.08)	1.06 (1.02–1.10)	1.06 (1.02–1.11)
Cardiopulmonary	1.06 (1.02–1.10)	1.08 (1.02–1.14)	1.09 (1.03–1.16)
Lung cancer	1.08 (1.01–1.16)	1.13 (1.04–1.22)	1.14 (1.04–1.23)
All other cause	1.01 (0.97–1.05)	1.01 (0.97–1.06)	1.01 (0.95–1.06)

(a) Estimated and adjusted based on the baseline random-effects Cox proportional hazards model, controlling for age, sex, race, smoking, education, marital status, body mass, alcohol consumption, occupational exposure and diet.

(b) The time periods (i.e. 1979–1983 and 1999–2000) given in the table refer to the time during which concentrations of fine particles were measured.

CI, confidence interval.

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The question of the likely causality of the reported association between long-term exposure to pollutants (especially fine particles, $PM_{2.5}$) and increased risk of mortality has been discussed on many occasions and was considered at some length in our earlier report (Department of Health, 2001). No evidence has come forward since 2001 to weaken our level of confidence in the likely causality of the association. On the contrary, evidence that we feel strengthens the likelihood of causality has appeared. We list the main strands of evidence that appear to us to be important in reaching a view on causality, below.

[7] We concentrate here on $PM_{2.5}$ for reasons explained further in Chapter 3, questions iii and iv. Results for other particle metrics and for gaseous pollutants are also given there.

a The searching reanalysis and extension of analysis of the ACS study provided by the HEI Reanalysis (Health Effects Institute, 2000) which confirmed and extended the findings of the original US cohort studies.

b The additional cohort studies reported from the USA, Canada and Europe that support the findings of the ACS study. The studies we have identified and their findings are recorded in Table 2.2.

c The studies from Dublin (Clancy *et al,* 2002) and Hong Kong (Hedley *et al,* 2002) that report the effects of sudden reductions in pollutant concentrations upon mortality rates. In the Dublin study both particles and sulphur dioxide declined; in the Hong Kong study, the main effect was on sulphur dioxide. (Although quantitative reductions in PM did not occur, qualitative changes in its composition did.)

d The consistent findings of the now very large number of time-series studies that find associations between daily average concentrations of particles and the daily mortality rate in cities and towns from many countries.

e The increasing toxicological evidence that suggests that exposure to low concentrations of particles can have significant effects both on the lung and, more importantly, on the cardiovascular system. The evidence relating to the latter has been considered in detail in the recent COMEAP report 'Cardiovascular Disease and Air Pollution' (Department of Health, 2006).

All this leads us to think that a lengthy discussion of causality is not needed here: it is our considered view that the associations reported in the literature of this field are likely to represent causal relationships with air pollution, especially particles, although we accept that there is a small possibility that some or all of the reported associations represent the effects of some as yet unidentified confounding factor or factors. We accept that the mechanisms underlying these effects are not yet fully understood but we think that the evidence that the main effects bear on the cardiovascular system is persuasive. The recent paper by Pope *et al* (2004) which looks at specific categories of effects on the cardiovascular system sustains us in reaching this conclusion.

A number of questions and problems have been identified and these have been examined in depth in Chapter 3. Detailed discussion papers on each problem (in some cases major problems were broken down into a series of further in-depth questions) were prepared and these are provided as working papers to this report. Summaries of our conclusions are presented in Chapter 4.

Table 2.2: Comparison of percentage increase in mortality associated with an increase in long-term particulate exposure as estimated from selected studies
Modified using table from Pope and Dockery (2006)

Study	Primary sources	Exposure increment $PM_{2.5}$ ($\mu g/m^3$)	All-cause	Cardio-pulmonary	Lung cancer
Harvard Six US Cities original	Dockery *et al* (1993)	10	13 (4.2–23) [a]	18 (6.0–32)	18 (-11–57)
Harvard Six US Cities HEI Reanalysis	Health Effects Institute (2000)	10	14 (5.4–23)	19 (6.5–33)	21 (-8.4–60)
Harvard Six US Cities extended follow-up	Laden *et al* (2006)	10	16 (7–26)	28 (13–44) [b]	27 (-4–69)
ACS original study	Pope *et al* (1995)	10	6.6 (3.5–9.8)	12 (6.7–17)	1.2 (-8.7–12)
ACS HEI Reanalysis	Health Effects Institute (2000)	10	7.0 (3.9–10)	12 (7.4–17)	0.8 (-8.7–11)
ACS extended analysis	Pope *et al* (2002)	10 Average exposure period	6 (2–11)	9 (3–16)	14 (4–23)
ACS, Los Angeles	Jerrett *et al* (2005)	10	17 (5–30)	12 (-3–30)	44 (-2–111)
California Cancer Prevention Study	Enstrom *et al* (2005)	10	1 (-0.6–2.6) All subjects, full follow-up period (1973–2002) [c]	–	–
Post-neonatal infant mortality	Woodruff *et al* (1997)	10 (PM_{10})	4 (2–7) [d]	–	–
	Woodruff *et al* (2006)	10	7 (-7–24) [d]	113 (12–305) [e]	
AHSMOG [f]	Abbey *et al* (1999)	10 (PM_{10})	1 (-5.8–7.8)	0.1 (-6.9–7.6)	36.9 (-6.1–99.6)
AHSMOG males only	McDonnell *et al* (2000)	10	8.5 (-2.3–21)	23 (-3–55) [g]	39 (-21–150)
US Veterans Administration (VA), preliminary results, males only	Lipfert *et al* (2000)	10	0.3 (NS) [h]	–	–

Table 2.2: Continued

Study	Primary sources	Exposure increment $PM_{2.5}$ (µg/m³)	All-cause	Cardio-pulmonary	Lung cancer
Other particle metrics					
Hamilton, Ontario, Canada	Finkelstein *et al* (2004)	100 m highway, 50 m major road	18 (2–38)	–	–
Netherlands	Hoek *et al* (2002)	10 background BS	17 (-24–78)	34 (-32–164)	–
		Living near a major road – BS	41 (-6–112)	95 (9–251)	–
France	Filleul *et al* (2005)	10 BS[i]	7 (3–10)	5 (-2–12)	3 (-8–15)
ACS county analysis	Willis *et al* (2003)	10 (sulphate)	22 (13–31)	32 (21–43)	–
ACS metropolitan area analysis	Willis *et al* (2003)	10 (sulphate)	12 (6–17)	14 (7.2–21)	–

(a) Note that 13% expressed as a relative risk is 1.13; (0.042–1.23), 95% confidence interval (CI).

(b) Cardiovascular only.

(c) Effect estimates for all-cause mortality are also reported for each decade of the full follow-up period. Results showed that for the first decade, a small positive risk (3.9%) on all-cause mortality for a 10 µg/m³ increase in $PM_{2.5}$ was found. For subsequent decades, the risk estimates were no longer statistically significant.

(d) Adjusted odds ratio.

(e) Adjusted odds ratio, respiratory only.

(f) Pooled estimates (random effects) for both males and females. Pollution associations were observed primarily in males and not females.

(g) Non-malignant respiratory mortality.

(h) Reported to be non-significant by author. Overall, effect estimates for various measures of particulate air pollution were highly unstable, not robust to selection of model and time windows, and extremely difficult to interpret.

(i) Percentage for 18 areas; 6 area monitors influenced by local traffic were excluded from model. Results for 24 areas were not statistically significant for any cause of death.

HEI, Health Effects Institute; ACS, American Cancer Society; AHSMOG, Adventist Health and Smog; and BS, Black Smoke.

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Chapter 3
Discussion

In this report, a great deal of evidence has been considered and carefully weighed. In addition, original work has been undertaken, particularly on the statistical aspects of interpreting the results of the leading cohort studies that report associations between long-term exposure to air pollutants, especially fine particles ($PM_{2.5}$), and effects on health. We present our conclusions as a series of answers to questions we believe to be of particular importance. Each of these questions is considered in summary form below and at greater length in the working papers attached to this report. The reader is asked to note that a series of boxes, which summarise our working conclusions, has been included in the text at different stages in this chapter as we consider the key questions presented below. The boxes show how our thinking developed as we worked through the questions.

i How has the evidence, linking long-term exposure to air pollution and increased risks of mortality, changed since our last report?

The evidence has strengthened. The Health Effects Institute (HEI) Reanalysis of the American Cancer Society (ACS) and the Six Cities cohort studies (Health Effects Institute, 2000), confirming the reliability of these studies and extending considerably the statistical analysis of them, was available for our last report. However, the extension of the ACS study (Pope *et al,* 2002), and the other North American and European cohort studies all confirm the association between long-term exposure to fine particles and the risk of death, and provide important new information about that relationship. Work by Pope *et al* (2004) has focused on specific causes of death, with particular reference to possible mechanisms. In addition, studies of policy interventions in Dublin (Clancy *et al,* 2002) and Hong Kong (Hedley *et al,* 2002) have confirmed that noteworthy and sustained reductions in death rates can occur soon after a major reduction in air pollution.

ii What is the primary source of evidence for quantifying the effects on mortality of long-term exposure to air pollution, specifically $PM_{2.5}$?

Like others, we consider that the ACS cohort study (Pope *et al,* 1995), and its extension (Pope *et al,* 2002), is the best single source of relevant coefficients because:

a it is the most extensive in terms of size, scale and coverage of different pollution mixtures;

b its data and statistical methods have been examined intensively, by various research groups, including the HEI Reanalysis (Health Effects Institute, 2000), and in separate though linked investigations (e.g. Abrahamowicz *et al,* 2003; Willis *et al,* 2003; Jerrett *et al,* 2005);

c its principal coefficients lie well within the range of available published coefficients (see Table 2.2, page 14), though they tend to the lower end of that range.

Within the many publications on the ACS study, we recommend choosing a coefficient from the Pope *et al* (2002) update, *provided that coefficients from suitable models have been reported there*, because the 2002 study:

d is based on substantially more data than the earlier ACS study – about three times as many deaths as reported in Pope *et al* (1995);

e uses the relevant extensions of statistical methods developed in the course of the HEI Reanalysis (Health Effects Institute, 2000).

Our strategy therefore was as follows:

a identify coefficients from Pope *et al* (2002) as a starting-point for quantification;

b consider the reasons why these estimates might ideally be modified, and whether the changes would lead to higher or to lower coefficients, and if possible estimate by how much;

c see whether suitable coefficients are available from Pope *et al* (2002) to quantify our 'idealised model', and if yes, choose them;

d if not, select from Pope *et al* (2002) those risk coefficients which, in our view, best approximate to the results we think an idealised model would produce, i.e. that best reflect the weight of evidence that we have reviewed taken as a whole.

e comment on our level of uncertainty regarding the chosen coefficients.

iii What index of the air pollution mixture should be considered as the principal metric to be used in quantifying the effects on mortality of long-term exposure to air pollution?

In answer to the previous question, we stated that the American Cancer Society (ACS) study (Pope *et al,* 2002) would provide the starting point for our work. The results for different pollutants in the HEI Reanalysis (Health Effects Institute, 2000) and the Six Cities study (Dockery *et al,* 1993) have been discussed previously in our report 'Cardiovascular Disease and Air Pollution' (Department of Health, 2006*)*. This section covers the most recent update of the ACS study (Pope *et al,* 2002).

It is clear that long-term exposure to particles is linked with mortality and we agreed that some index of ambient particles should be considered as the principal metric to be used in quantifying effects of the pollution mixture.

Table 3.1 compares the relative risks, at study mean concentrations, for different particle metrics measured over the same time period (chosen as 1979–1983 as this time period contained the widest range of particle metrics for comparison). Amongst the size-based particle metrics, in the ACS study, the evidence was strongest for $PM_{2.5}$ on the basis of the magnitude

of the relative risk and its statistical significance. It should be noted that $PM_{2.5}$ is a mass concentration term that denotes the mass of particles generally less than 2.5 μm diameter per cubic metre of air. $PM_{2.5}$ is sometimes described as 'fine particulate matter'. Particle deposition in the lung is dependent on particle size and particles below 2.5 μm in aerodynamic diameter deposit effectively in the alveoli, especially in high risk groups such as the sick and infirm, or children (Department of the Environment, 1996).

The relative risk for sulphate is also shown. This is a chemical, rather than size-based, particle metric but sulphate is, in fact, predominantly part of the $PM_{2.5}$ fraction. This relative risk is also positive and statistically significant. A discussion of the relative effects of sulphate and of $PM_{2.5}$ is provided later in answer to question v of this chapter.

Table 3.1: Comparison of relative risks (RR) (with 95% CI) of all-cause mortality for PM_{15}, $PM_{15\text{-}2.5}$, $PM_{2.5}$ and total suspended particulates (TSP) for the 1979–1983 measurement period (plus sulphate for 1980–1981) (Note that these relative risks are given at 'subject weighted mean concentrations') [a,b]

	PM_{15}	$PM_{15\text{-}2.5}$	$PM_{2.5}$	TSP	Sulphate (part of $PM_{2.5}$ fraction)
All-cause mortality	1.07 (0.99–1.15) per 40.3 μg/m³	1.01 (0.97–1.06) per 19.2 μg/m³	1.09 (1.02–1.16) per 21.1 μg/m³	1.02 (0.95–1.10) per 73.7 μg/m³	1.06 (1.04–1.08) per 6.5 μg/m³

(a) The relative risks given in the table were provided by Arden Pope III (2006), personal communication. These were only presented graphically in the Pope *et al* (2002) paper. The relative risks were adjusted for the factors listed in Table 2.1, page 12.

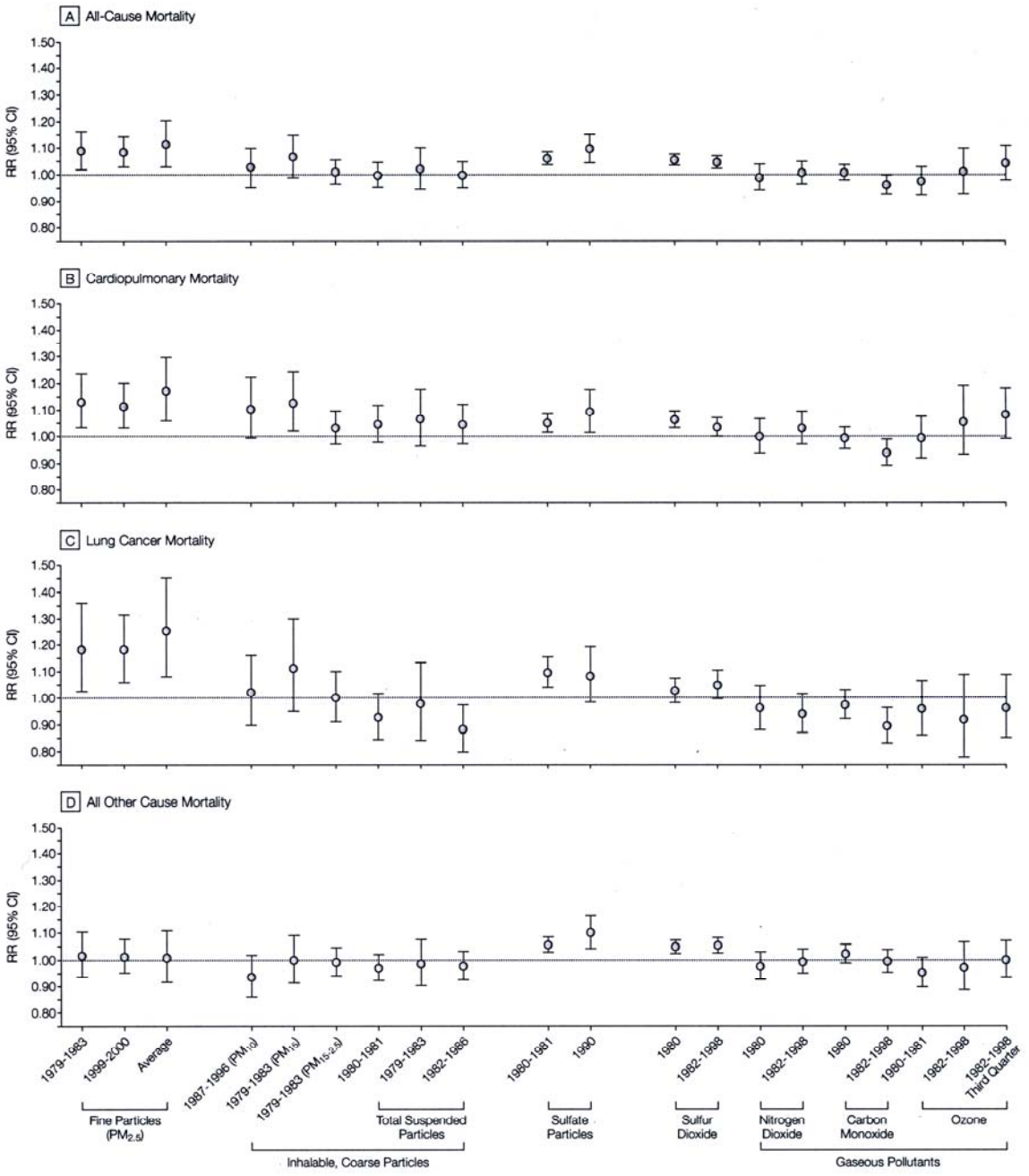
(b) The relative risks are from Figure 5 of Pope *et al* (2002) and are described as being 'at subject-weighted mean concentrations'. This is the risk at the mean concentration across the cities, weighted for the number of study subjects in each city, relative to the risk at a concentration of zero. The relative risks expressed on this basis take into account the fact that the value of the subject-weighted mean concentration is different for different pollutants. These estimates assume log-linear dependence of mortality across this range. Thus, a larger relative risk indicates a combination of the potency of the pollutant and the amount of the pollutant to which study subjects were exposed. The mean concentrations given in Table 1 of Pope *et al* (2002) are subject-weighted mean concentrations (Arden Pope III (2006), personal communication).

CI, confidence interval, and TSP, total suspended particles.

A relative risk for PM_{10} and all-cause mortality is not given in Table 3.1 as there is minimal overlap of its measurement period (i.e. years of data collection, 1982–1998) with those of the other particle metrics. The HEI Reanalysis (Health Effects Institute, 2000) of the ACS cohort does not provide relative risks for PM_{10}. In the extended analysis of the ACS study, Pope *et al* (2002) report a relative risk (and 95% CI), for the 1987–1996 measurement period, of 1.02 (0.95–1.10)[8] for all-cause mortality per 28.8 μg/m³ PM_{10}. Like the other particle metrics given in Table 3.1, PM_{10} appears to have a weaker effect on the relative risk of death from all-causes than $PM_{2.5}$ (i.e. the evidence was strongest for $PM_{2.5}$). The evidence as a whole points to $PM_{2.5}$ as the most satisfactory index of particulate air pollution to use in quantitative assessments.

[8] See Figure 5 of Pope *et al* (2002) (reproduced, with permission, as Figure 3.1 of this report). The relative risk (and CI) was provided by Arden Pope III (2006), personal communication.

Figure 3.1: Adjusted mortality relative risk (RR) ratio evaluated at subject-weighted mean concentrations (reproduced by permission of the American Medical Association)

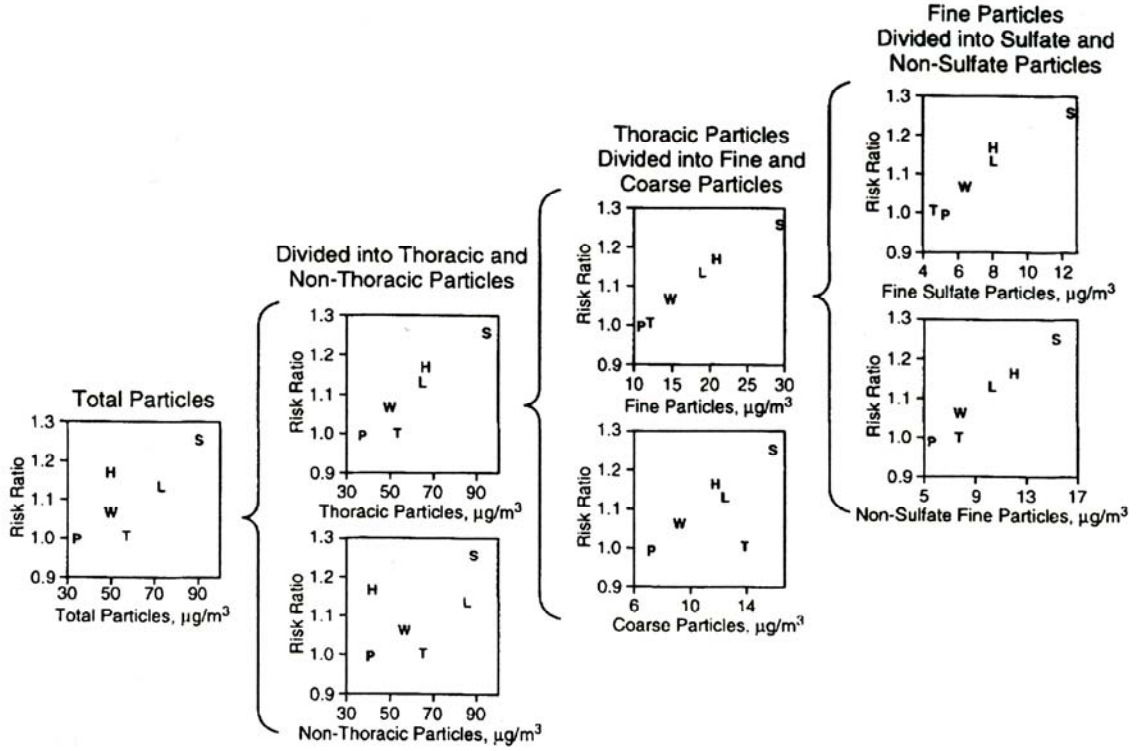


$PM_{2.5}$ indicates particles measuring less than 2.5 μm in diameter; PM_{10}, particles measuring less than 10 μm in diameter; PM_{15}, particles measuring less than 15 μm in diameter; $PM_{15\text{-}2.5}$, particles measuring between 2.5 and 15 μm in diameter; and CI, confidence interval.

A similar pattern was seen for cardiopulmonary mortality and lung cancer mortality, although the PM_{15} association was similar to that for $PM_{2.5}$ for cardiopulmonary mortality (Figure 3.1). The conclusion that $PM_{2.5}$ is the best particle metric agrees with the earlier reported evidence that showed $PM_{2.5}$ to be more closely related to mortality than PM_{10} (thoracic fraction) or total suspended particulate (TSP) (Dockery *et al,* 1993): see Figure 3.2, and with the conclusions of the HEI Reanalysis (Health Effects Institute, 2000).

The Subgroup agreed that primary quantification should be based on ambient particulate matter (PM), measured as $PM_{2.5}$.

Figure 3.2: Estimated adjusted mortality-rate ratios and pollution levels in the Six Cities study (reproduced by permission of The Royal Society of Chemistry)



Adjusted relative risks for annual mortality are plotted against each of seven long-term average particle indices in the Six Cities study, from largest size range [total suspended particulate matter (lower left), through sulphate and non-sulphate fine particle concentrations (upper right)]. Note that a relatively strong linear relationship is seen for fine particles, and for its sulphate and non-sulphate components. Topeka (T), which has a substantial coarse particle component of thoracic particle mass, stands apart from the linear relationship between relative risk and thoracic particle concentration (taken from Lippmann, 1998: Figure 5, page 87).

The thoracic fraction is defined as the mass fraction of inhaled particles penetrating the respiratory system beyond the larynx. As a function of total airborne particles, it is given by a cumulative lognormal curve with a median aerodynamic diameter of 10 µm and geometric standard deviation of 1.5 (Department of the Environment, 1996).

P = Portage, Wisconsin; T = Topeka, Kansas; W = Watertown, Massachusetts; L = St Louis, Missouri; H = Harriman, Tennessee; and S = Steubenville, Ohio.

iv Given that the effects are to be quantified using $PM_{2.5}$, does the evidence suggest the separate quantification of the effects of other pollutants?

The American Cancer Society (ACS) study (Pope *et al,* 2002) also examined the effects of gaseous pollutants. The results, given in Table 3.2, are based on subject-weighted mean concentrations.

Table 3.2: Comparison of adjusted relative risk (with 95% CI) of mortality from all-causes for SO_2, NO_2, CO and O_3 for the 1982–1998 measurement period [a,b]

	SO_2	NO_2	CO	O_3	O_3 (3rd quarter)
All-cause mortality	1.05 (1.02–1.07) per 6.7 ppb	1.01 (0.97–1.05) per 21.4 ppb	0.96 (0.93–0.997) per 1.1 ppm	1.01 (0.93–1.10) per 45.5 ppb	1.04 (0.98–1.10) per 59.7 ppb

(a) The relative risks given in the table were provided by Arden Pope III (2006), personal communication. These were only presented graphically in the Pope *et al* (2002) paper. The relative risks were adjusted for the factors listed in Table 2.1, page 12.

(b) Relative risks (RR) at subject-weighted mean concentrations for different pollutants.

CI, confidence interval.

Sulphur dioxide (SO_2)

Table 3.2 shows a positive and statistically significant association for sulphur dioxide and all-cause mortality. Positive, marginally significant, associations were found linking SO_2 and both cardiopulmonary mortality and lung cancer mortality. Unexpectedly, there was also a clear association with all other cause mortality (see Figure 3.1). Positive associations between SO_2 and mortality have also been found in many but not all other studies. There is much debate as to whether this is a direct effect or whether SO_2 is acting as a marker for pollutants emitted by sulphur-related combustion sources. Many of the studies that showed positive associations with SO_2 also showed positive associations with particles. The intervention study in Hong Kong (Hedley *et al,* 2002) showed a positive association with SO_2 in the absence of a change in particle concentrations, although there is evidence that the composition of the particles may have changed owing to the change in fuel composition. Where performed, the SO_2 association was generally maintained in two-pollutant models, although this was not the case in a study by Willis *et al* (2003) at a county rather than metropolitan area scale. We discuss these points in more detail below and in Working Paper 1. The discussion in the later section (see question xi, page 36) concludes that, overall, it is difficult to dismiss the possibility of a real effect of sulphur dioxide but even the ACS study may not have had the resolution to distinguish with confidence between a direct effect of sulphur dioxide and an apparent effect due to sulphur dioxide acting as a marker for combustion sources. For this reason, we have not chosen to recommend quantification of the possible direct effects of sulphur dioxide.

Nitrogen dioxide (NO_2) and carbon monoxide (CO)

The associations of all-cause mortality with nitrogen dioxide and with carbon monoxide are unconvincing (close to the null and not statistically significant). Nitrogen dioxide and carbon monoxide share a common source (traffic fumes) with primary particles and, in traffic-dominated areas, can be closely correlated with $PM_{2.5}$ in time-series studies. It does not necessarily follow that the same correlations are found spatially. Appendix G of the HEI Reanalysis (Health Effects Institute, 2000) gives the Pearson correlation coefficient between nitrogen dioxide and fine particles as -8% and between carbon monoxide and fine particles as -16%[9]. A similar lack of convincing positive associations between nitrogen dioxide and health was seen in the cause-specific mortality results (see Figure 3.1). Interestingly, the Six Cities study did find a positive and statistically significant association of all-cause and cardiopulmonary mortality with nitrogen dioxide but in that dataset there was a much closer correlation between nitrogen dioxide and particles (78%). Given the lack of a robust association in the ACS study, the positive associations in the Six Cities study may have been due to confounding by particles. In our opinion, there is currently insufficient evidence to attempt to quantify the possible but unproven effects of exposure to ambient concentrations of nitrogen dioxide and carbon monoxide on mortality.

Ozone (O_3)

The all-year ozone results for all-cause mortality are close to the null and non-significant although the coefficient for the 3rd quarter of the year (July to September) is slightly raised. For cardiopulmonary mortality (see Figure 3.1), the all-year coefficient was also raised and the 3rd quarter coefficient was greater and very close to statistical significance. A significant positive association between ozone and cardiopulmonary mortality was found for April to September in the HEI Reanalysis (Health Effects Institute, 2000) and for the whole year in one, but not all, of the spatial autocorrelation adjustment models used. The Pope *et al* (2002) paper does not give results for gaseous pollutants adjusted for spatial autocorrelation. Thus, there is some suggestion of an effect of long-term exposure to ozone on cardiopulmonary mortality in the summer but the overall evidence is weak in comparison with the evidence for $PM_{2.5}$. Overall, we do not recommend quantification of the effects of long-term exposure to ozone at present. However, we note that there is some evidence for an effect of long-term exposure to ozone on lung-function growth in children (WHO, 2003) and that effects on lung function growth increase the plausibility of an effect of long-term exposure to ozone on mortality.

Conclusions

Given the above discussion, the following sections concentrate on associations with $PM_{2.5}$ with further discussion of associations with sulphates in question v and sulphur dioxide in question xi of this chapter. We next consider the role of sulphates and, more generally, whether it is desirable and practicable to quantify, separately, the effects of some of the components of $PM_{2.5}$.

[9] These correlations were based on a slightly different dataset – 1980 pollution data and a subset of cities – but they nonetheless probably give a reasonable idea of the correlation coefficients on a spatial basis between these pollutants across the USA.

v Is it possible to separate the effects of 'sulphate' from those of the $PM_{2.5}$ mixture?

Particle mixtures contain a varying amount of sulphate, depending on the range of sources. This is measured as sulphate concentration. The significance of sulphate concentrations can be polarised into two viewpoints. If it were known that the sulphate component of the aerosol measured as $PM_{2.5}$ was toxicologically inert, it could be argued that policies aimed at reducing $PM_{2.5}$ by reducing the sulphate component would be pointless. Thus, the policy option of reducing $PM_{2.5}$ by imposing further restrictions on sources of sulphur dioxide would also be pointless. This case has been argued by Schlesinger and Cassee (2003). We believe, on the contrary, that the issue is more complicated than this. We see 'sulphates', as measured, as representing the formation of toxicologically active species such as sulphuric acid from sulphur dioxide emissions from the burning of sulphur-containing fuel.

In considering this question we developed three discussion papers: on the atmospheric chemistry of oxidants, sulphates and acid sulphates; on the toxicology of sulphates; and, lastly, on the epidemiological evidence linking sulphates with effects on health. These papers are attached as Working Papers 2–4.

Chemistry

An important conclusion from considerations of the atmospheric chemistry of sulphates is that sulphates (e.g. ammonium sulphate and bisulphate) do not occur as pure chemicals in the air. On the contrary, they occur in intimate mixtures with a wide range of other compounds, including transition metals which may also be a product of combustion of sulphur-containing fuels. This has led us to revise our initial thoughts regarding the toxicology of sulphates. Put starkly, though sulphates may be inert (in toxicological terms) in the pure state they might not be inert in the state in which they actually occur in the air. In addition, they are markers of complex chemical reactions yielding toxic products in air following emissions from sulphur-related combustion. This seems to us a very important conclusion.

Figure 3.3 illustrates some of the many different atmospheric processes that occur following the oxidation of SO_2 to sulphuric acid in the gas phase and its scavenging by two illustrative types of particles emitted either by power stations or diesel traffic. Internal mixing of the sulphuric acid, and its subsequent chemical reactions, forms sulphate salts and changes the properties of the particle allowing more efficient removal by wet scavenging processes.

Our thinking on the toxicological aspects of sulphates considered as pure salts is summarised below.

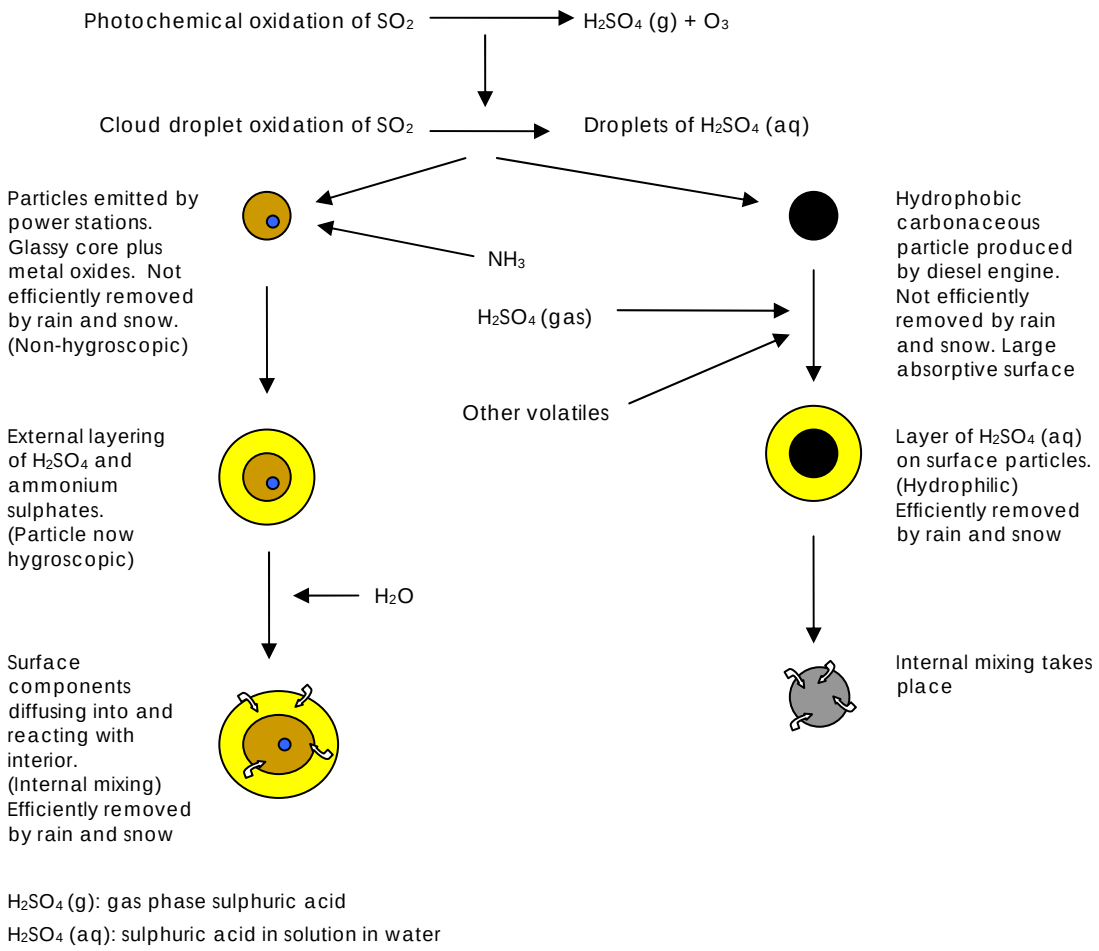
Toxicology

A literature review was conducted in order to ascertain whether there are any toxicological data available to support a role for secondary particles in driving the long-term toxicological effects of $PM_{2.5}$. Sulphates in $PM_{2.5}$ are likely to exist in the forms of sulphuric acid, ammonium bisulphate, ammonium sulphate, sodium sulphate and other metal sulphates. These species tend to become mixed with non-sulphate components in atmospheric particles.

A wide variety of forms of inorganic sulphate have been tested in a range of animal models to investigate potential acute and chronic respiratory effects including inflammation, fibrosis,

cancer and lung damage. Many of these studies have been previously reviewed in the report 'Sulphur Dioxide, Acid Aerosols and Particulates' produced in 1992 by the Advisory Group on the Medical Aspects of Air Pollution Episodes (MAAPE) (Department of Health, 1992). In general, these studies suggest that inorganic sulphate, even at high concentrations (up to 13 mg/m^3), does not induce significant toxicological effects. However, nearly all the studies identified used healthy animals.

Figure 3.3: Formation and fate of acidic particles



Relatively few studies were identified that investigated the effects of sulphates on the cardiovascular system. All of the studies identified conducted acute exposures and the results were generally negative. For example, H_2SO_4 at high doses (4 mg/m^3) did not induce any changes in heart rate, pulmonary and carotid arterial pressures, cardiac output and arterial blood gas tensions in dogs. Studies conducted in monocrotaline treated rats (pulmonary hypertension model) treated with residual oil fly ash (ROFA), identified that anthropogenic particles induced greater frequency and severity of arrhythmias. ROFA, however, is very different in composition from $PM_{2.5}$, containing much higher levels of metals in a form that is predominantly soluble. Studies using dogs with pre-existing cardiac abnormalities treated with

low doses of transition metal oxide or sulphate (0.05 mg/m^3, 3 hours per day, on 3 successive days) did not demonstrate any effect on the underlying clinical abnormalities.

The effects of sulphate-containing particles on the pH of lung lining fluid have not been widely studied. However, investigations of the lung lining fluid from individuals suffering from inflammatory diseases (e.g. asthma and cystic fibrosis) demonstrate both a lower pH and buffering capacity[10].

Since sulphates are usually associated with other components of the $PM_{2.5}$ mix, interactions are feasible. For example, it has been suggested that sulphate may play a role in mobilising transition metals from their oxide forms and in interacting with metals to drive the production of reactive oxidant species (Ghio *et al,* 1999). Sulphates could also interact with other components of the pollution mix; studies investigating interactions with ozone have generated mixed results.

In conclusion, there is no consistent toxicological evidence to suggest that long-term exposure to sulphates, in the forms investigated toxicologically, have significant effects on the cardiovascular system. In this we agree with the findings reviewed by Schlesinger and Cassee (2003). The toxicological data on nitrates are more limited than for sulphates and are insufficient to allow any firm conclusions on the effects of nitrates on human health.

Epidemiology

The epidemiological evidence bearing upon the possible role of sulphates in contributing to the effects on health attributed to $PM_{2.5}$ does not lead to clear-cut conclusions. In part this may be due to sulphate, as measured, acting as a surrogate for other more toxicologically active components, e.g. metals[11]. As regards the US cohort studies, the large contribution of sulphate to the aerosol monitored as $PM_{2.5}$ makes separation of the effects of sulphate and non-sulphate fine particles difficult and perhaps impossible.

The main evidence is from time-series studies; a detailed analysis of time-series studies that include sulphate as a variable is presented in Working Paper 4. The conclusions regarding sulphates are not clear. All the studies vary somewhat in the other pollutants studied concurrently. Qualitatively there was reasonably strong evidence of a positive effect, especially on mortality and this was supported by the quantitative meta-analysis which was dominated by two US studies and which found a small but significant association. The effects were variably robust to the inclusion of other pollutants and it should be noted that in the Wayne county analysis (Lippmann *et al,* 2000), which included the most extensive two-pollutant analysis, there was little evidence of independent effects of sulphate. The two European studies, from the Netherlands (Hoek *et al,* 2002) and West Midlands, UK (Anderson *et al,* 2001), did not show

[10] The buffering capacity of a solution is a measure of its ability to resist a change in pH when small amounts of acid or alkali are added. pH is a measure of acidity or alkalinity, an acidic solution has a low pH and an alkaline solution has a high pH.

[11] For example, recent work by Lippmann and colleagues in New York (Lippmann *et al,* 2006) has shown that nickel may be a toxicologically important component of the ambient aerosol. This study showed that a nickel-rich concentrated ambient aerosol had a greater effect on indices of cardiac function in mice predisposed to atherosclerosis (ApoE$^{-/-}$ mice) than a nickel-poor concentrated ambient aerosol. An examination of data from the NMMAPS (National Morbidity, Mortality, and Air Pollution Study) showed that, of measured chemical species, only nickel and vanadium were significantly associated with daily mortality rates.

convincing associations. A meta-analysis of panel studies from both Europe and North America found significant associations between sulphate concentrations and reductions in lung function and increases in symptoms and medication use.

Summary

We believe that regarding 'sulphate' in ambient air as toxicologically inert would be unwise, though we are persuaded that exposure to pure sulphate salts at ambient concentrations is unlikely to be harmful to health. We base this conclusion on our understanding that 'sulphate' as measured can best be regarded as a characteristic or descriptor or index of the fine particle aerosol and that interactions between sulphate salts or sulphuric acid and other components of that aerosol, including metal species, may lead to the formation and perhaps release of products that could well be damaging to health. We thus recommend that $PM_{2.5}$ should be used as the metric for quantification without consideration of an adjustment for that part of the fine particulate aerosol that comprises materials measured as sulphate. We note that nitrate species also contribute to $PM_{2.5}$. We recommend that, as in the case of sulphate species, nitrate species should not be treated separately from $PM_{2.5}$.

In the absence of clear evidence to the contrary, we consider that the recommended coefficient should apply to $PM_{2.5}$ as measured irrespective of the relative contributions of sulphate, nitrate or any other component to the total. This is not to say that all components of $PM_{2.5}$ do have the same toxicity – but that there is not, at present, evidence to quantify the effects of different components separately, in a way that would gain wide consensus.

vi Should quantification be based on all-cause or on cause-specific mortality?

It is conventional and helpful to base impact calculations primarily on all-cause mortality. This is principally in order to keep the process as simple as possible and to avoid problems caused by inaccuracies or local or national practices and customs in attributing deaths to specified causes. We support this approach. It should be noted that in contrast to time-series studies, where 'all-cause mortality' is generally understood as 'all internal (non-violent) causes', ICD 9: 000–799, in the American Cancer Society (ACS) study 'all-cause mortality' does mean exactly that, ICD 9: 000–999.

Use of all-cause mortality to estimate overall mortality impacts is a computational device; it should not be taken as implying that air pollution affects every cause of mortality. Deaths from cardiovascular disease and lung cancer appear to be the causes most significantly affected; surprisingly perhaps, on the evidence currently available, deaths from respiratory disease other than lung cancer seem to be little affected. There are several reasons for undertaking supplementary calculations of cause-specific impacts:

a it emphasises that the effects of air pollution on mortality are indeed cause-specific;

b estimating and aggregating cause-specific impacts gives a kind of cross-check on the all-cause results;

c it is easier to consider the issue of latency and/or cessation lag (see questions vii and xvi) when dealing with cause-specific mortality;

d use of life tables to derive impacts by linking the risk coefficients with demographic data takes account of age at death and, because the distribution of age at death varies by cause, cause-specific analyses lead to more accurate estimates of life expectancy[12].

We recommend therefore that supplementary calculations be based on:

a cardiovascular mortality, or alternatively – if suitable coefficients have not been published – on non-malignant cardiorespiratory mortality, where the majority of deaths are in any case from cardiovascular causes;

b lung cancer.

There is little evidence that long-term exposure to $PM_{2.5}$ increases the risks of mortality from other causes. Pope *et al* (2002) do report associations between all 'other' causes (i.e. other than cardiorespiratory and lung cancer) and both sulphates and SO_2, but it is difficult to interpret these associations and we do not recommend that they be quantified as effects of air pollution.

vii Risk coefficients from the American Cancer Society update vary according to the time period during which the annual average ambient $PM_{2.5}$ was measured. Which coefficients should be used? (Issues of latency and measurement error)

Pope *et al* (2002) present summary risk coefficients (all-cause and cause-specific mortality) relative to $PM_{2.5}$ as measured over three different time periods:

a in 1979–1983, i.e. near the start of the follow-up period (1982–1998);

b in 1999–2000, i.e. near the end of the follow-up;

c a third value derived as the average of (a) and (b), and representing pollution throughout the follow-up period.

We think that the choice of which of these is in principle most appropriate for quantification should be based mainly on the biological relevance of the time period, though other factors such as the accuracy and precision of the underlying measurements of annual average $PM_{2.5}$ should also be taken into account. In practice, of course, availability of coefficients is also relevant.

Biological relevance of the time period is closely linked to the issue of latency. If the time lag is short between exposure to pollution and the consequent effect on risks of death, then exposure throughout the follow-up period is the most biologically relevant of the three indices, given that exposure and deaths occurred throughout the period. If, however, there is a long latency, then exposure period 1979–1983 is the most relevant for deaths throughout the follow-up.

[12] Calculations of the impact of particles on life years lost give smaller results when using cause-specific mortality coefficients compared with all-cause mortality coefficients. This was thought to be due to an older average age at death for cardiovascular causes compared with deaths from all-causes (Institute of Occupational Medicine, 2003).

It is clear that the US cohort studies do not, and cannot, lead to any clear conclusion on the likely latency between a change in average pollution levels and the appearance of effects.

Nevertheless current thinking suggests that the exposure in the weeks, months and short number of years prior to death is the most biologically relevant time period of exposure for deaths from cardiovascular (or cardiorespiratory) causes, whereas the effect of exposure on lung cancer is likely to have a longer latency.

Judgements about latency also have an important bearing on whether the Pope *et al* (2002) coefficients may overestimate the mortality risk per $\mu g/m^3$ $PM_{2.5}$ at the current time and level of air pollution. It is possible that the American Cancer Society (ACS) study and other cohort studies reflect exposure to pollutants that took place some, or perhaps many, years before the air pollution measurements reported in the studies were made. The coefficients reported so far in the ACS study relate (adjusted) risk of death between the cities studied to the span of pollutant concentrations between those same cities with pollution measured near the start (1979–1983) and near the end (1999–2000) of the mortality follow-up period (Pope *et al,* 2002). Because $PM_{2.5}$ decreased in the USA in the decades prior to follow-up, the 'pollution span' between cities may well have been wider in the past than in 1979–1983 (or 1999– 2000); and so, if the mortality effects reported were due to either very long-term exposure or to exposure long ago, the reported coefficients may be inflated. This problem was discussed briefly in our recent report 'Cardiovascular Disease and Air Pollution' (Department of Health, 2006). However, this would not be a major problem if most of the effect occurred only after a short lag and the effect on risk was not persistent (Figure 3.4).

Regarding accuracy and precision of the underlying measurements of annual average $PM_{2.5}$, there are reasons for thinking that concentrations measured in 1999–2000, though based on only two years of data, may have been measured more accurately than concentrations in 1979–1983. However, the average concentration is possibly the most reliable of them all. This is discussed further in Working Paper 5.

On that basis we recommend that the risk coefficient for:

a cardiovascular (or cardiorespiratory) mortality be based on the average of the $PM_{2.5}$ concentrations measured in 1979–1983 and 1999–2000;

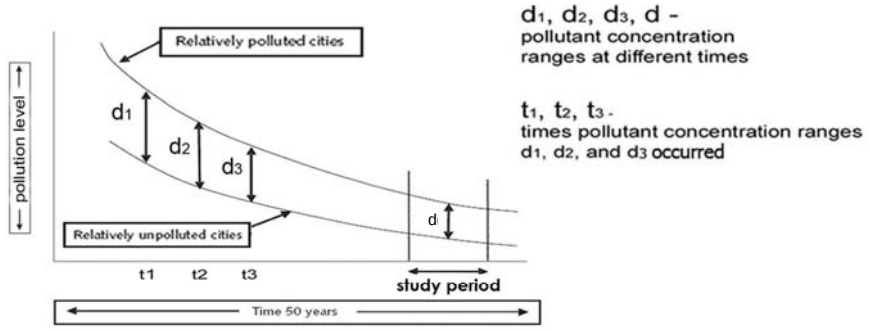
b lung cancer mortality be based on $PM_{2.5}$ concentrations measured in 1979–1983;

c all-cause mortality – where deaths are dominated by cardiovascular causes rather than lung cancer – be based on average of the $PM_{2.5}$ concentrations measured in the two periods.

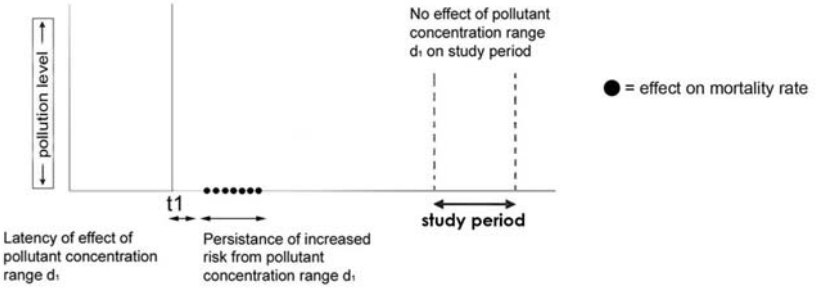
As noted above, an overestimation could occur if the earlier, rather than the more recent, exposure period mattered most.

Figure 3.4: Influence of past exposures on mortality rates in the study period

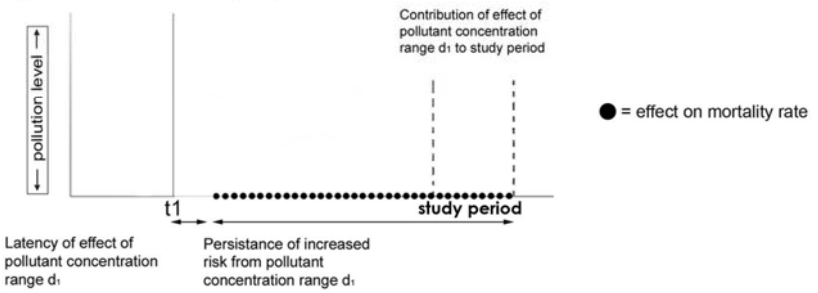
Panel A – Varying pollutant concentration ranges over time



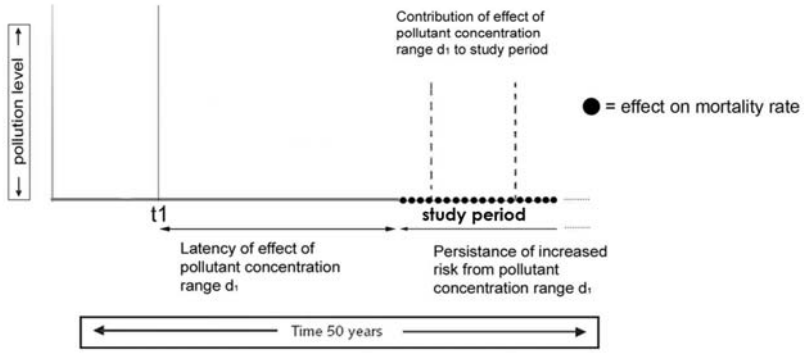
Panel B – Short latency/limited persistence of effect in response to pollutant concentration range d_1



Panel C – Short latency/extended persistence of effect in response to pollutant concentration range d_1



Panel D – Long latency and persistence of effect in response to pollutant concentration range d_1



Panel A illustrates that the pollutant concentration ranges between polluted cities and unpolluted cities may have been greater in the past. Panels B, C and D relate only to the effect of pollutant concentration range d_1 for simplicity. If the latency of the effect is short and the persistence of the increased risk is limited, then a large pollutant concentration range in the past may not have implications for the study period (Panel B). However, if the persistence of the increased risk due to pollutant concentration range d_1 is prolonged (Panel C) or the latency is long or both (Panel D), then allocating all of the increased risk to smaller pollutant concentration range d in the study period will overestimate the relative risk due to the contribution from the earlier and larger pollutant concentration range d_1.

viii Is there such evidence for the presence of a threshold or of non-linearity in the associations that deviations from linearity should be considered?

The possibility that the effects of air pollutants on health could be characterised by a threshold has long been a problem. Epidemiological studies are limited by the range of pollutant concentrations available for study and these do not usually include zero. Thus, hard evidence of the absence of a threshold is likely to be difficult to obtain. In general, it is accepted on the basis of time-series studies that no threshold of the effect of particulate matter on mortality can be defined for the population as a whole. This has caused some difficulties for toxicologists asked to explain effects at very low concentrations, but the likely distributions of exposure, together with the sensitivity of some individuals across large populations, make it plausible that there is some risk to some individuals even at very low background concentrations. The evidence regarding a threshold of effect occurring in the relationships between $PM_{2.5}$ and mortality reported in the cohort studies is discussed in Working Paper 6. We found that no evidence of a threshold has been produced – nor is there any sign of the line representing the association decreasing in slope as it approaches very low concentrations. On the contrary for lung cancer, models that do not impose linearity suggest an increase in steepness at low concentrations. On that basis, we assume that the relationship between $PM_{2.5}$ and mortality can reasonably be considered linear[13], within the range studied by the American Cancer Society (ACS) study, which fortunately includes values relevant to policy changes in the UK also. For extrapolation to higher values, attenuation of the effect should be considered – see question xiii.

Box 1: Working conclusions regarding our preferred choice of coefficients linking mortality to long-term exposure to $PM_{2.5}$

Our preferred coefficients linking long-term exposure to air pollution and mortality are derived from the largest and most extensively analysed study currently available: the extended form of the American Cancer Society study by Pope *et al* (2002). Several coefficients were reported in this study. On the basis of the considerations discussed so far, we regard the most appropriate coefficients to choose from the study to be as follows:

Coefficients based on particulate matter represented as $PM_{2.5}$, for all-cause mortality, supplemented by coefficients for cardiopulmonary and for lung cancer; and

of these, the coefficients which related the relative risk of death to the estimated average concentration of fine particles ($PM_{2.5}$) throughout the follow-up period are more appropriate, except for lung cancer where concentrations in the period 1979–1983 are more appropriate.

This leads to estimates (working conclusions at this stage), in terms of relative risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$, of:

1.06 (95% CI 1.02–1.11) for all-cause mortality;

1.09 (95% CI 1.03–1.16) for cardiopulmonary mortality;

1.08 (95% CI 1.01–1.16) for lung cancer mortality;

as presented in Table 2.1 (page 12).

[13] This linear relationship is of the logarithm of the relative risk against concentration (see Figure 2, of Pope *et al,* 2002) and it approximates to a linear relationship of relative risk against concentration for small concentration increments and small coefficients. This will simply be referred to as 'linear' in the remainder of the report, including the working papers.

We now turn to a consideration of those factors which might modify these working conclusions.

ix Should adjustment of coefficients for the possible effects of spatial autocorrelation be made?

Confounders are factors that are correlated both with exposure (air pollution) and, directly or indirectly, with the outcome (mortality). Confounders can bias (increase or decrease the size of the effect estimate) the relationship between air pollution and mortality. Studies usually adjust for them as well as possible but, inevitably, some residual confounding may remain as it is not possible to adjust for unidentified confounding factors, and even for identified factors adjustment may be incomplete.

If adjustment is made for factors that are correlated with $PM_{2.5}$ but are not, in fact, risk factors for mortality, then the confidence intervals for the $PM_{2.5}$ mortality risk coefficient will be widened. Despite widespread belief to the contrary, such adjustment will *not in general* bias the coefficient relating to the air pollutant towards zero (towards the null). However, bias towards the null will occur if there is classical measurement error[14] in the air pollution exposure measurements. Simulations (Working Paper 7) show that this is not too serious at low correlations but will get worse with increased correlation between the putative confounder and the exposure (air pollution). In the case of the American Cancer Society (ACS) study, it is likely that there is some classical measurement error. It is unknown whether it is large enough to affect the results, though the estimate made elsewhere in this report (Working Paper 5) suggests it is small, in which case bias from it would be small.

Thus, there is a trade-off between reducing bias by adjusting for confounders and the possibility of bias towards the null if measurement error is present and if the putative confounder is, first, not actually associated with mortality and, second, reasonably highly correlated with the exposure. We recommend that the ACS study relative risks adjusted, at least, for 'all individual covariates' be used. We now go on to consider the case for further adjustment.

Spatial autocorrelation, also called spatial clustering, occurs when a variable (e.g. mortality) shows more similar values nearby than at more distant locations. For example, mortality rates in cities close together in one region might be more similar than mortality rates in other parts of the country due to a regional factor (e.g. a common regional lifestyle). Spatial autocorrelation in model residuals indicates that there are relevant risk factors missing from the model. Models with no allowance for spatial autocorrelation, when it is present, will produce confidence intervals that are narrower than they should be and p-values smaller than they should be.

The missing risk factors might be confounders, although the presence of spatial autocorrelation does not prove that. Reducing vulnerability to confounding and avoiding incorrect confidence intervals can then be approached in two ways (the first being more reliable):

a incorporating the missing risk factors into the model;

b adjusting for the spatial autocorrelation using appropriate statistical techniques.

[14] Classical measurement error is the error between the measured mean concentration and the 'true' mean concentration.

However, the increase in bias to the null in the presence of measurement error, discussed in the paragraphs on confounding above, can also occur with adjustment for spatial autocorrelation. This bias increases with increased tightness of the spatial smooth[15]. Thus, it is not clear-cut that the coefficients with the most aggressive control for spatial autocorrelation in the Pope *et al* (2002) study are the best ones to adopt. Table 3.3 shows that the relative risk for all-cause mortality decreased with increased adjustment for spatial autocorrelation. (It should be noted that the analysis in Pope *et al* (2002) using the Bartlett test showed no evidence of statistically significant spatial autocorrelation in the data, i.e. in conventional interpretation, further adjustment is not required. Such adjustment may nevertheless be desirable, because lack of statistical significance is no guarantee that spatial autocorrelation is not present. In fact, Table 3.3 suggests that it was.)

Table 3.3: Relative risks (with 95% CI) for all-cause mortality associated with 10 μg/m³ increases in $PM_{2.5}$ concentrations for the 1979–1983 measurement period

		All covariates plus spatial smoothing		
	All individual covariates	**Least adjustment (Span – 50%)**	**Medium adjustment (Lowest variance)**	**Highest adjustment (Highest p-value)**
All-cause mortality	1.04 (1.01–1.08)	1.03 (0.999–1.06)	1.02 (1.00–1.05)	1.02 (0.995–1.04)

The relative risks given in the table were provided by Arden Pope III (2006), personal communication. These were only presented graphically in the Pope *et al* (2002) paper. The relative risks were adjusted for the factors listed in Table 2.1, page 12.

CI, confidence interval.

Unfortunately, coefficients adjusted for spatial autocorrelation are only given for $PM_{2.5}$ concentrations as measured in 1979–1983, not for the average of the 1979–1983 and 1999–2000 exposure periods.

For cardiopulmonary mortality, the unadjusted coefficient (all covariates) was 1.06 (95% CI 1.02–1.11), compared with 1.05 (1.02–1.09)[16] with most aggressive adjustment for spatial autocorrelation. Corresponding results for lung cancer were 1.08 (1.01–1.16) for the model with all covariates; and an almost identical estimate of 1.08 (1.01–1.15) with most aggressive adjustment for spatial autocorrelation. Aggressive adjustment for spatial autocorrelation changed the estimated coefficient for mortality from all-causes other than cardiopulmonary or lung cancer from 1.01 (0.97–1.05) (all covariates) to 0.98 (0.95–0.999) after adjustment for spatial autocorrelation, i.e. the adjusted coefficient is consistent with a beneficial effect of $PM_{2.5}$ on all 'other' causes. This of course does not make sense biologically. However, this artefact has a clear impact on the all-cause coefficient, while changing the cause-specific coefficients for cardiopulmonary and lung cancer mortality only a little.

In summary, our assessment of the impact of confounding and spatial autocorrelation favoured adjusting for all individual covariates and spatial autocorrelation at the highest adjustment level

[15] Smoothing refers to the process of fitting a smooth curve through the data.

[16] Figures provided by Arden Pope III (2006), personal communication. Relative risks were only shown graphically in Pope *et al* (2002).

undertaken. However, this preference was based on an uncertain trade-off of biases; and we note the preference of Pope *et al* for the estimate without spatial smoothing. In addition, no coefficient for $PM_{2.5}$ and all-cause mortality, adjusted for spatial autocorrelation, was available for our preferred exposure measure of the average of the 1979–1983 and 1999–2000 exposure periods.

x How should coefficients derived from studies conducted at a smaller spatial scale than the American Cancer Society study be used to estimate impacts on health in the UK?

A detailed discussion paper considering this issue is included as Working Paper 8.

The key American Cancer Society (ACS) study papers (Pope *et al,* 1995, 2002) compare mortality and pollution between regions, at the level of US metropolitan area (the central county including the city centre and other counties with more than 50% of the population living in the contiguous urban area). Some studies published in the last few years have focused on a finer spatial scale. These studies (e.g. Hoek *et al,* 2002; Willis *et al,* 2003; Finkelstein *et al,* 2004; Jerrett *et al,* 2005) have reported coefficients linking $PM_{2.5}$ with risk of death that are two or three times as large as those of the ACS study (see Figure 3.5). As an estimate of the magnitude of the difference, in the study most comparable to the ACS, Willis *et al* (2003) found that risk coefficients examined at a smaller spatial scale (i.e. at level of county rather than metropolitan area) estimated a relative risk (for an approximately 20 $\mu g/m^3$ range) of 1.32 compared with 1.17 unadjusted, i.e. a two-fold increase. Hoek *et al* (2002) and Jerrett *et al* (2005) also suggest higher factors. This raises some important questions, e.g.:

a Why does this difference occur?

b Which coefficients are most appropriate for estimating impacts on health in the UK – the ACS study coefficients or the larger coefficients reported by the 'smaller spatial scale' studies?

c More generally, how should coefficients derived from studies conducted at a smaller spatial scale than the ACS study be used to estimate impacts on health in the UK?

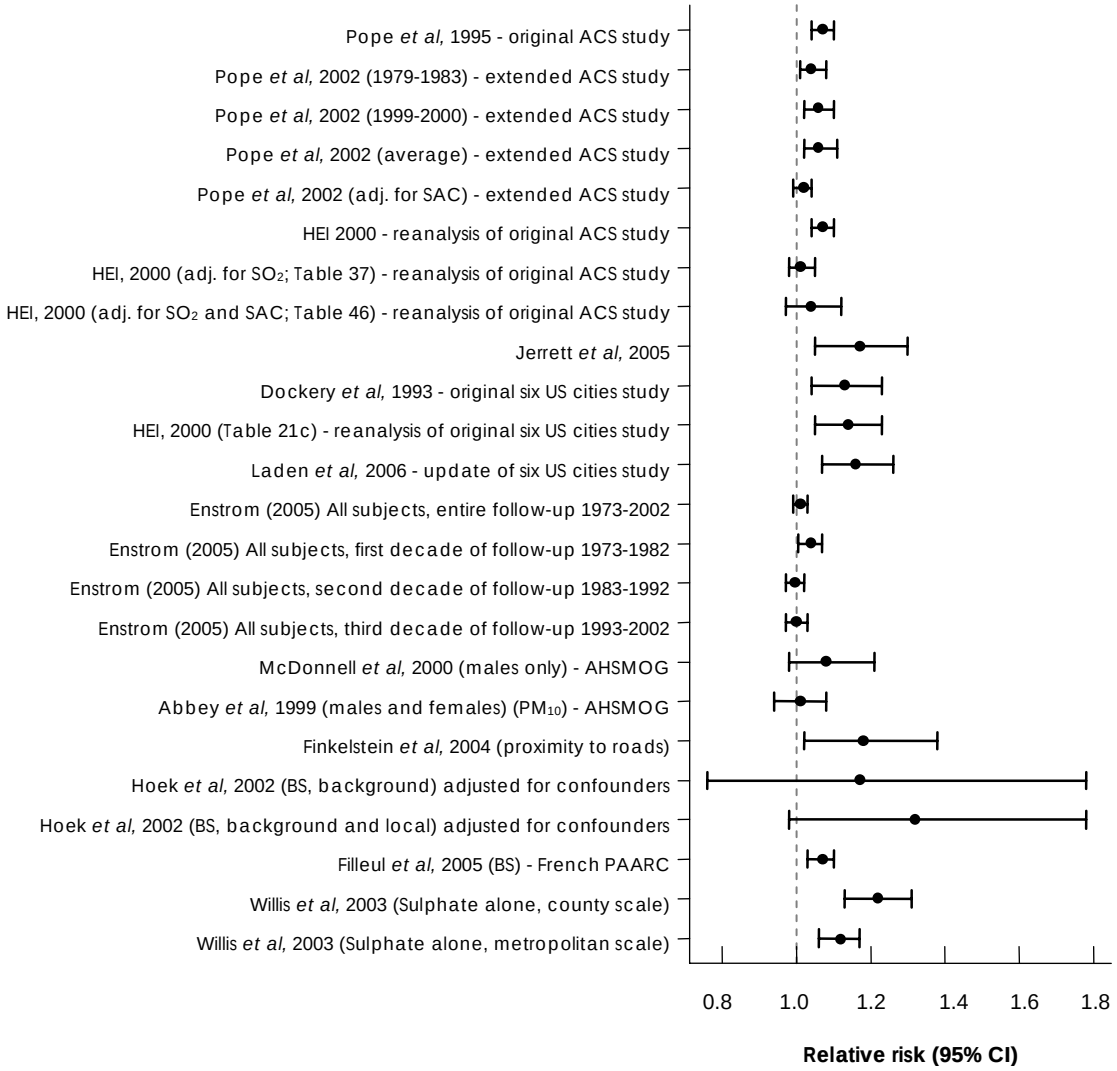
Two explanations for the larger coefficient in smaller scale studies deserve mention:

a Reduction of the spatial scale used in the studies would be expected to lead to a reduction of exposure measurement error. Some types of exposure measurement error ('classical') would bias coefficients downwards (attenuate them), so that reduced exposure measurement error in smaller scale studies might explain their higher coefficients. In this case the smaller scale study coefficients should be preferred. The argument is not clear-cut however. The most obvious reduction in measurement error in small compared to large area studies is of Berkson type error, which does not attenuate coefficients. It is likely that classical error will also be reduced, but if so this would only lead to reduced attenuation if the variation in true exposures in the smaller scale study reduced less. It is thus not clear which studies suffer most attenuation due to measurement error.

b Studies carried out on a smaller spatial scale and especially those focusing on proximity to roads, may be reflecting the effects of a different pollutant mixture than those which involve larger areas, i.e. by working on much smaller spatial scales, their studies may have specifically picked up effects of primary traffic-related pollution which, per μg/m^3, may have higher risks than $PM_{2.5}$ generally.

Thus the increase in the coefficient may be due to reduction of measurement error or greater exposure to a more toxic form of $PM_{2.5}$, but these are possibilities rather than conclusions.

Figure 3.5: Comparison of the relative risk of all-cause mortality per 10 μg/m^3 increase in $PM_{2.5}$ and other particle metrics



ACS, American Cancer Society; HEI, Health Effects Institute; Adj., Adjusted for; SAC, Spatial Autocorrelation; AHSMOG, Adventist Health and Smog; and BS, Black Smoke.

• = central estimate, 95% confidence interval (CI).

Some of the studies (Hoek *et al,* 2002; Jerrett *et al,* 2005) are specific to much smaller populations and geographical areas than the overall ACS study, while Willis *et al* (2003), who use the full coverage of the ACS study, use mortality data from the initial short follow-up period only, and report results for sulphates but not for $PM_{2.5}$. In addition, coefficients derived from some of the small spatial scale studies may be subject to error as a result of uncorrected effects of autocorrelation (see Working Paper 7) and be significantly affected by local (not easily generalisable) patterns of distribution of air pollutant concentrations. It is not known whether publication bias affects the studies on a smaller spatial scale. For these reasons, we prefer to select core estimates based on Pope *et al* (2002).

We recognise nevertheless that the thrust of these studies is towards higher coefficients than Pope *et al* (2002), and we think it is desirable to take account of this in selecting risk coefficients. In the absence of specifically relevant analyses on a smaller spatial scale, we think it reasonable to assume that adjustment for analyses on a smaller spatial scale would increase risk coefficients. In particular, the coefficients which we previously considered large (i.e. in the 2001 COMEAP report) are now more plausible.

xi Should the coefficient linking $PM_{2.5}$ and mortality reported in the American Cancer Society study and in revised form in the extension to that study, be adjusted for sulphur dioxide?

To determine whether the coefficient linking $PM_{2.5}$ and mortality should be adjusted for sulphur dioxide (SO_2), it is useful as a first step to consider whether the observed association with SO_2 is likely to be causal. This is followed by a discussion of other issues relating to the interpretation of two-pollutant models.

Cohort studies and intervention studies that have looked at associations with SO_2 are summarised in Table 1 of Working Paper 1. This shows that many, but not all, studies have shown positive associations between SO_2 and all-cause or cause-specific mortality. Whether these associations are causal is a far more complex question.

Many of the studies that showed positive associations with SO_2 also showed positive associations with particles. Correlations between SO_2 and particles in the studies varied from weak to reasonably strong. Where two-pollutant models were performed – e.g. the HEI Reanalysis (Health Effects Institute, 2000) – the SO_2 association was generally maintained in two-pollutant models. Evidence for an independent effect of SO_2 and its importance relative to particles was weaker when pollution was characterised at the smaller county scale than in larger metropolitan areas (Willis *et al,* 2003)[17]. The interpretation of two-pollutant models is discussed further below.

[17] The study by Willis *et al* (2003) at the county scale found that the SO_2 association adjusted for sulphate was not statistically significant. No association was given for SO_2 alone so it is not possible to judge whether the size of the association was reduced or maintained after adjustment for sulphate. In models including sulphates, the SO_2 coefficient was 1.12 (95% CI 0.97–1.28) in county scale analyses for a 27 ppb range (from the lowest to the highest concentration across counties) compared with 1.27 (1.15–1.40) in metropolitan area analyses. Conversely, in the same models, i.e. including SO_2, the coefficient for sulphates was higher in county scale analyses than in metropolitan area analyses – see question x and Working Paper 8.

The study by Hedley *et al* (2002) showed important short- and long-term reductions in mortality associated with a reduction in sulphur levels in transport and industrial fuels. The main change in monitored pollutants was a fall in SO_2. PM_{10} concentrations did not change overall, but there is emerging evidence that the composition of particles was affected, notably, there was a reduction in the transition metals, nickel and vanadium (Hedley *et al,* 2005).

There is reasonable evidence for respiratory effects of SO_2 but cardiovascular effects (which are likely to dominate the association with SO_2 in terms of cardiopulmonary mortality) are more unexpected. Time-series evidence supports this (see Figure 1 of Working Paper 1), although, as always, there is the issue of whether this could be explained by correlation with particles. There is very little toxicological evidence available on cardiovascular endpoints relating to long-term exposure to SO_2.

Overall, it is difficult to dismiss the possibility of a real effect of SO_2 but even the ACS study may not have had the resolution to distinguish with confidence between a direct effect of SO_2 and an apparent effect of SO_2 where it is acting as a marker for pollutants generated by combustion sources using sulphur-containing fuel. We have chosen to rely on $PM_{2.5}$ as the main metric due to the wider range of available evidence on this pollutant (including some mechanistic evidence). However, it must be borne in mind that $PM_{2.5}$ represents a potentially wide range of primary and secondary combustion sources. We have not chosen to recommend quantification of the possible direct effects of SO_2 as a sensitivity analysis, due to the possibility that it is acting as a marker for some of the same combustion sources as represented by $PM_{2.5}$.

The Health Effects Institute (2000) showed that adjustment for SO_2 caused a marked reduction in the $PM_{2.5}$ coefficient, whereas the SO_2 coefficient was stable to adjustment for $PM_{2.5}$. A crucial question is whether this indicates a real effect of SO_2 (or another factor for which SO_2 acts as a marker) or not. A real effect of SO_2 would suggest that it would be appropriate to quantify a direct effect of both pollutants and to use, for each, a coefficient adjusted for the other – and specifically to use the smaller adjusted $PM_{2.5}$ coefficient. Alternatively, both SO_2 and $PM_{2.5}$ could be markers for some of the same combustion sources in which case it would not be appropriate to adjust one for the other when they were both representing the same thing. It is also worth noting that Jerrett *et al* (2005) found a clear, large association with $PM_{2.5}$ in Los Angeles where levels of SO_2 are very low.

If SO_2 and $PM_{2.5}$ are closely correlated, it may be difficult or impossible to separate their effects in two-pollutant models. Appendix G[18] of the HEI Reanalysis gave a moderate Pearson correlation coefficient of 0.5 between SO_2 and $PM_{2.5}$. However, this leads to no immediate conclusion as to what percentage of the $PM_{2.5}$ mortality coefficient is explained by SO_2 as this also depends on the relative strength of the true relationships between these two pollutants and mortality. In addition, if the $PM_{2.5}$ and SO_2 measurements are subject to error, then the observed correlation, i.e. 0.5, will underestimate the true correlation.

The simulations in Working Paper 7 have shown that, if classical measurement error is present and the correlation between the putative confounder and the main pollutant of interest is high,

[18] Available on request from the Health Effects Institute.

then the main pollutant effect ($PM_{2.5}$) will be biased downwards. This suggests that the $PM_{2.5}$ coefficient could be reduced in a two-pollutant model with SO_2 even *without* SO_2 being truly associated with mortality.

There may be additional uncertainties if an adjusted coefficient is used to best represent the size of the 'true' effect of $PM_{2.5}$. For example, the number of cities with *both* SO_2 and $PM_{2.5}$ measurements may be much smaller than that with either alone[19].

It is preferable to adjust directly for known confounders but adjustment for spatial autocorrelation does reduce vulnerability to confounding by risk factors that are not in the model. Thus, taking adjustment for spatial autocorrelation into account may compensate for an absence of adjustment for SO_2 [20]. It is of interest to note that adjustment for SO_2 in the regional adjustment model in the HEI Reanalysis (Health Effects Institute, 2000) of the ACS study did not give such a marked reduction in the $PM_{2.5}$ coefficient (see Table 1 of Working Paper 1) as occurred in the main model. This suggests that adjusting for spatial autocorrelation in the regional adjustment model takes into account the effects of SO_2 or another spatially distributed confounder represented by SO_2.

The above complexities of interpretation, and the fact that resolving these points of finer detail may not be within the limit of resolution of the ACS study, persuade us against using an adjusted $PM_{2.5}$ coefficient for quantification. Qualitative judgements of the information discussed above have, however, informed our view on the uncertainty around the $PM_{2.5}$ coefficient from a single pollutant model.

xii Should the coefficient be adjusted for measurement error?

Working Paper 5 discusses how measurement error in the average between the exposure periods might be judged from the information on the correlations between the two measurement periods. Given certain assumptions, the amount by which the coefficient for $PM_{2.5}$ could be attenuated by measurement error can be estimated. Our estimates suggest that adjusting for measurement error would increase the coefficient by only a small amount and so we have not attempted to do so formally.

xiii Is the magnitude of the coefficient plausible?

Earlier sections, particularly that on smaller spatial scales, show that a range of coefficients have been reported. Are all these coefficients plausible? Here we consider the possibility that large coefficients are implausible but it should be recalled that very small coefficients might also be regarded as implausible in the light of the accepted effects of exposure to pollutants such as environmental tobacco smoke (Department of Health, 2006). As a rough cross-check, we have performed some calculations using historical pollution reductions and compared the predicted

[19] Appendix G of the HEI Reanalysis (Health Effects Institute, 2000) indicates that 38 cities had both $PM_{2.5}$ and SO_2 data compared with 50 cities with $PM_{2.5}$ data.

[20] Pope *et al* (2002) do not report results for a $PM_{2.5}$ coefficient adjusted for SO_2 but do give coefficients adjusted for spatial autocorrelation.

impact using the coefficients against the actual changes in life expectancy or death rates over the relevant time period. This can only be very approximate since there will be many other factors affecting death rates over the same time period. For example, in the period 1950–1980, several formal studies showed relationships between long-term exposure to air pollution and mortality (e.g. Daly, 1959; Reid, 1964); and these generally were not used to inform policy because adjustment for covariates was limited, at a regional rather than at an individual level. It was only with the cohort studies (Dockery *et al,* 1993; Pope *et al,* 1995) and their individual-level adjustment for covariates that the effects discussed in this report began to have a major effect on policy. It would therefore be very presumptuous of us to use historical UK mortality data to make strong judgements on the plausibility or otherwise of possible coefficients for the effect of $PM_{2.5}$ on mortality, based on informal assessments with no adjustment for confounding factors. But we may nevertheless be able to determine whether the coefficients are grossly implausible. The calculations are described in Working Paper 9.

This showed that, for the reductions in pollution since the 1970s, neither a coefficient of 6% nor a coefficient of 17% was grossly implausible, although for the higher coefficient the proportion of the overall decline in death rates predicted to be due to pollution was a high proportion of the observed reduction in age-standardised mortality rate. In men, the decline predicted using a coefficient of 17% closely approached the reduction in age-standardised mortality rate unexplained by smoking, calling into question its plausibility. The change in pollution in the UK since the 1970s is within the range covered by the American Cancer Society (ACS) study and so these estimates assume linearity of the concentration-response relationship – see question viii, page 31.

For reductions since the mid-1950s, the plausibility of the 6% coefficient is more doubtful when using a linear relationship, although as this involves pollution concentrations above the range of the ACS study, the shape of the relationship is unclear. A logarithmic[21] curve which flattens off at high concentrations has been suggested (Cohen *et al,* 2004) and this would give more plausible results. There is more uncertainty in estimating pollution concentrations further back in time and the nature of particulate pollution has been changing. Therefore, any calculations back to the mid-1950s would provide a weaker test of plausibility than the reductions since the 1970s. For reductions since the 1950s, the results using a coefficient of 17% would be implausible, assuming linearity.

The general impression from this consideration of plausibility was one of the factors informing the various views on uncertainty described in question xv.

In summary, assessment of the predicted changes in death rates from past changes in pollution did not suggest that the 6% coefficient was grossly implausible. This cross-check did not lead us to change our view on the preferred coefficient.

[21] Plotted against the logarithm of the concentration.

Box 2: Second working conclusions regarding our preferred choice of coefficients linking mortality to long-term exposure to $PM_{2.5}$

To what extent do the working conclusions given in Box 1 (see page 31) need to be adjusted in the light of the further considerations discussed in questions ix–xiii above?

Given the difficulty in distinguishing whether sulphur dioxide has a direct effect or whether it is acting as a marker for sulphur-related combustion sources, and our related decision not to attempt to quantify an effect of sulphur dioxide directly, we have not recommended adjustment for the possible effects of sulphur dioxide. As noted in the text, formal adjustment for several of the factors considered is not possible, in the sense that results have not been reported for models that incorporate all the characteristics that we see as desirable. However, in qualitative terms,

- **a** adjustment for spatial autocorrelation reduces the risk coefficients;
- **b** adjustment for finer spatial scale increases the coefficients, perhaps substantially, but the highest estimated coefficients stretch plausibility;
- **c** adjustment for measurement error increases them but only a little.

It is not possible, in the absence of exact results, to know how these factors play out relative to one another quantitatively. However, insofar as we have been able to derive approximate quantitative estimates for the scale of these adjustments on the ACS coefficients for all-cause mortality, then joint adjustment for the two main factors of spatial autocorrelation and analysis on a finer spatial scale may have no great effect overall.

This leads to the same estimates as before, in terms of relative risk per 10 $\mu g/m^3$ $PM_{2.5}$, of:

1.06 (95% CI 1.02–1.11) for all-cause mortality;

1.09 (95% CI 1.03–1.16) for cardiopulmonary mortality;

1.08 (95% CI 1.01–1.16) for lung cancer mortality

as presented in Table 2.1 (page 12). This is also broadly consistent with the recommendations of other expert groups, e.g. the WHO/UNECE Task Force on Health of the Convention on Long-Range Transboundary Air Pollution (CLRTAP) (World Health Organization, 2006), and the Health Effects Subcommittee of the Advisory Council on Clean Air Compliance Analysis (US Environmental Protection Agency, 2004).

There are some further questions still to be considered in arriving at our final view on the effect of long-term exposure to $PM_{2.5}$ on mortality.

xiv Transferability to the UK of results of studies undertaken abroad

The COMEAP 'Statement and Report on Long-Term Effects of Particles on Mortality' (Department of Health, 2001) raised the question of whether the findings of the major US cohort studies were transferable to the UK. Members discussed this in some detail in Section 2.2 of the 2001 report (pages 12–13, paragraphs 24–28). The discussion includes mention of exposure to co-pollutants and notes the HEI Reanalysis (Health Effects Institute, 2000) findings of a strong association with sulphur dioxide. This is discussed elsewhere in this report (see question xi, page 36).

The American Cancer Society (ACS) study has several major advantages regarding transferability of its coefficient to the UK. First, the ACS study is a general population study of people actually exposed to ambient air pollution, including to $PM_{2.5}$ in background concentrations very relevant to UK conditions and policies. Thus, there is no cross-species extrapolation, and no

extrapolation from very high to very low exposures – two issues that complicate quantified risk and impact assessment in many other contexts. Second, the ACS study is a large-scale, US-wide study, and so encompasses a very wide range of climate conditions, pollution mixtures and sub-populations. This strengthens it as a basis for use elsewhere. Finally, there are now strong precedents for use of the estimates of the ACS study outside the USA itself. For example, they have been used by the WHO to estimate the mortality impacts of urban air pollution in its global and regional burden of disease report (Cohen *et al,* 2004); they were recommended for use in Europe by the WHO/UNECE Task Force on Health of the CLRTAP (World Health Organization, 2006); and they were used in the recent cost-benefit analysis of the European Commission's Clean Air for Europe Programme (CAFE, 2005a,b). Indeed, arguably the UK is in several relevant respects more similar to the USA than it is to some other European countries.

Nevertheless, there are other factors that lead to uncertainties when using the ACS risk estimates in the UK rather than in the USA. These include different time periods of exposure, different patterns of change in long-term concentrations, different composition of the ambient aerosol (for example, concentrations of elemental carbon are generally higher in the UK), different mixtures of co-pollutants, and different response patterns due, perhaps, to different access to health care and different distributions of sensitivity. The last could be due to different age structures in the population, socioeconomic factors or, conceivably, to a different distribution of genetic polymorphisms. These factors could affect the magnitude of the coefficient linking $PM_{2.5}$ and mortality. We note that the factors affecting transferability could either increase or decrease the impact on health depending on the factor involved.

We considered (Working Paper 7) whether the different relative risks for different levels of higher education from Pope *et al* (2002) could be used when estimating effects in the UK by weighting for the different proportions of these groups in the UK population. However, the meaning of the groups 'more than high school', 'high school' and 'less than high school' would be different in the UK compared with the USA. We note nevertheless that, in the ACS study, the highest risks were found in the 'less than high school' education group, and that these were under-represented in the ACS study as a whole, suggesting a possible underestimate in transferring ACS risks to the UK population as a whole[22]. When impacts are calculated, differences in background mortality rates will also be important; the impact calculations will take these into account.

Members noted in 2001 that European studies were under way. Hoek *et al* (2002) have published a study showing an association between cardiopulmonary mortality and long-term exposure to traffic-generated air pollution in the Netherlands. Nafstad *et al* (2004) have also shown in Oslo that long-term exposure to urban pollutants is related to deaths from respiratory and cardiovascular causes. Filleul *et al* (2005) also report positive associations between all-cause mortality and measures of particles or nitrogen oxides in a cohort study in France. The intervention studies in Dublin and Hong Kong (Clancy *et al,* 2002; Hedley *et al,* 2002) show that a reduction in long-term exposure to pollutants (PM and sulphur dioxide) is associated

[22] We note that, subsequent to our cut-off for inclusion of studies in the report, an excellent review by Pope and Dockery (2006) was published. This included a reweighting of the ACS estimate to an 8–11% increase in mortality per 10 $\mu g/m^3$ $PM_{2.5}$, taking into account the proportion of those with different levels of education in the ACS cohort. This emphasises our point that there is a possible underestimation of risk in transferring ACS risks to the UK population as a whole.

with a reduction in deaths from cardiovascular diseases. These studies confirm effects outside the USA and so go some way to offering reassurance regarding transferability of the ACS coefficients as well as providing strong evidence that associations are causal.

xv How should we express uncertainty regarding the value of the coefficients given in our final recommendation above?

Sources of uncertainty

The coefficients listed in Table 2.1 (page 12) are expressed as best estimates of the true coefficients with the attendant 95% confidence intervals. The conventional statistical interpretation of the 95% confidence interval is that on average 95% of confidence intervals constructed in this way contain the true relative risk coefficient; however, it does not tell us where within that range the true value lies (or which confidence intervals fail to contain the true value). In the case of all-cause mortality our best estimate of the true coefficient is 1.06 and the 95% confidence interval is 1.02–1.11. It should be noted that it is possible to construct narrower confidence intervals which have a lower probability (e.g. 90 or 80%) of including the true value of the relative risk coefficient.

This 95% confidence interval represents only some of the overall uncertainty around the best estimate of the coefficient. It represents, in fact, the sampling error (statistical uncertainty) inherent in the particular study under consideration. No other cause of uncertainty is captured by the confidence interval. In moving from expressing the uncertainty in the results of a particular study to expressing the uncertainty in the choice of a representative coefficient for use in quantification, other considerations need to be taken into account. For example, there is variability in the results of studies from different locations and time periods (Figure 3.5). The reasons for this variability are unknown but may include variations in exposure assessment, toxicity of the air pollution mixture, population exposure or underlying vulnerability within the population. This forms part of the uncertainty around the best estimate to use for quantification.

One of the other causes of uncertainty is that arising from residual or unaccounted-for confounding. This is a component of what is sometimes termed 'model uncertainty'. The likely impact of this unaccounted-for confounding is, of course, unknown: indeed, the causes of this unaccounted-for confounding may well also be unknown, or known only partially. Another source of uncertainty is provided by information bias, also discussed in Working Paper 7. Other sources of model uncertainty include uncertainties about strategic judgements, e.g. linearity, adjustment for SO_2 or not, and relative toxicities of different components of the $PM_{2.5}$ mixture.

Approaches to quantifying uncertainty

We identified two principal means of quantifying some of the uncertainty due to these causes:

a making assumptions about the possible extent of information bias and/or residual confounding, combined with statistical uncertainty using Monte Carlo methods;

b use of a Delphic approach which involved elicitation of the views of Members on possible levels of uncertainty regarding the best estimate of the true coefficient.

These are discussed at some length in Working Paper 7.

Method (a) allowed us to calculate what might be described as extended confidence intervals around the best estimates of true coefficients published by Pope *et al* (2002), on the basis of (unverifiable) assumptions about the size of the residual confounding and information bias. As might be expected, increasing estimates of residual confounding and information bias produced extended uncertainty intervals which were wider than the original statistical confidence intervals and in some cases included (as a lower boundary) a relative risk (RR) of 1.00. In other words, under assumptions of more serious residual confounding and information bias, our uncertainty includes the possibility of no effect.

We found these calculations instructive in showing that the true extent of uncertainty around the best estimate of the true coefficients could be considerably greater than that represented by the conventional statistical confidence intervals. We decided, however, to base our uncertainty estimates on method (b). Our reasons for this lie, firstly, in our own uncertainty of the likely extent of residual or unaccounted-for confounding and of the extent of information bias present and, secondly, in that method (b) allows Members to incorporate other aspects of uncertainty, albeit informally.

Our approach – elicitation of Members' views

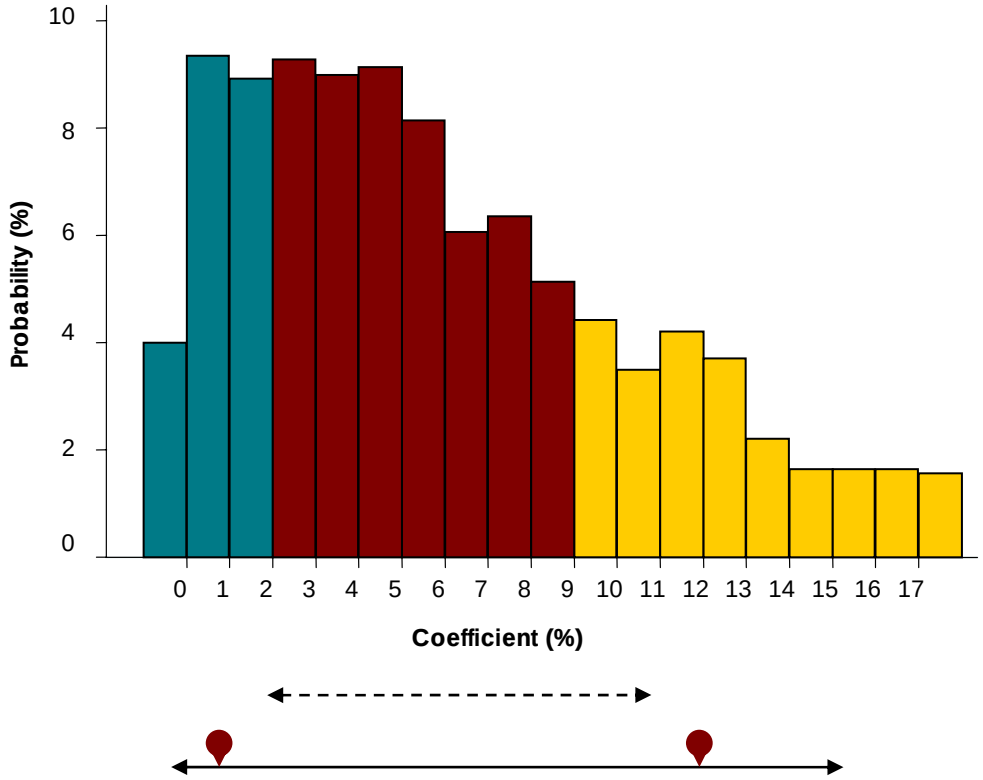
An approach was developed to discover Members' views of the value of the coefficient linking long-term exposure to $PM_{2.5}$ and relative risk of death from all-causes. In this, Members were asked to express their confidence in the sequential assertions that the real coefficient exceeded 0, 1, 2,…,17% by placing a percentage probability against each given value. Their contributions were collated and average probabilities, calculated as the arithmetic mean of the individual responses, were ascribed to each potential value of the real coefficient. Details of Members' individual responses are given in Working Paper 10.

Core results

The distribution of Members' aggregate probabilities is shown in Figure 3.6. Working Paper 10 also shows plots of Members' individual responses which were used in producing Figure 3.6.

Figure 3.6 shows, for possible values of the coefficient in the range 0–17%, the average (arithmetic mean) probability assigned by Members. For example, on average a 4% probability was assigned to the coefficient being zero or less (left-most bar), about a 9% probability was assigned to the coefficient being above 0 but not more than 1, i.e. including 1 (second bar), and so on.

Figure 3.6: Distribution of Members' aggregate probabilities (calculated as the arithmetic mean of the individual responses) of the uncertainty regarding the coefficient linking all-cause mortality and an increase in long-term exposure to $PM_{2.5}$



The first bar represents the probability of the coefficient being 0 or less (no adverse effect) and the last bar of it being more than 17%. The reader is asked to note that Members were not specifically asked to comment on coefficients less than 0%. Full details can be found in Working Paper 10.

The coloured areas of the histogram indicate the quartiles of the distribution:

blue – the 1st quartile, regarded as the 'low' band of the distribution;
red – the 2nd and 3rd quartiles, regarded as the 'middle' band of the distribution;
yellow – the 4th quartile, regarded as the 'high' band of the distribution.

The coefficients indicated on the abscissa refer to the relative risks discussed in the text, i.e. a coefficient of 5% corresponds to a relative risk of 1.05.

1.06 (1.02–1.11) relative risk of death of all-cause mortality and 95% statistical sampling confidence interval (CI) per 10 µg/m³ increase in $PM_{2.5}$ (as published by Pope *et al,* 2002).

1.06 (1.00–1.15) relative risk of death of all-cause mortality and Members' 95% plausibility interval per 10 µg/m³ increase in $PM_{2.5}$.

These indicate the typical 'low' (1%) and 'high' (12%) values suggested for use in sensitivity analysis. They represent the 12.5th and 87.5th percentiles of the overall plausibility distribution.

Summary description of the plausibility distribution

The plausibility distribution as a whole represents Members' aggregate uncertainty about the coefficient. It is possible to summarise the overall plausibility distribution in a number of ways, although no summary will capture all the characteristics of the distribution as a whole. One is by means of a 95% uncertainty interval. The corresponding range, from 0% to 15%, is wider than the confidence interval reported by Pope *et al* (2002), reflecting that the plausibility distribution incorporates a larger range of uncertainty issues.

Another summary of the uncertainty distribution can be given by a 75% plausibility interval, derived from the 12.5th and the 87.5th percentiles. This description of Members' aggregate probabilities indicates that the central coefficient was about 75% likely to fall in the interval between exceeding 1% and up to and including 12%, with a smaller chance given to the coefficient falling at 1% or lower, or higher than 12%; in other words there is a 25% chance of it (i.e. the central coefficient) falling outside this interval. Even the 75% plausibility interval is wider than the 95% statistical confidence interval (2–11%) published by Pope *et al* (2002) and demonstrates that a larger range of uncertainties have been taken into account.

At the median of the aggregate (arithmetic mean) distribution, where belief was evenly balanced between the coefficient being higher or lower, the coefficient exceeded 5%, i.e. close to the 6% estimate from Pope *et al* (2002).

Alternative summary of the plausibility distribution

The plausibility distribution is already a summary of the individual views of Members, and indeed alternative summaries are possible. For example, the overall distribution could have been constructed as the median (rather than the arithmetic mean) of the results of individual Members. This median distribution is given in Working Paper 10. Use of medians rather than arithmetic means has the effect of giving less weight to more extreme or 'outlier' views, whether extremely high or low; the individual results (Working Paper 10) show there were some such views.

The 95% plausibility interval of the overall (median) distribution is narrower, ranging from 1 to 13%, though still clearly wider than the confidence intervals published by Pope *et al* (2002). Additionally, the corresponding values of a 75% plausibility interval, derived using the median of Members' results, are 1.5–11.5%.

At the median of the aggregate (median) distribution the coefficient exceeded 6%.

Sensitivity analysis

One likely use of the plausibility distribution (derived from the arithmetic means) is when estimating the impact on mortality and life expectancy of policy interventions and initiatives designed to reduce levels of air pollutants. While it is natural to base 'best' estimates of impacts on the 'best' estimate of the risk coefficient, it is desirable, and arguably necessary, to take account of the uncertainties around that coefficient.

For the purposes of quantification, we need to consider how best to represent this uncertainty as a basis for sensitivity analysis. The most complete representation would be provided by using the probabilities from the aggregate plausibility distribution across the whole range of possible coefficients in Monte Carlo analysis. This method samples from the full plausibility

distribution of the risk coefficient – an approach which, with modern computing methods, is no longer prohibitively resource-intensive. Nevertheless, practitioners sometimes aim for a simpler approach, estimating impacts for a much more limited selection of 'low' and 'high' values. Sometimes these are selected as the extremes of the corresponding 95% uncertainty interval. However, these are clearly untypically 'low' and 'high' values, being respectively the 2.5th and 97.5th percentiles of the overall plausibility distribution. More representative 'low' and 'high' values are given by, for example, the 12.5th and 87.5th percentiles which are, respectively, the median values of the lower and upper quartiles of the overall plausibility distribution (see Figure 3.6) and between them contain 75% of that distribution. These lead to 'low' and high' values of the risk coefficient as 1 and 12%, respectively. While preferring a full Monte Carlo analysis, we suggest that these low and high values be considered when only a limited sensitivity analysis is practicable. We also recommend that the wider uncertainties (the 95% confidence interval, the 95% uncertainty range and perhaps other summaries of the plausibility distribution) be described in any reports on quantification.

We did not repeat the process of eliciting Members' views for the coefficients linking cardiopulmonary mortality or lung cancer mortality and $PM_{2.5}$. For these we recommend that the confidence intervals as published by Pope *et al* (2002) be used to express uncertainty, while recognising that there are important aspects of uncertainty not captured by these confidence intervals.

To summarise, we think that the coefficient linking all-cause mortality and long-term exposure to $PM_{2.5}$ in the UK can be best represented as 1.06 for a 10 μg/m³ increase in $PM_{2.5}$. We recommend that, when using this coefficient for quantification[23], an uncertainty section be included which describes:

a the 95% confidence interval (2 to 11%) around the coefficient in the original study (Pope *et al,* 2002);

b the aggregate view of Members that, taking wider sources of uncertainty into account, the coefficient was 95% probable to fall within the interval from exceeding 0 to 15%;

c typical 'low' and 'high' values of 1 and 12%.

It is recommended that the full distribution of probabilities in Figure 3.6 be used as an input into Monte Carlo analysis. Alternatively, the typical 'low' and 'high' values of 1 and 12% could be used in sensitivity analysis.

[23] The relative risk and percentage changes in this section are given for a 10 μg/m³ increase in $PM_{2.5}$. Linear scaling (i.e. the percentage change can be divided by two if the concentration change is divided by two) is a reasonable approximation for many applications. However, for larger coefficients and/or larger concentration increments, it is better to use a more precise equation based on multiplicative scaling of the original study RR (relative risk), e.g. 1.06 for an original concentration increase of 10 μg/m³. If the new concentration change in population-weighted mean for the policy of interest is $-x$ μg/m³ (with a negative sign as the analysis usually concerns reductions), then the new RR for an x μg/m³ reduction is calculated as $1.06^{-x/10}$. As this equation represents a curved relationship, concentration increments need to be identified as increases or decreases – the new RR will have a different value for a given concentration increment depending on whether it is for an increase or for a decrease.

xvi Lag time between reduction in pollution and reduction in mortality rates (cessation lag)

In question vii we discussed latency which, in the present context, may be defined as the time lag between mortality from cardiorespiratory causes or lung cancer and the earlier exposure to air pollution that may have contributed to it. This was relevant to the choice of time period of exposure within the American Cancer Society (ACS) study on which to base estimates of risks. In this section we consider the related but different concept of cessation lag, i.e. the lag time between reduction in pollution and consequent reduction in mortality rate. In addition to the coefficient and the uncertainty range around the coefficient, calculations of the likely impact on life expectancy require a view on cessation lag, because it reflects how quickly mortality risks are reduced and the associated public health benefits are attained, following reduced air pollution.

The time-series studies, showing on average higher (lower) mortality in the days immediately following higher (lower) air pollution, show (assuming causality) that some benefit is more-or-less immediate. We know, however, that the time-series studies capture only a small proportion of the overall impact on mortality implied by the cohort studies. Of greater relevance, therefore, are the studies of policy interventions in Dublin (Clancy *et al,* 2002) and in Hong Kong (Hedley *et al,* 2002). In both cities, reductions in air pollution were followed by mortality benefits in the subsequent five-year period. This suggests a reduction in pollution-related risks of mortality in the years shortly after the pollution is reduced. We do not know what further reductions in risks may have occurred after five years, or indeed may yet occur.

Having done a rapid examination of the rate at which the deaths fell in the Dublin study, we feel that though in principle it might take as long as 40 years for all of the mortality benefits to be achieved, in practice a bulk of the benefits is likely to occur significantly earlier than that, including a noteworthy proportion in the first five years. We believe this is particularly likely in the case of effects on the cardiorespiratory system but not in the case of lung cancer. As the cardiovascular effects dominate all-cause mortality we consider that the cessation lag for all-cause mortality is, on average, also substantially less than 40 years.

Thus, although the evidence is limited, our judgement tends towards a noteworthy proportion of the whole effect occurring in the years soon after pollution reduction rather than later.

xvii What additional issues need to be taken into account in calculations of total impact?

We see our primary focus as being on recommending a coefficient for use in quantifying the health impact of incremental changes in particles within the range of concentrations in the American Cancer Society (ACS) study. The lowest annual average $PM_{2.5}$ concentration in the metropolitan areas studied was around 7 $\mu g/m^3$ (Arden Pope III (2006), personal communication) and the highest was 30 $\mu g/m^3$. We wish to emphasise that there are additional uncertainties involved in extrapolating outside this range as might be done in calculations of the total impact of particles on life expectancy. Although the relationship with the logarithm of the relative risk (Figure 2 of Pope *et al,* 2002) appears to be linear within this range (and thus might be expected to continue at least just below and just above the range), the shape of the relationship is increasingly uncertain towards the outer end of the range as the number of cities with relatively low or relatively high concentrations is small.

Another issue that should be considered is whether to calculate the impact of anthropogenic particles only. While there is some evidence (see, e.g., World Health Organization, 2003, 2004) that different kinds of particles in the $PM_{2.5}$ size range have different toxicity, per $\mu g/m^3$, we agreed (see question v) not to recommend different quantifications for different components of the $PM_{2.5}$ mixture. So, for quantification, we do not propose different coefficients for anthropogenic and for non-anthropogenic $PM_{2.5}$. (This is a separate point from choosing to calculate the impact of anthropogenic particles on a policy basis, i.e. that component of the total particle concentration that man has the power to change.)

We agree that, for policy purposes, the primary focus of quantification should be on specified reductions in $PM_{2.5}$ in the range of the ACS study, i.e. 7–30 $\mu g/m^3$. This will avoid the need to extrapolate, to low concentrations, beyond the data provided by the key cohort studies. This point also applies to calculations of total impact. If these do extend to lower concentrations, the additional uncertainties in doing this should be acknowledged.

Box 3: Recommendation regarding our preferred choice of coefficients linking mortality to long-term exposure to $PM_{2.5}$

Now we have considered issues pertaining to transferability, our uncertainty regarding the central estimate and cessation lags, our final recommendations are as follows. The reader should note that in addition to the published confidence intervals from the ACS study (Pope *et al,* 2002), the recommended coefficient for all-cause mortality is qualified by a plausibility interval. See text on pages 42–46 for details.

For all-cause mortality:

Best estimate 1.06 with 95% confidence interval (CI) 1.02–1.11.

Our assessment of uncertainty led us to a 95% uncertainty interval of 1.00 to 1.15 about our best estimate of 1.06.

For the purposes of conducting impact assessments regarding all-cause mortality and assessing policy interventions designed to reduce levels of air pollutants, we have recommended that the full distribution of probabilities, given in Figure 3.6, be used as an input into Monte Carlo analysis. Alternatively, we suggest that the plausible 'low' and 'high' values of 1.01 and 1.12 could be used in sensitivity analysis.

We also recommend that the wider interval of 0 to 15% (RR 1.00 and 1.15) be included in any report on quantification of risks from long-term exposure to particulate air pollution represented by $PM_{2.5}$.

For cardiopulmonary mortality:

Best estimate 1.09 with 95% confidence interval (CI) 1.03–1.16; we did not assess a range of plausibility.

For lung cancer mortality:

Best estimate 1.08 with 95% confidence interval (CI) 1.01–1.16; again, we did not assess a range of plausibility.

All coefficients are expressed in terms of relative risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$ (annual average concentration).

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Chapter 4
Conclusions and Recommendations

An interim statement of our views on quantification of the effects of long-term exposure to air pollutants on mortality was published on 18th January 2006 (and is reproduced in this report, see page 59). The interim statement reported the findings of the first part of our work and identified areas that we intended to consider in more detail. The current report represents our final views. These may of course require modification as more evidence appears. Unsurprisingly the main conclusions reported in the interim statement have not been significantly modified.

Chapter 3 provides an in-depth analysis of the evidence we have examined and presents our findings as a series of questions and answers. For ease of reference the same numbering system has been used in this chapter. We have not reprinted the questions listed in Chapter 3: we record in this chapter our conclusions and recommendations in a more compressed form than used in Chapter 3. The Roman numerals given here correspond to the numbers of the questions considered in Chapter 3. Several points made in the interim statement have also been included here.

i We have agreed that the evidence base that links mortality to long-term exposure to air pollutants, and especially to particles, has strengthened since our last report on this topic published in 2001 (Department of Health, 2001). It is our considered view that the associations reported in the literature are highly likely to represent causal relationships with air pollutants, especially with particles. Nevertheless, we accept that there is a small possibility that some or all of the reported associations represent the effects of some as of yet unidentified confounding factor or factors. We have been impressed by the HEI review (Health Effects Institute, 2000) of the American Cancer Society (ACS) cohort study (Pope *et al,* 1995) and of the Six Cities study (Dockery *et al,* 1993), by the growing number of European studies and by the few studies of the effects of policy initiatives.

ii We have agreed that the ACS study, including the HEI review and the recently published extensions to this study (Pope *et al,* 2002), provides the most reliable source of coefficients, suitable for application in the UK, linking long-term exposure to air pollutants with mortality.

iii We have agreed that $PM_{2.5}$ is the most appropriate measure of particulate air pollution for use in quantification. In reaching this view we are aware of the reported associations with the component of $PM_{2.5}$ measured as sulphate and have discussed this in detail in Chapter 3. This point is taken up again below.

iv We have considered quantifying the possible effects on mortality of long-term exposure to other air pollutants including sulphur dioxide, nitrogen dioxide and ozone. In none of these cases have we been persuaded that the evidence base is yet sufficiently strong to warrant quantification. The problem is one of inadequate evidence rather than evidence for there being no effects. Better evidence might well lead us to change our views in this area.

v We considered whether quantification is improved by separating the effects of sulphate from those of other components of the particulate mixture. Our view is that particulate matter represented by $PM_{2.5}$ is a complex and possibly interacting mixture of many components, including sulphate, and though these components may differ from one another in terms of their toxicity, such data as we have do not allow confident separation of their effects on health. In the absence of clear evidence to the contrary we consider that the recommended coefficient should apply equally to all components of $PM_{2.5}$, including particulate matter measured as sulphate and nitrate. This is not to say that all components of $PM_{2.5}$ do have the same toxicity – but, rather, that there is not, at present, evidence to quantify different components differently, in a way that would gain wide consensus. This is clearly an area that requires further study.

vi We have agreed that all-cause mortality should be the primary health endpoint for use in quantification. However, we also recommend that quantification of effects of long-term exposure to $PM_{2.5}$ on cardiopulmonary mortality and on lung cancer mortality should be undertaken. We also agree that within the cardiopulmonary effects the major impact is likely to be on cardiovascular mortality and that effects on this endpoint should be considered for quantification as specific coefficients become available.

vii The coefficients linking mortality to long-term exposure to air pollution reported in the ACS study vary depending on the time period used for measuring the annual average ambient $PM_{2.5}$ level used in the regression analysis. This has led us to consider both the possibility of measurement error and the extent that the relationship between exposure and effect might be characterised by a degree of latency. We have considered these points in some detail and our conclusions regarding which coefficients should be used for quantification of effects in the UK are:

a cardiovascular (or cardiopulmonary) mortality should be based on the average of the $PM_{2.5}$ concentration measured in 1979–1983 and 1999–2000;

b lung cancer mortality should be based on $PM_{2.5}$ concentrations measured in 1979–1983;

c all-cause mortality where deaths are dominated by non-malignant cardiorespiratory deaths rather than by lung cancer should be based on the average of the $PM_{2.5}$ concentrations measured in the two periods.

viii In any calculation based on coefficients of the type discussed in this report questions regarding possible thresholds of effect and of the linearity or otherwise of the represented relationship arise. We found that the evidence did not point to a threshold in the data linking long-term exposure to particles and mortality. We also consider that the relationships represented by the coefficients reported in the ACS study can be considered to be linear within the range of concentrations studied. We note that this range included those concentrations likely to be relevant to policy development in the UK.

The conclusions reported above led us to what we described as sets of working conclusions (not to be confused with the interim statement) based on coefficients linking annual average $PM_{2.5}$ and mortality estimated from the ACS study. These are set out in Chapter 3, Boxes 1 and 2 (on pages 31 and 40) of this report. Further work focused on refinement of these working conclusions.

ix We first considered whether adjustment of the coefficients reported in the working conclusions for the possible effects of spatial autocorrelation should be undertaken. This is a complex issue and a detailed discussion is reported in Chapter 3. We concluded that there was a case for adjustment, though we noted that Pope and co-authors of the ACS study had preferred not to provide an adjusted coefficient as their headline figure. We later considered how adjustment for spatial autocorrelation might be offset by adjustment for other factors. This is reported below. For the moment it may be useful to note that adjustment for spatial autocorrelation led to a reduction in the reported coefficients.

x In looking at all the available evidence we noted that the coefficients reported from the large spatial scale studies, such as the main ACS analysis, were generally smaller than those from studies conducted at a finer spatial scale. A comparison of coefficients was presented in Figure 3.5 (page 35). We argued that the small spatial scale studies might better represent personal exposures to air pollutants but they might also be subject to certain uncorrected errors. While continuing to prefer the ACS study as our prime source of coefficients, we considered that some upward adjustment of the ACS coefficients might be justified. This was difficult to express in quantitative terms but we took note of it, as one factor among others, in our final discussion of our preferred coefficients.

xi We explored in some detail the case for adjusting the $PM_{2.5}$ coefficients for the possible effects of sulphur dioxide. This proved to be one of the more difficult questions we tackled. The epidemiological evidence that shows that long-term exposure to sulphur dioxide may be playing some part, either directly or as an indicator, is by no means negligible. But the possible correlation between sulphur dioxide and particles and the lack of persuasive hypotheses linking exposure to low concentrations of sulphur dioxide and deaths from cardiovascular disease also needs to be taken into account. Our main problem was distinguishing with confidence between a direct effect of sulphur dioxide and an apparent effect due to sulphur dioxide acting as a marker for combustion of sulphur-containing fuel; even the ACS study may not have the resolution to distinguish these with confidence. Overall, we concluded that we would not recommend quantification of the possible direct effects of sulphur dioxide, in the main analysis or in the sensitivity analysis, and that we would not recommend adjustment of the $PM_{2.5}$ coefficient.

xii We considered adjustment of the $PM_{2.5}$ coefficients for the possible effects of measurement error. Our estimates suggest that adjusting for measurement error would increase the coefficient by only a small amount and so we have not attempted to do so formally.

xiii Before taking the arguments for various adjustments discussed above into account we asked ourselves whether the ACS coefficients for $PM_{2.5}$ were, as they stood, plausible in the light of changes in air pollution levels in the UK over the past half century or so

and concomitant changes in mortality. We concluded that the best-estimate coefficient of the working conclusions was not implausibly large. Larger coefficients did seem implausible under an assumption of linearity above 30 μg/m^3 (the upper end of the range of annual average concentrations in the ACS study). A logarithmic curve which flattens off at high concentrations has also been suggested and this would give more plausible results.

Having considered the cases for a number of possible adjustments of the coefficients reported in our working conclusions, we set about considering the possible trade offs between these adjustments. Our views on this are reported in our second set of working conclusions (see Box 2, page 40). It will be seen that whilst some adjustments were thought to be likely to increase the coefficients, others seemed likely to diminish them. We concluded that holding to the 'best estimate' coefficients reported in the working conclusions was sensible. In fact the only further refinement made to these coefficients was that regarding the expression of uncertainty around the best estimate of the coefficient linking all-cause death and $PM_{2.5}$. This is discussed below.

xiv Transferability is a question that we have considered and expressed some unease about in earlier reports. Having reviewed the available literature we find ourselves reassured on this point. The appearance of European studies and the wide range of people and areas studied in the ACS work have helped us with this. We conclude that the coefficients reported in the ACS study and supported in this report can be used to predict impact on health in the UK with acceptable certainty.

xv The working conclusions in Boxes 1 and 2 (on pages 31 and 40) of this report are based on estimates from the ACS study (Pope *et al,* 2002). They are expressed in terms of a best estimate, with uncertainty represented by the corresponding 95% confidence interval. This is an incomplete representation of uncertainty, in that confidence intervals represent statistical uncertainty, i.e. they reflect only the sampling error of the study concerned. But there are also many other sources of uncertainty affecting a coefficient for use in impact estimation in the UK. These include not only unaccounted confounding from non-pollution factors, publication bias, and measurement error, but the many other issues also discussed in this report, such as which aspects of pollution increase the risks of mortality, what is the relevant spatial scale for an analysis, and how well do the US results transfer to the UK. A number of approaches that allow numerical description of the extent of overall uncertainty were considered. We adopted an approach that allowed the opinions of Members to be combined numerically. This process led us to a plausibility distribution for the coefficient linking all-cause mortality and annual average $PM_{2.5}$. This plausibility distribution, shown earlier in Figure 3.6 (page 44), is the best representation of Members' uncertainty about the coefficient. As noted in Chapter 3, it is possible to summarise the distribution in a number of ways. One is by means of a 95% uncertainty interval. The corresponding range, from 0 to 15%, is wider than the confidence interval reported by Pope *et al* (2002), reflecting that the plausibility distribution incorporates a fuller range of uncertainty issues.

One likely use of the plausibility distribution is when estimating the impact on mortality and life expectancy of policy interventions and initiatives designed to reduce levels of air pollutants. While it is natural to base 'best' estimates of impacts on the 'best' estimate of the risk coefficient, it is desirable, and arguably necessary, to take account of the uncertainties around that coefficient. For this, we recommend Monte

Carlo methods that sample from the full plausibility distribution of the risk coefficient. While preferring such an analysis, we suggest that typical 'low' and 'high' values be considered when only a limited sensitivity analysis is practicable. These typical 'low' and 'high' values can be given by, for example, the 12.5th and 87.5th percentiles which are, respectively, the median values of the lower and upper quartiles of the overall plausibility distribution. These lead to 'low' and high' values of the risk coefficient as 1 and 12%, respectively. We also recommend that the wider uncertainties (the 95% confidence interval, the 95% uncertainty range and perhaps other summaries of the plausibility distribution) be described in any reports on quantification.

We did not repeat the process for the coefficients linking cardiopulmonary mortality or lung cancer mortality and $PM_{2.5}$. For these we recommend that the confidence intervals be used to express uncertainty, while recognising that there are important aspects of uncertainty not captured by these confidence intervals.

xvi When coefficients of the sort discussed in this report are used to predict the impacts on health of policy initiatives it is important to understand whether the predicted effects (benefits) are likely to occur immediately after pollution levels fall or only after some latent period sometimes described as cessation lag. Evidence on this point is limited. However, our reading of the evidence provided by time-series studies and of the few studies of the impacts of policy interventions leads us to conclude that a noteworthy part of the predicted total benefits might well occur in the first five years after the reduction in pollution levels. We find it difficult to be as precise about this as we would wish.

xvii We are keen to emphasise that, in calculating the total impact of current levels of particulate air pollution (expressed as $PM_{2.5}$), such calculations are most reliable when limited to the concentration range of 7–30 μg/m^3 investigated in the ACS study.

Our final recommendations for coefficients linking mortality and long-term exposure to particulate air pollution expressed as $PM_{2.5}$ for use in estimating the benefits likely to be delivered by policy initiatives in the UK are set out below.

For all-cause mortality:

Best estimate 1.06 with 95% confidence interval (CI) 1.02–1.11.

Our assessment of uncertainty led us to a 95% uncertainty interval of 1.00–1.15 around our best estimate of 1.06.

For the purposes of conducting impact assessments regarding all-cause mortality and assessing policy interventions designed to reduce levels of air pollutants, we have recommended that the full distribution of probabilities, given in Figure 3.6 (page 44), be used as an input into Monte Carlo analysis. Alternatively, we suggest that the typical 'low' and 'high' values of 1.01 and 1.12 could be used in sensitivity analysis.

We also recommend that the wider interval of 0–15% (RR 1.00 and 1.15) be included in any report on quantification of risks from long-term exposure to particulate air pollution represented by $PM_{2.5}$.

For cardiopulmonary mortality:

Best estimate 1.09 with 95% confidence interval (CI) 1.03–1.16; we did not assess a range of plausibility.

For lung cancer mortality:

Best estimate 1.08 with 95% confidence interval (CI) 1.01–1.16; again, we did not assess a range of plausibility.

All coefficients are expressed in terms of relative risk per 10 μg/m^3 increase in $PM_{2.5}$ (annual average concentration).

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Committee on the Medical Effects of Air Pollutants

Quantification of the Effects of Air Pollutants on Health in the UK

Interim Statement 18th January 2006

A Subgroup of the Committee on the Medical Effects of Air Pollutants (COMEAP) is currently preparing a report which will, as far as possible, quantify the benefits to health of reducing air pollution in the UK. COMEAP has advised on quantification in earlier reports[1,2]. The Subgroup considered a draft of the first part of our report on the 20th December 2005, concerning the effects on mortality of long-term exposure to air pollutants, especially ambient particles. We agreed that the draft was sufficiently advanced and that our views were sufficiently developed to allow us to produce this interim statement. We understand that this is needed by Defra for use in their review of the Air Quality Strategy. We intend to publish a detailed report on the effects on health of long-term exposure to air pollutants later in 2006. This later report will include consideration of the effects of gaseous pollutants in addition to those of particles and of effects on morbidity in addition to those on mortality.

We have agreed that the evidence base that links long-term exposure to particles and mortality has been strengthened since our last report on this topic published in 2001[1]. It is our considered view that the associations reported in the literature of this field are likely to represent causal relationships with air pollution, especially particles, although we accept that there is a small possibility that some or all of the reported associations represent the effects of some as yet unidentified confounding factor or factors. We have examined the evidence regarding associations between long-term exposure to particles and increased risks of mortality. Our confidence in that evidence is such that we have been able to identify and agree a coefficient for use in quantifying the benefits to health of a reduction in ambient particle concentrations in the UK.

We also have agreed that careful expression of the value of this coefficient is needed. This will be reported in terms of our uncertainty regarding the value of the coefficient. While we have investigated many of the specific areas of uncertainty in detail, and that has enabled us to form interim conclusions about them, we have not yet completed our work on summarising and representing our overall uncertainty about the chosen coefficient. Thus the conclusion reported here must be regarded as an interim conclusion with regard to the assessment of uncertainty.

We have agreed that the American Cancer Society (ACS) study provides the single best source of information for quantifying the effects on mortality of long-term exposure to air pollution and that, from the ACS study, particulate matter measured as $PM_{2.5}$ is the most appropriate measure of air pollution for use in quantification. In saying this we point out that the identity of the individual components of the ambient aerosol that affect health remain unknown and thus we regard $PM_{2.5}$ as an index of a certain type of air pollution mixture. From the epidemiological evidence available, we consider that it is not possible to distinguish with confidence between the effects of the different components of the mixture, nor of different

sources. In the absence of clear evidence to the contrary, therefore, we consider that the coefficient should apply equally to all components of $PM_{2.5}$, including sulphate.

We have discussed the case for adjusting coefficients linking $PM_{2.5}$ and mortality for a variety of factors including sulphur dioxide, spatial autocorrelation and measurement error. We have also discussed the case for taking into account the higher coefficients found in studies at smaller spatial scales. We noted that some factors tend to decrease the coefficient whereas other factors tend to increase it. We concluded that we would not attempt to formally adjust the relevant ACS coefficients as published, to take account of the joint effect of these factors. Instead, we intend to reflect our discussions in an expression of uncertainty regarding the exact value of our preferred coefficient. Details of our discussions will be provided in our final report.

In defining a coefficient linking $PM_{2.5}$ and mortality and advising on its use for quantification we agreed the following points:

i $PM_{2.5}$ is our chosen index of pollution.

ii The coefficient will be expressed, as is conventional, as the percentage change in relative risk of death per 10 $\mu g/m^3$ change in annual average $PM_{2.5}$.

iii Calculations should focus on the benefits likely to be delivered by changes in $PM_{2.5}$ rather than on estimating the total impact on health of current $PM_{2.5}$. We accept that the latter can be calculated from our interim conclusions but we wish to consider, further, the uncertainties associated with such a calculation.

iv The effects chosen for quantification are all-cause, cardiorespiratory mortality and lung cancer mortality. We present, here, a coefficient relating to all-cause mortality; coefficients relating to all-cause, cardiorespiratory and lung cancer mortality will be included in our final report.

v We recognise the need to define the 'cessation lag', i.e. the time from reductions in $PM_{2.5}$ to the consequent reductions in risks of mortality. This is needed for calculations using the life-table methodology reported elsewhere[3]. Although the evidence is limited, our judgement tends towards a greater proportion of the effect occurring in the years soon after pollution reduction rather than later. We intend to discuss this further in our final report.

We have chosen the coefficient based on the averaged exposure period reported by Pope *et al*[4] as our best, current, estimate of that linking $PM_{2.5}$ and all-cause mortality in the UK. This coefficient is based on the largest available cohort study. In addition, the methodology of this study has been exposed to searching re-examination by the US Health Effects Institute[5]. The results of the ACS cohort are buttressed by those of the small number of other cohort studies published to date. We believe the coefficient can be transferred to the UK. There are uncertainties involved, but these could operate in either direction.

As noted, we have not completed our work on the expression of uncertainty and for the moment report the coefficient with only the 95% confidence intervals (95% CI) as provided by Pope *et al*[4]. We do not consider this to be satisfactory, for two reasons. First, it represents only the statistical (sampling) uncertainty associated with the coefficient, whereas, in addition, we wish to reflect uncertainty regarding adjustment of the coefficient for the factors noted above and with regard to its transferability to the UK. Second, and operating in the other direction, 95% confidence intervals may suggest a greater uncertainty than we intend: we consider it more

likely that the true coefficient lies close to the centre than close to the boundaries of the 95% confidence interval. We will explore these points in more detail in our further work on uncertainty.

Our interim conclusion is, then, that the effects on mortality of long-term exposure to a mixture of air pollutants, represented by $PM_{2.5}$, are best characterised by the following coefficient, expressed in terms of the percentage change in relative risk of all-cause mortality per 10 $\mu g/m^3$ change in annual average $PM_{2.5}$:

1.06 (95% CI 1.02–1.11)

We note that this represents a change from that provided in our last report. This reflects the expansion of the evidence-base in this area and our deeper understanding of the effects of pollutants, and other factors, on health.

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Working Papers

The following working papers have been produced by various Members of the Committee and Secretariat. These have been used in developing the recommendations given in the main chapters of this report.

Working Paper 1

Sulphur Dioxide (SO_2) – Is There an Association and Should the $PM_{2.5}$ Coefficient be Adjusted for SO_2?

Secretariat

To determine whether the coefficient linking $PM_{2.5}$ and mortality should be adjusted for sulphur dioxide, it is useful as a first step to consider whether the observed association with SO_2 is likely to be causal. This working paper contains a table summarising the available evidence on the effects on mortality of exposure to SO_2 from cohort and intervention studies. A forest plot containing studies which considered SO_2 exposure and cardiovascular mortality in time-series studies is also given.

The table shows that many, but not all, studies have shown positive associations between SO_2 and all-cause or cause-specific mortality. Whether these associations are causal is a far more complex question. Discussion of whether the coefficient linking $PM_{2.5}$ and all-cause mortality should be adjusted for SO_2 can be found in question xi in Chapter 3 of this report.

Table: Evidence from cohort and intervention studies of an effect of SO_2

Study	Effect of SO_2?	Correlation with PM	Notes
Hedley *et al* (2002) Hong Kong	Yes – biggest relative change in cause of death between the pre- and post-intervention period was seen in the 15–64 years age group for respiratory disease (4.8%; 1.2–8.3). Smaller, significant relative changes were seen with cardiovascular disease in >65 years (2.4%; 0.7–4.2) and all ages (2.0%; 0.3–3.7) categories only. For all-cause mortality significant relative changes were seen in all three age groups with the greatest change in >65 years (2.8%; 1.4–4.2)		Mean concentration of SO_2 at baseline was 44.2 μg/m³. Mean fall in the first year was 53% (20.8 μg/m³) and was sustained 5 years later (24.5 μg/m³). No great change in any of the other main pollutants (PM_{10}, NO_2), except O_3 (which showed a significant increase), was recorded over the 5 years after the restriction. Mean concentration of sulphate prior to the intervention was 8.9 μg/m³. This fell by 15–23% for 2 years but rose again in years 3–5 back to the baseline concentration. After the intervention was introduced, the average annual percentage change in deaths for 1990–1995 declined for all-causes, respiratory and cardiovascular (CV) deaths compared with the 5 years before the intervention
Hedley *et al* (2005) (Abstract) Hong Kong	Yes – post-intervention (5 years) there was a 2.2% reduction in all-cause mortality per year	Unavailable from abstract	Sharp reductions in annual ambient concentrations of vanadium and nickel. No sustained reductions in PM_{10}, NO_2 or O_3

Table: Continued

Study	Effect of SO_2?	Correlation with PM	Notes
Clancy *et al* (2002) Dublin	Yes – after adjustment for several factors, the estimated effects (% reductions in mortality) 5 years after vs. 5 years before the ban were reduced but remained highly significant for all-cause, cardiovascular and respiratory mortality. Greatest % reduction occurred with respiratory mortality (15.5%)	Probably close (coal)	Based on a ban on coal sales in 1990. Metrics measured were BS and SO_2. Total decline in the mean concentrations in SO_2 was 11.3 μg/m³; largest decline occurred in winter. Largest reduction in cardiovascular death rates occurred in winter
McDonnell *et al* (2000) (subset of AHSMOG) California (USA)	Possible independent effect of SO_2 on all-cause mortality in males was found; none with non-malignant respiratory disease listed as either the underlying or contributing cause of death	Weak SO_2 and $PM_{2.5}$ r=0.18 SO_4 and $PM_{2.5}$ r=0.33	Associations with $PM_{2.5}$ and all-cause or non-malignant respiratory disease (males only) were not changed by the addition of ambient SO_2 to the $PM_{2.5}$ model. Inclusion of SO_2 in two-pollutant models for lung cancer resulted in either minimal reductions or increases in the RR for $PM_{2.5}$ Note: the number of cases for lung cancer deaths is small – n=13 in males
Abbey *et al* (1999) (AHSMOG) California (USA)	Yes – SO_2 associated with lung cancer in both males (RR 1.99; 1.24–3.20) and females (RR 3.01; 1.88–4.84) per 3.72 ppb interquartile range SO_2. Note: the numbers of cases for lung cancer deaths are small – n=12 in females and n=18 in males SO_2 effect with lung cancer in females remained stable in two-pollutant models with PM_{10} (>100 μg/m³) and O_3 (>100 ppb); in males it remained stable with the addition of NO_2	For mean concentration, SO_2 and PM_{10} r=0.31	PM_{10} concentration (>100 μg/m³) showed significant associations with deaths from all-causes, non-malignant respiratory disease and lung cancer (also with mean PM_{10} concentration and lung cancer) in males only. PM_{10} coefficient remained stable in two-pollutant models (including when SO_2 was added). Significant association of NO_2 with lung cancer in females was lost when SO_2 was added (two-pollutant model)
Nafstad *et al* (2004) Oslo, Norway	No clear and meaningful associations between mortality and increased exposure; it was not the higher exposure levels but exposure between 10 and 19.99 μg/m³ that mainly increased risk ratios	SO_2 and NO_x r=0.63	Cohort = 16,209 males, aged 40–49 years. Analyses performed using the pollution exposures as either categorical or continuous variables. The risk of dying from a disease increased with increasing levels of NO_x exposure
Nafstad *et al* (2003) Oslo, Norway	No association with lung and non-lung cancer mortality. Authors thought this could be due to either low SO_2 concentration or levels indicating exposure was not associated with lung cancer. SO_2 declined over the period of the study		Cohort = 16,209 males, aged 40–49 years, followed from 1972/73 to 1998. NO_x associations with lung cancer were strengthened when SO_2 was added to the model

Table: Continued

Study	Effect of SO_2?	Correlation with PM	Notes
Filleul *et al* (2005) French PAARC study	No significant association with mortality – all-cause 1.01 (0.99–1.03), lung cancer 0.99 (0.92–1.07) or cardiopulmonary disease 0.97 (0.92–1.02) per 10 μg/m^3 SO_2 (24 areas). Results remained the same when 6 areas with high NO/NO_2 ratios were removed	SO_2 and TSP r=0.17	Cohort of 14,284 adults from 24 areas in 7 French cities. No significant associations observed for the 24 areas. TSP, BS, NO_2 and NO were significantly associated with all-cause mortality. TSP and NO_2 significantly associated with mortality from cardiopulmonary disease. NO_2 significantly associated with lung cancer mortality. Frailty methods used to take spatial correlation into account
Finkelstein *et al* (2003) Ontario, Canada	Low income – high SO_2 level (above 4.6 ppb) showed the largest association with mortality: all-cause 2.40 (1.61–3.58) and cardiopulmonary 3.36 (2.12–5.32)		Cohort = 5228 adults Similar associations attained for TSP across the income-pollutant categories
Pope *et al* (2002)	Of the gaseous pollutants, only SO_2 was associated with elevated mortality risk [a]: All-cause SO_2 (1980): 1.05 (1.03–1.08) SO_2 (1982–98): 1.05 (1.02–1.07) Cardiopulmonary SO_2 (1980): 1.06 (1.03–1.09) SO_2 (1982–98): 1.03 (0.999–1.07) Lung cancer SO_2 (1980): 1.03 (0.98–1.07) SO_2 (1982–98): 1.05 (0.996–1.10) All other causes SO_2 (1980): 1.05 (1.02–1.07) SO_2 (1982–98): 1.05 (1.03–1.08)		No adjustment of SO_2 coefficient for $PM_{2.5}$ or vice versa
ACS (Reanalysis) (HEI, 2000)	SO_2 alone for all-causes 1.49 (1.36–1.64)[b] SO_2 adjusted for $PM_{2.5}$, all-cause 1.46 (1.32–1.63) SO_2 alone for cardiopulmonary disease 1.59 (1.39–1.81) SO_2 adjusted for $PM_{2.5}$, cardiopulmonary disease 1.45 (1.25–1.69)	$PM_{2.5}$ and SO_2 r=0.5	RR for all-cause mortality for $PM_{2.5}$ 1.20 (1.11–1.29)[c] was reduced and lost significance after adjusting for SO_2 1.03 (0.95–1.13) (Table 37 of the HEI Reanalysis, 2000). Similar findings for cardiopulmonary mortality: RR for $PM_{2.5}$ 1.35 (1.21–1.51) was reduced, but maintained its significance after adjusting for SO_2 1.17 (1.03–1.33) (Table 38 of HEI Reanalysis, 2000). Because lung cancer mortality was not associated with $PM_{2.5}$, no adjustment for ecological covariates was attempted. In the regional adjustment model (Table 46 of the HEI Reanalysis, 2000): $PM_{2.5}$ alone for all-cause mortality 1.16 (0.99–1.37) per 24.5 μg/m^3. $PM_{2.5}$ adjusted for SO_2 1.11 (0.93–1.33) per 24.5 μg/m^3

Table: Continued

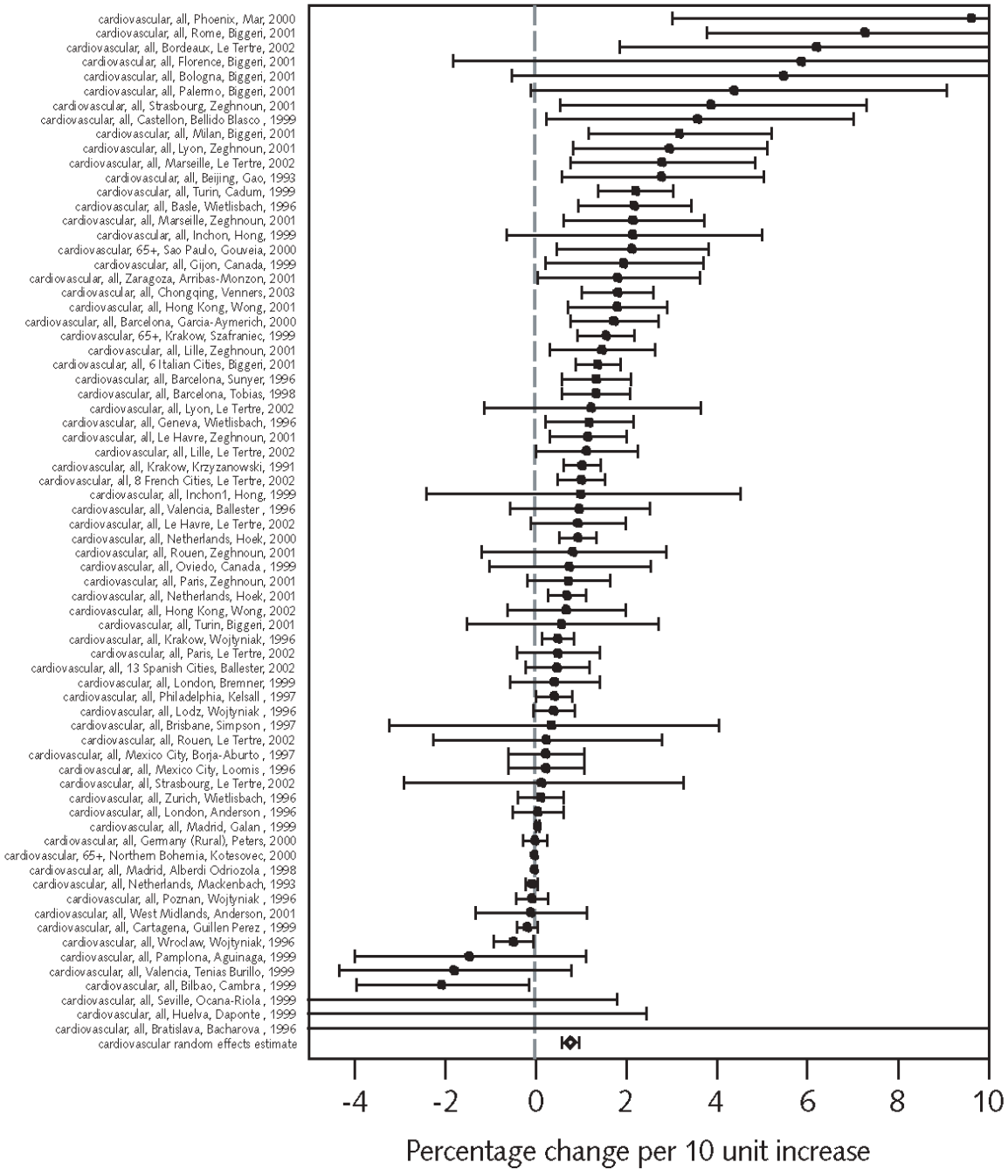
Study	Effect of SO_2?	Correlation with PM	Notes
Dockery *et al* (1993) Six US Cities study	Mortality was more strongly associated with the levels of fine, inhalable and sulphate particles than with the levels of total particulate pollution, aerosol acidity, SO_2 or NO_2. Results only presented graphically. Most cities were in a linear relationship between the SO_2 concentration and the mortality rate ratio but Harriman was not (higher rate ratio than expected for its SO_2 concentration)	Correlation between SO_2 and PM not given	Tightest linear relationship was with $PM_{2.5}$ RR 1.26 (1.08–1.47) for an 18.5 μg/m³ increase. Cohort = 8111 adults 14–16 year follow-up
Six US Cities (Reanalysis) (HEI, 2000)	SO_2 All-cause 1.26 (1.08–1.48) per 22.1 ppb Cardiopulmonary 1.24 (1.00–1.54) per 22.1 ppb Lung cancer 1.08 (0.63–1.88) per 22.1 ppb	Correlation of 85% between SO_2 and $PM_{2.5}$ (Table 17, p151)	Relative risk for $PM_{2.5}$ in Extended Model 1.28 (1.09–1.49)
Willis *et al* (2003) (county-scale study)	Unimportant covariate on the county scale. Although it emerged in the Reanalysis as an important confounder, it was not a significant confounder of the sulphate relative risk on the county scale. No relative risk given for SO_2 alone. RR for SO_2 adjusted for sulphate was 1.12 (0.97–1.28) for all-cause and 1.13 (0.93–1.37) for cardiopulmonary mortality for a 27 ppb range	Pearson correlation (%) SO_2 and sulphate 56%	

(a) Subject-weighted means.

(b) 29 ppb SO_2.

(c) Difference in mean concentration between the most and least-polluted city was 24.5 μg/m³.

Figure: Time-series studies on SO_2 and cardiovascular mortality



For a full list of the references given in the figure see the COMEAP report 'Cardiovascular Disease and Air Pollution' (Department of Health, 2006).

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Working Paper 2

Oxidants, Sulphates and Acid Sulphates

Dick Derwent

Oxidants

The atmosphere contains a number of strongly oxidising substances, of which the most prevalent is ozone, O_3. All of the ozone present in the atmosphere has been formed there by atmospheric chemical reactions driven by sunlight. Close to the populated and industrial centres of the northern hemisphere, much of this ozone has been formed by the sunlight-driven atmospheric chemical reactions involving organic compounds and oxides of nitrogen NO_x, the main ozone precursors. In the presence of intense ozone precursor emissions and strong sunlight, ozone concentrations may become elevated above levels thought to be harmful to human health. Under these conditions, the cocktail of primary pollutant precursors and atmospheric oxidants, such as ozone, is termed photochemical smog. At some time, photochemical smog has been observed in most urban and industrial centres worldwide.

The complex photochemical smog reactions may involve hundreds of different organic compounds from both man-made and natural biogenic sources. Taking the simple example of the production of photochemical ozone from the reactions of ethylene, an important man-made ozone precursor, the reactions generating ozone may be written as:

$$OH + C_2H_4 + O_2 = HOC_2H_4O_2$$

$$HOC_2H_4O_2 + NO = NO_2 + HOC_2H_4O$$

$$NO_2 + light = NO + O_3$$

$$HOC_2H_4O + O_2 = HO_2 + HCHO + HCHO$$

$$HO_2 + NO = OH + NO_2$$

$$NO_2 + light = NO + O_3$$

$$C_2H_4 + 2O_2 = 2HCHO + 2O_3$$

The above reactions appear to be catalytic in that NO_x (= NO + NO_2) and hydroxyl OH radicals are not consumed in the reaction system. Formaldehyde HCHO is an important oxidation product of ethylene and, indeed, of almost all organic compounds and its main fate is photolysis to produce more ozone.

Particles

The ambient atmospheric aerosol may be thought of as containing both primary and secondary particles of both organic and inorganic origins. Sulphates are an important secondary inorganic component of the urban and rural aerosol and are present as sulphuric acid H_2SO_4, partially neutralised ammonium bisulphate NH_4HSO_4 and neutral ammonium sulphate $(NH_4)_2SO_4$, calcium sulphate $CaSO_4$ and sodium sulphate Na_2SO_4. Collectively, they are termed particulate sulphate. Almost all of the particulate sulphate in the ambient aerosol has been formed in the

atmosphere by oxidation of man-made sulphur dioxide (SO_2), though natural sources of sulphate aerosol can be identified in pristine environments. In polluted locations, there appear to be no significant amounts of reduced sulphur compounds in the ambient aerosol and all of the sulphur is present in its fully oxidised state. Hence sulphate acts as an accurate marker for aerosol or particulate sulphur.

There are two principal routes, the homogeneous and heterogeneous routes, by which man-made gaseous sulphur dioxide is oxidised and converted into particulate sulphate. Sulphur dioxide may dissolve in cloud droplets and be oxidised by oxygen, hydrogen peroxide or ozone to form sulphuric acid. The dissolution of the SO_2 in the droplet is inhibited by the acidity formed by the oxidation processes and so would cease rapidly were it not for the presence of ammonia in the atmosphere which can dissolve in the reacting cloud droplet and partially neutralise the sulphuric acid. The cloud droplets may either fall as rain or evaporate, leaving an atmospheric aerosol that contains a mixture of sulphuric acid, ammonium bisulphate and ammonium sulphate depending upon the availability of SO_2, ammonia and the atmospheric oxidants. Because this oxidation route involves both gaseous and liquid phases, it is referred to as the heterogeneous oxidation route. The cloud droplets that act as chemical reactors for the SO_2 may be present in the frontal clouds associated with large synoptic systems, in convective clouds, in thunderstorms, in orographic clouds associated with hills and mountains or in low level mists and fogs. As a result, this oxidation route is active during much of the year, though its conversion rate is often limited to a few per cent per hour by the availability of SO_2, ammonia or atmospheric oxidants.

Sulphur dioxide may also be converted into particulate sulphate by the same reactions that produce photochemical smog. Here, sulphuric acid is formed by the oxidation of SO_2 with hydroxyl OH radicals in a reaction scheme that is closely analogous to the reaction scheme for ethylene described above:

$$OH + SO_2 + M = HOSO_2 + M$$

$$HOSO_2 + O_2 = HO_2 + SO_3$$

$$SO_3 + H_2O = H_2SO_4$$

$$HO_2 + NO = OH + NO_2$$

$$NO_2 + light = NO + O_3$$

$$SO_2 + 2O_2 + H_2O = H_2SO_4 + O_3$$

Again, the above reactions appear to be catalytic in that NO_x (= NO + NO_2) and hydroxyl OH radicals are not consumed in the reaction system. Because these reactions take place entirely in the gas phase, this mechanism is termed the homogeneous route.

Gaseous sulphuric acid either rapidly nucleates with water molecules to form a sulphuric acid droplet or sticks on to the pre-existing aerosol to form a highly acidic particle. At some later stage, atmospheric ammonia may dissolve in these droplets and act to partially neutralise them. Because ammonia does not take part in the rate-determining step of the homogeneous route, a large number of exceedingly acidic particles may form with little or no neutralisation. This is in complete contrast to the heterogeneous route where ammonia controls the rate of oxidation and some level of neutralisation is inevitable. Photochemical episodes are commonly associated with elevated levels of both ozone and acidic sulphate levels. Because particulate sulphate is an

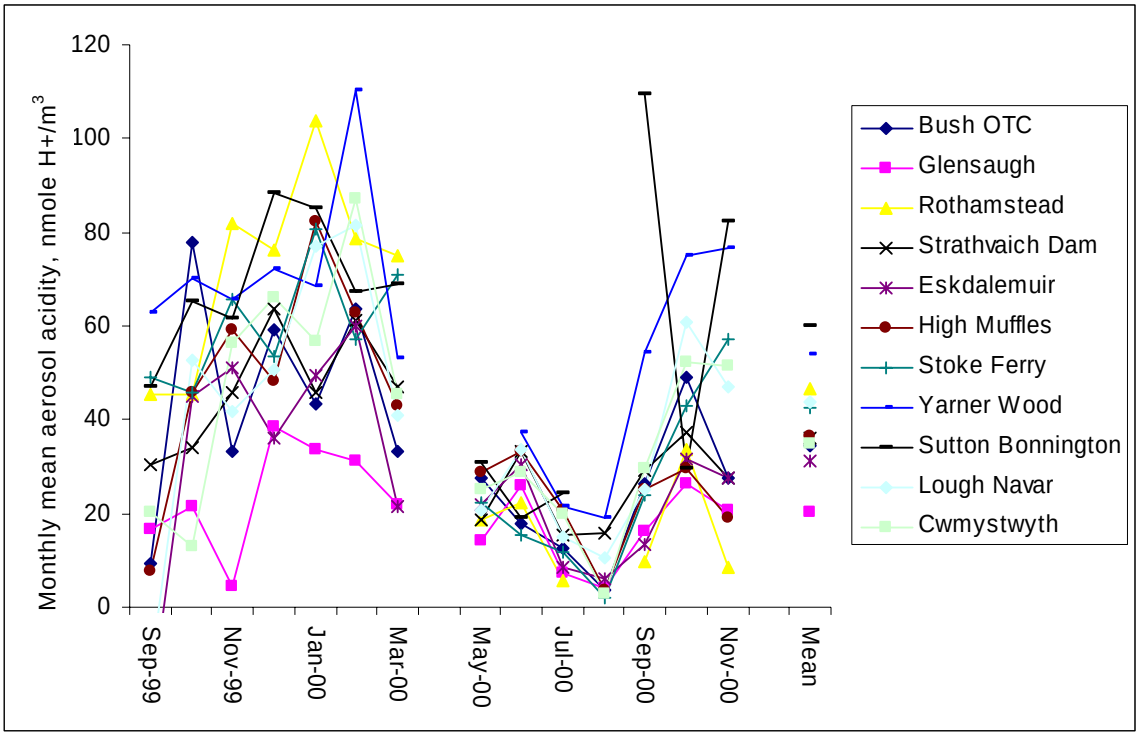
efficient light-scattering species, the photochemical oxidation of SO_2 produces haze and visibility reduction. Heat hazes are thus a common manifestation of the photochemical smog system.

There are no other inorganic sources of aerosol acidity other than sulphuric acid. Nitrate and chlorides are not present in the aerosol as free acids but only as fully neutralised salts of ammonium, sodium and calcium. There are, however, organic sources of aerosol acidity, including mono- and di-carboxylic acids and multi-functional acids. These acidic organic species are produced by the photochemical oxidation of organic compounds as side reactions to photochemical ozone production. There are, however, no routine observations of organic aerosol acidity in the UK.

UK Air Quality Data for total sulphates and acid sulphates

In Figure 1, the monthly mean aerosol composition is shown for a set of rural sites that are part of the UK Acid Rain Monitoring Network. Aerosol acidity is shown as net acidity by summing the observed aerosol anions: sulphate, nitrate and chloride and subtracting the cations: ammonium, sodium, magnesium and calcium. The plot shows the net aerosol acidity in nmoles H^+/m^3. The aerosol in the UK is most acidic during winter and is most neutralised during summer. This is because ammonia emissions from agriculture increase with ambient temperature and hence there is much more ammonia available to neutralise the aerosol during summer.

Figure 1: Monthly mean aerosol acidity (for sites that are part of the UK Acid Rain Monitoring Network)



In Figure 2, the daily time-series of particulate sulphate are shown for a single rural location, Stoke Ferry. Daily sulphate data show a wider dynamic range than monthly data. Evidence of daily peaks is found during May 1990, January 1991, April 1992, February 1993, May 1995, March 1996, November 1997 and December 2000, showing a mixture of spring and summer photochemical events and winter heterogeneous droplet events.

Little short-term, that is hourly, monitoring of aerosol acidity or sulphate has been carried out in the UK.

Figure 2: Daily time-series of particulate sulphate for Stoke Ferry

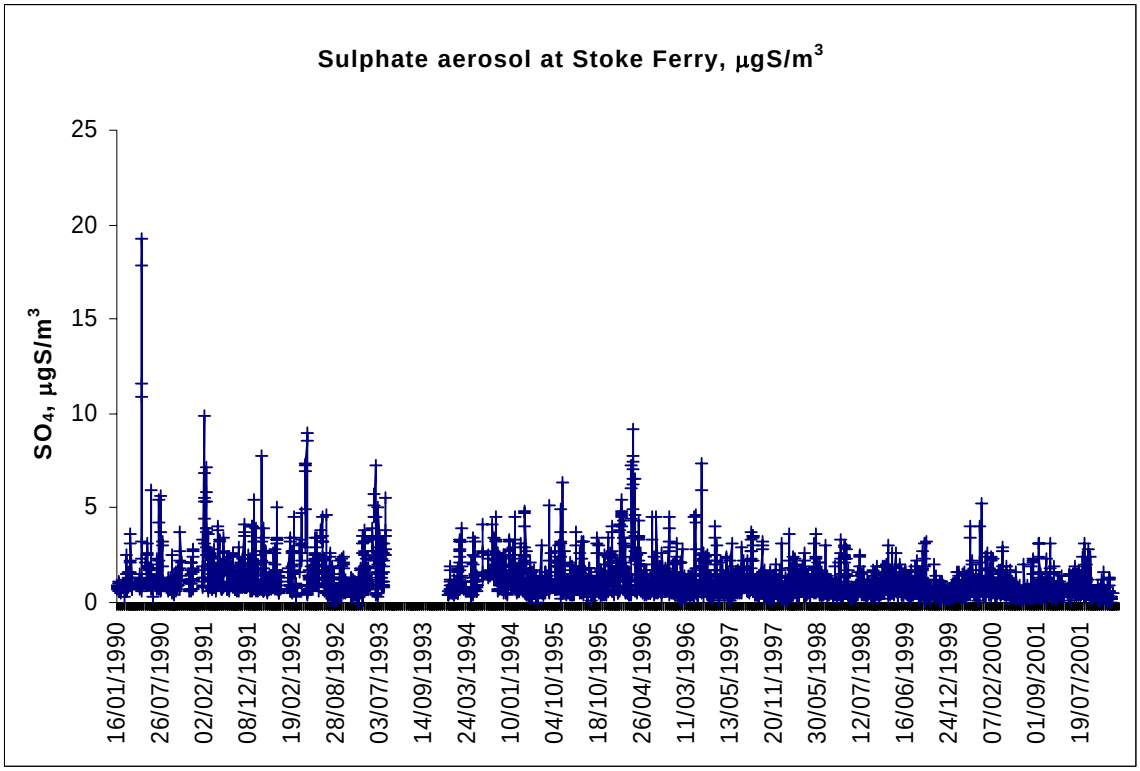
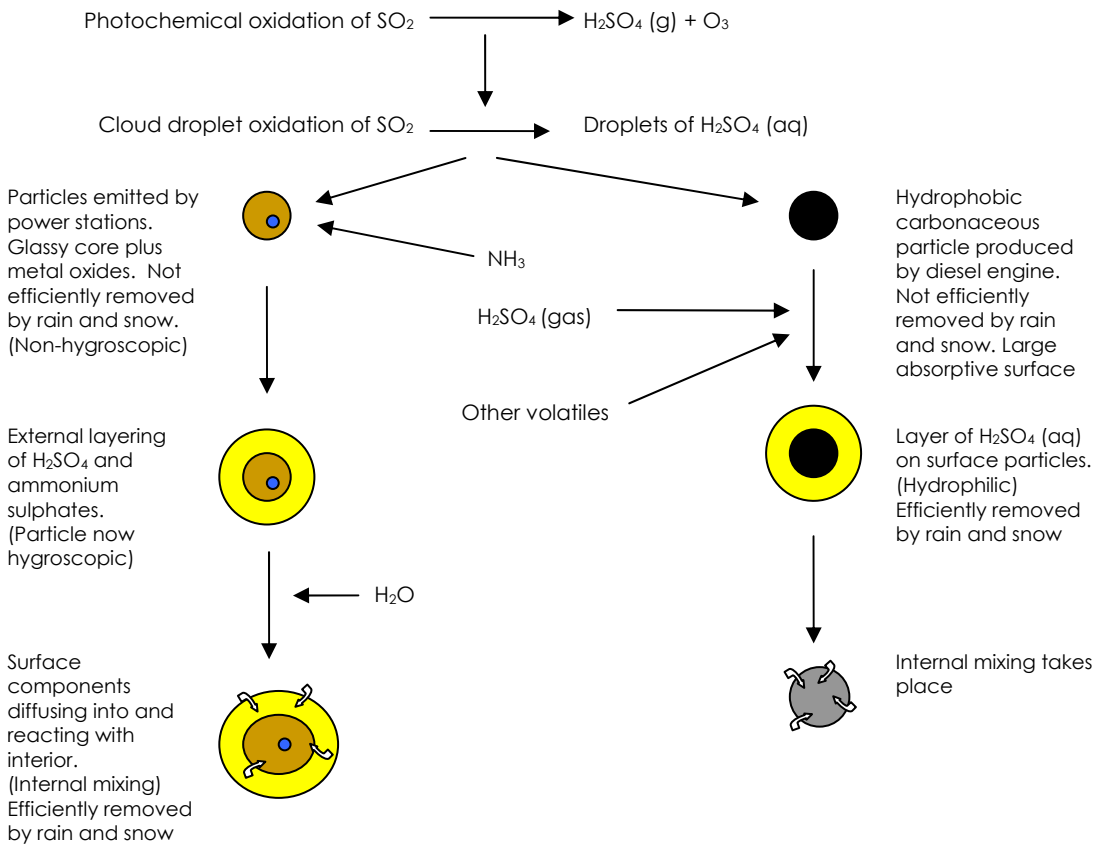


Figure 3 illustrates some of the many different atmospheric processes that occur following the oxidation of SO_2 to sulphuric acid in the gas phase and its scavenging by two illustrative types of particles emitted either by power stations or diesel traffic. Internal mixing of the sulphuric acid and its subsequent chemical reactions form sulphate salts and change the properties of the particle, allowing more efficient removal by wet scavenging processes.

Figure 3: Formation and fate of acidic particles



H_2SO_4 (g): gas phase sulphuric acid

H_2SO_4 (aq): sulphuric acid in solution in water

Working Paper 3

Secondary Particle Toxicology

Vicki Stone

Question: Do the toxicological data support a role for secondary particles in driving the long-term toxicological effects of $PM_{2.5}$?

In order to address this broad question the following specific questions must be addressed.

1 According to the toxicology literature could sulphate be an active component of $PM_{2.5}$ driving chronic adverse health effects?

Chronic exposure – impacts on respiratory health

The toxicological effects of sulphates and nitrates in the lung have been studied in a number of animal models using a variety of endpoints (see the table). The Advisory Group on the Medical Aspects of Air Pollution Episodes (MAAPE) produced a report in 1992, entitled 'Sulphur Dioxide, Acid Aerosols and Particulates' (Department of Health, 1992). Chapter 4 of that report described the 'Biochemical and Toxicological Effects of Sulphur Dioxide, Acid Aerosols and Particulates' that had been published at the time relating to both *chronic* and *acute* exposures. This report generated a number of useful summary diagrams (Figures 4.2 and 4.5) that illustrate the changes that occurred in animals exposed to a wide range of sulphur dioxide and acid aerosol concentrations, respectively. It is worth noting that most of these concentrations were orders of magnitude greater than those relevant to ambient air. Without distinguishing between acute and chronic exposures, the report made the following conclusions:

> "4.63 Sulphur dioxide is highly soluble and readily absorbed in the upper respiratory tract with the formation of a reactive sulphite species. The exact metabolic fate of sulphite can only be surmised but involves conversion to sulphate and removal in the urine.
>
> "4.64 Very high levels of inhaled sulphur dioxide and aerosols of sulphuric acid are surprisingly well tolerated by many animal species. Morphological damage of epithelial lining cells is detected in the upper respiratory tract after high or prolonged exposures. With acid aerosols, changes in airway resistance have been noted in the guinea pig, a particularly sensitive species and clearance effects noted in rabbits and donkeys on exposure to levels known to produce effects in man. It is impossible to predict the likely effects of exposure to ambient sulphur dioxide or acid aerosols upon man from animal studies.
>
> "4.65 Some investigations suggest that exposure of animals to sulphur dioxide in combination with particulates may be more damaging than the effects of the gas or sulphuric acid alone. However, relatively large concentrations of ultrafine particles, possibly of specific chemical composition, are required to produce reversible changes in some indices of lung function in the guinea pig, a particularly sensitive species."

Table: Main features of toxicological studies using animals to investigate the chronic respiratory effects of inorganic sulphur-containing compounds

Species studied	Endpoints measured	Chemical forms of inorganic sulphur studied
Rats	Mortality	SO_2
Mice	Lung function	H_2SO_4
Hamsters	Airway resistance	$(NH_4)_2SO_4$
Rabbits	Collagen production	$NaHSO_4$
Donkeys	Histopathology	Na_2SO_4
Guinea pigs	Fibrosis	$MgSO_4$
Monkey	Emphysema	
Humans	Clearance	
	Resistance to infection	
	Inflammation	
	T-lymphocyte proliferation	
	B cell function	
	Antigen processing	
	Carcinogenesis	
	Sensitivity to acetyl choline	
	Lung protein	

This report was unable to draw any conclusions as to the potential hazard of combined sulphur dioxide/particulate mixtures due to the "paucity of studies of this nature and the lack of monitoring of the nature of particulates at UK sites".

Subsequent to the 1992 report, there has been a relatively small number of studies that have investigated the chronic toxicological effects of 'sulphates'. These studies have been extensively reviewed (Grahame and Schlesinger, 2005; Lippmann, 2000; Schlesinger and Cassee, 2003) and such a review will not be attempted here.

It is worth noting the extensive studies conducted by Joachim Heyder's research group at the GSF, Munich (Heyder *et al,* 1999). These studies exposed beagle dogs for 13 months, to neutral sulphite (sodium metabisulphite) (1.5 mg/m^3) for 16.5 h per day, and to acidic sulphate particles (sodium bisulphate) carrying 15 μmol/m^3 hydrogen ions. The major conclusions of the study were that sulphur (IV) and particle-associated hydrogen ions, at concentrations close to those found at ambient concentrations, were unable to initiate disease in the healthy lungs of these animals. The endpoints investigated in this study were numerous and diverse, including measures of pulmonary inflammation, particle clearance, morphology, and structural and functional responses.

In general, studies relating to *chronic* exposures to sulphur-containing compounds, use variable concentrations, ranging from 100 μg/m^3 to 13 mg/m^3, but most of the studies have used exposure concentrations in the mg/m^3 range. Such concentrations are several orders of magnitude greater than those found in the UK, even during pollution episodes. The conclusions have not changed from those noted in the 1992 report; in general the findings of these studies tend to be negative, with effects only becoming significant after exposure to extremely high concentrations.

Exceptions include studies in donkeys demonstrating that exposure to sulphur dioxide, at 100 μg/m^3 for 1 hour per day, 5 days per week for 6 months, leads to a significant decrease in

particle clearance that the authors hypothesise could lead to an increased risk of chronic bronchitis (Lippmann *et al*, 1987).

These studies would suggest that chronic inhalation exposures to inorganic sulphur-containing compounds alone are unlikely to have chronic respiratory health effects.

Acute exposure – impacts on respiratory health

With respect to long-term health effects, it is worth considering the acute effects of exposure to the inorganic sulphur-containing component of $PM_{2.5}$. The long-term effects could simply be a consequence of exposure to moderate concentrations over a long period of time or, alternatively, they could be due to a number of intermittent episodes over the same period of time. The second option would suggest that the sulphur-containing compounds, if they are able to induce an acute response, may induce an impact that accumulates with time.

As mentioned previously, the MAAPE report 'Sulphur Dioxide, Acid Aerosols and Particulates' (Department of Health, 1992) concluded that inhaled inorganic sulphur-containing compounds have little impact on a number of animal models at exposure levels much greater than ambient concentrations. Again, a number of reviews (Amdur, 1989; Schlesinger and Cassee, 2003; Grahame and Schlesinger, 2005) have also been written that, in general, support the findings of the 1992 report. The types of endpoints measured have varied and include effects on inflammation, epithelial integrity, clearance, resistance to infection, histopathology, respiratory function, airway resistance and antigenic responses.

Returning to the suggestion that any effects of acute responses could accumulate over time, the general lack of response to acute exposures would suggest that this is unlikely. It is more likely that sulphate interacts with other pollutants that either acutely, or over time, induce a toxicological response (see below, questions 4 and 5).

Impacts on cardiovascular health

All of the toxicological studies identified have measured short-term effects of particulate matter on the respiratory system. Effects of inorganic sulphates on cardiovascular endpoints have not been extensively studied.

Sackner *et al* (1978) exposed anaesthetised dogs to a submicron aerosol of H_2SO_4 (4000 $\mu g/m^3$, for 4 hours) and found no effects on a variety of cardiac parameters including heart rate, pulmonary and carotid arterial pressures, cardiac output and arterial blood gas tensions. However, none of these endpoints corresponds to cardiovascular and neural changes that have been identified in animal and human models exposed to particulate matter. This has been reviewed in the recent COMEAP report 'Cardiovascular Disease and Air Pollution' (Department of Health, 2006).

In 2000, the Health Effects Institute published an extensive report (Godleski *et al*, 2000) which investigated the effects of concentrated ambient particles (CAPs) in Boston on cardiac function and respiratory inflammation in dogs. Half of the dogs tested were subjected to coronary occlusion, in order to simulate coronary artery disease. In the dogs subjected to the occlusion, CAPs induced a number of changes in the electrocardiogram (ECG), including an elevation of the ST segment, an effect which is suggestive of myocardial ischaemia. The healthy dogs exposed to CAPs did not demonstrate increased incidence of inflammation, but they did demonstrate a number of changes including heart rate variability, altered average heart rate,

decreased T-wave alternans, and changes in breathing rate and air flow rate. The authors suggest that CAPs influence the nervous system's control of the normal dog's heart without inducing arrhythmia and without the requirement for inflammation. The HEI report, however, questions the validity of the statistical approach used due to the small numbers of animals employed in the study.

In this study the animals' heart rates actually fluctuated widely from day to day during the study, but these changes were not related to the mass of exposure, suggesting that composition may be important. A number of parameters of composition were available (e.g. sulphate) in the study, but it was not possible to identify whether the variability in physiological response was due to particulate matter compositional changes. During the study period ammonium sulphate was the most prevalent ingredient quantified, making up 30.9±11.0% of $PM_{2.5}$ mass measured in the same area, giving a mean airborne concentration of 101.5 μg/m^3. (Organic carbon and elemental carbon made up 28% and 7% of the $PM_{2.5}$ mass, respectively.) Analysis of the air mass trajectory data indicated that when CAPs were derived from the northwest of Boston, high frequency (HF) powers for heart rate variability (HRV) and heart rate standard deviation (HR SD) were increased. These changes suggest increased vagal activity and that perhaps CAPs from the northwest had a pulmonary irritant effect. Conversely, when CAPs were derived predominantly from the continental USA, there was a significant decrease in HF HRV and HR SD with a corresponding increase in heart rate, suggestive of sympathetic activity. However, statistical analysis of these data did not find a significant effect of the source of CAPs on the high frequency component of HRV or on the standard deviation of the R-R interval.

In comparison, studies conducted in rats using residual oil fly ash (ROFA) identified that anthropogenic particles induced increased frequency and severity of arrhythmias in monocrotaline-treated rats (pulmonary hypertension model) (Watkinson *et al*, 1998). Other studies using ROFA have demonstrated that instillation of ROFA into rats leads to bradycardia, hypothermia and arrhythmogenesis (described in Campen *et al,* 2002). ROFA, however, is very different in composition to $PM_{2.5}$, containing much higher levels of metals in a form that is predominantly soluble. This would suggest, that there are forms of anthropogenic airborne particles that can impact on cardiovascular function in acute models, but that these effects are not necessarily dependent upon, or driven by, sulphate.

A number of studies have been conducted that investigate the role of metals in inducing the toxicological effects of ROFA. Such studies have often used the sulphate form of the metal salt as a surrogate for the ROFA components. For example, Campen *et al* (2002) exposed rats fitted with radiotelemetry transmitters to aerosolised nickel, vanadium or nickel plus vanadium in the form of a sulphate (0.3–2.4 mg/m^3), for 6 hours per day for 4 days. Nickel sulphate caused delayed bradycardia, hypothermia and arrhythmogenesis at concentrations greater than 1.2 mg/m^3. In contrast, even the highest concentration of vanadium sulphate failed to induce any significant change in heart rate (HR) or core temperature. The difference between these two metal salts suggests that the metal ion rather than the sulphate drives the cardiovascular effects.

Muggenburg *et al* (2003) studied old beagle dogs, with pre-existing cardiac abnormalities, and exposed them via oral inhalation to oxide and sulphate forms of transition metals (0.05 mg/m^3, for 3 hours per day, on 3 successive days). The study did not demonstrate an effect of the metal oxides or sulphates on the underlying clinical abnormalities observed in control conditions. The dose used in this study was relatively low, but the advantage is that this is a

good model of a suspected susceptible subpopulation. The fact that there was no difference between the sulphate and oxide treatments indicates that the sulphate was not inherently toxic or active in the dogs.

In a study exposing tissue samples of rat aorta and a small mesenteric artery to ambient particles (EHC-93), the soluble components of the particles failed to modify the resting tension of either tissue (Bagate *et al*, 2004). Since the soluble components include the sulphates, it seems unlikely that sulphates (at the unknown concentration employed) would impact on the contractility of the blood vessel musculature. In contrast, the whole PM fraction induced vasoconstriction of the phenylephrine pre-treated tissues. However, this effect is in complete contrast to some epidemiological and clinical studies that have demonstrated that PM is associated with increased blood pressure. The authors suggest that the *in vivo* effect is under neural regulation rather than being initiated directly by components of the PM mix.

In conclusion, none of the animal studies published demonstrated an ability of sulphate to induce cardiovascular effects. However, all of the effects measured were acute. No literature has been identified that investigates the chronic effects of sulphates on cardiovascular pathology or function.

2 Is the form of sulphate inhaled important in determining the toxicology?

The following forms of sulphur-containing compounds have been identified in atmospheric chemistry and are measured as sulphate in PM_{10}:

Sodium sulphate

Sulphuric acid

Ammonium sulphate

Ammonium bisulphate

Other metal sulphates

Sodium sulphate

Sodium sulphate is indicative of wind blown sea salt and such particles tend to occur in the $PM_{2.5}$ – PM_{10} size range.

Relatively few studies have investigated the pulmonary effects of sodium sulphate. Last *et al* (1986) used Na_2SO_4 as a neutral aerosol for comparison with ammonium sulphate or sulphuric acid. The study investigated synergistic interactions between sulphate aerosols and ozone. The authors concluded that it was the acidity of the particle rather than the sulphate content that was responsible for driving the synergistic effects on markers of lung fibrosis (lung protein and proline content).

Secondary particles

In contrast to sodium sulphate, the other inorganic sulphur-containing compounds listed occur in the $PM_{2.5}$ size range. This would suggest that inorganic sulphur-containing particles should reach the respiratory bronchioles and alveolar regions of the lung. In the humid environment of the respiratory airways, inorganic sulphur-containing particles are likely to grow considerably

and hence increase the tendency to deposit in the upper airways. This would hence decrease the tendency for interaction with the delicate respiratory parts of the lung, but increase the tendency for interaction with the mucociliary escalator. Experiments in a number of species suggest that high concentrations of H_2SO_4 decrease particle clearance from the lung (reviewed in Amdur, 1989).

H_2SO_4 and $(NH_4)_2SO_4$

Most of the studies investigating the effects of inorganic sulphates in animal models have been conducted using an aerosol of H_2SO_4 which is relatively well tolerated in acute and chronic studies, even at high exposure concentrations, in a wide variety of animal models.

H_2SO_4-coated particles

Sulphur-containing compounds may exist as discrete particles, droplets or as films on the surface of other particles. Studies have been conducted to investigate the effects of humidified sulphate and zinc oxide (ZnO) particle clouds on rats and guinea pigs (Amdur, 1989). In these studies SO_2 exposure was conducted in a humidified environment containing particles. The SO_2 is converted to H_2SO_4 that deposits on the particle surface. The resultant exposure consists of relatively low concentrations of H_2SO_4 (50 μg/m^3 for 3 hours) on the surface of ZnO particles (0.05 μm and 5 mg/m^3), which allow H_2SO_4 to reach the alveolar regions, which would not be possible if inhaled as droplets. The author suggests that this form of delivery leads to an increased potency of the H_2SO_4 as evidenced by a decrease in lung volume and diffusion capacity, centrilobular morphological damage, increased pulmonary oedema and epithelial permeability as well as inflammation. The airborne mass concentration of particles used in this study is large, although the deposited dose in the relatively short exposure time is not stated, but is unlikely to reach overload (4.5–5 mg required in a rat lung for overload).

Other metal sulphates

In a study by Amdur's research group, the role of iron sulphate ($FeSO_4$) in coal-dust-induced lung injury was investigated (Chen *et al*, 1996). The study demonstrated that exposure of guinea pigs to $FeSO_4$ (5% final concentration)-enriched carbon or coal dust (5 mg/m^3, for 3 hours) enhanced the decrease in phagocytic response of lavaged macrophages. Similar results were obtained by Jakab *et al* (1996) using mice exposed to SO_2 (10 ppm) and carbon black (10 mg/m^3) in a high relative humidity. Such conditions readily allow the formation of an H_2SO_4 film on the particle surface as studied by Amdur.

A number of studies have been conducted to investigate the respiratory and cardiovascular effects of ROFA (e.g. Dreher *et al*, 1997) and metal sulphates (e.g. Campen *et al,* 2002). The effects observed were invariably driven by the metals and not by the sulphate component of the treatment. This has been discussed in more detail in relation to cardiovascular effects under question 1.

3 A number of toxicological studies suggest that the acidity of the sulphate is related to its potency, how does the lung deal with H^+?

Holma (1985) studied the buffering capacity of fresh morning sputum, isolated from adult male smokers (20 cigarettes per day). The mucus samples were titrated with increasing amounts of H_2SO_4 and the pH monitored. The buffering capacity of the mucus (as measured by the ability to resist pH change on addition of acid) was found to vary from day to day. The buffering

capacity was found to be less than that of plasma, but greater than that of water. In a second experiment, after collection, the sputum was diluted 10-fold using distilled water and acidified with H_2SO_4 to pH3.33. The pH of the water was then monitored 2 and 10 minutes later. The pH increased, suggesting that the mucus acted as a buffer. Mucus with a pre-existing low pH was a less efficient buffer. Asthmatics and chronic bronchitics have been demonstrated to possess mucus of a low pH, and this would suggest they are less able to buffer the pH effects of acid aerosol inhalation. However, in the study by Holma (1985), the two asthmatics included in the study did not exhibit mucus of low pH, although their mucus did demonstrate a reduced capacity to buffer acid.

According to a recent review by Ng *et al* (2004) the pH of airway surface liquid (ASL) and alveolar subphase fluid (AVSF) is likely to be a major determinant of lung host-defence responses. They identified that ASL and AVSF are more acidic than plasma and that their pH is controlled via appreciable acid-base flux across the airway epithelium, but not across the alveolar epithelium. The buffering capacity of the ASL is thought to be due to mucins, and for AVSF due to surfactant proteins. Ng *et al* state that the pH of ASL and AVSF can be decreased by disease or inflammation. In addition to suppressing microbe clearance, Ng *et al* also indicate that a decrease in pH leads to increased pathogen survival in the airways and alveoli, and altered mediator release by macrophages and leukocytes, leading to increased potential for cellular damage.

If individuals with an inflammatory lung disease are part of a susceptible subgroup, then it is feasible that due to the lowered buffering capacity of their mucus, and hence lung surface, they are more sensitive to the effects of acid aerosols and/or inorganic sulphate exposure. Such exposure would lead to a reduced pH of lung fluids, resulting in decreased clearance of particles and pathogens. The resultant inflammation (either short- or long-term) could then be sufficient to exacerbate disease symptoms leading to death (through either respiratory or cardiovascular causes). This has been discussed in the recent COMEAP report 'Cardiovascular Disease and Air Pollution' (Department of Health, 2006). It is tempting to speculate that an individual with a pre-existing lung disease will die from lung rather than cardiovascular disease. However, it is also feasible that through the release of pro-inflammatory mediators into the general circulation, the inflammatory response initiated in the lung could result in increased blood clotting and increased activation of macrophages within atherosclerotic plaques. The epidemiology clearly demonstrates an increase in deaths due to cardiovascular causes, but does this mean that all of the deceased individuals identified in this group suffered from a pre-existing cardiovascular disease, or could they have had a pre-existing inflammatory disease, e.g. in the lung, that had secondary effects on the cardiovascular system?

In addition to measuring the effects of acid treatment on buffering capacity, Holma (1985) also measured the effects of pH change on mucus viscosity. Mucus viscosity was at its lowest at pH7.4, and a change in pH in either direction increased viscosity. An increase in mucus viscosity decreases the efficiency of the mucociliary clearance. Holma also suggested that increased mucus viscosity induced by H^+ may lead to increased airway obstruction, reduced vital capacity, forced expiratory volume and forced expiratory volume in one second. Since changes in mucus viscosity are associated with these variables in diseases such as chronic bronchitis and cystic fibrosis, this suggestion seems plausible.

4 Can sulphates interact with other components of $PM_{2.5}$ to alter their combined toxicity?

When trying to identify which components of $PM_{2.5}$ are responsible for driving the adverse health effects identified in epidemiological studies, it is tempting to consider the toxicity of each component individually. However, $PM_{2.5}$ is a complex mixture that varies with time and location. It is likely that some components are more potent than others, but due to the complexity of the mixture, it has not been possible to generate a firmly based ranking of hazard associated with each component (taking into account exposure dose and toxicity), or to identify components that definitely are or are not involved in generating the adverse health effects. There is clear toxicological evidence (Seaton *et al*, 1995; Donaldson *et al*, 2002) and some epidemiological evidence (Peters *et al*, 1997) that the insoluble, mainly carbonaceous ultrafine or nanoparticle component, derived from combustion sources, may play an important role in driving inflammation, but it is unlikely that this is the sole active component. It should be noted that particle size (e.g. ultrafine) does not imply complete uniformity of composition. A number of studies have also suggested a role for endotoxin (Becker *et al*, 1996; Schins *et al*, 2004), but some studies have also demonstrated no such role (Lightbody *et al*, 2002). Both toxicology (Frampton *et al*, 1999) and epidemiology (Pope, 1996) suggest a clear role for metals in driving the inflammatory response underlying PM-induced health effects, but again the metals are not able to explain all of the $PM_{2.5}$-induced toxicity. These findings would suggest that once deposited in the body, interactions between $PM_{2.5}$ components may occur, leading to potentiation or synergism of the toxic response.

Particles and sulphates

Wilson *et al* (2002) have demonstrated that both iron sulphate and iron chloride interact with carbon nanoparticles to potentiate the particle-driven production of reactive oxygen species in a cell-free system. There was no difference between the effects of sulphate and the chloride, suggesting that the sulphate ion did not play an especially significant role in the interaction.

As described previously (question 2), Amdur (1989) described how delivery of H_2SO_4 to the lung in the form of a film on the surface of ZnO particles enhanced the toxicological impact of the acid aerosol. Other groups have not conducted comparable studies, and the effects are limited to short-term respiratory studies. In general, these studies demonstrate enhanced effects on variables such as airway resistance and collagen synthesis, but it is difficult to come to firm conclusions due to the lack of comparable data from other sources.

Metals and sulphates

Ghio *et al* (1999) have suggested that sulphate may play a role in mobilising transition metals from their oxide forms during photo-reduction of ambient PM. They identified that a portion of the iron present in the atmosphere is present as sulphate. The study suggested that there was a relationship between the sulphate and metal content of the PM extracts and their ability to drive the production of reactive oxidant species. The sulphates alone (i.e. in the absence of metal species) were not able to generate these reactive intermediates, thought to be responsible for the metal toxicity.

5 Can sulphates interact with other pollutants in biological systems to alter their combined toxicity?

As suggested above, sulphates could interact with other components of the particle mixture leading to enhanced toxicity. The pollution mixture also consists of a number of oxidising gases including ozone and the oxides of nitrogen. A number of studies have been conducted to investigate such interactions, and while some studies have demonstrated enhanced toxicity, others have not.

Ozone

The research group of Jerold Last has published several papers on interactions between ozone (0.63 ppm, 1.3 mg/m^3) and either ammonium sulphate or sulphuric acid (1-5 mg/m^3 for 7 days) in animal models (Last *et al*, 1986; Last and Warren, 1987). The authors suggest that it is the acidity, rather than the sulphate content, that is responsible for the synergistic increases in lung protein and proline. Their studies indicated that neutral aerosols (Na_2SO_4 and NaCl) did not interact with ozone. These studies also employed aerosols of different mass median aerodynamic diameter.

Aranyi *et al* (1983) studied the effects of ozone (0.2 mg/m^3) and of a mixture of ozone, SO_2 (13.2 mg/m^3) and $(NH_4)_2SO_4$ on mice exposed for 5 hours per day, 5 days per week for up to 103 days. Both treatments increased susceptibility to streptococcal infection, but did not increase cellular markers of inflammation. Furthermore, both treatments increased the bactericidal activity of lavaged alveolar macrophages. With all of the endpoints measured there was no discernable difference between the effects of ozone alone and the mixture.

In a study exposing rats for 4 hours to ozone (0.8 ppm), ammonium sulphate, ferric sulphate or sulphuric acid (3.5 mg/m^3), ozone alone was found to slow early clearance of radioactive particles from the lung, but to stimulate later clearance (Phalen *et al*, 1980). In contrast, the sulphates had no significant impact on clearance. When ozone was combined with each of the sulphates, the effects observed were similar to ozone alone, with no evidence of synergy for ammonium sulphate or ferric sulphate. The results for sulphuric acid were less clear cut, and there may be some interaction between this acid and ozone with respect to effects on clearance. High humidity amplified the effects of ozone and most of the mixtures tested.

Oxides of nitrogen

In addition to investigating interactions between ozone and sulphates, the studies conducted by Last and co-workers (Last *et al*, 1986; Last and Warren, 1987) also investigated interactions with NO_2. Similar results were observed in relation to collagen production by lung minces, but to a lesser extent than for ozone.

Complex mixtures

Kleinman *et al* (1989) treated resting and exercising rats to multiple pollutants under conditions designed to generate an acidic aerosol. They measured the effects of these pollutants on the early and late clearance of inhaled radioactive particles from the lung and on inflammation. The paper is complex, and the exposure protocols are not clearly explained. In their abstract, the authors suggest that:

- The effects on clearance were dominated by the oxidant component of the mixture, but the effects were significantly greater than for ozone alone.

b H_2SO_4 alone did not induce inflammatory changes in the lung parenchyma, but effects on the nasal epithelium were noted.

c The mixture of ozone and NO_2 (forming nitric acid) induced damage to the lung parenchyma to a greater extent than ozone alone.

d Increasing the mixture complexity to include H_2SO_4, ozone and NO_2 led to damage in both the lung parenchyma and nasal epithelium.

e The effects observed at rest were dominated in the lung by the oxidant component of the gas mixture, and by the acid component in the nasal epithelium.

f Exercise significantly increased the effects of this complex mixture on the lung parenchyma to exceed the effects of ozone alone.

6 Since, according to the epidemiology, $PM_{2.5}$ impacts on cardiovascular deaths to a greater extent than respiratory deaths, is there sufficient toxicological evidence available to suggest that long-term exposure to sulphates may impact on the cardiovascular system?

The answer to this is simply no. The available toxicological data relating to the cardiovascular effects of sulphates are so few that it is not feasible to generate any clear conclusions. This does not mean that there is not a link, but, rather, that it has not been studied. There are plausible hypotheses that could be developed, but these are not substantiated in any way. Using the information outlined above, the following hypothesis could be generated:

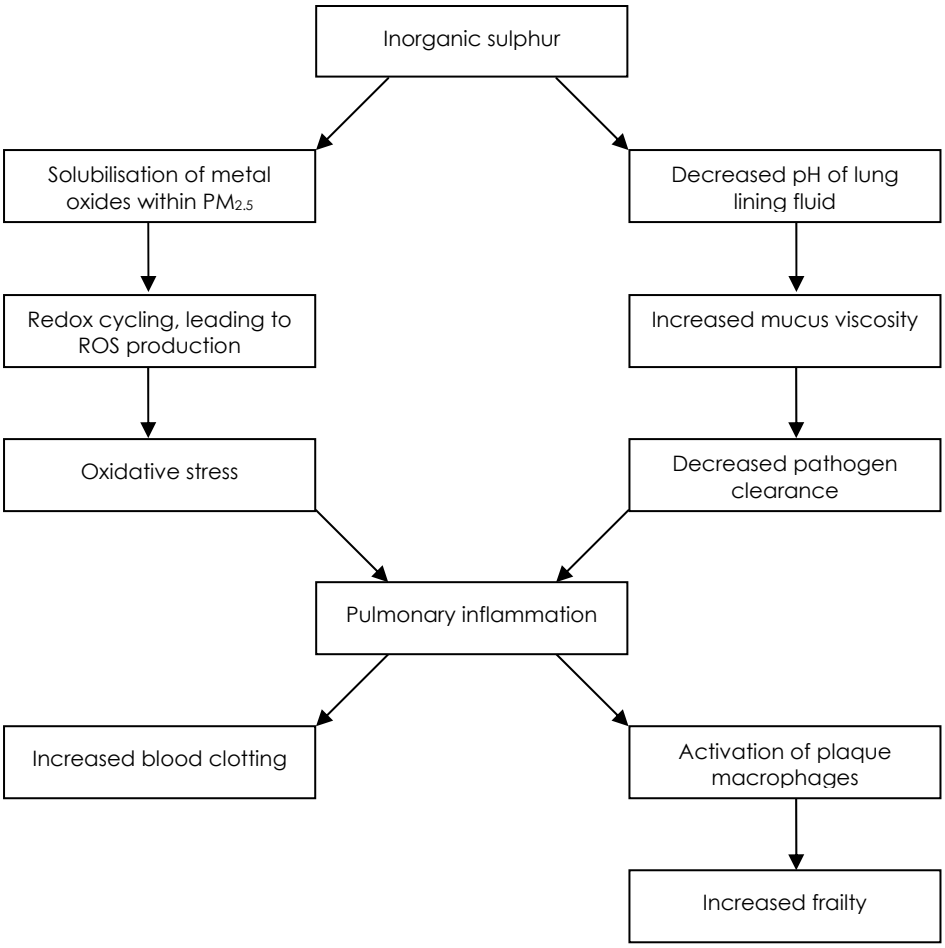
> Sulphates could play a role in the capacity of $PM_{2.5}$ to drive pulmonary inflammation via either increasing metal mobilisation from PM, and hence increasing the ability to drive oxidative stress leading to inflammation, or decreasing the pH of lung-lining fluid, leading to decreased pathogen clearance and hence increased inflammation. Inflammation in the lung could then initiate changes in blood clotting, and/or activation of macrophages in atherosclerotic plaques increasing their instability. The irritant effects of altered pH on neural reflexes cannot be ruled out, but it is difficult to explain how such changes could have long-term health effects (see the figure).

7 Is there sufficient toxicological evidence available to suggest that long-term exposure to nitrates may impact on human health?

There is even less information pertaining to the adverse health effects of inhaled nitrates. Studies with NH_4NO_3 (1 mg/m^3, for 6 hours per day, 5 days per week, 4 weeks) (Busch *et al*, 1986) failed to demonstrate any changes in lung volume or degree of emphysema in rats and guinea pigs treated with elastase.

Since the nitrates are only weakly acidic, the hypothesis generated for sulphates (question 6) is unlikely to be applicable, as nitrates are less likely to induce metal mobilisation or alterations in the pH of lung lining fluid.

Figure: Hypotheses to explain how inorganic sulphate could drive cardiovascular effects



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Working Paper 4

Epidemiology of Particulate Sulphate

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Background

The purpose of this brief review is to support QUARK II in coming to a decision about whether to estimate the impacts of particulate sulphate, or to adjust the $PM_{2.5}$ coefficient for sulphate or, alternatively, to adjust the sulphate coefficient for $PM_{2.5}$. This is a problem because generic particle measures based on size, such as PM_{10} and $PM_{2.5}$, are not specific for secondary aerosol arising from SO_2 emissions. The underlying importance of this question relates to what sources of particles should be the priority for regulation.

The main sources of evidence are time-series studies (population and panel), prevalence studies and cohort studies. Generally, sulphate has not been the main focus of investigation. Of more interest has been the acidity (H^+) which is associated (though not exclusively) with sulphur acids and sulphate compounds such as ammonium bisulphate. There seems to be good evidence that there is less acidity in Europe than in the north east of the USA, where most investigations have been done.

Because sulphate is a secondary particle with low settling velocity, it tends to have a relatively uniform distribution over large areas, such as comprise the focus for population time-series and cohort studies (though less so for panel studies which tend to be conducted in smaller areas) (Lippmann and Thurston, 1996). Particulate sulphate is likely to penetrate easily indoors, since it is largely in the fine fraction. For this reason exposure misclassification may be less than for particle measures which include primary components or the coarse fraction. Since exposure misclassification will generally bias estimates of health effects towards the null (Zeger *et al,* 2000), this complicates any analysis which attempts to compare the effects of different particulate fractions. This could lead to sulphate showing larger effects than PM_{10}, say, on account of less exposure misclassification.

Time-series studies

Although time-series evidence is less satisfactory for health impact assessment, it comprises the largest body of evidence. The Air Pollution Epidemiology Database (APED), at St George's, University of London, has systematically ascertained all time-series studies in the peer-reviewed literature and extracted estimates of effect for a range of pollutants, including sulphate, up to March 2005, and these will be reviewed.

A total of 29 population time-series studies (these will be referred to as time-series studies) with estimates for sulphate were identified. The numbers of studies with estimates for mortality, hospital admissions, emergency visits and ambulatory care visits were 14, 11, 5 and 1, respectively. Some of these studies reported estimates for a range of age and diagnostic subgroups.

Studies were divided by outcome into six categories: all-cause mortality (14 studies), respiratory mortality (7), cardiovascular mortality (7), respiratory hospital admissions (3), cardiovascular hospital admissions (3), and emergency visits (4). A summary of the number of studies and estimates is shown in Table 1.

For each of the above categories, a table listing the all-year, single pollutant, selected lag estimates was prepared together with an accompanying figure showing the estimates in the form of a forest plot. A semi-quantitative approach to assessing the results was employed in which the numbers of positive and negative estimates were counted, together with the numbers that were statistically significant at the 5% level. This is very limited however, because it does not take sufficient account of differences in power between the various studies. Quantitative meta-analysis was carried out for those groups containing four or more estimates from separate cities where the age-outcome category was sufficiently similar for the estimates to be grouped. Heterogeneity was tested for using the chi square test. The summary estimate was calculated using a fixed effect model if there was no evidence of heterogeneity, otherwise a random effects model was used. Where there were ten or more estimates tests for publication bias were done.

The results for all-cause mortality will be described in detail, since this is the largest dataset. The presentation for the other outcomes follows the same pattern. Fourteen studies reported effects on all-cause mortality (Anderson *et al,* 2001; Burnett *et al,* 1998, 2000; Dockery *et al,* 1992; Fairley, 1999; Goldberg *et al,* 2001a,b; Gwynn *et al,* 2000; Hoek *et al,* 2000; Klemm and Mason, 2000; Klemm *et al,* 2004; Lippmann *et al,* 2000; Schwartz *et al,* 1996; Villeneuve *et al,* 2003). Twelve were single-city studies (SCS) and two were multi-city studies (MCS) with six and eight cities, respectively. This gave a total of 27 cities (We have not allowed for double counting between SCS and MCS). Of the 15 estimates, 14 were positive and six out of 14 positive estimates were statistically significant (Figure 1). One study, that from the West Midlands, was negative, but not significantly so. A pooled estimate was obtained for 14 studies, 12 from North America and two from Europe. There was significant heterogeneity and the random effects estimate was 2.2 (95% CI 1.5–3.0) $p<0.0001$. There was visual evidence of publication bias but adjustment for this made little effect on the pooled estimate (Figure 2).

Seven studies reported respiratory mortality (Anderson *et al,* 2001; Fairley, 1999; Gwynn *et al,* 2000; Hoek *et al,* 2000; Lippmann *et al,* 2000; Villeneuve *et al,* 2003). Seven of eight estimates were positive, with one of five positive estimates being statistically significant (two estimates did not have standard errors) (Figure 3). The only negative estimate (not significant) was from the West Midlands. The results of the quantitative meta-analysis of six cities found no evidence of heterogeneity. The fixed effects estimate (for 10 $\mu g/m^3$) was 3.9 (95% CI 1.1–6.8) $p<0.006$.

For cardiovascular mortality, five of the following seven estimates were positive (Anderson *et al,* 2001; Fairley, 1999; Goldberg *et al,* 2001a; Gwynn *et al,* 2000; Hoek *et al,* 2000; Lippmann *et al,* 2000; Villeneuve *et al,* 2003). None of the five with standard errors was statistically significant (Figure 4). In a meta-analysis of five cities there was no evidence of heterogeneity. The fixed effect estimate (for 10 $\mu g/m^3$) was 1.0 (95% CI -0.3–2.3) $p< 0.1$.

Estimates for respiratory hospital admissions were available for only three cities (Anderson *et al,* 2001; Gwynn *et al,* 2000; Lippmann *et al,* 2000) and the ten estimates covered a range of ages and diagnoses (Figure 5). Seven out of ten estimates were positive, of which two were statistically significant. Three were negative (all from the West Midlands) but none significantly so. There were insufficient data for quantitative meta-analysis.

Table 1: Summary of studies, estimates, direction and significance

Outcome	Studies	Single-city studies	Multi-city studies	Total estimates adding in MCS cities	Total cities allowing for double counting with MCS	Estimates	Pos	Pos sig	Neg	Neg sig
All-cause mortality	14	12	2 (14)	27	22	15	14 of 15	6 of 14	1	0 of 1
Respiratory mortality	7	7	na	8	7	8	7 of 8	1 of 5	1	0 of 1
Cardiovascular mortality	7	7	na	7	7	7	5 of 7	0 of 5	2	0 of 2
Hospital admissions for respiratory diagnoses	3	3	na	10	3	10	7 of 10	2 of 7	3	0 of 3
Hospital admissions for cardiovascular diagnoses	3	3	na	9	3	9	9 of 9	1 of 9	0	na
Daily emergency room visits	4	4	na	23	3	23	13 of 23	4 of 13	10	3 of 10

Estimates for cardiovascular diagnoses were obtained from studies of three cities (Anderson *et al,* 2001; Gwynn *et al,* 2000; Lippmann *et al,* 2000) (Figure 6). Nine out of nine estimates were positive, with one significant. There were insufficient data for quantitative meta-analysis.

Four studies from two cities reported a range of estimates for emergency room visits (Metzger *et al,* 2004; Peel *et al,* 2005; Stieb *et al,* 2000; Tolbert *et al,* 2000) (Figure 7). Of 23 estimates, 13 were positive, with four being significantly so. Ten were negative with three significantly so. There were insufficient data for quantitative meta-analysis.

Ten studies reported the results of multi-pollutant models (Burnett *et al,* 1994, 1995, 1997, 1998; Delfino *et al,* 1997; Fairley, 1999; Goldberg *et al,* 2001a; Hoek *et al,* 2000; Lippmann *et al,* 2000; Thurston *et al,* 1994). The results are difficult to summarise. On inspection the impression is that the estimates tended to remain positive, though often reduced in size by including other pollutants in the model.

The most comprehensive analyses using two-pollutant models was found in the studies of Wayne County and the Netherlands (Hoek *et al,* 2000; Lippmann *et al,* 2000). In the Wayne County study, the interquartile values for sulphate were 7.8–13.6 $\mu g/m^3$ with a median of 10.2. The correlation with other pollutants was 0.48 with PM_{10}, 0.30 with O_3, and 0.27 with SO_2. The authors of the Wayne County study concluded as follows "… Our results are not consistent generally with our study hypothesis that the relative particle metric effect size and strength of association with mortality and morbidity outcomes, in descending order would be H^+, SO_4^{2-}, $PM_{2.5}$, PM_{10} and TSP. In general, the PM mass indices were associated more significantly with health outcomes than were H^+ or SO_4^{2-}. When both H^+ and SO_4^{2-} were significant, SO_4^{2-} was associated more strongly with the outcomes …."

In the Netherlands, sulphate ($\mu g/m^3$) ranged from 0.7 to 36.1 with a median of 3.8. The correlation with other pollutants was 0.84 with PM_{10}, 0.65 with black smoke (BS), 0.00 with ozone, 0.52 with SO_2, 0.44 with NO_2 and 0.55 with CO. SO_4^{2-} and, NO_3^- and BS were more consistently associated with mortality than was PM_{10}. Indicators of primary (BS) or secondary (SO_4^{2-} and NO_3^-) particles were relatively stable to inclusion of PM_{10}, but not vice versa. Although this study could not comment on the relative importance of secondary versus primary fine particles, both appeared to be important.

In the West Midlands, concentrations of SO_4^{2-} ranged from 1.3 to 7.7 (10^{th} to 90^{th} percentile) with a median of 2.7 ($\mu g/m^3$). This study did not tabulate two-pollutant estimates in the published paper, but some results are available in the report to EPAQS (Expert Panel on Air Quality Standards) (DETR, 2001). The effects of sulphate controlling for other particle metrics ($PM_{2.5}$, $PM_{2.5-10}$ and black smoke) were examined in relation to admissions for all cardiovascular and cardiac diseases for all ages and all respiratory diseases for all ages and ages 0–14 years. Generally, the effect of sulphate was less than that of black smoke for the 10^{th} to 90^{th} percentile range. The strongest effect (though non-significant) was on respiratory admissions aged 0–14 years and this was weakened by inclusion of $PM_{2.5}$ but unaffected by black smoke or the coarse fraction.

It is concluded that there is reasonably strong evidence of a positive effect, especially on mortality, and this is supported by the quantitative meta-analysis which found significant positive associations with all-cause and respiratory mortality. However, the two European studies, from the Netherlands and West Midlands, did not show convincing associations. The effects were variably robust to the inclusion of other pollutants and it should be noted that in the Wayne County analysis which included the most extensive two-pollutant analysis, there was little evidence of independent effects of sulphate.

Key to abbreviations in Figures 1–7

Diagnosis	Abbreviation	Age group	Definition (years)
Mortality	**AA**	All ages	All ages
	E	Elderly	60+
Respiratory morbidity	**A**	Adults	16+
	AA	All ages	All ages
	E	Elderly	64+
	C	Children	0-18
	YA	Young adults	5-64
Cardiovascular morbidity	**AA**	All ages	All ages
	E	Elderly	60+
Misc. Other (O)	**AA**	All ages	All ages

Figure 1: Sulphate and all-cause mortality

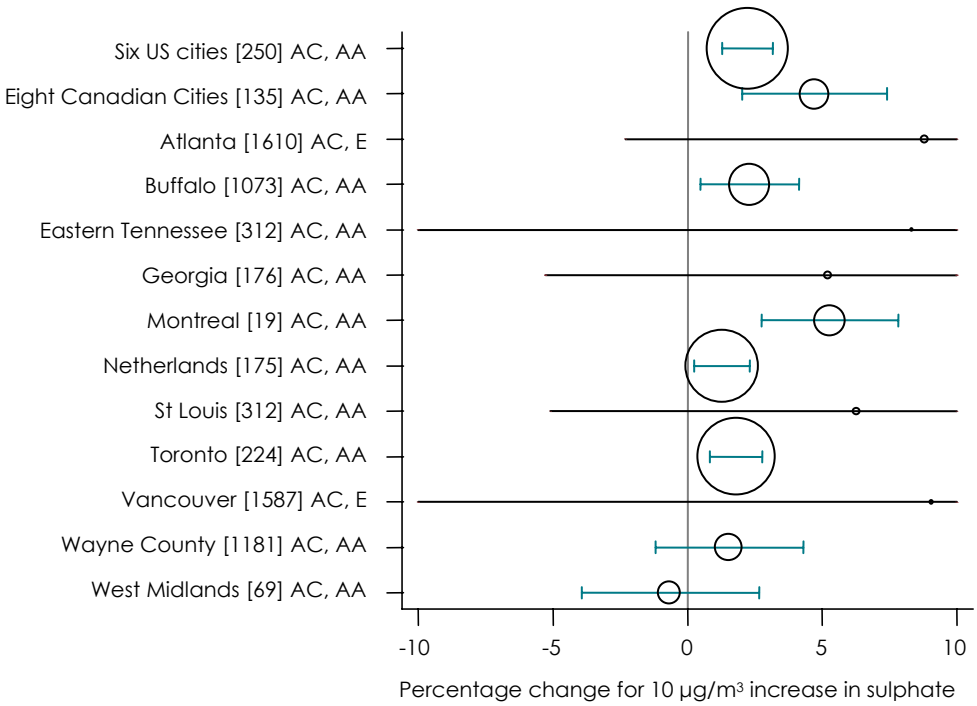


Figure 2: Sulphate and all-cause mortality: funnel plot. The dashed line indicates the pooled percentage change, the solid line the null effect and the dotted line the adjusted estimate

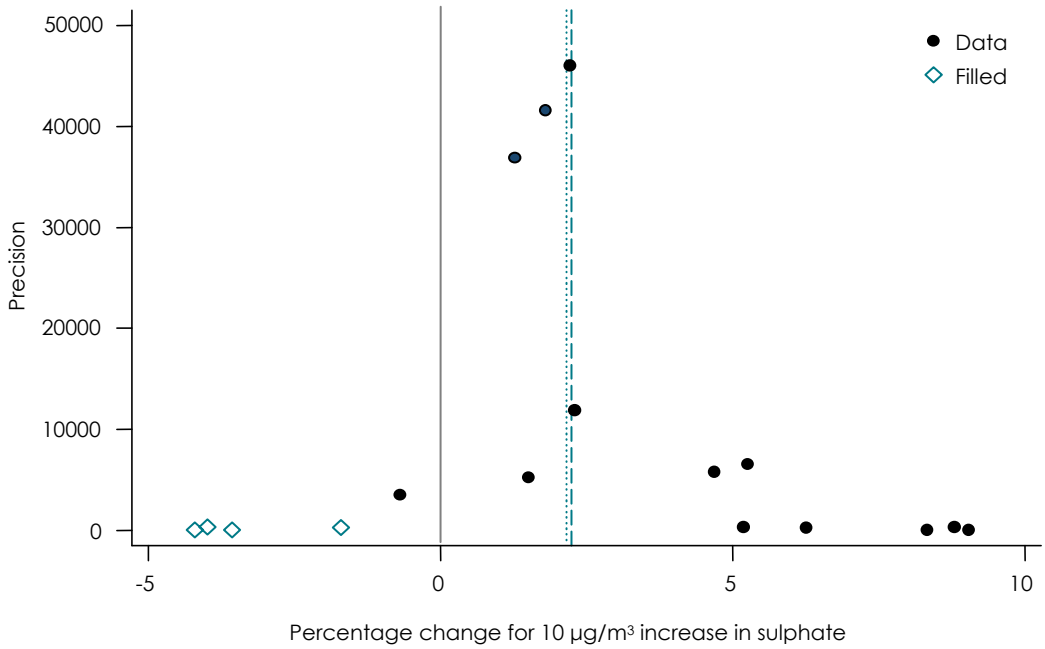


Figure 3: Sulphate and respiratory mortality

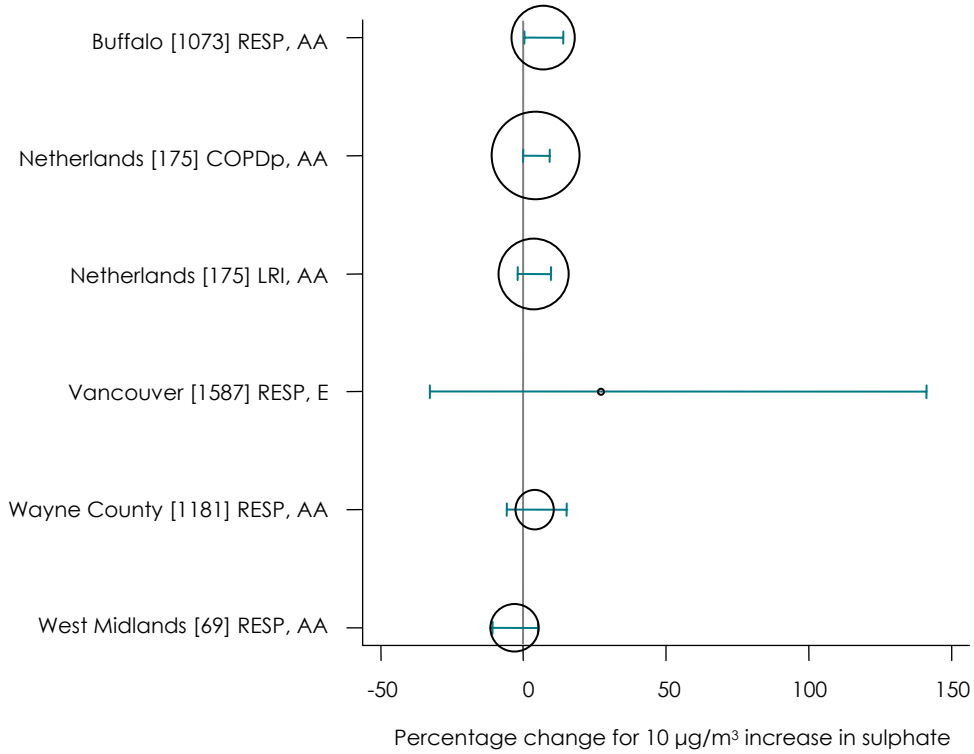


Figure 4: Sulphate and cardiovascular mortality

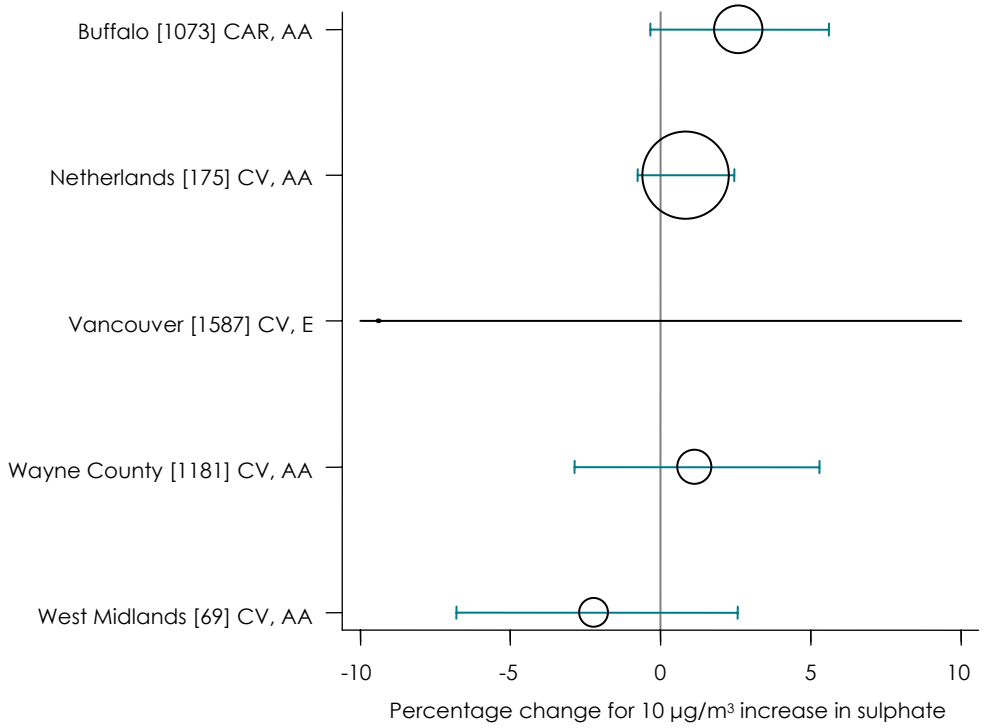


Figure 5: Sulphate and hospital admissions for respiratory diagnoses

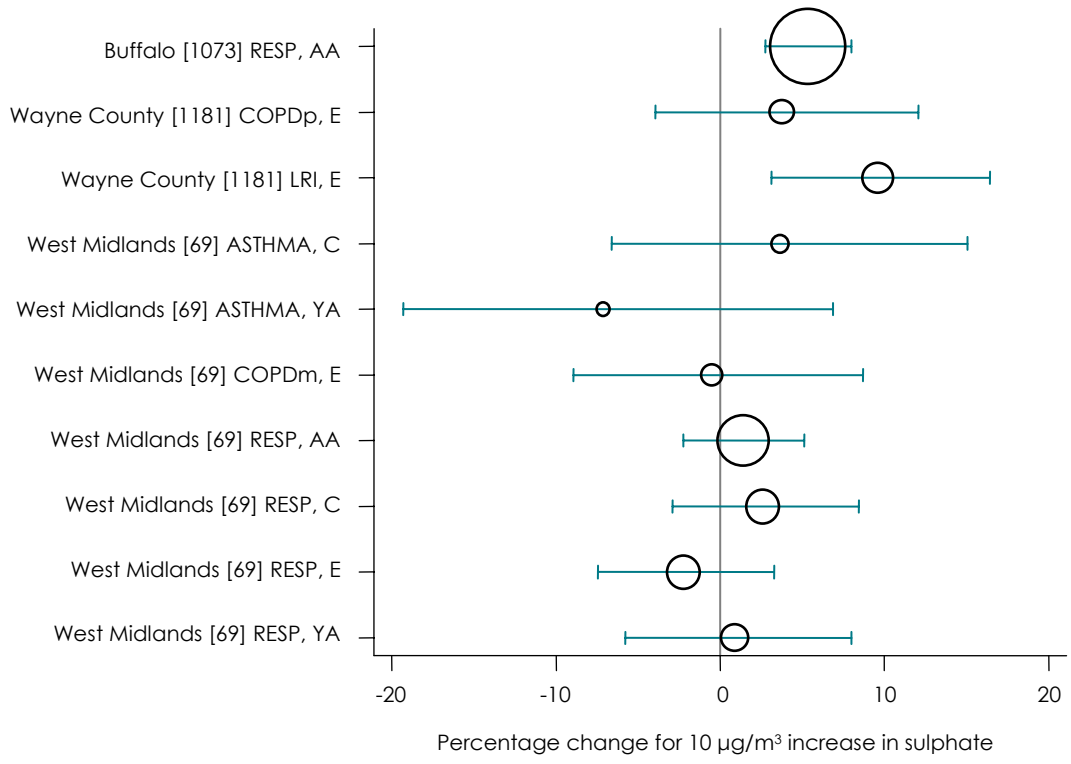


Figure 6: Hospital admissions for cardiovascular diseases

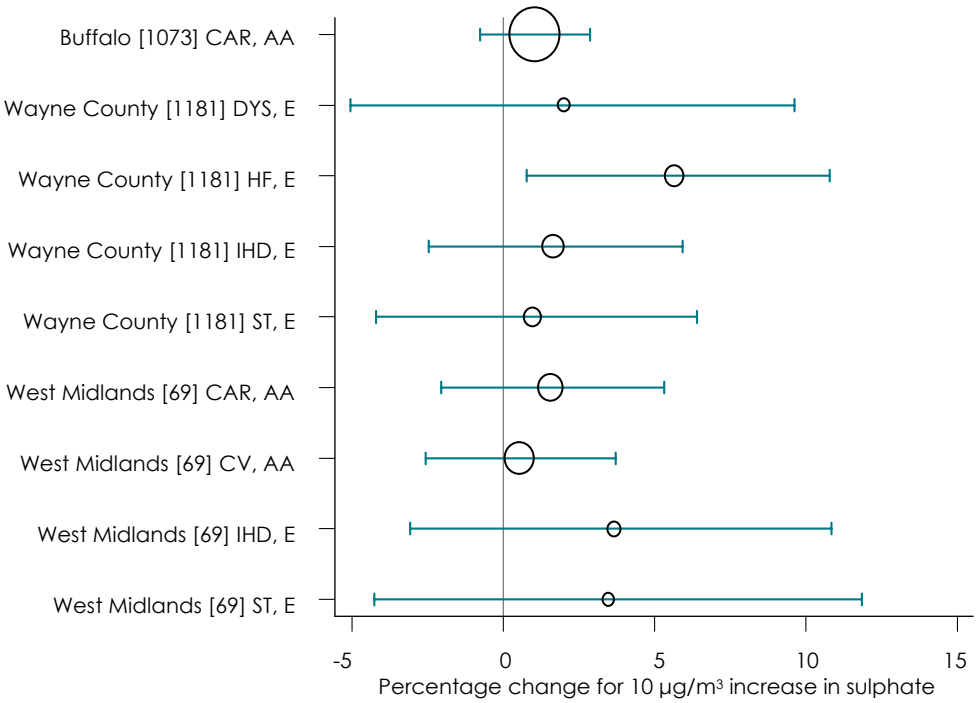
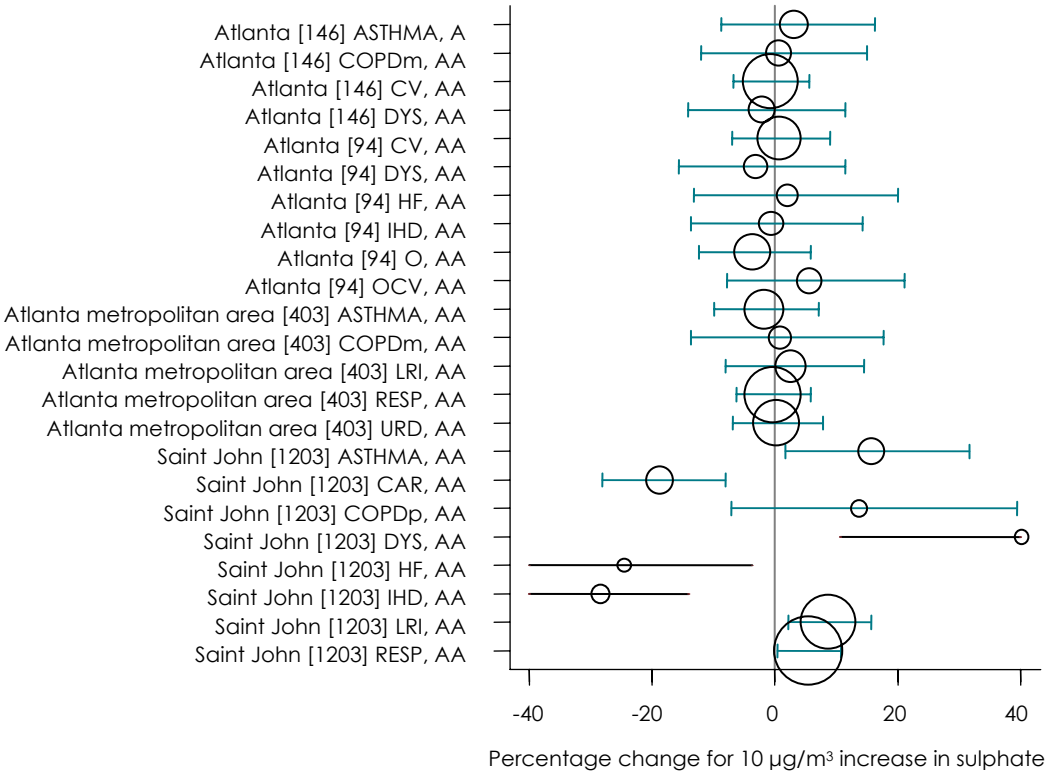


Figure 7: Sulphate and daily emergency room visits (see earlier for abbreviations)



Panel studies

A similar analysis of panel studies within APED was done. Quantitative meta-analysis was possible with four outcomes, all in children: peak expiratory flow rate (PEFR) winter and summer, cough and asthma medications. The results are summarised in Table 2.

Table 2: Quantitative meta-analysis of panel studies of sulphate and various outcomes

1 Sulphate and PEFR in children: summer period studies (5 estimates)
Fixed effects: -0.09 (-0.16 to -0.02) l/m Random effects: -0.16 (-0.32 to -0.01) l/m $P_{heterogeneity}$ = .08 Trim and fill: estimates unchanged P_{Begg} = 1–; P_{Egger} = 0.36
2 Sulphate and PEFR in children: winter period studies (5 estimates)
Fixed effects: -0.25 (-0.35 to -0.14) l/m Random effects: -0.25 (-0.35 to -0.14) l/m $P_{heterogeneity}$ = .8 Trim and fill: estimates: -0.26 (-0.36 to -0.16) l/m P_{Begg} = 0.22; P_{Egger} = 0.16
3 Sulphate and lower respiratory symptoms (cough) in children
4 estimates Fixed effects: 1.008 (1.004 to 1.013) Random effects: 1.008 (1.001 to 1.015) $P_{heterogeneity}$ = 0.1 Trim and fill: estimates: unchanged P_{Begg} = 0.5; P_{Egger} = 0.8
4 Sulphate and asthma medication in children
4 estimates Fixed effects: 1.020 (1.009 to 1.030) Random effects: 1.020 (1.007 to 1.033) $P_{heterogeneity}$ = 0.22 Trim and fill: estimates: unchanged P_{Begg} = 1–; P_{Egger} = 0.97

There were five estimates of sulphate and PEFR in children during a summer period from three studies, four estimates in the USA and one in Europe (Neas *et al,* 1995, 1996, 1999; Thurston *et al,* 1997; Ward *et al,* 2002). There was a negative effect on PEFR which was statistically significant. There were five estimates for sulphate and PEFR in children in the winter period, all from Europe (Brunekreef and Hoek, 1993; Hoek and Brunekreef, 1994; Peacock *et al,* 2003; Peters *et al,* 1997; Ward *et al,* 2002). The pooled effect on PEFR was negative and significant.

There were four estimates for sulphate and cough symptom in children, one from the USA and three from Europe (Peters *et al,* 1997; Thurston *et al,* 1997; vanderZee *et al,* 1999). The pooled effect was significantly positive.

There were four estimates for sulphate and use of asthma medications in children, one from the USA and the other three from Europe (Peters *et al,* 1997; Thurston *et al,* 1997; vanderZee *et al,* 1999). The effect was significantly positive, with a 2% increase in use of medication for a 10 $\mu g/m^3$ increase in sulphate.

It is concluded that there is good evidence associating sulphate concentration in particles with adverse effects on symptoms, lung function and medication use in children.

Prevalence studies

We have not undertaken a systematic review of prevalence (cross-sectional) studies. However, we shall examine the evidence from two major US studies.

Sulphate was one of a range of particle measures investigated in the Six Cities prevalence studies of children (Dockery *et al,* 1989). All of the particles investigated (TSP, PM_{15}, $PM_{2.5}$ and FSO_4 [1]) were positively associated with bronchitis, chronic cough and a history of chest illness. Due possibly to the low power of the analysis (only six cities), none of these associations was statistically significant. The analysis was closely controlled for confounding factors at the individual level. The size of effect of sulphate was similar to those of the other particles. The effects on respiratory symptoms were greater in those who had a history of asthma. There was no evidence of associations between any of the particles and symptoms of asthma.

In a study of children living in 24 communities in the USA and Canada, associations were also observed between sulphate concentrations and respiratory symptoms of reported bronchitis, chronic phlegm and any bronchitic symptoms (Dockery *et al,* 1996). There was no association with symptoms of asthma. The effects of sulphate were similar to those of particle strong acidity and somewhat greater than the effects of $PM_{2.5}$. These metrics were all closely correlated.

These two large and well-conducted cross-sectional studies have found associations between bronchitic type symptoms and sulphate, in the context of a high correlation between sulphate and acidity and $PM_{2.5}$. The results are therefore consistent with an adverse effect of particles rich in sulphate.

Cohort studies

The evidence associating sulphate with mortality in cohort studies is extensively dealt with elsewhere in the report.

Conclusion

Overall, there is reasonably consistent evidence that sulphate concentration in particulate matter is positively associated with adverse health effects in short-term exposure studies (population time-series and panel time-series studies) and long-term exposure studies (prevalence studies and cohort studies). Where there is evidence from multi-pollutant models the associations tend to persist though less strongly. This suggests that sources of particles that are related to sulphur-containing fuel combustion may have adverse health effects.

[1] FSO_4 represents the 'fine fraction aerosol sulphate'.

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Note: the reference ID shown at the end of each reference corresponds to that shown in the forest plots.

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Working Paper 5

Should Past, Recent or Long-Term Average Pollutant Levels be Used for Quantification?

David Strachan

Introduction

Pope *et al* (2002)[1] present adjusted relative risks for all-cause and cause-specific mortality in relation to $PM_{2.5}$ measurements derived at the city level for 1979–1983 (61 cities, 359,000 participants) and 1999–2000 (116 cities, 500,000 participants): "Although no network of $PM_{2.5}$ monitoring existed in the US between the early 1980s and late 1990s, the integrated average of $PM_{2.5}$ concentrations was estimated by averaging the $PM_{2.5}$ concentration for the early and later periods." These averages were available for 51 cities (319,000 participants).

The relative risk estimates differ: e.g. for all-cause mortality, per 10 $\mu g/m^3$ $PM_{2.5}$, they are 1.04 for 1979–1983, 1.06 for 1999–2000, and 1.06 for the average $PM_{2.5}$. Cause-specific mortality relative risks differ in similar proportions (Table 2 in Pope *et al,* 2002).

This paper discusses which of these three measures of $PM_{2.5}$ (and the associated sets of mortality relative risks) should be used for quantification purposes. Pope *et al* (2002) use the earlier $PM_{2.5}$ measures in most of their graphical presentation, but there is a case for using some measure of the long-term average or 'usual' exposure of the American Cancer Society (ACS) study cities, rather than the 1979–1983 pollutant estimates, as the basis for quantification.

Timing of exposure in relation to deaths

The period of mortality follow-up for the ACS cohort is 1982 onwards (presumably to around 2001), with about two-thirds of the deaths occurring in the later half of the follow-up period. Thus, the earlier pollutant estimates pre-date most of the deaths by a decade or more, whereas the later pollutant estimates post-date almost all of the deaths.

The use of the average measure as an estimate of the 'integrated average of $PM_{2.5}$ concentrations' is clearly oversimplified. Air pollution levels in the ACS cities have declined over the study period (Figure 1 in Pope *et al,* 2002) but probably not in a linear fashion year by year. In absolute terms, the decline was probably steeper in the 1980s than during the 1990s, so the average $PM_{2.5}$ measure tends to overestimate the actual 'integrated average' experienced in each of the ACS cities.

From time-series studies, there is evidence that air pollution levels *around the time of* death are influential. On the other hand, air pollution levels *after* death cannot influence mortality risk, whereas it is possible that air pollution levels *several years before* death may be biologically relevant. Thus, if the average $PM_{2.5}$ estimate derived by Pope *et al* (2002) deviates somewhat

[1] Pope, C.A., III., Burnett, R.T., Thun, M.J., Calle, E.E., Krewski, D., Ito, K., and Thurston, G.D. (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA.* **287,** 1132–1141.

from the 'integrated average' exposure for each of the fatal events during follow-up, it deviates in the desired direction – weighting somewhat towards prior exposure, rather than exposure after death.

Problem of scale

Although the 1979–1983 and 1999–2000 $PM_{2.5}$ estimates are fairly closely correlated ($r = 0.78$, Figure 1 in Pope *et al,* 2002), the range of the pollutant levels in the 51 cities with both sets of measurements differs: approximately 10–30 μg/m³ in 1979–1983, 5–20 μg/m³ in 1999–2000 (Figure 1 in Pope *et al,* 2002). More precise, but less comparable, are the standard deviations cited in Table 1 in Pope *et al* (2002) (which relate to different numbers of cities in each period): 4.6 μg/m³ in 1979–1983, 3.0 μg/m³ in 1999–2000, and 3.7 μg/m³ for the averages. Both types of evidence suggest that the spread of the cities on the $PM_{2.5}$ scale was about 1.5 times greater in 1979–1983 than in 1999–2000, with the scaling of the average, as expected, intermediate between the two. This scaling is also reflected in the mean levels of $PM_{2.5}$ in the three time periods (Table 1 in Pope *et al,* 2002).

Since the ACS study is essentially ecological, based on between-city differences in mortality rates (after adjustment for individual-level confounders such as smoking), the same spread of mortality rates implies different mortality relative risks (RR) per unit change in pollutant (e.g. per 10 μg/m³ $PM_{2.5}$), depending upon how the cities are spread out on the *x*-axis ($PM_{2.5}$).

Thus, it would be misleading to interpret the mortality relative risks associated with the 1999–2000 $PM_{2.5}$ values, as relevant throughout the follow-up period. For much of the preceding two decades, the ACS cities were presumably more widely spread on the $PM_{2.5}$ axis than they were in 1999–2000. On the other hand, the same cities were clustered more tightly on the *x*-axis for much of the follow-up period than they were in 1979–1983.

Mortality relative risks (RR) related to each of the $PM_{2.5}$ measures can be compared like-for-like by standardising to the range – or more precisely to the standard deviation – of the independent variable ($PM_{2.5}$).

On this basis, the estimated RR of 1.04 per 10 μg/m³ $PM_{2.5}$ for all-cause mortality and 1979–1983 pollution would be rescaled to exp[ln(1.04) x 4.6/10] = 1.018 per SD. (It should be noted that the correction to scale is implemented in relation to log-transformed mortality, as implied by the multiplicative model for relative risks.)

This is very similar to the estimated RR of 1.06 per 10 μg/m³ $PM_{2.5}$ for all-cause mortality and 1999–2000 $PM_{2.5}$, rescaled to exp[ln(1.06) x 3.0/10] = 1.018 per SD. Two conclusions may be drawn from this:

a The data for 116 cities are in line with what would be expected for the 61 cities (and presumably for the 51 contributing to the average $PM_{2.5}$).

b The estimates based on earlier and later pollution data, when rescaled appropriately, give remarkably similar values. Thus, there is no good evidence to prefer one over the other (or over their average).

On the same basis, the estimated RR of 1.06 per 10 μg/m³ $PM_{2.5}$ for all-cause mortality and average $PM_{2.5}$ would be rescaled to exp[ln(1.06) x 3.7/10] = 1.022 per SD. This is greater than

the standardised effects for 1979–1983 or 1999–2000. It can be shown (below) that this discrepancy may be explained by measurement errors in the pollutant estimates.

Measurement error and regression attenuation bias

The correlation of 0.78 shown in Figure 1 in Pope *et al* (2002) allows an estimate of the measurement error in each component of the average $PM_{2.5}$, as follows. Assume that we are measuring a 'true' long-term average $PM_{2.5}$ level between 1979–1983 and 1999–2000, and that each annual pollution measurement is an estimate of this. Assume, for simplicity, that the measurement error in the ranking of the 51 cities is similar (proportionately, in relation to the range of pollution levels) in 1979–1983 and 1999–2000. (This assumption could be challenged on the grounds that four years contribute to the earlier measurement, and only two years to the later one, but finer adjustments are unlikely to make a material difference to the conclusion.)

Then, 0.78 represents the 'coefficient of reliability' (r) for each of the measurements, that is the ratio of the 'measured' variance to 'true' variance at each time period. The reliability coefficient also, conveniently, represents the degree to which simple regression estimates using this exposure variable are attenuated by measurement error.

Taking the average of two measurements will improve reliability, by a known amount:

$$r' = nr/[(n - 1)r + 1]$$

where r' is the reliability of the average of n measurements. Thus, for two measurements, the reliability coefficient for the average $PM_{2.5}$ is 0.88.

(It should be noted that this is a measure of the imprecision in ranking of whole cities in relation to long-term, 'usual' or 'integrated average' $PM_{2.5}$ levels, not an estimate of the errors in imputing a city-wide measure of pollutant levels to the personal exposure of individuals within a city. The latter is not relevant to ecological analyses such as the ACS study.)

Thus, we can estimate that the log relative risks for 1979–1983 $PM_{2.5}$ are attenuated by 0.78 and those for average $PM_{2.5}$ are attenuated by 0.88. Standardising as above for scale of measurement, the all-cause mortality RR of 1.04 per 10 $\mu g/m^3$ $PM_{2.5}$ in 1979–1983 is compatible with:

$$\exp[\ln(1.04) \times (1/0.78) \times (4.6/3.7) \times 0.88] = 1.057 \text{ per } 10\ \mu g/m^3 \text{ average } PM_{2.5}$$

A B C D E

where A = log-transformed original relative risk, B = adjustment for measurement error in 1979–1983 pollution ranking (city-level), C = adjustment for different SDs of measurement in 1979–1983 and average $PM_{2.5}$, D = attenuation of 'true' effect of average $PM_{2.5}$, due to remaining measurement error, and E = 1.057 is fully consistent with the figure of 1.06 cited for average $PM_{2.5}$ in Table 2 of Pope *et al* (2002).

The conclusion is that the mortality relative risks for 1979–1983 $PM_{2.5}$ and for average $PM_{2.5}$, based on a similar set of cities, are consistent. Certainly, no strong evidence emerges to prefer the earlier pollution estimates.

The best estimate of the 'true' effect of $PM_{2.5}$ on mortality *throughout the follow-up period* is represented by the attenuation-adjusted coefficient for average $PM_{2.5}$:

$$\exp[\ln(1.06) \times (1/0.88)] = 1.068 \text{ per } 10\ \mu g/m^3 \text{ average } PM_{2.5}$$

Multi-pollutant models

The brief discussion paper on sulphur dioxide raised the possibility of adjusting the $PM_{2.5}$ effect for the SO_2 effect in multi-pollutant models. SO_2 levels were monitored annually for most of the study period (1982–1998) and so the 'integrated average' for each of the cities is well represented by the measured average. For simplicity, we may therefore assume that at the city level, long-term SO_2 levels are measured without error.

In Working Paper 7, Appendix B, the effect of adjustment for a correlate of air pollution (windspeed) in the situation where there is measurement error in the pollution levels has been modelled. An error variance of 4 was imposed onto a true PM variance of 25, implying a reliability coefficient of 25/29 = 0.86. This is a slightly greater measurement error than the $r = 0.88$ estimated for average $PM_{2.5}$ in the ACS cities.

With adjustment for SO_2 (correlated $r = 0.5$ with $PM_{2.5}$), the coefficient for average $PM_{2.5}$ would be attenuated by a factor of around 0.14/0.17, as shown in simulations in Working Paper 7, even if SO_2 were not a cause of between-city variation in mortality rates. If the attenuation of the $PM_{2.5}$ coefficient were substantially greater than that, it would imply some independent influence of SO_2 (i.e. that SO_2 is a confounder and should rightly be controlled in the model).

Which estimate to use for quantification?

I would propose the 'average $PM_{2.5}$' of Pope *et al* as the exposure measure of choice from the ACS study on the grounds that:

a. Its scale is intermediate between the earlier and later pollutant levels, therefore more representative of exposure in the ACS cities through the period of mortality follow-up.

b. Its (im)precision can be estimated and therefore a correction can be applied to measured relative risks, as above.

c. The improvement in reliability for the average, compared to single pollutant measures, means that the $PM_{2.5}$ coefficient will be less susceptible to attenuation by inclusion, in multi-pollutant models, of other exposures that may be more precisely measured (from one year to the next) and are moderately to highly correlated with $PM_{2.5}$.

If the correlation in Figure 1 of Pope *et al* (2002) is taken as a reasonable basis for estimating measurement errors, as above, then the actual association of average $PM_{2.5}$ pollution with all-cause mortality relative risk is:

$$\exp[\ln(1.06) \times 1/0.88] = \mathbf{1.068 \text{ per } 10\ \mu g/m^3}\ PM_{2.5} \text{ (throughout 1979–2000)}$$

Similar adjustments can be carried out for cause-specific mortality.

Working Paper 6

Thresholds and Other Non-Linearities

Fintan Hurley

Introduction

There is a widespread understanding that, overall, the epidemiological evidence linking air pollution and health does not support the idea that there is a population threshold for the effects of PM on health (Department of Health, 1998; World Health Organization, 2003, 2004). That evidence is dominated by the many time-series studies linking ambient PM and mortality.

This paper considers whether the American Cancer Society (ACS) study specifically supports the view that $PM_{2.5}$ at 'low' concentrations adversely affects the risks of mortality. We first consider the evidence, then the implications for quantifying the effects of PM on mortality, in particular in the UK.

It should be noted that here, as elsewhere throughout this report, when we speak of 'linear' we mean a linear relationship of the logarithm of relative risk against concentration, as shown for example in Figure 2 of Pope *et al* (2002). This is an implication of the proportional hazards modelling that underlies the ACS study analyses. As explained in Chapter 3 of the main text (footnote 13, page 31), this approximates to a linear relationship of relative risk against concentration for small concentration increments and small coefficients.

The evidence

HEI Reanalysis

Methods

The issue of threshold or not was investigated in some detail in the HEI Reanalysis (Health Effects Institute, 2000) and reported more fully by Abrahamowicz *et al* (2003). We focus on the latter, who used a *sample* of data from the original (Pope *et al,* 1995) ACS study and flexible (quadratic spline) modelling methods to describe the shape of the concentration-response (C-R) curve over the range of data in the ACS study. These methods allow the data to determine the shape of the C-R relationship, rather than have this shape determined *a priori* by the analysts. The range of data is described by annual average concentrations in the metropolitan areas with lowest and highest annual average concentrations. Abrahamowicz *et al* (2004) used concentration data from time periods at the start of follow-up.

Results

Abrahamowicz *et al* (2003) give results for PM expressed as $PM_{2.5}$ and as sulphates (SO_4), in Figures 2 and 3, respectively, of their paper. The most representative results are in Figures 2a and 3a, corresponding to Figures 10 and 11 of the original HEI Reanalysis. All analyses refer to mortality from all-causes.

a Results *for $PM_{2.5}$* cover the range from 9–33 μg/m³. The fitted curve (Figure 2a) shows statistically significant non-linearity in shape, with a *steeper* slope in the lower end of this range (e.g. up to about 15 μg/m³) than later. It therefore gives no evidence of a threshold in the study data.

b Results *for sulphates* cover the range from 3.6–23.5 μg/m³. Again, the fitted curve (Figure 3a) shows changes in shape over the range of the data. However, in contrast to the $PM_{2.5}$ results, in the lower end of this range (e.g. up to about 12 μg/m³), the estimated slope is small, rising rapidly after that. This implies suggestive evidence, not exactly of a threshold, but of much *lesser* effects at low ambient sulphate concentrations.

Commentary

It is usual to take PM expressed as $PM_{2.5}$ rather than as sulphates as the main index of particulate air pollution, for purposes of risk estimation. On that basis, it is reasonable to conclude that the ACS study does not support a threshold within the range of data that it covers, i.e. down to 7 μg/m³ $PM_{2.5}$. In fact, the authors say that: "In general, our results further reinforce the growing body of evidence against the hypothesis of a putative threshold below which exposure to fine particles does not affect public health" (page 1648). Furthermore they are guarded about a threshold for the effects of sulphates.

ACS update – Pope *et al* (2002)

Figure 2 of Pope *et al* (2002) shows non-parametric smoothed curves linking $PM_{2.5}$ and mortality from the major groups of causes.

a The graphs for all-cause mortality, for cardiopulmonary and for lung cancer all show curves that are approximately monotonically increasing over the range of the data. They do not suggest a 'levelling off' of the slope at the lowest observed concentrations.

b The only observably marked non-linearity is for lung cancer, where the fitted curve shows a somewhat *steeper* slope at lower concentrations, i.e. up to about 13 μg/m³ $PM_{2.5}$, than it does thereafter.

c There is no similar suggested change-point for all-cause or cardiopulmonary mortality.

d The fitted curve for 'all other causes' was approximately horizontal across the range of observed data.

e Evidence of departure from linearity was not statistically significant ($p>0.20$), presumably in any of the groups of causes studied.

Commentary

The evidence supports the authors' conclusion that the C-R function is monotonic and approximately linear over the range of the observed data, i.e. about 7–30 μg/m³ $PM_{2.5}$.

This result supports, and supersedes, the corresponding reanalysis results, which are based on fewer data.

Implications for quantification

Core analyses

a This conclusion suggests that effects be quantified at least down to the lower end of the ACS data, i.e. to 7–9 μg/m^3.

b Should effects be quantified at annual average concentrations of $PM_{2.5}$ lower than this? In the UK, annual average $PM_{2.5}$ is generally higher than the lower end of the ACS study data, and so the issue does not arise when looking at relatively small changes from the present position.

c It is however an issue in attempting to quantify the 'total mortality burden' attributable to $PM_{2.5}$. On this issue, the WHO/UNECE Task Force on Health of the Convention on Long-Range Transboundary Air Pollution recommended yes, to quantify *anthropogenic* $PM_{2.5}$ down to zero, i.e. with no threshold (see http://www.unece.org/env/documents/2004/eb/wg1/eb.air.wg1.2004.11.e.pdf). This is what was done in CAFE CBA (Clean Air for Europe Cost Benefit Analysis).

d I recommend the same approach, for the same reasons, for quantification in the UK.

Sensitivity analyses

The question arises: should quantification also include a threshold, perhaps as sensitivity analysis, and if so, at what concentration level? This implies an evaluation of what might be a threshold, at what probability (i.e. a subjective distribution over the range 0–7 μg/m^3 $PM_{2.5}$).

e Doing this would be difficult (expert elicitation process plus with-threshold calculations).

f If the answer is yes/no, then I think that analyses with no threshold are sufficient, in the sense that the 'no-threshold' assumption is reasonable and easy to implement.

Non-linearities

g Fortunately for ease of implementation, the evidence strongly suggests that implementation assuming linear relationships is sufficient.

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Working Paper 7

Spatial Autocorrelation, Confounding and Scale

Ben Armstrong and Richard W Atkinson

Responses to key questions

Question 1 What are the expected impacts on the estimated effects of air pollution from cohort studies of incompletely measured or modelled sources of variation in health over space?

a Confounding

Response

Confounding variables are those that are correlated with the exposure of interest (air pollution) and are direct or indirect risk factors for the outcome (mortality). Most studies have adjusted for many potential confounders, but this adjustment may incompletely control confounding because:

i some confounders may not be measured;

ii the model may be inappropriate (e.g. linear not curved);

iii confounders may be measured only approximately.

If any of these are operating, results will be biased due to 'residual' confounding, though the bias is, in general, less than that in unadjusted models.

However, there are negative consequences of adjusting for variables that are correlated with air pollution but *not* risk factors for the outcome. Doing this usually decreases the statistical precision of the air pollution coefficient, so its confidence interval is unnecessarily wide. However, such 'over-adjustment' does not in general bias the air pollution coefficient to the null, despite widespread belief to the contrary. The consequences of over-adjustment are illustrated using simulations in Appendix B.

The issue of over-adjustment is complicated further in situations where mean air pollution for 'areas' is measured with random error – as is usually the case. The bias to the null caused by that measurement error is increased if there is over-adjustment (also illustrated in Appendix B).

A distinction can be made in most cohort air pollution studies between individual confounders – available for each individual – and ecological confounders (available for areas – the level of the pollution measures). Both have the same potential to confound, which can be avoided by appropriate incorporation in modelling. In most studies, however, control for the two is incorporated separately. In the American Cancer Society (ACS) study reanalysis ecological confounder control was carried out in a second stage of a two-stage analysis, and there was no control for ecological confounders in the Pope *et al* (2002) report.

All the above comments apply to mutual confounding by pollutants; however, there is a difference when there is interest in more than one pollutant – as generally. Here there is a danger in considering just the relative risk (RR) and its confidence interval (CI) for each pollutant – neither may be statistically significant even when there is clear evidence that one or the other is associated with the outcome. This may be avoided by considering also single-pollutant models and/or joint tests. Each model answers a different relevant question.

b Spatial autocorrelation

Response

Spatial autocorrelation of a variable – also called spatial clustering – is a tendency for nearby values to be more similar than distant values. Residual spatial autocorrelation in mortality and air pollution has the following consequences:

i models with no allowance for autocorrelation will give estimates of air pollution effect with confidence intervals which are narrower than they should be, and p-values smaller than they should be;

ii the autocorrelation indicates that there are risk factors missing from the model. These risk factors may be confounders, although the autocorrelation does not prove that.

In a model of mortality rates that excludes or contains inadequately measured or modelled risk factors that are spatially autocorrelated, then the model residuals will also be spatially autocorrelated. In such a situation two things can be done to avoid the adverse consequences described above. First, more appropriate terms describing the risk factors can be found and incorporated in the model. Second, adjustment for the remaining spatial autocorrelation can be made in the model using appropriate statistical techniques. Both avoid incorrect confidence intervals (point i above). Both reduce vulnerability to confounding, but the first does this more reliably than the second (see below).

c Any other mechanism

Response

None identified.

Question 2 In what circumstances do models for autocorrelation (including regional adjustment) also control for confounding?

Response

If unmodelled confounders are spatially autocorrelated, models adjusted for autocorrelation will eliminate or reduce confounding. Such autocorrelation seems plausible for most confounders (Appendix C). Statistical adjustment for residual spatial autocorrelation therefore seems a prudent measure provided it does not lead to critical loss of precision in the pollution effect estimate.

However, most methods of adjusting for spatial autocorrelation, including that used in Pope *et al* (2002), are liable to increase bias due to classical measurement error, if present, as discussed for explicit confounders in response to question 1a above. This bias will increase as the 'wiggliness' (closeness to the data) of the spatial smooth increases. Thus in using a spatial smooth model there is a trade-off between reduced vulnerability to confounding bias and increased measurement error bias.

Questions 3–6 – for the ACS study (Pope *et al*, 2002) and the HEI Reanalysis (Health Effects Institute, 2000)

Question 3 Setting aside issues of spatial autocorrelation, what do *a priori* considerations and the sensitivity analyses that have been carried out lead us to conclude on:

a Which confounder-adjusted effect coefficient(s) do we prefer for risk assessment (subject to views on other factors)?
b What uncertainty remains from residual confounding?

Question 4 What do *a priori* considerations and the modelling that has been carried out lead us to conclude on:

a Which spatial autocorrelation model, if any, do we prefer for risk assessment (subject to views on other factors)?
b What uncertainty remains from residual spatial autocorrelation?

Response

We addressed these two questions together, for the following reasons: the absence of any increase in confidence intervals on introducing a spatial smooth (Pope *et al*, 2002 – Figure 3), which we found surprising though not contradictory, suggested that there was little problem of inappropriate standard errors in models without consideration of spatial autocorrelation. This leaves the confounding-reduction property of spatial autocorrelation models (see question 2 above) which was better considered under question 3.

We have indicated specific proposed choices in bold. These proposals are without reference to any considerations outside the ACS study.

Questions 3a and 4a Which point estimate?

We noted that the HEI Reanalysis but not Pope *et al* (2002) included estimates adjusted for 'ecologic confounders' and a fuller set of spatial models. However, given the greater follow-up of the Pope *et al* (2002) paper and the difficulty of choosing which ecological potential confounder to include, **we propose nevertheless to choose a preferred estimate from Pope *et al* (2002), with the HEI Reanalysis results considered for assessing uncertainty.**

We propose not considering estimates with less control for confounding than 'all [individual] covariates'.

The authors preferred using 1979–1983 pollution estimates to 1999–2000 or the average of the two. We agree that 1979–1983[1] is preferable to 1999–2000, but the choice between 1979–1983 and an average derived from the two periods is less clear. Follow-up was from 1982–1998 and most deaths in the latter half, so unless mean latency was substantial (at least five years), the average seems best. A long latency seems likely for lung cancer, but less so for cardiovascular deaths. We note that relative risk estimates from only one model (the 'all covariates' no spatial smooth model) is given for each cause of death using the average.

[1] Different measurement methods were used for the earlier and later periods. The comments here only relate to preferences regarding the timing of the measurements and do not discuss the quality of the measurements themselves.

We proceed to consider the estimates based on 1979–1983 exposures, for which more complete results are presented.

Spatial modelling: Pope *et al* (2002) included results from a model with spatial smooths at each of three bandwidths, but did not select one of these for the 'headline' result (e.g. abstract). **However, we considered that there was a strong case, on the basis of greater robustness to confounding in spatial smooth models without precision penalty, for preferring an estimate with spatial smooth, and among them those with the smallest bandwidth (last column of Figure 3).** The primary penalty for including spatial smoothing, or using a smaller bandwidth for the smooth surface, is loss of precision (wide confidence intervals). Because none of the results with spatial smooths appeared to lose precision, there seemed little reason not to prefer them, and among them the estimate with smallest bandwidth (last column on Figure 3). A second penalty for including spatial smoothing is increased bias to the null of coefficients if there is classical measurement error. However, simulations carried out in Appendix D together with other work in this report (Working Paper 5) suggest that increased classical measurement error is, in this study, a lesser concern than uncontrolled confounding.

We noted that inclusion of a spatial smooth reduced the estimate of the $PM_{2.5}$ effect for all-cause mortality, but not for cardiopulmonary and lung cancer deaths. For other causes $PM_{2.5}$ showed a beneficial effect in the spatial smooth model. This drew into focus an indirect approach to estimating impact of $PM_{2.5}$ on all-cause mortality: use the cardiopulmonary and lung cancer coefficients to estimate impacts on these causes; assume that there is no effect on other causes, and estimate the all-cause impact by summing the impacts from cardiopulmonary and lung cancer deaths. However, this had a 'cherry-picking' aspect to it – using the positive coefficients (cardiopulmonary, lung cancer) but not the negative one (other causes).

In summary, we considered three possible preferred estimates:

i the coefficients obtained without spatial smoothing selected for the abstract (4, 6, 8% for all-cause, cardiopulmonary and lung cancer mortality);

ii the coefficient from the model with spatial smooth of lowest bandwidth (about 2, 6, 8%);

iii the coefficients for cardiopulmonary and lung cancer mortality only, which are the same whether spatial smooth was included or not (6, 8% – by measuring from the figure), assume other causes coefficient = 0, and deduce all-causes = 6 x A + 8 x B, where A and B are proportions of deaths (in UK) from cardiopulmonary and lung cancer mortality.

Of these, we preferred the second. However, this preference is based solely on consideration of issues of confounding and spatial autocorrelation. In particular, if latency considerations suggest that coefficients based on 'average' exposures are preferable to those based on 1979–1983 exposure, only coefficients obtained without spatial smoothing are available.

Questions 3b and 4b Uncertainty

Confidence intervals will underestimate uncertainty, in omitting that due to residual confounding and information bias.

Residual confounding

i confounding from factors that have been adjusted for, but possibly incompletely (e.g. diet);

ii confounding from factors not adjusted for (e.g. all the 'ecologic confounders' considered at least to some extent in the HEI Reanalysis, such as climate, population change).

Information bias

Most likely source is error in measuring PM, this could be of three types:

i Systematic (e.g. period measured was consistently higher/lower than truly relevant period). If additive, there is no bias; if multiplicative, then bias is the factor by which exposure is underestimated or overestimated.

ii Random (not consistently too high or low):

Berkson (using a single measure for the population in a metropolitan statistical area (MSA), for whom true exposure varies). This causes little bias (Zeger *et al*, 2000).

Classical (the ambient measure used may be higher than the true mean level in some MSAs, lower in others). Classical error causes bias towards zero, by an amount roughly equal to $1/[1 + (\sigma_E/\sigma_T)^2]$, where σ_E = SD of error and σ_T = SD of true exposure (Armstrong, 1998).

Can we quantify the uncertainty?

Two approaches were considered:

i Monte-Carlo sensitivity analysis (MCSA), in which distributions are assumed for plausible information bias, and these combined with the sampling uncertainty to arrive at an uncertainty interval for a PM effect (Greenland, 2004, 2005). Details on how this approach was applied are given in Appendix D. In preliminary analyses we found confounding to dominate information bias for plausible values, so show results here for confounding only. We used three sets of distributional assumptions on confounding: low ($\pm$2%), mid ($\pm$5%), and high ($\pm$10%). (This is a subjective view of a range from the optimistic to pessimistic scale of expectation of residual confounding, motivated in Appendix D.)

It should be noted that confounding would usually be considered a source of bias, which would have a single direction. However, because we do not know the direction of bias we have considered confounding to contribute uncertainty equally likely in either direction.

Cause RR 95% uncertainty interval original*(CI) including possibility of residual confounding				
		Low	Central	High
All	1.02(0.99,1.04)	(0.97,1.07)	(0.92,1.13)	(0.84,1.24)
CP	1.06(1.03,1.09)	(1.01,1.11)	(0.96,1.17)	(0.87,1.29)
LC	1.08(1.01,1.15)	(1.00,1.17)	(0.96,1.21)	(0.88,1.33)

* Original values read from Figure 3 (Pope *et al*, 2002) last column.

We note that under 'central' assumptions of uncertainty, the 95% confidence intervals all include a relative risk increment of one, and hence the possibility of no adverse effect. However, the calculations on which these uncertainty estimates are based are sufficiently complex that it was difficult for members to contribute to deciding on the input values (meaning of 'low', 'central' and 'high') which determine final uncertainty.

ii Delphic method (expert judgement of several people directly on the limits of uncertainty of the coefficient). This method was used for the COMEAP Statement/Report (Department of Health, 2001). The method could have particular use to address the question: how likely do we think it is, given these studies, that air pollution has *no* effect on mortality?

Question 5 What should be concluded on effect-modification, in particular with respect to transportability of coefficients from the ACS study to the UK population?

Response

If the coefficient of air pollution is modified by another variable:

i The average effect in the study population (the coefficient ignoring the modifier) will not be the same as the average effect in another population (e.g. the UK) if the distribution of the modifier is different in the two.

ii Policy may wish to take account of the modification, as it indicates increased vulnerability to the effects of air pollution in some circumstances.

We noted that the only evidence for effect modification in the ACS study was that with education, which we considered a marker for social status/deprivation. For all-cause mortality, coefficients for the three education groups were about: 10%, 5%, and 0% (Pope *et al*, 2002 – Figure 4). The modification was unlikely to be caused by chance. It could be caused by biases (e.g. residual confounding), but we saw no obvious specific hypothesis explaining such bias.

These figures could, in theory, be used to estimate the average effect in the UK re-weighting for different proportions in each group compared to the ACS study. Doing so would not be easy, however. The meaning of the education levels used (<high school, high school, >high school) would not be the same in the UK and the USA. It has been suggested (UNECE/WHO, 2003) that the ACS sample is of higher social status than the USA in general. The USA has on average greater material wealth than the UK, although possibly greater variation in wealth.

Putting together all these factors, the overall impact of the modification of the air pollution effect on mortality by education on estimating a coefficient for the UK seems unlikely to be great.

Question 6 Do *a priori* considerations or the experience of the ACS study affect the interpretation of any other long-term exposure and mortality studies? (Even if the ACS study is the main one for deriving coefficients, other studies may be used to inform the conclusions, e.g. European studies may be used to inform issues of transferability.)

Response

Essentially the same considerations apply to the other studies (Abbey *et al*, 1999; Dockery *et al*, 1993; Filleul *et al*, 2005; Hoek *et al*, 2002; Nafstad *et al*, 2004; Willis *et al*, 2003).

Measured confounders varied from study to study. All estimated pollution exposure to a smaller spatial scale than did the ACS study, some (Hoek *et al*, 2002; Nafstad *et al*, 2004) to a quasi-individual scale, and some had study populations extending over a smaller overall geographical area. These factors would change the specific pattern of residual confounding and spatial autocorrelation, but there seems no obvious reason to assume that the impact of these things is in general either greater or less than on the ACS study.

Only Filleul *et al* (2005) allowed for spatial autocorrelation in the statistical analysis.

All studies had study populations that extended over a much smaller geographical area than did the ACS study, and the Hoek *et al* (2002) and Nafstad *et al* (2004) studies substantially so. To the extent that the studies controlled for the same measured confounding variables (they appear quite similar in this respect) this might be expected to reduce the potential for residual confounding (risk factors changing less over lower distances). However, the smaller spatial scale for pollution estimation adds potential for confounding at smaller spatial scales.

Thus we cannot conclude as to whether residual confounding would be either less or more.

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Additional Explanations and Support for Conclusions

Appendix A:
Spatial Autocorrelation Working Group – Key Questions

General questions

1 What are the expected impacts on the estimated effects of air pollution from cohort studies of incompletely measured or modelled sources of variation in health over space:

- a by confounding (this group will consider the statistical aspects of confounding by other pollutants and non-pollutant confounders);
- b by spatial autocorrelation;
- c by any other mechanism?

2 In what circumstances do models for autocorrelation (including regional adjustment) also control for confounding?

For the ACS study (Pope *et al*, 2002) and the HEI Reanalysis (Health Effects Institute, 2000)

3 Setting aside issues of spatial autocorrelation, what do *a priori* considerations and the sensitivity analyses that have been carried out lead us to conclude on:

- a which confounder-adjusted effect coefficient(s) do we prefer for risk assessment (subject to views on other factors);
- b what uncertainty remains from residual confounding?

4 What do *a priori* considerations and the modelling that has been carried out lead us to conclude on:

- a which spatial autocorrelation model, if any, do we prefer for risk assessment (subject to views on other factors);
- b what uncertainty remains from spatial autocorrelation?

5 What should be concluded on effect-modification, in particular with respect to transportability of coefficients from the ACS study to the UK population?

For other studies

6 Do *a priori* considerations or the experience of the ACS study affect the interpretation of any other long-term exposure and mortality studies? *(Even if the ACS study is the main one for deriving coefficients, other studies may be used to inform the conclusions, e.g. European studies may be used to inform issues of transferability.)*

Appendix B:
Over-adjustment

There is a common perception that adjusting 'too aggressively' for confounders, either directly or by including spatial terms in a regression, will bias coefficients for air pollution towards the null. Such bias in fact only occurs in the presence of classical measurement error in the pollution measure.

We illustrate this with some simulations. The results apply to any regression context, but for simplicity and concreteness we consider a time-series context. In each simulation run, we generated for each of 1000 days: (a) concentration of PM (Gaussian; mean = 20, SD = 5) and (b) a windspeed (Gaussian; mean = 10, SD = 2). The simulations build in a (negative) correlation between the two, as would be expected, which can be set to a different value for different simulation runs. We then generated mortality as a linear function of PM with coefficient 0.2 and random (Gaussian) noise so that mean=100 and SD=10. (Windspeed did not affect mortality.) Finally we regressed mortality on PM and windspeed and recorded the coefficient, i.e. we unnecessarily included a variable that was associated with PM but not in fact independently with mortality.

At each PM-windspeed correlation we simulated 1000 datasets and carried out the regression on each. We report below the mean of the 1000 coefficient estimates for each 100 simulations.

Corr (windspeed, PM)	Mean estimated coefficient	SD of estimated coefficient (empirical SE)	Mean SE of est coeff
Windspeed omitted	0.20	0.06	0.06
0	0.20	0.06	0.06
-0.00	0.20	0.06	0.06
-0.10	0.20	0.07	0.07
-0.30	0.20	0.08	0.08
-0.50	0.20	0.10	0.10
-0.70	0.20	0.13	0.13
-0.90	0.20	0.19	0.19
-0.95	0.20	0.26	0.26
-0.99	0.20	0.51	0.51

It can be seen that the mean of the coefficients remains 0.2 whether windspeed is included or not, whatever the correlation between PM and windspeed, but the standard error of the coefficients increases with increasing correlation. The increased standard deviation is correctly anticipated by the standard errors estimated for the coefficient at each simulation (last column), so confidence intervals would appropriately be wider in the model with windspeed.

Now we introduce classical measurement error by adding a random error component with a standard deviation of 2 to the generated PM before regressing:

Corr (windspeed, PM)	Mean estimated coefficient	SD of estimated coefficient (empirical SE)	Mean SE of est coeff
Windspeed omitted	0.17	0.06	0.06
0	0.17	0.06	0.06
-0.1	0.17	0.06	0.06
-0.3	0.16	0.07	0.07
-0.5	0.14	0.08	0.08
-0.7	0.13	0.10	0.10
-0.9	0.07	0.12	0.12
-0.95	0.06	0.14	0.13
-0.99	0.02	0.15	0.15

Here the estimate of PM effect is biased downwards, even when windspeed is omitted or uncorrelated with PM, as the standard measurement error theory predicts. However, this bias gets worse as the magnitude of correlation between PM and windspeed increases. (It should be noted that this bias is quite large – the SD is 40% the size of the SD of true exposure.)

Over-adjustment described by Abrahamowicz *et al* (2004)

Abrahamowicz *et al* (2004) describes an additional mechanism by which over-adjustment may occur in a particular context. The context is when an aggregated measure of a confounder at baseline time is used in a Cox regression. Entering such an aggregated variable in a Cox regression would give an estimate of PM effect less biased than the unadjusted estimate, but tending to 'overshoot' the true coefficient, if the true coefficient is not zero.

For example, if in the ACS study smoking had been controlled by including smoking prevalence of each area at the start of follow-up in the Cox regression, such over-adjustment would have occurred. An intuitive understanding of why is possible: over time smokers tend to die out – the prevalence of smoking reduces making the baseline measure inaccurate. Furthermore, because of the multiplicative combination of the effects of smoking and PM assumed in the Cox model, smokers die off faster in areas of high PM. Thus the areas of high PM have, over time, particularly overestimated smoking prevalence. The model therefore discounts what might otherwise be considered a high mortality in those areas because it expects a high mortality based on the increasingly incorrect information that smoking prevalence is high.

This mechanism appears not to be relevant for the Pope *et al* (2002) paper, which does not use aggregated risk factors. It could be relevant for those of the HEI analyses that adjusted for 'ecological' confounders which could be considered aggregated variables. However, the over-adjustment bias is small unless the strength of the association of the confounder and PM on

mortality are large and censoring (proportion of subjects alive at end of follow-up) is low – conditions that do not pertain for the ACS study. It seems likely, therefore, that the impact of this bias will be minimal in the ACS study, although a more formal sensitivity analysis would be required to quantify this.

In summary:

a Unless PM is measured with classical error over-aggressive control for confounding (inclusion of variables not actually associated with outcome) does not bias the PM coefficient but does reduce precision.

b If the PM is measured with classical error, there will be bias to the null with or without over-aggressive confounder control, but the bias will be greater with over-aggressive control.

c The over-adjustment bias described by Abrahamowicz *et al* (2004) does not apply to the Pope *et al* (2002) study and is likely to be minimal in the HEI Reanalysis.

Broadly the same trade-off is present for spatial (or time) smoothing: very aggressive modelling of spatial variation will increase standard errors, and if there is classical measurement error it will increase the magnitude of the bias to the null caused by this error.

Appendix C:

Effects on PM-Mortality Associations of Spatial Clustering of Mortality and of PM: Illustrations and Explanations

Introduction

We have summarised in a rather condensed form the impact of spatial autocorrelation and confounding on estimates of PM-mortality associations. It is the object of this appendix to describe these mechanisms in somewhat more detail, to assist an intuitive grasp of them.

We first expand on the responses given in the main text of this paper to Questions 1 and 2. We then illustrate the conclusions in simulations. We show that in general unmodelled spatial autocorrelation causes incorrect standard errors and confidence intervals. Further, we show that there are situations in which there is:

a confounding without spatial autocorrelation;

b spatial autocorrelation without confounding;

c elimination of confounding by using spatial autocorrelation models;

d reduction of confounding by using spatial autocorrelation models;

e increase of confounding by using spatial autocorrelation models.

We also discuss plausibility of these scenarios, concluding that it is most likely that spatial autocorrelation will be linked to confounding, and that using spatial autocorrelation models will reduce that confounding.

Expanded responses to Questions 1 and 2

Question 1 What are the expected impacts on the estimated effects of air pollution from cohort studies of incompletely measured or modelled sources of variation in health over space?

a Confounding

Response

We are concerned here with variation across the spatial units at which the mortality rates and pollution measures are available (e.g. metropolitan statistical areas in the ACS study). There are issues concerning spatial variation within these units, but these do not fall easily within the same framework.

Confounding variables are those that are correlated with the exposure of interest (air pollution) and are direct or indirect risk factors for the outcome (mortality). Most studies have adjusted for many potential confounders, but this adjustment may incompletely control confounding because:

i some confounders may not be measured;

ii the model may be inappropriate (e.g. linear not curved);

iii confounders may be measured only approximately.

If any of these is operating, results will be biased due to 'residual' confounding, though the bias is, in general, less than that in unadjusted models.

However, there are negative consequences of adjusting for variables that are correlated with air pollution but *not* risk factors for the outcome. Doing this decreases the statistical precision of the air pollution coefficient, so its confidence interval is unnecessarily wide. Such 'over-adjustment' does not, in general, bias the air pollution coefficient to the null, despite widespread belief to the contrary. The consequences of over-adjustment are illustrated using simulations in Appendix B.)

The issue of over-adjustment is complicated further in situations where mean air pollution for 'areas' is measured with random error. The bias to the null caused by that measurement error is increased if there is over-adjustment (also illustrated in Appendix B).

Because it is often not possible to be sure whether variables are risk factors for the outcome, investigators must, when choosing what to adjust for, balance the risk of residual confounding against that of over-adjustment.

All the above comments apply to mutual confounding by pollutants; however, there is a difference when there is interest in more than one pollutant – as generally. Here there is a danger in considering just the relative risk and its confidence interval for each pollutant – neither may be statistically significant even when there is clear evidence that one or the other is associated with the outcome. This may be avoided by considering also single-pollutant models and/or joint tests. Each answers a different relevant question.

b Spatial autocorrelation

Response

Spatial autocorrelation of a variable – also called spatial clustering – is a tendency for nearby values to be more similar than distant values. Spatial autocorrelation in mortality rates is due to the spatial distribution of risk factors rather than because the mortality rate in one location is influenced by mortality rates in nearby locations. These risk factors may, or may not, be confounders of the association between mortality and air pollution but both would generate spatial autocorrelation.

It is possible to have spatial confounding without spatial autocorrelation. For example, imagine that mortality and associated risk factors, including air pollution and factors that confound the association between mortality and air pollution, were measured in a number of geographical areas. Now it is likely that both mortality rates and risk factors would be more similar for adjacent than for more separated areas – hence spatial autocorrelation. Now imagine that the areas are 'jumbled up' over space in a random fashion. The clustering of similar areas will have gone but the risk factors and confounding factors will still be related in the same way. Hence spatial confounding without spatial autocorrelation is possible, although it is difficult to imagine a plausible example.

Residual spatial autocorrelation is such a tendency even after factors included in a model are adjusted for. We are concerned with residual spatial autocorrelation of mortality and air pollution.

Residual spatial autocorrelation in mortality and air pollution has the following consequences:

i Models with no allowance for autocorrelation will give estimates of air pollution effect with confidence intervals which are narrower than they should be, and p-values smaller than they should be.

ii The autocorrelation indicates that there are risk factors missing from the model. These risk factors may be confounders, although the autocorrelation does not prove that.

In a model of mortality rates that excludes or contains inadequately measured or modelled risk factors that are spatially autocorrelated, then the model residuals will also be spatially autocorrelated. In such a situation two things can be done to avoid the adverse consequences described above. First, more appropriate terms describing the risk factors can be found and incorporated in the model. Second, adjustment for the remaining spatial autocorrelation can be made in the model using appropriate statistical techniques. Both avoid incorrect confidence intervals ((point i) above). Both reduce vulnerability to confounding, but the first does this more reliably than the second (see below).

c Any other mechanism

Response
None identified.

Question 2 In what circumstances do models for autocorrelation (including regional adjustment) also control for confounding?

Response
Where there is residual spatial autocorrelation, models without allowance for this are likely to give incorrect confidence intervals and p-values and are vulnerable to uncontrolled confounding. Whereas models incorporating spatial autocorrelation will in general give more correct confidence intervals and p-values. In many but not all cases they will also reduce confounding.

In particular, where a fixed-effect regional adjustment smooth spatial surface is used (e.g. some ACS reanalysis results), no information is drawn from associations between mortality and air pollution across regions, so estimates are based entirely on these associations within regions. Hence any confounding in the between-region association (e.g. due to between-regional climate differences) is eliminated by this analysis. The factors causing such confounding may nevertheless cause confounding within regions, which will remain.

Random effect spatial autocorrelation models (some of the models described as including spatial autocorrelation) reduce rather than eliminate weight put on associations across wider areas. Thus they will reduce but not eliminate confounding in these associations.

Statistical adjustment for residual spatial autocorrelation therefore seems a prudent measure provided it does not lead to critical loss of precision in the pollution effect estimate. If the autocorrelation is due to risk factors correlated with air pollution, the adjustment may reduce the resulting confounding. Even if not, the adjustment will avoid bias in standard errors.

Scenarios

Although spatial autocorrelation is a more general concept than regional clustering, the latter is the simplest example of spatial autocorrelation. (With regional clustering two areas in the same region are likely to be more similar than two from different regions.) We use simulations in a simple scenario with regional clustering to explain the key concepts.

i 100 areas, 10 in each of 10 regions.

ii PM and background mortality may be set to have regional clustering or not. Technically, they are generated as sums of random (Gaussian) regional and area components. Non-zero regional variation implies regional clustering (spatial autocorrelation).

iii An unmeasured confounder is generated at the regional level and/or area level. Technically, variables are generated to be linear functions of air pollution at the specified level, plus random noise.

iv An increment to mortality is generated as a linear function of PM and the unmeasured confounder.

By setting some of these simulation components to zero the scenarios allow:

Clustering by region:	PM	YES/NO and extent
	Mort:	YES/NO and extent
Confounding:	Across regions	YES/NO
	Within regions	YES/NO
Air pollution effect:		YES/NO

Illustrations of clustering and confounding in different scenarios

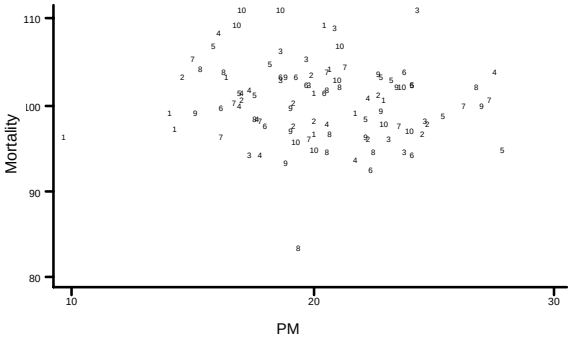
We illustrate in the figure (overleaf) the types of scenario considered. In none of these is there any true association between PM and mortality – the true PM coefficient is zero. Clustering where present is unrealistically severe, to make patterns clear visually. As single samples, some patterns may occur by chance, but the examples have been chosen to illustrate impacts of clustering demonstrated somewhat more formally by simulation results described later in this appendix.

Top four graphs

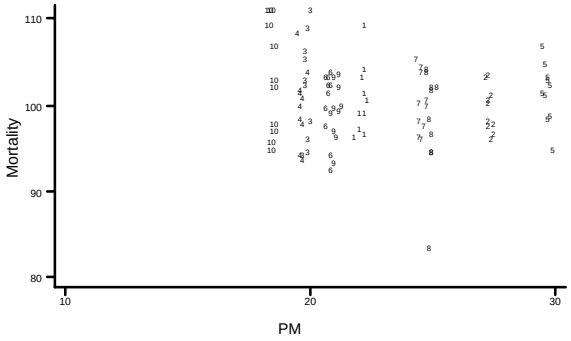
None of the top four graphs had any confounding in the simulation parameters, but they illustrate clustering (spatial autocorrelation) by air pollution, mortality, and both. PM-mortality graphs would give zero estimated coefficients, except for sampling error, whether the regression allowed for regional variation (clustering or spatial autocorrelation) or not. These thus illustrate the possibility of spatial autocorrelation without confounding. Where both PM and mortality are clustered, the confidence intervals from an analysis ignoring region will be spuriously narrow; an analysis with region as random effect (e.g. Filleul *et al,* 2005) would give a confidence interval of appropriate width; an analysis with region as fixed effect (e.g. some HEI Reanalysis) could be unnecessarily imprecise.

Figure: Illustrations of regional clustering and confounding

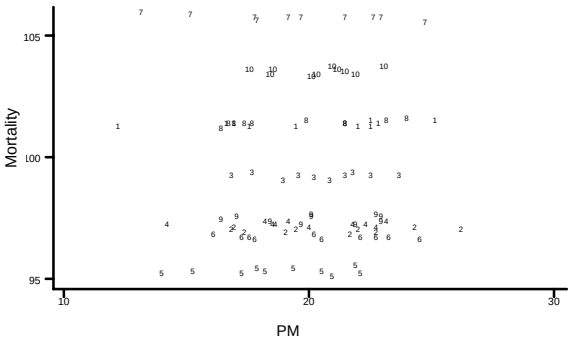
Clustering PM: NO, Mort: NO, Confounding Region: NO, Area, NO



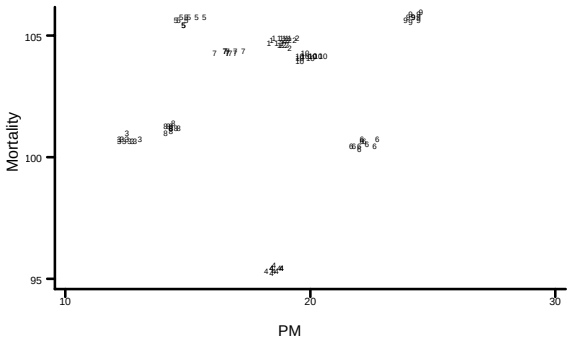
Clustering PM: YES, Mort: NO, Confounding Region: NO, Area, NO



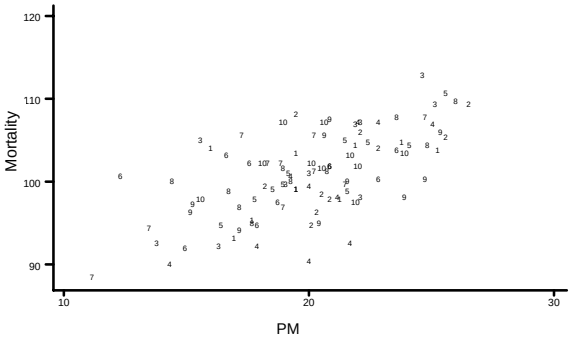
Clustering PM: NO, Mort: YES, Confounding Region: NO, Area, NO



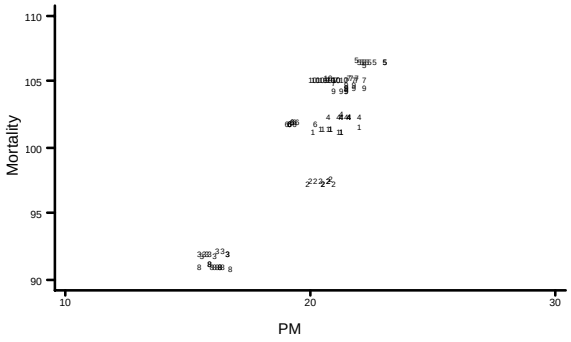
Clustering PM: YES, Mort: YES, Confounding Region: NO, Area, NO



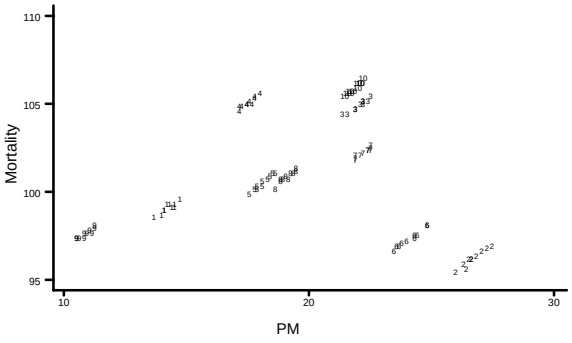
Clustering PM: NO, Mort: NO, Confounding Region: NO, Area, YES



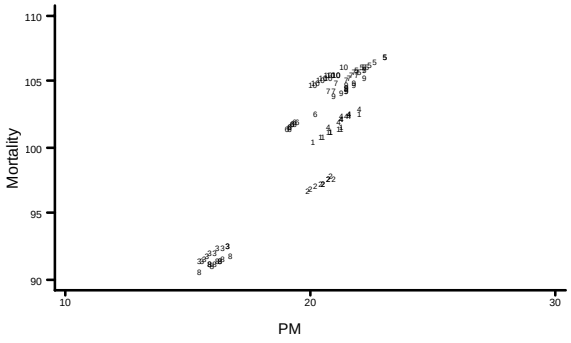
Clustering PM: YES, Mort: YES, Confounding Region: YES, Area, NO



Clustering PM: YES, Mort: YES, Confounding Region: NO, Area, YES



Clustering PM: YES, Mort: YES, Confounding Region: YES, Area, YES



Bottom four graphs

The bottom four all have confounding, some just across regions, and some just across areas. (The effect of the confounder on mortality cannot be shown directly on these two-dimensional graphs, but because the simulations did not assume a pollution effect any tendency for mortality to rise with PM can be assumed to be the result of confounding.)

i The first (third row, left) has no regional clustering of PM or mortality, but shows confounding nonetheless, illustrating the possibility, theoretically at least, of confounding unrelated to spatial autocorrelation.

All other figures have clustering of both PM and mortality:

ii The second (third row, right) has confounding across regions only. An analysis ignoring region would give a biased effect estimate and spuriously narrow confidence interval. An analysis including region as a fixed effect would give an unbiased estimate and confidence interval, although the confidence interval could be wide. An analysis with region as random effect would have some bias, but much less than that of the analysis ignoring region.

iii The third (bottom left) has confounding within regions only. An analysis ignoring region would give a slightly biased effect estimate. An analysis including region as a fixed effect or random effect would have substantial bias.

iv The final graph has confounding both within and across regions. No analysis without measurements of the confounder can give an unbiased estimate, but analyses with fixed or random region effects will give more appropriate confidence intervals.

Formal simulations

Under some of the specifications of simulation parameters as described above, we generated 1000 datasets. For each simulated dataset we carried out a regression analysis to estimate the pollution effect:

i ignoring region;

and two models allowing in different ways for 'spatial autocorrelation':

ii entering region as a fixed effect;

iii entering region as a random effect.

Simulation parameters								Summary results from 1000 simulations		
Mort SD		PM SD		Confounding		ICC		Beta: mean (estimated SE, actual SE)		
Area	Reg	Area	Reg	Area	Reg	Mort	PM	Crude	Fixed effect	Random effect
True beta = 0										
3	6	1	6	0	0	0.77	0.97	-0.01 (0.12,0.37)	-0.01 (0.32,0.32)	-0.01 (0.23,0.24)
3	6	1	6	0	1	0.86	0.97	0.95 (0.11,0.36)	-0.00 (0.32,0.31)	0.46 (0.23,0.30)
3	6	1	6	1	1	0.86	0.97	1.02 (0.12,0.39)	1.01 (0.32,0.31)	1.01 (0.23,0.25)
7	0	6	0	1	0	0.02	0.02	1.00 (0.12,0.12)	0.99 (0.12,0.12)	1.00 (0.12,0.12)
True beta = 0.1										
3	6	1	6	0	0	0.77	0.97	0.10 (0.12,0.38)	0.09 (0.32,0.32)	0.10 (0.23,0.25)
3	6	1	6	0	1	0.88	0.97	1.07 (0.12,0.37)	0.10 (0.32,0.31)	0.58 (0.23,0.29)
3	6	1	6	1	1	0.86	0.97	1.10 (0.11,0.37)	1.09 (0.32,0.32)	1.10 (0.22,0.24)
7	0	6	0	1	0	0.02	0.02	1.10 (0.12,0.12)	1.10 (0.12,0.12)	1.10 (0.12,0.12)

Notes: Reg = region, ICC = intra-class correlation (1 = maximally clustered, 0 = not clustered) the values given are the means over 1000 simulations.

Mean estimated SE is the average SE found in each regression (what would be used to make a CI);

Actual SE is the SD of estimates from the 1000 simulations – the true uncertainty of the estimated betas.

These results essentially bear out the statements on impact made in relation to the figures. In particular:

i Whenever the mortality and PM data are clustered, the crude estimate has estimated SE (first figure in brackets) much lower than the actual SE (second in brackets) – crude analyses will give spuriously narrow confidence intervals.

ii The first (and fifth) rows illustrate clustering without confounding – no bias in beta but bias in the standard error. The fourth and eighth rows illustrate confounding without clustering – bias in beta but no bias in the standard error.

iii The spatial 'autocorrelation' models (fixed and random region effects) always get the right SEs, and in some scenarios eliminate or reduce bias. They have higher SEs, however, than the model ignoring region – an unnecessary price if in fact there is no clustering. (The increase in SE is a consequence of the greater clustering of PM than mortality.)

iv The random effects model gives somewhat more precise estimates than the fixed effects model but controls confounding bias less effectively.

Discussion: theoretical and realistic spatial autocorrelation

The simulations above show the separation in theory between the phenomena of spatial autocorrelation and confounding. However, how realistic is such separation in practice?

Not very plausible

Factors that give rise to confounding but no spatial autocorrelation.

These factors would not be revealed as spatial autocorrelation, nor would spatial autocorrelation models control the confounding.

Examples seem contrived. One type of example supposes that some adverse health influence occurs sporadically across the USA, and that either by mechanism or chance these are atypical with respect to PM. Another type of example supposes that there is some resource that is fairly equally distributed across regions (thus no regional clustering), but not within (investment or federal support?) Further, the highly resourced areas tend to have lower or higher PM than others.

Moderately plausible

(a) Factors that give rise to spatial autocorrelation but not confounding, or at least not much confounding.

These factors would be revealed as spatial autocorrelation. Although they would not cause confounding if the autocorrelation was ignored, the confidence intervals would be incorrect if air pollution was also spatially autocorrelated.

Some elements of diet might be examples. It seems likely that there are regional variations in diet, but there is no particularly strong reason to suppose that the mechanism that gives rise to regional variations in diet would be related to that giving rise to regional variations in air pollution. This is not to say that such a correlation could not exist, however, so a cautious approach would accept the possibility that diet or other factors that vary between regions also confound.

(b) Confounding factors causing spatial autocorrelation and confounding at regional level only, or at least overwhelmingly predominantly at regional level.

These factors would be revealed as spatial autocorrelation. Models with regional effects or broad spatial smooths would control both confounding and distortion of confidence intervals.

The most plausible examples we can find are factors which do not vary, or not much, within regions. Some aspects of climate might partially conform to this.

Plausible

Factors causing confounding at different levels of spatial aggregation.

These factors would be revealed as spatial autocorrelation. Spatial autocorrelation models will control distortion of confidence intervals and partially control confounding.

Most unmeasured risk factors seem likely to fall into this category. Wealth-related factors make a good example. Although there are variations in wealth across regions, there are also variations within regions, and both of these could plausibly be related to air pollution. Migration, either as an example of a wealth-related factor or a variable in its own right, has similar properties.

We conclude that factors causing confounding are likely to cause some spatial autocorrelation, and that models incorporating that autocorrelation will control some but not all confounding by those factors.

Appendix D:
Quantifying Uncertainty

Less technical summary

We used recently developed methods (Greenland, 2005) to obtain 95% uncertainty intervals for the adjusted relative risks associated with 10 μg/m^3 $PM_{2.5}$ reported by Pope *et al* (2002). The intervals combined sampling uncertainty (conventional confidence intervals) with uncertainty due to unknown confounding and information bias (error in measuring exposure). These showed that for plausible bias parameters confounding dominated uncertainty, so we present the main results for this source of non-sampling uncertainty only.

We assumed no prior knowledge about the direction of confounding, so point estimates of relative risk were not affected. We show below uncertainty intervals corresponding to three benchmark assumptions about the likely extent of confounding:

Low: 33% probability of confounding in reported relative risks exceeding ±2%

Central: 33% probability of confounding in reported relative risks exceeding ±5%

High: 33% probability of confounding in reported relative risks exceeding ±10%

Uncertainty intervals were calculated for the relative risks reported by Pope *et al* for $PM_{2.5}$ without spatial modelling and with spatial smoothing using highest p-value criterion:

Cause	**RR**	**95% uncertainty interval**			
		Original CI including possibility of residual confounding			
			Low	**Central**	**High**
No spatial smoothing					
All-cause	1.04	1.01–1.08	0.99–1.10	0.94–1.15	0.85–1.27
Cardiopulmonary	1.06	1.02–1.10	1.00–1.12	0.95–1.18	0.87–1.29
Lung cancer	1.08	1.01–1.16	1.00–1.17	0.96–1.22	0.88–1.33
Spatial smoothing*					
All-cause	1.02	0.99–1.04	0.97–1.07	0.92–1.13	0.84–1.24
Cardiopulmonary	1.06	1.03–1.09	1.01–1.11	0.96–1.17	0.87–1.29
Lung cancer	1.08	1.01–1.15	1.00–1.17	0.96–1.21	0.88–1.33

* Original values read from Figure 3, last column, of Pope *et al* (2002).

Technical details

Objective: To quantify total uncertainty (due to sampling error and bias) in estimates of relative risk from Pope *et al* (2002) (principal reference: Greenland, 2005).

Simpler model for one bias only with normally distributed uncertainty (e.g. confounding)

We assume that RR (true exposure difference of x) = $\exp(\beta x)$ ($\mathrm{RR} = \exp(\beta)$ for short), but that we estimate β by $\hat{\beta}^*$, which is subject to both sampling error and unknown confounding bias.

Confounding bias: $\beta^* = \beta + c$, i.e. proportional bias is exp(c)

Sampling error: $\hat{\beta}^* = \beta^* + \upsilon$

We know from standard theory that asymptotically $\upsilon \sim N(0, \mathrm{SE}(\beta^*))$ with SE(β^*) the usual standard error given by standard software. We assume further that $c \sim N(0, \sigma_c)$, i.e. that uncertainty about extent of confounding can be modelled as a Gaussian distribution with SD = σ_c.

In summary: $\mathrm{RR} = \exp(\hat{\beta}^*)$, with $\hat{\beta}^* = \beta + \upsilon + c$, $\upsilon \sim N(0, \mathrm{SE}(\beta^*))$, $c \sim N(0, \sigma_c)$

If we knew υ and c, we could calculate

$$\beta = \hat{\beta}^* - \upsilon - c$$

In fact we only know the distributions of υ and c. From this we can find a posterior distribution of β given $\hat{\beta}^*$, SE(β^*), and σ_c:

$$E(\beta \mid \hat{\beta}^*) = \hat{\beta}^*$$

$$\mathrm{var}(\beta \mid \hat{\beta}^*) = \mathrm{SE}(\hat{\beta}^*)^2 + \sigma_c^2 \quad \left(\mathrm{SD}(\beta \mid \hat{\beta}^*) = \sqrt{\mathrm{SE}(\hat{\beta}^*)^2 + \sigma_c^2}\right)$$

and $$(\beta \mid \hat{\beta}^*) \sim N\left[\hat{\beta}^*, \mathrm{SD}(\beta \mid \hat{\beta}^*)\right]$$

From this distribution we can determine in particular 95% uncertainty limits as the 2.5th and 97.5th centiles, $\left[\hat{\beta}^* - 1.96\ \mathrm{SD}(\beta \mid \hat{\beta}^*), \hat{\beta}^* + 1.96\ \mathrm{SD}(\beta \mid \hat{\beta}^*)\right]$.

Finally but most problematically, we need to decide on a value for σ_c, which determines the range of confounding we think is likely. For small values, $\exp(\sigma_c) \approx 1 + \sigma_c$, and we can think of σ_c as being the proportion by which the relative risk is likely to be biased by confounding. For example, if we think that bias up to $\pm$10% is fairly likely, we set $\sigma_c = 0.1$. (To be more precise, 'fairly likely' here means 67% likely – the above example describes a belief that there is a 67% chance of bias within $\pm$10%, and a 33% chance of bias above $\pm$10%, and we allow a 5% chance that the bias will be above $\pm$20%, etc, from the properties of the normal distribution.)

Our choice of σ_c should be informed by the likelihood of residual confounding (important confounders being omitted, or confounders being importantly mis-measured or modelled), and also by the scale of the relative risk. It would not make sense to assume as high a value for σ_c for relative risk presented per 1 μg/m^3 and per 100 μg/m^3. Pope *et al* (2002) present the relative risk per 10 μg/m^3 $PM_{2.5}$, which comprises (for 1979–1983) about two standard deviations (SD = 4.6, from Table 1 of Pope *et al*, 2002). Thus the relative risk presented is for an exposure difference such as there would be between about the 16th and 84th centiles of exposure (±1 SD), though a more precise estimate would assume a log-normal rather than normal distribution.

A key simplification occurs if we then specify the relative risk due to the hypothesised omitted confounder, say $\exp(\beta_c)$ using the same centile range as used of the PM. Then we need only the correlation r between the confounder and the PM to determine the confounding bias r (deduced mathematically – see derivation at the end of this appendix):

$$c = \beta_c r, \text{ or } \exp(c) = \exp(\beta_c)^r$$

It is useful to see how this expression evaluates for some benchmark confounder relative risks (RR) and confounder-PM correlations (r):

Proportional confounding bias by strength of confounder-mortality association and confounder-PM correlation

RR*	Confounder-PM correlation (*r*)					
	0.0	**0.1**	**0.2**	**0.5**	**0.8**	**0.9**
1.0	1.00	1.00	1.00	1.00	1.00	1.00
1.1	1.00	1.01	1.02	1.05	1.08	1.09
1.2	1.00	1.02	1.04	1.10	1.16	1.18
1.5	1.00	1.04	1.08	1.22	1.38	1.44
2.0	1.00	1.07	1.15	1.41	1.74	1.87

RR*: relative risk of confounding variable across the same percentile range as that used to express the exposure RR.

Thus if an omitted confounder with a relative risk of 1.5 across the 16th–84th percentile range and correlated at 0.5 with the exposure was considered plausible, then a confounding bias of 1.22 would be present. (For a correlation of -0.5 or relative risk of 1.5^{-1} the bias would be 1.22^{-1}, so separate table entries for negative correlations and/or protective factors are unnecessary.) Under this bias, a PM relative risk of 1.22 would be expected if there were no true exposure effect. Conversely with the negative correlation or protective factor a PM relative risk of 1.00 would be expected even if there were a true exposure relative risk of 1.22.

We can use the table to inform our choice of σ_c, the standard deviation of the distribution describes our uncertainty in c. We use three benchmarks:

Low: $\sigma_c = \log(1.02) = 0.02$ (assuming that combinations of r and RR outside the top left of the table are implausible)

Central: $\sigma_\varepsilon = \log(1.05) = 0.05$ (slightly widening the plausible range of possible *r* and RR)

High: $\sigma_\varepsilon = \log(1.10) = 0.10$ (allowing that confounders with quite substantial values of *r* and RR might be present but omitted)

Our subjective view is that this range runs from the optimistic to the pessimistic ends of scales of expectation of residual confounding.

[It should be noted that the HEI Reanalysis presents PM relative risks for a greater PM contrast – the maximum to the minimum area, which is about twice the value of the Pope 10 μg/m^3. To apply the above procedure we would have to choose different confounder relative risks for the two studies (16th–84th percentile range and minimum–maximum range for Pope *et al* (2002) and the HEI Reanalysis (Health Effects Institute, 2000), respectively). In particular, the empirical confounding ratio of 1.15/1.06 = 1.08 found for population change in relation to sulphates and mortality (HEI Reanalysis, Table 34) would translate to a more moderate confounding ratio of $\sqrt{1.08} = 1.04$ with the relative risk scale used by Pope *et al* (2002).]

We apply these benchmark values of σ_ε to the relative risks for all-cause, cardiopulmonary and lung cancer deaths reported by Pope *et al* (2002) for $PM_{2.5}$ without spatial modelling and with spatial smoothing using the highest p-value criterion:

Cause	**RR**	**95% uncertainty interval**			
		Original CI including possibility of residual confounding			
			Low	**Central**	**High**
No spatial smoothing					
All-cause	1.04	1.01–1.08	0.99–1.10	0.94–1.15	0.85–1.27
Cardiopulmonary	1.06	1.02–1.10	1.00–1.12	0.95–1.18	0.87–1.29
Lung cancer	1.08	1.01–1.16	1.00–1.17	0.96–1.22	0.88–1.33
Spatial smoothing*					
All-cause	1.02	0.99–1.04	0.97–1.07	0.92–1.13	0.84–1.24
Cardiopulmonary	1.06	1.03–1.09	1.01–1.11	0.96–1.17	0.87–1.29
Lung cancer	1.08	1.01–1.15	1.00–1.17	0.96–1.21	0.88–1.33

* Original values read from Figure 3, last column, of Pope *et al* (2002).

Discussion

i This approach has not explicitly considered confounding by more than one factor. It can be extended to do so, however, by interpreting the omitted confounder as a score comprising components from each omitted specific confounder. Thus if we do not think confounding by a single omitted factor could plausibly cause confounding by a factor of 1.05 but thought that several omitted factors could in total cause such confounding, it would be appropriate to focus on the central benchmark σ_ε.

ii If we use an estimate allowing for spatial autocorrelation, we might assume less residual confounding.

iii This approach does not draw on information external to the study – for example, the exclusion of very large relative risks because they are incompatible with calendar trends in mortality and in air pollution in the UK. Such an exercise could be combined with this one.

iv Arguably, different confounding bias is plausible for different causes of death.

More complex case: considering both confounding and information bias

We assume:

RR(true exposure difference of x) = $\exp(\beta x)$, where x = true mean exposure in study population of area of residence of x.

Studies use approximate observed exposure $\tilde{x}$:

$$\tilde{x} = bx + a + \varepsilon$$

where b (constant) is average proportional error (e.g. observed pollution on average 50% of true pollution),

a (constant) is average additive error (e.g. observed pollution on average 1 $\mu g/m^3$ higher than true pollution),

and $\varepsilon \sim N(0, \sigma_\varepsilon)$ is random error (classical).

Then RR(mortality at observed exposure $\tilde{x}$ Vs 0) = $\exp(\beta^* \tilde{x})$

with $$\beta^* = \frac{\beta}{b[1 + (\sigma_\varepsilon / \sigma_x)^2]}$$

where σ_x is the standard deviation of exposure in the study population (Armstrong, 1998).

We also assume residual confounding:

$$\exp(\beta^{**}) = c\exp(\beta^*) = c\exp\left(\frac{\beta}{b\left[1 + (\sigma_\varepsilon / \sigma_x)^2\right]}\right)$$

where c is the factor by which the true relative risk has been distorted by residual confounding and the double asterisk on the leftmost beta indicates a regression coefficient subject to both information bias and residual confounding.

Finally, the study yields an estimate

$$\hat{\beta}^{**} = \beta^{**} + \upsilon$$

where $\upsilon \sim N(0, \mathrm{SE}(\hat{\beta}))$ is the sampling variation.

From this, given the bias parameters b, $\sigma_\varepsilon / \sigma_x$, and c, and sampling error υ we could deduce β from $\hat{\beta}**$ as

$$\exp(\beta) = \frac{\exp\left\{(\hat{\beta}** - \upsilon) b[1 + (\sigma_\varepsilon / \sigma_x)^2]\right\}}{1 + c} \qquad (1)$$

However, we do not know these parameters. Monte-Carlo sensitivity analysis proceeds by assuming distributions for the bias parameters to represent our uncertainty about the sources of bias, simulating from these distributions and from that for υ to get a distribution for β, from which we can estimate a 95% uncertainty interval as the 2.5th to 97.5th centile.

We assume:

$$b \sim \text{log-normal}(\text{GM} = 1, \text{GSD} = 1 + \sigma_b)$$
$$\sigma_\varepsilon / \sigma_x \sim \text{log-normal}(\text{GM} = \mu_e, \text{GSD} = 1 + \sigma_e)$$
$$c \sim \text{log-normal}(\text{GM} = 1, \text{GSD} = 1 + \sigma_c)$$

Numerical values must be found for the hyperparameters $\sigma_b, \mu_e, \sigma_e$ and σ_c. As a subjective but informed benchmark, we take:

$\sigma_b = 0.1$	(observed exposure may systematically be from about 0.8 to 1.2 of true exposure)
$\mu_e = 0.1$	(best guess for random error in exposure is that it has SD = 10% of SD of true exposures)
$\sigma_e = 0.5$	(we are very uncertain of this 10%; it could be as low as 4% or as high as 22%)
$\sigma_c = 0.05$	(residual confounding could distort the RR by a factor of 0.9 to 1.1)

(ranges given show 2.5th–97.5th centiles of distributions).

To show the contribution to total uncertainty from bias from these sources we also assume in different simulations zero-bias values: $b = 1$, $\sigma_\varepsilon / \sigma_x = 0$, and $c = 0$.

From these distributions we can simulate a distribution of values of β from the observed $\hat{\beta}**$ using expression (1).

For example, for all-cause mortality vs sulphate from Pope *et al* (2002) we have:

$$\hat{\beta}** = \log(1.04) = 0.04$$

with 95% CI (0.01-0.08), and hence SE($\hat{\beta}**$)=0.07/3.92 = 0.018.

Simulated total uncertainty in regression slope for all-causes on sulphate (10^6 replicates)				
Bias parameters				**RR (95% uncertainty interval)**
σ_b	μ_e	σ_e	σ_c	
systematic exposure error	**random exposure error**		**confounding**	
No non-sampling uncertainty				
0.0	0.0	0.0	0.0	1.040 (1.006–1.075)*
Benchmark uncertainty				
0.1	0.0	0.0	0.0	1.040 (1.006–1.078)
0.0	0.1	0.5	0.0	1.041 (1.006–1.077)
0.0	0.0	0.0	0.05	1.040 (0.940–1.151)
0.1	0.1	0.5	0.05	1.040 (0.938–1.157)
Double benchmark uncertainty				
0.0	0.0	0.0	0.0	1.040 (1.006–1.075)
0.2	0.0	0.0	0.0	1.039 (1.006–1.084)
0.0	0.2	1.0	0.0	1.043 (1.006–1.089)
0.0	0.0	0.0	0.1	1.040 (0.860–1.257)
0.2	0.2	1.0	0.1	1.043 (0.841–1.314)

* Some difference from published RR and 95% CI 1.04(1.01–1.08) because these are given to two decimal places only; hence simulation parameters for log(RR) and its SE are approximate.

Conclusion

At these bias parameter distributions and observed relative risks, confounding is overwhelmingly the largest source of uncertainty additional to sampling error. (This is not surprising since the exposure measurement error effects are proportional to the excess relative risk, which is small here.) There is discussion of uncertainty due to residual confounding earlier in this appendix in the section on the simpler model.

Derivation of expression for bias due to omission of a variable (i.e. confounding):

$$E(x_2 \mid x_1) = a + bx_1 \qquad \text{with}\,\text{corr}(x_1, x_2) = r_{12}\ \text{and}\,\text{SD}(x_i) = \sigma_i$$

so $$b = r_{12}\frac{\sigma_2}{\sigma_1}$$

$$E(y \mid x_1 x_2) = \alpha + \beta_1 x_1 + \beta_2 x_2$$

But x_2 is omitted, so

$$E(y \mid x_1) = \alpha + \beta_1 x_1 + \beta_2 E(x_2 \mid x_1)$$

$$E(y \mid x_1) = \alpha + \beta_1 x_1 + \beta_2 (a + bx_1)$$

$$E(y \mid x_1) = \alpha + \beta_2 a + (\beta_1 + \beta_2 b) x_1$$

or $$E(y \mid x_1) = \alpha' + \beta_1' x_1 \qquad \text{where}\ \ \beta_1' = \beta_1 + \beta_2 b$$

i.e. $$\text{bias} = \beta_2 b = \beta_2 r_{12}\frac{\sigma_2}{\sigma_1}$$

Working Paper 8

Studies on a Small Spatial Scale

Fintan Hurley and John Stedman

Introduction

The American Cancer Society (ACS) study is the main cohort study used in quantifying the effects of long-term exposure to particles (PM) on mortality. It is based on contrasts *between* cities (metropolitan areas) in annual average pollution concentrations. It shows risk coefficients (linking concentration and changes in all-cause mortality hazards) in the order of 4–6%, per 10 μg/m^3 $PM_{2.5}$ (ACS update: Pope *et al*, 2002).

In recent years several studies have appeared giving risk coefficients for mortality in relation to long-term PM exposure, based on contrasts on a finer scale than metropolitan area – for example, contrasts *within* cities (metropolitan areas). For any scale of analysis larger than the individual, the result of the analysis may be different at different geographical scales of data, and typically, these studies at a finer spatial scale than the ACS study have reported *higher* risk coefficients than the 4–6% figures from the ACS update.

The purpose of this note is to review some of these studies in order to indicate their reliability, and the kinds of results they give; and then to draw some conclusions and implications, for quantification.

The studies

Hoek *et al* (2002)

Design and subjects

This is the study which first drew attention to the phenomenon. It is based on a case-cohort study of 5000 subjects from within a prospective cohort study of more than 120,000 people in the Netherlands (the Netherlands Cohort Study on Diet and Cancer – NLCS). Subjects were aged 55–69 years on enrolment (mean 61 years), which started in 1986.

Assessment of air quality

Three components of ambient pollution

This study nominally considers concentrations of nitrogen dioxide (NO_2) and black smoke (BS). Overall, concentrations are looked on as the aggregate of three components: regional, urban background, and roadside. Some components of the concentrations have been estimated by models related to surrogate statistics or are represented by indicators.

> *Regional:* by interpolation from regionally representative monitoring sites
>
> *Urban:* estimated from mapped population density. Relationship with population density established by regression analysis of available urban monitoring data
>
> *Roadside:* constant increments within fixed distances from the road (50 m and 100 m). Increments defined in previous studies.

All of these were expressed as long-term average ambient concentrations of BS and NO_2 at the subject's 1986 home address. In addition, Hoek *et al* 'quantified small-scale spatial variations in air pollution concentrations by calculating proximity [of 1986 home address] to major roads', using GIS methods (Arcinfo). Only 5% of the study participants lived close to a major road. Adding the roadside increment to black smoke gave clearly higher 'background + local' concentrations to this small subset; they are clearly visible in the overall frequency distribution of concentrations (see Figure 2 in Hoek *et al,* 2002).

Comparison with mapping methods used in the UK

Regional: by interpolation from regionally representative monitoring sites

Urban: derived from emission inventories using a dispersion model. A limitation of the Hoek *et al* approach is that they will only have included the spatial variations in concentrations related to population density. The impact from the emissions from major roads in less populated areas will not have been included in the estimates of background concentrations. This may have tended to decrease the impact of traffic emissions within the estimate of urban background exposure and increase the impact within the roadside exposure estimate.

Roadside: we use a similar approach but only within 10 m and the magnitude of the roadside increment varies with traffic flow. There will be a large variation in the magnitude of the impact of traffic emissions within 100 m from a road. UK studies suggest that the roadside concentrations beyond about 20–50 m from the edge of the road will be essentially indistinguishable from the local background. Thus Hoek *et al* may have tended to add too large a roadside increment at distances greater than about 20 m from the roadside.

Modelling of concentration-response relationships; risk coefficients

Relationships with mortality, assessed over an 8-year period 1986–1994, were examined using Cox proportional hazards modelling, with detailed adjustment for confounders at the individual level. Major roads were included in the models either as an indicator or as a component of the total exposure. In the latter case, the roadside increment was added as one of two constant values, i.e. for BS or for NO_2. Thus these two approaches are quite similar.

Results

In models adjusting for covariates *and including estimates of background pollution,* the coefficient linking all-cause mortality with an indicator variable for living near a major road was elevated, and statistically significant when analyses were restricted to 2788 people who had been living 10+y at their 1986 address (RR 1.53, 95% CI 1.01-2.33 when adjusting for black smoke; similar results when adjusting for NO_2).

The coefficient for *background* BS, adjusted for confounders, in the wider study sample of 3464 with confounder information, was elevated, though far from significant statistically (RR 1.17; 95% CI 0.76-1.78, per 10 $\mu g/m^3$ BS). This coefficient was robust to whether the indicator variable for closeness to roads was included or not.

However, the estimated effect of all-source BS (i.e. background plus local, in models without the indicator variable for closeness to roads), was higher, and very close to statistical significance at the conventional 5% level (RR 1.32; 95% CI 0.98-1.78, per 10 $\mu g/m^3$ BS).

Mortality from non-cardiopulmonary causes was not associated with background pollution, with living near roads, or with 'total' BS or NO_2. This is consistent with the Pope *et al* (2002) results for $PM_{2.5}$, and in contrast to the ACS update results for SO_2 and sulphates.

Discussion and interpretation

These results strongly suggested that exposure estimation at a smaller spatial scale might lead to higher estimates of risk, and were interpreted as such by the authors. Direct comparison with Pope *et al* (2002) is not possible, because of the different exposure metrics used, and the relationship between BS and $PM_{2.5}$ varies by time, place and, especially, sources of pollution. BS is likely to be a reasonable indicator, but not necessarily quantitatively of the primary combustion component of both $PM_{2.5}$ and PM_{10} (PM from traffic emissions is probably 'darker' than PM from domestic coal fires). It is also likely that a greater proportion of primary PM emitted from traffic is in the fine fraction than from stationary combustion sources (Dore *et al,* 2004). Nevertheless, the disparity of coefficients in the two studies (e.g. RR 1.32 per 10 μg/m³ BS from Hoek *et al*, 1.06 per 10 μg/m³ $PM_{2.5}$ from Pope *et al*, 2002) is very marked.

Interpretation may be linked with another finding, from within the study, that living near a major road (whether represented by an indicator variable, or by 'local' concentrations of BS or NO_2) was found to lead to a greater association with health impacts than variations in urban background concentrations. We note the following:

a. The concentrations of 'traffic related' NO_2 and black smoke in urban background locations were only represented by the spatial variation in population density; measured concentrations were not used directly.

b. The composition of the air pollution mixture is likely to differ between the local, urban background and regional scales. PM concentrations at local traffic related 'hot-spots' will include a larger proportion of local combustion emissions than at background locations, where the emissions will have aged further and include a greater proportion of sulphates and nitrates.

c. The World Health Organization (2004), in its answers to the follow-up questions from CAFE (Clean Air for Europe) (Question 5.4 there), noted that the case for attributing significant health effects of air pollution to vehicle emissions is strong.

Taking these points together suggests two possible explanations. It is possible that the greater coefficients obtained in studies at a smaller spatial scale could be due to:

a. less exposure misclassification, and so less attenuation of the true concentration-response relationship;

b. a greater variability in concentrations *compounded with greater toxicity (per μg/m³ PM) at higher concentrations*.

These two explanations are not mutually exclusive in that both may be contributing and, to an extent, these may be different ways of saying the same thing.

Willis *et al* (2003)

Assessment of air quality

Willis *et al* (2003) aimed to reanalyse the original ACS study data, but using concentration data on a finer spatial scale than the ACS. In practice, this meant annual average concentrations at the county scale rather than at the scale of metropolitan statistical area (MSA: the central county including the city centre and other counties with more than 50% of the population living in the contiguous urban area).

a In the ACS study, concentrations were defined as averages over available monitoring sites in each MSA and individuals assigned according to three digit zip codes.

b Willis *et al* used a spatial resolution of counties and defined concentrations of sulphate using single monitoring sites in each county. Their focus was on sulphates rather than $PM_{2.5}$, in order to ensure basic measurement data were available at fine enough resolution. In addition, individuals were assigned to counties using five digit zip codes, i.e. a more refined method than had been used in assigning to MSAs in the original study.

There are various problems in using zip codes to assign individuals to MSAs (cities) or counties. Zip codes are not polygons (areas) but postal delivery routes. Therefore assignments are not precise. In particular, the three digit zip code areas used in the ACS study tend to be larger than MSAs. This may have led to additional misclassification on top of that introduced by using MSA rather than county data.

Design and subjects

The 151 MSAs of the original ACS study sulphate analysis corresponded to 513 counties, of which only 139 met the criteria of at least 10 measurements of sulphates in 1980–1981, i.e. near the start of the ACS mortality follow-up. Some individuals were excluded because their location (zip code) data were not sufficiently detailed, or did not sufficiently match the county boundaries chosen. After exclusion, the study was nevertheless based on almost 250,000 subjects in the 139 counties included.

Modelling of concentration-response relationships; risk coefficients

A two-stage random effects model was used, as had been developed for the HEI Reanalysis (Health Effects Institute, 2000), involving adjustment for confounders at the individual level using Cox regression methods, followed by regression of the adjusted county-specific mortality rates on ecological-level risk factors, including sulphate pollution.

Results

The rate ratios (RRs) of mortality from sulphate exposure are much higher in the county analysis than in the metropolitan analysis. For example, adjusted for multiple covariates, the county analysis gave an estimated RR of 1.32 (95% CI 1.12–1.56) compared with 1.17 (95% CI 1.05–1.31) for the MSA analysis. Cross-reference with results from Pope *et al* (1995) strongly suggests that these RRs refer to the difference in annual average sulphates between lowest and highest polluted counties or MSAs. The range of sulphate pollution was similar in both analyses, at about 20 $\mu g/m^3$ (mean 11.2, range 3.8–24.1 $\mu g/m^3$ county scale, mean 10.6, range 3.6-23.5 $\mu g/m^3$ for MSAs – Table 2 of Willis *et al*). Also, the proportion of those with high school education – identified in Pope *et al* (1995, 2002) as the major individual-level confounder and effect modifier – was similar in both analyses, at 68%.

In addition, analyses at the county scale were more robust to the inclusion of other ecologic variables in the analysis. In particular, in two-pollutant models, SO_2 was not statistically significantly associated with either all-cause or cardiopulmonary mortality, when sulphates were in the model. The sulphate coefficient in county scale analyses, with inclusion of SO_2 in the model, was reduced but not markedly so, and remained clearly significant statistically (Tables 4 and 5 of Willis *et al*). In models including sulphates, the SO_2 coefficient for all-cause mortality was 1.12 (0.97–1.28) in county scale analyses compared with 1.27 (1.15–1.40) in metropolitan area analyses. Conversely, in the same models, i.e. including SO_2, the coefficient for sulphates was higher in county scale analyses than in metropolitan area analyses.

Thus, analyses at the county scale did not support an independent effect of SO_2. (The Pearson correlation coefficient between SO_2 and sulphates was similar, at 0.48 and 0.56, respectively, in the metropolitan area and the county-scale analyses.)

Discussion, interpretation, implications

The authors attribute the difference in risk coefficients between their study and the ACS study (Pope *et al*, 2002) to using sulphate concentration data at a finer (county) scale rather than at the scale of city/metropolitan area.

We do not know very much about the spatial scale of variability in sulphate concentrations in the UK. It is expected to be less variable than $PM_{2.5}$ for which the primary component is variable across urban areas.

Filleul *et al* (2005)

Design and subjects

This is a cohort mortality study based on 24 areas in seven French cities, selected to provide contrasting kinds and concentrations of air pollution. It comprises a mortality follow-up from enrolment in 1974–1976 up to June 2001(all-cause) or end of 1998 (cause-specific) of subjects of the PAARC survey of air pollution and chronic respiratory diseases. Subjects were to be enrolled if, in 1974–1976, they were French, aged 25–59 years, had been resident in the area for at least three years and were not manual workers. Information (1974–1976) was available on characteristics including age, sex, physique, smoking habits, educational status and occupational exposures. Results are based on 14,284 subjects whose vital status was determined. Results from a 10% random sample showed that, after 25 years, 60% still lived in the same region, 41% in the same town.

Assessment of air quality

The study areas were quite localised, varying in diameter from 0.5 to 2.3 km. A special monitoring site was set up in a central location in each of the 24 study areas, with daily measurements over three years 1974–1976. Pollutants measured were PM (TSP by gravimetric method, BS by reflectometry), sulphur dioxide (specific SO_2 and acidimetric method), nitrogen dioxide (NO_2, colorimetric analysis), and nitric oxide (NO). Sulphates were measured over shorter periods within 1974–1976.

Results showed that measurements from six of the 24 areas were strongly influenced by local ('roadside') traffic pollution, i.e. with ratios of NO/NO_2 higher than three. These were excluded from some analyses, leaving 18 areas in six cities.

Data from ongoing monitoring networks were available in most of the cities for the later years of 1990–1997. These showed very much lower annual average concentrations in 1990–1997 than in 1974–1976 for BS and for SO_2, but not for NO_2. Data, available only for the four areas of Bordeaux, showed clear reductions in BS within five years. Limited information suggested that the reductions in BS and SO_2 over 20 years did not much affect the rankings of the areas and cities.

Modelling of concentration-response relationships; risk coefficients

Cox proportional hazards modelling was used, with age as the underlying time dimension, to estimate the effects of pollution 1974–1976 on the age-specific risks of mortality over the 25-year follow-up period. Analyses adjusted for individual-level confounders, stratifying by gender. A random effects component based on frailty modelling was used to take account of spatial autocorrelation. Results suggested that the adjustment did not entirely remove spatial autocorrelation.

Results from all 24 areas showed no clear or consistent effects of air pollution on mortality. However, after exclusion of six areas whose pollution data were dominated by local traffic sources, particles (both TSP and BS) and oxides of nitrogen (both NO_2 and NO) were statistically significantly related to mortality from all non-accidental causes. The adjusted risk ratios (95% CI) for TSP, BS, NO_2, and NO for non-accidental mortality were 1.05 (1.02–1.08), 1.07 (1.03–1.10), 1.14 (1.03–1.25), and 1.11 (1.05–1.17) for 10 $\mu g/m^3$, respectively.

All four pollutants also showed elevated risks of cardiopulmonary mortality, with estimated risks for TSP and NO_2 being statistically significant. NO_2 was the only pollutant clearly related to risk of lung cancer mortality. Restricting analyses to the first ten years of mortality follow-up gave similar risk estimates but greater variability, because of the smaller numbers of deaths.

Discussion and interpretation

This is a European cohort mortality study which showed statistically significant associations between annual average air pollution in 18 areas of six cities (1974–1976) and the subsequent age-specific mortality of adults resident in those areas at start of follow-up. Within this framework, however, there are issues/questions to be considered.

> *Exclusion of areas with monitoring stations heavily influenced by local (roadside) traffic*
> The authors' view seems reasonable, that measurements from these stations were not representative of general background pollutant concentrations as experienced by the resident populations, and so that these areas should be excluded from the main analyses.
>
> *Associations with oxides of nitrogen, especially with NO_2* No such associations were found in the ACS study. Associations with NO_2 are often interpreted as reflecting a more general effect of traffic pollution, rather than a substance-specific effect of NO_2 *per se*. It is notable that, in contrast to PM (i.e. TSP and BS) and to SO_2, annual average concentrations of NO_2 did not decline over the 25 years of mortality follow-up. It is plausible that the observed reductions reflect control of domestic and industrial emissions from burning fossil fuels, without corresponding reductions in traffic pollution, so that by the end of follow-up traffic pollution was the major source of pollution, and so of between-area differences. If so, it would not be surprising that associations with pollution were evident with NO_2 as a marker of traffic-related pollution.

Lack of associations with SO_2 While contrasting with the general ACS study results, a lack of association with SO_2 is consistent with the results from Willis *et al* (2003), discussed earlier. Results from the Hong Kong intervention study (Hedley *et al*, 2002) show, however, that it would be a mistake to generalise that SO_2 associations are not observable for analyses at a small spatial scale.

Associations with PM These of course are of particular interest. Superficially, the results might seem to be straightforward. Black smoke is the measure closest to $PM_{2.5}$ as used in the ACS study; and the 'headline' coefficient of 1.07 (95% CI 1.03–1.10), per 10 μg/m^3 annual average, is very similar to that for $PM_{2.5}$ from the ACS study. However, the Filleul *et al* (2005) results refer to exposure at the start of follow-up, rather than averaged over the follow-up period; and the estimated reduction in BS over the period of the 25-year follow-up in the PAARC study is much greater than the corresponding reductions in $PM_{2.5}$ in the ACS study. Thus, the absolute annual average concentrations used in Filleul *et al* (2005) may be substantially too high as surrogates for concurrent pollution throughout the follow-up. Also, though the rankings of areas and cities have been preserved, concentrations at the start of follow-up will have increasing measurement error as follow-up progresses; and, with an ageing cohort, much of the mortality will have occurred late in the follow-up. (Data from the paper show about 20% of deaths occurred in the first ten years, covering 40% of the follow-up period.) These considerations suggest that concurrent measurement of pollution might have led to considerably higher estimates of the risks associated with BS than those given in the paper.

In conclusion, then, the results of Filleul *et al* (2005) do seem consistent with a general pattern, that in cohort mortality studies, analyses based on small spatial areas lead to higher estimates of PM-related risks of mortality than the analyses on the wider scales of US metropolitan areas which underlie the main ACS study results.

Jerrett *et al* (2005)

Design and subjects

Jerrett *et al* (2005) set out to study the association between long-term exposure to air pollution and mortality *between communities within a city*, using data from the ACS study. They chose Los Angeles because it is a large area, with large differences in air pollution between locations, and sufficient ACS subjects. Collating and analysing data at the zip code scale, their study involved 22,905 ACS subjects (5956 deaths) from 267 zip code areas.

Assessment of air quality

$PM_{2.5}$ concentrations have been interpolated from measurement data at 23 locations. This number of sites is consistent with providing estimates of the variation in urban background concentrations at zip code centroids. Concentrations have been estimated for the centroids of zip code areas, which have a typical area of about 22.5 km^2, which would be a square with sides of roughly 5 km. The zip code centroid locations are typically 3–4 km apart with a minimum distance of about 1 km.

A map is presented of $PM_{2.5}$ concentrations in the Los Angeles area in 2000 (HEI Reanalysis). This map is consistent with the monitoring results and map provided on the South Coast Air Quality Management District website (www.aqmd.gov). $PM_{2.5}$ concentrations are highest in the east of the area at Riverside. Sulphate and NO_2 are, however, generally highest in central Los Angeles.

The paper states that the interpolation was calculated on to a 25 m grid. Variations in concentrations at a scale of 25 m will not be captured by an interpolation of monitoring data. Such an analysis would require detailed emission inventory based dispersion modelling and would not provide representative data for the zip code area average in any case. Thus the scale of analysis is not 25 m but is closer to a scale of 1–5 km. This is intermediate between the MSA-type analysis of the ACS and small scale analyses of Hoek *et al* and similar to the spatial scale at which UK concentrations will be assessed when illustrative calculations are carried out within QUARK II.

It should be noted that the range of modelled $PM_{2.5}$ concentrations within Los Angeles was, at 20 μg/m^3, greater than the range of 16 μg/m^3 between cities as studied by Pope *et al* (2002).

Any interpolation will, of course, be dependent on the spatial distribution of the monitoring sites, how representative they are, and the interpolation methods used. Starting from paragraph 565, the Air Quality Expert Group (AQEG) PM report (Defra, 2005) describes a similar interpolation study for PM_{10} in London. In this instance the interpolated surfaces were not considered to be representative of gradients across the city.

In addition, the impact of traffic was assessed "by assigning buffers that included zip code-area centroids within either 500 or 1000 meters of a freeway". The zip code areas are quite large compared with the 500 or 1000 m buffers applied to assess proximity to freeways. It is therefore likely that exposure to additional $PM_{2.5}$ from freeways will not have been very well classified (the paper acknowledges the imprecision).

Peak ozone concentrations only were considered, using interpolation from measurement data from 42 sites. There was no assessment of average ozone levels.

Limited information on residential mobility suggested that mobility, and associated exposure misclassification, were limited. There is of course some misclassification in that many individuals will spend a substantial amount of time away from their zip code of residence.

Modelling of concentration-response relationships; risk coefficients

An extension of Cox regression analysis methods was used, adjusting for 44 individual confounders and eight ecological confounders.

Controlling only for individual-level confounders gave an estimated relative risk (RR) of 1.17 (95% CI 1.05–1.30) compared with the corresponding estimate of 1.06 in Pope *et al* (2002), using recent or average exposure data. Further adjustment for ecological confounders reduced the estimated relative risk from 1.17 to 1.11 (95% CI 0.99–1.25). There was only weak evidence of a further effect of living near freeways.

Discussion and interpretation

Los Angeles has seen amongst the smallest decline in $PM_{2.5}$ since 1980 within the ACS cities. The ranking of $PM_{2.5}$ concentrations at eight monitoring sites in 2000 is similar to that of PM_{10} in 1993. Taking these two facts together, the 2000 $PM_{2.5}$ exposure is probably the best exposure measure for this study.

Jerrett *et al* consider that modelling concentrations at a finer spatial scale contributed to, and substantially explained, the higher coefficients found in their study, relative to the ACS update.

Some differences between the ACS sub-cohort in Los Angeles and the full cohort would have been expected to lead to *smaller* risk coefficients in Los Angeles. Less reduction in air pollution may have increased the Los Angeles coefficient, but not greatly.

However, the paper notes that the proportion of primary $PM_{2.5}$ from traffic is higher in Los Angeles (3.7%) than in the USA as a whole (0.75%) in 1999. It should be noted that this is only primary PM emissions, there is also a large component from secondary PM, not directly emitted. Jerrett *et al* conjecture also that the greater 'loading' from traffic of PM in Los Angeles compared with the ACS cities generally may have contributed to the higher coefficients.

Conclusions and implications

Conclusions

These results variously show higher estimated relative risks linking particulate pollution and mortality when concentration data are gathered at a finer spatial scale than the metropolitan areas used in the main analyses of the ACS study (Pope *et al*, 1995, 2002; Health Effects Institute, 2000). They strongly suggest, and indeed in their different ways both the county-scale analyses of Willis *et al* (2003) and the within metropolitan area analyses of Jerrett *et al* (2005) actually show that were it possible to analyse the ACS cohort as a whole on a fine spatial scale, then this would lead to higher estimates of relative risks than those of the main ACS study – whether original, reanalysis or update.

The reasons for the differences appear to be a combination of the following:

a. the use of concentration data at a finer spatial scale reduces misclassification error and the associated attenuation of risk estimates;

b. there may be a correlation between high local concentrations and PM that is relatively 'dense' with traffic pollution.

Implications

Risk coefficients for the USA

These studies on a smaller spatial scale do not give risk coefficients which are easily generalisable, transferable and so usable for quantification in the UK. They do, however, strongly suggest that, rather than being unfeasibly high, the risk coefficients from the main ACS analyses, including the update study, may substantially *underestimate* the true relationships between long-term (annual average) exposure to PM and mortality.

Transferability to Europe – traffic contribution to PM

These values of the traffic contribution are much lower than for European situations, where we have an additional PM source of diesel cars and light goods vehicles, in addition to the diesel heavy-duty vehicles seen in the USA and in Europe. Traffic exhaust emission contributed 25% of total UK primary PM_{10} emissions in 2002 according to the NAEI (Dore *et al,* 2004) and 34% of primary $PM_{2.5}$. The proportion of total emissions from traffic exhaust is expected to decline to about half the 2002 value by 2020 as a result of tighter European standards for new vehicles.

Coefficients for use in Europe

These studies on a smaller spatial scale do not give risk coefficients that can easily be generalised, transferred and so used for quantification in the UK. We think that the working policy of basing coefficients on the Pope *et al* (2002) ACS update remains the best policy. However, the joint implication of the results, summarised in the previous two paragraphs, is that

a the ACS design and analyses may *underestimate* the coefficients that would have been found had modelling on a finer spatial scale been possible;

b the ACS coefficients may further *underestimate* effects in the UK (in Europe) because of the greater contribution of traffic to PM in UK (in Europe).

The linked issues of spatial scale and traffic pollution alone therefore support the use of risk coefficients at the higher end of those reported by Pope *et al* (2002), or higher (e.g. from the Six Cities study, Dockery *et al*, 1993). We recognise, however, that other factors are also important, and may operate in the opposite direction. These are being considered by others within QUARK II.

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Working Paper 9

Plausibility of Coefficients for Long-Term Exposure to Particles and Mortality[1]

Heather Walton and Ben Armstrong

A range of coefficients has been reported for long-term exposure to particles and mortality from 1% right up to 17% (see Figure 3.5, in the main text, page 35). Are all of these coefficients plausible?

We approached this by

a taking a historical change in air pollution;

b predicting the expected effect on death rates or life expectancy from this change in air pollution using the relevant coefficient;

c comparing the prediction against the actual change in death rates or life expectancy that occurred.

This approach is very approximate because:

a particle metrics were different in the past;

b the composition of particle mixtures changes over time;

c many other factors that change over time affect death rates and life expectancy.

Thus, this approach is only intended to pick up whether any of these coefficients is *grossly* implausible.

The first section in this paper examines more recent pollution changes. The second examines longer term pollution changes while acknowledging the greater uncertainties that this entails.

Pollution change from 1970–2000

Coefficient of 6% per 10 μg/m^3 increase in $PM_{2.5}$

Stedman (2002) developed a model relating emissions of particles to concentrations and validated this against measured data. This model was then used to calculate retrospectively what PM_{10} concentrations might have been in the years before PM_{10} monitoring started in 1992. PM_{10} estimates for selected years were extracted from Figure 2 of the paper. These were

[1] It has been suggested that the analysis of the plausibility of the coefficients could be refined by examining trends in rural mortality rates (that might be expected to give a rough representation of trends in mortality rates less affected by air pollution) and by examining trends in cardiovascular mortality rates in addition to trends in all-cause mortality rates. These are useful ideas and, subject to availability of appropriate data, we hope to look into this at a later date.

Table 1: Estimated annual mean $PM_{2.5}$ at London, Bloomsbury, 1970–2000 and resulting predicted percentage change in age-standardised mortality rate using coefficient of 6%

Year	$PM_{2.5}$ µg/m³ (estimated from PM_{10})* (TEOM)	Predicted % change in age-standardised mortality rate at 1.06 per 10 µg/m³ increase in $PM_{2.5}$	Actual % change in age-standardised mortality rate relative to 1970 (men)	Actual % change in age-standardised mortality rate relative to 1970 (women)	Predicted % change from changes in smoking prevalence (men)	Predicted % change from changes in smoking prevalence (women)
1970	26.4	Reference	Reference	Reference	Reference	Reference
1980	20.4	-3.4%	-11.0%	-11.1%	-5.5%	+1.6%
1990	18.6	-4.4%	-25.4%	-23.9%	-11.7%	-0.8%
2000	12.6	-7.7%	-39.4%	-33.5%	-17.2%	-4.1%

* Derived from retrospective modelling by Stedman (2002), $PM_{2.5}$ assumed to be PM_{10} multiplied by 0.6. Measured using a tapered element oscillating micro-balance (TEOM).

then converted to $PM_{2.5}$ estimates using a factor of 0.6. Table 1, column 2, shows the estimates for London, Bloomsbury, for the selected years.

The concentration changes in 1980, 1990 and 2000 relative to 1970 were then calculated. The predicted changes in age-standardised mortality rate corresponding to these concentration changes were then derived using the appropriate coefficient from the ACS study (in this case 1.06 per 10 µg/m³ increase in $PM_{2.5}$)[2]. (For simplicity, there was assumed to be no lag between change in pollution and change in mortality rate.) These predicted changes are shown in column 3 of Table 1.

These predicted changes were then compared with the actual change in age-standardised mortality rate. Age-standardised mortality rates for men and women in England and Wales (relative to the European standard population) were obtained from the Office for National Statistics (Griffiths and Brock, 2003)[3]. Columns 4 (men) and 5 (women) give the actual percentage change in age-standardised mortality rate in the relevant year relative to the age-standardised mortality rate in 1970. These can be compared with the predicted change in

[2] Percentage change derived from $(1.06^{0-\Delta c/10}) - 1$ where Δc = concentration change for the relevant time period relative to the reference concentration in 1970 (26.4 µg/m³), e.g. Δc = 6.0 µg/m³ for 1980 and the predicted % change is $(1.06^{0-6/10}) - 1 = -0.034$ or -3.4%. (For small relative risks, simple multiplication of the 0.6% hazard rate reduction per µg/m³ $PM_{2.5}$ by the relevant concentration change gives a reasonable approximation. The more complex equation is used because the model used by Pope *et al* (2002) is on a multiplicative scale.)

[3] The age-standardised mortality rates in 1970 (reference) were 1,395.68 per 100,000 for men and 851.99 per 100,000 for women. The equivalent rates for 1980, 1990 and 2000 were 1,290.08, 1,040.65 and 845.50 for men and 757.06, 648.66 and 566.33 for women.

mortality rate due to the pollution change in the third column[4]. The table shows that, over the 30-year interval from 1970 to 2000, age-standardised mortality rates declined by 39.4% for men and 33.5% for women. Estimated $PM_{2.5}$ declined by 13.8 μg/m^3 over this time, giving a predicted mortality decline of 7.7% over the same period for a relative risk of 1.06 per 10 μg/m^3 increase in $PM_{2.5}$. This is a substantial but not excessive proportion of the observed decline.

The predicted changes in mortality rates in the third column only take account of pollution changes and there are of course many other factors influencing the observed age-standardised mortality rate changes in columns 4 and 5. One of the more obvious other factors is smoking. It is possible to derive an approximate prediction of the likely contribution of changes in smoking trends to the changes in age-standardised mortality rates. The relative risk for a smoker compared with a non-smoker is around two for all-cause mortality[5]. This relative risk can be applied to the number of smokers in the population to give the predicted change in mortality rate for the population as a whole. The effect of smoking is not apparent instantly, so some account needs to be taken of the delay before risks change. Smoking affects mortality predominantly through three causes of death: lung cancer (long average latent interval), respiratory disease (medium latent interval) and cardiovascular disease (short latent interval). For all-cause mortality, there will be a compromise between these effects of past smoking and recent smoking for the different causes. Because cardiovascular disease is dominant in terms of numbers of smoking-related deaths overall (Doll *et al,* 2004), we will use smoking prevalence five years before the year for which the rate adjustment is required.

Smoking prevalence has decreased from 45% in men over 60 years of age in 1965 (five years before the reference year 1970) to 20% in 1995 (Peto *et al,* 2000)[6]. In women over 60 it has declined from 23% in 1965 to 18% in 1995. The predicted changes in age-standardised mortality rate as a result of these changes in prevalence are shown in columns 6 and 7 of Table 1[7]. Compared with the actual decline in age-standardised mortality rates of 39.4% for men and 33.5% for women over the 30-year interval from 1970 to 2000, the predicted

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[4] This comparison assumes that the pollution reductions at London, Bloomsbury, are reasonably representative of changes across England and Wales (age-standardised mortality rates are for the whole of England and Wales). In fact, the decline in London is probably amongst the largest declines in the UK so probably overestimates the overall changes in England and Wales. The comparison also assumes that the relative risk for $PM_{2.5}$ of 6% for both sexes combined can be used in a comparison with separate age-standardised mortality rates for men and women. Pope *et al* (2002) looked at relative risks for $PM_{2.5}$ separately for men and women. The relative risk was higher in men than in women but the confidence intervals overlapped and the sex differences were not statistically significant.

[5] In the HEI Reanalysis of the ACS study the relative risk for current smokers was 2.07 (Health Effects Institute, 2000).

[6] The prevalence in men over 60 years of age was 16% in 1998 and 20% in 1995 (five years before 2000). Equivalent figures for 1975 and 1985 were 37% and 25%. The prevalence in women over 60 years of age was 16% in 1998 and 18% in 1995. Equivalent figures for 1975 and 1985 were 25% and 22%. (The over 60 age group was chosen as this is the age group for most of the deaths.)

[7] The predicted changes were calculated as follows. We assumed that, for a given sex, overall mortality in year y is

$$M_{NS,y}[(1 - p_{y-5}) + R\,p_{y-5}]$$

where $M_{NS,y}$ is the mortality in non-smokers in year y, p_{y-5} is the prevalence of smoking in the year relevant to y (ie y-5), and R is the relative risk for all-cause mortality in smokers relative to non-smokers. Thus the change due to smoking change alone (i.e. if $M_{NS,y} = M_{NS}$) in year y relative to year 1970 is

$$[(1 - p_{y-5}) + R\,p_{y-5}]/[(1 - p_{70-5}) + R\,p_{70-5}]$$

changes due to smoking were a decline of 17% in men and a more modest decline of 4% in women over the same period. The declines in actual rates *unexplained by smoking* are thus 39.4 – 17 = 22.4% and 33.5 – 4 = 29.5%, still considerably larger than the 7.7% decline predicted to be due to the decline in $PM_{2.5}$. The decline unexplained by smoking was considerably larger than the decline predicted from changes in $PM_{2.5}$ for each decade as well as overall.

Coefficient of 17% per 10 μg/m³ increase in $PM_{2.5}$

It was considered useful to use this approach to test the plausibility of some of the higher possible coefficients. These coefficients may not be likely to be chosen as the central coefficient but they will form part of the discussion of uncertainty. A 'reality check' would help inform the weight that might be given to these coefficients when commenting on uncertainty ranges around the central coefficient.

A coefficient of 17% per 10 μg/m³ increase in $PM_{2.5}$ was chosen to investigate. This size of coefficient was found by Jerrett *et al* (2005) in Los Angeles and by Hoek *et al* (2002) for black smoke in the Netherlands. It is just above the coefficient found in the Six Cities study. The calculations performed are analogous to those for the coefficient of a 6% increase in age-standardised mortality rate per 10 μg/m³ increase in $PM_{2.5}$. The results are shown in Table 2.

Table 2: Estimated annual mean $PM_{2.5}$ at London, Bloomsbury, 1970–2000 and resulting predicted percentage change in age-standardised mortality rate using coefficient of 17%

Year	$PM_{2.5}$ μg/m³ (estimated from PM_{10}) (TEOM)	Predicted % change in age-standardised mortality rate at 1.17 per 10 μg/m³ increase in $PM_{2.5}$	Actual % change in age-standardised mortality rate relative to 1970 (men)	Actual % change in age-standardised mortality rate relative to 1970 (women)	Predicted % change from changes in smoking prevalence (men)	Predicted % change from changes in smoking prevalence (women)
1970	26.4	Reference	Reference	Reference	Reference	Reference
1980	20.4	-9.0%	-11.0%	-11.1%	-5.5%	+1.6%
1990	18.6	-11.5%	-25.4%	-23.9%	-11.7%	-0.8%
2000	12.6	-19.5%	-39.4%	-33.5%	-17.2%	-4.0%

The proportion of the observed decline predicted by air pollution using this higher coefficient is less easily believable at up to around 60% of the total. However, it is not impossible if the decline is counterbalanced by increases in death rates due to other factors. In other words, the observed decline is a *net* decline.

An increase in death rates due to smoking is an obvious candidate for counterbalancing a possible reduction in death rates due to air pollution. However, over the period covered in Table 2 smoking rates have been declining in both sexes. If, as has been assumed, there is less

delay for smoking-related circulatory diseases and these deaths dominate overall smoking-related deaths, then smoking does not in fact counterbalance but rather also predicts a decline. Indeed, for men, the actual decrease in mortality unexplained by smoking (22.4%) is close to the total 19.5% decrease predicted using this higher coefficient for $PM_{2.5}$, though this is not true for women(29.5% vs 19.5%).

There were examples of other factors which were increasing death rates at the same time as the predicted reduction in death rates due to pollution (e.g. those causing increasing death rates for suicide, prostate cancer, diabetes and liver disease) (Office for National Statistics, 2003). Therefore, although the higher coefficients might predict a greater reduction in death rates than occurred in practice, this could potentially be explained by a counterbalancing increase in death rates due to other factors. Of course, other factors might also have decreased mortality, making the predicted reduction due to $PM_{2.5}$ less plausible.

In summary, calculations which use a 6% unit increment in mortality due to $PM_{2.5}$ and do not involve concentrations above the range of the American Cancer Society (ACS) study do not produce predicted mortality changes implausible in relation to actual changes. For the higher coefficient of 17% the predicted drop in age-standardised mortality rate is quite a high proportion of the actual drop in age-standardised mortality rate observed and in men closely approaches the reduction unexplained by smoking, calling into question its plausibility. It is possible that this is counterbalanced by increases in death rates due to other factors, though we have not explored this further.

Pollution change from 1954–2000

This section considers whether the coefficients examined (6 and 17%) would be plausible when considering the larger pollution changes that have occurred since the mid-1950s. There are more uncertainties in this, as UK particle levels in the 1950s were above the top end of the range of 1979–1983 particle levels in the ACS study (although probably not above the range experienced in the USA in the 1950s). In addition, the nature of the pollution has changed from coal-smoke-dominated to traffic-dominated pollution. Use of coefficients from the ACS study to cover this period thus involves additional extrapolation.

The paper by Stedman (2002), used to derive $PM_{2.5}$ in the previous section, did not estimate particle levels back further than 1970. So a more approximate approach would have to be taken to estimate earlier $PM_{2.5}$ levels[8]. It is clear that steep declines in $PM_{2.5}$ are likely to have occurred. Black smoke levels declined from 200–275 $\mu g/m^3$ in the 1950s[9] to around 40 $\mu g/m^3$ in 1970 to around 7 $\mu g/m^3$ in 2000[10].

[8] There are data on black smoke levels and on sulphate and nitrate levels back to 1954. In combination with approximate scaling factors, possible $PM_{2.5}$ levels could be inferred but these would be subject to considerable uncertainty.

[9] Mean across all London sites derived from Warren Spring Laboratory Annual Reports published by the Ministry of Technology or Department of Scientific and Industrial Research each year from 1954 to 1961.

[10] Mean across all London sites derived from the Air Quality Archive: www.airquality.co.uk.

Age-standardised mortality rates dropped by around 40% in both men and women from 1954 to 2000 and smoking prevalence in the over 60 age group dropped by 19% and 4% in men and women, respectively, from 1949 to 1995[11].

Broadly, declines in air pollution from 1954–2000 were much greater than from 1970–2000, whereas the drop in age-standardised mortality rate from 1954–2000 was only slightly greater than that from 1970–2000. If the relationship with air pollution were linear, a greater observed reduction in age-standardised mortality rate might have been expected. This is not likely to be explained by a counterbalancing increase in mortality rates due to smoking as smoking prevalence fell overall during this period.

The above view assumes no change in the shape of the relationship at concentrations above the range of the ACS study. This may not be the case. It is known from time-series studies that concentration-response relationships tend to flatten off at high concentrations (Schwartz *et al,* 2002). A curve in the logarithm of exposure as well as a linear relationship can be fitted to the ACS data. This curve flattens off at higher concentrations. This was used in sensitivity analysis in the Global Burdens of Disease project (Cohen *et al,* 2004). If such a curve does apply, then a less dramatic reduction in age-standardised mortality rate might be more compatible with the steep decline in air pollution over the same period.

So, for larger increments going back further in time, the plausibility of the 6% coefficient may be more doubtful if the relationship is still linear but not if the relationship flattens off.

As there was a question over the plausibility of the 17% coefficient for the smaller decline in pollution from 1970–2000, this is also likely to be true for 1954–2000. (The coefficient of 17% comes from studies conducted at a smaller spatial scale at which contrasts in exposure to particles from traffic are likely to be greater. The applicability of this coefficient to past changes in coal-smoke-derived particles thus probably has a greater degree of uncertainty than for the 6% coefficient.)

Conclusions

In conclusion, using the relative risk of 1.06 per 10 μg/m^3 increase in $PM_{2.5}$ to predict expected changes in mortality rate due to pollution changes over the last 30 years does not give implausible results compared with the observed decline. There is more uncertainty about the plausibility when predicting expected changes due to larger pollution reductions over the last 46 years. The earlier 16 years are less relevant for the plausibility of the coefficient for lower concentrations. Overall, the 6% coefficient would not be regarded as grossly implausible.

The changes predicted by using a relative risk of 1.17 per 10 μg/m^3 increase in $PM_{2.5}$ are less believable, although for pollution changes over the last 30 years, the changes could perhaps be counterbalanced by other factors increasing mortality rates. For pollution changes over the last 46 years, the predicted changes are likely to be more clearly implausible, particularly when a linear relationship is assumed.

[11] Smoking prevalence in the over 60 age group rose slightly in men in the 1960s and 1970s and in women in the 1970s and 1980s.

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Working Paper 10

Members' Expression of Uncertainty Regarding the Coefficient Linking the Relative Risk of Death from All-Causes to Long-Term Exposure to $PM_{2.5}$

Secretariat

Typically the 95% confidence interval is used to express the sampling (statistical) uncertainty (around the coefficient) inherent in a particular study. This interval, however, does not capture other aspects of uncertainty considered by the Committee in choosing a coefficient for use in quantification[1]. The Committee thought it important that these additional sources of uncertainty be reflected in their final recommendation.

After consideration, an exercise was conducted to elicit Members' views regarding the uncertainty surrounding their recommended estimate of the coefficient relating all-cause mortality to $PM_{2.5}$ (annual average concentration). It was agreed that Members should be asked to indicate their views regarding the range of uncertainty from all-causes in such a way that their views could be synthesised and reported.

Members were asked to express their confidence in the sequential assertions that the real coefficient exceeded 0, 1, 2,…, 17% by placing a percentage probability against each given value[2,3]. Their contributions were collated and average probabilities, calculated as the arithmetic means of the individual responses, were ascribed to each potential value of the real coefficient.

The collated results are given in Table 1. The individual responses, given in this table, were used to derive the aggregate probabilities assigned to each potential value of the real coefficient [see Figure 3.6 (page 44), repeated again, as Figure 4, in this working paper].

Figure 1 shows plots of the distribution of each Member's probabilities assigned to the range of coefficients. Figure 2 is another way of representing the same information. However, the reader can readily note the differences, between Members, in the probabilities assigned to a particular coefficient. Figure 3 shows the cumulative probabilities, derived from the arithmetic means of the individual responses.

Table 1 shows the average (arithmetic mean) and median probabilities assigned by Members to indicate their belief that the true coefficient exceeded a given value in the range of 0 to 17% (seen at the top of each column). For example, on average, a probability of 96% was assigned to the coefficient being of any value greater than 0%.

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[1] A more detailed description of some sources of uncertainty is given in question xv, Chapter 3.

[2] Readers are asked to note that Members were not specifically asked to comment on coefficients less than 0%.

[3] Members were provided with a version of the forest plot – Figure 3.5 (page 35)– for the elicitation exercise as a summary of the evidence across the range of coefficients.

Table 2 shows for possible values of the coefficient, in the range of 0% to 17%, the arithmetic mean and median aggregate probabilities for each interval (e.g. >0≤1) derived from the percentage probabilities (given in the first shaded row in Table 1) averaged across the responses of Members. For example, on average a 4% probability (based on arithmetic means) was assigned to the coefficient being zero or less and about a 9% probability was assigned to the coefficient being above 0% but not more than 1% (i.e. including 1%).

The aggregate probabilities assigned to the coefficients above were used to generate the distribution given in Figure 4.

Table 1: Members' percentage probabilities assigned to a range of coefficients (0 to 17%) to indicate their belief in the true coefficient exceeding a given value

	Coefficient (%)																		
Member	**>0.99**	**>0**	**>1**	**>2**	**>3**	**>4**	**>5**	**>6**	**>7**	**>8**	**>9**	**>10**	**>11**	**>12**	**>13**	**>14**	**>15**	**>16**	**17**
A		99	95	90	80	75	70	65	60	50	45	40	35	30	25	20	15	10	5
B		99	95	80	60	50	45	40	35	30	25	20	15	10	5	4	3	2	1
C		87	82	77	71	64	57	50	43	36	29	24	19	15	11	8	6	4	3
D		95	50	40	35	30	25	20	15	10	7.5	5	4	3	2	1.5	1	0.5	0
E		99	97	92	88	77	65	55	47	42	38	32	26	19	13	10	7	4	2
F	97.5*	95	92.5	75	60	45	30	15	12.5	10	7.5	5	2.5	0	0	0	0	0	0
G		98	95	90	85	75	60	50	40	30	20	15	15	10	5	2	2	2	0
Average probability (%) (arithmetic mean)		**96.0**	**86.6**	**77.7**	**68.4**	**59.4**	**50.3**	**42.1**	**36.1**	**29.7**	**24.6**	**20.1**	**16.6**	**12.4**	**8.7**	**6.5**	**4.9**	**3.2**	**1.6**
Median probability %		**98.0**	**95.0**	**80.0**	**71.0**	**64.0**	**57.0**	**50.0**	**40.0**	**30.0**	**25.0**	**20.0**	**15.0**	**10.0**	**5.0**	**4.0**	**3.0**	**2.0**	**1.0**

* Readers are asked to note that Members were not specifically asked to comment on coefficients less than 0%.

The average (arithmetic means and medians) probabilities have been rounded to one decimal place. All other data in Table 1 are reported as provided by Members.

Table 2: Members' aggregate percentage probabilities assigned to a range of coefficients (0 to 17%)

	Coefficient (%)																	
Aggregate probability	**≤0**	**>0≤1**	**>1≤2**	**>2≤3**	**>3≤4**	**>4≤5**	**>5≤6**	**>6≤7**	**>7≤8**	**>8≤9**	**>9≤10**	**>10≤11**	**>11≤12**	**>12≤13**	**>13≤14**	**>14≤15**	**>15≤16**	**>16≤17**	**>17**
Arithmetic mean	**4.0**	**9.4**	**8.9**	**9.3**	**9.0**	**9.1**	**8.1**	**6.1**	**6.4**	**5.1**	**4.4**	**3.5**	**4.2**	**3.7**	**2.2**	**1.6**	**1.6**	**1.6**	**1.6**
Median	**2.0**	**3.0**	**15.0**	**9.0**	**7.0**	**7.0**	**7.0**	**10.0**	**10.0**	**5.0**	**5.0**	**5.0**	**5.0**	**5.0**	**1.0**	**1.0**	**1.0**	**1.0**	**1.0**

Figure 1: Distribution of probabilities assigned by Members to a range of coefficients (0 to 17%)

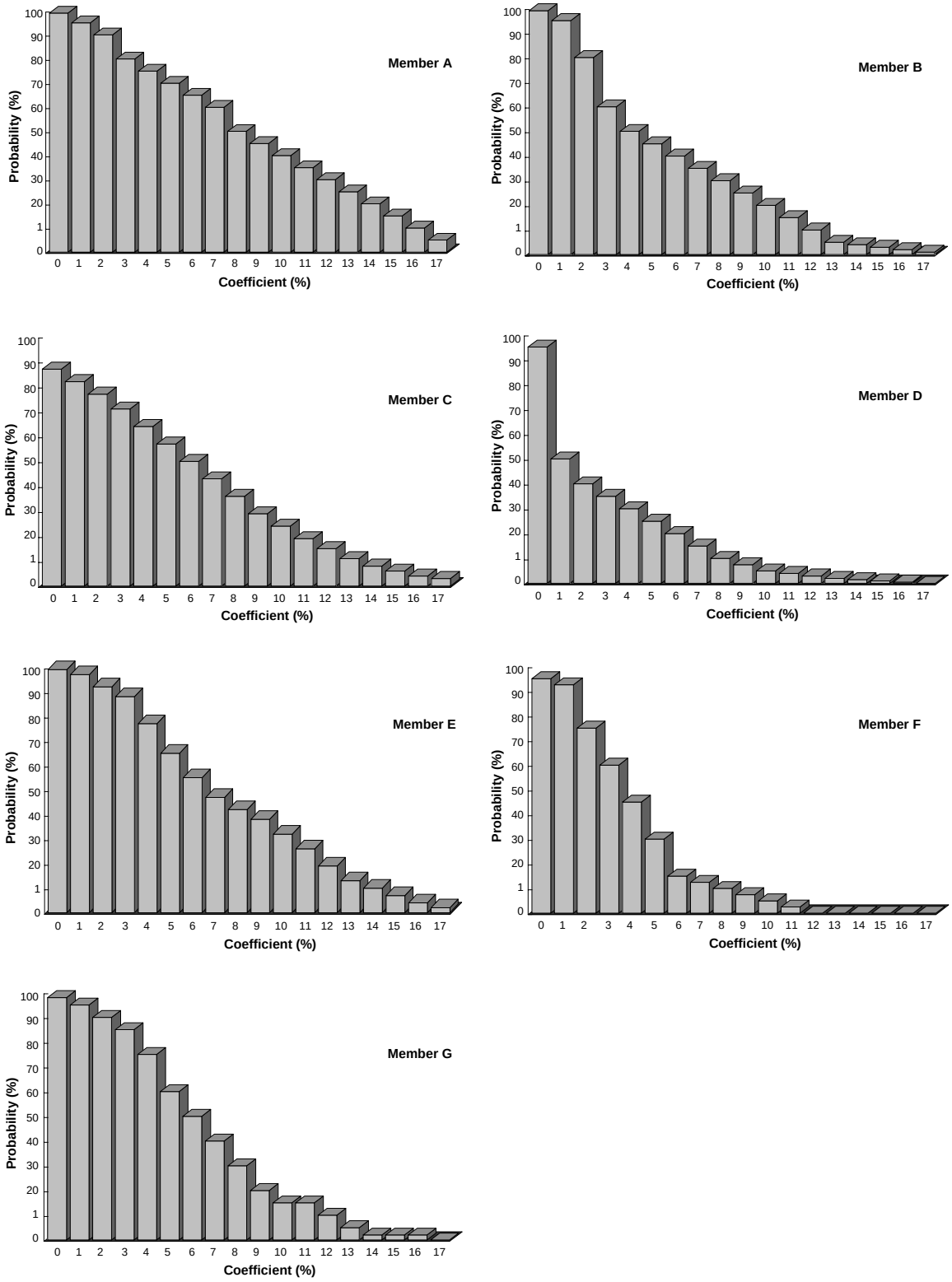


Figure 2: Comparison of probabilities assigned by Members to a range of coefficients (0 to 17%)

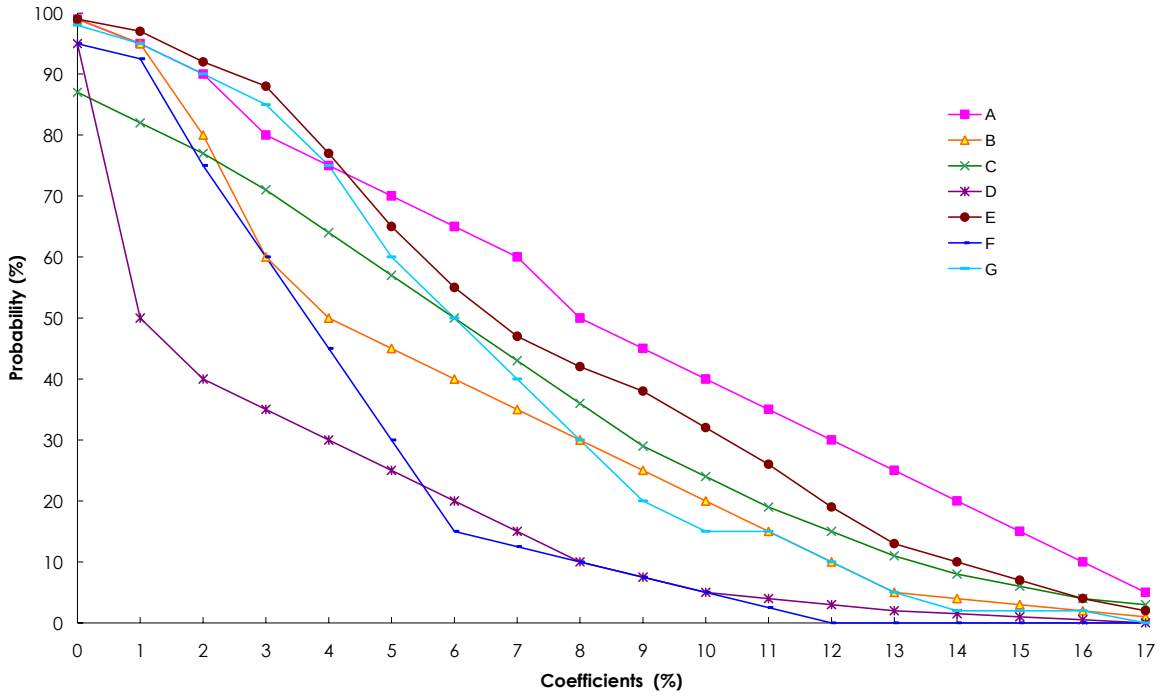


Figure 3: Cumulative average probabilities assigned by Members to a range of coefficients (0 to 17%)

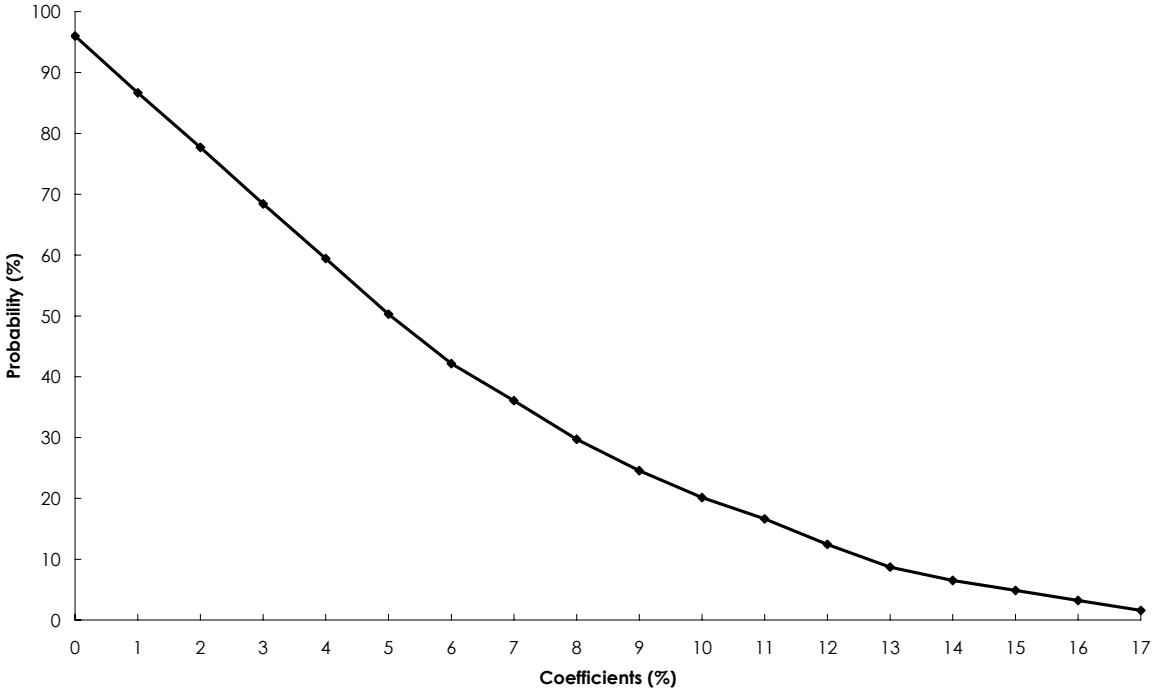
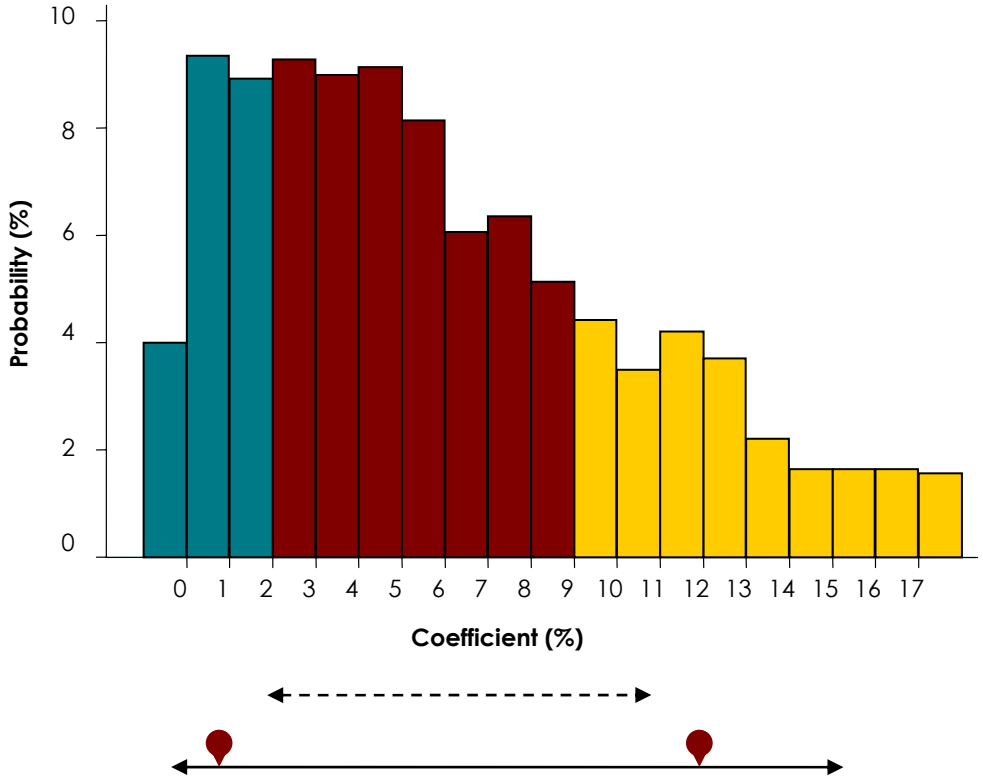


Figure 4: Distribution of Members' aggregate probabilities (calculated as the arithmetic mean of the individual responses) of the uncertainty regarding the coefficient linking all-cause mortality and an increase in long-term exposure to $PM_{2.5}$



The first bar represents the probability of the coefficient being 0 or less (no adverse effect) and the last bar of it being more than 17%.

The coloured areas of the histogram indicate the quartiles of the distribution:

blue – the 1st quartile, regarded as the 'low' band of the distribution;
red – the 2nd and 3rd quartiles, regarded as the 'middle' band of the distribution;
yellow – the 4th quartile, regarded as the 'high' band of the distribution.

The coefficients indicated on the abscissa refer to the relative risks discussed in the text, i.e. a coefficient of 5% corresponds to a relative risk of 1.05.

1.06 (1.02–1.11) relative risk of death of all-cause mortality and 95% statistical sampling confidence interval (CI) per 10 μg/m³ increase in $PM_{2.5}$ (as published by Pope *et al*, 2002).

1.06 (1.00–1.15) relative risk of death of all-cause mortality and Members' 95% plausibility interval per 10 μg/m³ increase in $PM_{2.5}$.

These indicate the typical 'low' (1%) and 'high' (12%) values suggested for use in sensitivity analysis. They represent the 12.5th and 87.5th percentiles of the overall plausibility distribution.

Appendices and Membership Lists

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

Professor of Occupational and Environmental Medicine
Medical Research Council (MRC)
Epidemiology Resource Centre (University of Southampton)

1.2 Professor P K Hopke

Bayard D Clarkson Distinguished Professor
Director of Center for Air Resources Engineering and Science (CARES)
Department of Chemical and Biomolecular Engineering, Clarkson University
Potsdam, New York
USA

1.3 Dr M Krzyzanowski

Regional Adviser, Air Quality and Health
Head of European Centre for Environment and Health, Bonn
World Health Organization

1.4 Dr B Ostro

Chief, Air Pollution Epidemiology Unit
California Environmental Protection Agency
Office of Environmental Health Hazard Assessment
Oakland, California
USA

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 35–36 [1] 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 SO_2, 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 report [2].

[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

Ito, K., Christensen, W.F., Eatough, D.J., Henry, R.C., Kim, E., Laden, F., Lall, R., Larson, T.V., Neas, L., Hopke, P.K., and Thurston, G.D. (2006) PM source apportionment and health effects: 2. An investigation of inter-method variability in associations between source-apportioned fine particle mass and daily mortality in Washington, DC. *J. Exp. Sci. Environ Epidemiol.* **16,** 300–310.

Laden F., Neas, L.M., Dockery, D.W., and Schwartz, J. (2000) Association of fine particulate matter from different sources with daily mortality in six US cities. *Environ. Health Perspect.* **108,** 941–947.

Laden, F., Schwartz, J., Speizer, F.E., and Dockery, D.W. (2006) Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard six cities study. *Am. J. Respir. Crit. Care Med.* **173,** 667–672.

Mar, T.F., Norris, G.A., Koenig, J.Q., and Larson, T.V. (2000) Associations between air pollution and mortality in Phoenix, 1995–1997. *Environ. Health Perspect.* **108,** 347–353.

Mar, T.F., Ito, K., Koenig, J.Q., Larson, T.V., Eatough, D.J., Henry, R.C., Kim, E., Laden, F., Lall, R., Neas, L., Stölzel, M., Paatero, P., Hopke, P.K., and Thurston, G.D. (2006) PM source apportionment and health effects. 3. Investigation of inter-method variations in associations between estimated source contributions of $PM_{2.5}$ and daily mortality in Phoenix, AZ. *J. Exp. Sci. Environ. Epidemiol.* **16,** 311–320.

Sarnat, J.A., Brown, K.W., Schwartz, J., Coull, B.A., and Koutrakis, P. (2005) Ambient gas concentrations and personal particulate matter exposures: implications for studying the health effects of particles. *Epidemiology* **16,** 385–395.

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.

Venkatachari, P., Hopke, P.K., Brune, W.H., Ren, X., Lesher, R., Mao, J., and Mitchell, M. (2007) Characterization of wintertime reactive oxygen species concentrations in Flushing, New York. *Aerosol Sci. Technol.* **41,** 97–111.

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 33 [3], 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 $\mu g/m^3$ decrease in annual average $PM_{2.5}$ levels. In addressing this question, the experts first specified a functional form for the $PM_{2.5}$ 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 $PM_{2.5}$), 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 (5^{th}, 25^{th}, 50^{th}, 75^{th}, and 95^{th}).

Of note, while the Pope *et al* (2002) study that you have used for your estimates suggests a 6% change in mortality per 10 $\mu g/m^3$ change in $PM_{2.5}$, the median estimate of the experts was from 7 to 16% per 10 $\mu g/m^3$ change in annual average $PM_{2.5}$ concentration. Experts in this study tended to be confident that $PM_{2.5}$ 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-μg/m³ increase in $PM_{2.5}$ 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 μg/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 5 [1]: 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

[1] 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

estimate per μg/m^3 than does generic $PM_{2.5}$ 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 $PM_{2.5}$.

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 μg/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 μg/m^3 than generic $PM_{2.5}$. Of those few studies that have examined both $PM_{2.5}$ 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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Appendix 2

COMEAP Response to Public Comment and Peer Review on the Draft Report *Long-Term Exposure to Air Pollution: Effect on Mortality*

The Committee wishes to thank all those who submitted comments to the Secretariat on its draft report *Long-Term Exposure to Air Pollution: Effect on Mortality* between July and August 2007. We respond here to some of the comments made on aspects of our report.

1 Additional publications

We note the comments made by reviewers regarding papers not considered in this report. That recent material could not be included was inevitable because much time needed to be devoted to considering evidence and distilling our conclusions after the evidence-collection phase was completed. A cut-off in early 2006 was adopted for published work which was considered in detail. We note that this, unfortunately, excludes an important and influential review by Pope and Dockery (2006) and recommend reading of that review to readers of this report.

2 Elicitation exercise

Another area of interest to those providing comments was our use of an elicitation exercise to provide a 'plausibility interval' around the central estimate for the coefficient relating long-term exposure to fine particles and mortality. Some welcomed this innovative approach; others were concerned that the elicitation process was insufficiently defined or that it was too subjective. Dr Bart Ostro provided particularly insightful and helpful comments reflecting his valuable experience and his involvement in an elicitation process run by the US Environmental Protection Agency (http://www.epa.gov/ttn/ecas/ria.html).

Those who contributed views for the elicitation exercise in this report were members of the COMEAP subgroup on quantification of air pollution risk (QUARK), and had thus been involved in reading circulated papers, contributing to discussions and drafting material as the main report developed. This familiarity was an advantage. The exercise also provided transparency as to the range of views amongst those that prepared the whole report.

We accept that different approaches to the elicitation exercise could have been taken. Any process like this is open to the argument that the conclusion could be influenced by the sophistication of the process. How important is this influence? A subtle difference in emphasis seems to us more likely than a major difference in the conclusion, if based on similar material at a similar date. We also accept that any view on the uncertainty around the central estimate could change substantially over time as new information becomes available. Nonetheless, we are firmly of the opinion that it is right to provide an assessment of uncertainty, provided it is acknowledged that this is based on information available at a particular point in time.

The main report discusses in detail many of the lines of reasoning that will have contributed to the judgements that individual members made. We are content that the elicitation exercise adequately represents our opinions and describes appropriately the uncertainties as we saw them. We note the debate that this relatively new approach has generated and we encourage further discussion of methodological issues amongst researchers and regulators in the field.

3 Larger coefficients

Another theme raised in the comments was a view that the central estimate of the coefficient linking long-term exposure to fine particles and mortality should be larger than 6%. This view was based on several studies that gave higher coefficients. These studies often defined exposure at a finer spatial scale than that used in the ACS study. We examined many of these studies in detail (see Working Paper 8) and discuss some of the possible reasons for the higher coefficients in Chapter 3, Section x. We explain at the end of Section x why we did not select one or more of these studies as an alternative to the large and extensively reanalysed ACS study for our core estimate. Nonetheless, these studies were not dismissed and were important in developing our views. A balance was struck between various counterbalancing factors – the large size and statistical power of the ACS study, the possibility that adjustment for spatial autocorrelation would reduce the coefficient and the possibility that allowance for exposure misclassification would increase it (see Box 2, page 40). These studies were also important in defining the uncertainty around the central estimate – the uncertainty range reflects the possibility that the best estimate of the true coefficient might be higher. Taking all the various factors into account, we are content with recommending a coefficient of around 6% at the present time. In the meantime, there is a need for studies evaluating exposure to $PM_{2.5}$ or related pollutants at a small spatial scale that approach the size and statistical power of the ACS study.

4 Plausibility of the coefficient

It has been suggested to us that the analysis of the plausibility of the coefficients could be refined by examining trends in rural mortality rates (that might be expected to give a rough representation of trends in mortality rates less affected by air pollution) and by examining trends in cardiovascular mortality rates in addition to trends in all cause mortality rates. These are useful ideas and, subject to availability of appropriate data, we hope to look into this at a later date.

5 Sulphate

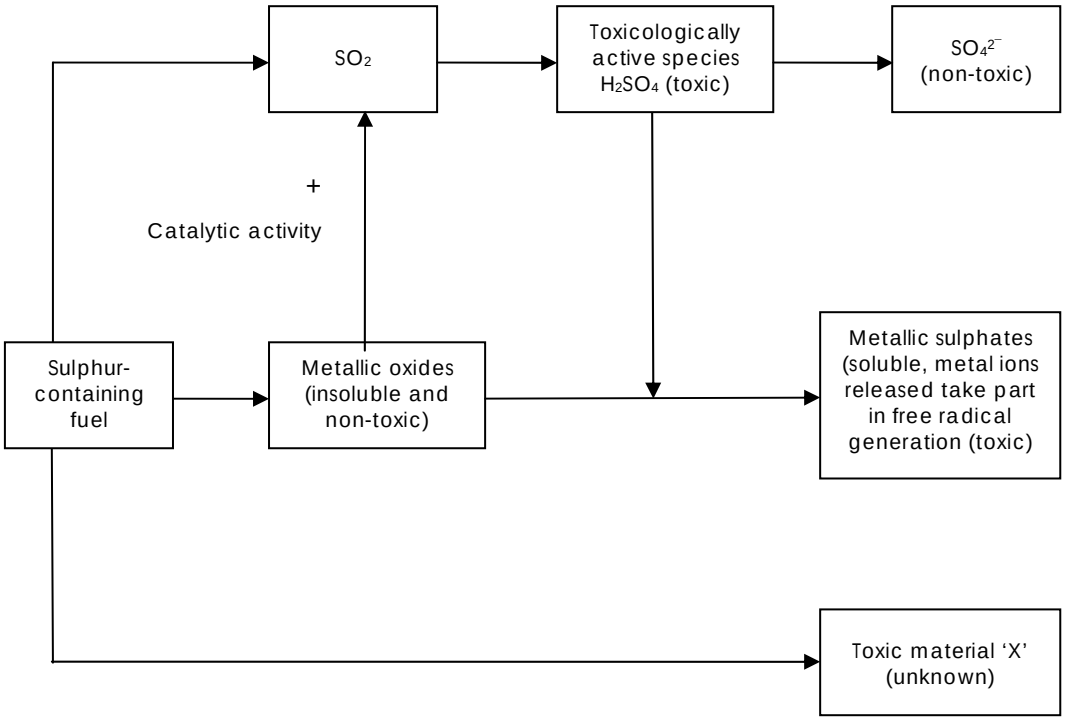
We note the comments made by the Joint Environmental Programme (JEP) regarding the benefits to health that may be delivered by reducing the sulphate component of $PM_{2.5}$ by reducing, further, emissions of sulphur dioxide. This is a complex issue. We have made some amendments to the report to increase clarity and we expand further on the issue here. We accept that if sulphate[1], itself a non-toxic material, were acting merely as a marker for toxic components of the $PM_{2.5}$ mixture then reducing sulphate concentrations, *per se,* would not reduce effects on health. Some policies to reduce emissions from sulphur-containing fuels might also reduce a toxic component produced by the same source but, as noted by JEP, this is

[1] We use the term 'sulphate' here to mean sulphate compounds such as ammonium sulphate and sodium sulphate. Particulate sulphate as measured will also include sulphuric acid (see Working Paper 2).

not necessarily the case. We think, however, that the actual role of sulphate is more complicated than this. We think that sulphate represents a chain of chemical reactions from sulphur dioxide that produces toxicologically active species: these include sulphurous and sulphuric acids, sulphites, bisulphites and bisulphates. Some of these are acidic species and on reaction with water generate hydrogen ions. Hydrogen ions are themselves toxicologically active and may also react with metal oxides leading to the release of soluble and toxic metal species (Ghio *et al*, 1999). As was mentioned in our report, it has been suggested that certain metal ions could play a role at the surface of particles leading to the formation of oxidative free radicals. These are known to be very toxicologically active. Sulphate, then, acts as a marker for the *formation* of, rather than simply the *presence* of, toxicologically active species and we argue that by reducing sulphate, by limiting its production from sulphur dioxide, the formation of a number of active species will also be reduced (see question v in Chapter 3). This, we think, will have a beneficial effect on health.

These points are illustrated in the figure below.

Figure: Sulphate as an indicator of toxicologically active species produced as a result of combustion of sulphur-containing fuel



SO_4^{2-} will remain an index of toxicity if the SO_4^{2-}/X ratio is maintained as fuel usage is reduced.

SO_4^{2-} will remain an indicator of toxicity even if X does not exist because SO_4^{2-} production will indicate the formation of H_2SO_4 and metallic ions.

Several of the points raised in the comments relate to atmospheric chemistry and policy issues, and would benefit from wider discussion – we suggest that this should form a separate strand of work from this report.

6 Latency

We note Professor David Coggon's comments relating to latency and agree that the persistence of effects on risk is important in addition to the latency between exposure and first elevation of risk. We have included a diagram (Figure 3.4, page 30) to explain this more clearly and intend to develop discussion of this issue in future work.

7 Particle composition

We agree with the comment that too little is understood about how the composition of particles (such as the capacity to generate reactive oxygen species) is related to effects on health. This is particularly true in the case of the effects of long-term exposure to particles. Creative research in this area is to be encouraged.

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Appendix 3

Glossary of Terms and Abbreviations

ACS	American Cancer Society
AHSMOG	Adventist Health and Smog Study
Ambient air	Outdoor air
Black smoke (BS)	Non-reflective (dark) particulate matter, measured by the smoke stain method
CAFE	Clean Air for Europe
Carbon monoxide (CO)	A poisonous gas produced by incomplete oxidation of fossil fuels
Cardiovascular disease	Disorders of the heart and circulatory system
COMEAP	Committee on the Medical Effects of Air Pollutants
Confidence interval	If it is possible to define two statistics t_1 and t_2 (functions of sample values only) such that, θ being a parameter under estimate, $$P(t_1 \leq \theta > t_2) = \alpha$$ where α is some fixed probability (e.g. 0.95 or 95%), the interval between t_1 and t_2 is called a confidence interval. The assertion that θ lies in this interval will be true, on average, in a proportion α of the cases when the assertion is made. For example, 95% confidence intervals are calculated in such a way that, in the absence of bias, 95% of such intervals will include the parameter that is being estimated
EPAQS	Expert Panel on Air Quality Standards
Epidemiological studies	Investigations of diseases conducted at a population level
HEI	Health Effects Institute
International Classification of Disease (ICD)	The International Classification of Disease is an internationally agreed system for classifying diseases in which code numbers are allocated to disease categories and subcategories
MAAPE	Advisory Group on the Medical Aspects of Air Pollution Episodes
Meta-analysis	A statistical method used to combine the results of a number of individual studies
Nitrogen dioxide (NO_2)	A gas produced during combustion by the oxidation of atmospheric nitrogen
Ozone (O_3)	A strongly oxidant gas produced from oxygen

Particle	A minute portion of matter – frequently a very small solid or liquid particle (or droplet) of micrometre or nanometre dimensions
PM	Particulate matter
$PM_{2.5}$	Mass per cubic metre of particles passing through the inlet of a size selective sampler with a transmission efficiency of 50% at an aerodynamic diameter of 2.5 micrometres
PM_{10}	As above, with 10 micrometres
QUARK II	Quantification of Air Pollution Risks in the UK (subgroup of COMEAP)
ROFA	Residual oil fly ash
Relative risk (RR)	Relative risk is used in this report to compare age-specific death rates in two groups that differ in terms of exposure or other characteristics, e.g. in terms of their average annual exposure to $PM_{2.5}$. It is derived as the ratio of age-specific death rates in the two groups (assuming other factors are equal) because exposure is expected to increase age-specific death rates by some multiplicative factor, to be estimated from epidemiological studies. Relative risk is a measure of that factor
SD	Standard deviation
Six Cities Study	A long-term cohort study conducted in the USA
Spatial autocorrelation (spatial clustering)	Occurs when a variable (e.g. mortality) shows more similar values nearby than at more distant locations
Sulphur dioxide (SO_2)	An acidic gas formed by oxidation of sulphur found in fossil fuel
Sulphate (SO_4^{2-})	Small airborne particles comprising mainly ammonium sulphate or bisulphate and formed by the reaction between sulphuric or sulphurous acid and ammonia
TEOM	Tapered element oscillating microbalance. A method of measuring mass of particles in real time
TSP	Total suspended particles
UNECE	United Nations Economic Commission for Europe
µm	Abbreviation for micrometre or micron (a unit of length). 1 µm = one thousandth of a millimetre
µg/m³	Micrograms per cubic metre. 1 µg = 1 millionth of a gram
WHO	World Health Organization

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